Formulation and evaluation of water-insoluble matrix drug delivery systems and modelling of drug release

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List of abbreviations

DC –	direct compression, directly compressed
EC –	ethyl cellulose
FDA –	U.S. Food ad Drug administration
GRAS –	generally recognized as safe
HME –	hot melt extrusion, hot melt extruded
HPC –	hydroxypropyl cellulose
HPMC –	hydroxypropyl methyl cellulose, hypromellose
IVIVC –	in vivo – in vitro correlation
MCC –	microcrystalline cellulose
PEG –	polyethylene glycol
PVAc –	polyvinyl acetate
PVP –	polyvinylpyrrolidone, povidone
SLS –	sodium lauryl sulphate
WG –	wet granulation, wet granulated

Introduction

Tablets

Tablets have been known as pharmaceutical dosage forms since the middle of the 19th century (Friedrich 2000, www.deutsches-apotheken-museum.de). With the start of mass production they became the dosage form of choice, due to their favorable handling properties and cost effectiveness. The application of single units, each containing a fixed dose of active material, confined the risk of over- or under-dosing associated with liquid formulations and increased patient compliance all over the world.

Still today, more than 50 % of all new drugs approved by the FDA are formulated as tablets. Modern tableting machines yielding over 1 million tablets/h make tablets a very economical dosage form and yet allow for memorable designing by the use of dies, flavors, tailored tablet shapes and printings.

Controlled release

Most of the marketed tablet formulations release the drug immediately after administration, but in the therapy of several diseases, like asthma or psychological affections, a controlled drug supply to the body is desired. It can be roughly distinguished between timed and sustained/extended release drug deliveries (Burger 1998), the latter forming one target of this work.

The build-up of new drug approvals of the FDA in the categories “new molecular entity” and “new formulation” of the last 5 years (01/2007-09/2012) is depicted in Fig. 1. It can be clearly seen that immediate release formulations still play a major role in the formulation of new molecular entities but also in approved reformulations (78 % and 33 %, respectively). Extended release formulations already make 5 % of all approvals of “new molecular entities”. After reformulation their proportion increases to 20 %.

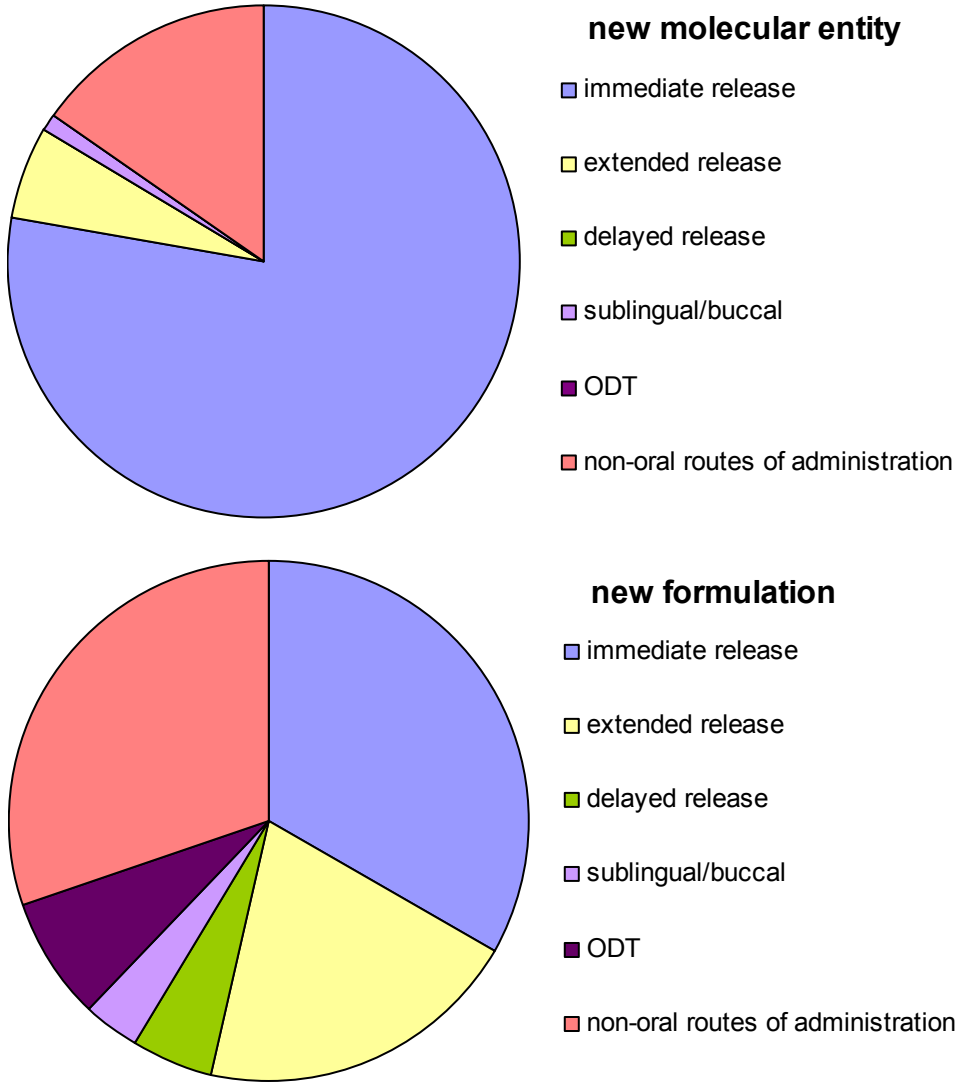

Fig. 1. Schematic representation of the constitution of the FDA approvals of the last 5 years for new molecular entities and new formulations.

Generally, two different approaches are used to achieve the desired extended drug release profile, i.e. coated systems and matrix systems.

Coated tablets

Coated tablets commonly consist of a drug containing tablet core and a release controlling barrier, usually applied by film or compression coating. Most coatings use functional polymers to form this barrier and thereby determine the drug release pattern (Table 1).

Table 1. Tablet application dependent on the polymer film's properties.

Polymer film properties		Example	Application
Erodible		HPMC	Sustained release
Soluble	pH-dependent (pH > 5)	Eudragit L, S	Delayed release (Enteric dosage forms)
Insolube	Brittle	Ethyl cellulose	Delayed release Repeated release
	Flexible	Kollicoat SR	Sustained release

According to the desired release profile, the coating polymer is selected. In case of soluble/erodible polymers, the coating prevents medium penetration to the core until it is dissolved or eroded, liberating the drug containing core (Maffione 1993). In case of insoluble polymers, medium penetration and drug diffusion through the coating are limited (Ozturk 1990), (Fig. 1).

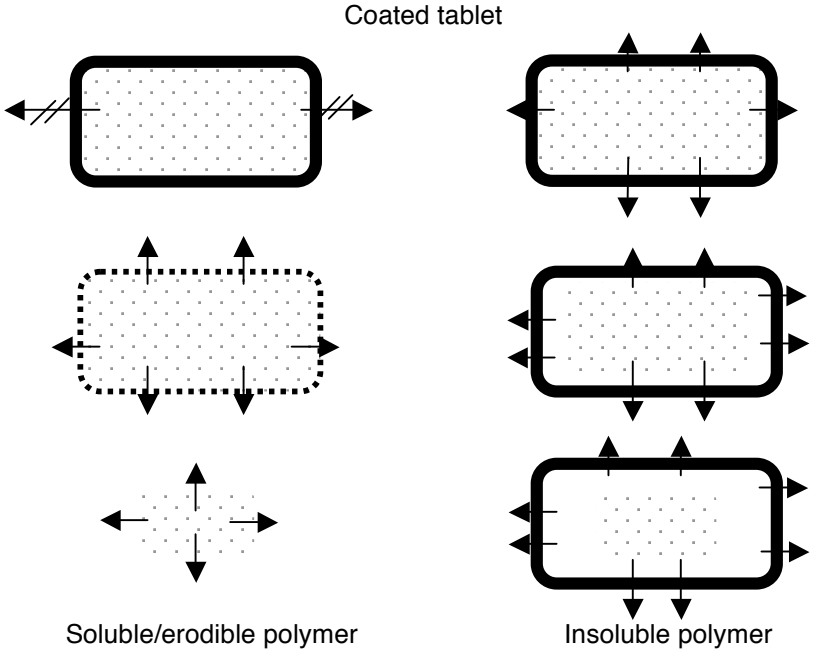

Fig. 1. Release behavior of coated tablets with soluble/erodible or insoluble polymers.

Matrix tablets

In contrast to reservoir tablets, matrix tablets, which are the main focus of this work, contain the drug embedded in a functional carrier.

Formulation and manufacturing of matrix tablets are well known and established processes resulting in highly reproducible drug release and in vitro-in vivo correlation (IVIVC) of drug release has been evaluated (e.g. Dalton 2001, Dutta 2005). Furthermore, the development of innovative functional excipients (entirely new substances as well as derivatives or co-processed existing materials) and evaluation of the drug delivery potential of these systems make matrix tablets an interesting field of research (Colombo, 2009).

According to the nature of the carrier material, lipidic and polymeric matrices can be distinguished.

In case of lipidic matrices waxes and lipids embed the active compounds and have been classified with regard to their interaction with aqueous media (Small 1968). These interactions govern the release mechanism of lipidic matrices being either diffusion or erosion controlled (Khan 2003, Pivette 2012). Drug release patterns from a few hours up to several days can be achieved according to the composition of the matrix and its preparation method (see Matrix preparation).

Table 2. List of common polymers for matrix preparation (examples).

Polymer properties		Example
Soluble/ Erodible	Swellable	Hydroxypropyl methyl cellulose, Sodium carboxymethylcellulose, Poly ethylene oxide Pectin, Alginate, Xanthan gum
	Non-swellable	Polyvinylpyrrolidone Hydroxypropyl cellulose
Insoluble	Non-swellable	Ethyl cellulose Cellulose acetate
	Swellable	Kollidon® SR Eudragit® RS

In case of polymeric carriers, the substances are further subdivided into groups considering the solubility and swelling characteristics of the carrier materials (water soluble/erodible - water insoluble, swellable - non-swellable polymers). A few examples are summarized in Table 2.

Generally, the dissolution medium penetrates the matrix tablets more or less hindered by the functional excipient that makes the carrier (Fig. 3). The tablets deliver the drug in a sustained fashion due to their barrier-free structure. Hence, delayed release profiles can only be achieved by coating of matrix tablets.

In case of swellable soluble/erodible polymers the dimensions of the swollen matrix exceed the dimensions of the dry tablet. The medium causes the polymer to transform to the rubbery state and form a gel preventing fast progress of the wetting front. Two more fronts can be identified: the diffusion front, where the particles of the active compound are dissolved and ready for diffusion through the gel layer and the erosion front, where a critical concentration of the polymer is underrun leading to chain disentanglement and the erosion of the polymer gel (Colombo 2000, Escudero 2012, Li 2005). Soluble drugs are released via diffusion through the gel, whereas in case of insoluble drugs, the diffusion front falls together with the erosion front and the drug is liberated via erosion of the surrounding matrix structure (Maderuelo 2011).

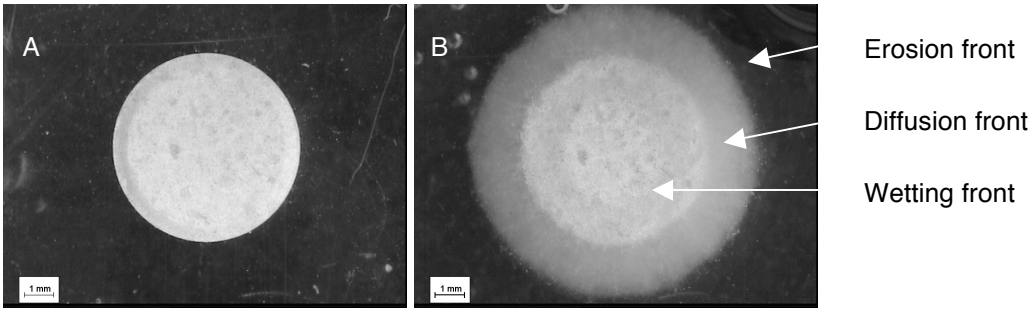

Fig. 3. Macroscopic pictures of Alginate matrices in A) dry state and B) after 60 min of incubation with dissolution media at 37 °C.

On the other hand, for non-swellable soluble/erodible polymers the erosion front falls together with the wetting front and the drug particles are solely released by erosion of the tablet surface. Here, the tablet dimensions decrease over time (Fig. 4).

Generally, the gel strength is the key parameter affecting drug release and can be influenced for example by the polymer itself, its molecular weight and content, the substitution type, the interactions with the dissolution medium, the drug and other excipients (Maderuelo 2011).

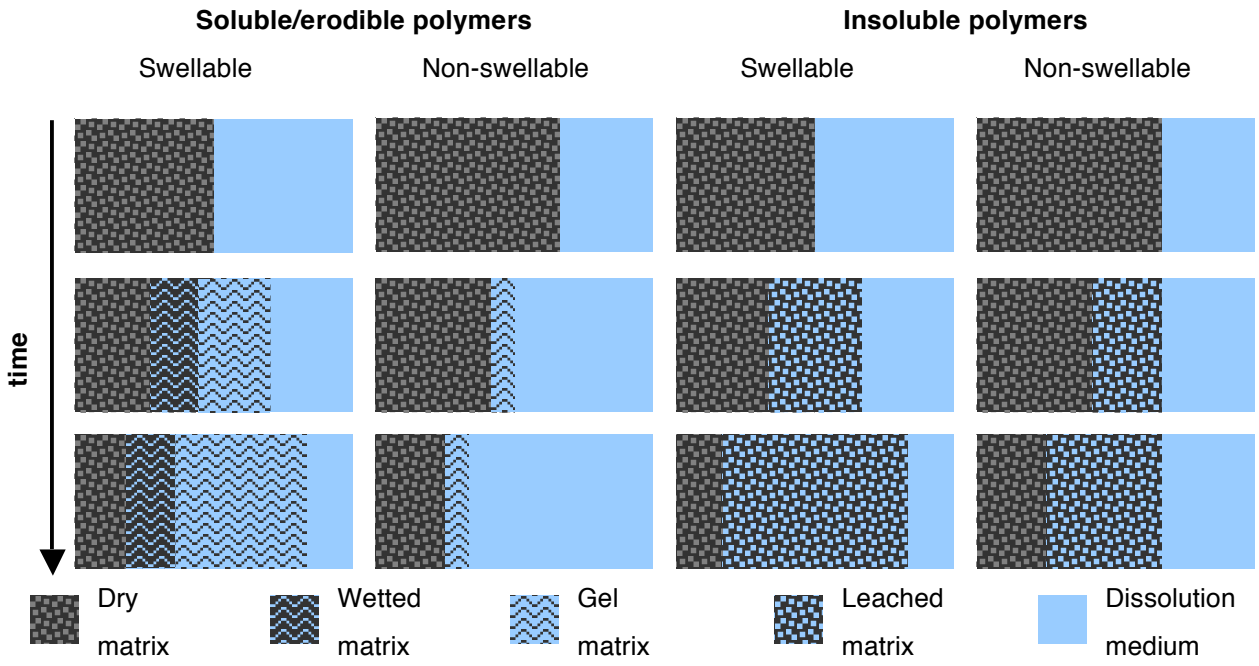

Fig. 4. Schematic representation of fronts' movement in different types of matrices.

