

Preparation of taste masked orally disintegrating tablets by compression of coated pellets

Inaugural-Dissertation
to obtain the academic degree
Doctor rerum naturalium (Dr. rer. nat.)

submitted to the Department of Biology, Chemistry and Pharmacy
of Freie Universität Berlin

by

KATHRIN EVA BÜRKI

from Aarau, Switzerland

2016

Die vorliegende Arbeit wurde von November 2011 bis Mai 2016 unter der Leitung von Prof. Dr. Roland Bodmeier im Institut für Pharmazie angefertigt.

1. Gutachter: Prof. Dr. Roland Bodmeier

2. Gutachter: Prof. Dr. Philippe Maincent

Disputation am 12.07.2016

Acknowledgements

I would like to express my deepest thankfulness to all those who helped me during the work on my thesis at the Freie Universität Berlin.

First of all, I want to thank my supervisor Prof. Dr. Roland Bodmeier for giving me the opportunity to work and study in his research group, for his supervision, and scientific support.

I kindly thank Prof. Dr. Philippe Maincent for his readiness to evaluate my thesis.

I am deeply grateful to Rahul, Marina, Benjamin, Gaith, Jelena Marco, Rick, Zoha, and Marius for proofreading parts of my thesis and for their valuable comments and suggestions.

I thank my lab mates Agnieszka, Benjamin and Miriam for the always friendly atmosphere in R133, for their support, the motivating discussions and for their friendship.

Special thanks also to Frau Ewest, Andreas Krause, Stefan Walther and Gabriela Karsubke for helping me to master the challenges of labwork and paperwork.

Furthermore, I thank all my colleagues of the research group for the scientific discussions, for their valuable input and assistance, and for the unforgettable lunchbreaks and group activities.

Finally, I would like to express my deepest gratitude to my family and friends for their love and encouragement during this time and throughout my life.

Table of contents

1	Introduction	1
1.1	Taste masking	1
1.1.1	Taste perception	1
1.1.2	Taste masking techniques.....	2
1.1.2.1	Sweeteners and flavors	2
1.1.2.2	Coating.....	2
1.1.2.3	Granulation	4
1.1.2.4	Complexation.....	6
1.1.2.5	Inhibition of taste receptors.....	6
1.1.2.6	Improved texture	7
1.1.3	Taste tests	8
1.1.3.1	<i>In vivo</i> taste tests	8
1.1.3.2	<i>In vitro</i> taste tests	10
1.2	Orally disintegrating tablets.....	12
1.2.1	Preparation	12
1.2.1.1	Lyophilisation (freeze-drying)	12
1.2.1.2	Compression	13
1.2.1.3	Molding.....	16
1.2.2	Disintegration testing	16
1.2.2.1	<i>In vitro</i> disintegration tests.....	16
1.2.2.2	Disintegration media	19
1.3	Preparation and compaction of coated pellets	20
1.3.1	Fluid-bed coating of pellets.....	20
1.3.2	Compaction process	21
1.3.3	Factors affecting coating damage during compaction.....	21
1.3.3.1	Coating properties	22

1.3.3.2	Pellet cores	23
1.3.3.3	Tableting excipients	24
1.3.3.4	Tableting process	27
1.4	Excipients and drugs.....	28
1.4.1	Polymers for taste-masking coatings.....	28
1.4.2	Drugs	29
1.5	Research objectives	31
2	Materials and methods	32
2.1	Materials	32
2.2	Methods	34
2.2.1	Pellet preparation.....	34
2.2.2	Pellet characterization	35
2.2.3	Drug release tests	36
2.2.4	Microscopic pictures	38
2.2.5	Compressed density of tableting excipients	38
2.2.6	Tableting.....	38
2.2.7	Characterization of tablets.....	39
2.2.8	Preparation of free films.....	39
2.2.9	Characterizations of free films	40
2.2.10	Drug solubility.....	41
2.2.11	Scanning electron microscope (SEM) pictures	41
2.2.12	Calculation of difference factor.....	41
3	Results and discussion.....	43
3.1	Effect of coating properties	44
3.1.1	Water-soluble, acid-soluble and insoluble polymers as coating material for taste masking	44
3.1.1.1	Drug release from uncompressed pellets	44

3.1.1.2	Effect of buffer concentration and ionic strength on coating disintegration and drug release from pellets with acid-soluble coatings.....	50
3.1.1.3	Compression sensitivity of Kollicoat Smartseal, Eudragit E, and ethyl cellulose coatings	53
3.1.2	Subcoatings	55
3.1.3	Mechanical properties	62
3.1.3.1	Plasticizer type and concentration.....	62
3.1.3.2	Admixing of the more flexible polymer Kollicoat SR to Kollicoat Smartseal	68
3.1.3.3	Magnesium stearate content.....	70
3.1.4	Coating level	71
3.2	Effect of drug solubility and drug layer composition.....	73
3.2.1	Drug solubility.....	73
3.2.2	Acid-soluble or highly viscose polymers as binder in the drug layer	77
3.2.3	Drug loading.....	79
3.3	Effect of mechanical stress during tableting.....	81
3.3.1	Compression force.....	81
3.3.2	Pellet fraction in tablets.....	82
3.3.3	Pellet core type	84
3.3.4	Tableting excipients (excipient powders and layers)	86
3.3.4.1	Density of excipients and coated pellets for volume based calculation of tablet compositions.....	87
3.3.4.2	Lubricant selection for tablets prepared of coated pellets with excipient layers	89
3.3.4.3	Cushion and disintegration layers versus excipient powders	90
3.3.4.4	Cushion layer composition	94
3.3.4.5	Disintegration layer composition	96
3.3.4.6	Glidant layer.....	97

3.3.4.7	Release in pH 1.0	100
3.3.4.8	Tablet wetting time	101
4	Summary	105
5	Zusammenfassung	110
6	Appendix	116
6.1	Coating formulations	116
6.2	Excipient layer formulations	118
7	References	119
8	Curriculum vitae.....	131

Abbreviations

C.I.	Coating level
EC	Ethyl cellulose
FDA	Food and drug administration
HCl	Hydrochloric acid
HEC	Hydroxyethyl cellulose
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
L-HPC	Low-substituted hydroxypropyl cellulose
MCC	Microcrystalline cellulose
Mg stearate	Magnesium stearate
NaCl	Sodium chloride
PEG	Polyethylene glycol
PEO	Polyethylene oxide
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
ODT	Orally disintegrating tablet
RH	Relative humidity
S.D.	Standard deviation
TA	Triacetin
TBC	Tributyl citrate
Tramadol HCl	Tramadol hydrochloride
USP	United states pharmacopoeia

1 Introduction

The present thesis deals with the preparation and characterization of taste-masked orally disintegrating tablets (ODTs) prepared by compaction of coated pellets. In this introductory chapter, a review is given on various topics related to this subject. It starts with an introduction to taste perception and a review of several taste masking techniques as well as test procedures to measure taste intensity. Next, the research on preparation techniques for ODTs is reviewed, followed by an introduction and evaluation of disintegration testing methods. Finally, problems associated with the compaction of coated pellets are highlighted and factors discussed which influence coating damage during compression.

1.1 Taste masking

1.1.1 Taste perception

The taste of a drug product is an important parameter as it affects patient acceptance and compliance. Ultimately, it will also influence prescribing practice and thus the commercial viability of a product [1].

The organoleptic sensation in the oral cavity is a combination of taste, odor and texture of the ingested material. There are only five primary taste qualities: sweet, sour, salty, bitter and umami, whereas there is a large number of odor qualities [2]. Together, these gustatory and olfactory sensations make up for the flavor of a substance [3].

Taste receptor cells are organized in taste buds. These taste buds are located in papillae on the tongue epithelium. Papillae located at the back of the tongue are especially sensitive to bitter taste, whereas the ones on the posterior lateral edge are particularly sensitive to sour and bitter and the ones at the front of the tongue are most sensitive to sweet taste [4].

The taste of a substance is the result of complex interactions of the dissolved molecules with taste cells. Interactions of Na^+ or H^+ with ion channels lead to salty or sour taste, respectively [5, 6]. Molecules with bitter, sweet and umami taste are recognized by G protein-coupled receptors [4, 7-10]. Receptors responsible for bitter taste detection belong to the TAS2R/T2R family of G protein-coupled receptors [11].

Taste provides valuable information about food and the reactions range from attraction and pleasure to aversion [9]. Sweet-tasting molecules include carbohydrates and some amino acids which are important in nutrition and sweet taste is generally considered pleasant. Monovalent

cations, which are crucial for the electrolyte balance, mediate a salty taste. Sour taste is produced by protons and umami taste by monosodium glutamate and disodium guanylate. Bitter taste sensation is triggered by a large variety of compounds including divalent cations, alkaloids and some amino acids. Many bitter-tasting chemicals are toxic. Thus, bitter taste functions as a warning signal and is usually considered unpleasant [6]. Furthermore, how a certain taste is perceived is influenced by the individual's experience and age and also by the culture in which the person grew up [2, 12].

1.1.2 Taste masking techniques

Many drugs have an unpleasant taste and taste masking is thus necessary to obtain palatable formulations. Taste masking can be achieved by three main principles: covering the unpleasant taste sensation by a pleasant one, preventing contact of trigger molecule and taste receptors, and inhibiting the taste receptor response. Different techniques used for taste masking of pharmaceutical products are discussed in the following paragraphs.

1.1.2.1 Sweeteners and flavors

Bitter taste sensation is reduced in the presence of sweet or salty substances [13]. A sweet taste is generally considered pleasant. Therefore, almost all marketed orally disintegrating tablets (ODTs) contain either sugar or an artificial sweetener. Most commonly, the artificial sweetener aspartame is used. The palatability of ODTs is also improved by flavors such as mint, orange or strawberry flavor [14]. The taste-masking effect of sweeteners and flavors is limited and often insufficient for drugs with a high bitterness intensity, a high water solubility or a high dose. In these cases, other taste-masking techniques have to be used in addition [15].

1.1.2.2 Coating

Coating is an efficient taste-masking technique. The drug is completely covered by a polymer film which delays its dissolution. Thus, the interaction of drug and taste receptors is prevented. Water-soluble, water-insoluble and acid-soluble (reverse-enteric) polymers are used for taste-masking coatings as well as mixtures thereof. The coating can be applied either by spray coating or the film is generated in a microencapsulation process.

Spray coating

A polymer solution or dispersion is sprayed onto drug containing cores (e.g. drug particles, granules, pellets or tablets). In the case of tablets, coating is usually performed in a drum coater whereas fluid-bed coaters are used for particles, granules or pellets [16].

Water soluble polymers such as hydroxypropyl methylcellulose (HPMC) or hydroxyethyl cellulose (HEC) have been used as taste-masking coatings. For example, taste-masked chewable or orally disintegrating tablets of ibuprofen have been prepared by coating drug pellets with HEC or HPMC [17, 18]. An HPMC coating was also used for taste masking of tablets containing acetylsalicylic acid [19]. An advantage of water-soluble polymers is that they only delay the drug release for a short time and do not retard it afterwards [17]. However, as a consequence, they provide only short taste masking periods and their taste-masking efficiency is inferior to that of polymers which are insoluble in saliva [18, 19].

Another approach to achieve a low drug release in the oral cavity followed by a fast release in the stomach is the use of acid-soluble polymer coatings. Quinine sulfate pellets were coated with the acid-soluble polymer Eudragit E PO [20]. At a coating level of 20%, taste masked pellets were obtained. These pellets provided immediate release in acidic medium. Eudragit E was also used in a dry powder coating process to produce taste masked theophylline tablets [21]. Orally disintegrating tablets were prepared of acetaminophen pellets coated with 3% Kollicoat Smartseal [22]. A human taste panel confirmed that the taste of the drug was masked for at least 30 seconds.

When water-insoluble polymers are used, they are often combined with water-soluble or acid-soluble polymers to ensure a fast drug release in the stomach. For example, coatings containing a combination of the water-insoluble ethyl cellulose and the water soluble HPMC were applied to mask the taste of sparfloxacin [23] or lafutidine [24]. By adjusting the ratio of the two polymers, it was possible to achieve the lag time necessary for taste masking followed by a fast drug release. The drug release rate after the lag time was also increased by the addition of low substituted hydroxypropyl cellulose (L-HPC) to the pellet cores [23]. It swelled and thus led to rupturing of the polymer coating. The combination of acid-soluble Eudragit E 100 and water-insoluble cellulose acetate was used to prepare taste masked levofloxacin powder for reconstitution [25].

Aside from polymers, also hydrogenated oils have been used for taste-masking coatings [26]. They were applied on drug granules in a fluid bed coating apparatus. However, this process required the use of the toxic solvent methylene chloride.

Microencapsulation

Taste-masked microparticles can be prepared by coacervation techniques (phase separation methods). With this technique, drug particles are completely covered by the wall material.

For example, taste-masked microcapsules of diclofenac sodium were prepared with ethyl cellulose and a solvent/non-solvent system of toluene and petroleum ether [27]. Ueda et al. developed a wet agglomeration technique to prepare spherical cores of drug, lactose and disintegrant [28]. The cores were subsequently encapsulated with Eudragit RL by phase separation. With Primojel as disintegrant in the core, microcapsules exhibited rapid drug release after the lag time due to rupturing of the capsule wall.

1.1.2.3 Granulation

By means of granulation, the drug is embedded in a matrix of polymeric or lipidic binder. Contrary to coating, the drug is not completely covered by the polymer or lipid. Nevertheless, the delay of drug dissolution can be enough to provide sufficient taste masking. Furthermore, taste masking of granules which have a matrix structure is expected to be less affected by compaction compared to coated particles [29]. Several techniques are used to produce granules which include wet or melt granulation in high-shear mixers, spray drying/congealing, and hot-melt extrusion.

Granulation in mixers

Taste-masked acetaminophen granules were prepared in a high shear mixer using polyvinyl pyrrolidone (PVP) as binder [30]. Three different wet-granulation methods were applied: water granulation, steam granulation or granulation with an aqueous PVP solution. Steam granulation was the most effective technique with regard to taste masking. Compared to the other methods, steam granulation led to the smoothest particle surface and slowest dissolution rate. In an invention of Mukherji et al. the drug is granulated with an aqueous granulation fluid containing a dissolved binder (e.g. sucrose) and dispersed particles of the water-insoluble polymer Eudragit NE [31].

Spray drying/congealing

The model drugs roxithromycin and ibuprofen were dispersed either in a solution of HPMC or a dispersion of Eudragit L followed by spray-drying [32]. The combination with Eudragit L led to an improved taste as determined with an electronic tongue. The formulation containing HPMC had the same taste signal as pure drug. In another study, famotidine was spray-dried in a colloidal solution of Eudragit E PO and the particles were compressed to obtain ODTs [33]. The taste was significantly improved compared to ODTs containing unprocessed famotidine powder. Taste-masked particles of the macrolide antibiotic clarithromycin were developed by spray-congealing the drug powder in a matrix of glycerol monostearate and Eudragit E PO [34, 35]. The reconstituted liquid dosage form of spray-congealed powder had a better palatability compared to that of spray-coated particles.

Hot melt extrusion and gel extrusion

Extrusion is another well-known technique to embed drug in a polymer or lipid matrix. Most commonly, the polymeric or lipidic carrier is in the molten state during extrusion (hot melt extrusion). However, the extrusion of gels has also been reported. The drug is either dissolved or suspended in the carrier.

Ibuprofen granules were produced by hot-melt extrusion with Eudragit E PO [36]. The extrusion was performed at 140 °C where the drug dissolved in the molten polymer. The extrudates were milled with a cryogenic mill and compressed to ODTs. A human taste panel confirmed that the tablets had no bitter taste. Paracetamol granules were prepared by hot-melt extrusion with either Eudragit E PO or Kollidon VA64 followed by grinding with a ball mill [37]. Taste masking efficiency was similar for both polymers and increased with decreasing drug loading.

Gel-extrusion was performed with Eudragit E 100 [38]. The polymer powder was mixed with drug (pirenzepine or oxybutynin) and 10% ethanol was added to obtain a gel. This was then extruded using a syringe. The dry extrudates were crushed in a mortar and compressed to ODTs. The tablets disintegrated *in vivo* in less than 30 seconds and had no bitter taste. The same procedure was also used to prepare taste-masked ODTs of chlorpheniramine maleate [39].

Witzleb et al. developed a method for continuous solid lipid extrusion and milling [40]. Investigated lipids included glyceryl monostearate, glyceryl tristearate, cetyl palmitate and solid paraffin. Problems with electrostatics could be overcome by the addition of PEG. Granules

with glyceryl monostearate and PEG containing up to 70% of the anthelmintic drug praziquantel were well accepted by cats.

1.1.2.4 Complexation

When the drug is bound to polymers or cyclodextrins, it cannot interact with taste receptors and thus will not cause an unpleasant taste.

Ion exchange resins are polymers with ionic functional groups to which oppositely charged drugs can bind by ionic interaction. After ingestion, the drug is gradually exchanged by electrolytes from the gastro-intestinal fluids and thus released from the resin. Taste-masked ODTs of tramadol HCl were prepared by binding the drug to Tulsion 335, a cation exchange resin with carboxylic groups [41]. The drug/resin complex did not release any drug within 300 seconds in phosphate buffer pH 6.8. The antihistaminic drug doxylamine succinate was formulated as taste-masked ODT using the cation exchange resin Indion 243 [42].

Cyclodextrins (CD) are cyclic oligosaccharides. Due to their characteristic molecular structure, they have a hydrophilic outside and a hydrophobic interior. In their apolar cavity, a big variety of hydrophobic guest molecules can be entrapped. The most commonly used CD for pharmaceutical applications is β CD which consists of seven glucopyranose units [43]. Drug/CD complexes can be prepared by adding drug solutions to highly concentrated CD solutions. The complexes precipitate and are collected by filtration [44]. Several marketed products are available which contain cyclodextrins to mask the taste of bitter drugs such as cetirizine hydrochloride or nicotine [43, 45, 46]. The taste-masking efficiency of cyclodextrins complexes containing the drug famotidine increased when HPMC was included as a third component [46]. The ternary complexes had a higher stability constant compared to binary complexes which led to improved taste masking but did not retard the release in 900 mL of buffer pH 4.5.

1.1.2.5 Inhibition of taste receptors

While bitter taste receptors are activated by a wide variety of chemical substances, only few substances are known as inhibitors [47]. An ideal bitter blocker should prevent the bitter taste sensation caused by variety of different chemicals. Furthermore, the inhibition should be selective for bitter receptors and reversible, and the intake of the inhibitor must be safe.

Lipoproteins (e.g. phosphatic acid with β -lactoglobulin) reduce the bitter taste of various bitter drugs including quinine, promethazine, theophylline and propranolol [48]. The inhibition is reversible and independent of whether the lipoprotein is administered together or just before the bitter stimuli. The perception of saltiness of sodium chloride and sweetness of sucrose is not reduced. An additional advantage of lipoproteins is that they originate from food (soybeans, milk, eggs) and are considered as safe.

Probenecid, which is approved for the treatment of gout, inhibits a subset of TAS2Rs bitter taste receptors [47]. *In vivo* it reduced the bitter taste of salicin but not of saccharin which binds to another subtype of TAS2R. Thus, probenecid was suggested as a tool to investigate bitter taste reception on a molecular level and as a lead for the development of bitter blockers.

A high-throughput screening was used approach to search for molecules which inhibit the activation of the bitter taste receptor hTAS2R31 by the artificial sweeteners saccharin and acesulfame [49]. The molecule GIV3727 was identified as inhibitor and its suppression of bitter taste perception was confirmed *in vivo*.

1.1.2.6 Improved texture

Not only taste is important for the palatability of ODTs but also their texture or “mouthfeel”. Insoluble excipients or drugs can cause an unpleasant gritty, rough or dry feeling. Approaches to improve the mouthfeel include reducing the particle size of excipients, increasing the viscosity of the slurry, and increasing the fraction of soluble excipients.

Microcrystalline cellulose (MCC) with a mean particle size of 7 μm (Avicel PH-M-06) was superior with regard to texture compared to MCC having a mean particle size of 100 μm (Avicel PH-102) [50]. However, the small particle size grade exhibited poor flowability. On the other hand, large granules (approx. 500-600 μm) of the soluble fillers sucrose, lactose and mannitol, did not cause a gritty feeling. They could thus be used in combination with Avicel PH-M-06 to improve its flowability.

Siebert et al. suggested the use of HPMC in ODTs to increase the viscosity of the slurry [51]. To achieve an organoleptically pleasant slurry, the viscosity should be in the range of 25`000 to 500`000 cps.

ODTs prepared of MCC, lactose and Ac-Di-Sol had an unpleasant mouthfeel due to the high amount of insoluble MCC [52]. Therefore, the percentage of MCC in the excipient mixture was

reduced to 40%. Additionally, taste and texture of the ODTs were improved by the sugar alcohol erythritol which has a negative heat of solution and leads to a cool and sweet taste sensation.

1.1.3 Taste tests

1.1.3.1 *In vivo* taste tests

Human taste panels

The most widely used method to assess the taste of pharmaceutical products is the evaluation by a human taste panel. In such studies, the gustatory sensation is determined by healthy human volunteers under well-controlled conditions. Clinical testing on children is restricted due to ethical considerations. Therefore, also pediatric formulations are usually evaluated by adults even though their taste perception and preferences may differ from those of children. Volunteers are included or excluded from the panel based on parameters such as age, health, intake of medication, smoking behavior or impaired taste perception. Panelists are instructed regarding sample application method and correct rating of taste sensations. In some industries (e.g. wine, coffee, beer), well trained specialists, so called expert tasters, are responsible for the evaluation of a particular product. However, for pharmaceutical products, panel members are typically laypersons [53-55].

Methods of taste evaluation can be grouped into descriptive tests, discrimination tests and scaling tests. In descriptive methods, the product's sensory characteristics are described in words or numbers. Discrimination tests include difference tests and ranking. Difference tests evaluate whether there is a perceivable difference between products. In ranking tests, a series of samples is ranked with regard to a certain attribute [54]. In scaling tests, taste qualities are rated using a given scale. Different kinds of scales have been applied. For example, bitterness was evaluated on an intensity scale ranging from 0 (none at all) to 4 (maximum imaginable intensity). In some studies, the panelists were trained before the test with standard solutions [13, 56]. Quinine HCl solutions with concentrations between 0.01 and 1.00 mM were used and the bitterness scores defined as 0, 1, 2, 3, and 4, respectively. The label magnitude scale is a semantic scale ranging from "barely detectable" to "strongest imaginable" with a quasi-logarithmic spacing between the labels (Fig. 1) [57, 58]. Contrary to the scale described above, it yields intensity data with ratio properties (i.e. a sample with twice the score is twice as bitter). Affective or hedonic scales provide information about how much volunteers like or dislike a

product. This method is also called acceptance test. For example, products are rated on a nine-point scale ranging from “like extremely” to “dislike extremely” [54].

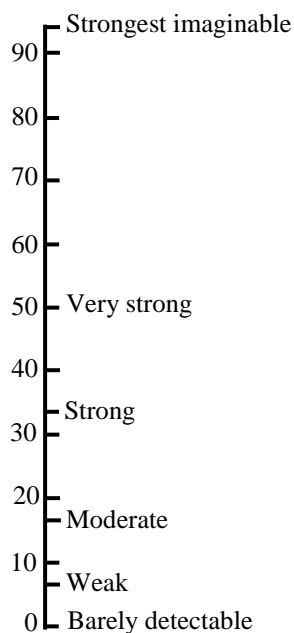


Fig. 1. Label magnitude scale developed by Green et al. [58].

Animal studies

Animals used for taste tests include rats, mice, cats and dogs [53]. Most common test methods are brief-access tests, conditioned taste aversion test or two-bottle preference tests in rats.

In a brief-access test, rats are trained before the test to drink immediately when they have access to a bottle [59, 60]. During the test, bottles with sample solutions are presented to the rat for 10 or 30 seconds. The number of licks is measured and serves as indicator for the palatability of the solution. Rats are able to detect various bitter drugs and can distinguish between different concentrations of bitter compounds.

Conditioned taste aversion tests make use of the fact that animals avoid the ingestion of solids or liquids which have led to aversive postingestional consequences [61]. During the conditioning phase, an aversion to a certain taste (conditioned stimulus) is created. The more the test stimulus resembles this conditioned stimulus, the stronger the aversion (i.e. suppression of the intake).

In a two-bottle preference test, rats have unrestricted access to two bottles, one with water and one with the test solutions [61]. The amount of fluid intake from each bottle is determined over a relatively long time (e.g. 24 h).

1.1.3.2 *In vitro* taste tests

In vivo taste evaluation has several drawbacks such as subjective results with a high variability, expensiveness and ethical considerations due to potential adverse effects. Therefore, *in vitro* taste tests are becoming more and more popular using either dissolution tests or electronic tongues [55].

Dissolution tests

Dissolution tests provide helpful information if taste masking of a formulation relies on the suppression of drug release. They cannot provide information about the effect of sweeteners or flavors on taste perception. Results of dissolution studies depend on the type and amount of fluid used as well as on the dissolution apparatus (i.e. mechanical stress). Ideally, the test conditions should mimic those in the oral cavity.

Most commonly used fluids for *in vitro* taste tests are phosphate buffers with a pH between 6.2 and 6.8 [21, 35, 41, 62-65] or distilled water [20, 23, 66]. Even though in some cases such buffer solutions are called simulated salivary fluid, they resemble saliva only with regard to pH but not with respect to buffer capacity or electrolyte composition and concentration[67]. Only rarely, researchers have used release media with a composition similar to that of saliva [68].

In some studies, a standard volume of 900 mL dissolution medium was used [20, 21, 35]. However, this is much more than the amount of saliva in the oral cavity. Therefore, in other studies, *in vitro* taste tests were performed using a reduced amount of fluid (5-10 mL) [23, 41, 62-65].

Tests with 900 mL of medium are operated in a compendial dissolution apparatus (USP apparatus I or II). On the other hand, tests with a small fluid volume are performed in test tubes, volumetric flasks or syringes with or without agitation. Yajima et al. [69] and Hoang Thi et al. [70] developed methods in which the sample is placed in a small column and the release medium is pumped through the column.

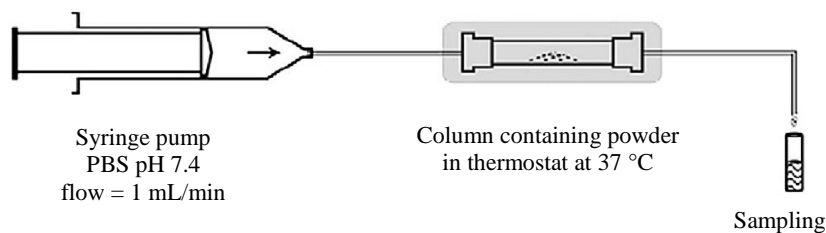


Fig. 2. Mini column apparatus used by Hoang Thi et al. (reproduced with permission from [70]).

Results of dissolution tests have been evaluated with the help of *in vivo* studies in which the bitterness threshold of the particular drug was determined) [23, 63, 65, 66]. This concentration was then set as the limit which must not be exceeded during the release test (usually 60 seconds). All of this release test were performed in 10 mL of medium which will lead to a higher dilution than during the intake of ODTs. However, this was not considered in the evaluation of the results.

Electronic tongues

Electronic taste sensing systems or electronic tongues are sensor array systems which imitate the interaction of molecules with human taste receptors. The chemicals interact with the surface of a sensor and initiate changes in electric potentials. These electrochemical signals are recorded and evaluated by a computer. Two electronic tongues are commercially available (α Astree electronic tongue and Insent taste sensing system) which use a set of seven or eight sensors for the measurements. Data evaluation is complex and typically done with multivariate data evaluation using algorithms included in the particular software. The α Astree electronic tongue has a bitterness prediction module. To predict the bitterness of an unknown substance, the electronic tongue is first calibrated by measuring a set of bitter substances and correlating the results to *in vivo* data [71]. Contrary to dissolution tests, electronic tongues can also be used to predict the effect of sweeteners [72].

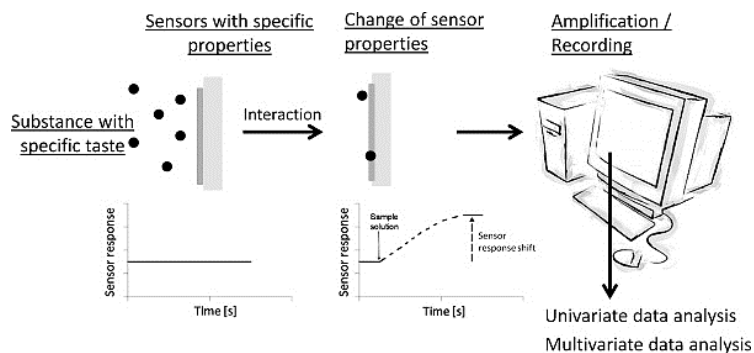


Fig. 3. Basic principle of electronic tongues (reproduced with permission from [71])

1.2 Orally disintegrating tablets

Orally disintegrating tablets (ODTs) are tablets which quickly dissolve or disintegrate in the oral cavity. Chewing or drinking of liquids is not needed. ODT is the term used by the American Food and Drug Administration (FDA) whereas in the European Pharmacopeia they are called orodispersible tablets. Other terms used in the literature are fast disintegrating, fast melting, fast dispersing, rapid dissolve, rapid melt, and quick disintegrating tablet [73]. The FDA recommends an *in vitro* disintegration time of 30 seconds or less [74] while the European Pharmacopeia allows for an *in vitro* disintegration time of three minutes [75].

ODTs have been on the market since the early 90s [76]. They were developed for patients who have difficulties to swallow conventional tablets. For example, this applies to pediatric and geriatric patients and people suffering from diseases which impair swallowing (e.g. Parkinson disease, invasive tumors) [74]. Swallowing difficulties are a prevalent problem: it is estimated that about 26% of the total patient population have problems to swallow a tablet [77]. In nursing homes, about 40% of the patients have swallowing difficulties [78].

Compared to liquid dosage forms, which are also easy to swallow, ODTs are superior regarding stability, dosing accuracy and small packaging size. Furthermore, they are used by the pharmaceutical industry as a new dosage form in the life cycle management of drugs [73].

1.2.1 Preparation

ODTs have been prepared by lyophilisation, compression and molding. The preparation of ODTs is challenging since several of their desired characteristics are in conflict with each other: very fast disintegration, high tensile strength, small size (i.e. low amount of excipients) and a simple manufacturing process. A number of platform technologies has been developed for the manufacturing of ODTs: e.g. Zydis (Cardinal Health), OraSolv/DuraSolv (Cima Labs), and FlashDose (Biovail) [73]. They are discussed in the context of the following paragraphs reviewing the above mentioned preparation techniques.

1.2.1.1 Lyophilisation (freeze-drying)

For the production of freeze-dried ODTs, drug solutions or suspensions are placed in molds and frozen. The solvent (typically water) is then removed in vacuum. The main advantage of ODTs prepared by freeze-drying is their almost instantaneous disintegration due to the highly porous

structure. Drawbacks are the time-consuming and expensive production and the poor physical stability [73].

The most well-known lyophilisation technique is Zydis (Cardinal Health) [79]. The matrix of Zydis tablets is composed of polymers such as gelatin, dextran or alginates and of saccharides such as mannitol or sorbitol. The polymers lead to a glassy-amorphous structure whereas the saccharides induce crystallinity and increase tablet hardness. A maximum of about 400 mg of water-insoluble drug and 60 mg of water-soluble drug can be included. The tablets are hygroscopic and require a relative humidity of less than 40% during storage.

1.2.1.2 Compression

Compression of tablets is a fast and inexpensive technique to manufacture ODTs. Different techniques have been applied to obtain compressed tablets which exhibit fast disintegration as well as sufficient hardness. They include granulation, spray drying or flash heating of excipients before compaction, the addition of superdisintegrants or effervescent couples, as well as humidity/heat treatment of tablets.

Granulation

Rapid disintegration granules were prepared by spray-coating of saccharides with a suspension of corn starch and a disintegrant [80]. The formulation with the best disintegration time to hardness ratio was mannitol spray-coated with a suspension of corn starch and crospovidone (2.5:1 w/w). Tablets with a breaking force of 70 N disintegrated in less than 30 seconds in the oral cavity.

Granules consisting of a plastic material (Mannogem EZ spray) and a water penetration enhancer (Maltrin QD 580) were prepared by wet granulation with sucrose solution [81]. Tablet hardness dramatically increased after this wet granulation process compared to directly compressed tablets. The porous structure of the excipients was maintained after compression which enabled fast water penetration. Tablets with a breaking force of 62 N and a disintegration time of 22 seconds were obtained.

Spray drying

Mannitol, MCC and aspartame were spray-dried together with either Kollidon CL, Ac-Di-Sol or sodium starch glycolate as disintegrant [82]. This excipient powders were then compressed

with 5% valdecoxib or metoclopramide as model drugs of poor and high solubility, respectively. Disintegration time and dissolution rate was faster for tablets with the spray-dried excipient base compared to directly compressed tablets. The fastest disintegration was achieved with Kollidon CL as disintegrant (< 20 seconds).

Similarly, mannitol, MCC and saccharine were spray-dried and the disintegrants Kollidon CL, Ac-Di-Sol or sodium starch glycolate were added to the formulations either before or after spray-drying [83]. When the disintegrants were added to the spray-drying fluid, disintegration times were in the same range as for directly compressed tablets. However, when the disintegrants were added after the spray-drying step, the disintegration of tables prepared with spray-dried excipients was faster.

In both studies described here, tablet hardness was between 3-4 kg for spray-dried formulations. Unfortunately, no values were reported for directly compressed tablets. Therefore, no conclusion can be drawn regarding the effect of spray drying on tablet hardness.

Candy floss technology

The candy floss technology is similar to the production of cotton candy. This flash heat technique has been patented by Fuisz Technologies (Chantilly, Virginia) and is known as FlashDose technology [73]. With this method, sucrose was subjected to a flash heat process in combination with hygroscopic sugar alcohols (e.g. sorbitol, xylitol) and Tween 80 as crystallization modifier [84]. The floss was chopped and partially recrystallized to obtain a free flowing powder with good compactibility. Recrystallization was achieved by treating the floss with ethanol or with heat and humidity. Drug or coated drug pellets were then mixed with the floss and compressed into tablets.

Marketed co-processed fillers for compression of ODTs

Several companies offer fillers especially designed for the compaction of ODTs: e.g. Ludiflash (BASF), Pardeck ODT (Merck), Pearlitol Flash (Roquette), Pharmaburst 500 (SPI Pharma) and Prosolv ODT (JRS Pharma) [85]. All of these fillers are based on mannitol which is co-processed with other excipients such as MCC, maize starch, crospovidone, croscarmellose sodium to improve flowability, compactibility and tablet disintegration.

Superdisintegrants

So called superdisintegrants are excipients which accelerate tablet disintegration at a relatively low concentration in the formulation (typically 1-10%). They act by wicking and extensive swelling. A high hydration capacity, swelling volume and swelling pressure are the key properties of efficient superdisintegrants [86]. The most commonly used superdisintegrants are cross-linked PVP (Kollidon CL, Polyplasdone), croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate (Explotab, Primojel) and L-HPC [36, 50, 52, 80, 87, 88].

Effervescent couples

Effervescent couples consist of a carbonate source and an acid. Upon contact with water, the chemical reaction leads to the formation of carbon dioxide gas which disrupts the tablet. The Orasolv technology (by Cima Labs) uses sodium bicarbonate and citric acid to prepare orally disintegrating tablets which disintegrate in less than one minute [89]. However, these tablets have a low hardness and a special packaging system is needed [73, 90]. To improve tablet hardness, a non-direct compression filler (powdered mannitol) in combination with a relatively high amount of lubricant (1.5%) is used in the Durasolv technology (Cima Labs) [91]. Durasolv tablets have a friability of less than 2% and disintegrate in less than one minute.

After treatment

Treating tablets with humidity after compaction is another technique to improve tablet hardness while at the same time maintaining fast disintegration properties.

For example, tablets made of granulated mixtures of various sugars and sugar alcohols (e.g. mannitol, lactose, glucose, maltose and fructose) were stored at 35°C/85% RH or 25°C/70% RH for 20 min up to 24 hours [92]. After drying at 30-40 °C, they had a hardness of 3-6 kp and disintegrated in less than 30 seconds.

Heat and humidity treatment was also used to prepare tablets of materials processed by candy floss technique [93]. After floss and drug were mixed and tamped into molds, partial recrystallization of the sugar was induced by exposing the tablets to 40°C/85% RH for 15 minutes. The ODTs had sufficient hardness for handling and dissolved in the mouth within seconds.

1.2.1.3 Molding

Tablets are molded from wet powder or granules either without the application of pressure or at compression forces significantly lower than in common tableting processes (compression molding or wet compression). Therefore, molded tablets have a higher porosity than conventional tablets which is advantageous for fast tablet disintegration. Typical excipients used for molded tablets are sugars, sugar alcohols and gums [94-97].

Low tablet hardness is often a problem for tablets prepared by molding. The higher the amount of excipients dissolved during the kneading step, the more solid bridges are formed. Therefore, tablet breaking force increased when more water was added or when sugars of higher solubility were used (sucrose or trehalose instead of mannitol or lactose) [98]. A high porosity and fast disintegration was ensured by the addition of a swellable disintegrant.

Lactose tablets made by wet compression had a ten times higher tensile strength than tablets of the same porosity (0.31) prepared by conventional compression technique [99]. Besides increasing the water content in wet granules, also reducing the particle size of lactose led to increased tensile strength.

1.2.2 Disintegration testing

1.2.2.1 *In vitro* disintegration tests

Compendial disintegration test

There is no compendial disintegration test designed specifically for ODTs. Therefore, the compendial disintegration test for conventional uncoated tablets is often also applied for ODTs. Six tablets are placed in a basket having a mesh at the bottom with 1.8-2.2 mm apertures. The basket is placed in 800-900 mL of water and moves up and down during the test. The endpoint is reached when all tablets have disintegrated in pieces small enough to pass through the mesh. The European Pharmacopoea requests for orodispersible tablets a maximum disintegration time of 3 min while the FDA suggests a disintegration time of not more than 30 seconds [74, 75].

The conditions in the compendial test do not at all resemble the situation in the oral cavity. Therefore, several alternative tests have been developed to provide results with a better correlation to *in vivo* disintegration times of ODTs.

Disintegration in small volume of water in test tubes

In a very simple test, tablets are placed in test tubes with 2 mL of water and the disintegration is observed visually [100]. An exact detection of the endpoint is difficult with this method. The test tubes had to be rotated gently at a 45° angle to check for remaining, undisintegrated parts.

Tablet wetting

In this tests, tablets are placed in a Petri dish with small amounts of water or on a wet filter paper in such a way that the tablet is not completely covered with fluid [85, 100-104]. The time needed for complete wetting of the tablets is determined. Some researchers suggest the addition of a dye to facilitate endpoint detection [85, 102, 104]. Test conditions resemble the *in vivo* situation with regard to the small amount of fluid available for disintegration. However, the test does not simulate the mechanical stress induced by tongue movement and tablet disintegration depends entirely on wicking. In a set-up developed by Kakutani et al., these forces are simulated by two weights placed on top of the tablet: one weight at the center of the tablet surface (inner weight) and one at the margins of the surface (outer weight) (Fig. 4) [105].

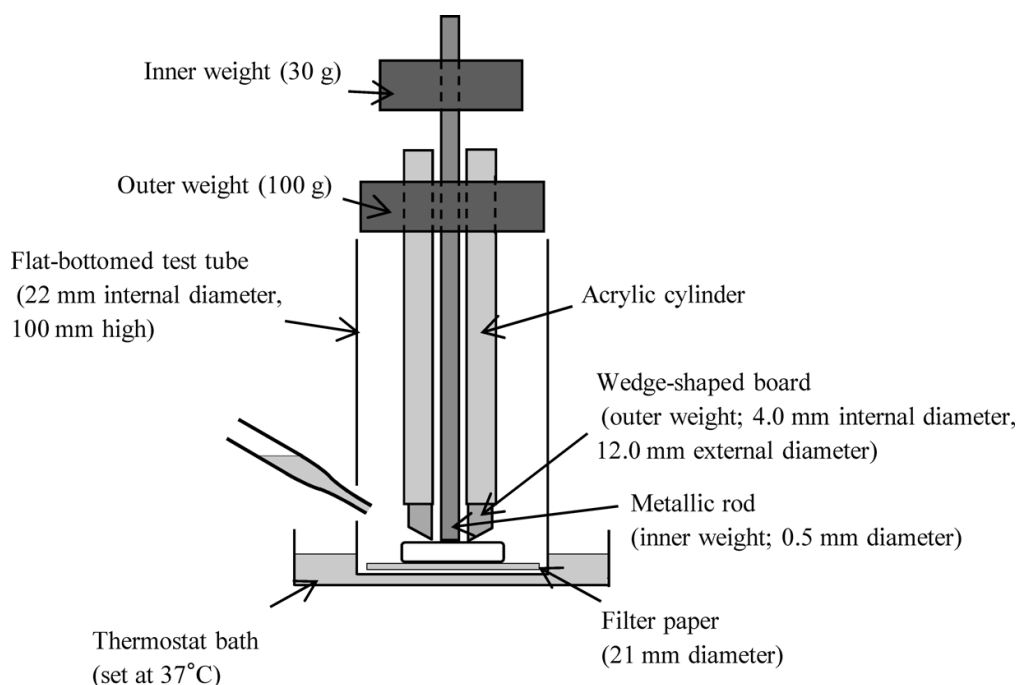


Fig. 4. Device for disintegration testing of ODTs developed by Kakutani et al. (reproduced from [105]).