In case of insoluble polymers, the matrices ideally stay intact during drug release experiments. The medium penetrates the tablet dissolving the drug on its way, so that the molecules can diffuse through the polymer network. Again a wetting front and a dissolution front might be distinguishable depending on the solubility of the incorporated drug. The matrix dimensions will increase with time in case of swellable polymers, while they stay the same for non-swellable polymers.

This work focuses on insoluble matrix tablets. Therefore, some polymers belonging to this group are discussed in detail within the formulation section of the introduction (see Excipients - Polymers).

Formulation

The formulation of matrix tablets is rather straightforward. Only an active ingredient and a matrix carrier are necessary to form a matrix drug delivery system, but the preparation process often requests other excipients to enable manufacturing.

Marketed tablet formulations usually contain a variety of different ingredients. Besides active compound and release retarding excipient, filler, binder, lubricant, glidant and die can be distinguished. Table 3 lists the inactive ingredients in exemplary marketed matrix formulations.

Table 3. List of inactive ingredients of marketed extended release products.

Function	Mirapex® ER	Jenloga®	Intuniv®
Binder, Matrix polymer	Hypromellose, Carbomer homopolymer	Hypromellose	Hypromellose, Methacrylic acid copolymer
Filler, Binder	Corn starch	Pregelatinized starch, Lactose monohydrate	Lactose, Microcrystalline cellulose
Binder	-	-	Povidone
Disintegrant	-	-	Crospovidone
Emulsifying agent	-	Sodium lauryl sulphate	-
pH modifier	-	-	Fumaric acid
Glidant	Colloidal silicon dioxide	Colloidal silicon dioxide	-
Lubricant	Magnesium stearate	Magnesium stearate	Glyceryl behenate

Excipients – Polymers

Ethyl cellulose

Ethyl cellulose (EC), a cellulose derivative substituted with ethoxy groups, is an insoluble, non-swellable polymer and by itself impermeable to water. It is GRAS listed and monographs exist in the European, Japanese and United States Pharmacopoeia.

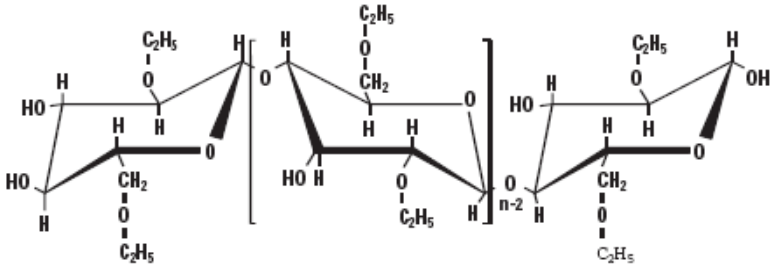

Fig. 5. Chemical structure of ethyl cellulose.

It is frequently used as coating material or matrix polymer for sustained release because it forms a water penetration barrier (Ethocel® technical handbook).

Ethyl cellulose compacts were formed by plastic deformation of the particles (Katikaneni 1995a). The degree of elasticity was higher for larger particles resulting in weaker tablets. The viscosity grade also affected tablet hardness (Upadrashta 1994) - harder tablets were obtained with EC 10 cP than EC 100 cP, which was explained by differences in the polymers' degree of order.

Drug is released by diffusion through pores and cracks in the polymer network, which initially exist or form due to dissolution of soluble compounds. Hence, with increasing solubility of the drug its release was increased (Neau 1999).

The polymer content and particle size have also been identified as important formulation parameters affecting drug release from controlled release EC matrix tablets. Prolonged release patterns were obtained with increasing polymer levels and decreasing particle sizes (Katikaneni 1995b, Barra 2000, Khan 2007). The viscosity grade only slightly affected drug release (Upadrashta 1994).

Addition of hydrophilic polymers to ethyl cellulose matrices resulted in modified drug release, dependent on the amount of additive and its viscosity grade. When a high viscosity grade of HPMC (HPMC K4M) was used, drug release was decreased with increasing additive content (Dabbagh 1996), whereas, drug release increased for a low viscosity grade HPMC (HPMC E50) with increasing amounts of HPMC acting as channelling agent (Khan 2007). Ethyl cellulose matrices strongly responded to the preparation method. Fastest drug releases were obtained for directly compressed

matrices, followed by wet granulation and hot melt extrusion (Crowley 2004, Khan 2007) (see Matrix preparation).

Eudragit® RS

Eudragit® RS, a methacrylate copolymer with quaternary ammonium groups, is permeable and swellable (Eudragit® application guidelines). Monographs exist in the European, Japanese and United States Pharmacopoeia.

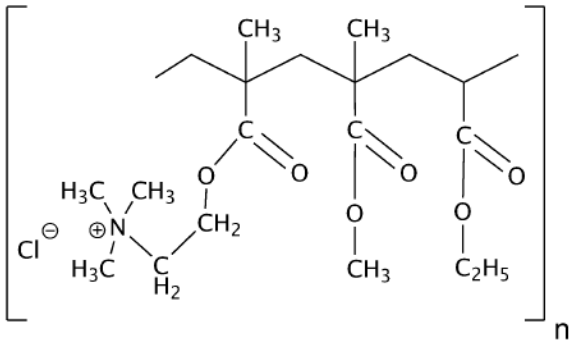

Fig. 6 Chemical structure of Eudragit® RS.

Similar to ethyl cellulose matrices, the drug is mainly released by diffusion through water filled pores in the tablet but diffusion through the hydrophilic regions of the polymer is also possible. Eudragit® RS has been used as matrix former in direct compression and wet granulation. The polymer as well as the drug particle size affect the drug release, and a linear relationship between drug percolation threshold and mean particle size has been detected (Caraballo 1996, Millán 1998). The percolation threshold increased with increasing drug/polymer particle size ratios.

Tablet preparation using an ultrasound-assisted press resulted in decreased drug release due to fusion of the polymer particles during compaction. A low percolation threshold has been determined for these matrices (13.4 - 20.2 % v/v, Caraballo 2000). Fused matrices can also be obtained by hot melt extrusion of drug/polymer blends and exhibit strongly decreased drug release profiles (Kidokoro 2001).

Another method to promote fusion of the polymer particles and thereby decreasing the drug release rate is thermal treatment of the tablets above the glass transition temperature. Eudragit RS matrices prepared by direct compression were sensitive to such treatments (Azarmi 2002), whereas hot melt extruded tablets exhibited no further decrease in drug release (Kidokoro 2001).

Kollidon® SR

Kollidon® SR is the most permeable polymer within this work. It is a co-processed and spray-dried mixture of approximately 80 % polyvinyl acetate (PVAc) and 19 % polyvinylpyrrolidone (PVP), furthermore, 0.8 % sodium lauryl sulphate (SLS), and 0.6 % silica as stabilizers. No monographs exist for the co-processed material yet, but the constituents PVAc and PVP can be found in the European Pharmacopoeia and PVP also appears in the Japanese and United States Pharmacopoeia.

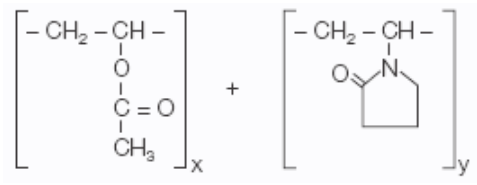

Fig. 7 Chemical structure of Kollidon® SR (ratio x/y = 8/2) (Bühler 2008).

The polymer shows better compactibility than microcrystalline cellulose, good flow and compression due to plastic deformation (Hauschild 2006), making it a favorable excipient for direct compression of matrix tablets. Utilizing this property, ultra hard tablets with tensile strengths of at least 4 MPa were developed to reduce the risk of drug abuse in the therapy of opiate addicts and severe pain (Cailly-Dufestel 2009).

In contact with dissolution fluids, the soluble PVP will dissolve and leach out increasing the porosity of the matrix (Shao 2001). At the same time the glass transition temperature of the insoluble PVAc is further reduced at elevated humidities (Hauschild 2006) resulting in a rubbery mass forming a swelling matrix during dissolution. Swelling kinetics follow an exponential relationship described by Therien-Aubin in 2003. Maximum tablet diameter and height increases of approximately 10 % and 30 %, respectively, have been determined (Strübing 2008, Siepmann 2010).

Various researchers described controlled release matrix tablets. The minimum content of Kollidon® SR to form a non-disintegrating matrix tablet was evaluated using different fillers (Agnese 2010). The concentration was filler type as well as compression force dependent, ranging from 30 to 75 % polymer. The manufacturer's application guidelines suggest a content to achieve sustained release dependent on the solubility of the active ingredient: for low solubility drugs a concentration of 15 - 25 % is recommended, whereas 25 - 40 % and 40 - 55 % are necessary for sparingly soluble and freely soluble APIs, respectively (Bühler 2008). Hence, eroding as well as non-eroding matrices are proposed as drug delivery systems, implying a reproducible erosion of the matrix.

The working group of Siepmann showed in 2010 that the drug release from Kollidon® SR matrices is governed majorly by diffusion through the matrix. It can be described by a solution of Fick's second

law of diffusion (Vergnaud 1993, see Mathematical modelling). This model allowed for drug release prediction for matrices of different dimensions, thereby facilitating the formulation step in product development.

Drug release was independent of the dissolution medium (Kranz 2005), but dependent on drug solubility (Reza 2003). With increasing solubility the drug release increased. Therefore, addition of poorly soluble acids or bases affected the release of drugs whose solubility depends on pH due to changes in the microenvironment of the matrices (Kranz 2005, Riis 2007). The drug particle size did not affect drug release (Kranz 2006).

Furthermore, the polymer content played an important role in drug release modification. The retardation was stronger at higher polymer levels due to lower porosity of the matrices (Shao 2001, Draganoiu 2003, Siepmann 2010). The addition of fillers to matrices containing ≤ 47 % Kollidon® SR resulted in excipient properties dependent drug release (Shao 2001, Kranz 2005, Riis 2007).

Moreover, the preparation method had a great impact on drug release (Kranz 2006). Wet granulated matrices prepared with water as granulation fluid exhibited faster release profiles compared to direct compression. This could be explained by increased porosity of the wet granulated tablets due to cluster formation of the soluble PVP during granulation process. Consequently, the manufacturer's guidelines recommend the application of Kollidon® SR in the extra-granular phase for wet granulated preparations. Another technique used to prepare Kollidon® SR matrices was hot melt extrusion, where processing temperature, drug loading and plasticizer content were the main formulation parameters (Özgüney 2009).

Kollidon® SR could also be used to develop floating matrix tablets (Strübing 2008). At initial porosities of 25 - 35 % matrix tablets containing propranolol hydrochloride maintained buoyancy over 24 h.

Matrix tablets were further tested regarding stability against thermal treatment. The effects on drug release were dependent on treatment conditions, duration and polymer content (Shao 2001, Engineer 2004, Kranz 2005). Slight decreases of release profiles were seen for storage at 40 °C/75 % relative humidity due to polymer relaxation.

Extensive research has been undertaken in the topic of insoluble matrix tablets, but parameters like porosity or matrix dimensions have been neglected in most studies, reducing the comparability and generality of the results. Furthermore, the application of percolation theory would allow deeper insight into mechanisms of matrix formation and drug release.

Drugs

The drugs utilized as active ingredients in the formulations of this work were selected for their physicochemical properties only. They serve as model compounds and do not imply a special therapeutic intention.

They can be divided into non-ionic and basic materials, and ordered according to their solubility in aqueous media.

Table 4. Overview: model drugs.

Name	Molecular weight, g/mol	Solubility, mg/ml
Non-ionic drugs		
Diprophylline	254.2	≈ 200
Pentoxyfylline	278.3	≈ 75
Caffeine	194.2	≈ 25
Theophylline	180.2	≈ 12
Carbamazepine	236.3	≈ 0.1
Basic drugs		
Metoprolol tartrate	684.8	≈ 1000
Propranolol hydrochloride	295.8	≈ 250

Excipients-Filler/Binder

The most commonly used excipients are fillers and binders. They are added to give the tablet its mass and strength. Generally, fillers used for direct compression exhibit the required binding capacity, so that the excipient amount can be kept low (Bolhuis, Chowhan 1996). As already discussed above, the admixing of fillers to matrix tablet formulations has an effect on the release pattern (e.g. Shao 2001, Kranz 2005). Especially for low dose drugs the addition of fillers to the powder blend of matrix tablets is necessary to obtain the desired release profile. This effect was attributed to a polymer content reduction. Hence, higher filler amounts in the formulation resulted in accelerated drug release (e.g. Draganoiu 2003, Caraballo 1994).

The discussion of the effect of filler type on drug release is more controversial. Kranz et al. found considerable differences between matrices containing different types of fillers (Kranz 2005), whereas Ford et al. described type independent drug release below a critical concentration (Ford 1987). Above this concentration the properties of the filler became evident. Hence, percolation theory should be applied to better understand these phenomena (see Percolation theory).

The excipients utilized as filler in the formulations of this work have also been chosen for their physicochemical properties. They serve as model compounds and display the most commonly used materials in tablet preparation by direct compression.

They can be categorized into non-ionic and ionic substances, and according to their behavior in aqueous media.

Table 5. Overview: excipients.

Brand name	Description	Properties
Non-ionic		
Avicel® PH102	Microcrystalline cellulose	Insoluble, Swellable
Flowlac®	Spray-dried lactose	Soluble
Methocel® E5	Low viscosity HPMC	Swellable, Soluble
Ionic		
e.g. DI-CAFOS	Dicalcium phosphate	Insoluble
-	Sodium chloride	Soluble

Excipients-Lubricant/Glidant

Almost every tablet formulation contains lubricants and glidants. Lubricants aid the compaction process by reducing die wall friction and facilitating tablet ejection (Bolhuis, Hölzer 1995). They prevent adhesion and sticking of the tablet material to the tooling (Moody 1981).

Usually magnesium stearate, stearic acid, sodium stearyl fumarate, glyceryl behenate, polyethyenglycol or talc is used as lubricant in tablet formulations (Wang 2010). A drawback in their use is the simultaneous reduction of tablet strength (Lerk 1977) limiting the lubricant content to concentrations of 0.5 – 2 %.

Glidants improve flowability of the powder blend, and thereby increase mass uniformity of the tablets. Most lubricants also act as glidants. Typically, colloidal silicon dioxide is added to powder blends due to its high surface area and moisture sorption potential. It has been shown to compensate the tablet strength reducing properties of magnesium stearate (Lerk 1977).

Matrix preparation

Compression

During tablet manufacturing different stages of compaction have to be passed (Nyström, Karehill 1996). At low applied forces particle rearrangement will occur until friction inhibits further densification. Increased forces then lead to deformation of the particles, which can be plastic, elastic or a combination of both, dependent on the material properties. In some cases deformation is followed by particle fracture and the newly formed particles run through the same steps with further increasing forces. During all stages inter-particular bonds are formed, causing cohesion of the particles and therefore tablet strength.

Bonding mechanisms can be subdivided into A) solid bridges that are formed due to melting, self-diffusion or recrystallization of particle material (they can be either of covalent or ionic nature); B) intermolecular forces that operate over some distance and comprise hydrogen bonds, van der Waals forces, or electrostatic forces; and C) mechanical interlocking, which is dependent on particle shape. To determine the dominant bonding mechanism sophisticated techniques like application and removal of lubricant films or compaction in liquids or vacuum has been used (Nyström, Karehill 1996).

Generally matrix compacts are characterized regarding their mass and content uniformity, their dimensions and strength. Furthermore, instrumented tabletting machines or compaction simulators are employed to give insight into the distribution of applied forces during compaction (e.g. Katikaneni 1995).

To investigate the heat of friction during tabletting, infrared imaging has been applied and revealed a compression force and lubricant concentration dependent increase in tablet temperature for a directly compressible powder mixture (Bechard 1992).

Direct compression

The most time and cost efficient way to produce tablets is direct compression of powder mixtures (Bolhuis, Chowhan 1996). Less labor, equipment, space and lower power consumption are necessary in production compared to other procedures (Fig. 8). For heat- and humidity-sensitive drugs it is usually the process of choice because unlike granulation and extrusion, no solvents or elevated temperatures are necessary (Jivraj 2000).

Prerequisites for this preparation technique are good flow and compactibility of the blends to allow a reproducible tablet quality. Directly compressible excipients have been developed to compensate poor flowability and compactibility of active substances (Table 6). Due to sophisticated or patented production techniques, these excipients are more expensive than the basic materials. Processes like spray-drying and particle coating are used to manufacture excipients for direct compression. It can be distinguished between single materials and combinations that bring together desired properties of the original substances (Kegel 2010).

Table 6. Directly compressible excipients.

Brand name	Substances	Manufacturer
Single materials		
Avicel® PH102	MCC	FMC BioPolymer, USA
Emcompress®	Calcium phosphate	J. Rettenmaier & Söhne GmbH + Co. KG, Germany
Flowlac®	Lactose	Molkerei Meggle Wasserburg GmbH & Co. KG, Germany
Material combinations		
Avicel® CE 15	MCC, guar gum	FMC BioPolymer, USA
Cellactose®	MCC, lactose	Molkerei Meggle Wasserburg GmbH & Co. KG, Germany
Ludipress®	Lactose, PVP, Crospovidone	BASF, Germany
Kollidon® SR	PVAc, PVP	BASF, Germany
Prosolv® SMCC	MCC, colloidal silicon dioxide	FMC BioPolymer, USA
StarLac®	Lactose, maize starch	Molkerei Meggle Wasserburg GmbH & Co. KG, Germany

Co-processing results in products that exhibit superior properties compared to simple physical mixtures due to enhanced interactions of the substances. The raw material is only changed physically, not chemically, which reduces the regulatory time and effort.

Furthermore, directly compressible drug preparations, like Rhodapap DCP™, exist. Spray drying seems to be the method of choice, because smooth spherical particles with good flow properties are obtained. Gonissen et al. evaluated the processibility of spray dried drug formulations with immediate release and achieved good results with loadings of approximately 70 % (Gonissen 2008).

However, for sustained release matrix tablets functional excipients need to be added in effective concentrations (see Percolation theory). This should be kept in mind when studying the literature about directly compressed matrix systems (examples summarized in Table 7).

Subsequently the limited loading of active compounds forms a major drawback of direct compression. At high drug loadings matrix integrity can be an issue but also low loadings can be problematic due to inhomogeneity of the matrices.

Another disadvantage of direct compression is the segregation of the powder blends prior to compaction, caused by density and particle size differences. The risk can be reduced by matching size and density of the materials in use (Gohel 2005) but not fully avoided.

Table 7. List of carrier materials in direct compression of sustained release matrices.

Category	Substances	Reference
Celluloses	HPMC	Dabbagh 1996, Fuertes 2010, Gambhire 2007 Goncales-Araújo 2008, Khan 2007, Miranda 2007, Reza 2003, Streubel 2000
	Ethyl cellulose	Barra 2000, Bonny 1993, 1995, Boza 1999, Crowley 2004, Dabbagh 1996, Katikaneni 1995b, Khan 2007, Neau 1999, Pather 1998, Streubel 2000
(Meth)Acrylates	Eudragit RS	Agabeyoglu 1985, Azarmi 2002, 2005, Boza 1999, Cameron 1987, Caraballo 1999, Lin 1990, Melgoza 1998
Polyvinyls	PVAc	Novoa 2005
	PVAc/PVP	Draganoiu 2003, Engineer 2004, Kranz 2005, Kranz 2006, Reza 2003, Riis 2007, Shao 2001, Siepmann 2010, Strübing 2008
	PVP	El-Arini 1995
	Polyvinyl stearate	Hastedt 2006
Polysaccharides	Alginate	Tapia 2004
	Carrageenan	Tapia 2004
	Chitosan	Kristmundsdottir 1995, Tapia 2004
	Karaya gum	Munday 2000, Murali Mohan Babu 2001
	Pectine	Ashford 1993, Rubinstein 1993, Wakerly 1997
	Xanthan gum	Baumgartner 2008, Munday 2000, Vendruscolo 2005
Fats	Glycerol behenate	Gambhire 2007, Ghimire 2011
Waxes	Carnauba wax	Reza 2003

Granulation

In granulation techniques, the tablet ingredients are consolidated into granules prior to compression. According to the mechanism of solid bridge formation, three different techniques can be distinguished: dry, wet and melt granulation.

In dry granulation bonds between the powder particles are formed due to deformation of a plastic material under high pressure. The prepared compacts are ground down to granule size in a second process step (List 1985). One efficient and fully automated process for dry granulation is roller compaction, which has been reviewed by Kleinebudde (Kleinebudde 2004).

In wet granulation solvents, solutions or dispersions are used and solid bridges are formed due to recrystallization of dissolved material during solvent removal, whereas in melt granulation thermo-responsive excipients are exposed to high temperatures fusing the powder particles to larger aggregates. Naturally, these techniques are not suitable for humidity-sensitive and thermo-labile drugs.

Main advantages of granulation prior to compaction are improved flowability in the hopper, decreased segregation of the particles, and reduced dust during tabletting (Bauer, Frömming, Führer 1999). Moreover, achieving required tablet hardness is facilitated because the blend has already been densified. For low dose drugs the incorporation of the active substance in the granulation fluid leads to homogeneous distribution and therefore increased content uniformity. The downsides of this process are its longer duration and higher costs due to the additional formulation steps (Fig. 8).

Similar to directly compressed matrix formulations, percolation theory should be considered when studying the literature on granulated matrix tablets (examples in Table 8).

Key parameters in matrix preparation by compaction are the homogeneity of the material mixture (see Percolation theory), the compression force and the dwell time, i.e. the residence time of the upper punch on the lowest position of the amplitude.

The compression force is limited by the compressibility of the substances and the tooling, because higher forces also increase the wear and tear of the materials. The smaller the tooling, the higher the wear and the lower the acceptable compression force (www.ritter-pharma-technik.de). The dwell time depends on the equipment and, even more important, on the tabletting speed and usually ranges in the millisecond region.

Table 8. List of carrier materials in wet granulation of sustained release matrices.

Category	Substances	Reference
Celluloses	HPMC	Goole 2007, Nellore 1998
	Ethyl cellulose	Khan 2007, Kuksal 2006, Shaikh 1987
(Meth)Acrylates	Eudragit NE	Billa 1998
	Eudragit RL	Abbaspour 2007, Caraballo 1994, Kuksal 2006
	Eudragit RS	Abbaspour 2007, Agabeyoglu 1985, Caraballo 1994, de Haan 1986, Fernandez-Arevalo 1993, Kuksal 2006
Polyvinyls	PVAc/PVP	Draganoiu 2003, Kranz 2006, Riis 2007
Polysaccharides	Chitosan	Amrutkar 2009
	Guar gum	Krishnaiah 2002
	Karaya gum	Murali Mohan Babu 2001
	Pectine	Ahrabi 2000
	Xanthan gum	Fan 2008
Fats	Glycerol behenate	Ghimire 2011, Goole 2007, Obaidat 2001
Waxes	Carnauba wax	Huang 2006

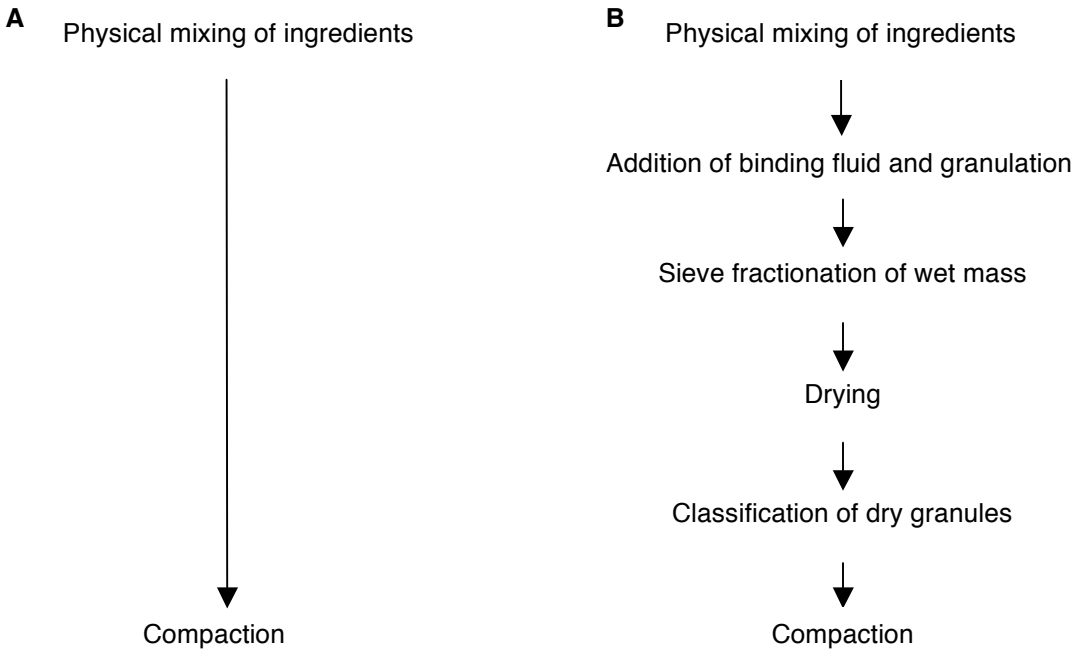

Fig. 8. Flow chart of process steps for A) Direct compression and B) Wet Granulation.

Matrix tablets prepared by compaction are porous binary systems of solids and gas with air contents of approximately 1 - 25 % depending on the compressibility of the materials used (Fig. 9). The ratio of apparent and true density of the tablets is used to assess its porosity. This simple approach offers a non-destructive means to obtain the overall porosity but fails to provide more detailed information on pore size distribution, structure and accessibility. Hence, more elaborate methods such as mercury intrusion porosimetry, gas pycnometry, ultrasound, NIR imaging and tetrahertz spectroscopy have been evaluated (e.g. Brohede 2007, Hastedt 2006, Nordström 2013, Leskinen 2010, Lim 2011, Peiponen 2013). Knowledge of the porosity of a compacted system is crucial since it affects diffusional processes and tablet integrity (Nordström 2013).

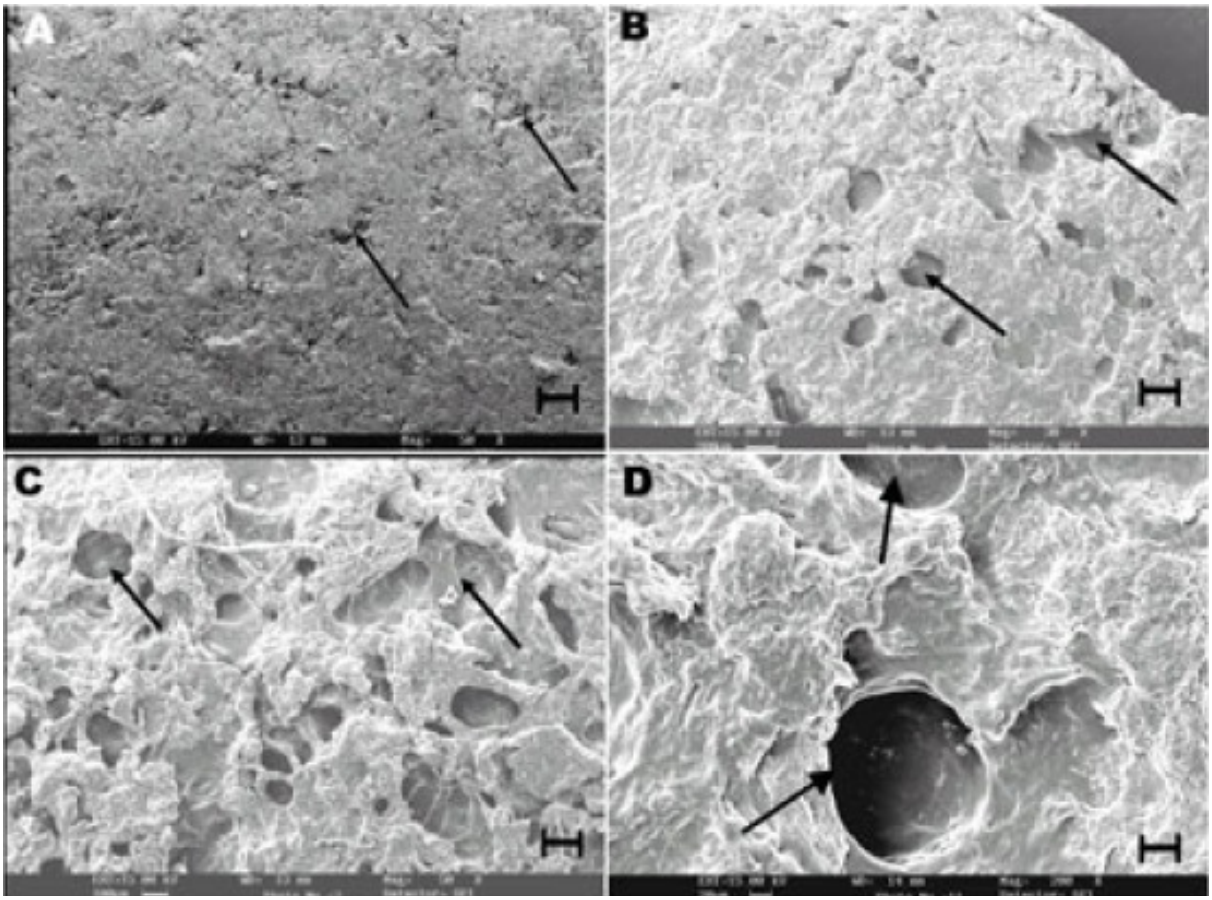

Fig. 9. SEM pictures of wet granulated matrix tablet (containing 300 mg Zidovudine, 30 mg Eudragit RS, 30 mg Eudragit RL and 60 mg ethyl cellulose) after 0 h (A, 5000x), 2 h (B, 6000x), 5 h (C, 5000x), and 10 h (D, 4000x) of dissolution, (arrows indicate pores) (Kuksal 2006).