Sieve methods

Tablets are placed on a sieve which is slightly immersed in the disintegration medium. The medium is stirred or agitated on a reciprocating shaker. The amount of fluid is limited depending on the depth of immersion, e.g. to 1 mL [73, 106]. Alternatively, instead of placing the sieve into the medium, water is dropped on the tablets at a constant rate (4 mL/min) [107]. Stirring or agitation of the medium as well as dropping it on the tablets creates a shear force simulating the force of slight tongue movement. Generally, tablets are considered disintegrated when all parts passed through the mesh. Alternatively, a camera and image analysis have been used to determine the remaining surface of the tablets and the endpoint of disintegration [106].

Rotating shaft methods

Rotating shaft devices have been developed to simulate the mechanical stress occurring during disintegration of ODTs in the oral cavity [108]. As for the sieve methods, tablets are placed on a wire gauze immersed in a disintegration medium. Additionally, a wetting sponge is placed on top and a rotating shaft with adjustable weight exerts force on the tablets during disintegration (Fig. 5). An automatic endpoint detection was developed for this test method using electric sensors [109].

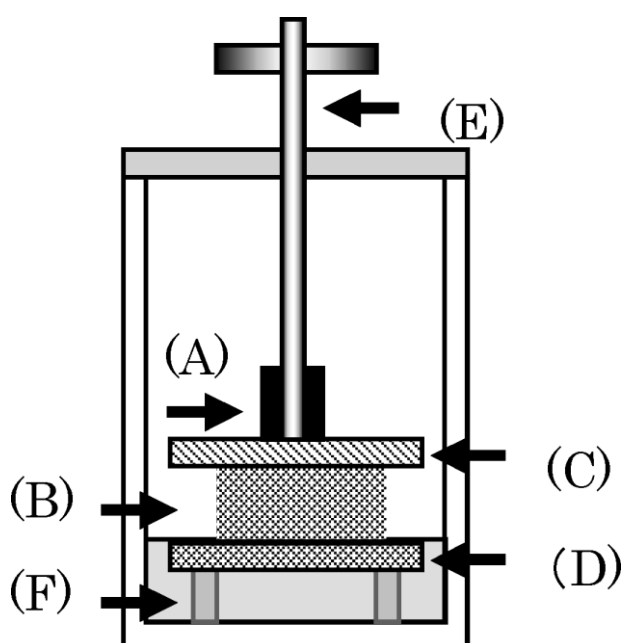


Fig. 5. Device for disintegration testing of ODTs developed by Narazaki et al. ((A) Weight, (B) RDT, (C) wetting sponge, (D) wire gauze, (E) rotary shaft, (F)) (reproduced from [108]).

Methods with texture analyzer

Texture analyzers have been used to evaluate disintegration characteristics of ODTs [110-112]. Tablets are fixed to the probe which moves down, thereby partially immersing the tablets into the disintegration medium. Once the trigger force is reached, the probe moves with constant speed or by applying a constant force. In some set-ups, the use of a perforated grid or mesh allows for disintegrated parts to move away from the tablet's surface [111, 112]. The disintegration time can be determined from the force/time or distance/time curves. Furthermore, the profiles provide information about different disintegration mechanisms and possibly even about the "mouthfeel" [110].

1.2.2.2 Disintegration media

Water is the most commonly used disintegration media for ODTs and it is the media suggested in the compendial disintegration procedure [75, 100, 103-109]. Some researchers use artificial saliva containing electrolytes and buffer salts [101, 110, 111]. For several ODT formulations, artificial saliva led to faster disintegration than water [111]. Only rarely, viscosity enhancers are used even though the viscosity of saliva is higher than that of water. A good *in vivo/in vitro* correlation of tablet disintegration was achieved when the disintegration fluid contained a combination of PVP and glycerol as viscosity enhancers [112].

1.3 Preparation and compaction of coated pellets

1.3.1 Fluid-bed coating of pellets

Pellets are generally coated in fluid-bed apparatuses. Heated air flows through the product container. It keeps the pellets in motion and ensures quick drying of the coating fluid which is sprayed on the pellets. Most commonly, the coating fluid is atomized by a two fluid nozzle. This nozzle type has a liquid outlet which is surrounded by an outlet for pressurized air.

Several set-ups of fluid-bed apparatuses exist which differ in spraying direction and pellet movement (Fig. 6) [113-115]. A particularly homogeneous coating with minimal pellet aggregation can be attained by the so called Wurster set-up. With this set-up, a controlled pellet flow is achieved through a column which is mounted in the middle of the product container. Due to a higher air flow rate in the column, pellets move upwards inside the column and downwards on the outside. The coating fluid is sprayed inside the column co-current to the flow of pellets. This allows for a maximum drying time before the pellets come into close contact again at the bottom of the product container. In top-spray set-ups, pellets move in a random way while the liquid is sprayed from the top. Rarely, also tangential-spray or rotary set-ups are applied. In this type of coaters, pellets move in a circular course and the liquid is sprayed tangentially to the pellet flow.

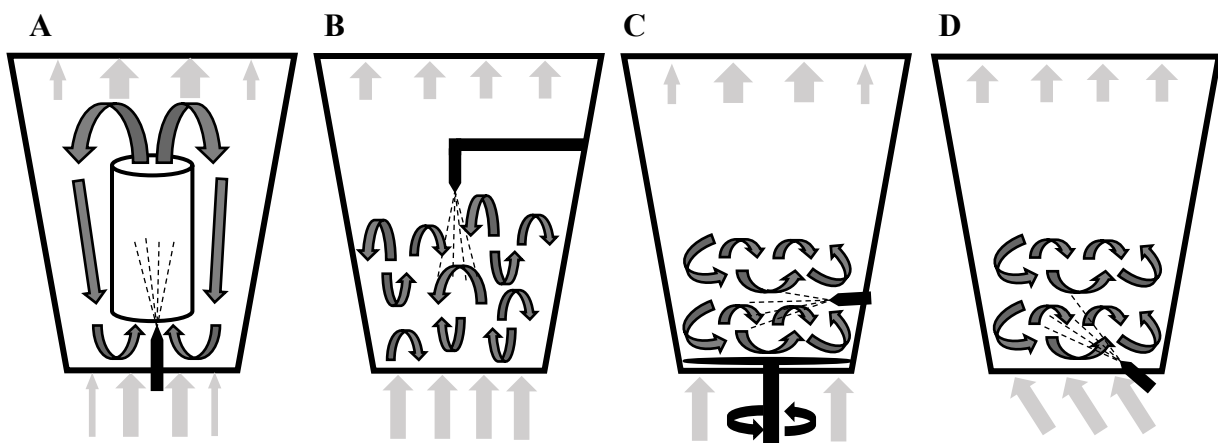


Fig. 6. Set-ups of fluid bed coaters. A: Wurster coater, B: top-spray coater, C: rotary coater, D: tangential bottom-spray coater (dark gray arrows: pellet flow, light gray arrows: air flow).

1.3.2 Compaction process

Tablets are prepared by compaction of solid particles such as powders, granules or pellets. The material is filled into a die and then compressed by punches. In the first phase of the compaction process, particles rearrange until a highly dense packing is reached. In this phase, the compression force is still low. In the second phase, the force increases as particles now undergo elastic and plastic deformation and brittle fracture. The dominating mode of deformation and the pressure needed to form a tablet are depending on the nature of the material. In the third phase of the process, the pressure is released and the lower punch moves upwards to eject the tablet. In this phase, the tablet expands slightly due to elastic recovery of the material [16, 113].

1.3.3 Factors affecting coating damage during compaction

Compressing coated pellets without damaging the coating is highly challenging. The polymer film must withstand changes in shape as well as friction between particles without rupturing, otherwise the functionality of the coating is lost. Due to this issue, only few tablets containing coated pellets are available on the market: Antra MUPS, Beloc ZOK and Prevacid SoluTab [116]. Factors affecting coating damage during compaction are listed in Fig. 7 and further described in the following paragraphs.

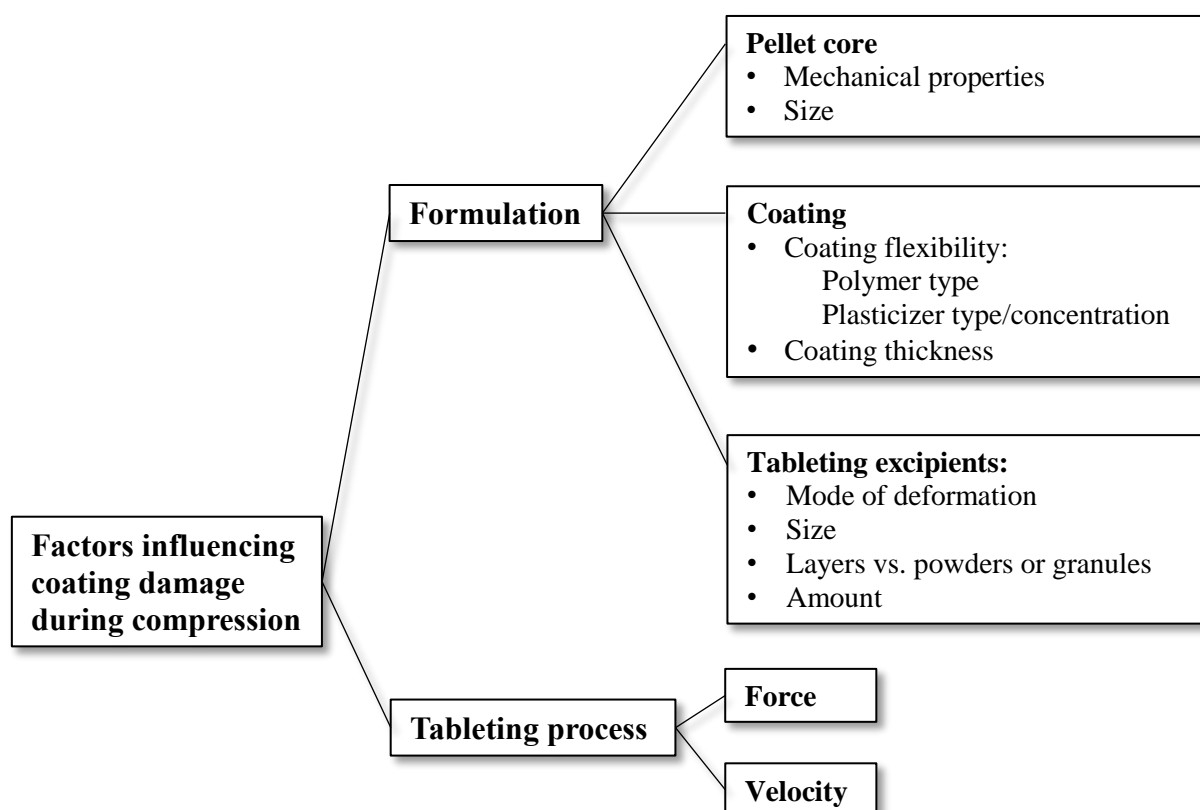


Fig. 7. Factors influencing coating damage during compression.

1.3.3.1 Coating properties

Coating flexibility

The mechanical properties of the coating are one of the most critical factors influencing compression-induced coating damage [117]. Brittle polymers (e.g. ethyl cellulose) can generally not be compacted without loss of functionality [118-121]. In contrast, coatings with a high flexibility stay intact during compression, independent of other formulation or process parameters [120, 122]. The elongation at break of polymer films depends on the polymer type [123]. To reduce compression-induced coating damage, the flexibility of coatings has been increased by the addition of plasticizers or by admixing highly flexible polymers as described in the following examples.

Films of Kollicoat SR had an elongation at break of only 1% (film thickness: 350 μm) [120]. The maximum elongation increased to 137% when 10% triethyl citrate (TEC) was added as plasticizer. The release from pellets coated with unplasticized Kollicoat SR strongly increased upon compression. In contrast, the release rate of the plasticized formulation was not affected by compression.

Compressed pellets coated with the enteric polymer Eudragit L (10% TEC) released 27% of the drug within two hours in 0.1 N HCl [117]. Films of this formulation had an elongation at break of less than 5%. The elongation increased to 112% when 50% Eudragit NE were added. Compressed pellets coated with this mixture released less than 10% of the drug within two hours in 0.1 M HCl and therefore fulfilled the requirements for enteric formulations.

Similarly, fast disintegrating tablets of enteric coated granules were achieved by mixing Eudragit L and Eudragit NE in a ratio of 9:1 and adding 20% TEC [124]. In another study, the enteric polymer Kollicoat MAE was mixed with Kollicoat EMM at a ratio of 70:30 to obtain a coating with sufficient flexibility to withstand compression [120].

Besides the film composition, also the physical interlocking of polymer chains has an influence on the mechanical properties of film coatings. When polymers are applied as solution, the molecules are more interwoven than if they are applied as dispersion. This is one reason why ethyl cellulose and Eudragit RS showed better resistance to compression when they were applied as organic solutions in comparison to aqueous dispersions [125]. Other reasons could be drug migration into the coating during the application of aqueous dispersions or the influence of additives in aqueous dispersions.

While the effect of compression on extended release coatings has been studied extensively, only little is known about its effect on the functionality of taste masking coatings. For example, acetaminophen particles were coated with the acid-soluble polymer Eudragit E and compressed to tablets [126]. Uncompressed particles were taste masked for 59 seconds *in vivo*. For compressed pellets, only *in vitro* release data was reported with a first sampling point after five minutes. Therefore, no conclusion can be drawn about the taste masking properties after compaction. In another study, ibuprofen pellets were coated with 15% Eudragit E and compressed into orally disintegrating tablets [18]. These tablets were taste masked. However, the study provides no information about the compression sensitivity of Eudragit E since release profiles of uncompressed pellets were not reported. Kollicoat Smartseal, another acid-soluble polymer, was used to coat paracetamol pellets [22]. A human taste panel study confirmed that ODTs prepared from these pellets were taste masked for at least 30 seconds. Also this study does not provide information about coating damage caused by compaction since drug release in neutral pH was not measured. Furthermore, the acetaminophen pellets were prepared with ethyl cellulose as binder (30% w/w regarding drug, corresponding to 15% w/w of the tablet formulation). Since acetaminophen is a sparingly soluble drug, this can lead to a remarkable delay of drug dissolution not attributed to the Kollicoat Smartseal coating.

Coating thickness

The thicker the film, the more force is required to rupture it [127]. Therefore, a sufficient coating thickness is important to prevent coating damage during compression. Drug pellets were coated with 12.5% and 25% Eudragit FS and compressed to tablets. Only at the higher coating level, an increased plasticizer content led to a reduced drug release in 0.1 N HCl [128]. Similarly, films of Eudragit L ruptured regardless of their mechanical properties when the coating level was 12.5% [117]. When the coating level was increased to 25%, a higher film flexibility led to a reduced release after compaction.

1.3.3.2 Pellet cores

Pellet cores vary regarding mechanical properties, size, and dissolution or swelling behavior. Pellet hardness has controversial effects on compression-induced coating damage. Hard pellets deform less leading to reduced straining of the polymer film. However, compression of harder pellets will lead to higher stress at points where pellets are in contact with each other or with the compaction tooling.

Pellets of microcrystalline cellulose and salicylic acid with different porosities were coated with ethyl cellulose [129]. Even though the shape and density of pellets with high initial porosity changed more, their release was less affected by compression. In contrast, compressed soft bisacodyl pellets coated with Eudragit L released a higher amount of drug in 0.1 N HCl compared to hard pellets [117].

A small pellet size is generally considered advantageous regarding coating integrity after compression. This can be explained by a higher number of contact points to which the energy is distributed. In a study on pellets coated with Eudragit L, larger pellets had a lower sphericity after compression than smaller ones indicating that they were deformed more [122]. They also released more drug in 0.1 N HCl. Also pellets coated with ethyl cellulose, cellulose acetate butyrate or Eudragit RL/RS exhibited a higher degree of coating damage after compression when larger pellets were used [130-132].

1.3.3.3 Tableting excipients

Excipients are added to coated pellets prior to tableting to serve as cushioning agents, to increase tablet hardness, and to ensure fast disintegration. Deformation behavior as well as particle size of tableting excipients have an influence on prevention of coating damage. Generally, tableting excipients are added to pellets as powders or granules. However, they can also be applied as layers onto the pellets similar to a coating process.

Mode of deformation

Powder particles deform under pressure by elastic and plastic deformation and by brittle fracture (Voigt). Commonly used tableting excipients with a brittle nature are lactose, mannitol and calcium hydrogen phosphate whereas microcrystalline cellulose mainly deforms plastically and starch shows a high degree of elastic deformation [122, 133, 134].

In several studies, coated pellets were better protected by plastically deforming materials with a low yield pressure than by brittle ones. If the excipient matrix deforms more easily than the pellets, compression force is mainly absorbed by the matrix and the coating stays intact. For example, pellets coated with Eudragit RS exhibited the lowest degree of film damaged when compressed with polyethylene glycol, followed by those compressed with microcrystalline cellulose (MCC), crospovidone, lactose and calcium hydrogen phosphate, respectively [135]. The order corresponded well to the order of yield pressures derived from Heckel plots of these materials. An optimized formulation with minimal coating damage and fast disintegration was

proposed. It contained MCC, PEG and crospovidone in a ratio of 2:1:1. However, tablet breaking force was only 9 N for tablets containing 25% coated granules and 13 N for tablets with 5% coated granules.

Hard pellets coated with Eudragit L released less drug after compression with the plastically deforming MCC compared to the more brittle lactose/cellulose 75:25 (Cellactose) or calcium hydrogen phosphate [117]. However, for soft pellets with the same coating, the amount of drug released in 0.1 N HCl was high, irrespective of the type of tableting excipients.

Excipient pellets were prepared of microcrystalline cellulose with low and high porosity and with small and large pellet size [129]. Ethyl cellulose coated drug pellets were compressed with these excipient pellets. The best cushioning effect was achieved with small, highly porous pellets. They led to compressed coated pellets which were less indented and with had the most regular shape.

In other studies, excipients which mainly deform elastically offered an even better cushioning effect than plastically deforming [133, 134]. Enteric-coated pellets released less drug in 0.1 N HCl when they were compacted together with highly elastic carrageenans (e.g. Gelcarin GP-379) or alginates (e.g. Protanal LF 240 D) compared to MCC. It was hypothesized, the elastic deformation led to reduced mechanical stress during compression. However, the lower release rate could also be owed to a prolonged tablet disintegration caused by the gel forming excipients. Unfortunately, data regarding this parameter was not reported.

Particle size

Particle size of tableting excipients is another which factor influences their cushioning efficiency. The protective properties of lactose were improved by micronization [136]. Compressing ethyl cellulose coated pellets together with micronized lactose resulted in a much smaller increase in release rate compared to tablets with lactose of larger particle size. To improve flowability, the micronized powder was spray-dried together with water soluble polymers. This reduced the cushioning efficiency only slightly.

A superior protection by small particle grades was also found for mannitol, lactose, microcrystalline cellulose, cornstarch, and carmellose calcium [137]. Below a critical size of 20 μm , they all offered effective cushioning for ethyl cellulose coated theophylline particles.

In contrast, in a study of Haslam et al., the release rate increased less when coarse grades of microcrystalline cellulose and lactose were used for the compression of pellets coated with cellulose acetate butyrate [131].

Excipient layers

Different types of excipient layers have been applied on coated pellets to prevent compression induced changes of drug release. They can be divided in sealing, cushioning and glidant layers. The most effective protection was provided by glidant layers or by glidant containing cushion layers. A glidant layers of magnesium stearate or sodium stearyl fumarate (3% weight gain) was applied onto ethyl cellulose coated pellets followed by a microcrystalline cellulose cushion layer (97% weight gain) [138]. These pellets were compressed without additional excipients. Due to the glidant layer, the excipient layer detached from the coated beads during compaction and the coating stayed intact. The same effect was achieved without glidant layer if at a least 3% magnesium stearate were added to the microcrystalline cellulose layer.

Layers of microcrystalline cellulose without glidant did not provide a protective effect [138, 139]. On the contrary, the coating damage was more pronounced compared to physical mixtures of pellets and microcrystalline cellulose. This was attributed to a better dissipation of the pressure by the loose powder.

An HPMC cushion/sealing layer reduced the change in release rate after compression for pellets coated with cellulose acetate butyrate [131]. The effect the HPMC overcoat was more pronounced when higher amounts were applied (25% vs. 10%) and when smaller pellets were used (0.5 mm vs. 1.0 mm). However, the reduced release rate could at least partially be due to a prolonged tablet disintegration, but disintegration times were not reported.

A cushion layer of polyethylene glycol (PEG) provided little benefit for the prevention of coating rupturing [140]. Consecutive layers of polyethylene oxide (PEO), microcrystalline cellulose and sodium starch glycolate were applied onto ethyl cellulose coated pellets [140]. During 2 hours in simulated gastric fluid, the release was slower than from uncompressed pellets, although the tablets disintegrated within 20 minutes. This was attributed to the gelling properties of PEO which led to sealing of cracks in the coating. After the change to simulated intestinal fluid, the release rate increased and was faster than for uncompressed pellets.

Amount of tableting excipients

On one hand, a high pellet load is essential to achieve a small tablet size which is more convenient for patients. Furthermore, a higher pellet content leads to better drug content uniformity of the tablets [122, 141].

On the other hand, the higher the amount of tableting excipients, the better the cushioning effect. More energy is absorb by the deformation of excipients and the number of points where pellets come in contact with each other is reduced. In several studies, coating damage during

compression increased with increasing pellet load [117, 122, 128]. The effect was more pronounced for coatings with a low plasticizer content and thus low flexibility [122]. Other drawbacks of a high pellet content are the fusion of pellet coatings which leads to delayed or incomplete tablet disintegration [128] and low tablet hardness [122].

1.3.3.4 Tableting process

Polymer films have viscoelastic mechanical properties. Therefore, the extent to which coated pellets are deformed (compression force) as well as the deformation rate (tableting speed) can influence the degree of coating damage.

For pellets coated with ethyl cellulose (Aquacoat ECD, 25% TEC), the drug release rate continuously increased with increasing compression force [120]. For other coatings (e.g. ethyl cellulose with 5% propylene glycol, Kollicoat SR 30D, Eudragit L 30D 55) the release rate increased dramatically after compression but differences between various compression forces were negligible [117, 119, 120].

Polymer films exhibit a lower maximum elongation at higher strain rates [127]. Therefore, increasing tableting speed slightly increased coating damage for pellets coated with Eudragit L or Eudragit FS [122, 128].

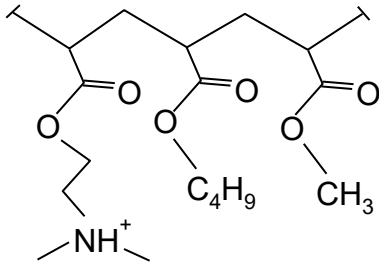
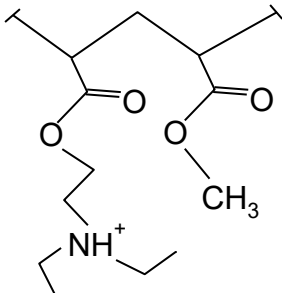
1.4 Excipients and drugs

1.4.1 Polymers for taste-masking coatings

Acid-soluble polymers

Acid-soluble polymers are used for taste masking and as protective coatings (e.g. as moisture barrier). Two acid-soluble polymers are commercially available: Eudragit E (Evonik) and Kollicoat Smartseal (BASF). Both are methacrylate polymers. Side chains with tertiary amines lead to their pH dependent solubility. The main characteristics of the two polymers are listed in Table 1 [142, 143].

Table 1. Eudragit E and Kollicoat Smartseal

	Eudragit E	Kollicoat Smartseal
Chemical structure	 <p style="text-align: center;">2 : 1 : 1</p>	 <p style="text-align: center;">3 : 7</p>
Molecular weight	47'000 Da	200'000 Da
Soluble at pH	< 5.0	< 5.5
Glass transition temperature	45 °C	63 °C
Product grades	PO: powder for preparation of aqueous colloidal solution 100: granules for preparation of organic solution 12.5: organic solution	30D: aqueous dispersion

Water-soluble polymers

Water-soluble polymers used for film coatings belong to the groups of cellulose ethers (e.g. hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC)) or vinyl polymers (e.g. polyvinyl acetate (PVA) (Opadry amb II) or polyethylene glycol/polyvinyl acetate copolymer (PVA-PEG) (Kollicoat IR)).

Two fully-formulated coating systems based either on HPMC (Opadry tm) or on PVA (Opadry amb II) were used in this study. Besides the polymers, they contain additives such as talc and titan dioxide.

Water-insoluble polymers

Water-insoluble polymers generally used for coating include cellulose ethers (e.g. ethyl cellulose, cellulose acetate), vinyl polymers (e.g. polyvinyl acetate (Kollicoat SR)) and methacrylate polymers (e.g. Eudragit RL, Eudragit RS). When water-insoluble polymers are used for taste masking, they are often combined with water-soluble ones to ensure a fast drug release once the dosage form has been swallowed [23-25, 144].

In this study, ethyl cellulose (Ethocel Standard 7 Premium) was used in combination with PVP (Kollidon 30) as pore former.

1.4.2 Drugs

Tramadol HCl

Tramadol HCl is a bitter drug with a bitterness threshold of 20 µg/mL [41, 62]. In comparison, the bitterness threshold of quinine HCl is about 3 µg/mL, of diclofenac sodium 20 µg/mL, of caffeine 230 µg/mL and of acetaminophen 1000 µg/mL [30, 63, 66, 145]. Tramadol HCl was selected as bitter model drug due to its high solubility (948 mg/mL). Taste masking of highly soluble drugs is especially challenging. Furthermore, the release of tramadol HCl is a sensitive indicator for coating damage due to its fast dissolution upon contact with release medium. Tramadol HCl is an opioid analgesic of low potency. Typical oral doses for adults are 50 mg or 100 mg. Extended release dosage forms are also available with up to 400 mg tramadol HCl per tablet [146].

Acetaminophen

Acetaminophen was used as sparingly soluble model drug (17 mg/mL in water [147]) to study the effect of drug solubility in comparison to the very soluble tramadol HCl. Its bitterness intensity is lower than that of tramadol HCl. However, this was not considered for the evaluation of *in vitro* taste tests. Acetaminophen is an analgesic and antipyretic drug. Single doses for adults are 500-1000 g [146].

1.5 Research objectives

The objective of this work was to prepare taste masked orally disintegrating tablets (ODTs) of the highly soluble drug tramadol HCl by compression of coated pellets. The tablets should fulfill the following requirements:

- *Disintegration*: tablet wetting time of less than three minutes, ideally less than 30 seconds

The target for tablet wetting time was set on the basis of requirements regarding the disintegration time of ODTs described in the European pharmacopoeia and in an FDA guidance [74, 75]. However, a wetting test was performed instead of the compendial disintegration test.

- *Taste masking*: less than 1.5 mg tramadol HCl released within one minute in phosphate buffer (pH 6.8)

Tramadol HCl has a bitterness threshold of 20 $\mu\text{g/mL}$ [41, 62]. This is in the same range as the threshold for promethazine HCl and diclofenac sodium (10 $\mu\text{g/mL}$ and 20 $\mu\text{g/mL}$, respectively) [63, 66]. ODTs of these drugs were rated “tasteless” by human taste panels when the tablets had an *in vitro* release of 1.56 mg or 1.64 mg within one minute, respectively [63, 64]. Therefore, to achieve taste masking for tramadol HCl, the upper limit for drug release in pH 6.8 was set to 1.5 mg within one minute.

- *Immediate release in the stomach*: at least 85% tramadol HCl released within 15 minutes in 0.1 N HCl (pH 1.0)

The target for drug release in acidic medium was set on the basis of an FDA guidance regarding immediate release dosage forms [148].

2 Materials and methods

2.1 Materials

Pellet cores

Microcrystalline cellulose (MCC) pellets, Celphere[®] 203 (Asahi Kasei Corporation, Chiyoda, Japan); sugar pellets, Neutralpellets (Hanns G Werner GmbH & Co. KG, Tornesch, Germany)

Drugs

Tramadol HCl (Heumann Pharma GmbH, Feucht, Germany); acetaminophen (Fagron GmbH & Co KG, Barsbüttel, Germany)

Binders

Polyvinyl pyrrolidone (PVP), Kollidon[®] 30 and Kollidon[®] 90 (BASF SE, Ludwigshafen, Germany); ethyl cellulose, Ethocel[™] Standard 100 Premium (Colorcon, Dartford Kent, UK); aminoalkyl methacrylate copolymer, Eudragit[®] E 100 (Evonik Industries AG, Essen, Germany)

Polymers for coating

Aminoalkyl methacrylate copolymer, Eudragit[®] E 100 (Evonik Industries AG, Essen, Germany) and Kollicoat[®] Smartseal 30 D (BASF SE, Ludwigshafen, Germany); ethyl cellulose, Ethocel[™] Standard 7 Premium (Colorcon, Dartford Kent, UK); polyvinyl acetate/polyethylene glycol, Kollicoat[®] SR 30 D (BASF SE, Ludwigshafen, Germany); HPMC-based readymix, Opadry[®] tm (Colorcon, Dartford Kent, UK); PVA-based readymix, Opadry[®] amb II (Colorcon, Dartford Kent, UK); hydroxypropyl cellulose (HPC), Klucel[®] EXF (Kremer Pigmente GmbH & Co. KG, Aichstetten, Germany); polyvinyl pyrrolidone (PVP), Kollidon[®] 30 (BASF SE, Ludwigshafen, Germany)

Coating additives

Tributyl citrate (BASF SE, Ludwigshafen, Germany); triacetin (Carl Roth GmbH + Co. KG, Karlsruhe, Germany); magnesium stearate Pharma Veg (Baerlocher GmbH, Unterschleissheim, Germany); butylhydroxy toluol (Sigma-Aldrich Chemie GmbH, Steinheim, Germany)

Tableting excipients

MCC, Avicel[®] PH-102 and Avicel PH-105 and Avicel PH-200 (FMC BioPolymers, Philadelphia, USA); mannitol, Pearlitol[®] 100-SD (Roquette Frère, Lestrem, France); colloidal silicon dioxide, Aerosil[®] 200 (Evonik Degussa GmbH, Essen, Germany); maize starch B (Roquette Frère, Lestrem, France); sorbitol, C*Sorbidex[™] S 16606 (Cargill Incorporated, Wayzata, USA); lactose, FlowLac[®] 90 (Molkerei MEGGLE Wasserburg GmbH & Co. KG, Wasserburg, Germany) and Lachotchem[®] microfine (DMV-Fonterra Excipients GmbH & Co. KG, Goch, Germany), magnesium stearate Pharma Veg (Baerlocher GmbH, Unterschleissheim, Germany); stearic acid 50 (Caesar & Loretz GmbH, Hilden, Germany); sodium stearyl fumarate, Pruv[®] (JRS Pharma GmbH & Co, Rosenberg, Germany); glyceryl dibehenate, Compritol[®] 888 ATO (Gattefossé, Saint-Priest, France); cross-linked PVP, Kollidon[®] CL and Kollidon[®] CL-SF (BASF SE, Ludwigshafen, Germany) and Polyplasdone[™] XL-10 (Ashland, Covington, USA), sodium starch glycolate, Explotab[®] (JRS Pharma GmbH & Co, Rosenberg, Germany), cross-linked sodium carboxymethyl cellulose, Ac-Di-Sol[®] (FMC BioPolymers, Philadelphia, USA)

For reasons of simplicity, [®] and [™] are not used in the text below.

2.2 Methods

2.2.1 Pellet preparation

Drug layering

Tramadol HCl was layered onto 700 g of Celphere 203 (microcrystalline cellulose pellets, 150-300 μm) in a fluidized bed coater (Glatt GPCG-1, Glatt AG, Binzen, Germany). It was applied as solution (16% w/w) in isopropanol/water 88:12 with Kollidon 30 as binder (3% w/w regarding the drug). The nozzle diameter was 1.2 mm, the atomization air pressure 1.2 bar and the air flow rate 50-70 m^3/h . The inlet air temperature was adjusted to achieve a product temperature of 40 °C. After spraying, the product was dried in the fluid bed at 40 °C for 15 minutes. Drug loading of layered pellets was 20% w/w unless mentioned otherwise.

Acetaminophen was layered onto 90 g of Celphere 203 in a fluidized bed coater (Mini-Glatt, Glatt AG, Binzen, Germany). The drug was dissolved (10% w/w) in ethanol 96% with Kollidon 30 as binder (3% w/w regarding the drug). The nozzle diameter was 0.5 mm, the atomization air pressure 0.9 bar and the process air pressure 0.2 bar. The inlet air temperature was adjusted to reach a product temperature of 30 °C. Drug loading of layered pellets was 20% w/w.

Coating

Drug loaded pellets were coated in a fluidized bed coater (Mini-Glatt, Glatt AG, Binzen, Germany) using a batch size of 65-95 g. The nozzle diameter was 0.5 mm, atomization air pressure 0.9 bar and process air pressure 0.15-0.2 bar. The inlet air temperature was adjusted to achieve a product temperature between 20-23 °C for Eudragit E and Kollicoat Smartseal and 40-42 °C for Opadry tm, Opadry amb II and ethyl cellulose. Coatings were applied with a spray rate of 1.0-1.3 g/min for Eudragit E, Kollicoat Smartseal and ethyl cellulose and about 0.6 g/min for Opadry tm and Opadry amb II. Coating compositions are described in detail in the appendix (6.1).

After coating, pellets were mixed with Aerosil 200 (0.5% w/w) to prevent sticking during storage. Pellets coated with Kollicoat Smartseal were cured for 18 hours at 50 °C unless mentioned otherwise.

Application of excipient layers

Excipients were layered onto 70 g of coated pellets in a fluidized bed coater (Mini-Glatt, Glatt AG, Binzen, Germany). The nozzle had a diameter of 0.5 mm, the atomization air pressure was 0.9-1.0 bar and process air pressure 0.15-0.2 bar. The inlet air temperature was adjusted to achieve a product temperature between 20-23 °C. The spray rate was between 1.2 and 1.4 g/min. Excipient layer compositions are described in detail in the appendix (6.2).

2.2.2 Pellet characterization

Crushing strength of pellets

The crushing force of pellet cores was measured with a Texture Analyser (TA.XT plus, Stable Micron Systems, Winopal Forschungsbedarf GmbH, Ahnsbeck, Germany) using a cylindrical probe with a diameter of 2 mm (n = 3). The trigger force was 1 g and the test speed 1.2 mm/min. The pellet diameter was determined from the height of the probe relative to the table at the point when the trigger force was reached. The following equation (Eq. 1) was used to calculate the surface tensile strength of pellets [149]:

$$\sigma_f(s) = \frac{1.6 * F}{\pi * d^2}$$

(Eq. 1)

$\sigma_f(s)$: surface tensile strength

F: crushing force

d: diameter

Apparent density of pellets

A modified version of the method described by Braun was used to determine the apparent density of coated pellets [122]. A known amount of coated pellets was placed in a 50 mL volumetric flask. The flask was filled to the mark with paraffin highly liquid. The density of the pellets was calculated using from the amount of paraffin displaced by the pellets (n = 3). The density of paraffin was determined beforehand using also a 50 mL volumetric flask.

2.2.3 Drug release tests

Taste test in USP dissolution apparatus II (drug release in pH 6.8)

Unless mentioned otherwise, the *in vitro* taste test was performed in a USP dissolution apparatus II [150] (VK 7000, Vankel Industries, Edison, NJ, USA) at 37 °C (n = 3). A paddle rotation speed of 100 rpm was chosen to accelerate tablet disintegration and to minimize its effect on drug release. The dissolution medium was 100 mL phosphate buffer pH 6.8 (50.0 mM KH_2PO_4 , 22.4 mM NaOH, according to USP 38 [151]). To determine the total drug content of formulations with water-soluble or water-insoluble coatings, another sample was taken 30 minutes or two hours after the tests, respectively. For formulations with acid-soluble coatings, 30 mL of 0.1 N HCl were added after the test. This reduced the pH below 5 and thus, the acid-soluble polymers dissolved. Another sample was taken after approximately 30 minutes. Samples were centrifuged for 25 minutes at 17000 rpm to eliminate turbidity caused by insoluble excipients (Heraeus™ Biofuge™, Thermo Fisher Scientific Inc., Waltham, MA, USA). The drug concentration was determined by UV spectrophotometry at a wavelength of 271 nm for tramadol HCl and 243 nm for acetaminophen (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany). When the absorption was below 0.1 (less than 1.5 mg tramadol HCl released), a small volume taste test was performed as described in the next paragraph in order to achieve a lower limit of quantification.

Small volume taste test

Tablets were placed in test tubes and 1 mL of 12.5 mM phosphate buffer pH 6.8 was added (37 °C) (n = 3). After one minute, 4 mL of phosphate buffer were added, the solution was stirred for about two seconds with a spatula. Then, a sample was collected through a filter using a syringe. Samples were centrifuged and the drug content determined as described for the taste test in the dissolution apparatus II. Additionally, the mean drug content of three tablets from the corresponding batch was determined in acidic media.

Drug release in buffers of different concentration and ionic strength

Phosphate buffer pH 6.8 was prepared according to the US pharmacopeia 38 (50.0 mM KH_2PO_4 , 22.4 mM NaOH) [151]. It had a buffer capacity of 23.3 mEq/pH unit as calculated using Equation 2. To determine the effect of buffer capacity, the drug release was measured in this buffer, in water and in buffer/water mixtures of the ratios 1:1 and 1:3. To study the influence

of ionic strength, 25, 50, 100 or 200 mM NaCl was added to the buffer/water 1:1 mixture leading to an ionic strength of 35-135 mM.

300 mg coated drug pellets were placed in a test tube and 5 mL of medium were added (n = 3). Before sampling, the medium was stirred with a spatula for 4 seconds. After the pellets had settled (4-5 seconds), a sample was taken with a syringe through a needle (d = 0.45 mm). The test was performed at room temperature (21-22 °C). The samples were centrifuged and the drug content determined as described for the taste test in the dissolution apparatus II. Additionally, the mean drug content of pellets from the corresponding batch was determined in acidic media where the top-coating dissolved.

$$\beta = 2.303 * C * \frac{K_a * [H_3O^+]}{(K_a + [H_3O^+])^2}$$

(Eq. 2)

β: buffer capacity

C: buffer concentration

K_a: dissociation constant of buffer species

[H₃O⁺]: proton concentration = 10^(-pH)

Drug release test in acidic medium

To simulate drug dissolution in the stomach, drug release in 900 mL of 0.1 N HCl (pH 1.0) was measured in a USP dissolution apparatus II [150] (VK 7000, Vankel Industries, Edison, NJ, USA) at 37 °C (n = 3). Although the FDA recommends 50 rpm as paddle rotation speed for immediate release dosage forms (FDA guideline), a speed of 100 rpm was used. The faster rotation speed was chosen to ensure a homogeneous concentration in the vessel during the fast release of the drug. Drug concentration was determined by UV spectrophotometry at a wavelength of 271 nm for tramadol HCl and 243 nm for acetaminophen (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany).

2.2.4 Microscopic pictures

Coated pellets were soaked in 50 mM phosphate buffer pH 6.8, in water or in buffer/water mixtures. The pellets were observed under a microscope (Zeiss Axioscope with AxioCam 105 color, Carl Zeiss Jena GmbH, Jena, Germany; magnification 20x).

2.2.5 Compressed density of tableting excipients

Tableting excipients were compressed individually using a manually operated hydraulic press (P/N 25.011, Specac Limited, Orpington, England) (n = 5). The punch size was 13 mm and the compression force 10 tons which resulted in a pressure of about 740 MPa. This pressure was maintained for one minute. Thickness and radius of the compacts were measured directly after ejection using a digital sliding caliper (profi scale precise PS 7215, Burg Wächter, Wetter, Germany). The density was calculated from the weight and volume of the compacts.

2.2.6 Tableting

Tableting of pellets with excipient powders (chapters 3.1-3.3.3)

Coated pellets were mixed manually with 50% w/w tableting excipients. The excipient mix consisted of 72% w/w Avicel PH-102, 23% w/w Pearlitol 100-SD, 4% w/w Aerosil 200 and 1% w/w magnesium stearate. Tablets of 600 mg powder/pellet mixture (containing approx. 50 mg tramadol HCl) were weighed individually and compressed using an instrumented single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany). The punch diameter was 12 mm and the compression force was adjusted to 10 kN.

Tableting of pellets with excipient layers (chapter 3.3.4)

The weight of the tablets was adjusted so that each tablet contained 300 mg coated pellets (corresponding to approximately 50 mg tramadol HCl) and 50% V/V tableting excipients. The tableting excipients included the substances layered onto coated pellets and in some cases an external disintegrant. Additionally, 0.5% w/w stearic acid were added as lubricant. Before tableting, pellets with excipient layers were stored for at least two days at a relative humidity of approx. 50% (over a saturated solution of magnesium nitrate hexahydrate) to control the effect of moisture content on tablet hardness. Pellets, lubricant and external disintegrant were

mixed with a Turbula[®] mixer (Willy A. Bachofen AG, Muttenz, Switzerland) for one minute. Each tablet was weighed individually and compressed using an instrumented single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany). The compression force was adjusted to achieve a tablet hardness of 40-50 N.

2.2.7 Characterization of tablets

Breaking force of tablets

The tablet breaking force was measured using a hardness tester (MultiCheck, Erweka GmbH, Heusenstamm, Germany) (n = 8).