According to the content of matrix former, tablets stay intact during drug release or disintegrate into granules in case of granulation prior to tableting or into powder in case of direct compression (see Percolation theory). As already discussed in previous chapters matrix integrity is strongly affected by compressibility and particle size of the constituents.

Extrusion

Extrusion processes in the pharmaceutical industry can be subdivided into extrusion of wet granulation masses and melt-extrusion. The first is usually followed by a spheronization step and drying of the product to form matrix pellets. The use of granulation liquids and the complex, usually discontinuous process are major disadvantages of this technique.

Melt-extrusion, the main process in manufacturing of extruded matrices, has two key characteristics: first, the employment of thermoplastic excipients and second, the subjection of the compounds to heat (Breitenbach 2010). There is no need for liquids or solvents and continuous production of matrices is feasible. Melt extruded matrices are applicable in oral, transdermal, trans-mucosal as well as subcutaneous drug delivery systems (Repka 2008).

Suitable excipients for matrix preparation are listed in Table 9 to display the variety of materials used. Their glass transition temperatures have great impact on the process and plasticizers can be added if high process temperatures and melt viscosities are an issue (Crowley 2007, Repka 2007).

The excipients are compounded with the actives before or in the mixing zones of the extruder, then molten (resulting in a viscous mass) and finally extruded through an orifice (Fig. 10). The polymer or wax strands are then cooled down and cut into appropriate size, forming granules, films or finished tablets by a special shaping technique called calendering.

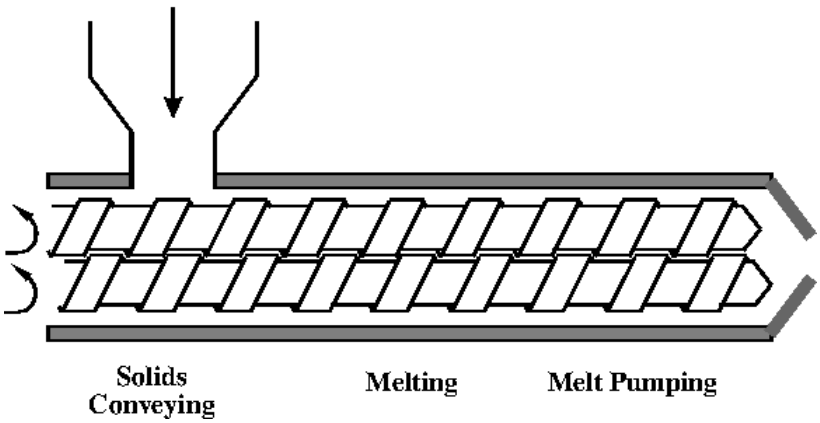

Fig. 10. Schematic drawing of a twin-screw extruder (www. polymerprocessing.com).

Key process parameters are the barrel temperature, the screw speed and the feed rate, which affect the torque, representing melt viscosity, and residence time of the material (Kolter 2010). Residence times as short as 0.5 - 5 min even allow the incorporation of some thermo-labile drugs in hot-melt extruded matrices (Crowley 2007).

The active ingredient can be included in three different ways (Breitenbach 2000): it can be dissolved in the molten polymer, forming a uniphase system, or it can be homogeneously dispersed resulting in

biphasic systems where the particles exist either in their amorphous or crystalline form. Naturally, stability of the solid solutions or amorphous dispersions is an important issue because recrystallization might occur during storage (Bruce 2007).

Table 9. List of thermoplastic substances used in hot-melt extrusion of sustained release matrices.

Category	Substances	Reference
Celluloses	Cellulose acetate butyrate	Sprockel 1997
	HPMC	Liu 2001
		Crowley 2004
	Ethyl cellulose	De Brabander 2002
		Follonier 1995
(Meth)Acrylates	Eudragit RS	Follonier 1994
		Kidokoro 2001
		Zhu 2002
Polyvinyls	PVAc	Sprockel 1997
		Zhang 2000
	PVAc/PVP	Özgüney 2009
Polysaccharides	Xanthan gum	Fukuda 2006
	Pectine	Follonier 1995
	Chitosan	Fukuda 2006
Polylactides	PLGA	Ghalanbor 2010
		Shuwisitkul 2011
Fats	Gelucire	Siepmann 2006
	Glyceryl behenate	Pivette 2011
	Glyceryl palmitostearate	Liu 2001
	Glyceryl trimyristat	Güres 2011
	Glyceryl tristearate	Güres 2011
Waxes	Carnauba wax	Miyagawa 1996
		Sato 1997
	Microcrystalline wax	De Brabander 2000
		Zhou 1996

Besides the incorporation of API powders, more sophisticated approaches like the inclusion of granules or pellets (Schilling 2010) or the co-extrusion of core-coat systems have been investigated (Quintavalle 2008).

The existence of incorporated air cannot be fully excluded but usually the formed matrices are much denser than their compacted equivalents (Crowley 2004). Due to the formation of solid bridges

between the polymer particles lower percolation thresholds can be assumed. Still, drug loadings are limited to approximately 50 % dependent on drug properties due to processing issues (Özgyney 2009).

Drug is released via diffusion through the polymer or water-filled pores; hence formulation, air content and addition of pore formers strongly affect release by changing the total porosity (see also Mathematical modelling of drug release from porous insoluble matrices). Fig. 11 illustrates the pore distribution after release of wax matrices containing no pore former, HPC SL or sodium chloride, respectively.

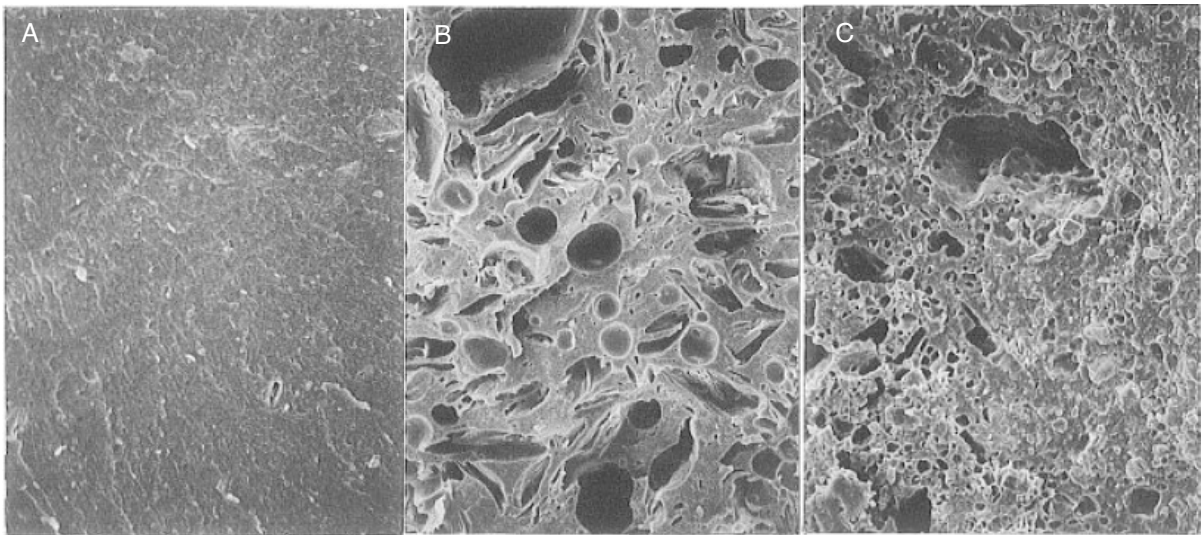

Fig. 11. SEM pictures of wax matrix granules prepared by hot-melt extrusion after dissolution study. A) without pore former, B) 40 % w/w HPC-SL, C) 55 % w/w sodium chloride (Sato 1997).

Other techniques

Besides the well-established compaction and extrusion technique there are other methods like coating, gelation and spray congealing for the preparation of matrices for oral drug delivery.

Coating is the most time-consuming process in this list. The active and the release-retarding polymer are simultaneously sprayed onto pellet cores. Coated matrices have the ability to sustain the release of highly soluble drugs (Rahman 2005) and the decreasing release rate could be avoided by spraying different drug/polymer ratios resulting in near zero-order release (Scott 1991). But simple coated matrices also exhibited very slow and incomplete drug release due to encapsulation of the drugs (Mota 2010). Hence, there is still room for improvement for this preparation technique.

Gelation and spray congealing are simple encapsulation techniques, where drug is either dissolved or dispersed in a polymer solution or melt that is further subjected to ion or temperature induced precipitation. Pectinate formulations were developed for colon drug targeting by dropping drug containing pectin solutions into Ca^{2+}- or Zn^{2+}- solutions (El-Gibaly 2002, Sriamornsak 1998) and molten glycerol monostearate was employed to encapsulate acetaminophen (Nitanai 2012).

In all cases the obtained matrices deliver the drug by diffusion through the matrix material and pore formers can be incorporated to increase the release rate.

Special formulations

Gastro-retentive systems

Gastro-retentive systems can be roughly classified into density-based (floating/sinking delivery systems), expandable and muco-adhesive retention systems (Talukder 2004). In each category, matrix tablets can be found:

Floating

As previously mentioned for Kollidon® SR (Strübing 2008), floating matrix tablets have been formulated. Another commonly utilized polymer for this purpose is hypromellose (e.g. Li 2003, Streubel 2003). Generally, an apparent density of the tablet of less than 1 g/ml is targeted by either incorporation of air during processing or by addition of excipients that generate gas after medium penetration (Baumgartner 2000). In both cases the air volume entrapped in the matrix weakens the carrier network, increasing the risk of matrix disintegration. The loss of buoyancy due to dissolution of the gas is minimized by dissolution of solutes with densities > 1 g/ml, so that the matrices stay afloat for extended time periods.

Expansion

The swelling behavior of hydrophilic polymer matrices, made of polysaccharides or cellulose ethers for example, has been used for gastro-retention of drug delivery systems. In this approach fast expansion of the tablet from swallowable sizes to sizes larger than the pyloric opening and hence, entrapment of the system in the stomach is aimed for. Klausner has reviewed simple matrix tablets as well as more sophisticated geometries for gastro-retention in 2003. Waterman has criticized the reliability of these systems in 2007.

Mucoadhesion

Polymers such as hypromellose, polyvinylpyrrolidone, guar gum and sodium carboxymethylcellulose also showed muco-adhesion. This might prolong the transit time of matrix formulations through the gastro-intestinal tract (Chary 1999).

Generally, gastro-retention can be realized with matrix formulations and only in case of insoluble and slowly eroding matrices, the risk of tablet accumulation in the stomach after repeated administration has to be considered.

Solubility enhancement

The embedding of poorly soluble drugs in hydrophilic matrices was found to increase their dissolution rate by improved wetting and increased available surface area of the drug molecules by the polymers (Leuner 2000). Typical polymers employed for this purpose are hypromellose, polyvinylpyrrolidone, polyethylene gycol and Soluplus® (polyvinyl caprolactam – polyvinyl actetate – polyethylene glycol graft polymer). The matrices form solid dispersions or solid solutions dependent on the particle size and the solubility of the drug in the carrier.

Multi-layer tablets

Multi-layered tablets result in a highly flexible drug delivery system. In addition to the control of the drug release kinetics, multi-layer tablets also offer the possibility of formulating incompatible substances. Abdul, in 2004, and Vaithiyalingam, in 2010, have reviewed their design and production issues.

Geomatrix®

A multilayer tablet design is the base of the Geomatrix® technology (Colombo 1989). According to the desired release profile, erodible or swellable polymer layers hinder release from a drug and hypromellose containing core layer by restricting the surface available for medium penetration and drug diffusion (Fig. 12). A quasi-constant delivery rate is the result of careful formulation of the drug containing and rate controlling barrier layers.

Marketed products that use the geomatrix technology are for example Xatral® once daily (Sanofi-synthelabo), Sular® (Sciele), ZYFLO CR™ (Critical therapeutics), diclofenac-ratiopharm® uno (ratiopharm) and Madopar® DR (Roche) (www.skyepharma.com).

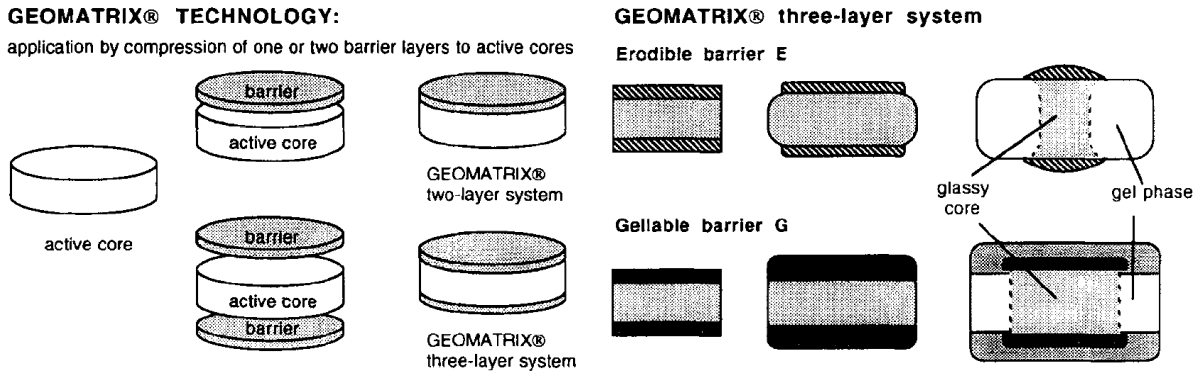

Fig. 12. Geomatrix® system, composition and swelling behavior (Conte 1996).

RingCap technology

Insoluble bands surround a capsule shaped matrix tablet in the RingCap technology (Wong 1996, 1997). These bands reduce the surface area of the tablet available for dissolution medium and hence, hinder matrix swelling and drug diffusion from these parts. The drug release pattern can be adjusted by number and thickness of the bands (Fig. 13).

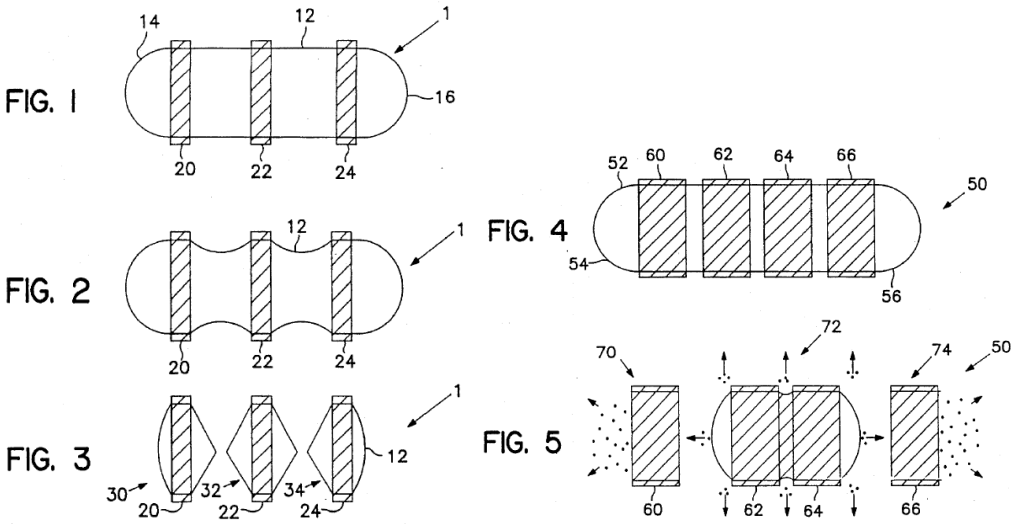

Fig. 13 Schematic representation of the RingCap technology (Wong 1996).