Tablet wetting time

Tablet wetting time was measured using a set-up similar to that described by Bi et al. [103]. A cotton pad was placed in a petri dish of the same diameter as the pad and soaked with 7 mL of water. A tablet was placed on the wet cotton pad and the time needed until the center of the upper tablet surface was wetted was measured (n = 8). The test was performed at room temperature.

2.2.8 Preparation of free films

Free films were prepared by spraying the coating formulations on a rotating Teflon-layered disc. Heat and air flow were provided with a hair dryer. Spraying was continued until the films had a thickness of approx. 120 µm for the water uptake test and 230-270 µm for measurements of mechanical properties. Films thickness was measured with a film thickness meter (Minitest 600 FB, Erichsen GmbH + CO KG, Hemer, Germany). Like coated pellets, Kollicoat Smartseal films were cured for 18 hours at 50 °C or 75 °C. Free films were also prepared by casting of coating formulations (without magnesium stearate) into Teflon-layered Petri dishes. The amount of fluid was adjusted to obtain films with a thickness of 230-270 µm. Organic solutions were dried at room temperature whereas aqueous dispersions were dried in an oven at 50-75 °C (same temperature as for curing of pellets with the respective coating formulation).

2.2.9 Characterizations of free films

Mechanical properties of free films

Films were stored for at least three days in a desiccator over saturated solutions of magnesium nitrate hexahydrate (approx. 50% RH) before the measurements. Mechanical properties were determined using a method similar to that described by Bodmeier and Paeratakul [127]. Films were fixed between two plates with a circular hole ($d = 10$ mm). Force and displacement were measured using a Texture Analyzer (TA.XT plus, Stable Micron Systems, Winopal Forschungsbedarf GmbH, Ahnsbeck, Germany). A stainless steel probe with spherical tip ($d = 5$ mm) penetrated into the hole with a constant speed of 10 mm/min and elongated the film until it ruptured. Puncture strength and maximum elongation were then calculated according to Equations 3 and 4, respectively. Six measurements were performed for each formulation. Mean values for maximum elongation and puncture strength were calculated from the three samples with the highest maximum elongation assuming that lower values were due to imperfections of the specimens rather than a characteristic of the formulation.

$$\text{Puncture strength} = \frac{F}{A_{cs}} \quad (\text{Eq. 3})$$

F: puncture force

A_{cs} : cross-sectional area of the edge of the film located in the path of the cylindrical opening of the film holder

$$\text{Maximum elongation (\%)} = \frac{\sqrt{R^2 + D^2} - R}{R} * 100 \quad (\text{Eq. 4})$$

R: radius of the opening of the film holder

D: displacement of the probe from the point of contact to the point of film rupture

Water uptake of free films

Free films were cut into circles with a diameter of 2.5 cm and immersed in phosphate buffer pH 6.8 at 37 °C. After removal from the medium, films were blotted dry and weighed. They were dried to constant weight at 50 °C. The water content was calculated from weight loss during drying in relation to the final weight (n = 3 for each sampling point).

2.2.10 Drug solubility

An excessive amount of tramadol HCl was added to phosphate buffer pH 6.8. The drug concentration in the supernatant after equilibration in an incubation shaker (37 °C) for 7 days was determined with a spectrophotometer ($\lambda = 271$ nm).

2.2.11 Scanning electron microscope (SEM) pictures

Tablets were cut in half with a razor blade and coated with gold. Pictures of the tablets were then obtained with a FEI Quanta 200 scanning electron microscope (FEI, Hillsboro, USA) at 15 kV.

2.2.12 Calculation of difference factor

The difference between dissolution profiles in pH 6.8 (*in vitro* taste test) of different formulations was characterized using the difference factor. The difference factor f_1 is one of the approaches suggested by the FDA for the comparison of dissolution curves. It calculates the mean of the relative difference of two curves at each time point (in percentage) (Eq. 5). Release profiles with f_1 values up to 15 were considered similar.

$$f_1 = \left(\sum_{t=1}^n |R_t - T_t| \right) / \left(\sum_{t=1}^n R_t \right) * 100$$

Eq. 5)

n: number of sampling points

R_t : percentage released by the reference sample at time t

T_t : percentage released by the test sample at time t

The similarity factor f_2 is generally used in combination with the difference factor to determine whether dissolution curves are similar. However, this factor was not used in this study to compare drug release curves derived from the *in vitro* taste test. During this tests only a small fraction of the dose was released. Therefore, a comparison of the differences between two curves relative to the total dose was not considered meaningful.

3 Results and discussion

Many patients have problems to swallow tablets or capsules and prefer orally disintegrating tablets (ODTs) [77, 78, 152, 153]. Since ODTs remain in the oral cavity for a longer time than conventional tablets, it is important to mask the taste of bitter drugs in order to ensure patient acceptance and compliance [1, 153]. One approach to prepare taste masked ODTs is coating of drug containing pellets followed by compression into tablets. In the oral cavity, these tablets disintegrate rapidly and the pellets are swallowed as a slurry (Fig. 8). The coating prevents drug dissolution until the pellets reach the stomach and thus the drug cannot interact with taste receptors. However, the main challenge associated with the compaction of coated pellets is to prevent film damage and consequent loss of coating functionality [117-122, 135, 138-140].

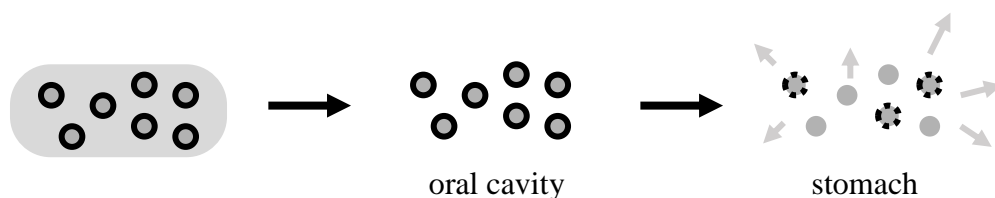


Fig. 8. Principle of taste masked orally disintegrating tablet prepared of coated pellets.

The objective of this study was to prepare taste masked ODTs of the highly soluble drug tramadol HCl. MCC pellets were layered with tramadol HCl and coated with different polymer formulations followed by compression into ODTs. The effectiveness of formulation and process parameters to prevent compression-induced coating damaged and to achieve taste masked ODTs was evaluated. The investigated parameters can be divided into three main groups. The first group includes parameters which have an influence on the properties of the coating such as polymer type, plasticizer content, and coating level. The second group comprises parameters which concern the drug and the drug layer. The third group deals with parameters which affect the mechanical stress on the coating during compaction, e.g. compression force, pellet content in tablets, and excipient layers.

3.1 Effect of coating properties

3.1.1 Water-soluble, acid-soluble and insoluble polymers as coating material for taste masking

Polymers with different dissolution characteristics were used as coatings for tramadol HCl pellets and their suitability to provide taste masking as well as a fast drug release in pH 1.0 was evaluated. The release was determined in phosphate buffer (pH 6.8) and 0.1 N HCl (pH 1.0) to simulate the pH conditions of the oral cavity and the stomach.

Opadry tm and Opadry amb II are coating formulations containing the water-soluble polymers HPMC and PVA, respectively. Kollicoat Smartseal and Eudragit E are acid-soluble methacrylic polymers which dissolve at a pH below 5. Therefore, they are not soluble in saliva (pH 6-8 [154]) but dissolve in the acidic environment of the stomach. Ethyl cellulose is insoluble in aqueous media irrespective of the pH. Therefore, PVP was included in the ethyl cellulose coating formulation as pore former (20% w/w) to achieve a fast release after the lag phase.

3.1.1.1 Drug release from uncompressed pellets

The drug release of uncompressed pellets was evaluated in order to select suitable coating formulations for the subsequent preparation of ODTs.

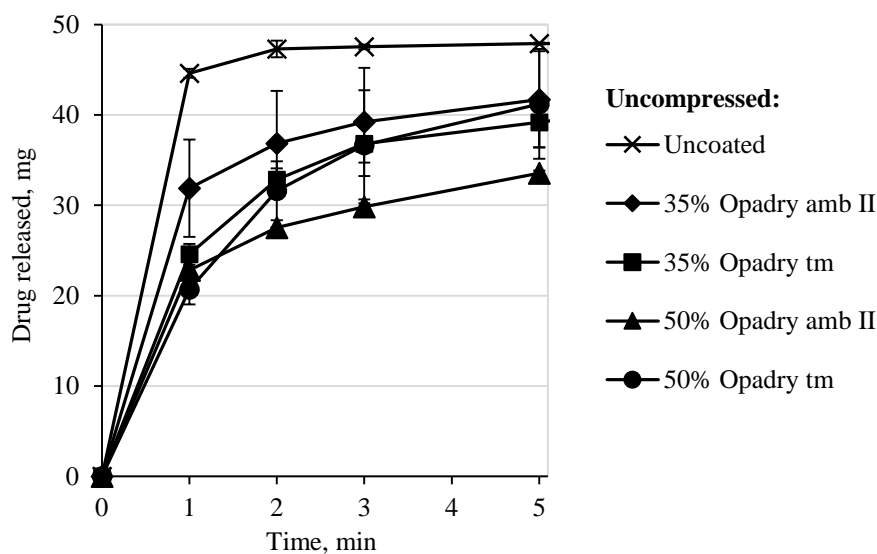


Fig. 9. Tramadol HCl release in pH 6.8 from pellets coated with Opadry tm or Opadry amb II.

Tramadol HCl dissolved rapidly from uncoated pellets due to its high solubility. After one minute in phosphate buffer pH 6.8, 44.6 mg were released from pellets containing 50 mg tramadol HCl (Fig. 9).

Also pellets with water-soluble coatings released the drug quickly. Pellets containing a dose of 50 mg tramadol HCl coated with 50% w/w Opadry tm or Opadry amb II released 20.7 mg and 22.8 mg of drug within one minute, respectively (Fig. 9). A coating level of considerably more than 50% w/w would be required to achieve taste masking. Therefore, water-soluble polymers were not used as coatings for further experiments.

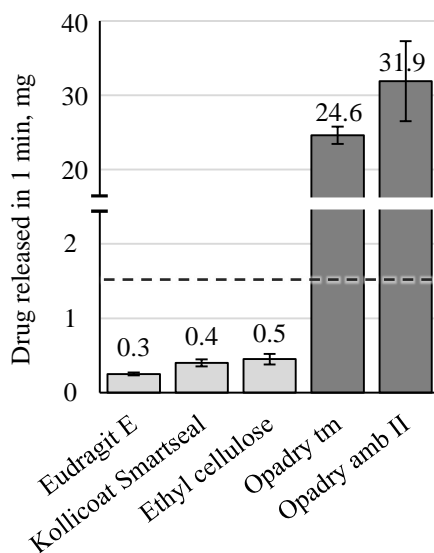


Fig. 10. Tramadol HCl released after one minute in pH 6.8 from uncompressed pellets coated with polymers of different solubility (35% w/w coating level).

In contrast, the insoluble ethyl cellulose coating as well as the acid-soluble coatings with Kollicoat Smartseal or Eudragit E, released less than 1.5 mg tramadol HCl in the first minute (35% w/w coating level) and thus provided taste masked pellets (Fig. 10). However, the release profiles achieved with the different polymers varied with regard to the duration of the lag phase (Fig. 11).

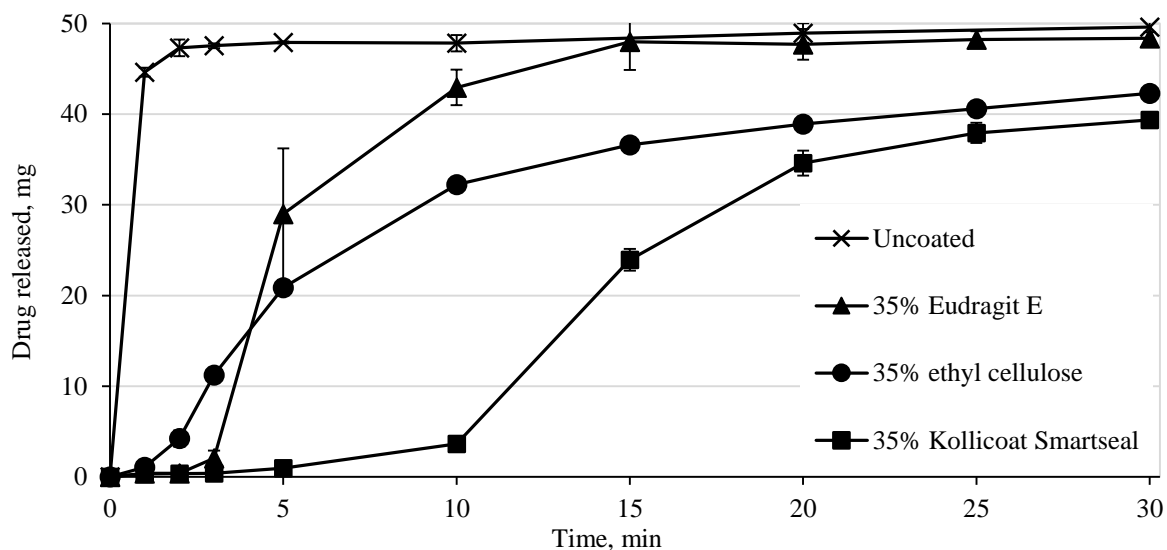


Fig. 11. Tramadol HCl release in pH 6.8 from pellets coated with Eudragit E, Kollicoat Smartseal and ethyl cellulose.

Ethyl cellulose coated pellets exhibited the shortest lag time (one minute). A relatively high amount of pore former (20% w/w PVP) was included in the formulation to ensure a fast drug release in the stomach. Therefore, the tramadol HCl release in the first minute was sufficiently low to provide taste masking (0.5 mg) but reached already 4.2 mg after two minutes and after 30 minutes 42.3 mg (85%) was released.

Pellets coated with Eudragit E had a lag time of two minutes in phosphate buffer pH 6.8. After three minutes, the formulation exhibited a burst release leading to complete liberation of the drug within 15 minutes. The burst release is caused by the disintegration of the coating which is further discussed below. Pellets coated with Kollicoat Smartseal had a longer lag phase. They released only 1.0 mg of tramadol HCl in five minutes. After 30 minutes, 78% (39.4 mg) of the drug was released. A long lag phase is not necessary for ODTs but it would be an advantage for dosage forms where the pellets are dispersed in water or mixed with food before intake.

The drug release was also determined in 0.1 N HCl (pH 1.0), simulating the acidic environment of the stomach. In this medium, the release should be fast (> 85% in 15 minutes). The test was performed with uncompressed pellets. If those release the drug rapidly, compressed pellets (ideally with undamaged coatings) will provide fast drug release as well.

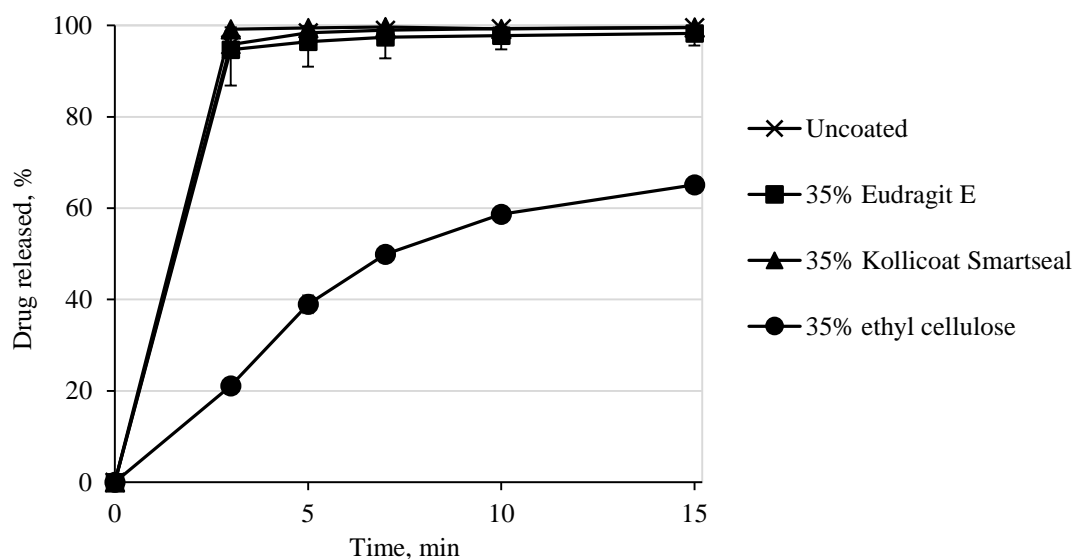


Fig. 12. Tramadol HCl release in pH 1.0 from pellets coated with Eudragit E, Kollicoat Smartseal or ethyl cellulose.

The acid soluble polymers Kollicoat Smartseal and Eudragit E dissolved quickly in pH 1.0 and, as for uncoated pellets, the drug was completely released after three minutes (Fig. 12).

In contrast, the release from pellets coated with ethyl cellulose was relatively slow even though the film contained 20% w/w PVP as pore former. Only 65% of the drug was released after 15 minutes which was below the desired level of at least 85%. For taste masking coatings, the pH independent characteristics of ethyl cellulose are a drawback because good taste masking has to be traded off against a fast drug release after swallowing.

In conclusion, coatings with the acid-soluble polymers Kollicoat Smartseal and Eudragit E provided taste masked tramadol HCl pellets with rapid drug dissolution in acidic media (35% coating level). The insoluble ethyl cellulose coating also led to taste masked pellets. However, the release in pH 1.0 was too slow. With the water soluble coatings Opadry tm or Opadry amb II, taste masking was not achieved with coating levels up to 50% w/w.

Drug release mechanisms in pH 6.8

For a better understanding of the release mechanisms provided by the different polymer coatings, coated tramadol pellets were soaked in phosphate buffer pH 6.8 and observed over time using a microscope (magnification: 20x). Furthermore, the water uptake of free films of Kollicoat Smartseal and Eudragit E was determined in phosphate buffer pH 6.8. The films had the same composition as the coatings and were prepared by spraying.

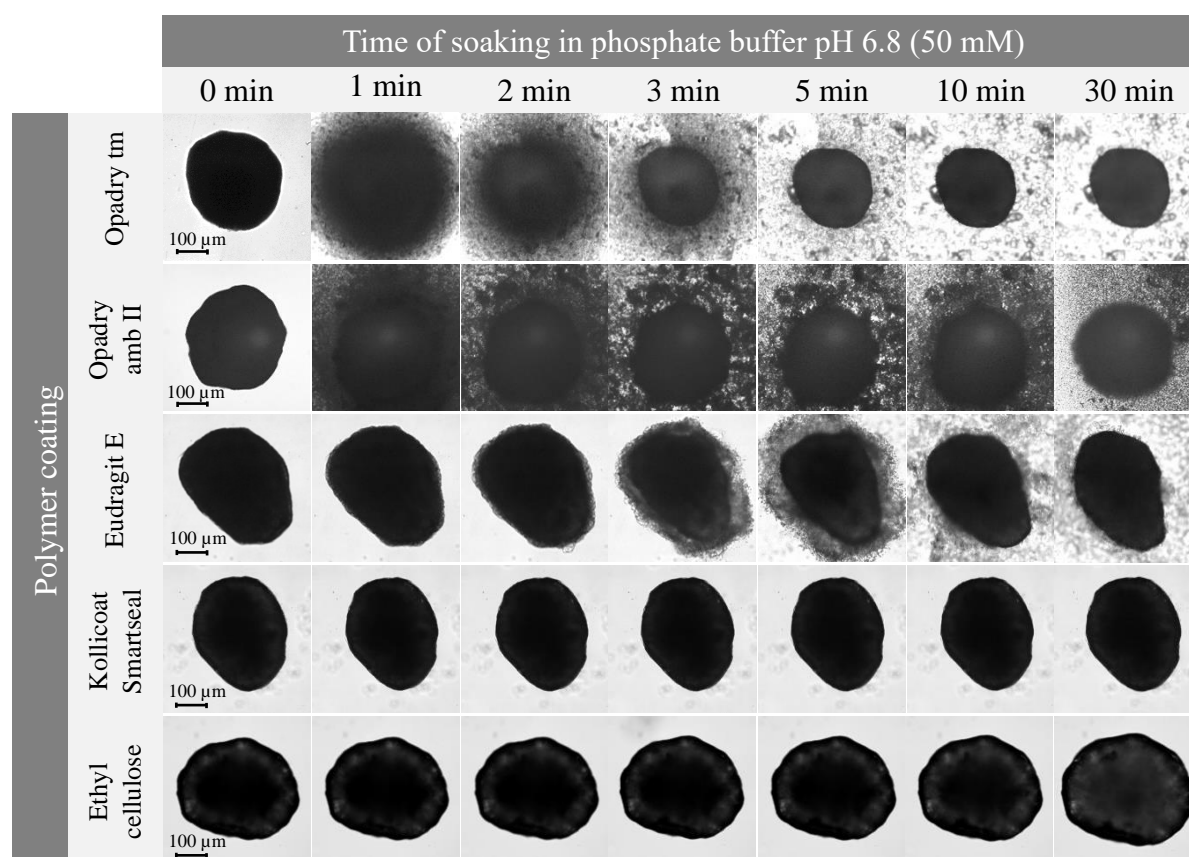


Fig. 13. Microscopic pictures of pellets coated with polymers of different solubility soaked in 50 mM phosphate buffer pH 6.8 (coating level 35% w/w).

The microscopic observations correlated well with the release profiles (Fig. 13). Opadry tm and Opadry amb II swelled, disintegrated and dissolved immediately which led to a fast drug release. The remaining particles which surrounded the MCC cores are insoluble pigments. Eudragit E is insoluble at pH 6.8. However, it swelled visibly in the first two minutes. Then the coating ruptured and disintegrated, leading to a burst release of the drug. For pellets with a Kollicoat Smartseal coating, no change was visible over a period of 30 minutes even though almost 80% of the drug was released within this time. Therefore, the drug diffused either through the intact coating or through microcracks formed due to the osmotic pressure inside the

pellets. Also for ethyl cellulose coated pellets, no rupturing or disintegration was visible. However, the pellets swelled slightly. This is probably due to the swelling of PVP which was included in the film as pore former.

The different behavior of Kollicoat Smartseal and Eudragit E coatings can be explained by differences in the chemical structure. Both polymers have a methacrylate backbone and side chains with tertiary amines. At pH 6.8, tertiary amines are mostly protonated (approx. 99.9%) which gives the polymers a hydrophilic nature. However, Eudragit E has a higher percentage of side chains with tertiary amines than Kollicoat Smartseal (50% vs. 30%). Therefore, it takes up water faster and to a higher extent as confirmed by a water uptake study on free films (Fig. 14). The fast influx of water quickly leads to a high osmotic pressure inside the pellets. Furthermore, the hydrated Eudragit E films have poor mechanical strength. Thus, the swollen coating can be easily disrupted.

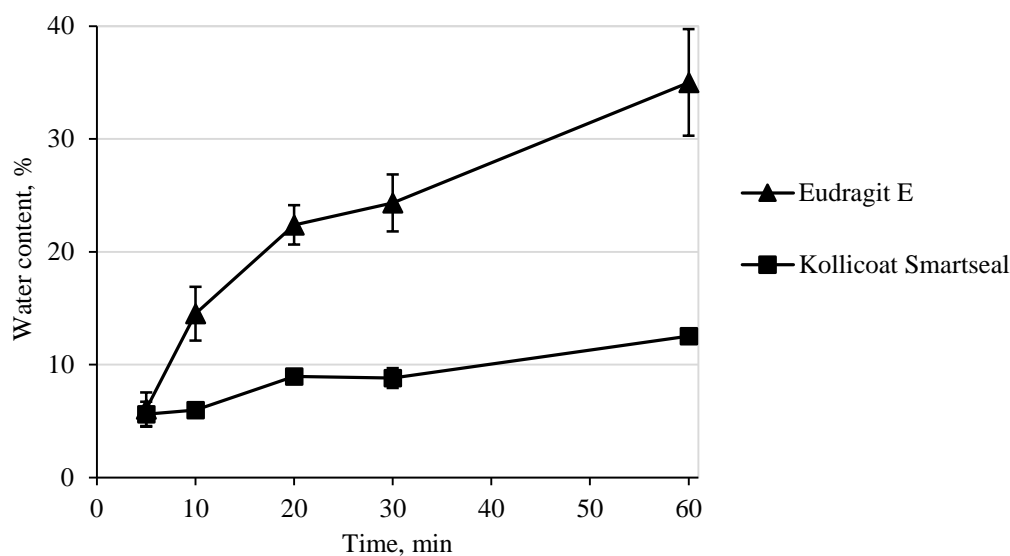


Fig. 14. Water uptake of free films of Kollicoat Smartseal and Eudragit E soaked in 50 mM phosphate buffer pH 6.8 (18 or 15% w/w TBC and 10 or 33% w/w magnesium stearate in Kollicoat Smartseal and Eudragit E, respectively).

3.1.1.2 Effect of buffer concentration and ionic strength on coating disintegration and drug release from pellets with acid-soluble coatings

The rate and extent of protonation of amine groups of Kollicoat Smartseal and Eudragit E not only depend on the pH of the medium but also on its buffer capacity. Buffer capacity and electrolyte concentration of human saliva vary between individuals as well as between unstimulated and stimulated salivation [67, 154]. Furthermore, they differ greatly from those of compendial buffer solutions. Therefore, the influence of buffer capacity and ionic strength of the release medium on coating disintegration and drug release was investigated for Eudragit E and Kollicoat Smartseal.

Pellets coated with Eudragit E were soaked in media of different buffer capacity and observed under a microscope (magnification: 20x). Furthermore, tramadol HCl pellets with a Kollicoat Smartseal or Eudragit E coating were incubated in test tubes with different media and the amount of drug released after five minutes was determined. The investigated media were water and 12.5, 25.0 and 50.0 mM phosphate buffer pH 6.8. The 50 mM buffer solution corresponds to the phosphate buffer pH 6.8 described in the United States Pharmacopoeia (USP) [151]. The buffer solutions have buffer capacities of 5.8, 11.6 and 23.3 mEq/pH unit, respectively. In comparison, the buffer capacity of human saliva is in the range of 6.0 ± 1.7 mEq/pH unit for unstimulated whole saliva and 7.9 ± 1.4 mEq/pH unit for stimulated whole saliva [154]. Furthermore, 0-100 mM NaCl was added to 25 mM phosphate buffer which has itself an ionic strength of 35 mM. These solutions cover the range of ionic strength of saliva (approx. 30-100 mM) [67].

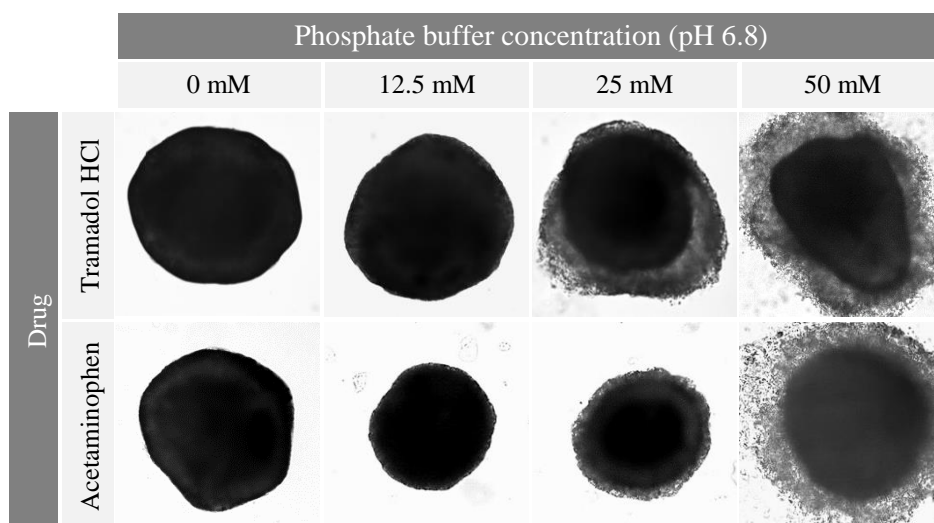


Fig. 15. Microscopic pictures of tramadol HCl and acetaminophen pellets coated with 35% w/w Eudragit E soaked for five minutes in water or phosphate buffer pH 6.8 of different concentration.

Swelling and disintegration of Eudragit E strongly depended on the buffer concentration (Fig. 15). A sufficiently high buffer capacity is needed for fast and complete protonation of the amine groups. Therefore, the coating was visually intact after five minutes in water and 12.5 mM phosphate buffer, whereas in 25 mM and 50 mM phosphate buffer it had ruptured and disintegrated. The effect was not related to the properties of the drug or caused by a drug/polymer interaction as it was observed for pellets containing tramadol HCl as well as for pellets containing acetaminophen. In contrast to tramadol HCl, acetaminophen is a non-ionizable drug and its solubility is lower by a factor of about 50 (17 mg/mL [147] vs. 948 mg/mL).

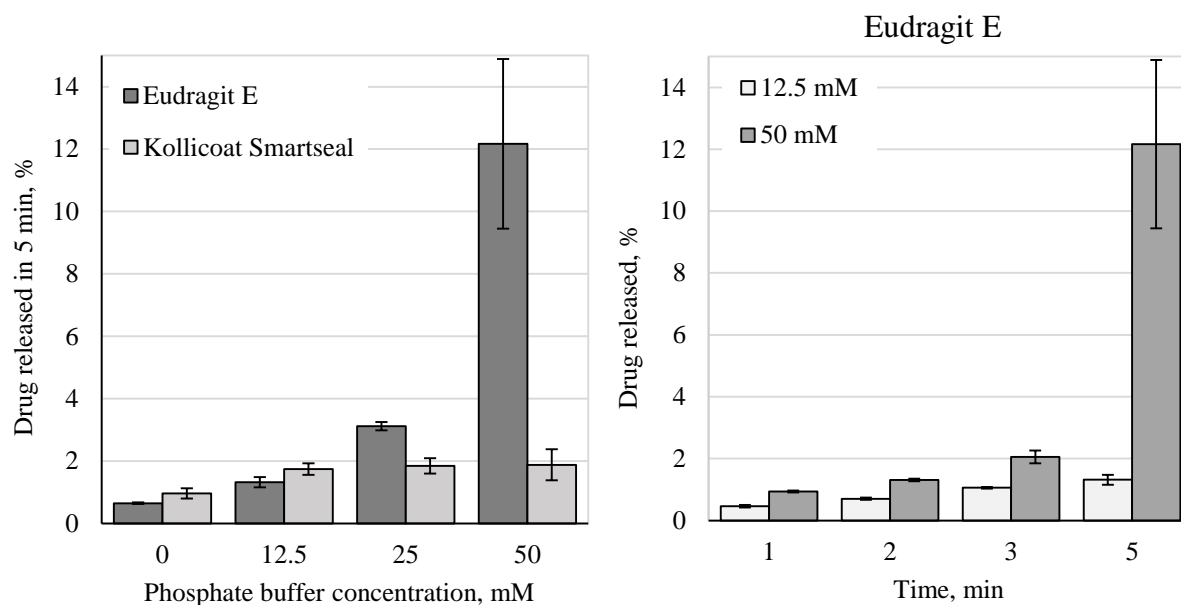


Fig. 16. Left: tramadol HCl released after five minutes in water and phosphate buffer pH 6.8 of different strength from pellets coated with 35% w/w Eudragit E or 35% w/w Kollicoat Smartseal.

Right: tramadol HCl released over time in 12.5 mM or 50 mM phosphate buffer from pellets coated with 35% w/w Eudragit E.

As discussed above, Kollicoat Smartseal is less hydrophilic and did not show swelling or rupturing even in 50 mM phosphate buffer (Fig. 13). Thus, buffer capacity had only a small effect on pellets coated with Kollicoat Smartseal (Fig. 16, left). The drug release was slightly higher in buffer solutions than in water: 1.7% after five minutes in 12.5 mM phosphate buffer compared to 1.0% after five minutes in water. However, it remained almost the same when the buffer concentration was increased to 50.0 mM (1.9%).

In contrast, buffer capacity greatly influenced the drug release from pellets coated with Eudragit E due to the effect on coating hydration and rupturing (Fig. 16, left). The release continuously increased with increasing buffer concentration, ranging from 0.6% after five

minutes in water to 12.2% in 50 mM phosphate buffer. The difference between 50 mM buffer (prepared according to USP) and 12.5 mM buffer (buffer capacity similar to saliva), was small in the first minutes and then became more pronounced with increasing incubation time (Fig. 16, right). Thus, the buffer capacity of the release medium is of minor importance for *in vitro* taste tests with a short incubation time (e.g. for ODTs). However, if the taste masking functionality is measured over a longer time, buffer capacity should be carefully adjusted in order not to over- or underestimate the release.

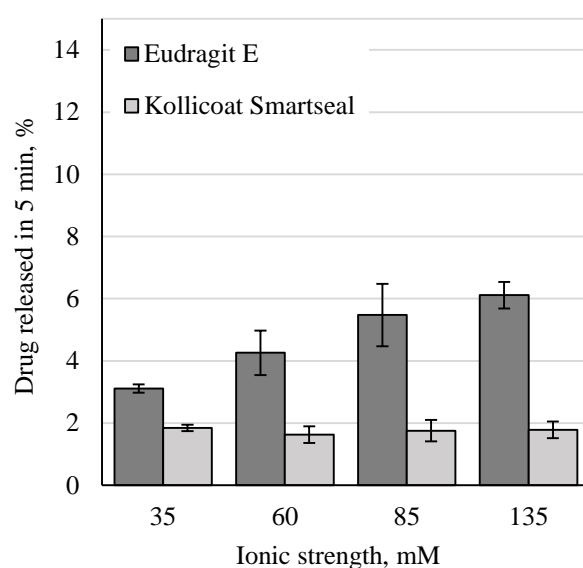


Fig. 17. Tramadol HCl released after five minutes in 25 mM phosphate buffer with different ionic strength (i.e. NaCl concentration) from pellets coated with 35% w/w Eudragit E or 35% w/w Kollicoat Smartseal.

Increasing the ionic strength of the buffer solution from 35 to 135 mM through the addition of sodium chloride had no influence on the release from pellets coated with Kollicoat Smartseal (Fig. 17). The release from pellets coated with Eudragit E slightly increased with increasing ionic strength. This is contradictory to the findings of Sjöqvist et al. [155], who observed a decreasing release rate from Eudragit E microcapsules with increasing sodium chloride concentrations. However, the concentrations in that study were in the range of 1-4.5 M which is far higher than the electrolyte concentration of saliva (approx. 30-100 mM [67]).

Overall, the release from pellet coated with Kollicoat Smartseal was more robust regarding the composition of the medium compared to pellets coated with Eudragit E.

3.1.1.3 Compression sensitivity of Kollicoat Smartseal, Eudragit E, and ethyl cellulose coatings

Among the investigated polymer coatings, Kollicoat Smartseal, Eudragit E as well as ethyl cellulose provided taste masked tramadol HCl pellets (35% w/w coating level). These pellets were compressed into orally disintegrating tablets together with 50% w/w tableting excipients. The tablets contained 50 mg of tramadol HCl and had a total weight of 600 mg and a diameter of 12 mm. The compression force was set to 10 kN. The release in phosphate buffer pH 6.8 was determined to evaluate the taste masking efficiency and the comparison of the release before and after compaction served as an indicator for coating damage caused by compression.

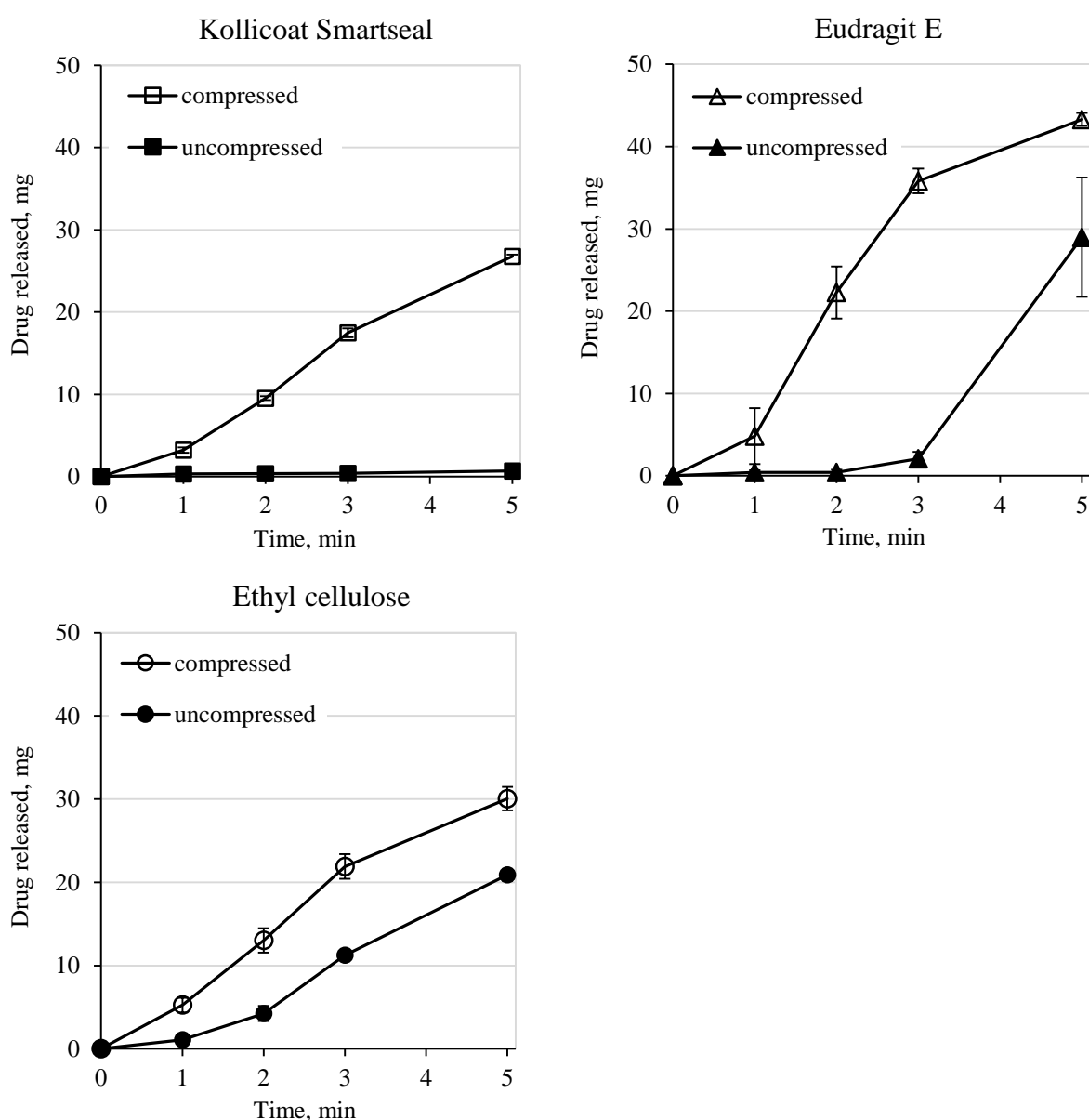


Fig. 18. Tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with Kollicoat Smartseal, Eudragit E or ethyl cellulose (35% w/w coating level, 18 or 15% w/w TBC in Kollicoat Smartseal and Eudragit E, 20% w/w PVP in ethyl cellulose, 10 kN compression force).

All investigated coatings released the drug faster after compression, indicating that the films were damaged. The difference factor (representing the mean difference in %) was 3080, 234, and 88 for Kollicoat Smartseal, Eudragit E and ethyl cellulose, respectively. Compressed pellets did not exhibit a lag time before the drug was released. After one minute, 3.2 mg of tramadol HCl was released from compressed pellets coated with Kollicoat Smartseal, 4.8 mg with Eudragit E and 5.3 mg with ethyl cellulose, leading to insufficient taste masking of the ODTs.

Therefore, the effect of several formulation and process parameters was studied in order to reduce the coating damage caused by compaction and to obtain taste masked tramadol HCl tablets. The different approaches are described in the following chapters. Ethyl cellulose was only used as subcoating and not as main coating for further experiments, since the drug release in pH 1.0 was too slow even in the compressed state (81% after 15 minutes with 35% w/w coating level).

3.1.2 Subcoatings

To reduce the amount of drug released from compressed pellets in pH 6.8, subcoatings were applied under Eudragit E or Kollicoat Smartseal topcoatings. The subcoatings either had a lower permeability to provide an additional barrier for drug diffusion or gel-forming properties to seal cracks in the topcoating. The total coating level was kept constant at 35% w/w.

Ethyl cellulose subcoating under Eudragit E

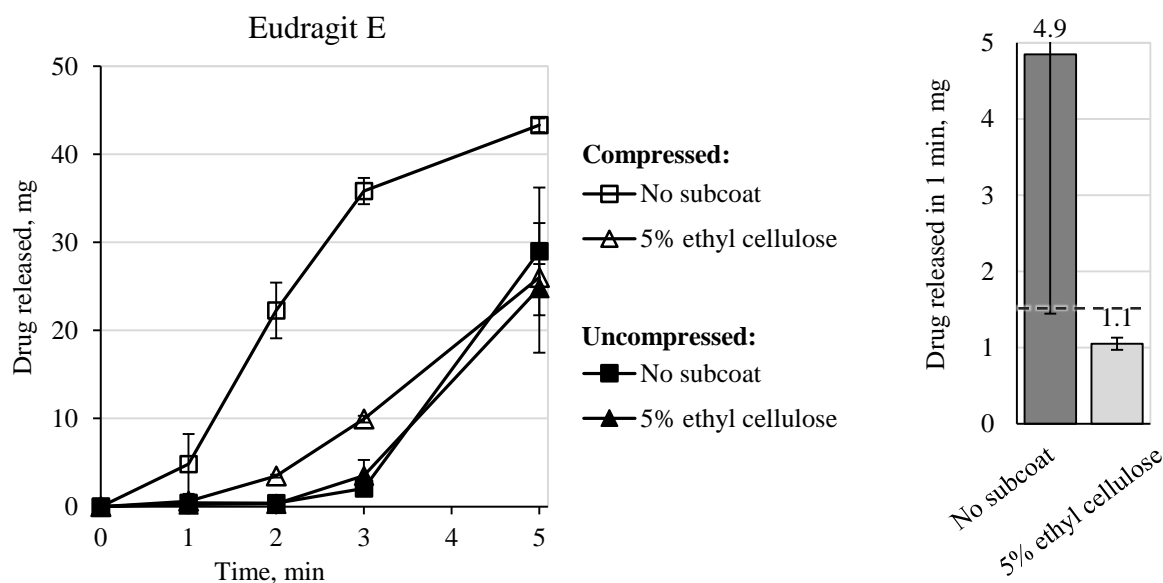


Fig. 19. Left: Effect of ethyl cellulose subcoating on tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with Eudragit E (35% w/w total coating level, 20% w/w PVP in ethyl cellulose, 15% w/w TBC in Eudragit E, 10 kN compression force).

Right: Effect of ethyl cellulose subcoating on tramadol HCl released after one minute in pH 6.8 from compressed pellets coated with Eudragit E (35% w/w total coating level, 20% w/w PVP in ethyl cellulose, 15% w/w TBC in Eudragit E, 10 kN compression force).

In the uncompressed state, a subcoating of 5% w/w ethyl cellulose (20% w/w PVP) under Eudragit E had no effect on the release in phosphate buffer pH 6.8 ($f_1 = 18.5$). However, the release rate of compressed pellets was reduced compared to pellets without subcoating ($f_1 = 62.3$). Compressed pellets coated with 5% w/w ethyl cellulose and 30% w/w Eudragit E released less than 1.5 mg of tramadol HCl in the first minute and thus provided taste masked ODTs (Fig. 19).

The subcoating alone had almost no retarding effect on the release from compressed pellets (Fig. 20). Its higher effectiveness in combination with the Eudragit E topcoating could be due to reduced rupturing during compression because some of the mechanical stress is absorbed by the topcoating. Furthermore, the topcoating might retard pore former leaching.

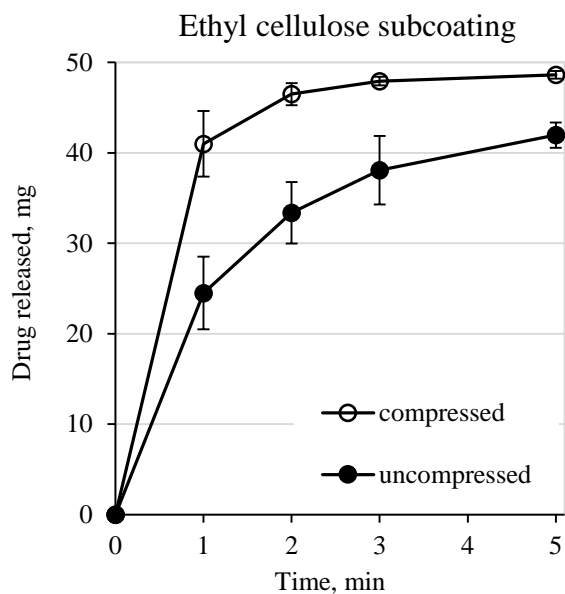


Fig. 20. Tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with 5% w/w ethyl cellulose containing 20% w/w PVP as pore former (10 kN compression force).

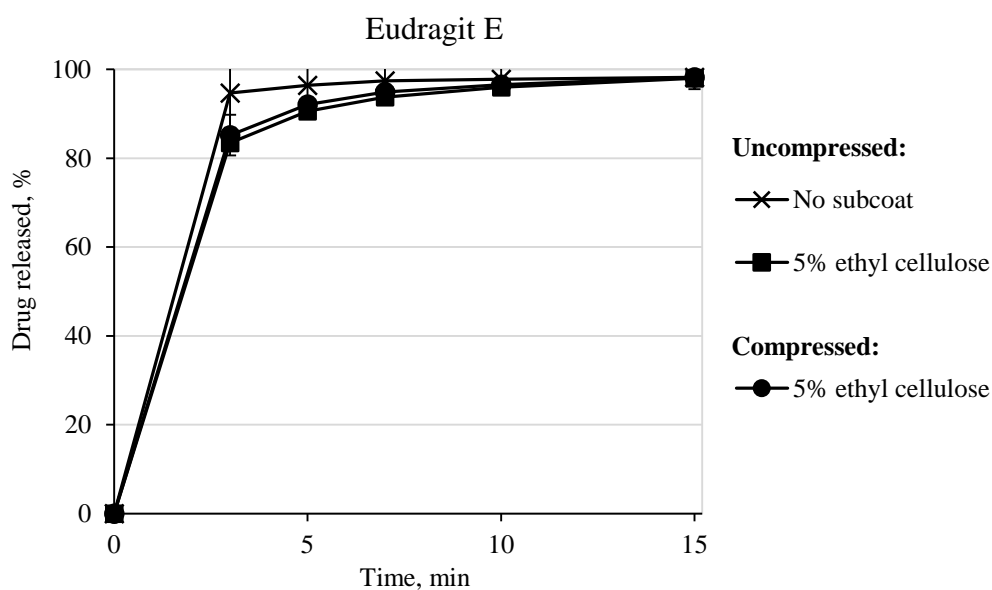


Fig. 21. Effect of ethyl cellulose subcoating on tramadol HCl release in pH 1.0 from compressed and uncompressed pellets coated with Eudragit E (35% w/w total coating level, 20% w/w PVP in ethyl cellulose, 15% w/w TBC in Eudragit E, 10 kN compression force).

In pH 1.0, the 5% w/w ethyl cellulose subcoating very slightly reduced the release rate (Fig. 21). However, this is probably not of practical relevance since more than 90% tramadol HCl was released within five minutes from compressed as well as from uncompressed pellets. As the subcoating is very thin, the pore former PVP can easily dissolve and leach out once the topcoating has dissolved.

Subcoatings of ethyl cellulose, Eudragit E or HCP under Kollicoat Smartseal

Since tramadol HCl is highly water-soluble, it partially dissolved during the coating process with the aqueous dispersion of Kollicoat Smartseal. This led to stickiness and the coating could only be applied at a low spray rate. Furthermore, drug migration into the film during coating can have unwanted effects on drug release by increasing the film's permeability [125]. Therefore, organic solutions of polymers were applied as subcoatings under Kollicoat Smartseal. Additional benefits with regard to taste masking of compressed pellets were expected from subcoatings with a lower permeability (ethyl cellulose) or with gel-forming properties (hydroxypropyl cellulose (HPC)).

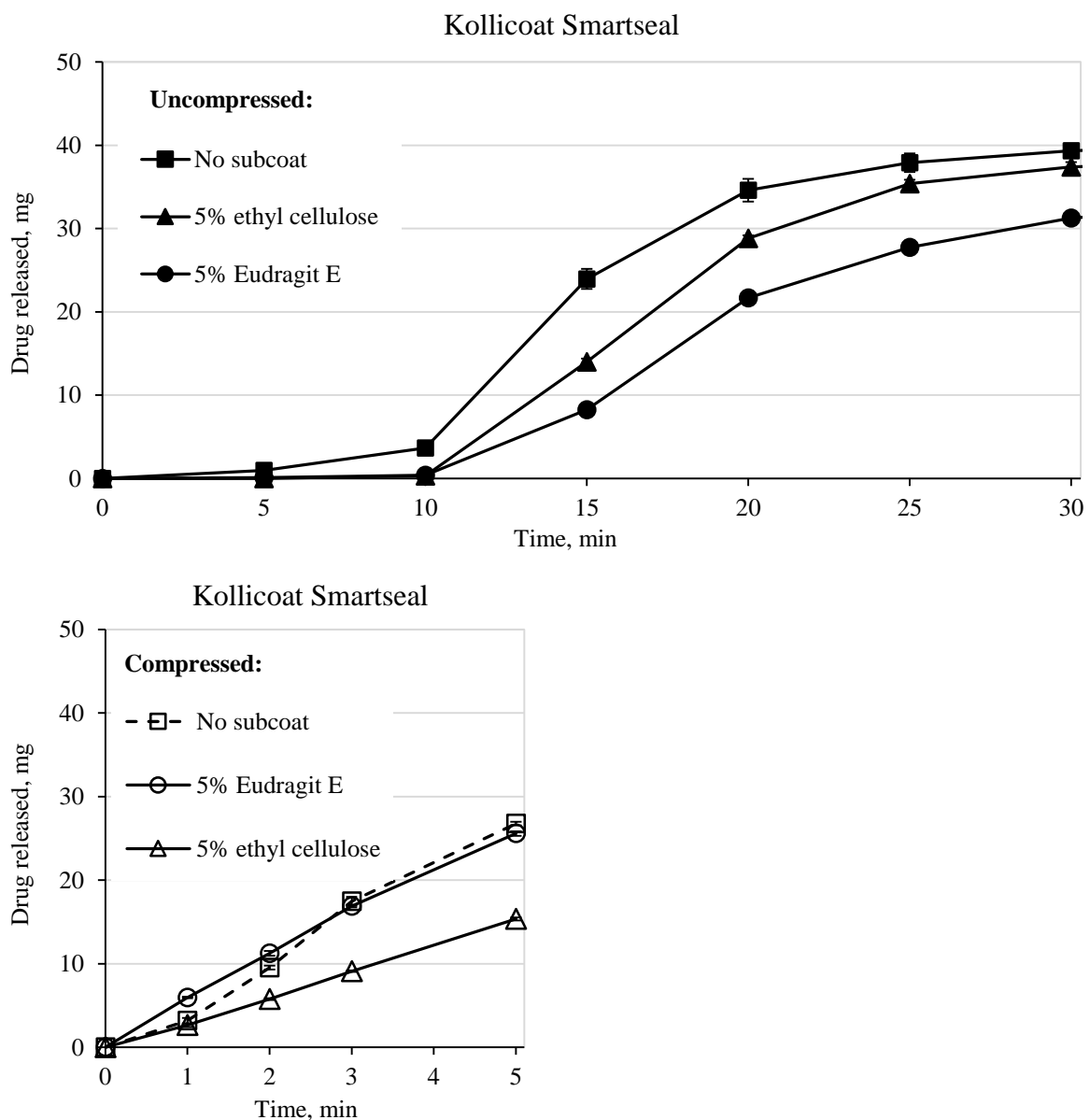


Fig. 22. Effect of Eudragit E and ethyl cellulose subcoatings on tramadol HCl release in pH 6.8 from uncompressed (top) and compressed (bottom) pellets coated with Kollicoat Smartseal (35% w/w total coating level, 20% w/w PVP in ethyl cellulose, 18 or 15% w/w TBC in Kollicoat Smartseal and Eudragit E, 10 kN compression force).

Organic solutions of ethyl cellulose or Eudragit E were applied as subcoatings under Kollicoat Smartseal. A coating level of 5% w/w was sufficient to prevent dissolution of tramadol HCl during the application of the aqueous topcoating. Consequently Kollicoat Smartseal, could be sprayed at a faster rate (1.2 g/min vs. 0.5 g/min for 70 g of pellets) and no stickiness was observed. Furthermore, the permeability of the coating was reduced as indicated by the increased lag time in pH 6.8 for uncompressed pellets (Fig. 22, top).

Even though the Eudragit E subcoating increased the lag time of uncompressed pellets, it had no effect on the release in pH 6.8 after compression ($f_1 = 10.9$). In contrast, the more hydrophobic ethyl cellulose subcoating reduced the drug release rate of compressed pellets compared to pellets without a subcoating ($f_1 = 42.3$) (Fig. 22, bottom). Yet, these pellets still released 2.6 mg tramadol HCl in the first minute leading to insufficient taste masking.

To further reduce the release in pH 6.8 while maintaining a fast release in pH 1.0, different ratios of subcoating/topcoating were evaluated and the amount of pore former in the subcoating was varied. Furthermore, the effect of pore former type was investigated. The water-soluble pore former PVP was either replaced by an acid-soluble polymer (Kollicoat Smartseal) or by a water-soluble substance of low molecular weight (lactose). The total coating level was kept constant at 35% w/w.

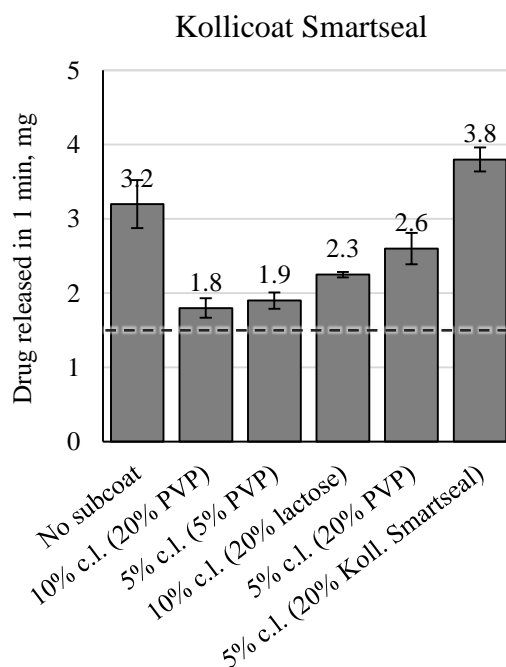


Fig. 23. Effect of coating level (c.l.), pore former type and pore former content of the ethyl cellulose subcoating on tramadol HCl released after one minute in pH 6.8 from compressed pellets with a Kollicoat Smartseal topcoating (35% w/w total coating level, 18% w/w TBC in Kollicoat Smartseal, 10 kN compression force).

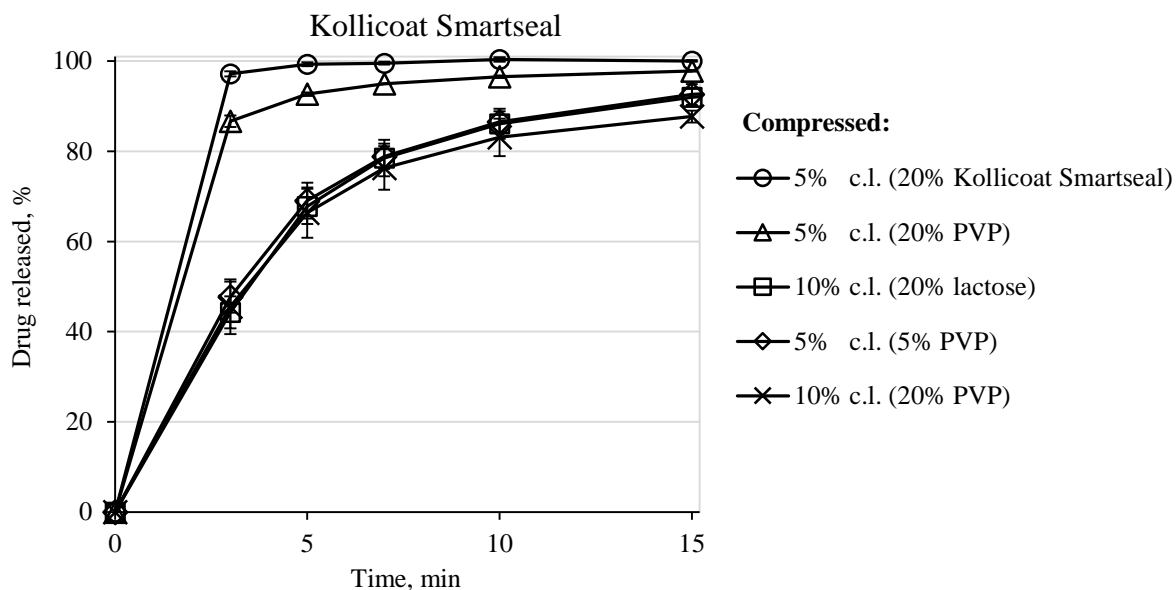


Fig. 24. Effect of coating level (c.l.), pore former type and pore former content of the ethyl cellulose subcoating on tramadol HCl release in pH 1.0 from compressed pellets with a Kollicoat Smartseal topcoating (35% w/w total coating level, 18% w/w TBC in Kollicoat Smartseal, 10 kN compression force).

The amount of tramadol HCl released from compressed pellets after one minute at pH 6.8 was reduced to 1.8 mg or 1.9 mg when the coating level of the ethyl cellulose subcoating was increased to 10% w/w, or the amount of PVP in the subcoating was reduced to 5% w/w (Fig. 23). This is still slightly higher than the threshold for taste masking. Additionally, there was a pronounced reduction of the release rate in pH 1.0 (Fig. 24). All formulations met the target of 85% drug release after 15 minutes. However, the difference compared to tablets with uncoated pellets, which released 99% in three minutes, could cause problems if the criteria for bioequivalence have to be met.

To increase the release rate in pH 1.0, lactose was used as an alternative pore former. After the topcoating has dissolved, soluble pore formers diffuse out of the subcoating and thereby generate pores. As a substance of low molecular weight, lactose was expected to diffuse out more rapidly compared to the polymer PVP. However, there was no difference between the release of the two formulations at pH 1.0 ($f_1 = 3.4$) (Fig. 24). Also Kollicoat Smartseal was included as pore former in the ethyl cellulose subcoating. Contrary to PVP and lactose it dissolves only in acidic media but not at pH 6.8. Nevertheless, the drug release rate of compressed pellets increased not only in pH 1.0 but also in pH 6.8 compared to pellets with PVP or lactose as pore former (Fig. 23 and Fig. 24). Aside from the different pore former, this could also be due to increased compression-sensitivity caused by magnesium stearate which was included as anti-tacking agent in subcoatings containing Kollicoat Smartseal [156, 157].

Gel-forming polymers like hydroxypropyl cellulose (HPC) generate solutions of high viscosity. They might seal cracks in the topcoating for a short time and thus lead to the desired lag phase even if the coating is damaged after compression. A 10% w/w HPC (Klucel EXF) subcoating was applied under Kollicoat Smartseal (35% w/w total coating level).

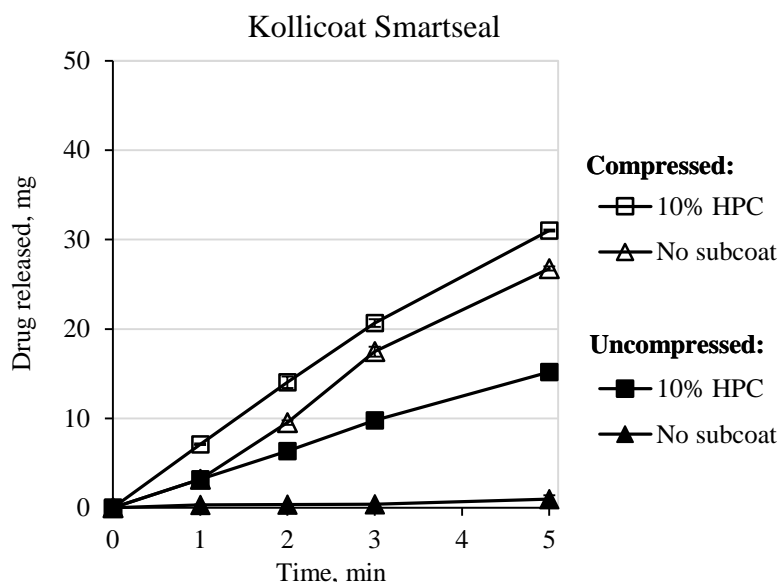


Fig. 25. Effect of hydroxypropyl cellulose (HPC) subcoating on tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with Kollicoat Smartseal (35% w/w total coating level, 18% w/w TBC in Kollicoat Smartseal, 10 kN compression force).

The release of uncompressed pellets with an HPC subcoating was increased compared to pellets without subcoating (Fig. 25). This could be due to a higher permeability of HPC compared to Kollicoat Smartseal. Furthermore, swelling of the HPC subcoating could lead to crack formation in the topcoating. This might be avoided by applying the gel-forming polymer as overcoat. However, this approach is known to lead to long disintegration times [140] and is, therefore, not an option for ODTs. Also in the compressed state, the HPC subcoating did not delay the release of tramadol HCl through the damaged coating. As for uncompressed pellets, the release rate was slightly higher compared to pellets coated only with Kollicoat Smartseal ($f_1 = 27.9$) (Fig. 25). A gel-forming polymer as subcoating was therefore not a suitable approach to improve the taste masking efficiency of compressed pellets coated with Kollicoat Smartseal.

In conclusion, applying an ethyl cellulose subcoating with 20% w/w PVP as pore former (5% coating level) under Eudragit E coatings reduced the release rate of compressed pellets in pH 6.8 and taste masking was maintained after compaction (35% w/w total coating level). At

the same time, this subcoating had almost no effect on the release in pH 1.0. Ethyl cellulose subcoatings also reduced the release of compressed pellets with Kollicoat Smartseal as topcoating. However, all of the investigated subcoating/topcoating ratios, pore former types and pore former contents led to a release of more than 1.5 mg tramadol HCl after one minute at pH 6.8. Insufficient taste masking is therefore expected. A gel-forming HPC subcoating under Kollicoat Smartseal increased, rather than decreased, the release rate in pH 6.8.

3.1.3 Mechanical properties

Film damage upon compression mainly depends on the mechanical properties of the coating. Films should be flexible and strong in order to be able to deform during compaction without rupturing. High film flexibility can be achieved by the addition of suitable plasticizers or by admixing a highly flexible polymer [117, 120, 124].

3.1.3.1 Plasticizer type and concentration

Plasticizers were included in coating formulations for two reasons. On one hand, they increase the mobility of polymer chains and thus the flexibility of polymer films. Therefore, the coating can be elongated to a higher extent without rupturing and the effect of compaction on drug release is reduced or eliminated [117, 120, 124, 127]. Furthermore, plasticizer was added to the aqueous dispersions of Kollicoat Smartseal to reduce the minimum film forming temperature. Above this temperature, polymer particles exhibit sufficient plasticity to form a coherent film [158]. The coalescence can already take place during the coating process. However, in some cases, an additional curing step is needed after the coating has been applied.

Effect of plasticizer type in Eudragit E coatings

Tramadol HCl pellets were coated with Eudragit E containing 10% w/w TBC or triacetin (TA) as plasticizer (no subcoating). In contrast to TA, TBC is a water-insoluble plasticizer. It provides films with low water uptake, a low glass transition temperature and good plasticizer permanence during storage [159]. Also TA leads to Eudragit E films with good flexibility [126, 160].

Since it is difficult to measure mechanical properties of coatings applied on tablets or pellets, they are commonly studied on free films [117, 120, 123, 127]. Free films were prepared either by casting or by spraying the coating formulations on a rotating Teflon disc. In the formulation of sprayed films, also the anti-tacking agent magnesium stearate was included (10% w/w). Elongation at break and puncture strength of the films were determined using a Texture Analyzer.

Table 2. Effect of plasticizer type on mechanical properties of free films of Eudragit E (film thickness: 230-260 μm).

	Maximum elongation (S.D.), %		Puncture strength (S.D.), MPa	
	Cast films	Sprayed films	Cast films	Sprayed films
10% w/w triacetin	123 (3)	25 (0)	3.37 (0.15)	1.25 (0.04)
10% w/w tributyl citrate	219 (23)	63 (6)	1.70 (0.11)	2.56 (0.15)

Irrespective of the preparation method, Eudragit E films containing TBC as plasticizer had a higher maximum elongation compared to films with TA.

The method of preparation had a big influence on the mechanical properties of free films. The maximum elongation was lower for sprayed films compared to cast films (Table 2). This could be due to the anti-tacking agent magnesium stearate which was not included in cast films and which is known to reduce maximum elongation and puncture strength of films [156, 157]. Another reason could be a better entanglement of polymer chains in cast films. The films prepared by spraying are expected to better represent the properties of pellet coatings since they contain all components of the coating formulation and the preparation closely resembles the coating process. On the other hand, casting is less time-consuming and thus a good tool for screening.

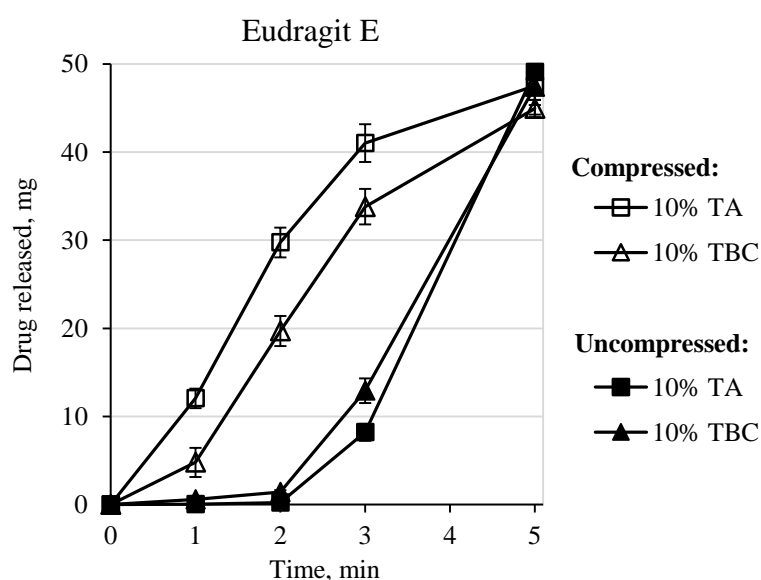


Fig. 26. Effect of plasticizer type on tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with Eudragit E (35% w/w coating level, 10 kN compression force, TBC = tributyl citrate, TA = triacetin).

Even though TBC and TA differ in their solubility, they had no influence on the drug release from uncompressed pellets ($f_1 = 13.2$) (Fig. 26). This indicates, that plasticizer leaching did not play a significant role. After compression, the release in the first minute was lower with coatings containing TBC than with those containing TA. Coatings with TBC could better withstand compression forces which is in good agreement with the higher maximum elongation measured for free films (63% vs. 25% for sprayed films) (Table 2). After one minute, the drug was released rapidly regardless of the plasticizer type due to film disintegration.

Effect of tributyl citrate concentration in Eudragit E and Kollicoat Smartseal coatings

The effect of plasticizer concentration on the release in pH 6.8 was investigated for uncompressed and compressed pellets coated with Kollicoat Smartseal or Eudragit E. Tramadol HCl pellets with an ethyl cellulose subcoating were coated with Kollicoat Smartseal containing 0-25% w/w TBC or with Eudragit E containing 0-15% w/w TBC. The TBC content in Eudragit E formulations could not be increased further because the coating became too sticky.

Additionally, free films of Kollicoat Smartseal and Eudragit E with different concentrations of TBC were prepared by spraying and casting. Sprayed films contained the anti-tacking agent magnesium stearate analogous to coating formulations. The properties of unplasticized Kollicoat Smartseal formulations could not be measured because they were too brittle and cracks formed already during the drying step.

For both polymers, increasing concentrations of TBC led to an increased maximum elongation and decreased film strength (Table 3). The only exception was cast films of Eudragit E which had a lower maximum elongation with 15% w/w than with 10% w/w TBC (180% vs. 219%). Eudragit E exhibited a higher maximum elongation than Kollicoat Smartseal at the same plasticizer content. This is probably related to the lower molecular weight and glass transition temperature of Eudragit E (47'000 Da vs. 200'000 Da and 45 °C vs. 63 °C) [142, 143]. Also the fact that Kollicoat Smartseal was applied as aqueous dispersion and Eudragit E as organic solution could play a role [123, 125].

3 Results and discussion

Table 3 Effect of tributyl citrate (TBC) content on mechanical properties of free films of Kollicoat Smartseal and Eudragit E (film thickness: 230-260 μm).

	Maximum elongation (S.D.), %		Puncture strength (S.D.), MPa	
	Cast films	Sprayed films	Cast films	Sprayed films
Kollicoat® Smartseal				
No plasticizer	n.d.	n.d.	n.d.	n.d.
10% w/w TBC	36 (3)	13 (1)	5.75 (0,35)	1.95 (0.08)
18% w/w TBC	151 (1)	52 (1)	3.70 (0.01)	1.79 (0.04)
25% w/w TBC	253 (26)	73 (8)	1.11 (0.03)	0.49 (0.02)
Eudragit® E				
No plasticizer	53 (23)	17 (1)	3.12 (0.28)	3.19 (0.35)
10% w/w TBC	219 (23)	63 (6)	1.70 (0.11)	2.49 (0.13)
15% w/w TBC	180 (18)	75 (3)	1.44 (0.11)	0.55 (0.03)

n.d. = not determined because films were too brittle to handle

The highest maximum elongation achieved for cast films of Kollicoat Smartseal was 253% with 25% w/w TBC and for cast films of Eudragit E it was 219% with 10% w/w TBC. In other studies, plasticized films of Eudragit L and Eudragit NE with a maximum elongation of 198% did not rupture upon tableting of coated pellets [117]. This was also the case for Kollicoat SR coatings with 10% w/w plasticizer, which had a maximum elongation of 137% [120]. Thus, the plasticized Eudragit E and Kollicoat Smartseal coatings should be flexible enough to withstand compaction without loss of functionality. However, the comparability of results from different studies is limited because many factors, such as method of film preparation, storage humidity, and elongation speed have a big influence on the results [127, 161]. Furthermore, coating damage during compaction does not depend on coating flexibility alone. For example, in studies with Eudragit FS or Eudragit L/Eudragit NE, coatings ruptured regardless of their mechanical properties, if the coating thickness was too low [117, 128].

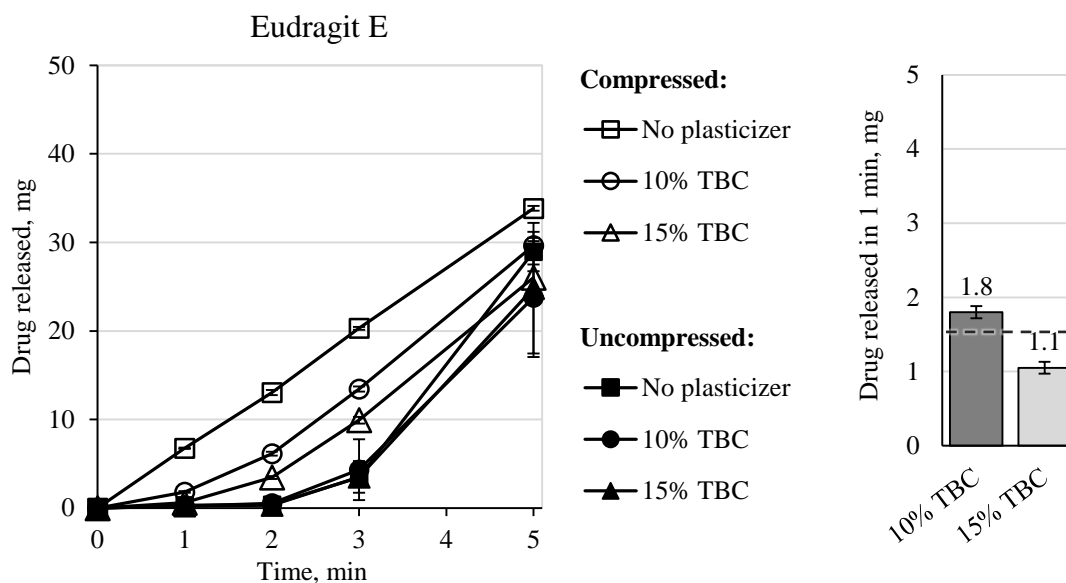


Fig. 27. Left: Effect of tributyl citrate (TBC) content on tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with Eudragit E (5% w/w EC subcoating, 35% w/w total coating level, 10 kN compression force).

Right: Effect of TBC content on tramadol HCl released after one minute in pH 6.8 from compressed pellets coated with Eudragit E (5% w/w EC subcoating, 35% w/w total coating level, 10 kN compression force).

For uncompressed pellets coated with Eudragit E, the addition of plasticizer had no influence on the release in pH 6.8 (Fig. 27, left). Eudragit E was applied as organic solution. When polymer solutions are used, the polymer chains form an interwoven network once the solvent has evaporated and the plasticity of the formulation is not important for film formation. Therefore, regardless of the TBC content, uncompressed pellets had a lag phase of two minutes followed by a fast release due to coating disintegration (Fig. 13). In the compressed state, pellets without plasticizer no longer exhibited a lag phase. They released 6.7 mg tramadol HCl within one minute. In contrast, plasticized films were less damaged and taste masked ODTs were achieved when the coating contained 15% w/w TBC. With this coating, only 1.1 mg tramadol HCl was released after one minute in pH 6.8 (Fig. 27, right). The reduction of coating damage with increasing TBC content correlated well with the increasing maximum elongation of free films prepared by spraying. Also in the compressed state, the release rate after two minutes was not affected by the plasticizer concentration since the drug release in this phase is governed by coating disintegration.

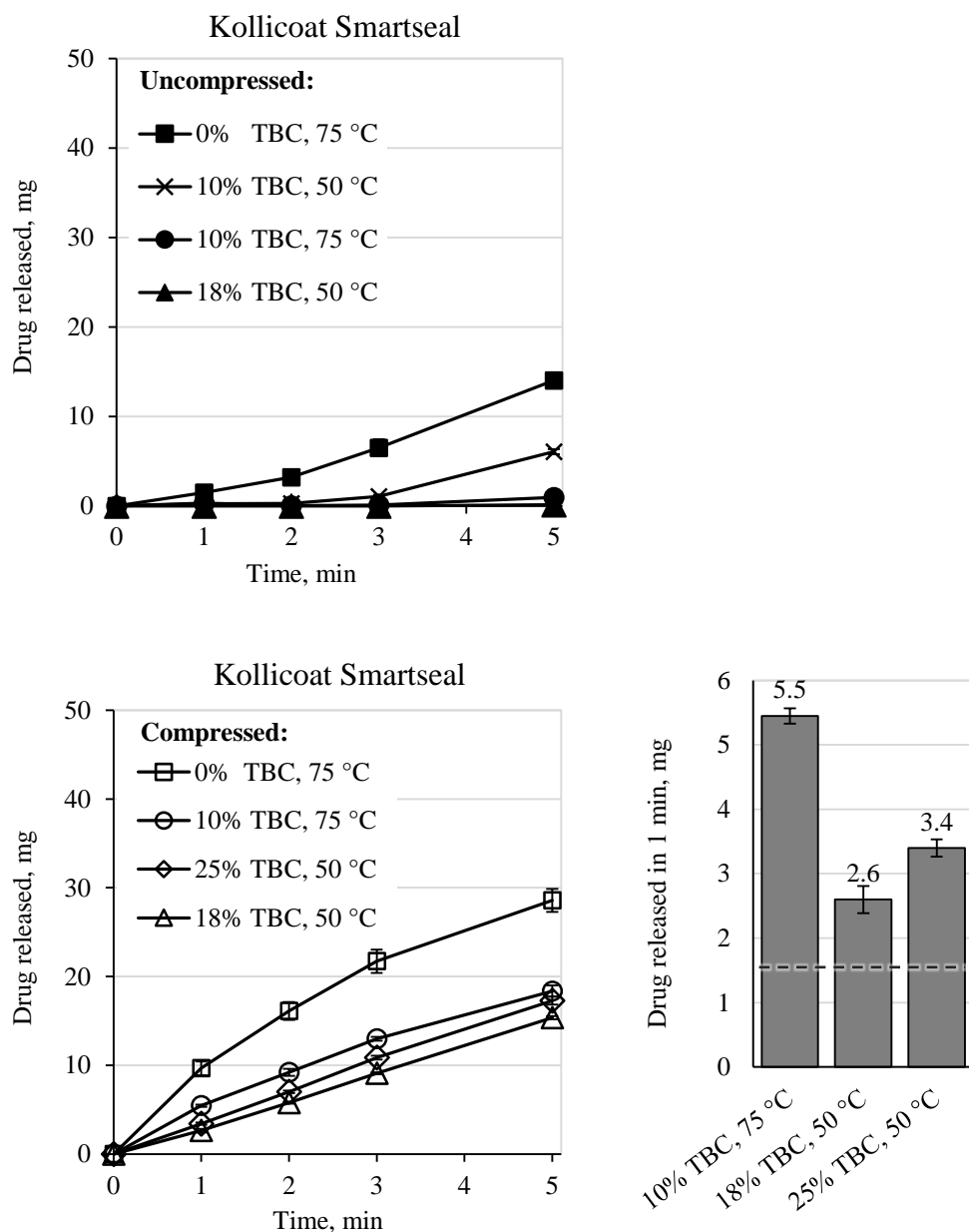


Fig. 28. Top: Effect of tributyl citrate (TBC) content and curing temperature on tramadol HCl release in pH 6.8 from uncompresssed pellets coated with Kollicoat Smartseal (5% w/w EC subcoating, 35% w/w total coating level, 10 kN compression force).

Bottom: Effect of tributyl citrate (TBC) content on tramadol HCl release in pH 6.8 from compressed pellets coated with Kollicoat Smartseal (5% w/w EC subcoating, 35% w/w total coating level, 10 kN compression force).

Kollicoat Smartseal was applied as aqueous dispersion. Release profiles in pH 6.8 of uncompresssed pellets indicated that without plasticizer, polymer particles did not coalesce even though the pellets were cured for 18 hours at a relatively high temperature (75 °C) (Fig. 28, top). With 10% w/w TBC as plasticizer, the film coalescence was not complete after curing at 50 °C. The drug release could be further reduced when the curing temperature was increased to 75 °C. With 18% w/w TBC, a curing temperature of 50 °C was sufficient for polymer particles

to merge. Only 0.07 mg tramadol HCl were released from uncompressed pellets within five minutes. Coating damage during compression was reduced, when the TBC content was increased from 0 to 10 or 18% w/w as indicated by the lower drug release rate in pH 6.8 (Fig. 28, bottom). However, when the TBC concentration was further increased to 25% w/w, no additional decrease of drug release was achieved even though the maximum elongation of free films was higher. A direct correlation of mechanical properties of free films and coating damage during compaction is difficult because of the complex interplay of many factors. A higher plasticizer concentration not only increases the maximum elongation of films but at the same time reduces their puncture strength. The two effects counteract each other with regard to the film's ability to undergo compaction without rupturing. Furthermore, high film flexibility decreases the risk of rupturing but the films will be deformed more and thus become thinner. This reduction in coating thickness is another reason for an increased release rate after compaction.

A TBC concentration of 18% w/w in Kollicoat Smartseal coatings led to the lowest degree of coating damage after compaction. Nevertheless, 2.6 mg tramadol HCl was released after one minute in pH 6.8 through this coating (with 5% w/w ethyl cellulose subcoating) Hence, the tablets were not completely taste masked (Fig. 28, bottom).

In summary, increasing the TBC concentration increased the maximum elongation of free films of Kollicoat Smartseal and Eudragit E and decreased their strength. Including TBC in coatings reduced the release from compressed pellets compared to unplasticized formulations. For Kollicoat Smartseal, 18% w/w TBC was the optimal concentration, but still too much tramadol HCl was released for complete taste masking. On the other hand, taste masked ODTs could be achieved with pellets coated with Eudragit E if 15% w/w TBC was added (5% w/w ethyl cellulose subcoating).

3.1.3.2 Admixing of the more flexible polymer Kollicoat SR to Kollicoat Smartseal

Besides the addition of plasticizers, admixing of highly flexible polymers to the coating formulation is another approach to increase film flexibility [120, 124].

Kollicoat SR consists of polyvinyl acetate and PVP in a ratio of 9:1 and is used for extended release formulations. The drug release from pellets coated with Kollicoat SR (10% w/w TEC as plasticizer) was not affected by compaction [120]. Aqueous dispersions of Kollicoat

Smartseal and Kollicoat SR were mixed in ratios of 70:30 or 50:50 and applied on tramadol HCl pellets (5% w/w ethyl cellulose subcoating). The formulations contained 18% w/w TBC as plasticizer. The drug release from compressed pellets was determined in pH 6.8. Furthermore, mechanical properties were determined for corresponding free films prepared by casting.

Table 4. Effect of admixing Kollicoat SR to Kollicoat Smartseal on mechanical properties of free films (18% w/w TBC, film thickness: 230-260 μm).

Kollicoat Smartseal/ Kollicoat SR	Maximum elongation (S.D.), %	Puncture strength (S.D.), MPa
100:0	151 (1)	3.70 (0.01)
70:30	350 (17)	2.25 (0.20)
50:50	490 (41)	1.67 (0.14)

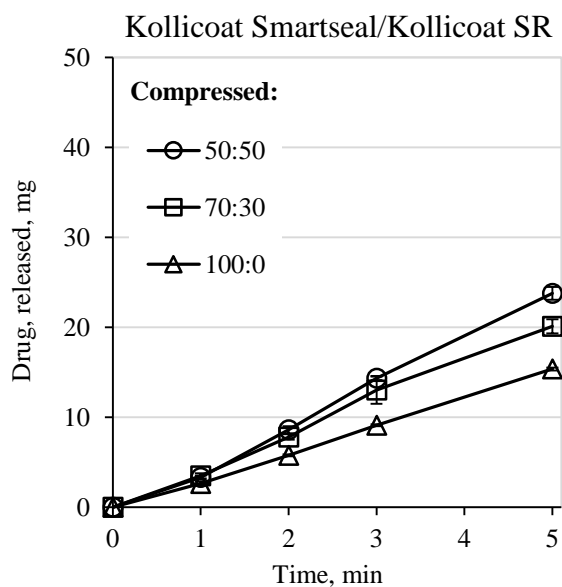


Fig. 29. Effect of Kollicoat Smartseal/Kollicoat SR ratio in the coating on tramadol HCl release in pH 6.8 from compressed pellets (5% w/w EC subcoating, 35% w/w total coating level, 18% w/w TBC in the topcoating, 10 kN compression force).