Core-in-cup technology

The formulation of core-in-cup matrices has already been studied in the late 1980s (Seta 1988, Shenouda 1990), but production was simply manually then. Only Danckwerts developed a technique ready for industrial scale up in 1994, represented Fig. 14. The aim of this system was the restriction of the release surface to one face of the matrix tablet only, thereby obtaining zero-order-release kinetics. While the tablet core contained a high-dosed hydrophilic matrix (5-15 % hypromellose in drug), the cup consisted of carnauba wax in ethyl cellulose (Fig. 15).

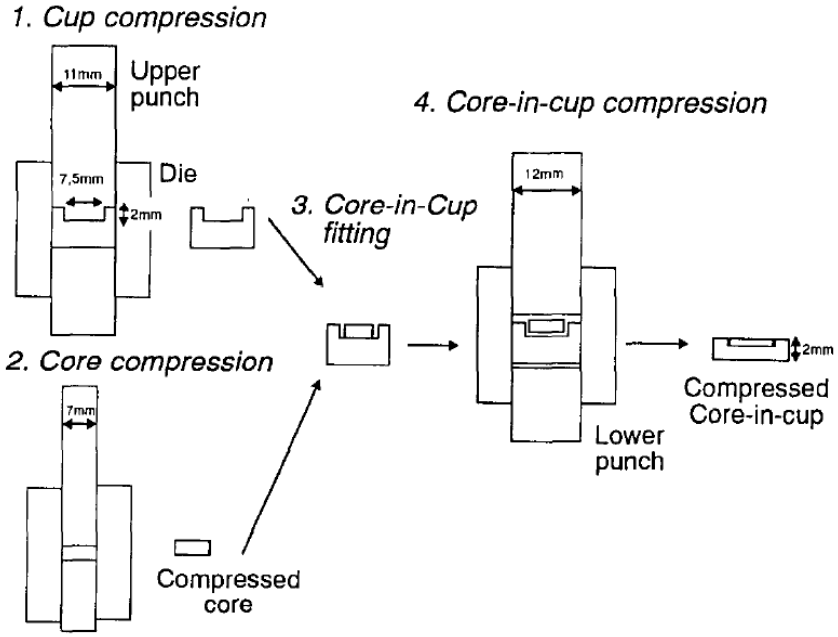

Fig. 14. Production scheme of core-in-cup matrices (Danckwerts 1994).

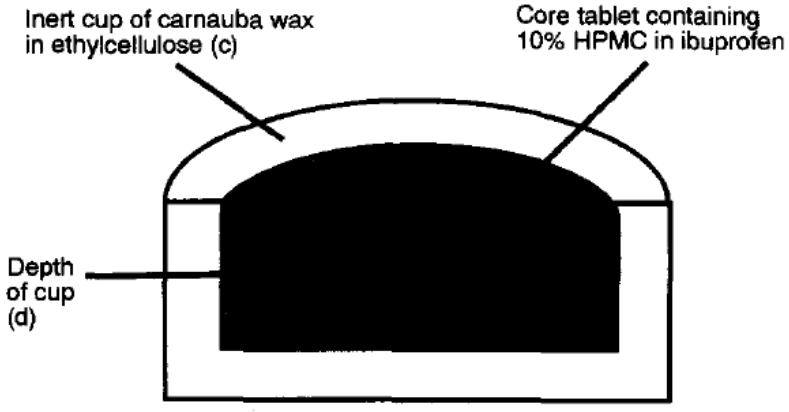

Fig. 15. Composition of Ibuprofen containing core-in-cup formulation (Danckwerts 1995).

Dome Matrix®

Assembling of modules to achieve flexibility in dosing, release kinetics and drug combination was the idea of this approach (Fig. 16). A “snap and click” design allows interlocking of the modules for safe administration to the patient. The void between two center pieces can be used for gastro-retention by entrapment of air (Colombo 2009).

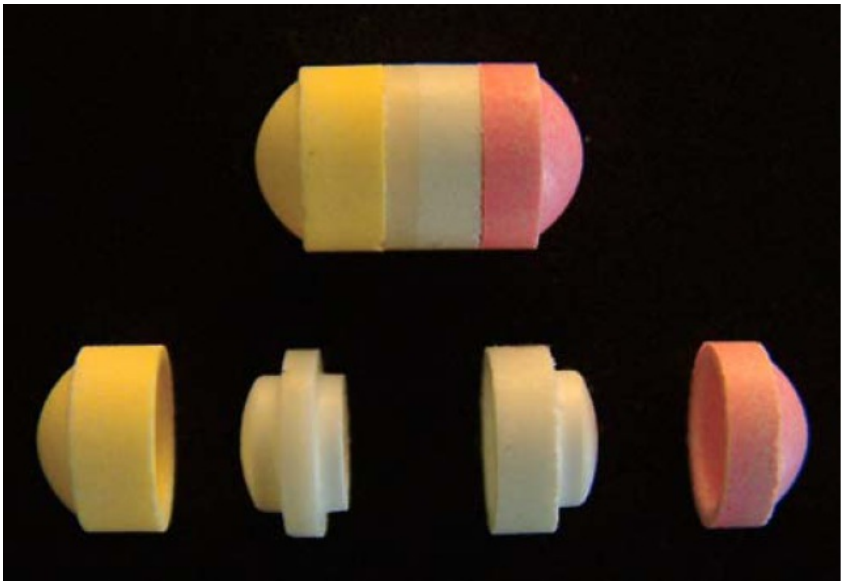

Fig. 16. Assembly of different modules of the Dome Matrix® technology (Colombo 2009).

Multi Matrix System (MMX technology)

The MMX technology targets the delivery of 5-aminosalicylic acid to the colon. The drug is embedded in hydrophobic and hydrophilic matrices that are enterically coated. After dissolution of the coat, the drug is released via diffusion from the eroding matrix core (Kamm 2007). Lialda® (Shire Pharmaceuticals Inc.) uses the MMX technology.

TIMERx®

Another blend of polymers forms the principle of the TIMERx® technology. Xanthan gum and locust bean gum blends offer synergistic gel formation. The release profile can be adjusted via the ratio of polysaccharides and the addition of divalent cations such as Ca^{2+} as stimulator for ionic cosslinking of the saccharide chains or sugars as gel formation modifiers. Hence, zero-order, first-order or multiple-phase release patterns can be obtained. Procardia® XL (Pfizer) and Cystin® CR (Leiras OY) use the TIMERx® technology (Staniforth 2005).

Mathematical modelling of drug release from porous insoluble matrices

Understanding of the underlying release mechanisms is a prerequisite to predicting the drug release from matrix tablets. Lists of the processes that have to be considered have been compiled, e.g. by Siepmann et al. in 2008:

- wetting of the system with water
- water penetration into the device
- phase transitions of the excipients
- drug and excipient dissolution
- hindrance of the dissolution by limited solubility or dissolution rates
- drug and excipient degradation
- creation of water filled pores
- pore closing due to polymer swelling
- hydrostatic pressure within the delivery system
- convection driven drug release along pressure gradient
- creation of acidic or basic microenvironments
- pH-dependence of dissolution, degradation
- physical drug-excipient interactions
- diffusion of drug and/or excipients out of the dosage form
- penetration of acids, bases or salts from the bulk fluid into the dosage form
- sink-conditions
- chemical reactions between drugs and excipients and/or water
- changes of the device geometry.

According to the properties of the device itself or the used ingredients, some mechanisms will become more important than others. For processes that run in parallel the fastest, and for processes that follow one another the slowest step is rate limiting (van Veen 2005).
Ritger and Peppas published a simple exponential relationship in 1987 that has been widely used to verify the general drug release mechanism (Ritger 1987):

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{(Eq. 1)}$$

where M_t is the mass of drug released at time t and M_∞ is the mass of drug released as time approaches infinity, k is a proportionality factor and n is the release exponent, indicating the underlying mechanism. It is a short term approximation of drug release from polymeric systems, $M_t/M_\infty < 0.6$.
Table 10 summarizes exponent values with corresponding release mechanisms for systems with thin film-like, spherical and cylindrical geometries. Subsequently, matrix tablets exhibiting an exponent of 0.45 release the drug via diffusion, an exponent between 0.45 and 1.0 is attributed to anomalous (non-Fickian) diffusion, whereas an exponent of 1.0 indicates zero-order release, caused by swelling and

erosion of the device (Siepmann 2008). Literature applying this equation to matrix tablets observed also values below 0.45 (e.g. Caraballo 1999, Goncalves-Araújo 2008), which is not covered by the original equations the model is based on.

Table 10. Diffusional exponent n and mechanism of drug release from systems of different geometries (Ritger 1987).

Exponent, *n*			Drug release mechanism
Thin film	Sphere	Cylinder	
0.50	0.43	0.45	Fickian diffusion
$0.50 < n < 1.0$	$0.43 < n < 1.0$	$0.45 < n < 1.0$	Anomalous transport
1.0	1.0	1.0	Zero-order release

Hence, with regard to matrix tablets two major mechanisms can be distinguished, which change in dependence of the composition of the matrix: diffusion and erosion. The dimensions of the matrix, the distribution of the drug in the matrix and the content and properties (like wettability and solubility) of the matrix former are key parameters affecting the processes governing drug release (see also Percolation theory).

Diffusion

On the topic of diffusional drug release a vast amount of research has been done. A classification according to the key parameters just mentioned is depicted in Fig. 17 (Siepmann 2012). The two special cases of cylindrical matrices (tablets), monolithic solutions and monolithic dispersions, are reviewed below.

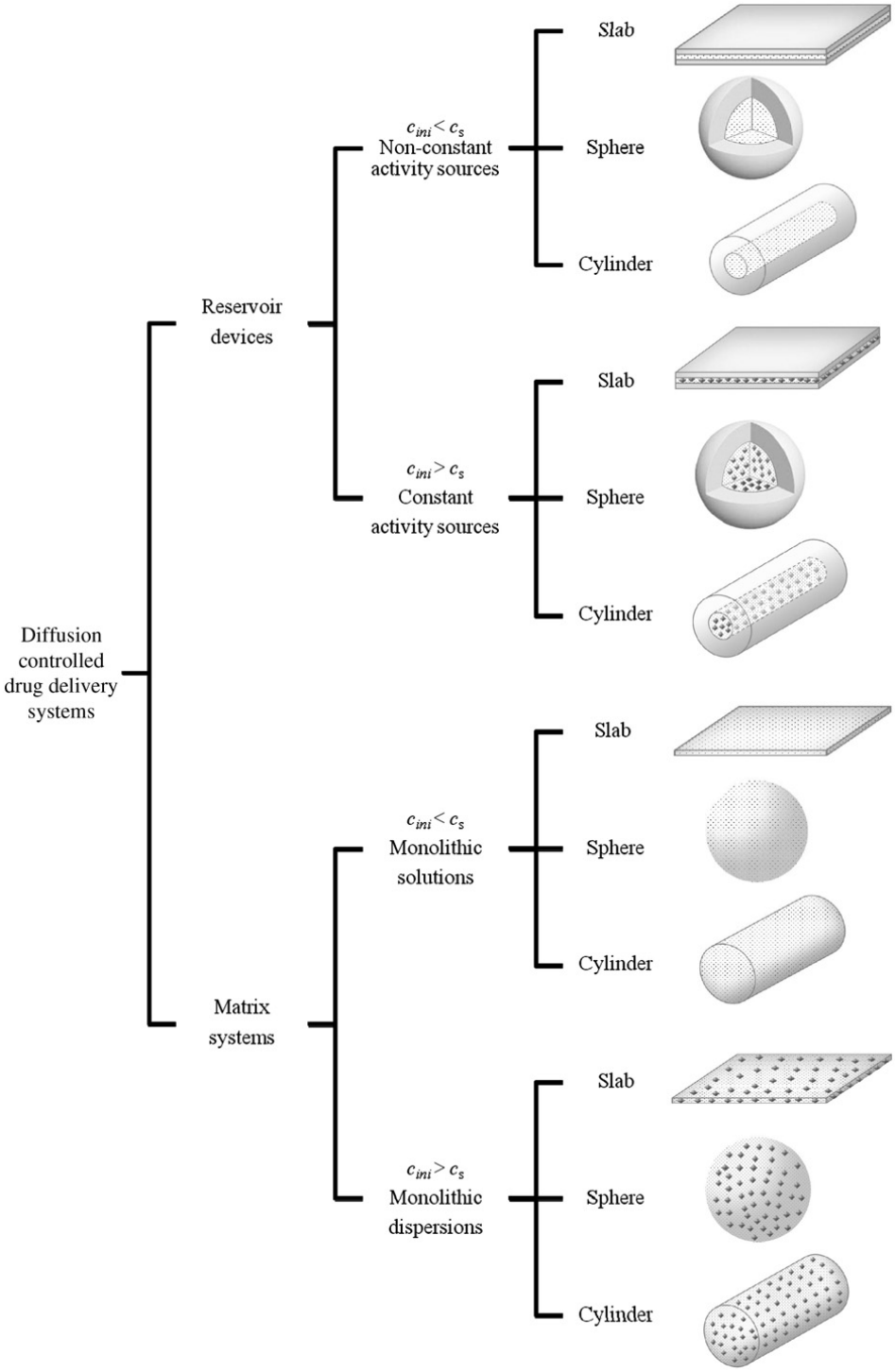

Fig. 17. Classification scheme of predominantly diffusion-controlled drug delivery systems (Siepmann 2012).

Monolithic solutions refer to systems where the drug is either molecularly dispersed in the carrier material, or, upon medium imbibition into the system, the dissolution front moves alongside the penetration front. Fick's second law of diffusion can describe drug release from these kinds of systems in radial as well as axial direction (Crank 1975):

$$\frac{\partial c}{\partial t} = \frac{1}{r} \cdot \left\{ \frac{\partial}{\partial r}\left(rD\frac{\partial c}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D}{r}\cdot\frac{\partial c}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD\frac{\partial c}{\partial z}\right)\right\} \qquad \text{(Eq. 2)}$$

where *c* is the concentration of the diffusing molecule, *t* is the time, *r* and *z* represent the radial and axial coordinates, *θ* the angle perpendicular to the *r*-*z*-plane and *D* the apparent diffusion coefficient in the matrix.
A solution to this differential equation can be found in Vergnaud 1993:

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D_{app} t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \cdot \exp\left(-\frac{(2p+1)^2 \cdot \pi^2}{H^2} \cdot D_{app} t\right) \qquad \text{(Eq. 3)}$$

where M_t is the mass of drug released at time *t* and M_∞ is the mass of drug released as time approaches infinity, *R* and *H* denote the radius and the height of the tablet respectively, *n* and *p* are real numbers and q_n are the roots of the Bessel function of the first kind of zero order $(J_0(q_n) = 0)$.
Prerequisites for the application of this equation are:

- uniform dispersion of the drug molecules in the matrix
- drug release by diffusion through water-filled pores
- constant diffusivity in axial and radial direction
- constant dimensions (cylindrical tablet)
- maintained sink-conditions throughout the release period

This equation has been applied to matrices of Gelucire 50 02 (Aïnaoui 1998) and Kollidon SR (Siepmann 2010), where the prediction of drug release from tablets of different dimensions could be shown.
In case of Gelucire 50 02 the conditions are easily met but in case of Kollidon® SR the dimensions of the matrix change during release due to swelling of the polymer. The latter author further investigated the swelling behavior (see Kollidon® SR) and replaced the initial dimensions with the dimensions of the swollen tablet, justified by the immediate and complete water uptake. Hence applicability of the equation was confirmed and independent experiments were compared to predictions with good agreement. The apparent diffusion coefficient has been used as fitting parameter: D was adapted until the best fit with an existing set of data was obtained. Employing the derived D and the dimensions of the matrix allowed for prediction of drug release for matrices with exactly the same composition.
Moreover the effect of drug loading on release was investigated. Apart from the determination of different diffusion coefficients for 10, 20 and 40 % drug and the exclusion of matrices with 60 % drug,

due to collapse of the swollen tablet during release, no further benefit was obtained with the equation, limiting its predictability to the dimension of a system with known apparent diffusion coefficient.

Monolithic dispersions contain an excess of drug that cannot be rapidly dissolved by the penetrating dissolution medium, so that dissolved and dispersed drug coexist in the wetted areas of the tablet. The famous model designed by Takeru Higuchi, initially developed for ointments (Higuchi 1961) but later extended to thin films of granular matrices describes drug release from this kind of matrix (Higuchi 1963):

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t} \qquad \text{(Eq. 4)}$$

where Q is the release rate per unit surface area, D represents the diffusivity of the drug in the permeating fluid, ε denotes the porosity and τ the tortuosity of the matrix, A is the amount of drug per unit volume, C_s represents the solubility of the drug in the permeating fluid and t is the time.
For reasonable application of this equation the following conditions have to be met (Siepmann 2011):

- drug transport through the film is the rate limiting step
- the drug concentration in the matrix is much higher than its solubility
- the drug is finely and homogeneously dispersed
- the particle size is much smaller than the film thickness
- dissolution of the drug particles is rapid compared to diffusion
- constant diffusion coefficient of the drug within the film
- sink-conditions are maintained
- edge effects are negligible
- drug diffusion is restricted to one direction
- the film does not swell or dissolve

Its simplicity often tempted researchers to erroneously apply this equation to matrix tablets, but especially the underlined conditions are often violated.
First, the drug loading has to exceed the solubility. Hence, only tablets with high loadings of poorly or sparingly soluble drugs can be considered. Furthermore, keeping the concentration gradient and therefore the diffusion coefficient constant, the prediction is limited to a cumulative drug release of maximum 60 %.

Second, drug diffusion has to be restricted to one direction only; thus valid systems comprise ointment films, transdermal patches, films for oral delivery or partially coated tablets (Siepmann 2011).
A mathematical model for cylinders of monolithic dispersions also exists but diffusion is similarly limited to one dimension only (radial diffusion):

$$\frac{M_t}{M_\infty} + (1 - \frac{M_t}{M_\infty}) = \frac{4D}{R^2} \cdot \frac{c_S}{c_{ini}} \cdot t \qquad \text{(Eq. 5)}$$

where *D* represents the diffusion coefficient, *R* denotes the radius of the cylinder and c_s and c_{ini} represent the saturation concentration and the initial loading, respectively.

Last but not least, the matrix film has to be non-swelling and insoluble, in other words no change in dimensions occurs. That condition alone limits the applicability with regard to oral matrix devices to only a few matrix carriers that comprise non-swellable, insoluble polymers and hydrophobic substances (see Matrix tablets).

Despite all the limitations of applicability the Higuchi equation still provides the most detailed description of parameters affecting the drug release process.

The higher the solubility of the drug, the steeper is the concentration gradient between the surface of the matrix and the location of the drug. This gradient is kept constant as long as there is undissolved drug that can replace liberated molecules. Therefore, this equation can only be a short-term approximation and its validity is limited to the first 60 % of cumulative drug release.

As the drug is dissolved and diffuses out of the matrix its position is filled with dissolution medium leaving pores for the adjacent drug particles. The higher the initial loading, the higher is the final porosity of the leached matrix. Besides the volume fraction of pores their distribution also plays a role for drug diffusion. Large pores leave short ways for the diffusing molecules whereas small winded pores form long, tortuous paths. Moreover, a high surface area is beneficial for fast drug liberation from the matrix system but the volume is also important. The higher the surface area/volume ratio the shorter is the diffusional path length.

To extend this model to monolithic solutions a modification has been proposed by Bunge in 1998:

$$\frac{M_R}{M_o} = \sqrt{\frac{2DtR}{L^2}(1 - \frac{R(\pi-2)}{\pi})} \qquad \text{(Eq. 6)}$$

where M_R/M_o is the fraction released, *D* represents the effective diffusivity of the drug in the permeating fluid (see below), *R* denotes the ratio of solubility concentration and original drug concentration ($R= C_S/A$), *L* is the thickness of the matrix, and *t* is the time. An error of 0.5 % compared to an exact solution has been postulated.

Although the original and the modified Higuchi equations are initially developed for thin films of matrix with diffusion restricted to one direction only, the derived parameters influencing drug release might still be valid for matrices with cylindrical dimensions.

As Siepmann pointed out in 2011, the composition of the matrix has to be closely examined with regard to properties affecting on the one hand the microenvironment of the matrix and thereby the solubility and diffusivity of the active ingredient, and on the other hand the porosity of the matrix. This is equally true for both monolithic solutions and dispersions.

Frenning has reviewed the key parameters of drug release from porous matrix structures in 2011. A pronounced impact has been attributed to the matrix porosity affecting in turn the effective diffusion coefficient D_{eff}.

$$D_{eff} = \frac{\varepsilon D}{\tau} \quad \text{(Eq. 7)}$$

where D is the diffusivity of the drug in the permeating fluid, ε represents the porosity and τ the tortuosity of the matrix. The importance of the probability of the pores to form a coherent network was simultaneously treated (see Percolation theory).

Workers of the same group recently published a model based on the Weibull function for the description of the pore network (Jämstorp 2011). They investigated the relationship between porosity, connectivity of the pores and the effective diffusion coefficient derived from fittings to a solution of Fick's second law of diffusion finding good agreement between predictions and experimental data.

Erosion

With regard to swellable matrix carriers, again a variety of approaches to drug release prediction and modelling can be found. An advantage of these eroding systems is their more constant release rate (zero-order kinetics).

Assuming a constant rate of erosion and uniform drug distribution within a matrix, Aïnaoui published a rather simple equation based on the Hopfenberg model (Aïnaoui 2000, Hopfenberg 1976):

$$\frac{M_t}{M_{in}} = 1 - \left[1 - \frac{vt}{R}\right]^2 \left[1 - \frac{vt}{H}\right] \qquad \text{(Eq. 8)}$$

where M_t is the amount of drug released at time *t*, M_{in} represents the initial amount of drug in the matrix, *H* and *R* denote the half height and the radius of the tablet ($H < R$) and *v* is the erosion rate.

Because, besides erosion, diffusion usually also plays a role, additive equations have been postulated referring to contribution of both mechanisms to different extends, for example by Peppas and Sahlin 1989:

$$\frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n} \qquad \text{(Eq. 9)}$$

where M_t represents the mass of drug released at time *t* and M_∞ represents the mass of drug released as time approaches infinity, k_1 is the Fickian kinetic constant and k_2 is the relaxational/erosion rate constant and *n* is the release exponent, dependent on the geometry of the matrix.

Siepmann has reviewed models explicitly treating the drug release from hypromellose in 2001. For further study of erodible matrices the reader is referred to this and other reviews (e.g. Lin 2006, Siepmann 2001).

However, the mathematical modelling of drug release governed by erosion of the insoluble matrix scaffold is rare compared to the abundant treatment of release by diffusion. The statistical nature of the erosion rate from matrices prepared with non-swellable insoluble polymers hinders straight forward approaches for drug release modelling. Moreover, a drawback that has to be pointed out is the comparatively fast drug release from these devices, summarizing to rather non-controlled drug liberation.

To be able to distinguish between diffusion and erosion controlled drug release, the percolation theory represents an interesting approach in matrix formulation.

Percolation theory

Percolation theory, coming up in mathematics in the 1950s, generally treats the probability of connectivity in random systems. A broad range of disciplines since, such as physics, chemistry but also epidemiology and geography, has utilized this theory. Leuenberger first applied it to pharmaceutics in 1987.

Binary mixtures are regarded as random systems of component A and B and their site occupation probability is *p* and *1-p*, respectively (Fig. 18A - D). At a low content *p*, component A will be dispersed in component B (Fig. 18A), increasing contents of A will lead to cluster formation of that component (Fig. 18B) and above a critical content, the percolation threshold p_c, these clusters will interconnect and span the whole system from top to bottom and left to right (Fig. 18C). Further increase of the content of component A will expand the percolating clusters until they start to insulate the clusters of component B, dispersing B in A (Fig. 18D).

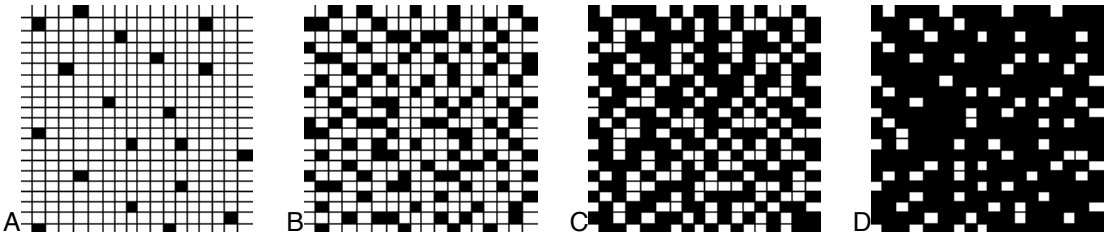

Fig. 18. Distribution of compound A (black squares) in compound B (white squares) with A) $p = 0.05$, B) $p = 0.30$, C) $p = 0.59$, D) $p = 0.80$.

Furthermore, the percolating material will govern the properties of the system. That means if, in a binary mixture of components A and B, component A exceeds a critical content, it will dominate the properties of the system. The same holds true for component B. If both components exceed the percolation threshold, a continuous sponge-like network is formed. Both constituents percolate the system and therefore affect its properties simultaneously.

Binary blends of solid particles like powders, compacts or liquid mixtures of immiscible droplets can be easily imagined as such systems, making percolation theory an interesting approach for pharmaceutical science. The percolation models developed in mathematics or other disciplines usually are not easily transferable, because pharmaceutical mixtures are not as ideal. Interactions between the components have to be considered and more often the systems under investigation consist of three or more constituents, complicating the examination.

The simplest system investigated in pharmaceutical sciences was the binary mixture of air and powder particles. According to literature, site and bond percolation have to be distinguished (e.g. Stauffer 1985). Two particles of the same material can be regarded as a cluster that has two sites in common

or one bond. Therefore, for the same system a site percolation threshold and a bond percolation threshold should exist (site percolation threshold > bond percolation threshold).
Leu and Leuenberger calculated these thresholds in 1993, finding that the bond percolation threshold could be described by values between the relative poured and tapped density of a powder, because the weak inter-particular bonds connecting the particles became evident at relative densities in that range. The site percolation threshold, where the connectivity of the particles is based on neighboring sites rather than bonds and the compact exhibits measurable cohesion (a tablet is formed), was located at relative densities between 0.5 and 0.8. Plots of tablet hardness vs. relative density showed two linear ranges, allowing for estimation of the site percolation threshold, which confirmed the calculated results. A third threshold, where the air entrapped in the compact would be insulated by the solid particles, could not be identified experimentally. Further investigations of the compaction process suggested that the compaction stress is conducted via the bonds of the particles and can be interpreted as a two-dimensional percolation process (Leuenberger 1997).
Binary systems of gas and solid particles with different contents of each phase can be used to illustrate these findings (Fig. 19).

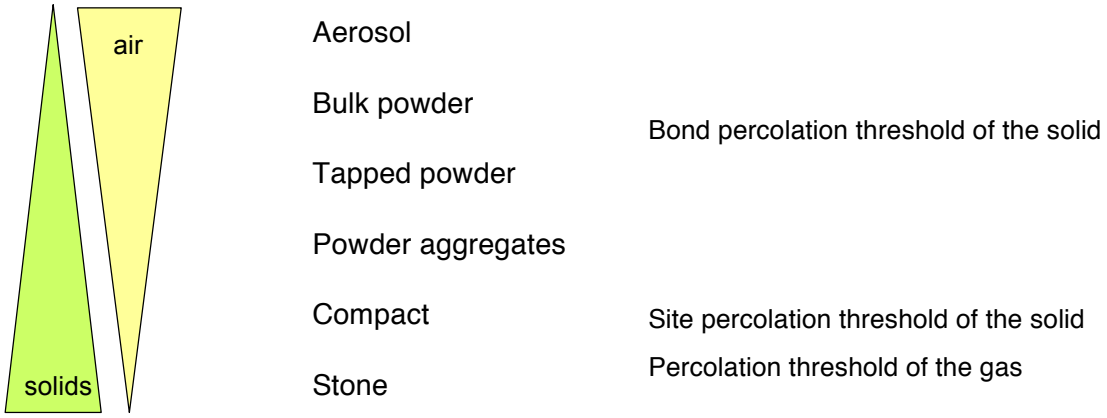

Fig. 19. Example of binary system gas/solid.

At very low solid content a homogeneous gas/solid system contains the solid particles dispersed in the gas. The gas insulates the particles and the probability of contact is very low. These systems are also called aerosols and the only coherent phase is the gas phase. With increasing solid content, the probability of contact between the solid particles is increased.

Any powder gives a system where the particles touch and therefore form a coherent network. The air content of the system is usually pretty high, resulting in a low bulk density compared to the true density of the solid. Weak intermolecular forces that can be easily disrupted by gravity, for example, connect the particles. Still the solid is percolating the system because the bond percolation threshold is exceeded.

By tapping the powder, part of the air can be removed and a closer particle packing and higher apparent density is obtained. The particles are still linked via weak forces, only the connected surface area is increased. By compressing the powder this surface area can be further increased and the occurrence of stronger intermolecular forces or mechanical interlocking is likely (see Compression). The more force is applied the bigger the powder aggregates will be, that cannot be disrupted as easily as the bulk powder. Gradually a network of particles linked by strong forces is formed. Finally, the excess of site percolation threshold is associated with the formation of a compact, which still contains considerable amounts of air. Stronger compression leads to denser compacts until all air is removed and true density of the solid is reached.

More often than simple gas/solid systems, binary mixtures of two components A and B were investigated. These can generally be considered as matrix tablets with one component being the active pharmaceutical ingredient and the other being the carrier. Both components belong to the solid phase of the blend and therefore the site percolation threshold, indicated by the onset of tablet formation, will be a product of the solid fraction of the tablet. Binding of component A (e.g. the drug) to itself and to component B (e.g. the excipient), and vice versa, will occur during compaction to an extend that depends on the compactibility of the components. Therefore, the site percolation threshold might change with different weight fractions of the compounds in the binary blend if they differ in their compactibility. Kuentz and Leuenberger were the first to distinguish between critical solid fraction for tablet integrity (considered as site percolation threshold earlier) and critical mass fraction (excipient percolation threshold) that strongly affects the solid fraction (Kuentz 2000). With increasing mass fractions of the poorly compressible drug, the site percolation threshold increased.