The addition of Kollicoat SR to Kollicoat Smartseal strongly increased the maximum elongation of free films (Table 4). Films with a ratio of Kollicoat Smartseal/Kollicoat SR 50:50 (18% w/w TBC) had a maximum elongation of 490%. However, the higher maximum elongation did not lead to a reduced compression sensitivity of the coating. This could be due to the reduced puncture strength which nullified the benefit of a higher flexibility. The amount

of drug released from compressed pellets after one minute in pH 6.8 was almost the same regardless of the amount of Kollicoat SR added to the formulation. All formulations exhibited insufficient taste masking. After one minute, the release rate increased with increasing Kollicoat SR content. This was attributed to the pore former PVP included in Kollicoat SR. It dissolves and consequently increases coating permeability (Fig. 29).

3.1.3.3 Magnesium stearate content

Magnesium stearate was included in coating formulations as anti-tacking agent. However, it can reduce maximum elongation and puncture strength of polymeric films [156, 157]. A lower magnesium stearate content might thus lead to less coating rupturing and slower drug release from compressed pellets. Tramadol HCl pellets were coated with Eudragit E (no subcoating) containing either 10 or 33% w/w magnesium stearate and the release of uncompressed and compressed pellets in pH 6.8 was determined.

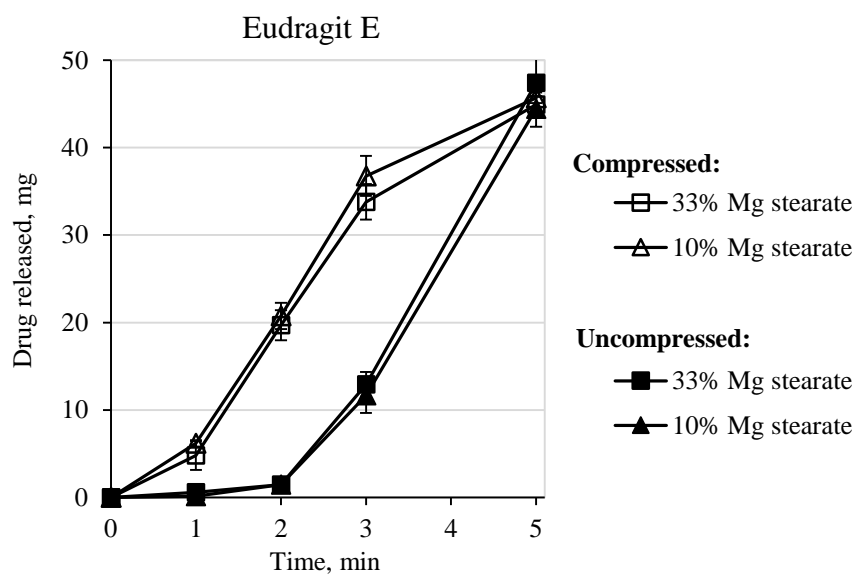


Fig. 30. Effect of magnesium stearate content on tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with Eudragit E (35% w/w coating level, 10% w/w TBC, 10 kN compression force).

There was no difference between the drug release profiles of pellets coated with Eudragit E containing 10 or 33% w/w magnesium stearate, neither before nor after compression ($f_1 = 8.1$ and 6.0, respectively) (Fig. 30). This indicates that the reduced magnesium stearate content did not substantially improve the mechanical properties of Eudragit E films.

3.1.4 Coating level

The coating level of pellets affects taste masking of ODTs in two ways. First, a higher coating level reduces the drug release rate due to longer diffusion pathways. Furthermore, thicker coatings can better withstand mechanical stress during compression because a higher force is necessary to rupture the films [127]. For Eudragit FS and Eudragit L/Eudragit NE coatings, increasing film flexibility only reduced drug liberation when the coating thickness was sufficiently high [117, 128]. On the other hand, a low coating level is desirable with regard to drug loading of the dosage form and process time.

The effect of Kollicoat Smartseal and Eudragit E coating level was studied for tramadol HCl pellets with a 5% w/w ethyl cellulose subcoating (20% w/w PVP). The investigated total coating levels ranged from 15 to 50% w/w corresponding to approximately 0.7 to 2.4 mg/cm².

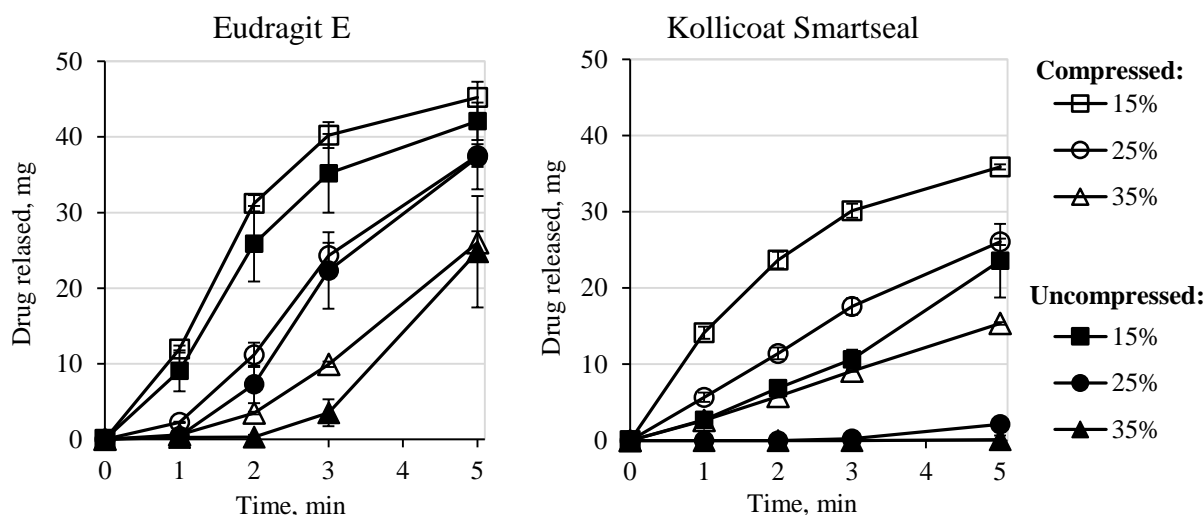


Fig. 31. Effect of coating level on tramadol HCl release in pH 6.8 from uncompressed and compressed pellets coated with Eudragit E (left) or Kollicoat Smartseal (right) (EC subcoating accounts for 5% w/w of the coating level, 20% w/w PVP in ethyl cellulose, 15 or 18% w/w TBC in Eudragit E and Kollicoat Smartseal, 10 kN compression force).

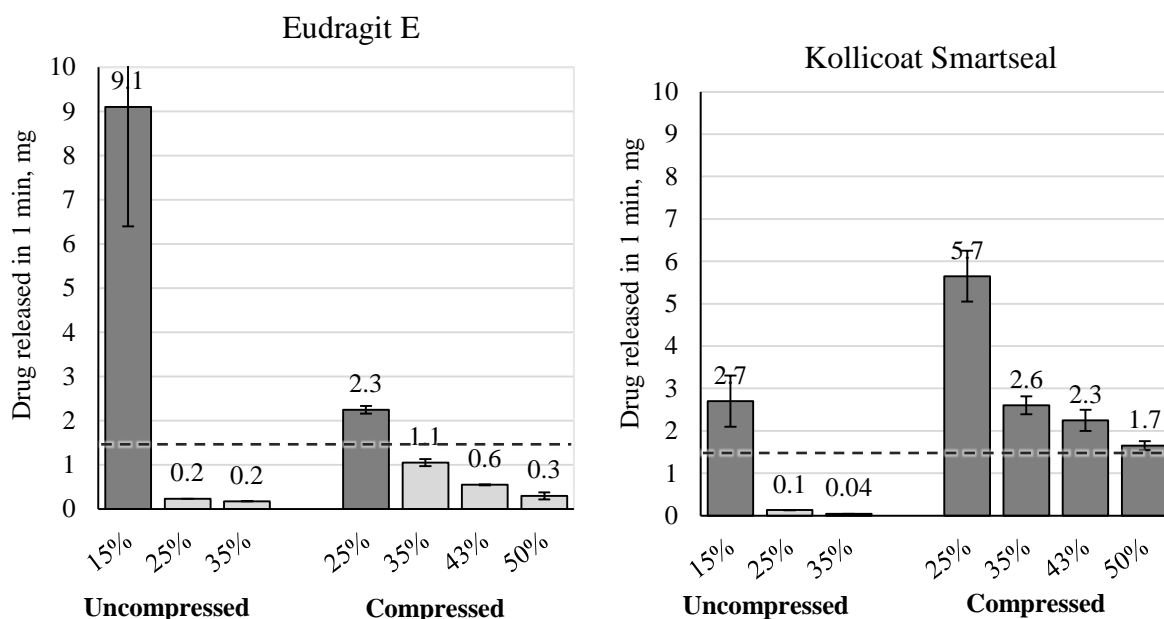


Fig. 32. Effect of coating level on tramadol HCl released in pH 6.8 after one minute from uncompressed and compressed pellets coated with Eudragit E (left) or Kollicoat Smartseal (right) (EC subcoating accounts for 5% w/w of the coating level, 20% w/w PVP in ethyl cellulose, 15 or 18% w/w TBC in Eudragit E and Kollicoat Smartseal, 10 kN compression force).

For uncompressed pellets with topcoatings of either Eudragit E or Kollicoat Smartseal, a total coating level of 25% w/w (5% w/w ethyl cellulose subcoating) was sufficient to obtain taste masked pellets with a drug release of less than 1.5 mg after one minute in pH 6.8 (Fig. 32).

Differences between release profiles of uncompressed and compressed pellets were smaller for Eudragit E than for Kollicoat Smartseal, indicating that this coating was less damaged during compaction (Fig. 31). With Eudragit E as topcoating, a total coating level of 35% w/w was sufficient to prepare taste masked ODTs which released of 1.1 mg in one minute. A further increase of coating thickness reduced the release to only 0.3 mg after one minute at a coating level of 50% w/w (Fig. 32, left).

Also with Kollicoat Smartseal as topcoating, an increased coating thickness reduced the drug release from compressed pellets (Fig. 32, bottom right). However, a higher coating level is needed compared to Eudragit E. At a coating level of 50% w/w, the release in pH 6.8 is still slightly above the target (1.7 mg was released in one minute) and the total coating level would have to be increased beyond 50% w/w to achieve fully taste masked ODTs.

3.2 Effect of drug solubility and drug layer composition

3.2.1 Drug solubility

Very soluble tramadol HCl and sparingly soluble acetaminophen

The drug diffusion rate through coatings is directly proportional to the concentration gradient. It is assumed that the concentration inside the pellets is close to saturation, whereas outside it is negligibly low. Therefore, concentration gradient and diffusion rate depend on the drug's solubility. Furthermore, drugs of higher solubility generate a higher osmotic pressure inside the pellets. This pressure can lead to the formation of cracks in the film and increase the drug release rate. Reducing the solubility of a drug by modifying its chemical structure is usually not an option because of potential effects on efficacy and safety. However, drug solubility inside the pellets can be reduced by adjustment of microenvironmental conditions.

To study the effect of drug solubility, release profiles of acetaminophen and tramadol HCl were compared. Acetaminophen is a sparingly soluble drug (17 mg/mL in water [147]) whereas tramadol HCl is a very soluble drug (948 mg/mL in phosphate buffer pH 6.8). The lower bitterness intensity of acetaminophen was not considered for the evaluation of the results. Additionally, the solubility of tramadol HCl inside the pellets was reduced by the application of a sodium chloride layer on top of the drug layer.

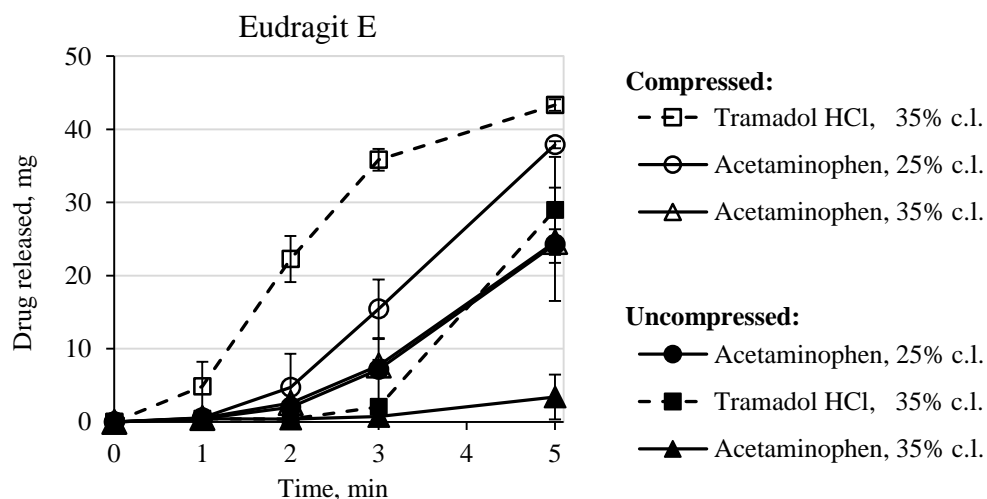


Fig. 33. Release in pH 6.8 of drugs with different solubility from uncompressed and compressed pellets coated with Eudragit E (15% w/w TBC, c.l. = coating level, 10 kN compression force).

For uncompressed pellets coated with Eudragit E, the effect of drug solubility on the release in pH 6.8 was small because the drugs were not released by diffusion through the film but due to the disintegration of the coating (Fig. 33 and Fig. 15). The time until the coating ruptured

depended mostly on its thickness and not on drug properties. The lag time of tramadol HCl pellets with 35% w/w coating level was between the lag times of acetaminophen pellets with 25 and 35% w/w coating level.

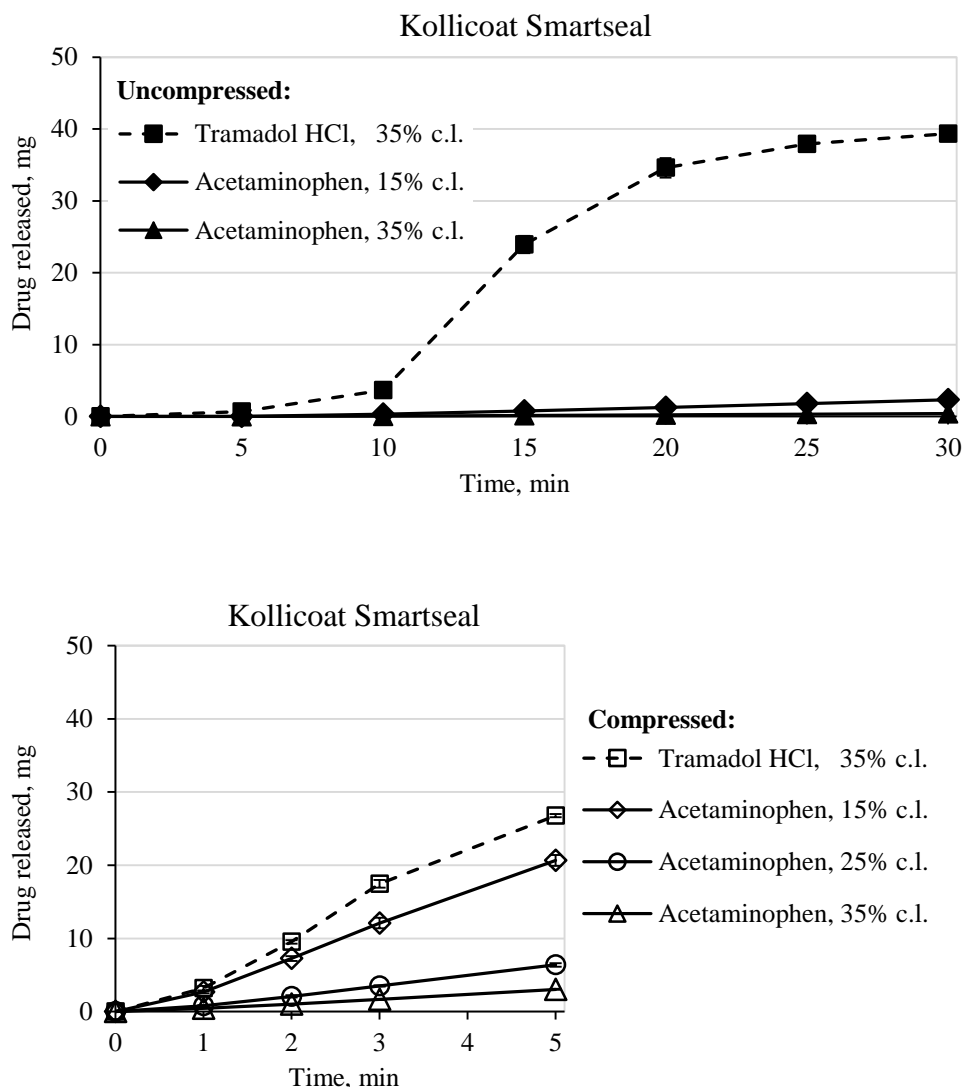


Fig. 34. Release in pH 6.8 of drugs with different solubility from uncompressed (top) and compressed (bottom) pellets coated with Kollicoat Smartseal (18% w/w TBC, c.l. = coating level, 10 kN compression force).

In contrast, for uncompressed pellets coated with Kollicoat Smartseal, the solubility of the drug had a big influence on the release in pH 6.8 (Fig. 34). After 30 minutes, only 2.3 mg acetaminophen was released at a coating level of 15% w/w compared to 39.4 mg tramadol HCl at a coating level of 35% w/w (Fig. 34).

As discussed above, Kollicoat Smartseal and Eudragit E coatings were both damaged by compression. For the highly soluble drug tramadol HCl, this led to insufficient taste masking at coating levels up to 35% w/w (no subcoating) (Fig. 33 and Fig. 34). For the sparingly soluble acetaminophen, on the other hand, the damaged coatings still provided a barrier which led to

an adequate delay of drug release (Fig. 33 and Fig. 34). With Eudragit E, a coating level of 25% w/w was sufficient to reduce the release in pH 6.8 to less than 1.5 mg in one minute. With Kollicoat Smartseal, a coating level of 35% w/w was required (Fig. 35).

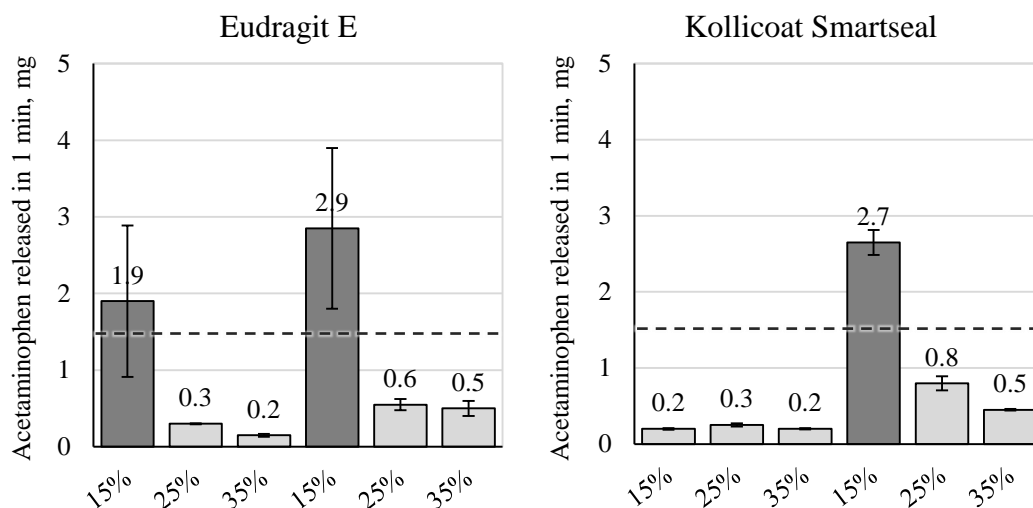


Fig. 35. Effect of coating level on acetaminophen release in pH 6.8 from uncompressed and compressed pellets coated with Eudragit E (left) or Kollicoat Smartseal (right) (15 or 18% w/w TBC in Eudragit E and Kollicoat Smartseal, 10 kN compression force).

Reducing the solubility of tramadol HCl through the application of a sodium chloride layer

As indicated by the release profiles of the sparingly soluble acetaminophen, reducing the solubility of tramadol HCl inside the pellets could be an effective approach to achieve taste masked ODTs. In solutions of sodium chloride, the solubility of tramadol HCl is reduced due to the common ion effect. At a sodium chloride concentration of 3 M, the solubility of tramadol HCl is reduced by a factor of two to 469 mg/mL and in a 5 M sodium chloride solution it is only 9 mg/mL [162]. To achieve a microenvironment with a high sodium chloride concentration, sodium chloride was layered on top of the drug layer (7.5% w/w weight gain). The pellets were then coated with 5% w/w ethyl cellulose as subcoating and 30% w/w Kollicoat Smartseal as topcoating.

A saturated sodium chloride concentration inside the pellets was expected based on the following considerations. If the salt layer dissolves, while drug layer and core remain mainly undissolved, the sodium chloride concentration inside the pellets will be equal to the apparent density of the salt layer. Assuming that the apparent density of the salt layer is similar to that of the rest of the pellets (1.305 mg/cm³), a saturated sodium chloride solution will be achieved.

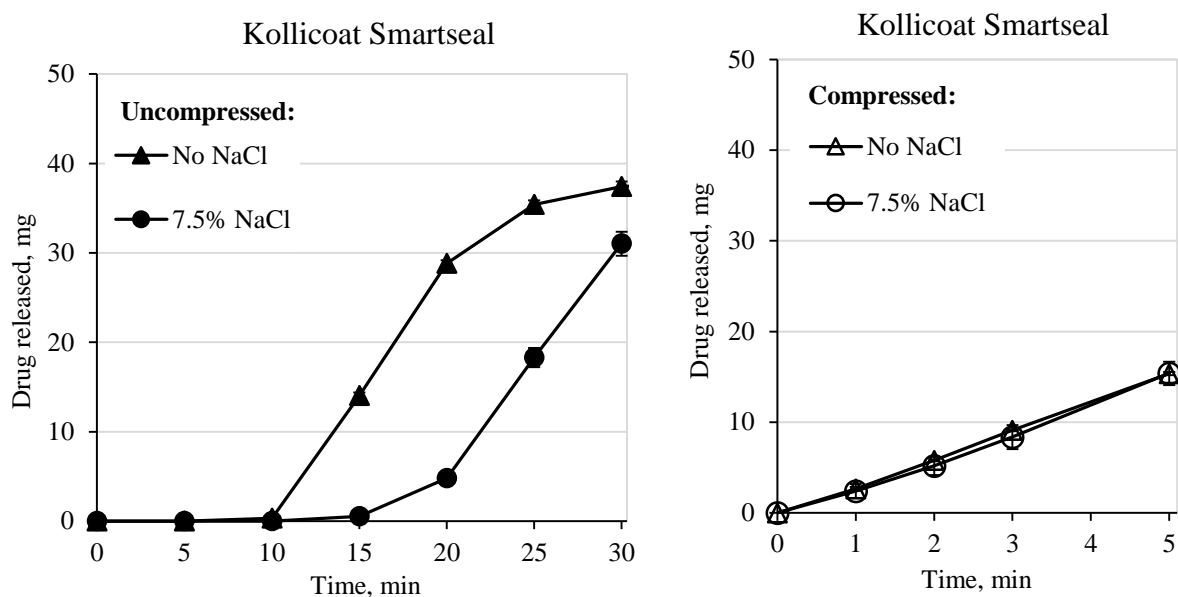


Fig. 36. Effect of sodium chloride layer on tramadol HCl release in pH 6.8 from uncompressed (left) and compressed (right) pellets coated with Kollicoat Smartseal (5% w/w EC subcoating, 35% w/w total coating level, 20% PVP in ethyl cellulose, 18% w/w TBC in Kollicoat Smartseal, 10 kN compression force).

For uncompressed pellets, the sodium chloride layer increased the lag time from 10 minutes to 15 minutes (Fig. 36, left). Once the coating becomes permeable and sodium chloride is released, the solubility of tramadol HCl increases again. Therefore, the lag time was not as long as for acetaminophen and the release rate after the lag phase was approximately the same compared to pellets without salt layer. On the release of compressed pellets, the salt layer had no effect ($f_1 = 4.9$) (Fig. 36). Possibly, sodium chloride was released too quickly through the damaged coating. Therefore, taste masked ODTs were not achieved by this approach.

Briefly, for uncompressed pellets, the effect of drug solubility was more pronounced for Kollicoat Smartseal due to the diffusion controlled release mechanism. After compaction, drug solubility played a big role for both Kollicoat Smartseal and Eudragit E. At a coating level of 35% w/w, tramadol HCl was released too quickly to provide adequate taste masking. In contrast, 25% w/w Eudragit E or 35% w/w Kollicoat Smartseal were sufficient to obtain taste masked ODTs with the sparingly soluble acetaminophen (if it would have the same bitterness intensity as tramadol HCl). Reducing the solubility of tramadol HCl by applying a sodium chloride layer increased the lag phase of uncompressed pellets coated with Kollicoat Smartseal. However, it had no effect on the release from compressed pellets and thus did not improve the taste masking of ODTs.

3.2.2 Acid-soluble or highly viscose polymers as binder in the drug layer

When drug suspensions are layered onto pellet cores, binders are needed to ensure adhesion of drug particles to the cores. Also if drugs are sprayed from a solution, a binder is often added to improve layering efficiency. Commonly, water-soluble binders of low viscosity are used. If they are exchanged for water-insoluble binders, a lower coating level is required to achieve the same release rate because the binder represents an additional barrier for drug diffusion [163]. Furthermore, such matrix-like systems are less affected by compression than reservoir systems [29]. Another approach is to use water-soluble binders which provide solutions of high viscosity. This might delay the drug release for a short time, even if the coating is ruptured.

For the other experiments of this study, tramadol HCl was applied on the MCC cores from a solution with 3% w/w Kollidon 30, a low viscosity grade of PVP. To evaluate the effect of the binder, 10 or 50% w/w Eudragit E (acid-soluble polymer) or 10% w/w Kollidon 90 (high viscosity grade of PVP) were used instead. The percentage of binder was calculated relative to the amount of drug. After drug layering, the pellets were coated with 10% w/w Eudragit E as subcoating and 25% w/w Kollicoat Smartseal as topcoating followed by compression into tablets.

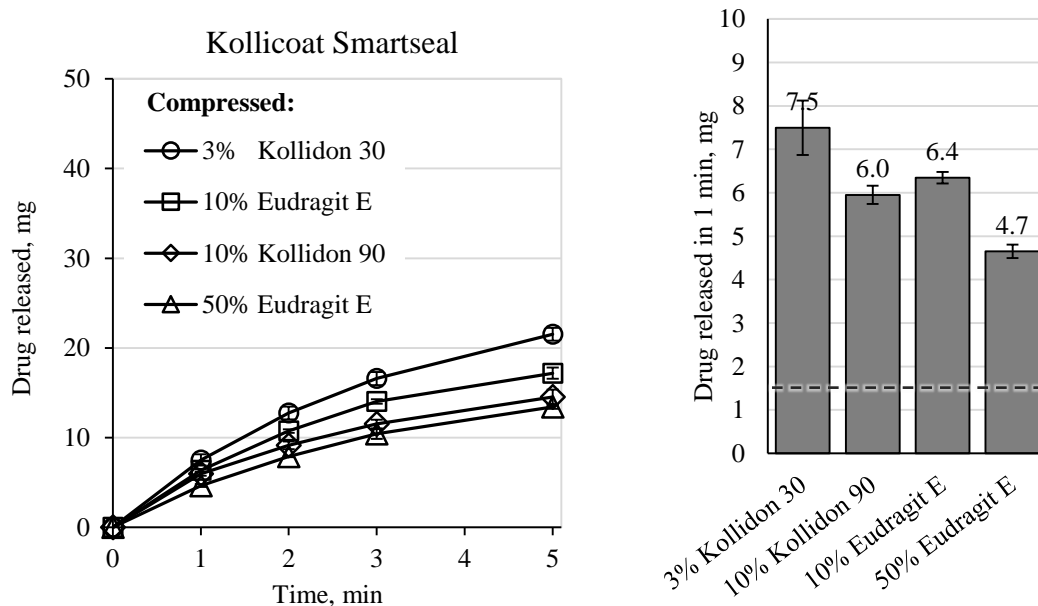


Fig. 37. Effect of binder type and content in the drug layer on tramadol HCl release in pH 6.8 from compressed pellets coated with 10% w/w Eudragit E subcoating and 25% w/w Kollicoat Smartseal topcoating (15 or 18% w/w TBC in Eudragit E and Kollicoat Smartseal, 10 kN compression force).

When 10% w/w Kollidon 90 was used as binder in the drug layer, the release was reduced compared to 3% w/w Kollidon 30 ($f_1 = 29.4$). Also Eudragit E reduced the release rate ($f_1 = 37.6$ with 50% w/w Eudragit E) (Fig. 37). A high amount of carrier is necessary to retard the release of highly soluble drugs in matrix systems [163]. It must be considered that for pellets with 20% w/w drug loading, 50% w/w binder in the drug layer corresponds to the same weight gain as a coating level of 10% w/w. Nonetheless, water-soluble binders of high viscosity or acid-soluble binders can be used in combination with other approaches to improve taste masking of ODTs.

3.2.3 Drug loading

The drug loading of pellets was increased from 20 to 40% w/w to achieve tablets with a higher dose of tramadol HCl (100 mg instead of 50 mg). The pellets were coated with 5% w/w ethyl cellulose as subcoating and 30% w/w Kollicoat Smartseal or Eudragit E as topcoating. The amount of coated pellets per tablet was kept at 300 mg (50% w/w).

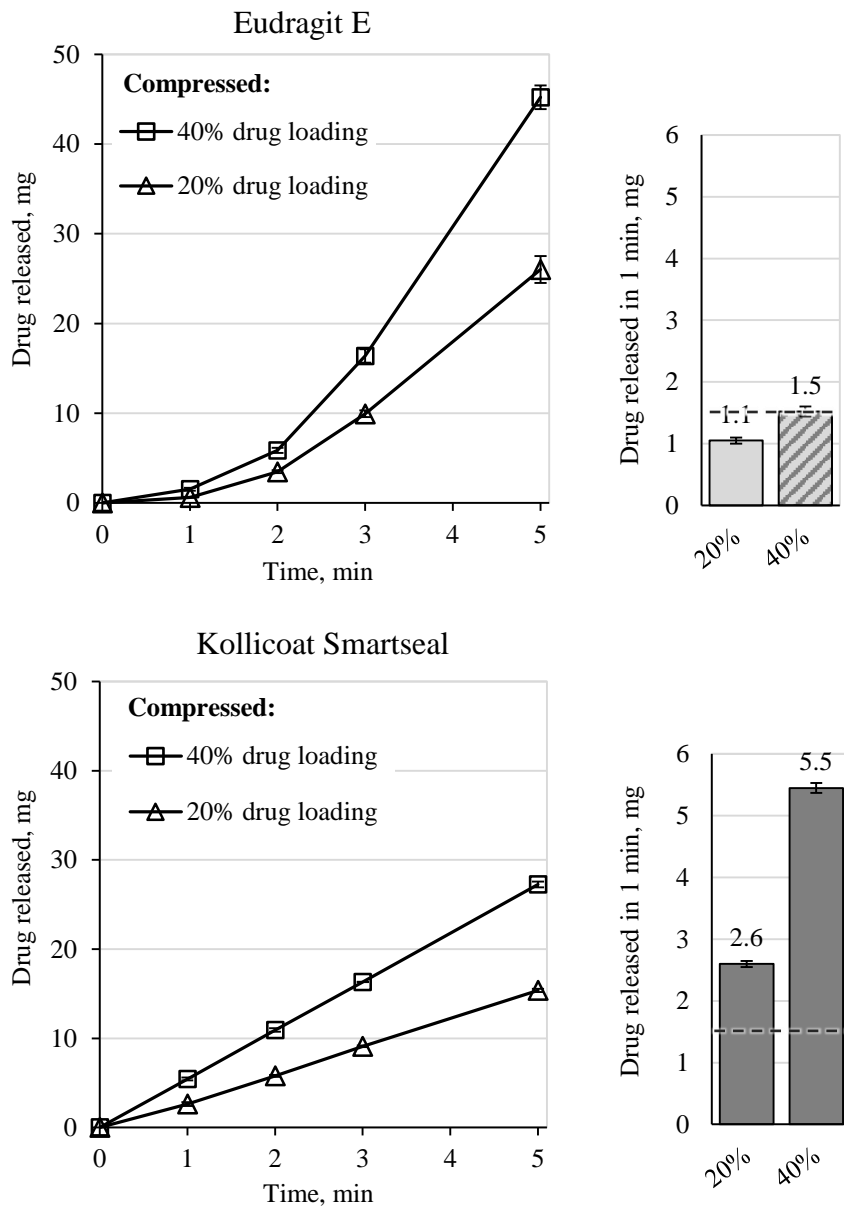


Fig. 38. Effect of pellet drug loading on tramadol HCl release in pH 6.8 from compressed pellets coated with Eudragit E (left) or Kollicoat Smartseal (right) (5% w/w EC subcoating, 35% w/w total coating level, 15 or 18% w/w TBC in Eudragit E and Kollicoat Smartseal, 10 kN compression force).

For pellets with a higher drug loading, a slower relative dissolution rate is expected due to the lower ratio of surface area to dose. However, with both Kollicoat Smartseal and Eudragit E, the relative dissolution rate in pH 6.8 was almost the same for compressed pellets with 20 or

40% w/w drug loading (Fig. 38). Thus, the absolute amount released - which is more relevant for taste masking - was higher for tablets with 100 mg tramadol HCl compared to those with 50 mg. At both drug loadings, the amount released from compressed pellets coated with Kollicoat Smartseal was too high to achieve taste masked tablets. With Eudragit E coatings, on the other hand, even from tablets with 100 mg tramadol HCl only 1.5 mg tramadol HCl was released in the first minute. This is just equal to the limit of *in vitro* drug release which is expected to provide taste masked ODTs.

3.3 Effect of mechanical stress during tableting

The higher the mechanical stress on the coating during tableting, the more likely it will rupture or at least become thinner. Mechanical stress during compaction depends on the degree of densification (compression force), the percentage of pellets in the tablet, and the mechanical properties of pellet cores and tableting excipients. Coatings with good mechanical properties can undergo compaction without rupturing irrespective of compression force and type of tableting excipients [120, 122]. However, for compression-sensitive coatings, optimization of these parameters can help to protect the coating during tableting [117, 120, 128, 129, 133, 134, 138].

3.3.1 Compression force

The lower the compression force, the lower the degree of densification and deformation (for the same pellet/excipient mixture). Therefore, several coating formulations exhibit less coating damage at lower compression forces [117, 119, 120].

Tramadol HCl pellets with an ethyl cellulose subcoating and a Kollicoat Smartseal or Eudragit E topcoating were mixed with tableting excipients at a ratio of 1:1. The mixture was compressed into ODTs using a compression force of either 5 kN or 10 kN.

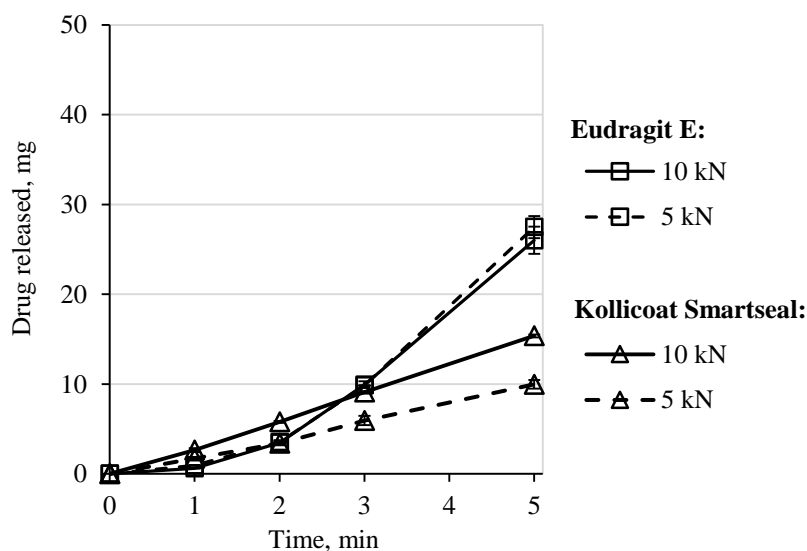


Fig. 39. Effect of compression force on tramadol HCl release in pH 6.8 from pellets coated with Eudragit E or Kollicoat Smartseal (5% w/w EC subcoating, 35% w/w total coating level, 20% w/w PVP in ethyl cellulose, 15 or 18% w/w TBC in Eudragit E and Kollicoat Smartseal).

Reducing the compression force from 10 kN to 5 kN had no effect on the release in pH 6.8 for pellets coated with Eudragit E ($f_1 = 4.9$) (Fig. 39). Even at 10 kN compression force, coating damage was small. Furthermore, after two minutes, the release rate is governed by coating swelling and disintegration.

In contrast, for pellets coated with Kollicoat Smartseal, a reduced compression force led to a reduced drug release rate ($f_1 = 36.1$). However, also tablets compressed at 5 kN released still too much tramadol HCl (1.7 mg) to ensure complete taste masking. Moreover, tablet breaking force decreased from 45 N to 19 N which is insufficient for packaging, transport and handling by patients. Therefore, reducing the compression force was not a practicable method to achieve taste masked ODTs.

3.3.2 Pellet fraction in tablets

Reducing the fraction of pellets in the tablets is another method to reduce the stress on the coating during compression [117, 122]. Contrary to reducing the compression force, tablet hardness will not be reduced by this approach.

On condition that dose and tablet weight have to be kept constant, drug loading of pellets must be increased when the pellet content in tablets is reduced. Therefore, pellets were layered with 40% w/w of tramadol instead of 20% w/w. They were then coated with 5% w/w ethyl cellulose subcoating and 30% w/w Kollicoat Smartseal or Eudragit E topcoating. Pellets with 40% w/w drug loading were compressed with 75% w/w tableting excipients and pellets with 20% w/w drug loading with 50% w/w tableting excipients. This led to tablets containing 50 mg tramadol HCl.

Reducing the pellet fraction led to a pronounced reduction of drug release rate in pH 6.8 for pellets coated with Kollicoat Smartseal ($f_1 = 64.9$) (Fig. 40, bottom). Contrary to tablets with 50% w/w pellets, tablets with 25% w/w pellet content released less than 1.5 mg tramadol HCl in the first minute. Thus they provided taste masking. Additionally, they had an increased breaking force (80 N vs. 49 N).

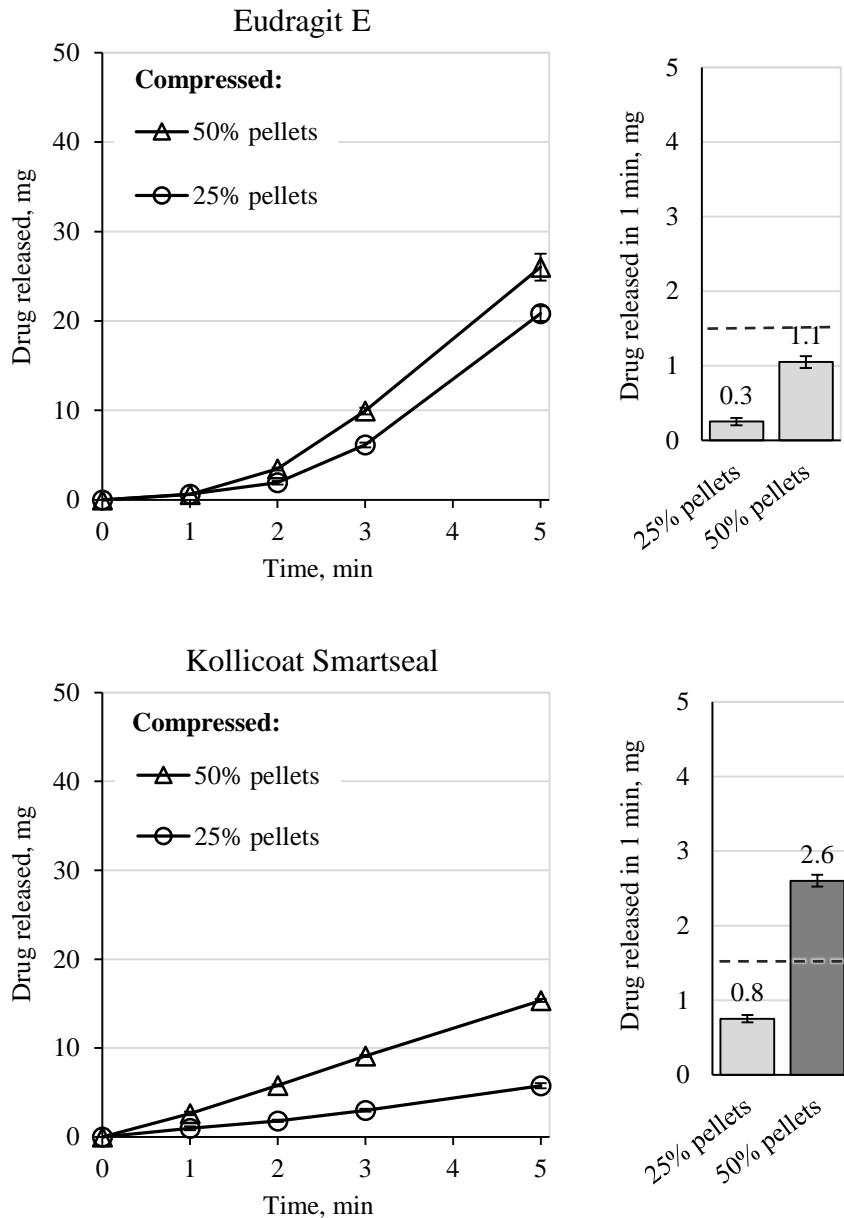


Fig. 40. Effect of pellet content in tablets on tramadol HCl release in pH 6.8 from compressed pellets coated with Eudragit E (top) or Kollicoat Smartseal (bottom) (5% w/w EC subcoating, 35% w/w total coating level, 15 or 18% w/w TBC in Eudragit E and Kollicoat Smartseal, 10 kN compression force, same dose per tablet).

The Eudragit E coating led to taste masked tablets at both pellets contents (Fig. 40, top). The difference between drug release profiles of tablets with different pellet fractions was smaller ($f_1 = 26.3$). This is in agreement with the results regarding the effect of compression force discussed above as it confirms that the Eudragit E coating is less affected by changes of the mechanical stress than Kollicoat Smartseal.

3.3.3 Pellet core type

Also pellet cores have an effect on the mechanical stress acting on the coating during compaction. A core which deforms or densifies more easily will absorb more pressure but also lead to a greater degree of deformation.

The investigated cores were composed either of MCC or sugar. After layering with tramadol HCl, the cores were coated with 10% w/w Eudragit E as subcoating and 25% w/w Kollicoat Smartseal as topcoating. The release in pH 6.8 was determined after compaction at 10 kN.

Table 5. Tensile strength of uncoated pellet cores.

Core (uncoated)	Tensile strength (S.D.), MPa
Microcrystalline cellulose	22.2 (2.7)
Sugar	4.7 (0.9)

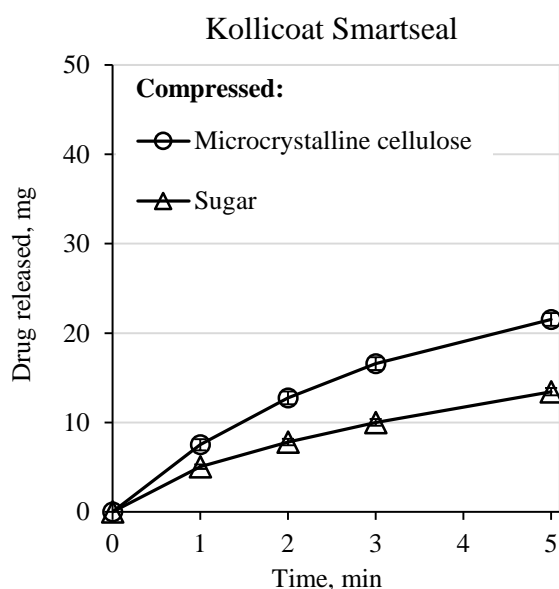


Fig. 41. Effect of pellet core type on tramadol HCl release in pH 6.8 from compressed pellets coated with Kollicoat Smartseal (5% w/w EC subcoating, 35% w/w total coating level, 18% w/w TBC in Kollicoat Smartseal, 10 kN compression force).

The sugar cores used in this study had a lower crushing strength compared to the MCC cores (Table 5). This led to a lower degree of compression-induced coating damage as indicated by the lower tramadol HCl release rate ($f_1 = 37.7$) (Fig. 41). The lower release rate could also be partially due the slightly larger size of the sugar cores (212 -300 μm vs. 150-300 μm) which will lead to a thicker coating film at the same coating level. The higher osmotic pressure, created by the dissolution of the sugar core, seems not to be of major importance. Also for pellets with MCC cores, the osmotic pressure is high due to the high solubility of tramadol HCl.

3.3.4 Tableting excipients (excipient powders and layers)

Mechanical properties of tableting excipients play an important role for the protection of coated pellets during compression. Generally, excipients with a low yield pressure are best suited for the compaction of coated pellets [117, 135]. Also elastically deforming excipients reduce coating damage during compression [133, 134]. On the other hand, brittle substances generally lead to extensive coating damage [117, 135].

Besides coating damage, segregation is a major challenge when pellets are compressed together with excipient powders due to the difference in size and flowability. Variation of mass and drug content increase with decreasing pellet content and increasing pellet diameter [122]. Different approaches have been applied to overcome segregation problems: layering of tableting excipients on the pellets [138, 140], use of excipient granules/pellets of similar size as the drug pellets [164], granulation of pellets with excipients [165] or special feeding techniques during tableting [166].

Layering of tableting excipients on coated pellets not only prevents segregation but also eliminates direct contact of pellets with each other and with the die wall and punches. This could minimize mechanical stress on pellets during compaction and reduce coating damage. Similar release profiles of uncompressed and compressed pellets have been achieved with a glidant layer under a MCC cushion layer or with a glidant-containing MCC layer [138]. Other excipient layers consisting of MCC without glidant, HPMC, PEG or PEO provided only small or no advantage [131, 139, 140].

To our knowledge, no ODTs have been prepared where the main part of the tableting excipients was applied as layer onto the coated pellets. ODTs should ideally disintegrate in less than 30 seconds [74] which presents a big challenge for such systems. Tablets of pellets with a MCC cushion layer containing 10% HPMC as binder and 15% Ac-Di-Sol as disintegrant needed nine minutes to disintegrate [138]. Pellets with layers composed of PEO, MCC and sodium starch glycolate led to tablets which disintegrated in 20 minutes. Pellets with a PEG layer produced non-disintegrating matrices. When 5% sodium starch glycolate was added to these tablets, the disintegration time was still more than 30 minutes [139]. Tablets of coated lansoprazole pellets with a layer of either mannitol or PEG disintegrated in less than 30 seconds [167]. However, in these ODTs, pellets with excipient layer accounted only for about 40% w/w of the tablet formulation. The rest of the excipients was added as powders.

In order to obtain taste masked tablets with rapid oral disintegration, the effect of different excipient layers on the prevention of compression-induced coating damage and on tablet disintegration was investigated and compared to the effect of excipient powders.

3.3.4.1 Density of excipients and coated pellets for volume based calculation of tablet compositions

The cushioning effect of excipients depends on how well they enclose the pellets. Formulations based on weight per weight ratios are most common in studies about the effect of tableting excipients on coating damage [117, 135]. However, the packing of pellets in tablets depends on the volume ratio of pellets and excipient matrix [122]. Thus, for all experiments in this study regarding the effect of different tableting excipients, the amount of excipients was adjusted so as to keep the volume ratio of pellets and excipients constant.

For this purpose, the density of tableting excipients was determined using a simplified version of the method developed by Sun [168]. Excipient powders were compressed at 740 MPa for one minute using a hydraulic press. This pressure is much higher than the pressure reached during tableting (approx. 50-170 MPa). After releasing the pressure, the density was calculated from weight and size of the compact (Table 2). This method of determining the density of compressed excipients is very simple in contrast to measurements of true density. Moreover, it is expected to be more relevant for the preparation of tablets due to the resemblance of the two processes.

The apparent density of the coated pellets used in this part of the study was determined based on the amount of paraffin displaced by the pellets. It was 1.305 g/cm³ for tramadol HCl pellets with an MCC core coated with 5% w/w ethyl cellulose and 30% w/w Kollicoat Smartseal.

The density of compressed excipients and the apparent density of pellets were used to calculate the amount of excipients needed for a volume based ratio of 1:1. Only the lubricant was added on a weight per weight basis. All tablets contained 300 mg of coated pellets which corresponds to an apparent volume of 0.230 cm³. The tablets had a volume of about 0.509-0.565 cm³ (d = 12 mm, h = 4.5-5 mm). Therefore, it was theoretically possible that the pellets were not densified during compaction.

Table 6. Density of tableting excipients compressed at 740 MPa.

	Density (S.D.), g/cm ³
Ac-Di-Sol	1.445 (0.007)
Avicel 200	1.483 (0.009)
Avicel 105	1.476 (0.016)
Ethocel Standard 100 Premium	1.036 (0.010)
Explotab	1.412 (0.017)
FlowLac 90	1.305 (-, n=1)
Kollidon CL	1.050 (0.006)
Kollidon CL-SF	1.060 (0.079)
Kollidon 30	1.199 (0.004)
Kollidon 90	1.126 (0.004)
Lactochem microfine	1.369 (0.030)
Magnesium stearate	0.992 (0.005)
Maize starch B	1.341 (0.004)
Pearlitol 100SD	1.446 (0.009)
Polyplasdone XL-10	1.096 (0.002)

3.3.4.2 Lubricant selection for tablets prepared of coated pellets with excipient layers

Lubricants are added to tablet formulations to reduce the friction between powder or tablet and die wall. The most commonly used lubricant is magnesium stearate. However, in preliminary experiments, the desired tablet breaking force of 40-50 N could not be reached when pellets with excipient layers were compressed with 0.5% w/w magnesium stearate as lubricant. Reduced tablet hardness is a well-known drawback of magnesium stearate [169-171]. To find a suitable lubricant type and concentration for the compression of pellets with excipient layers, tablets were prepared with different amounts of magnesium stearate, stearic acid, sodium stearyl fumarate (Pruv) or glyceryl dibehenate (Compritol 888 ATO). The compression force was set to 10 kN and axial ejection pressure and tablet breaking force were determined.

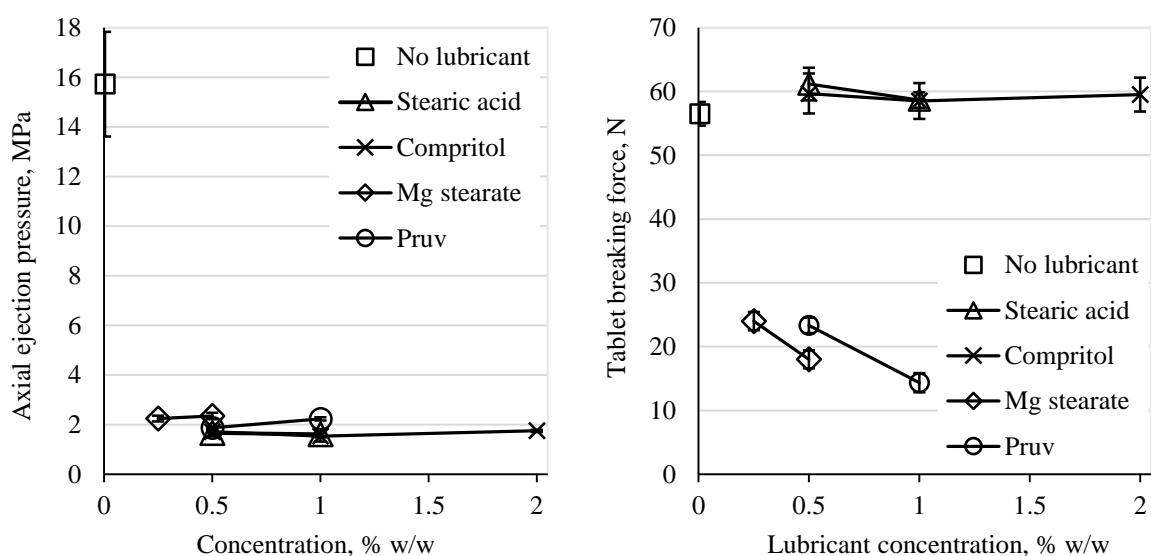


Fig. 42. Effect of lubricant type and concentration on axial ejection pressure (left) and tablet breaking force (right) of tablets prepared of coated pellets with 15% V/V MCC/lactose 3:1 layer and 35% V/V mannitol/MCC 2:1 layer.

The axial ejection pressure is the force needed to eject the tablet relative to the contact area of tablet and die wall. It serves as indicator for the effectiveness of a lubricant. It was reduced from 15.7 MPa for tablets without lubricant to about 2 MPa with all of the investigated lubricant types and concentrations (Fig. 42, left). Thus, they were all well suited with regard to lubrication.

In contrast, tablet breaking force strongly depended on the type of lubricant used (Fig. 42, right). It was reduced from 57 N without lubricant to 18 N or 23 N with 0.5% w/w magnesium stearate or Pruv, respectively. Decreasing the magnesium stearate content to 0.25% w/w only slightly increased the breaking force (24 N). On the other hand, the addition of stearic acid or

Compritol 888 ATO did not reduce the tablet breaking force. It was in the range between 59 N and 61 N for 0.5-1% w/w stearic acid and 0.5-2% w/w Compritol 888 ATO. With Compritol 888 ATO, residues of tableting material were sticking to the punches. Therefore, stearic acid was selected as lubricant for further experiments.

3.3.4.3 Cushion and disintegration layers versus excipient powders

Excipients with low yield pressure, like MCC or polyethylene glycol (PEG), offer the best protection of coated pellets during compression [135]. Also carrageenans and alginates have good cushioning properties which was ascribed to their high degree of elastic deformation [133, 134]. For this study, MCC was selected as plastic material and starch as elastic material. PEG, carrageenans or alginates were not used because they were expected to prolong tablet disintegration.

For the cushion layer, a suspensions of MCC/lactose 3:1 in ethanol was layered onto coated tramadol HCl pellets. Small particle size grades were used since the coated pellets had a size of less than 400 μm (Avicel PH-105, Lactochem microfine). 5% w/w PVP and 2% w/w ethyl cellulose were added as binders. Layered pellets were compressed into tablets with and without the addition of external disintegrants. Coated pellets (without excipient layers) accounted for 50% V/V of the tablet formulation (see 3.3.4.1). The compression force was adjusted to obtain tablets with a breaking force of 40-50 N.

The wetting time of tablets prepared of pellets with a MCC/lactose 3:1 cushion layer was too slow for orally disintegrating tablets (> 3 min) (Table 8, F1). This was ascribed to the presence of polymeric binders in the cushion layer. Long disintegration times have also been described in other studies for tablets of pellets with HPMC, PEO or PEG in excipient layers [138, 140]. The addition of Kollidon CL, Ac-Di-Sol or Explotab as external disintegrants (3 or 6% V/V) did not reduce tablet wetting time to less than three minutes (Table 8, F2-F4). Therefore, these cushion layered pellets were not suited for the preparation of orally disintegration tablets.

To reduce the disintegration time, a so called disintegration layer was applied on top of the cushion layer. This disintegration layer did not contain a polymeric binder. The layering fluid consisted of an aqueous solution of mannitol in which MCC (Avicel PH-105) was suspended. The dissolved mannitol served as binder in the layering process. MCC was added to improve compactibility and promote tablet disintegration through swelling.

Coated pellets were layered first with 25% V/V cushion layer (MCC/lactose 3:1 with PVP and EC as binders) and subsequently with 19 or 25% V/V disintegration layer (mannitol/MCC 2:1). Additionally, coated pellets were layered only with the disintegration layer (44% V/V or 50% V/V.) Tablets with a breaking force of 40-50 N were prepared with and without 6% V/V Kollidon CL as external disintegrant. For comparison, coated pellets were compressed with powder mixtures of the same composition as the cushion layer (without binder) or the disintegration layer (both with 6% V/V Kollidon CL). For these tablets, excipient grades for direct compression were used (FlowLac 90, Avicel 200, Pearlitol 100-SD).

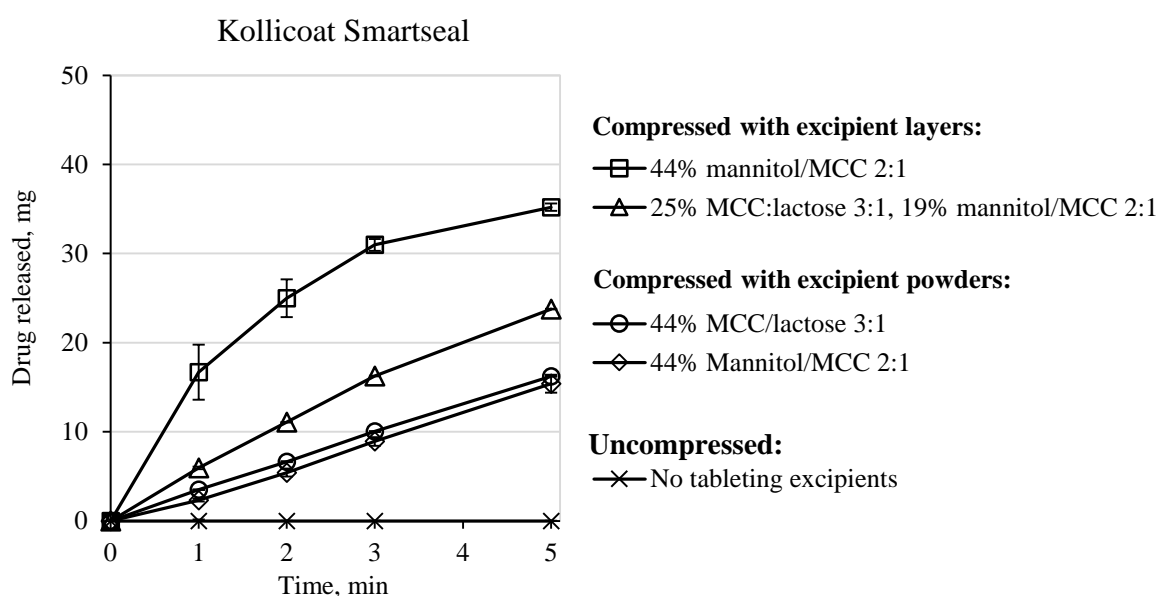


Fig. 43. Effect of a cushion layer under the disintegration layer on tramadol HCl release in pH 6.8 from compressed pellets and comparison with release of pellets compressed with excipient powder mixtures (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% w/w TBC); disintegrant: 6% V/V Kollidon CL; tablet breaking force: 40-50 N).

Tablets of pellets with cushion and disintegration layers had a wetting time of more than three minutes when no external disintegrant was added. With 6% V/V Kollidon CL, the wetting time was 12 seconds (Table 8, F14).

Compressed pellets with a cushion and a disintegration layer released 6.0 mg tramadol HCl in the first minute in pH 6.8 (Fig. 43). Taste masking was thus not achieved. Furthermore, the release rate was faster compared to pellets compressed with analogues powders mixtures. This could be attributed to a better distribution of the compression force by the loose powder [138]. Pellets with excipient layers have only few points of contact. During compaction, the force is concentrated at these points.

Coating damage of compressed pellets with a cushion layer (MCC/lactose 3:1) under the disintegration layer (mannitol/MCC 2:1) was considerably lower compared to pellets layered only with the disintegration layer (Fig. 43). In contrast, the two corresponding powder mixtures led to tablets with almost the same drug release rate. The better cushioning effect of the cushion layer compared to the disintegration could be due to a higher porosity. The bulk density of layered pellets increased with increasing ratio of disintegration to cushion layer (Table 7) and also on scanning electron microscope images, the MCC/lactose cushion layer appeared more porous than the mannitol/MCC disintegration layer (Fig. 44).

Table 7. Bulk density of coated pellets with different ratios of MCC/lactose 3:1 cushion layer and mannitol/MCC 2:1 disintegration layer

Ratio of cushion to disintegration layer	Bulk density, g/mL
88:0	0.576
50:38	0.715
0:88	0.806

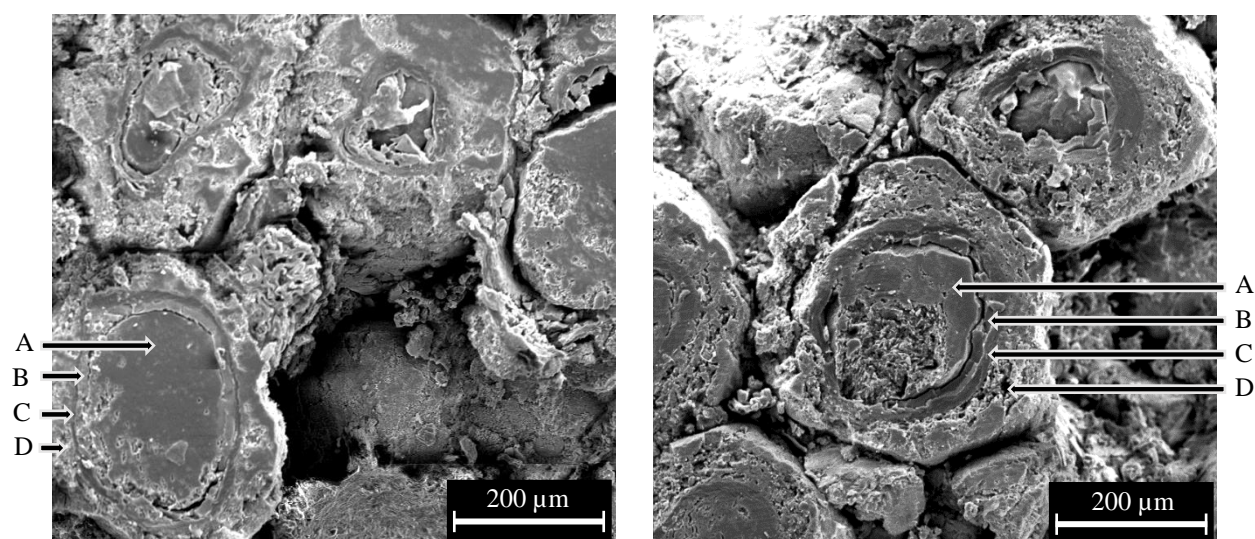


Fig. 44. Scanning electron microscope images of compressed coated pellets with excipient layers. Left: with 44% V/V mannitol/MCC 2:1 disintegration layer, right: with 25% V/V MCC/lactose 3:1 cushion layer and 19% V/V mannitol/MCC 2:1 disintegration layer (A: pellet core, B: drug layer, C: coating, D: excipient layers)

The addition of Kollidon CL had no influence on the drug release in pH 6.8, although a slightly higher compression force was needed to achieve tablets of the same hardness when the formulations contained Kollidon CL (Fig. 45).

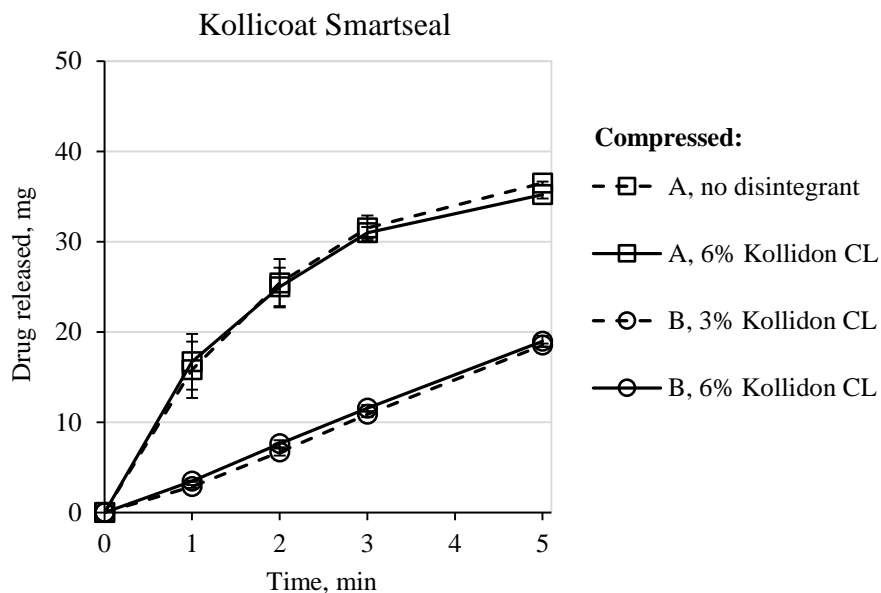


Fig. 45. Effect of Kollidon CL as external disintegrant on tramadol HCl release in pH 6.8 from tablets prepared of coated pellets with excipient layers, A: 50% V/V or 44% V/V mannitol/MCC 2:1 disintegration layer, B: 25% V/V MCC/lactose 3:1 cushion layer with 3% w/w Mg stearate and 22% V/V or 19% V/V mannitol/MCC 2:1 disintegration layer (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% w/w TBC); tablet breaking force: 40-50 N).

3.3.4.4 Cushion layer composition

Filler type

To improve the protective effect of the cushion layer and thus obtain taste masked ODTs, the filler type in the cushion layer was varied. Formulations with either MCC/lactose 3:1, starch/lactose 3:1 or only MCC were applied on coated tramadol HCl pellets followed by the application of a disintegration layer (mannitol/MCC 2:1 or mannitol/starch 2:1). The layered pellets were compacted and the release in pH 6.8 was determined.

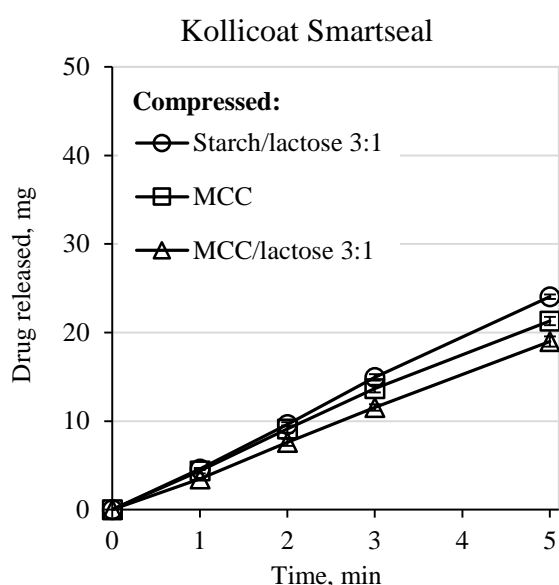


Fig. 46. Effect of filler type in the cushion layer on tramadol HCl release in pH 6.8 from tablets prepared of coated pellets with excipient layers (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% TBC); excipient layers: 25% V/V cushion layer with different fillers incl. 3% w/w Mg stearate and 19% V/V mannitol/MCC 2:1 or starch/MCC 2:1 disintegration layer; disintegrant: 6% V/V Kollidon CL; tablet breaking force: 40-50 N).

The type of filler in the cushion layer had only a small influence on the drug release rate from compressed pellets (Fig. 46). Using only MCC as filler and thus omitting the brittle lactose had no remarkable effect on the drug release in pH 6.8 ($f_1 = 16$). When the highly plastic MCC was replaced by the more elastic starch, a higher compression force was needed to obtain tablets of the same hardness (13.2 ± 0.2 kN vs. 9.7 ± 0.1 kN). The release rate increased slightly ($f_1 = 28$). The small effect of the filler type in the cushion layer could be due to the small particle size of the excipients (Avicel PH-105: $d = 20 \mu\text{m}$ [172], maize starch: $d = 5-25 \mu\text{m}$ [173], Lactochem microfine: $d = 3 \mu\text{m}$ [174]). In a study on compaction of pellets coated with ethyl cellulose, all excipients had a similar cushioning effect when their particle size was below $20 \mu\text{m}$ [137].

Magnesium stearate content

In studies of Hosseini et al., an MCC layer protected the ethyl cellulose coating from damage during compression when 3% w/w magnesium stearate were added to the layer. The excipient layer detached from the coating upon compaction and the coating remained intact. Therefore, the effect of magnesium stearate in the cushion layer was evaluated here. 3-33% w/w magnesium stearate was included in the layer while the ratio of MCC/lactose was kept at 3:1. Subsequently, the pellets were layered with a disintegration layer (mannitol/MCC 2:1) and compressed into tablets together Kollidon CL (6% V/V).

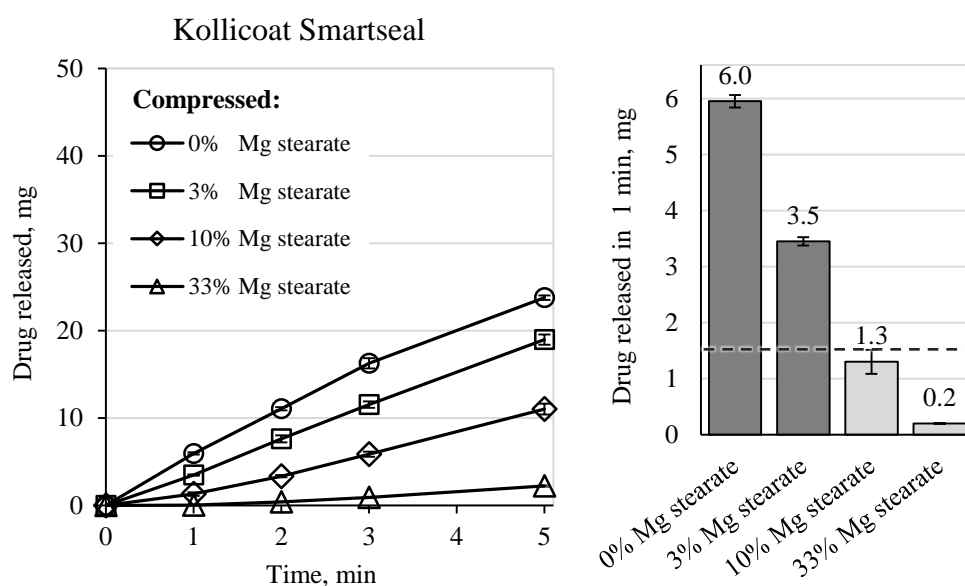


Fig. 47. Effect of magnesium stearate content the cushion layer on tramadol HCl release in pH 6.8 from tablets prepared of coated pellets with excipient layers (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% w/w TBC); excipient layers: 25% V/V MCC/lactose 3:1 cushion layer with different Mg stearate content and 19% V/V mannitol/MCC 2:1 disintegration layer; disintegrant: 6% V/V Kollidon CL; tablet breaking force: 40-50 N).

The higher the glidant concentration in the cushion layer, the lower was the release rate after compression (Fig. 47). A magnesium stearate content of 10% w/w was needed to reduce the tramadol HCl release in the first minute to less than 1.5 mg and thus obtain taste masked ODTs. With 33% w/w magnesium stearate the release was further reduced to only 0.2 mg in one minute. Aside from the good taste masking, these tablets exhibited also a fast wetting time of 17 seconds (Table 8, F16).

3.3.4.5 Disintegration layer composition

The effect of disintegration layer composition on compression-induced coating damage was evaluated. Sorbitol was added because it has a higher compactibility than mannitol [175]. Mannitol/MCC disintegration layers with and without 20% w/w sorbitol were layered on top of coated tramadol HCl pellets with a MCC/lactose 3:1 cushion layer (containing 3% w/w magnesium stearate). Layered pellets were compressed into ODTs with 6% V/V Kollidon CL.

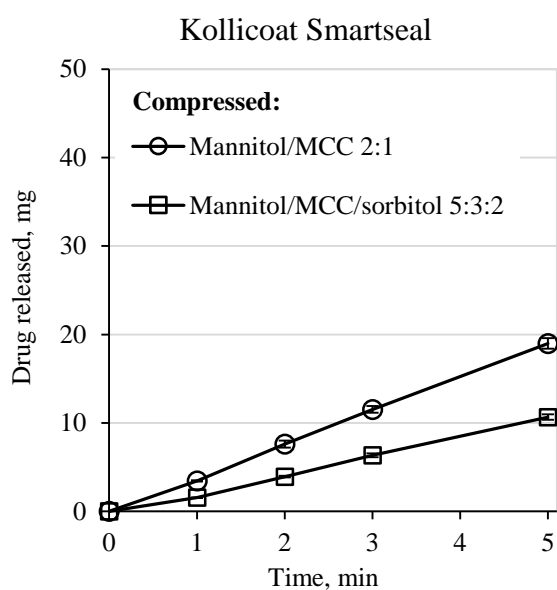


Fig. 48. Effect of sorbitol content in the disintegration layer on tramadol HCl release in pH 6.8 from tablets prepared of coated pellets with excipient layers (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% w/w TBC); excipient layers: 25% V/V MCC/lactose 3:1 cushion layer with 3% w/w Mg stearate content and 19% V/V disintegration layer of different compositions; disintegrant: 6% V/V Kollidon CL; tablet breaking force: 40-50 N).

The addition of sorbitol reduced the compression force needed to achieve tablets with a breaking force of 40-50 N (4.3 ± 0.1 kN vs. 9.6 ± 0.1 kN). This led to a reduction of coating damage and thus to a reduced drug release rate (Fig. 48). However, pronounced sticking to the punches occurred during tableting which was ascribed to the hygroscopic nature of sorbitol. Magnesium stearate or Pruv can be used to reduce sticking caused by sorbitol [176] but tablets of sufficient hardness could not be achieved with these lubricants (Fig. 42). The addition of 1% w/w Aerosil 200 to the tablet formulation prevented sticking but also prolonged tablet wetting (> 3 min). Thus, the addition of sorbitol was not a practicable approach to reduce coating damage during compaction.

3.3.4.6 Glidant layer

Instead of adding a glidant to the excipient layer, applying a separate glidant layer between coating and cushion layer can also prevent coating rupturing caused by compaction [138].

A magnesium stearate glidant layer was applied on coated tramadol HCl pellets (10% V/V regarding coated pellets corresponding to 5% V/V of the tablet formulation). On top, different ratios of cushion layer (MCC/lactose 3:1 with 3% magnesium stearate) and disintegration layer (mannitol/MCC 2:1) were applied and the pellets were compressed to tablets of 40-50 N breaking force. Kollidon CL was added as external disintegrant. Alternatively, coated pellets with a magnesium stearate layer were compressed with excipient powders of compositions analogues to the cushion layer or the disintegration layer (including Kollidon CL).

Glidant layer under excipient layers

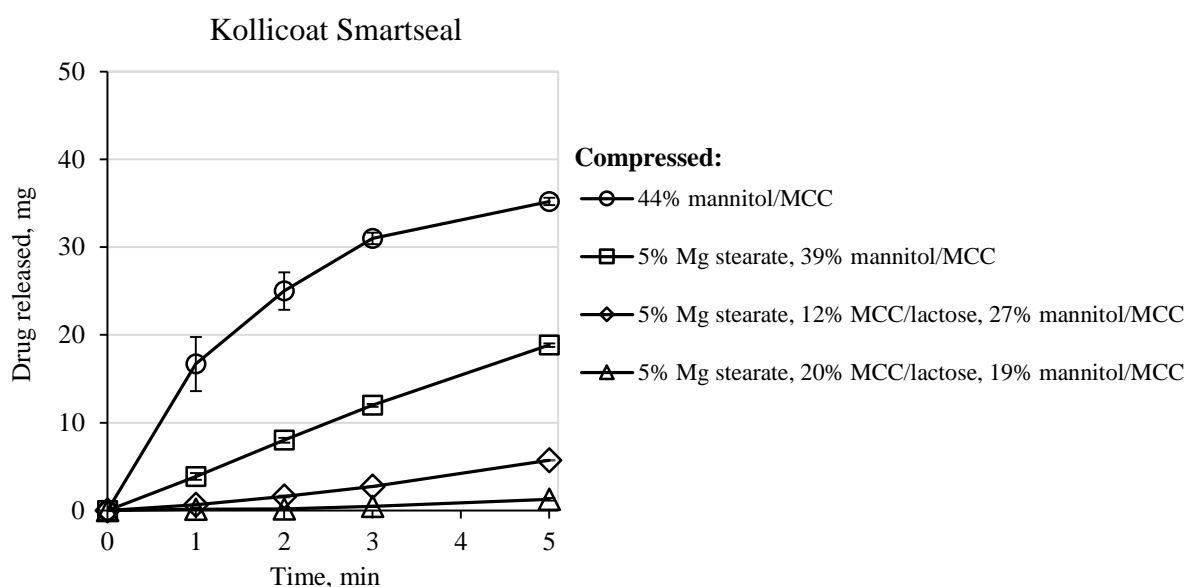


Fig. 49. Effect of magnesium stearate glidant layer on tramadol HCl release in pH 6.8 from tablets prepared of coated pellets with different excipient layers (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% w/w TBC); MCC/lactose 3:1 cushion layer contains 3% w/w Mg stearate content; disintegrant: 6% V/V Kollidon CL; tablet breaking force: 40-50 N).

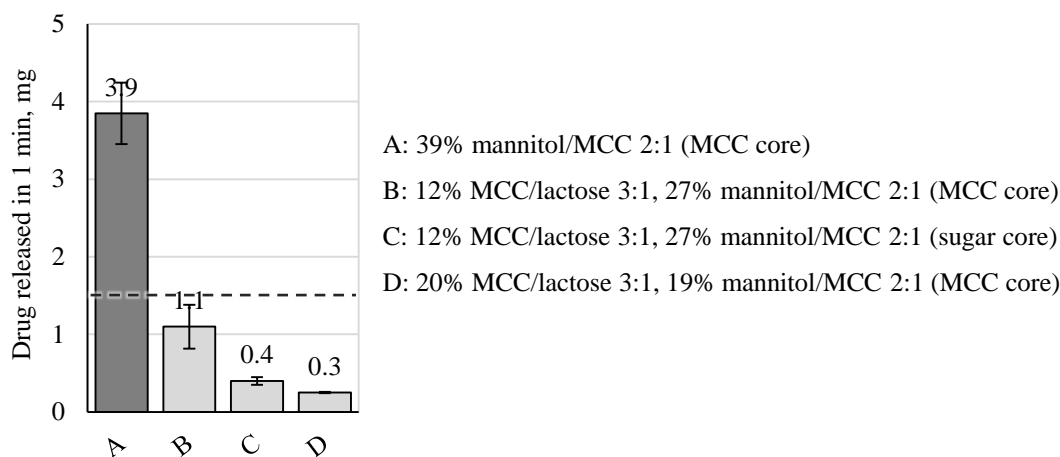


Fig. 50. Tramadol HCl released after one minute in pH 6.8 from compressed pellets with 5% V/V magnesium stearate layer and different excipient layers (coating: 5% w/w EC (20% w/w PVP), 30% Kollicoat Smartseal (18% w/w TBC); MCC/lactose 3:1 cushion layer contains 3% w/w Mg stearate content; disintegrant: 6% V/V Kollidon CL; tablet breaking force: 40-50 N).

The glidant layer between coating and excipient layers reduced coating damage during compaction and thus the release rate in pH 6.8. However, taste masking of ODTs was only achieved in combination with a cushion layer (Fig. 49 and Fig. 50). This indicates that both - lubricants and cushioning agents - are crucial to protect film coatings during compaction. Lubricants minimize the friction between coating and tableting excipients and cushioning agents absorb mechanical stress by being deformed and densified. Only excipient layers which combine both qualities – either in separate layers or in a single layer as described above – can efficiently protect the coating. Taste masked ODTs were achieved with pellets with 5% V/V magnesium stearate glidant layer, 12% V/V cushion and 27% V/V disintegration layer. Using sugar cores instead of MCC cores or increasing the amount of cushion layer to 20% V/V further decreased the release rate and only 0.4 mg or 0.3 mg tramadol HCl were released in one minute, respectively (Fig. 50). The wetting time was 31 seconds for tablets with 20% V/V cushion layer (with 6% V/V Kollidon CL) (Table 8, F17).

Glidant layer with excipient powders

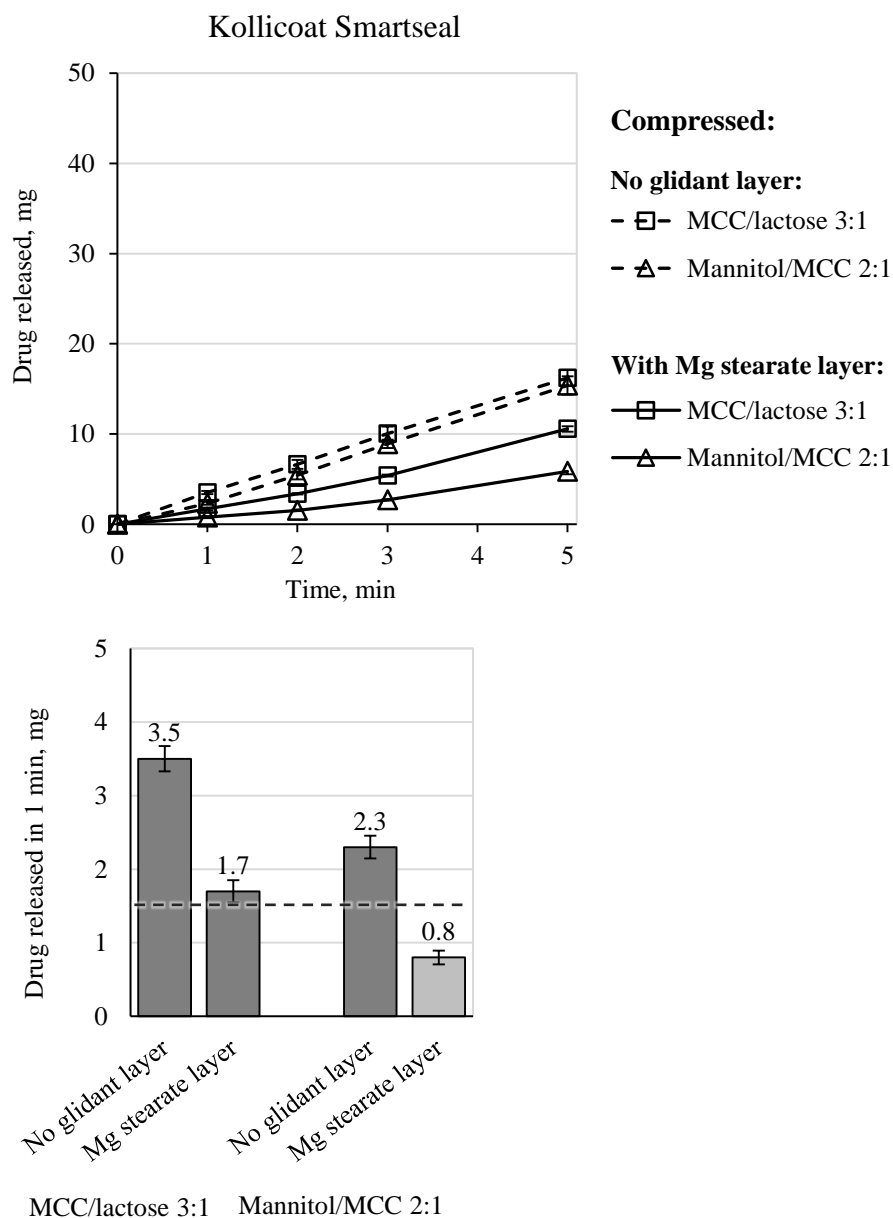


Fig. 51. Effect of 5% V/V magnesium stearate glidant layer on tramadol HCl release in pH 6.8 from tablets prepared of coated pellets and different excipient powder mixtures (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% w/w TBC); disintegrant: 6% V/V Kollidon CL; tablet breaking force: 40-50 N).