Kuentz and Leuenberger also investigated the excipient percolation threshold. A value of 20% w/w was obtained for MCC by calculation and experiment, depicting the minimum binder amount necessary to form a tablet with considerable strength. The power law used to calculate the excipient percolation threshold was later extended to consider an initial strength parameter (explainable by bond percolation) and the percolation thresholds of binary mixtures containing different sieve fractions were obtained (Ramirez 2004).

Distinct percolation thresholds of the binary blend with regard to other properties of the compact (like tensile strength or disintegration time, Leuenberger 1987) could be identified by the abrupt change of

these properties, called critical phenomena. The obtained threshold was attributed to the percolation of the compound affecting the said properties (such as binders affecting the hardness of tablets etc.)
Leuenberger investigated the percolation threshold of excipients used as disintegrants that were only effective below their percolation threshold. Above that concentration the disintegration time strongly increased and the materials acted as release retarding agents.
In 1988 Holman and Leuenberger verified the application of percolation theory to pharmaceutical compacts by developing a mathematical model of Young's modulus or tablet hardness in dependence of solid fraction of the compressed materials. Further investigations of binary blends of compounds with different compactibilities revealed that compaction was a function of the weight ratio of the constituents and the percolation threshold was particle size dependent (Blattner 1990).
Patel and Bansal derived a predictive model for binary blends by single material characterization and applying a percolation model or the Ryshkewitch-Duckworth model (Patel 2011).

Meanwhile, other researchers evaluated percolation theory with regard to another critical phenomenon: drug release kinetics from insoluble matrices, which will indicate the percolation threshold of the active ingredient.
As the matrix is immersed in aqueous media and the soluble compounds will dissolve during drug release, a different phase system has to be considered. One phase will be aqueous (comprising volume fractions that were formerly occupied by drug or air) and the other solid. If systems of more than two components are formulated, their solubilities determine the phase affiliation. Soluble compounds will add up to the solute phase including the drug and insoluble substances contribute to the excipient percolation.
An equation to calculate the drug percolation threshold based on the Higuchi equation was developed and used to determine the percolation threshold of ethyl cellulose and hydrogenated castor oil matrix tablets containing caffeine as model drug (Bonny Leuenberger 1991, 1993). The drug percolation threshold was similar for both kinds of matrices with regard to total porosity of the system (volume fractions of 0.35 vs. 0.36), but differed expressed as a weight fraction (28 % vs. 41 %, respectively). The excipient percolation threshold was estimated from the disintegration behavior of the matrices. Tablets containing a volume fraction of less than 0.29 of ethyl cellulose or 0.06 of hydrogenated castor oil disintegrated during drug release and therefore marked the threshold of the matrix system. The smaller value of the oil was explained by the lower particle size. The working group of Caraballo investigated the particle size dependence of the percolation threshold of the drug as well as the excipient further. Linear relationships between percolation threshold and particle size ratio were obtained (Caraballo 1997, Millán 1998). Although the results seem reasonable, the methodology has to be doubted. The release kinetics was determined by the Higuchi-derived tablet property ß, even though drug release was not limited to one-dimensional diffusion only. Moreover, comparability of the binary systems was limited, because the preparation process did not control tablet dimensions and porosity. Finally, only part of the experimental matrix was considered in further analysis of the data, which was not reasoned.

The Bonny and Leuenberger approach to identify the drug percolation threshold has also been applied by Brohede et al 2007. Tablets were prepared carefully controlling the particle size of the constituents, the dimensions and the porosity of the matrices. A drug percolation threshold of 0.22 (total porosity) was measured and the comparably low value explained by the testing conditions. Drug release was not limited to one direction only, so that cluster connectivity throughout the whole matrix was not necessary to allow drug release. The same study provided another break of slope of the release rate vs. porosity plot at 0.44 (total porosity), which was called a “cross-over to effective medium behaviour” and an excipient percolation threshold of 0.84 (total porosity).

The importance of the knowledge of the excipient percolation threshold is easily justified. Matrix integrity and therefore controlled drug release via diffusion through aqueous pores can only be obtained if the solids content of the leached matrix still exceeds the percolation threshold. However, the excipient percolation thresholds obtained in the latter studies (0.06 - 0.3) do not reach the values for site percolation (0.5-0.8) described earlier but coincide with bond percolation thresholds. Hence, also a site percolation threshold should exist, where the excipient particles not only form clusters that span the matrix but present a coherent network. This threshold would be marked by the onset of surface erosion, as the bond percolation threshold is marked by the onset of disintegration (Fig. 20). The second break of slope obtained in the previous study (Brohede 2007) of 0.44, equal to a volume fraction of the polymer of 0.56 can be assumed as site percolation threshold, but confirmation is required.

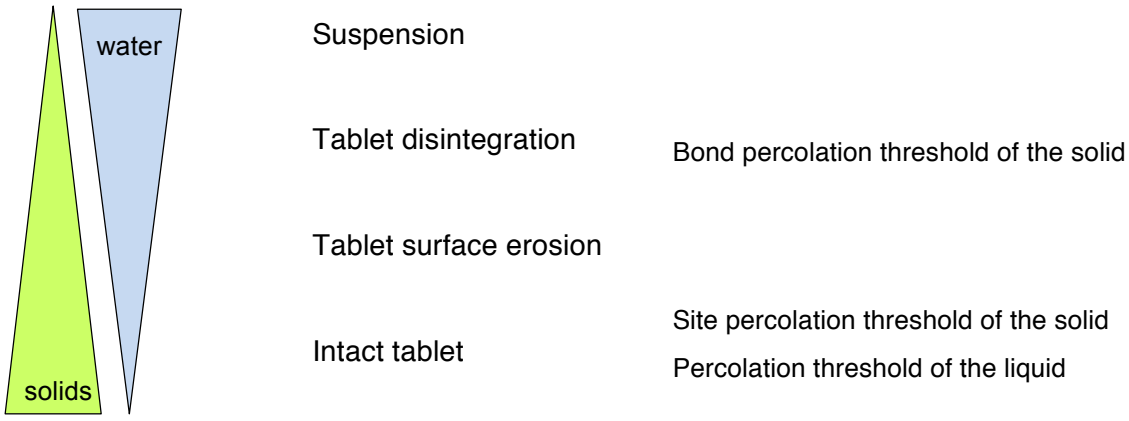

Fig. 20. Example of binary system liquid/solid

Similar to the excipient percolation threshold, the drug percolation threshold is an essential formulation parameter. Below this percolation threshold the matrix material entraps the drug particles. If diffusion through the carrier is too slow (e.g. regarding the transit time of oral delivery systems) this can lead to bioavailability issues. The part of the drug that is fully enclosed by the carrier cannot be released and

therefore is not available for the body (Leuenberger 1995). A Monte Carlo simulation of drug release from inert matrix tablets with zero porosity was performed. A sigmoidal shape was obtained for plots of entrapped drug vs. initial drug loading (Fig. 21) and further described by an error function (Villalobos 2005). Although the simulation lacks natural characteristics like tablet porosity and erosion above the excipient percolation threshold, the results still confirm experimental data obtained by Leuenberger 1995.

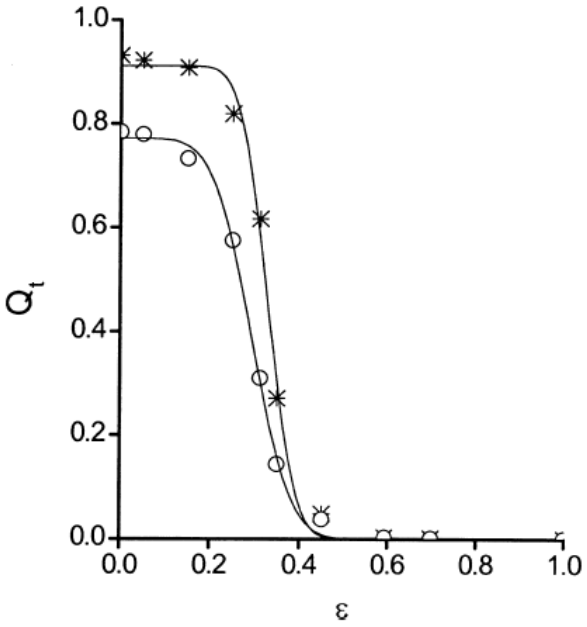

Fig. 21. Fraction of dose trapped in the matrix vs initial drug load. Symbols represent experimental data - total area exposed during release (○), only tablet faces exosed (*); solid lines represent prediction. (Villalobos 2005).

Barra et al. tested a different approach to matrix tablet design (Barra 2000). They formulated binary mixtures (1:1) that differed only in particle size of the drug and the matrix former. The release data were fitted to the Higuchi equation and the derived release rate was plotted against the particle size ratio. As in binary mixtures of 1:1 both compounds should percolate the system and therefore dominate the drug release kinetics, the deviations found were explained by changes in the excipient percolation threshold. At drug to particle size ratios above one, erosion of the matrix occurred, opposing the percolation of the polymeric carrier, while drug release was independent of the particle size of the constituents. Only at particle size ratios below one, a size dependent kinetic could be observed and percolation of the polymer was assumed. Particle size dependent binding of the polymer was also considered, since differences in tablet strength and porosity could be observed. SEM pictures taken from released matrices give a good impression of the approach (Fig. 22).
Hence, besides actual amounts, the distribution of a compound plays an important role in formulation of matrix systems. In solid state a broader distribution can be achieved for identical volume fractions

with smaller particle sizes as demonstrated in the previous study (Barra 2000). As this approach is limited by processibility of powder blends other strategies are used. Dissolution or melting of the matrix polymer also generates an increased surface area and wider spreading, explaining the decreased drug release from wet granulated or hot melt extruded matrices (Kidokoro 2001).

Hydrophilic matrices (HPMC) have also been studied regarding percolation thresholds. Miranda et al. investigated the particle size effect on drug and polymer percolation threshold and a linear relationship similar to insoluble matrices was found (Miranda 2007). Goncalves-Araújo et al. studied multicomponent systems with additional excipients (Goncalves-Araújo 2008). A minimum content of 10 – 20 % HPMC independent of the evaluated viscosity grade was necessary to form sustained release matrices. The impact of other excipients was not further evaluated. Fuertes et al. evaluated the excipient percolation threshold in dependence of the active's solubility, revealing no correlation (Fuertes 2010).

Distinction between bond and site percolation does not seem adequate, because the polymer chains of different particles entangle and disentangle as HPMC transforms to the rubbery state and forms a gel during dissolution experiments. The falling below the percolation threshold of the polymer will be associated with polymer erosion, similar to insoluble matrix carriers. Hence, application of percolation theory might give rise to more thorough understanding of this type of matrix tablets.

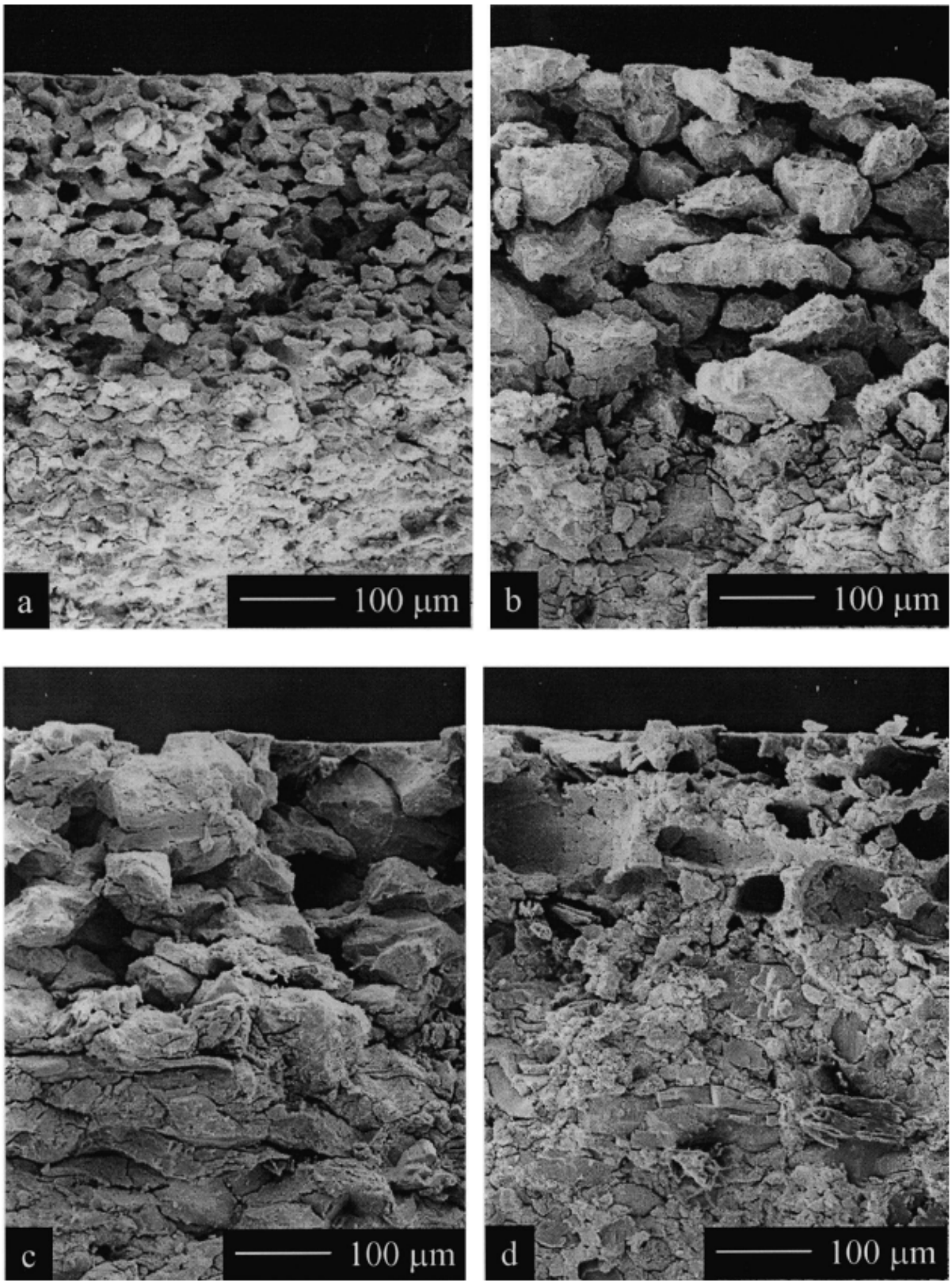

Fig. 22. Cross-sections of tablets after 16 h of release: a) 20-32 μm/20-32 μm, b) 20-32 μm/63-125 μm, c) 63-125 μm/63-125 μm d) 63-125 μm/20-32 μm.