The glidant layer reduced coating damage also when the additional tableting excipients were added as powders instead of excipient layers (Fig. 51). However, the protective effect of excipient powders was inferior. Contrary to excipient layers, powders mixtures cannot completely prevent the contact of pellets with each other or with die wall and punches. At these points, the cushioning effect is missing and the coating ruptures despite of the glidant layer. Nonetheless, the application of a thin magnesium stearate layer (10% V/V regarding coated pellets) presents a simple method to reduce compression-induced coating damage and taste masked ODTs were obtained in combination with the mannitol/MCC 2:1 powder mixture.

3.3.4.7 Release in pH 1.0

After the pellets are swallowed, the drug should be released rapidly. Tramadol HCl pellets coated with 5% w/w EC (20% w/w PVP) and 30% w/w Kollicoat Smartseal exhibited a fast drug release in pH 1.0 as discussed in chapter 3.1.2. However, excipient layers applied on coated pellets might reduce the release rate if the layers disintegrate too slowly. Therefore, the effect of excipient layers on the release in pH 1.0 was evaluated. The two formulations with the lowest drug release in pH 6.8 after compression were selected for this study. The release in pH 1.0 was measured in the uncompressed state.

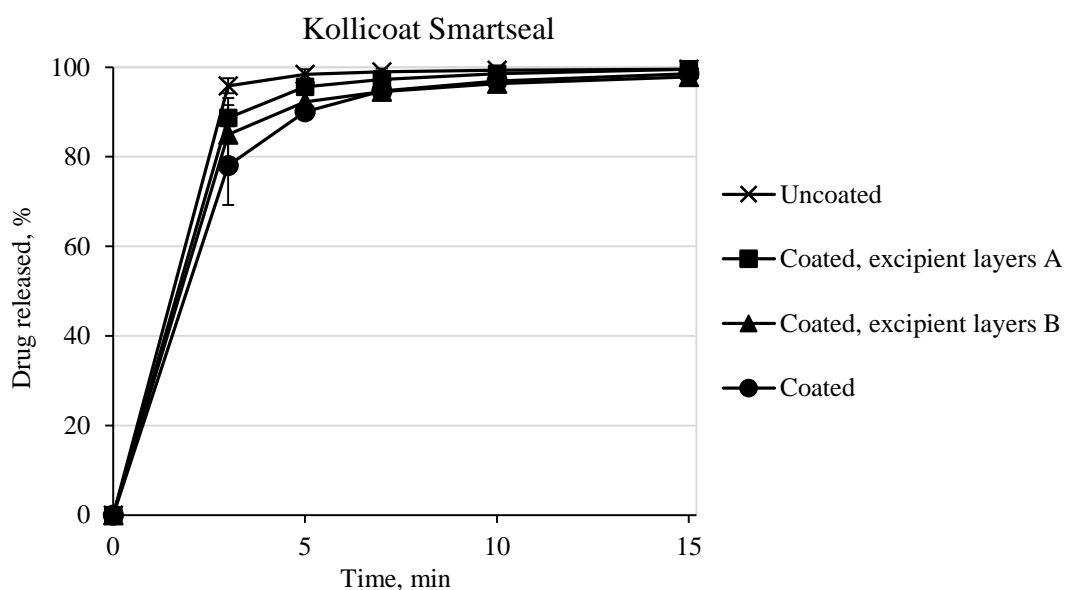


Fig. 52. Effect of excipient layers on tramadol HCl release in pH 1.0 from uncompressed pellets (coating: 5% w/w EC (20% w/w PVP), 30% w/w Kollicoat Smartseal (18% w/w TBC); excipient layers: A: 5% V/V Mg stearate glidant layer and 20% V/V MCC/lactose 3:1 cushion layer with 3% w/w Mg stearate and 19% V/V mannitol/MCC 2:1 disintegration layer, B: 25% V/V MCC/lactose 3:1 cushion layer with 33% w/w Mg stearate and 19% V/V mannitol/MCC 2:1 disintegration layer).

The release rate in pH 1.0 was not reduced by glidant, cushion or disintegration layers. Both investigated formulations released more than 90% of tramadol HCl within five minutes. Thus, the target of > 85% released in 15 minutes was easily met. The fast release indicates that the layers disintegrated quickly and did not act as an additional barrier for drug diffusion.

3.3.4.8 Tablet wetting time

One of the biggest challenges for the formulation of ODTs is to achieve fast tablet disintegration. The European Pharmacopoeia requests a disintegration time of less than three minutes for orodispersible tablets [177]. The FDA recommends a disintegration time of less than 30 seconds [74]. Conditions in the oral cavity differ greatly from those in the compendial disintegration test which is performed by placing the tablets in a basket which moves up and down in a beaker containing about 800 mL of water. There is no pharmacopoeial disintegration test designed especially for ODTs but several researchers have developed alternative test setups which more closely resemble the conditions *in vivo* [85, 100-112]. For this study, tablet wetting time was measured with a method similar to that described by Bi et al. [103]. Tablets were placed on a wet cotton pad and the time until the water reached the center of the tablet's upper surface was measured. The influence of excipient layer composition was evaluated as well as the effect of different types and concentrations of internal and external disintegrants.

Table 8. Wetting time of tablets prepared from coated pellets with excipient layers (composition in % V/V, 40-50 N tablet breaking force)

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
Coated pellets																					
5% w/w EC, 30% w/w Koll. Smarts.	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Glidant layer																					
Magnesium stearate (MgSt)																	5	5	5	5	5
Cushion layers																					
Starch/lactose 3:1, 3% w/w MgSt													25								
MCC/lactose 3:1, 3% w/w MgSt	50	44	44	44										25			20	20	20	20	20
MCC/lactose 3:1, 10% w/w MgSt							25	25	25	25	25	25			25						
MCC/lactose 3:1, 33% w/w MgSt																25					
Disintegration layers																					
Mannitol/starch 2:1													19								
Mannitol/MCC 2:1					50	44	25	22	19	22	19	22		19	19	19	19				
Mannitol/Polyplasdone 2:1																		25			
Mannitol/MCC/Polypl. 67:15:18																			25		
Mannitol/MCC/Polypl. 67:23:10																				25	
Mannitol/MCC/Koll. CL-SF 67:23:10																					25
External disintegrants																					
Kollidon CL		6				6		3	6				6	6		6	6				
Ac-Di-Sol			6							3	6										
Explotab				6								3			6						
Disintegration time (S.D.), s	> 180	> 180	> 180	> 180	46 (7)	9 (3)	> 180	40 (17)	18 (8)	> 180	> 180	> 180	13 (7)	12 (4)	> 180	17 (7)	31 (17)	> 180	> 180	> 180	> 180

Tablets of pellets with an MCC/lactose 3:1 cushion layer (3% w/w magnesium stearate) had a wetting time of more than three minutes (Table 8, F1). This was ascribed to the binders used in the cushion layer. PVP increased the viscosity of the fluid entering the tablet and ethyl cellulose increased the tablet's hydrophobicity. The addition of 6% V/V Kollidon CL, Explotab or Ac-Di-Sol as external disintegrants did not reduce the wetting time to less than three minutes (Table 8, F2-F4).

The mannitol/MCC 2:1 disintegration layer contained no polymeric binder. Tablets of pellets with this layer were completely wetted after 46 seconds (Table 8, F5). With 6% V/V Kollidon CL as external disintegrant, the wetting time was reduced to nine seconds (Table 8, F6).

Tablets of pellets with 25% V/V cushion layer (containing 10% w/w magnesium stearate) and 25% V/V disintegration layer were not wetted after three minutes if no external disintegrant was added (Table 8, F7). With 3% V/V Kollidon CL (Table 8, F8), tablets were wetted at the center of the upper tablet surface after 40 seconds. However, for several tablets a dry part remained on one side which was not wetted after three minutes (Fig. 53). This was probably due to an inhomogeneous distribution of the disintegrant at this low concentration. In contrast, tablets with 6% V/V Kollidon CL were fully wetted after 18 seconds (Table 8, F9, and Fig. 53). Tablets with Ac-Di-Sol or Explotab as external disintegrant were not wetted after three minutes (Table 8, F10-F13).

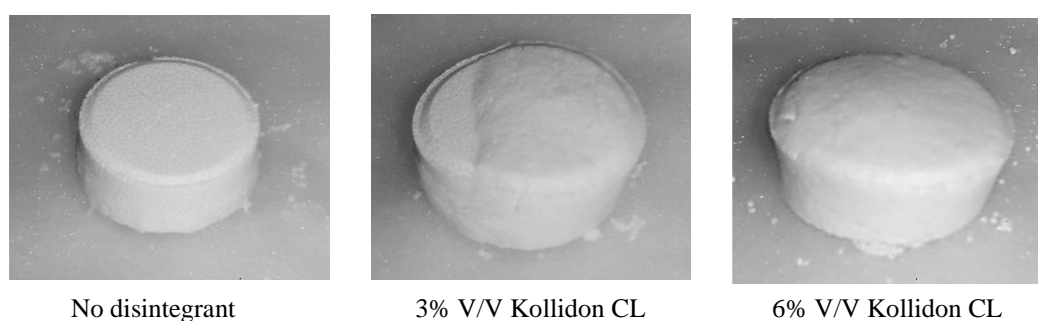


Fig. 53. Effect of Kollidon CL as external disintegrant on the wetting behavior of tablets prepared of pellets with an MCC/lactose 3:1 cushion layer and a mannitol/MCC 2:1 disintegration layer.

Whether starch or MCC was used as filler in the cushion and disintegration layers had no significant influence on the wetting time for tablets with 6% V/V Kollidon CL (13 seconds and 12 seconds, respectively ($p = 0.668$)) (Table 8, F14 and F15).

Increasing the magnesium stearate content in the MCC/lactose 3:1 cushion layer from 3 to 10 or 33% w/w led to slightly higher wetting times (with 6% V/V Kollidon CL) (12 seconds vs. 18 and 17 seconds, respectively; $p = 0.029$ and 0.044) (Table 8, F9, F14 and F16). This phenomenon is well-known for magnesium stearate and is due to its hydrophobic nature [170]. With a magnesium stearate glidant layer under the cushion and disintegration layers, the wetting time increased to 31 seconds (with 6% V/V Kollidon CL) (Table 8, F17). Moreover, for some of these tablets, a dry part remained on one side as described above for tablets with 3% V/V Kollidon CL.

Including the disintegrant in the excipient layers would be preferable because internal disintegrants cannot segregate and ensure a homogeneous distribution within tablets. Since the coated pellets have diameter of less than 400 μm , a small particle size grade of cross-linked PVP (Polyplasdone XL-10) was selected as internal disintegrant. It was included in the mannitol/MCC 2:1 disintegration layer at concentrations of 10, 18 or 33% w/w. This results in concentration of 3, 6 and 11% V/V in the tablet formulation. Kollidon CL-SF, another grade of cross-linked PVP of small particle size, was also included in the disintegration layer at a concentration of 10% w/w. All tablets prepared of layered pellets with an internal disintegrant exhibited wetting times of more than three minutes (Table 8, F18-21). This might be due to lower effectiveness of disintegrants in the internal phase [83] and due to slower water uptake and lower swelling pressure of small particle size grades of cross-linked PVP [178].

In summary, tablets of pellets layered with only the disintegration layer exhibited fast wetting even without external disintegrant. If the pellets had only a cushion layer, wetting times exceeded three minutes also with Kollidon CL, Ac-Di-Sol or Explotab as external disintegrants. For tablets of pellets with combinations of cushion and disintegration layers, wetting times of less than 30 seconds could be achieved by the addition of 6% V/V Kollidon CL. It was not possible to reach wetting times of three minutes or less through the addition of internal disintegrants (Polyplasdone XL-10 or Kollidon CL-SF).

4 Summary

Many patients have problems to swallow tablets or capsules and prefer orally disintegrating tablets (ODTs). ODTs remain in the oral cavity for a longer time than conventional tablets and taste masking of bitter drugs is important to ensure patient compliance. One of the approaches to formulate taste masked ODTs is the preparation of coated drug pellets followed by compression into tablets. In the oral cavity, these tablets disintegrate rapidly and the pellets are swallowed as a slurry. The coating prevents drug dissolution in the oral cavity and thus the interaction of drug and taste receptors. However, compression of coated pellets is challenging. Rupturing of the film must be prevented to preserve the coating's functionality.

The target of this work was to prepare taste masked ODTs of the highly soluble drug tramadol HCl by compression of coated pellets. The tablets should disintegrate quickly, ideally in less than 30 seconds. An in vitro release of 1.5 mg tramadol HCl within one minute in phosphate buffer pH 6.8 was set as upper limit to ensure sufficient taste masking. On the other hand, the drug should be released rapidly once the pellets reach the stomach to ensure that bioavailability is not governed by drug dissolution. Therefore, the formulations should exhibit a drug release of at least 85% after 15 minutes in 0.1 N HCl (pH 1.0).

Microcrystalline cellulose (MCC) pellets were layered with 20% w/w tramadol HCl. When the pellets were not coated, tramadol HCl dissolved rapidly due to its high solubility. Coatings with polymers of different solubility were evaluated for their suitability to provide taste masked tramadol HCl pellets. Uncompressed pellets with water-soluble coatings (Opadrytm or Opadry amb II) released the drug too quickly. Taste masking was not achieved with coating levels up to 50% w/w. The insoluble ethyl cellulose coating led to taste masked pellets at a coating level of 35% w/w. However, drug release in pH 1.0 was too slow (65% after 15 minutes) even though 20% w/w PVP was included as pore former. In contrast, the acid-soluble polymers Kollicoat Smartseal and Eudragit E provided taste masked tramadol HCl pellets at a coating level of 35% w/w while leading to a fast drug dissolution in acidic media.

Coated pellets (35% w/w coating level) were compressed into ODTs applying a compression force of 10 kN. The tablets contained 50% w/w pellets with a dose of 50 mg tramadol HCl. The drug release rate of pellets coated with Kollicoat Smartseal, Eudragit E or ethyl cellulose was increased after compression, indicating that the films were damaged. Compressed pellets did not exhibit a lag time before the drug was released which led to ODTs with insufficient taste masking. Therefore,

the effects of several formulation and process parameters were evaluated in order to reduce coating damage caused by compaction and thus obtain taste masked tramadol HCl tablets.

First, the effect of parameters which influence the coating properties were investigated. This included application of subcoatings, variation of plasticizer type and content, and increase of coating level.

Applying subcoatings with lower permeability or with gel-forming properties was evaluated as a method to reduce the drug release from compressed pellets. An ethyl cellulose subcoating with 20% w/w PVP as pore former (5% w/w coating level) under Eudragit E coatings reduced the release rate of compressed pellets in pH 6.8 and taste masking was maintained after compaction (35% w/w total coating level). At the same time, the subcoat had almost no retarding effect on the release in pH 1.0. Ethyl cellulose subcoats also reduced the release in pH 6.8 of compressed pellets with Kollicoat Smartseal as topcoat. However, more than 1.5 mg tramadol HCl was released within one minute even when the coating level of the subcoat was increased to 10% w/w or the amount of pore former reduced to 5% w/w. Insufficient taste masking is therefore expected for these ODTs. A gel-forming HPC subcoating was applied under Kollicoat Smartseal to act as a sealing for film cracks. However, taste masking could not be achieved by this method.

Plasticizer type and content were varied to achieve a high coating flexibility which is crucial to prevent coating damage during compression. Tributyl citrate (TBC) was preferable as plasticizer for Eudragit E in comparison to triacetin (TA). TBC led to less coating damage during compression and thus a lower drug release rate in pH 6.8. For compressed pellets coated with Eudragit E, increasing the TBC concentration reduced the drug release. Taste masked ODTs were obtained at a plasticizer content of 15% w/w (with 5% w/w ethyl cellulose subcoat). For Kollicoat Smartseal, a TBC content of 18% w/w led to the lowest coating damage during compression. However, too much tramadol HCl was released through this coating for complete taste masking (2.6 mg after one minute; with 5% w/w ethyl cellulose subcoat).

Admixing of polymers with high flexibility is another approach to improve the mechanical properties of film coatings. Kollicoat Smartseal was mixed with the more flexible polymer Kollicoat SR at a ratio of 70:30 and 50:50 (18% w/w TBC content). Even though the maximum elongation of free films increased with increasing Kollicoat SR content, the amount of drug released from compressed pellets after one minute in pH 6.8 was unchanged. Therefore, taste masked ODTs were not obtained by this method.

The coating level of pellets affects taste masking of ODTs in two ways. First, a higher coating level reduces the drug release rate due to longer diffusion pathways. Furthermore, thicker coatings can better withstand mechanical stress during compression because a higher force is necessary to rupture the films. With Eudragit E as topcoat, a total coating level of 35% w/w was sufficient to

prepare taste masked ODTs which released of only 1.1 mg tramadol HCl within one minute in pH 6.8 (5% w/w ethyl cellulose subcoat). With Kollicoat Smartseal as topcoat, a higher coating level was required compared to Eudragit E. At a total coating level of 50% w/w, the amount of tramadol HCl released within one minute was 1.7 mg which is slightly above the target. Thus, the coating level would have to be increased beyond 50% w/w to achieve fully taste masked ODTs with Kollicoat Smartseal.

In further experiments, the influence of drug solubility, drug loading and binder type in the drug layer were evaluated.

A lower solubility generally leads to a lower drug release rate for reservoir-type dosage forms. Release profiles of the sparingly soluble drug acetaminophen (17 mg/mL) were compared to those of the very soluble tramadol HCl (948 mg/mL). For acetaminophen, a coating level of 25% w/w Eudragit E or 35% w/w Kollicoat Smartseal was sufficient to prepare taste masked ODTs which released less than 1.5 mg in one minute. In contrast, 35% w/w coating level (no subcoating) was insufficient to provide taste masking for tramadol HCl with either polymer. Therefore, a sodium chloride layer was applied on tramadol HCl pellets before coating to reduce the solubility of tramadol HCl inside the pellets. This increased the lag phase of uncompressed pellets coated with Kollicoat Smartseal, but did not affect the release from compressed pellets. Thus, it did not lead to taste masked ODTs.

The drug loading of tramadol HCl pellets was increased from 20 to 40% w/w to achieve a higher dose per tablet at the same pellet content (100 mg vs. 50 mg). Tablets with a dose of 100 mg tramadol HCl were taste masked when the pellets were coated with Eudragit E (with 5% w/w ethyl cellulose subcoat). They released 1.5 mg tramadol HCl in the first minute in pH 6.8. With Kollicoat Smartseal, the amount of tramadol HCl released in pH 6.8 from compressed pellets was above the threshold at both drug loadings.

Different types and amounts of binder were used for the application of tramadol HCl on pellet cores. Subsequently, pellets were coated and compressed into ODTs. Generally, water-soluble binders of low viscosity are used for drug layering (Kollidon 30 in this study). When a binder with a higher viscosity was used (Kollidon 90), the drug release rate in pH 6.8 from compressed pellets was reduced due to the additional barrier for drug diffusion. This was also the case when the acid-soluble polymer Eudragit E was used as binder. Therefore, highly-viscous or acid-soluble binders can be used to improve taste masking of ODTs in combination with other approaches.

In the following experiments, the effects of parameters which reduce the mechanical stress during compaction were evaluated. This included process parameters (compression force) as well as

formulation parameters (pellet content in tablets, pellet core type, and application of excipient layers).

Reducing the compression force from 10 kN to 5 kN reduced the drug release rate from pellets coated with Kollicoat Smartseal. However, also tablet hardness was reduced from 45 N to 19 N. This would be insufficient for packaging, transport and handling by patients.

The amount of pellets in the tablets was reduced from 50 to 25% w/w to reduce the stress on pellets during compaction while maintaining a compression force of 10 kN. To keep the dose constant, pellets with 40% w/w instead of 20% w/w drug loading were used. Reducing the pellet fraction led to a pronounced reduction of the drug release rate for pellets coated with Kollicoat Smartseal. With 25% w/w pellet content, taste masked ODTs were obtained.

Also pellet cores have an influence on the mechanical stress acting on the coating during compaction. In this study, MCC cores and sugar cores were used which differed regarding their crushing strength (22.2 vs. 4.7 MPa, respectively). The pellets were layered with drug and coated with 10% w/w Eudragit E as subcoating and 25% w/w Kollicoat Smartseal as topcoating. The release rate after compaction was lower for pellets with a sugar core. This indicates that pellets with a lower crushing strength were preferable to prevent compression-induced coating damage of the investigated polymers.

The effect of applying excipient layers on coated pellets is discussed in the following paragraphs. Tableting excipients have to provide cushioning for coated pellets during compaction and ensure sufficient tablet hardness and fast disintegration. Compared to excipient powders, layers have two main advantages: the segregation of excipients and pellets is omitted and pellets have no direct contact with each other or with the compaction tooling. For this part of the study, pellets coated with 5% w/w ethyl cellulose as subcoating and 30% w/w Kollicoat Smartseal as topcoating were used. After the application of excipient layers, pellets were compressed into ODTs with or without external disintegrant. The amount of tableting excipients was kept constant at 50% V/V and the compression force was adjusted to obtain tablets of 40-50 N breaking force.

A cushion layer composed of MCC/lactose 3:1 with PVP and ethyl cellulose as binders was sprayed onto coated pellets. Tablets prepared from these pellets exhibited wetting times of more than three minutes which is not fast enough for ODTs. Adding external disintegrants (Kollidon CL, Explotab und Ac-Di-Sol) did not reduce the wetting time to below three minutes. Therefore, a disintegration layer of mannitol/MCC 2:1 was applied on top of the cushion layer. No polymeric binder was added to this layer. Instead, the dissolved mannitol acted as binder. Tablets prepared of these pellets had a wetting time of 12 seconds with 6% V/V Kollidon CL as external disintegrant. However, the tablets were not taste masked since 6.0 mg tramadol HCl was released after one minute in pH 6.8. Furthermore, the cushioning effect of excipient layers was inferior compared to that of analogues powder mixtures.

Including glidants in excipient layers or applying a glidant layer under excipient layers is known to reduce compression-induced coating damage. Therefore, the influence of magnesium stearate content in the cushion layer and the effect of a separate magnesium stearate layer were studied. When 10% w/w magnesium stearate was added to the MCC/lactose 3:1 cushion layer, taste masked ODTs were obtained. These tablets had a wetting time of 18 seconds when 6% V/V Kollidon CL was added as external disintegrant. Applying magnesium stearate as a separate layer between coating and excipient layers also reduced coating damage caused by compaction. However, to achieve taste masked ODTs, a cushion layer under the disintegration layer was still necessary. This indicates that both – cushioning and reduced friction – are crucial to effectively protect film coatings during compaction. The glidant layer reduced coating damage also when pellets were compressed with excipient powders instead of excipient layers but the protective effect was slightly inferior. Nevertheless, this presents a simple method to reduce compression-induced coating damage and taste masked ODTs were obtained with a powder mixture of mannitol/MCC 2:1.

In conclusion, taste masked tramadol HCl pellets with rapid drug release in pH 1.0 were obtained with coatings of the acid-soluble polymers Kollicoat Smartseal or Eudragit E (35% w/w coating level). Compaction of these pellets led to coating damage and the taste masking functionality was lost. Taste masked ODTs were obtained when an ethyl cellulose subcoating was applied under the Eudragit E coating. Thereby, a plasticizer content of 15% w/w TBC in the Eudragit E coating and a total coating level of 35% w/w were required. For pellets coated with Kollicoat Smartseal, taste masked ODTs were achieved when 18% w/w TBC were added, an ethyl cellulose subcoating was applied and the pellet content in the tablets was reduced to 25% w/w. The application of excipient layers also provided taste masked ODTs of Kollicoat Smartseal coated pellets. Thereby, glidant and cushioning agents in the excipient layers were important to prevent coating damage during compaction. On the other hand, a disintegration layer which contained no polymeric binder was essential to achieve fast tablet wetting.

5 Zusammenfassung

Viele Patienten haben Probleme Tabletten zu schlucken und bevorzugen deshalb oral zerfallende Tabletten (ODTs). ODTs verbleiben länger im Mund als herkömmliche Tabletten. Daher ist Geschmacksmaskierung wichtig, um die Compliance zu verbessern. Eine Methode um geschmacksmaskierte ODTs herzustellen besteht darin, Wirkstoffpellets zu überziehen und sie anschließend zu Tabletten zu verpressen. Im Mund zerfallen diese Tabletten wieder in einzelne Pellets, die dann geschluckt werden. Der Überzug reduziert die Wirkstofffreisetzung im Mund und dadurch die Interaktion des Wirkstoffs mit den Geschmacksrezeptoren. Das Verpressen von überzogenen Pellets stellt jedoch eine große Herausforderung dar. Das Reißen des Films muss verhindert werden, damit die Funktion des Überzugs erhalten bleibt.

Ziel dieser Arbeit war es, durch das Verpressen von überzogenen Pellets geschmacksmaskierte ODTs mit dem leicht löslichen Wirkstoff Tramadol HCl herzustellen. Die ODTs sollten schnell zerfallen, idealerweise innerhalb von weniger als 30 Sekunden. Eine *in vitro* Freisetzung von 1.5 mg Tramadol HCl innerhalb einer Minute in Phosphatpuffer pH 6.8 wurde als Obergrenze festgelegt, um ausreichende Geschmacksmaskierung sicherzustellen. Andererseits soll der Wirkstoff schnell freigesetzt werden, sobald die Pellets im Magen sind, um zu verhindern, dass die Bioverfügbarkeit durch die Auflösungsgeschwindigkeit des Wirkstoffs bestimmt wird. Das Ziel war daher eine Wirkstofffreisetzung von mindestens 85% nach 15 Minuten in 0.1 N HCl (pH 1.0).

Pellets aus mikrokristalliner Cellulose (MCC) wurden mit 20% w/w Tramadol HCl beschichtet. Wenn die Pellets keinen Überzug hatten, löste sich das Tramadol HCl aufgrund der hohen Löslichkeit schnell auf. Überzüge mit Polymeren unterschiedlicher Löslichkeit wurden bezüglich ihrer Eignung für die Geschmacksmaskierung von Tramadol HCl-Pellets untersucht. Unverpresste Pellets mit wasserlöslichen Überzügen (Opadry tm oder Opadry amb II) setzten den Wirkstoff zu schnell frei. Geschmacksmaskierung wurde nicht erzielt Beschichtungsgraden bis zu 50% w/w. Ein Überzug mit dem wasserunlöslichen Polymer Ethylcellulose führte bei einem Überzugslevel von 35% w/w zu geschmacksmaskierten Pellets. Die Freisetzungsgeschwindigkeit in pH 1.0 war aber zu langsam (65% nach 15 Minuten), obwohl 20% w/w PVP als Porenbildner zugesetzt wurden. Im Gegensatz dazu führten die säurelöslichen Überzüge Kollicoat Smartseal und Eudragit E bei einem Überzugslevel von 35% w/w zu geschmacksmaskierten Tramadol HCl-Pellets und erzielten gleichzeitig eine schnelle Freisetzung in saurem Medium.

Überzogene Pellets (35% w/w Überzugslevel) wurden mit einer Presskraft von 10 kN zu ODTs verpresst. Die Tabletten enthielten 50% w/w Pellets mit einer Dosis von 50 mg Tramadol HCl. Die Freisetzungsgeschwindigkeit von Pellets mit einem Überzug aus Kollicoat Smartseal, Eudragit E

oder Ethylcellulose war nach dem Tablettieren erhöht. Dies ist ein Zeichen dafür, dass die Filme durch das Verpressen beschädigt wurden. Die verpressten Pellets wiesen keine Lag-Phase auf, bevor der Wirkstoff freigesetzt wurde, was zu einer unzureichenden Geschmacksmaskierung der ODTs führte. Daher wurde der Einfluss verschiedener Formulierungs- und Prozessparameter untersucht, um Filmschäden durch das Verpressen zu vermindern und geschmacksmaskierte Tramadol HCl-Tabletten zu erhalten.

Zuerst wurde der Effekt verschiedener Parameter untersucht, die einen Einfluss auf die Eigenschaften des Überzugs haben. Dies beinhaltete das Auftragen von Basisüberzügen, das Variieren des Weichmachertyps und -gehalts und das Erhöhen des Beschichtungsgrades.

Das Auftragen von Basisüberzügen mit geringerer Permeabilität oder mit gelbildenden Eigenschaften wurde untersucht als Methode, um die Wirkstofffreisetzung von verpressten Pellets zu reduzieren. Ein Ethylcellulose-Basisüberzug mit 20% w/w PVP als Porenbildner (5% w/w Überzugslevel) unter dem Eudragit E-Überzug reduzierte die Freisetzungsgeschwindigkeit in pH 6.8 und die Geschmacksmaskierung blieb nach dem Verpressen erhalten (35% w/w Gesamtüberzugslevel). Die Freisetzung in pH 1.0 wurde durch den Basisüberzug kaum verlangsamt. Auch bei verpressten Pellets mit Kollicoat Smartseal als Hauptüberzug reduzierten Ethylcellulose-Basisüberzüge die Freisetzungsrates in pH 6.8. Jedoch wurden mehr als 1.5 mg Tramadol HCl innerhalb einer Minute freigesetzt, auch dann, wenn das Überzugslevel des Basisüberzugs auf 10% w/w erhöht oder der Porenbildnergehalt auf 5% w/w reduziert wurde. Für diese ODTs ist daher eine unzureichende Geschmacksmaskierung zu erwarten. Ein gelbildender HPC-Basisüberzug, der Risse im Hauptüberzug verschließen sollte, wurde unter Kollicoat Smartseal aufgetragen. Jedoch konnte mit dieser Methode keine Geschmacksmaskierung von ODTs erzielt werden.

Weichmachertyp und -gehalt wurden variiert um Überzüge mit einer hohen Flexibilität zu erzielen. Dies ist essenziell um Filmschäden während des Verpressens zu vermeiden. Tributylcitrat (TBC) war als Weichmacher in Eudragit E im Vergleich zu Triacetin (TA) vorzuziehen. TBC führte zu geringeren Filmschäden beim Verpressen und zu einer niedrigeren Wirkstofffreisetzungsrates in pH 6.8. Für verpresste Pellets mit einem Eudragit E-Überzug führte eine Erhöhung des TBC-Gehalts zu einer niedrigeren Wirkstofffreisetzung. Geschmacksmaskierte ODTs wurden mit einem Weichmachergehalt von 15% w/w erzielt (mit 5% w/w Ethylcellulose-Basisüberzug). Für Pellets mit einem Kollicoat Smartseal-Überzug führte ein TBC-Gehalt von 18% w/w zu den geringsten Filmschäden beim Verpressen. Jedoch wurde zu viel Tramadol HCl freigesetzt um eine ausreichende Geschmacksmaskierung zu gewährleisten (2.6 mg nach einer Minute; mit 5% w/w Ethylcellulose-Basisüberzug).

Das Beimischen eines Polymers mit hoher Flexibilität ist eine andere Methode um die mechanischen Eigenschaften von Filmüberzügen zu verbessern. Kollicoat Smartseal wurde mit dem flexibleren Polymer Kollicoat SR im Verhältnis 70:30 und 50:50 gemischt (18% w/w TBC-Gehalt). Obwohl die Reißdehnung der gecasteten Filme zunahm, war die Wirkstoffmenge, die nach einer Minute in pH 6.8 aus verpressten Pellets freigesetzt wurde, unverändert. Daher wurde mit dieser Methode keine ausreichende Geschmacksmaskierung erzielt.

Die Überzugsmenge auf den Pellets beeinflusst die Geschmacksmaskierung von ODTs auf zwei Arten. Zum einen führt ein höherer Beschichtungsgrad aufgrund längerer Diffusionswege zu einer langsameren Freisetzungsrates. Zum anderen können dickere Überzüge der mechanischen Beanspruchung während des Tablettierens besser standhalten, da eine größere Kraft nötig ist um diese zu zerreißen. Mit Eudragit E als Hauptüberzug reichte ein Gesamtüberzugslevel von 35% w/w aus, um geschmacksmaskierte ODTs zu erzielen (5% w/w Ethylcellulose-Basisüberzug). Mit Kollicoat Smartseal als Hauptüberzug waren höhere Überzugslevel nötig im Vergleich zu Eudragit E. Bei einem Gesamtbeschichtungsgrad von 50% w/w wurden 1.7 mg Tramadol HCl innerhalb einer Minute freigesetzt. Dies liegt leicht über der festgelegten Grenze. Die Überzugsmenge müsste demnach auf mehr als 50% w/w erhöht werden, um geschmacksmaskierte ODTs mit Kollicoat Smartseal herzustellen.

In weiteren Experimenten wurde der Einfluss der Wirkstofflöslichkeit, der Wirkstoffbeladung und des Bindemitteltyps in der Wirkstoffschicht untersucht.

Eine niedrigere Wirkstofflöslichkeit führt bei Reservoir-Arzneiformen im Allgemeinen zu niedrigeren Freisetzungsrates. Die Freisetzungsprofile des leicht löslichen Arzneistoffs Tramadol HCl (948 mg/mL) wurden mit denjenigen des gering löslichen Paracetamols (17 mg/mL) verglichen. Für Paracetamol reichte ein Überzugslevel von 25% w/w Eudragit E oder 35% w/w Kollicoat Smartseal aus, um geschmacksmaskierte ODTs zu erhalten, welche weniger als 1.5 mg innerhalb einer Minute freisetzten. Im Gegensatz dazu war mit beiden Polymeren ein Beschichtungsgrad von 35% w/w nicht ausreichend um Geschmacksmaskierung für Tramadol HCl zu erzielen (ohne Basisüberzug). Daher wurde vor dem Überziehen eine Natriumchlorid-Schicht auf Tramadol HCl-Pellets aufgetragen um die Löslichkeit von Tramadol HCl zu reduzieren. Dies verlängerte die Lag-Phase von unverpressten Pellets mit einem Kollicoat Smartseal-Überzug. Auf die Wirkstofffreisetzung aus verpressten Pellets hatte es aber keinen Einfluss, so dass damit keine Geschmacksmaskierten von ODTs erzielt werden konnte.

Die Wirkstoffbeladung von Tramadol HCl-Pellets wurde von 20 auf 40% w/w erhöht um bei gleichem Pelletgehalt in den Tabletten eine höhere Dosis zu erreichen (100 mg statt 50 mg). Tabletten mit einer Dosis von 100 mg Tramadol HCl waren geschmacksmaskiert, wenn die Pellets mit Eudragit E überzogen waren (mit 5% w/w Ethylcellulose-Basisüberzug). Sie setzten 1.5 mg

Tramadol HCl innerhalb einer Minute bei pH 6.8 frei. Mit Kollicoat Smartseal war die freigesetzte Menge Tramadol HCl bei beiden Wirkstoffbeladungen über dem Limit.

Verschiedene Bindemitteltypen und -mengen wurden für das Auftragen von Tramadol HCl auf die Pellets benutzt. Danach wurden die Pellets überzogen und zu ODTs verpresst. Normalerweise werden wasserlösliche Polymere mit niedriger Viskosität als Bindemittel für das Auftragen von Wirkstoffen verwendet (Kollidon 30 in dieser Arbeit). Wenn ein Bindemittel mit höherer Viskosität verwendet wurde (Kollidon 90), verringerte sich die Freisetzungsgeschwindigkeit in pH 6.8 aus verpressten Pellets aufgrund der zusätzlichen Diffusionsbarriere. Dies war auch der Fall, wenn das säurelösliche Polymer Eudragit E als Bindemittel verwendet wurde. Somit können hochviskose oder säurelösliche Bindemittel eingesetzt werden, um die Geschmacksmaskierung von ODTs in Kombination mit anderen Maßnahmen zu verbessern.

In den folgenden Experimenten wurde der Effekt von Parametern untersucht, welche die mechanische Beanspruchung der überzogenen Pellets während des Tablettierens reduzieren. Dazu gehörten sowohl Prozessparameter (Presskraft) als auch Formulierungsparameter (Pelletgehalt in Tabletten, Art des Pelletkerns und Auftragung von Hilfsstoffschichten).

Wenn die Presskraft von 10 kN auf 5 kN reduziert wurde, verringerte sich die Freisetzungsrates aus Pellets mit einem Kollicoat Smartseal-Überzug. Jedoch reduzierte sich auch die Tablettenhärte von 45 N auf 19 N. Dies wäre für das Verpacken, den Transport und die Handhabung durch Patienten nicht ausreichend.

Der Pelletgehalt der Tabletten wurde von 50 auf 25% w/w reduziert, um die Beanspruchung der Pellets während des Tablettierens bei unveränderter Presskraft (10 kN) zu verringern. Um die Dosis konstant zu halten, wurden Pellets mit 40 statt 20% w/w Wirkstoffgehalt verwendet. Das Reduzieren des Pelletgehalts führte zu einer starken Reduktion der Freisetzungsrates aus Pellets, die mit Kollicoat Smartseal überzogen waren. Mit einem Pelletgehalt von 25% w/w konnten geschmacksmaskierte ODTs erzielt werden.

Auch die Pelletkerne haben einen Einfluss auf die mechanische Beanspruchung der Überzüge während des Verpressens. In dieser Untersuchung wurden MCC-Kerne und Zuckerkerne verwendet, welche sich in ihrer Bruchfestigkeit unterschieden (22.2 und 4.7 MPa). Die Pellets wurden mit Wirkstoff beschichtet und mit 10% w/w Eudragit E als Basisüberzug und 25% w/w Kollicoat Smartseal als Hauptüberzug überzogen. Die Freisetzungsrates aus verpressten Pellets war niedriger, wenn die Pellets einen Zuckerkernel hatten. Dies deutet darauf hin, dass sich Pelletkerne mit einer niedrigeren Bruchfestigkeit besser eignen, um Filmschäden der untersuchten Polymere während des Verpressens zu vermeiden.

Die folgenden Abschnitte beschreiben den Effekt von Hilfsstoffschichten, welche auf die überzogenen Pellets aufgetragen wurden. Tablettierhilfsstoffe müssen während des Verpressens die Kräfte, die auf die Pellets wirken, abdämpfen (Cushioning). Außerdem müssen sie für eine ausreichende Tablettenhärte und eine schnelle Zerfallszeit (resp. Durchnässungszeit) sorgen. Hilfsstoffschichten haben im Vergleich zu Hilfsstoffpulvern zwei Vorteile: das Entmischen von Pellets und Hilfsstoffen wird verhindert und außerdem haben die Pellets keinen direkten Kontakt zueinander und zu den Tablettierwerkzeugen. Für diesen Teil der Arbeit wurden Pellets mit einem Überzug von 5% w/w Ethylcellulose und 30% w/w Kollicoat Smartseal verwendet. Nach dem Auftragen der Hilfsstoffschichten wurden die Pellets mit oder ohne zusätzliche Zerfallsmittel zu ODTs verpresst. Der Pelletgehalt in den Tabletten betrug 50% V/V und die Presskraft wurde jeweils angepasst um Tabletten mit einer Bruchfestigkeit von 40-50 N zu erzielen.

Eine Cushioning-Schicht aus MCC/Laktose 3:1 mit PVP und Ethylcellulose als Bindemittel wurde auf die überzogenen Pellets aufgetragen. Die Tabletten, die aus diesen Pellets hergestellt wurden, wiesen eine Durchnässungszeit von mehr als drei Minuten auf. Dies ist nicht schnell genug für ODTs. Die Zugabe von Zerfallsmitteln (Kollidon CL, Explotab und Ac-Di-Sol) reduzierte die Durchnässungszeit nicht auf unter drei Minuten. Daher wurde eine Zerfalls-Schicht aus Mannitol/MCC 2:1 auf die Cushioning-Schicht aufgetragen. Für diese Schicht wurde kein Polymer als Bindemittel verwendet, sondern das gelöste Mannitol diente als Bindemittel. Tabletten, hergestellt aus diesen Pellets zusammen mit 6% V/V Kollidon CL als Zerfallsmittel, hatten eine Durchnässungszeit von 12 Sekunden. Jedoch waren die Tabletten nicht geschmacksmaskiert, da 6 mg Tramadol HCl innerhalb von einer Minute freigesetzt wurden bei pH 6.8. Außerdem war der Cushioning-Effekt der Hilfsstoffschichten dem analoger Hilfsstoffpulvermischungen unterlegen. Bekanntermaßen führen das Zugeben von Schmiermittel zu Hilfsstoffschichten und das Auftragen von Schmiermittel-Schichten unter Hilfsstoffschichten zu einer Reduktion der Filmschäden während der Tablettierung. Daher wurden der Einfluss des Magnesiumstearat-Gehaltes in der Cushioning-Schicht und der Effekt einer separaten Magnesiumstearat-Schicht untersucht. Durch die Zugabe von 10% w/w Magnesiumstearat zur Cushioning-Schicht konnten geschmacksmaskierte ODTs hergestellt werden. Diese Tabletten hatten eine Durchnässungszeit von 18 Sekunden, wenn 6% V/V Kollidon CL als Zerfallsmittel zugegeben wurde. Auch das Auftragen einer separaten Magnesiumstearat-Schicht verringerte den Filmschaden beim Verpressen. Jedoch war eine Cushioning-Schicht unter der Zerfallsschicht trotzdem nötig, um geschmacksmaskierte ODTs zu erzielen. Dies zeigt, dass beides – Dämpfung der Presskraft und Reduzieren der Reibung – wichtig ist um Filmüberzüge beim Tablettieren effektiv zu schützen.

Als Fazit ist festzuhalten, dass geschmacksmaskierte Tramadol HCl-Pellets mit schneller Wirkstofffreisetzung in pH 1.0 erzielt wurden mit Überzügen aus den säurelöslichen Polymeren

Kollicoat Smartseal und Eudragit E (35% w/w Überzugslevel). Beim Verpressen wurden diese Überzüge beschädigt und die geschmacksmaskierende Funktion ging verloren. Geschmacksmaskierung von ODTs wurde erreicht, wenn ein Basisüberzug aus Ethylcellulose unter Eudragit E aufgetragen wurde. Dabei war ein Weichmacheranteil von 15% w/w TBC im Eudragit E-Überzug und eine Gesamtüberzugsmenge von 35% w/w nötig. Für Pellets mit einem Kollicoat Smartseal-Überzug wurden geschmacksmaskierte ODTs erzielt, wenn 18% w/w TBC zugegeben, ein Ethylcellulose-Basisüberzug aufgetragen und der Pelletgehalt in den Tabletten auf 25% w/w reduziert wurde. Auch durch das Auftragen von Hilfsstoffschichten konnten geschmacksmaskierte ODTs aus Pellets mit einem Kollicoat Smartseal-Überzug hergestellt werden. Schmiermittel sowie Cushioning-Hilfsstoffe waren wichtig, um Filmschäden während des Verpressens zu minimieren. Das Auftragen einer Zerfalls-Schicht, die kein Polymer als Bindemittel enthielt, war essenziell, um eine schnelle Durchnässungszeit der Tabletten zu gewährleisten.

6 Appendix

6.1 Coating formulations

Table 9. Coating formulation with Kollicoat Smartseal.

Excipient	Function	Concentration in solution, % w/w	Concentration in dry film, % w/w regarding the polymer
Kollicoat Smartseal 30D	Film forming polymer	33.33 (dispersion) 10 (polymer)	100
Tributyl citrate (TBC)	Plasticizer	1.80*	18*
Butyl hydroxyl toluol (BHT)	Anti-oxidant	0.18	1.8
Magnesium stearate	Anti-tacking agent	1.00	10
Water	Dispersant	63.67	-
Acetone	Dispersant	2.00	-

* unless mentioned otherwise

BHT was dissolved in TEC. The solution was added to Kollicoat Smartseal 30 D and stirred overnight (about 15 hours). Magnesium stearate was mixed with acetone prior to the addition of water in order to improve dispersibility. The acetone was then evaporated before the addition of the plasticized polymer dispersion.

Table 10. Coating formulation with Opadry amb II

Excipient	Function	Concentration in solution, % w/w	Concentration in dry film, % w/w
Opadry amb II	Ready-to-use mixture containing polymer and additives	20	100
Water	Solvent	80	-

Table 11. Coating formulation with Opadry tm.

Excipient	Function	Concentration in solution, % w/w	Concentration in dry film, % w/w
Opadry tm	Ready-to-use mixture containing polymer and additives	8	100
Isopropanol/water 70:30	Solvent	92	-

Table 12. Coating formulation with Eudragit E.

Excipient	Function	Concentration in solution, % w/w	Concentration in dry film, % w/w regarding the polymer
Eudragit E 100	Film forming polymer	6.25	100
Tributyl citrate (TBC)*	Plasticizer	0.94**	15**
Magnesium stearate	Anti-tacking agent	2.08**	33**
Isopropanol/acetone 4:6	<i>Solvent</i>	90.73	-

* or triacetin if mentioned so, ** unless mentioned otherwise

Table 13. Coating formulation with ethyl cellulose.

Excipient	Function	Concentration in solution, % w/w	Concentration in dry film, % w/w regarding the polymer
Ethocel Standard 7 Premium	Film forming polymer	7.00	100
Kollidon 30*	Pore forming polymer	1.40**	20**
Isopropanol/water 88:12	Solvent	91.60	-

* or Kollidon 90 or Eudragit E 100 if mentioned so, ** unless mentioned otherwise

6.2 Excipient layer formulations

Table 14. Cushion layer formulations.

Excipient	Function	Concentration in solution, % w/w	Concentration in dry layer, % w/w
*	Filler/cushioning agent	30	90
Magnesium stearate	Glidant	1.2**	3**
Kollidon 90	Binder	2	5
Ethocel Standard 100 Premium	Binder	0.8	2
Ethanol 96%	Solvent/dispersant	60	-

* The filler/cushioning agent was Avicel PH-105 for MCC layers, Avicel PH-105 and Lactochem microfine 3:1 for MCC/lactose layers, maize starch and Lactochem microfine 3:1 for starch/lactose layers, ** unless mentioned otherwise.

Table 15. Disintegration layer formulations.

Excipient	Function	Concentration in solution, % w/w	Concentration in dry layer, % w/w
Pearlitol 100-SD*	Water soluble filler	16.7	67
Avicel 105**	Water-insoluble, swelling filler	8.3	33
Water	Solvent/dispersant	75	-

* with 20% w/w C*Sorbidex S 16606 if mentioned so, **or maize starch in combination with starch/lactose cushion layers.

Table 16. Glidant layer formulation.

Excipient	Function	Concentration in solution, % w/w	Concentration in dry layer, % w/w
Magnesium stearate	Glidant	26.7	80
Kollidon 30	Binder	6.7	20
Isopropanol	Solvent/dispersant	66.7	-

7 References

1. Nunn, T. and J. Williams, *Formulation of medicines for children*. British Journal of Clinical Pharmacology, 2005. **59**(6): p. 674-676.
2. Mennella, J.A. and G.K. Beauchamp, *Optimizing oral medications for children*. Clinical Therapeutics, 2008. **30**(11): p. 2120-32.
3. Rozin, P., "*Taste-smell confusions*" and the duality of the olfactory sense. Percept Psychophys, 1982. **31**(4): p. 397-401.
4. Hoon, M.A., et al., *Putative mammalian taste receptors: a class of taste-specific GPCRs with distinct topographic selectivity*. Cell, 1999. **96**(4): p. 541-51.
5. Stewart, R.E., J.A. DeSimone, and D.L. Hill, *New perspectives in a gustatory physiology: transduction, development, and plasticity*. American Journal of Physiology, 1997. **272**(1 Pt 1): p. C1-26.
6. Kinnamon, S.C. and T.A. Cummings, *Chemosensory transduction mechanisms in taste*. Annual Review of Physiology, 1992. **54**: p. 715-31.
7. McLaughlin, S.K., P.J. McKinnon, and R.F. Margolskee, *Gustducin is a taste-cell-specific G protein closely related to the transducins*. Nature, 1992. **357**(6379): p. 563-9.
8. Spielman, A.I., et al., *Rapid kinetics of second messenger production in bitter taste*. American Journal of Physiology, 1996. **270**(3 Pt 1): p. C926-31.
9. Adler, E., et al., *A novel family of mammalian taste receptors*. Cell, 2000. **100**(6): p. 693-702.
10. Xu, H., et al., *Different functional roles of T1R subunits in the heteromeric taste receptors*. Proceedings of the National Academy of Sciences of the United States of America, 2004. **101**(39): p. 14258-63.
11. Conte, C., et al., *Identification and characterization of human taste receptor genes belonging to the TAS2R family*. Cytogenetic and Genome Research, 2002. **98**(1): p. 45-53.
12. Lanfer, A., et al., *Predictors and correlates of taste preferences in European children: The IDEFICS study*. Food Quality and Preference, 2013. **27**(2): p. 128-136.
13. Nakamura, T., et al., *The effect of various substances on the suppression of the bitterness of quinine-human gustatory sensation, binding, and taste sensor studies*. Chemical & Pharmaceutical Bulletin (Tokyo), 2002. **50**(12): p. 1589-93.
14. Goel, H., et al., *Orally disintegrating systems: innovations in formulation and technology*. Recent Patents on Drug Delivery & Formulation, 2008. **2**(3): p. 258-74.
15. Ayenew, Z., et al., *Trends in pharmaceutical taste masking technologies: a patent review*. Recent Patents on Drug Delivery & Formulation, 2009. **3**(1): p. 26-39.
16. Bauer, K.H., et al., *Lehrbuch der Pharmazeutischen Technologie*. 8 ed. 2006, Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft mbH Stuttgart.
17. Roche, E.J., S.M. Papile, and E.M. Freeman, *Rotogranulations and taste masking coatings for preparation of chewable pharmaceutical tablets*, in US 5260072 A. 1993.

18. Kumar, K.N. and D. Sandeep, *Formulating taste-masked orally disintegrating tablets of bitter drug ibuprofen*. International Research Journal of Pharmacy, 2013. **4**(11): p. 71-78.
19. Pearnchob, N., J. Siepmann, and R. Bodmeier, *Pharmaceutical applications of shellac: moisture-protective and taste-masking coatings and extended-release matrix tablets*. Drug development and industrial pharmacy, 2003. **29**(8): p. 925-38.
20. Kayumba, P.C., et al., *Quinine sulphate pellets for flexible pediatric drug dosing: formulation development and evaluation of taste-masking efficiency using the electronic tongue*. European Journal of Pharmaceutics and Biopharmaceutics, 2007. **66**(3): p. 460-5.
21. Cerea, M., et al., *A novel powder coating process for attaining taste masking and moisture protective films applied to tablets*. International journal of pharmaceutics, 2004. **279**(1-2): p. 127-39.
22. Sujitha, V., B. Sayani, and T. Geetha, *Preparation and evaluation of orally disintegrating taste masking tablet of paracetamol with Kollicoat Smart Seal 30 D*. Der Pharmacia Lettre, 2014. **6**(2): p. 82-89.
23. Shirai, Y., et al., *A novel fine granule system for masking bitter taste*. Biological and Pharmaceutical Bulletin, 1993. **16**(2): p. 172-7.
24. Nishiyama, T., T. Ogata, and T. Ozeki, *Preparation of bitter taste-masking granules of lafutidine for orally disintegrating tablets using water-insoluble/soluble polymer combinations*. Journal of Drug Delivery Science and Technology, 2016. **32**, Part A: p. 38-42.
25. Yu, D. and E. Roche, *Taste masked pharmaceutical liquid formulations*, in US6586012. 2003.
26. Sugao, H., et al., *Taste masking of bitter drug powder without loss of bioavailability by heat treatment of wax-coated microparticles*. Journal of Pharmaceutical Science, 1998. **87**(1): p. 96-100.
27. Al-Omran, M.F., et al., *Taste masking of diclofenac sodium using microencapsulation*. Journal of Microencapsulation, 2002. **19**(1): p. 45-52.
28. Ueda, M., et al., *Preparation of microcapsules masking the bitter taste of enoxacin by using one continuous process technique of agglomeration and microencapsulation*. Journal of Microencapsulation, 1993. **10**(4): p. 461-73.
29. Pai, R. and K. Kohli, *Extended release matrix pellets: preparation and compression into disintegrating tablet*. International Journal of Drug Delivery; Vol 3, No 2 (2011): International Journal Of Drug Delivery, 2011.
30. Albertini, B., et al., *Characterization and taste-masking evaluation of acetaminophen granules: comparison between different preparation methods in a high-shear mixer*. European Journal of Pharmaceutical Sciences, 2004. **21**(2-3): p. 295-303.
31. Mukherji, G., et al., *Taste masked oral compositions*, in WO 2001035930 A1. 2003.
32. Janczyk, M., et al., *Electronic tongue for the detection of taste-masking microencapsulation of active pharmaceutical substances*. Bioelectrochemistry, 2010. **80**(1): p. 94-8.
33. Xu, J., L.L. Bovet, and K. Zhao, *Taste masking microspheres for orally disintegrating tablets*. International journal of pharmaceutics, 2008. **359**(1-2): p. 63-9.

34. Yajima, T., et al., *Particle Design for Taste-Masking Using a Spray-Congeaing Technique*. Chemical & Pharmaceutical Bulletin, 1996. **44**(1): p. 187-191.
35. Yajima, T., N. Umeki, and S. Itai, *Optimum spray congealing conditions for masking the bitter taste of clarithromycin in wax matrix*. Chemical & Pharmaceutical Bulletin (Tokyo), 1999. **47**(2): p. 220-5.
36. Gryczke, A., et al., *Development and evaluation of orally disintegrating tablets (ODTs) containing Ibuprofen granules prepared by hot melt extrusion*. Colloids and Surfaces B: Biointerfaces, 2011. **86**(2): p. 275-84.
37. Maniruzzaman, M., et al., *Taste masking of paracetamol by hot-melt extrusion: an in vitro and in vivo evaluation*. European Journal of Pharmaceutics and Biopharmaceutics, 2012. **80**(2): p. 433-42.
38. Ishikawa, T., et al., *Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter-taste-masked granules by the compression method*. Chemical & Pharmaceutical Bulletin (Tokyo), 1999. **47**(10): p. 1451-4.
39. Shishu, A. Bhatti, and T. Singh, *Preparation of tablets rapidly disintegrating in saliva containing bitter taste-masked granules by compression method*. Indian Journal of Pharmaceutical Sciences, 2007. **9**(1): p. 80-84.
40. Witzleb, R., et al., *Solid lipid extrusion with small die diameters--electrostatic charging, taste masking and continuous production*. European Journal of Pharmaceutics and Biopharmaceutics, 2011. **77**(1): p. 170-7.
41. Madgulkar, A.R., M.R. Bhalekar, and R.R. Padalkar, *Formulation design and optimization of novel taste masked mouth-dissolving tablets of tramadol having adequate mechanical strength*. AAPS PharmSciTech, 2009. **10**(2): p. 574-81.
42. Puttewar, T.Y., et al., *Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin*. Journal of King Saud University - Science, 2010. **22**(4): p. 229-240.
43. Szejtli, J. and L. Szente, *Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins*. European Journal of Pharmaceutics and Biopharmaceutics, 2005. **61**(3): p. 115-25.
44. Freudenberg, K.D., F.D. Cramer, and H.D. Plieninger, *Verfahren zur Herstellung von Einschlussverbindungen physiologisch wirksamer organischer Verbindungen*. 1953, DE 000000895769 B.
45. Carlsson, T. and S.B. Andersson, *Smoking substitute*, in WO1991009599 A1. 1991.
46. Patel, A.R. and P.R. Vavia, *Preparation and Evaluation of Taste Masked Famotidine Formulation Using Drug/ β -cyclodextrin/Polymer Ternary Complexation Approach*. AAPS PharmSciTech, 2008. **9**(2): p. 544-550.
47. Greene, T.A., et al., *Probenecid inhibits the human bitter taste receptor TAS2R16 and suppresses bitter perception of salicin*. PLoS One, 2011. **6**(5): p. e20123.
48. Katsuragi, Y., et al., *Selective inhibition of bitter taste of various drugs by lipoprotein*. Pharmaceutical Research, 1995. **12**(5): p. 658-62.
49. Slack, J.P., et al., *Modulation of bitter taste perception by a small molecule hTAS2R antagonist*. Current biology : CB, 2010. **20**(12): p. 1104-9.

50. Ishikawa, T., et al., *Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M series) and low substituted-hydroxypropylcellulose or spherical sugar granules by direct compression method*. Chemical & Pharmaceutical Bulletin (Tokyo) 2001. **49**(2): p. 134-9.
51. Siebert, J.M., et al., *Orally disintegrable tablet forming a viscous slurry*. 2000, WO 2000009090 A1.
52. Bi, Y.X., et al., *Evaluation of rapidly disintegrating tablets prepared by a direct compression method*. Drug development and industrial pharmacy, 1999. **25**(5): p. 571-81.
53. Anand, V., et al., *The latest trends in the taste assessment of pharmaceuticals*. Drug Discovery Today, 2007. **12**(5-6): p. 257-65.
54. Anand, V., et al., *Taste assessment trials for sensory analysis of oral pharmaceutical products*. Pakistan Journal of Pharmaceutical Sciences, 2008. **21**(4): p. 438-50.
55. Gittings, S., et al., *Dissolution methodology for taste masked oral dosage forms*. Journal of Controlled Release, 2014. **173**: p. 32-42.
56. Ishizaka, T., et al., *Bitterness Evaluation of Medicines for Pediatric Use by a Taste Sensor*. Chemical and Pharmaceutical Bulletin, 2004. **52**(8): p. 943-948.
57. Green, B.G., et al., *Evaluating the 'Labeled Magnitude Scale' for measuring sensations of taste and smell*. Chem Senses, 1996. **21**(3): p. 323-34.
58. Green, B.G., G.S. Shaffer, and M.M. Gilmore, *Derivation and evaluation of a semantic scale of oral sensation magnitude with apparent ratio properties*. Chemical Senses, 1993. **18**(6): p. 683-702.
59. Contreras, R.J., C.A. Carson, and C.E. Pierce, *A novel psychophysical procedure for bitter taste assessment in rats*. Chemical Senses, 1995. **20**(3): p. 305-12.
60. Boughter, J.D., Jr., et al., *A brief-access test for bitter taste in mice*. Chemical Senses, 2002. **27**(2): p. 133-42.
61. Scalera, G., *Acid taste thresholds assessed by conditioned taste aversion and two-bottle preference in rats*. Physiol Behav, 2004. **82**(2-3): p. 411-23.
62. Shrotriya, S.N., et al., *Taste Masking of Tramadol Hydrochloride by Polymer Carrier System and Formulation of Rapidly Disintegrating Tablets using Factorial Design*. Indian Journal of Pharmaceutical Education and Research, 2013. **47**(1): p. 34-40.
63. Sona, P.S. and C. Muthulingam, *Formulation and Evaluation of Taste Masked Orally Disintegrating Tablets of Diclofenac Sodium*. International Journal of PharmTech Research, 2011. **3**(2): p. 819-826.
64. Sharma, G., et al., *Taste masking of Promethazine Hydrochloride using Eudragit E100 via solid dispersion technique to develop fast disintegrating tablets*. Der Pharmacia Lettre, 2010. **2**(3): p. 83-94.
65. Bhalekar, M.R., et al., *Comparative evaluation of taste masking methods of ondansetron HCl*. World Journal of Pharmacy and Pharmaceutical Sciences, 2014. **3**(8): p. 982-995.
66. Haware, R.V., et al., *Development of a Melting Tablet Containing Promethazine HCl Against Motion Sickness*. AAPS PharmSciTech, 2008. **9**(3): p. 1006-1015.
67. Aps, J.K. and L.C. Martens, *Review: The physiology of saliva and transfer of drugs into saliva*. Forensic Science International, 2005. **150**(2-3): p. 119-31.

68. Guhmann, M., et al., *Development of oral taste masked diclofenac formulations using a taste sensing system*. International Journal of Pharmaceutics, 2012. **438**(1–2): p. 81-90.
69. Yajima, T., et al., *Method of evaluation of the bitterness of clarithromycin dry syrup*. Chemical & Pharmaceutical Bulletin (Tokyo), 2002. **50**(2): p. 147-52.
70. Hoang Thi, T.H., et al., *Development and evaluation of taste-masked drug for paediatric medicines – Application to acetaminophen*. International Journal of Pharmaceutics, 2012. **434**(1–2): p. 235-242.
71. Woertz, K., et al., *Taste sensing systems (electronic tongues) for pharmaceutical applications*. International journal of pharmaceutics, 2011. **417**(1-2): p. 256-71.
72. Woertz, K., et al., *Rational development of taste masked oral liquids guided by an electronic tongue*. International journal of pharmaceutics, 2010. **400**(1-2): p. 114-23.
73. Fu, Y., et al., *Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies*. Critical Reviews™ in Therapeutic Drug Carrier Systems, 2004. **21**(6): p. 433-475.
74. *Guidance for Industry: Orally Disintegrating Tablets* 2008 [cited 02.04.; Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf>].
75. *Zerfallszeit von Tabletten und Kapseln*, in *Europäisches Arzneibuch*. 2014, Deutscher Apotheker Verlag: Stuttgart. p. 397-399.
76. Brniak, W., R. Jachowicz, and P. Pelka, *The practical approach to the evaluation of methods used to determine the disintegration time of orally disintegrating tablets (ODTs)*. Saudi Pharmaceutical Journal, 2015. **23**(4): p. 437-443.
77. Andersen, O., et al., *Problems when swallowing tablets. A questionnaire study from general practice*. Tidsskrift for den Norske laegeforening, 1995. **115**(8): p. 947-9.
78. Nogueira, D. and E. Reis, *Swallowing disorders in nursing home residents: how can the problem be explained?* Clinical Interventions in Aging, 2013. **8**: p. 221-227.
79. Seager, H., *Drug-delivery products and the Zydis fast-dissolving dosage form*. The Journal of Pharmacy and Pharmacology, 1998. **50**(4): p. 375-82.
80. Okuda, Y., et al., *A new formulation for orally disintegrating tablets using a suspension spray-coating method*. International journal of pharmaceutics, 2009. **382**(1-2): p. 80-7.
81. Fu, Y., S.H. Jeong, and K. Park, *Fast-melting tablets based on highly plastic granules*. Journal of Controlled Release, 2005. **109**(1–3): p. 203-210.
82. Mishra, D.N., et al., *Spray dried excipient base: a novel technique for the formulation of orally disintegrating tablets*. Chemical & Pharmaceutical Bulletin (Tokyo), 2006. **54**(1): p. 99-102.
83. Alanazi, F.K., *Evaluation of spray and freeze dried excipient bases containing disintegration accelerators for the formulation of metoclopramide orally disintegrating tablets*. Saudi Pharmaceutical Journal, 2007. **15**(2).
84. Misra, T.K., et al., *Fast-dissolving comestible units formed under high-speed/high-pressure conditions*. 1999, WO 1999008658 A1.

-
85. Stoltenberg, I. and J. Breitzkreutz, *Orally disintegrating mini-tablets (ODMTs)--a novel solid oral dosage form for paediatric use*. European Journal of Pharmaceutics and Biopharmaceutics, 2011. **78**(3): p. 462-9.
 86. Quadir, A. and K. Kolter. *A Comparative Study of Current Superdisintegrants*. 2006 [13.04.2016]; Available from: <http://www.pharmtech.com/comparative-study-current-superdisintegrants>.
 87. Fini, A., et al., *Fast dispersible/slow releasing ibuprofen tablets*. European Journal of Pharmaceutics and Biopharmaceutics, 2008. **69**(1): p. 335-341.
 88. Nagendra, K., et al., *Fast dispersible/slow releasing ibuprofen tablets*. International Journal of PharmTech Research, 2009. **1**(4): p. 1585-1588.
 89. Wehling, F., S. Schuehle, and N. Madamala, *Effervescent dosage form with microparticles*. 1993, US 5178878 A.
 90. Amborn, J. and V. Tiger, *Apparatus for handling and packaging friable tablets*. 2001, WO1999046168A1.
 91. Khankari, R.K., et al., *Rapidly dissolving robust dosage form*. 1998, WO 1998046215 A1.
 92. Mizumoto, T., et al., *Tablets quickly disintegrating in the oral cavity and process for producing the same*. 1999, WO 1999047124 A1.
 93. Myers, G.L., G.E. Battist, and R.C. Fuisz, *Process and apparatus for making rapidly dissolving dosage units and product therefrom*. 1998, US 5851553 A.
 94. Okada, M., et al., *Preparations solides rapidement solubles*. 1999, WO 1999018936 A1.
 95. Humbert-Droz, P., M. Seidel, and R. Martani, *Fast disintegrating oral dosage form*. 1997, WO 1997038679 A2.
 96. Nakamichi, K., S. Izumi, and H. Yasuura, *Fast soluble tablet*. 1993, WO 1993015724 A1.
 97. Makino, T., M. Yamada, and J. Kikuta, *Fast dissolving tablet and its production*. 1996, US 5501861 A.
 98. Oshima, T., et al., *Formation mechanism of wet-compressed rapidly disintegrating tablets containing a poorly water-soluble model drug*. Journal of Drug Delivery Science and Technology, 2006. **16**(3): p. 211-215.
 99. Bi, Y., Y. Yonezawa, and H. Sunada, *Rapidly disintegrating tablets prepared by the wet compression method: mechanism and optimization*. Journal of Pharmaceutical Science, 1999. **88**(10): p. 1004-10.
 100. Rawas-Qalaji, M.M., F.E. Simons, and K.J. Simons, *Fast-disintegrating sublingual tablets: effect of epinephrine load on tablet characteristics*. AAPS PharmSciTech, 2006. **7**(2): p. E41.
 101. Hobbs, D., et al., *An in vitro analysis of disintegration times of different formulations of olanzapine orodispersible tablet: a preliminary report*. Drugs in R&D, 2013. **13**(4): p. 281-8.
 102. Wu, S.H., et al., *An Alternative to the USP Disintegration Test for Orally Disintegrating Tablets*. Pharmaceutical Technology. **32**(8).

103. Bi, Y., et al., *Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity*. Chemical & Pharmaceutical Bulletin, 1996. **44**(11): p. 2121-7.
104. Segado, F.J., *Orally disintegrating tablets and process for obtaining them*, in WO2003103629 A1. 2003.
105. Kakutani, R., H. Muro, and T. Makino, *Development of a new disintegration method for orally disintegrating tablets*. Chemical & Pharmaceutical Bulletin (Tokyo), 2010. **58**(7): p. 885-90.
106. Morita, Y., et al., *Evaluation of the disintegration time of rapidly disintegrating tablets via a novel method utilizing a CCD camera*. Chemical & Pharmaceutical Bulletin (Tokyo), 2002. **50**(9): p. 1181-6.
107. Ohta, M., et al., *Intrabuccally rapidly disintegrating tablet*. 2001, WO1997047287A1.
108. Narazaki, R., et al., *A new method for disintegration studies of rapid disintegrating tablet*. Chemical & Pharmaceutical Bulletin (Tokyo), 2004. **52**(6): p. 704-7.
109. Harada, T., et al., *Evaluation of the disintegration properties of commercial famotidine 20 mg orally disintegrating tablets using a simple new test and human sensory test*. Chemical & Pharmaceutical Bulletin (Tokyo), 2006. **54**(8): p. 1072-5.
110. El-Arini, S.K. and S.D. Clas, *Evaluation of disintegration testing of different fast dissolving tablets using the texture analyzer*. Pharmaceutical Development and Technology, 2002. **7**(3): p. 361-71.
111. Abdelbary, G., et al., *Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration*. International Journal of Pharmaceutics, 2005. **292**(1–2): p. 29-41.
112. Szakonyi, G. and R. Zelkó, *Prediction of oral disintegration time of fast disintegrating tablets using texture analyzer and computational optimization*. International Journal of Pharmaceutics, 2013. **448**(2): p. 346-353.
113. Voigt, R., *Pharmazteutische Technologie*. 10 ed. 2006, Stuttgart, Germany: Deutscher Apotheker Verlag.
114. *Coating-Verfahren* 2016 [cited 2016 06.04.]; Available from: <http://www.glatt.com/de/verfahren/coating/>.
115. *Laboratory and pilot units_Mixing, Drying, Granulating, Coating*. 2016 [cited 2016 06.04.]; Available from: <https://boschpackagingpharmana.files.wordpress.com/2011/12/laboratory-and-pilot-units.pdf>.
116. Abdul, S., A.V. Chandewar, and S.B. Jaiswal, *A flexible technology for modified-release drugs: Multiple-unit pellet system (MUPS)*. Journal of Controlled Release, 2010. **147**(1): p. 2-16.
117. Beckert, T.E., K. Lehmann, and P.C. Schmidt, *Compression of enteric-coated pellets to disintegrating tablets*. International Journal of Pharmaceutics, 1996. **143**(1): p. 13-23.
118. Bansal, P., et al., *Effect of compression on the release properties of polymer coated niacin granules*. Journal of Controlled Release, 1993. **27**(2): p. 157-163.
119. Sarisuta, N. and K. Punpreuk, *In vitro properties of film-coated diltiazem hydrochloride pellets compressed into tablets*. Journal of Controlled Release, 1994. **31**(3): p. 215-222.
120. Dashevsky, A., K. Kolter, and R. Bodmeier, *Compression of pellets coated with various aqueous polymer dispersions*. International Journal of Pharmaceutics, 2004. **279**(1–2): p. 19-26.

121. Béchard, S.R. and J.C. Leroux, *Coated pelletized dosage form: Effect of compaction on drug release*. Drug Development and Industrial Pharmacy, 1992. **18**(18): p. 1927-1944.
122. Braun, M., *Einflussfaktoren bei der Tablettierung magensaftresistent überzogener Pellets auf Exzenter- und Rundlauftablettenpresse*, in *Mathematisch-Naturwissenschaftliche Fakultät*. 2003, Rheinische Friedrich-Wilhelms-Universität Bonn: Bonn.
123. Bodmeier, R. and O. Paeratakul, *Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms*. Pharmaceutical Research, 1994. **11**(6): p. 882-8.
124. Shimizu, T., et al., *Formulation study for lansoprazole fast-disintegrating tablet. I. Effect of compression on dissolution behavior*. Chemical & Pharmaceutical Bulletin (Tokyo), 2003. **51**(8): p. 942-7.
125. Chang, R.-K. and E.M. Rudnic, *The effect of various polymeric coating systems on the dissolution and tableting properties of potassium chloride microcapsules*. International Journal of Pharmaceutics, 1991. **70**(3): p. 261-270.
126. Klimkowsky, D. *Moisture Protection and Taste-Masking with Polymethacrylate Coatings*. [cited 2016 06.04.]; Available from: <http://www.phexcom.cn/uploadfiles/200899112713336.pdf>.
127. Bodmeier, R. and O. Paeratakul, *Dry and wet strengths of polymeric films prepared from an aqueous colloidal polymer dispersion, Eudragit RS30D*. International Journal of Pharmaceutics, 1993. **96**(1): p. 129-138.
128. Wagner, K.G., et al., *Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press*. European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50**(2): p. 285-92.
129. Tunon, A., et al., *Drug release from reservoir pellets compacted with some excipients of different physical properties*. European Journal of Pharmaceutics and Biopharmaceutics, 2003. **20**(4-5): p. 469-79.
130. Ragnarsson, G., et al., *Development of A New Controlled Release Metoprolol Product*. Drug Development and Industrial Pharmacy, 1987. **13**(9-11): p. 1495-1509.
131. Haslam, J.L., et al., *Tableting of controlled release multiparticulates, the effect of millisphere size and protective overcoating*. International Journal of Pharmaceutics, 1998. **173**(1-2): p. 233-242.
132. Kühl, P., *Tablettieren von Pellets: Komprimierbarkeit, Kompaktierbarkeit und Integrität in Kombination mit mikrokristalliner Cellulose und Polyethylenglykol*, in *Fachbereich Chemie*. 1999, Universität Hamburg: Hamburg.
133. Picker, K.M., *"Soft tableting": a new concept to tablet pressure-sensitive materials*. Pharmaceutical Development and Technology, 2004. **9**(1): p. 107-21.
134. Schmid, W. and K.M. Picker-Freyer, *Tableting and tablet properties of alginates: characterisation and potential for Soft Tableting*. European Journal of Pharmaceutics and Biopharmaceutics, 2009. **72**(1): p. 165-72.
135. Torrado, J.J. and L.L. Augsburg, *Effect of different excipients on the tableting of coated particles*. International Journal of Pharmaceutics, 1994. **106**(2): p. 149-155.
136. Lin, X., et al., *Development of potential novel cushioning agents for the compaction of coated multi-particulates by co-processing micronized lactose with polymers*. European Journal of Pharmaceutics and Biopharmaceutics, 2011. **79**(2): p. 406-15.

137. Yao, T., et al., *Tableting of Coated Particles. II. Influence of Particle Size of Pharmaceutical Additives on Protection of Coating Membrane from Mechanical Damage during Compression Process*. Chemical and Pharmaceutical Bulletin, 1998. **46**(5): p. 826-830.
138. Hosseini, A., M. Korber, and R. Bodmeier, *Direct compression of cushion-layered ethyl cellulose-coated extended release pellets into rapidly disintegrating tablets without changes in the release profile*. International journal of pharmaceutics, 2013. **457**(2): p. 503-9.
139. Altaf, S.A., S.W. Hoag, and J.W. Ayres, *Bead compacts. I. Effect of compression on maintenance of polymer coat integrity in multilayered bead formulations*. Drug development and industrial pharmacy, 1998. **24**(8): p. 737-46.
140. Altaf, S.A., S.W. Hoag, and J.W. Ayres, *Bead compacts. II. Evaluation of rapidly disintegrating nonsegregating compressed bead formulations*. Drug development and industrial pharmacy, 1999. **25**(5): p. 635-42.
141. Beckert, T.E., K. Lehmann, and P.C. Schmidt, *Compression of enteric-coated pellets to disintegrating tablets: uniformity of dosage units*. Powder Technology, 1998. **96**(3): p. 248-254.
142. *Eudragit E*. 2016 [cited 2016 06.04.]; Available from: <http://eudragit.evonik.com/product/eudragit/en/products-services/eudragit-products/protective-formulations/e-100/pages/default.aspx>.
143. *Kollicoat Smartseal 30D Technical Information*. 2011 [cited 2016 06.04.]; Available from: http://www.pharma-ingredients.basf.com/statements/technical%20informations/en/pharma%20solutions/03_101002e_kollicoat%20smartseal%2030%20d.pdf.
144. Gandhi, R., C. Issa, and R. Malik, *Coating composition for taste masking coating and methods for their application and use*, in WO 2004052345 A8. 2004.
145. Keast, R.S. and J. Roper, *A complex relationship among chemical concentration, detection threshold, and suprathreshold intensity of bitter compounds*. Chem Senses, 2007. **32**(3): p. 245-53.
146. *Arzneimittel-Kompendium Schweiz*. 2016 [cited 2016 06.04.]; Available from: <https://compendium.ch>.
147. Granberg, R.A. and A.C. Rasmuson, *Solubility of Paracetamol in Pure Solvents*. Journal of Chemical & Engineering Data, 1999. **44**(6): p. 1391-1395.
148. *Guidance for Industry - Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. 1997 [cited 2016 08.04.]; Available from: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070237.pdf>.
149. Kállai, N., et al., *Evaluation of Drug Release From Coated Pellets Based on Isomalt, Sugar, and Microcrystalline Cellulose Inert Cores*. AAPS PharmSciTech, 2010. **11**(1): p. 383-391.
150. *711 Dissolution*, in *United States Pharmacopoeia*. 2015, The United States Pharmacopoeial Convention: Rockville, USA. p. 486-496.
151. *Buffer solutions*, in *United States Pharmacopoeia*. 2015, The United States Pharmacopoeial Convention: Rockville, USA. p. 7206-7207.
152. Carnaby-Mann, G. and M. Crary, *Pill swallowing by adults with dysphagia*. Archives of Otolaryngology - Head & Neck Surgery, 2005. **131**(11): p. 970-5.

153. Brown, D., *Orally Disintegrating Tablets - Taste Over Speed Drug Development and Delivery*, 2003. **3**(6).
154. Bardow, A., et al., *The buffer capacity and buffer systems of human whole saliva measured without loss of CO₂*. *Archives of Oral Biology*, 2000. **45**(1): p. 1-12.
155. Sjoqvist, R., et al., *In vitro-in vivo evaluation of bacampicillin hydrochloride from microcapsules of water-insoluble and an acid-soluble polymer*. *Journal of Microencapsulation*, 1985. **2**(2): p. 123-36.
156. Poonpun, S., et al., *Mechanical and adhesive properties of cellulosic film coats containing polymeric additives*. *Pharmazie*, 2015. **70**(5): p. 300-5.
157. Kriangkrai, W., et al., *Magnesium Stearate as Anti-tacking Agent in Acrylic Polymer Films Intended for Gas-entrapped Floating Delivery System*. *Advanced Materials Research*, 2012. **506**: p. 497-500.
158. Felton, L.A., *Mechanisms of polymeric film formation*. *International Journal of Pharmaceutics*, 2013. **457**(2): p. 423-427.
159. Lin, S.Y., K.S. Chen, and L. Run-Chu, *Organic esters of plasticizers affecting the water absorption, adhesive property, glass transition temperature and plasticizer permanence of eudragit acrylic films*. *Journal of Controlled Release*, 2000. **68**(3): p. 343-50.
160. Lin, S.Y., C.J. Lee, and Y.Y. Lin, *The effect of plasticizers on compatibility, mechanical properties, and adhesion strength of drug-free Eudragit E films*. *Pharmaceutical Research*, 1991. **8**(9): p. 1137-43.
161. Obara, S. and J.W. McGinity, *Properties of free films prepared from aqueous polymers by a spraying technique*. 1994. **11**(11): p. 1562-7.
162. Rathore, G.S., et al., *Solubility Modulation of High Water Soluble Drugs for Osmotically Controlled Release Systems*. *International Journal of Pharmaceutical Sciences*, 2009. **1**(1): p. 21-27.
163. Zoubari, M.G., *Water-insoluble polymers as binders for controlled release matrix pellets and reservoir pellets*, in *Fachbereich Biologie, Chemie, Pharmazie*. 2015, Freie Universität Berlin: Berlin.
164. Lundqvist, Å.E.K., F. Podczeck, and J.M. Newton, *Influence of disintegrant type and proportion on the properties of tablets produced from mixtures of pellets*. *International Journal of Pharmaceutics*, 1997. **147**(1): p. 95-107.
165. Pan, X., et al., *Novel compaction techniques with pellet-containing granules*. *European Journal of Pharmaceutics and Biopharmaceutics*, 2010. **75**(3): p. 436-42.
166. Voegelé, J. *Solving Segregation Challenges in MUPS Production*. 2014 [cited 2016 17.01.]; Available from: <http://www.gea.com/de/de/stories/mups-production.jsp>.
167. Roy, S.B., S.K. Kulkarni, and H.M. Mamania, *Delayed release oral disintegrating pharmaceutical compositions of lansoprazole*. 2011, WO 2011138797 A2.
168. Sun, C.C., *A novel method for deriving true density of pharmaceutical solids including hydrates and water-containing powders*. *Journal of Pharmaceutical Science*, 2004. **93**(3): p. 646-53.
169. Shotton, E. and C.J. Lewis, *Some observations on the effect of lubrication on the crushing strength of tablets*. *Journal of Pharmacy and Pharmacology*, 1964. **16**(S1): p. 111T-120T.

-
170. Strickland, W.A., et al., *The physics of tablet compression IX. Fundamental aspects of tablet lubrication*. Journal of the American Pharmaceutical Association, 1956. **45**(1): p. 51-55.
171. De Boer, A.H., G.K. Bolhuis, and C.F. Lerk, *Bonding characteristics by scanning electron microscopy of powders mixed with magnesium stearate*. Powder Technology, 1978. **20**(1): p. 75-82.
172. *Avicel*. 2016 [cited 2016 02.04.]; Available from: <http://www.fmcbiopolymer.com/Pharmaceutical/Products/Avicelforsoliddoseforms.aspx>.
173. *Maize Starch*. 2016 [cited 2016 02.04.]; Available from: <http://www.roquette-pharma.com/maize-starch-filler-disintegration-diluent-tablets-capsules-powders>.
174. *Lactochem microfine*. 2016 [cited 2016 02.04.]; Available from: <http://www.dfepharma.com/en/excipients/lactose/micronised-lactose/lactochem-microfine.aspx>.
175. Liu, F.Y., et al., *Water soluble polymer-based rapidly dissolving tablets and production processes thereof*, in WO1999047126A1. 2002.
176. Saniocki, I., *New Insights into Tablet Sticking: Characterization and Quantification of Sticking to Punch Surfaces during Tablet Manufacture by Direct Compaction*, in *Fachbereich Chemie der Fakultät für Mathematik, Informatik und Naturwissenschaften* 2014, Universität Hamburg.
177. *Tabletten*, in *Europäisches Arzneibuch*. 2014, Deutscher Apotheker Verlag: Stuttgart. p. 1206.
178. Bühler, V. *Kollidon Polyvinylpyrrolidone excipients for the pharmaceutical industry*. 2008 [cited 2016 02.04.]; Available from: http://www.kollidon.com/Documents/ENP/Brochure/EN/G-EMPMD256_Kollidon_Polyvinylpyrrolidone_excipients_for_the_pharmaceutical_industry.pdf.

8 Curriculum vitae

The CV is not shown in the online version for reasons of data privacy protection.

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.