Research objectives

Characterization of insoluble carrier materials for matrix tablets prepared by direct compression

Evaluation of essential polymer properties concerning tablet manufacturing

Investigation of drug release behavior from insoluble matrix tablets

Evaluation of essential polymer properties concerning drug release

Comparison of commonly used insoluble polymeric carriers

Modelling of drug release from insoluble matrix tablets

Verification of the derived model with independent experiments

Evaluation of the limitations of applicability of the derived mathematical model with regard to formulation and key characteristics of the active ingredient, the polymeric carrier and the preparation process

Insoluble matrix systems for controlled delivery of high drug doses

Background

In compression of controlled release matrix tablets, different excipients are usually utilized to form tablets with sufficient hardness, low friability and reliable drug release profiles. To keep the final tablet mass low, ideally one excipient should combine all of these functions and the necessary amount should be as low as possible. Especially, controlled release matrices of high drug doses (500-1000 mg) require excipients meeting high demands with regard to compaction and release retarding properties.

One approach is the employment of insoluble matrix polymers such as Kollidon SR, Eudragit RS and ethyl cellulose (Crowley 2004, Kranz 2005, Neau 1999). These polymers differ in various properties such as chemical structure, glass transition temperature, permeability, compressibility, density, and many more (Bühler 2008, Eudragit® application guidelines, Ethocel 2005).
The evaluation of their potential for flexible controlled delivery of drugs with different physicochemical properties in highly loaded systems is intended here.

Materials and methods

Ethocel Std. 10 FP (The Dow chemical company, Midland, MI, USA), Kollidon SR, coarse theobromine and micronized caffeine, theophylline, diprophylline (BASF SE, Ludwigshafen, Germany), carbamazepine (F.I.S. - Fabbrica Italiana Sintetici S.p.A., Alto de Montevecchio, Italy), Aerosil 200 and Eudragit RS (Evonik Industries AG, Darmstadt, Germany), and magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany) were used as received.

Blends for tabletting

Drug and polymer powders were physically mixed in different ratios (100/0 – 5/95) on a weight base to obtain 10 g of blend. In case of wet granulation these mixtures were wetted with isopropanol/water (88/12 w/w) to form granules and dried overnight.
Finally, 1 % w/w Aerosil and Mg stearate were added to the powder mixtures or the granules as lubricant and glidant.

Compaction

Matrix tablets were prepared by compressing the blends into tablets of different diameters (2 – 13 mm) with an equipped single punch tabletting machine (EK0, Korsch AG, Berlin, Germany) at a compression speed of 10 rpm and recording compression force (MGCplus, catman, HBM, Darmstadt, Germany). The tablets were further characterized regarding their dimensions and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany).

To investigate the impact of thermal treatment, tablets containing Kollidon SR and Eudragit RS as matrix former were subjected to dry heat at 40 and 60 °C (oven Heraeus T6000, Thermo Fischer Scientific GmbH, Dreieich, Germany).

Dissolution tests were performed using a USP paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), 900 ml phosphate buffer pH 6.8, at 50 rpm and 37 °C. Samples were taken at predetermined time points and analyzed spectrophotometrically (272, 290 and 295 nm, n=3).

Results and Discussion

The most time and cost effective preparation method, direct compression, was selected for matrix tablet formulation for controlled release of active material. Simple binary mixtures of different drugs and Kollidon SR as polymer (ratio 1:1) were compressed. Drug release was determined (Fig. 23) and followed the active's solubility, due to its impact on the concentration gradient within the matrix. Freely soluble drugs were released fast (within 1 h) and soluble drugs were retarded up to 8 h. Release was incomplete after 15 h in case of sparingly soluble drugs. Only 37 % of the drug content of carbamazepine containing tablets was liberated while the majority was trapped inside the matrix.
The graph illustrates clearly, that one formulation cannot provide controlled release for all drugs. The obtained profiles vary between almost immediate and incomplete release. Therefore, different approaches have to be used to realize controlled release of the active, according to its solubility.

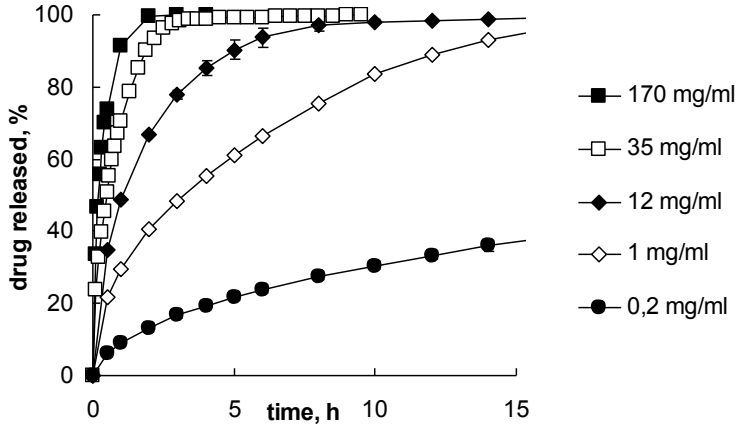

Fig. 23. Effect of drug solubility on release from 2 mm Kollidon SR matrix tablets containing 50 % drug.

Drug release of very and freely soluble drugs has to be further retarded to obtain controlled release whereas drug release of sparingly soluble drugs has to be accelerated to avoid incomplete release.
In the literature several parameters have been investigated to modify drug release from matrices (i.e. drug loading, post compaction treatment, matrix preparation method, and matrix size; e.g. Azarmi 2005, Caraballo 2000, Crowley 2004, El Arini 1997, Melgoza 1998, Siepmann 2010).

Drug loading

For the soluble drug caffeine, blends with polymer in weight ratios of 100/0 to 5/95 were prepared and compressed on a single punch tablet press. Eudragit RS and ethyl cellulose were considered as alternative polymer candidates, but ethyl cellulose powder exhibited flowability problems. Therefore, this polymer was excluded from the direct compression studies. All investigated blends with Kollidon SR and Eudragit RS resulted in tablets with considerable strength. This confirmed the suitability of the polymers as single excipient for matrix tablet formulation, apart from the obligatory glidant and lubricant. However, the obtained tablet hardness at similar compression forces differed with regard to

polymer type and content (Fig. 24). In case of Eudragit RS the tablet strength decreased with increasing polymer content while it increased for Kollidon SR. Thus, a higher compactibility can be concluded for the latter polymer.

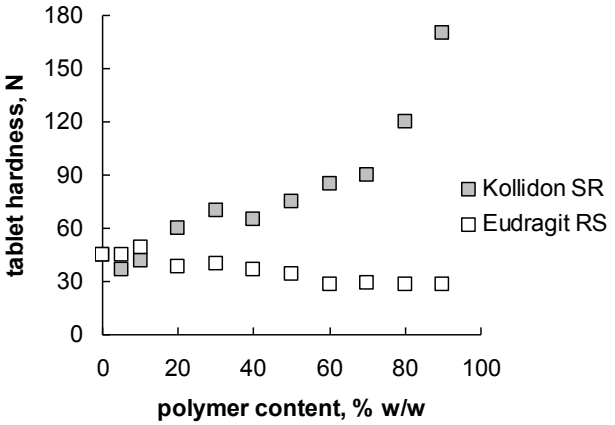

Fig. 24. Effect of polymer content on the tablet hardness of binary drug / polymer blends compressed at 10 kN compression force.

The obtained tablets were investigated concerning their drug release profiles. The caffeine dose was liberated with a declining rate over time in 20 min – 40 h dependent on the composition of the matrix (Fig. 25). In case of Kollidon SR (Fig. 25A) the release retardation increased with decreasing drug loading and consequently increasing polymer content. This can be explained by a decreased porosity of the matrix at higher polymer content (Shao 2001). Moreover, with up to 20 % polymer the matrices visibly eroded during release, which led to an increased surface area and rather uncontrolled release. Above that polymer concentration the tablets stayed intact and drug was released by diffusion through the polymer matrix (Siepmann 2010). Defining high dose formulations as matrices with at least 50 % drug, controlled release profiles of 5 – 7 h can be achieved for caffeine with Kollidon SR.

In case of Eudragit RS (Fig. 25B), similarly the release duration increased with decreasing drug content up to 50 %. These tablets all showed erosion during release, so that high dosed matrices could not be formulated with this polymer by direct compression. Only below drug concentrations of 50 % the tablets stayed intact, but interestingly exhibited similar profiles. With increasing polymer content no further decrease of drug release was obtained.

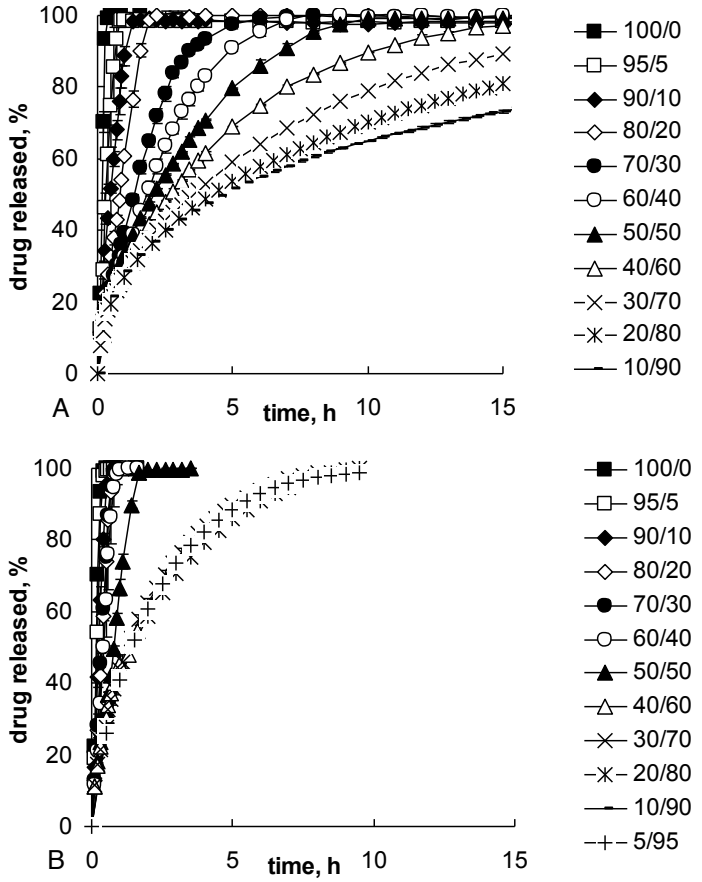

Fig. 25. Effect of drug loading on caffeine release from directly compressed 6 mm tablets containing A) Kollidon SR and B) Eudragit RS.

The release from Eudragit RS matrices was overall faster compared to Kollidon SR.

A different behaviour of the polymers due to differences in tablet strength was hypothesized. The stronger Kollidon SR tablets generally showed slower release than the weaker Eudragit RS tablets and withstood erosion at higher drug content. Subsequently the excipient percolation threshold that determines matrix integrity was located at Kollidon SR concentration of 20 – 30 % w/w and Eudragit RS concentration of 50 – 60 % w/w. Further evaluations about drug release affecting polymer properties were aimed at (see 'The effect of polymer properties').

Post-compression treatment

Post-compression treatment with heat was investigated as an approach to reduce the release rate from the directly compressed tablets (Azarmi 2002). Polymer concentrations slightly below the excipient percolation threshold (80/20 Kollidon SR, 50/50 Eudragit RS) were selected, because these formulations would show the strongest response in changing the release mechanism from erosion-controlled to diffusion-controlled.

On the one hand, Kollidon SR matrices (Fig. 26A) were neither affected by treatment with temperatures of 40 °C nor 60 °C. Dry heat alone had no impact on drug release. Hence, further investigations on this subject were intended (see 'The effect of polymer properties'). On the other hand Eudragit RS tablets (Fig. 26B) already responded to storage at room temperature and showed diffusion controlled release after thermal treatment. Fusion of the polymer particles during heat treatment is likely resulting in strengthened matrix structures. These results hint that special attention has to be paid to Eudragit RS formulations with regard to storage induced changes of the matrix characteristics.

Even though the release profile was slowed down for formulations with 50/50 Eudragit RS, Kollidon SR tablets of the same composition still exhibited the lower release rate. Therefore, thermal treatment has its limitations with regard to formulation of controlled drug delivery systems, but can be used for stability evaluation of the matrix tablets.

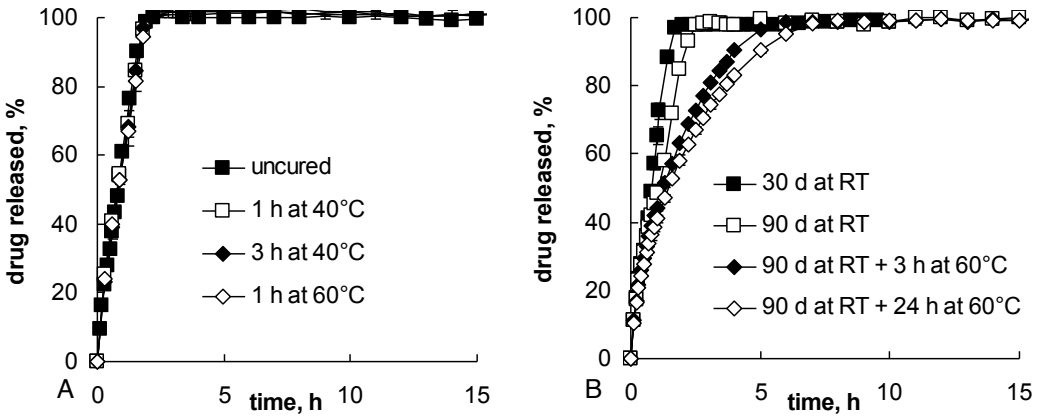

Fig. 26. Effect of thermal treatment and storage on caffeine release from directly compressed 6 mm tablets containing A) drug/Kollidon SR (80/20) and B) drug/Eudragit RS (50/50).

Direct compression can be used to formulate controlled release matrices for actives that are slightly soluble to soluble, but would fail to sufficiently retard freely and very soluble drugs.

Preparation method

Hence, another method to prepare controlled release matrices was evaluated: wet granulation of the powder blend with subsequent compression of the granules. With this technique the flowability issues of ethyl cellulose could be overcome, allowing for matrix preparation with this polymer. Lower amounts of polymer (only 10 %) were necessary to form a compact that visibly stayed intact during release independent of the polymer type. The drug release was decreased with increasing polymer content similar to directly compressed matrices (e.g. Eudragit RS, Fig. 27).

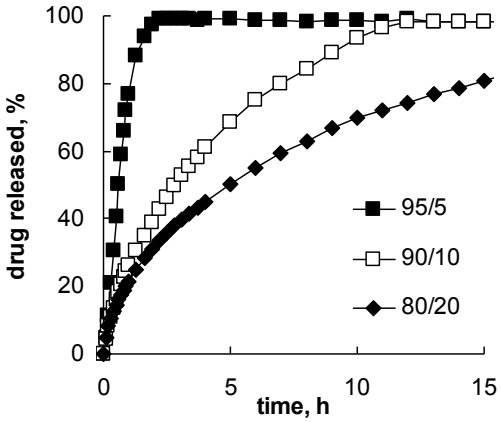

Fig. 27. Effect of drug loading on caffeine release from wet granulated Eudragit RS matrices (13 mm).

Release profiles obtained for tablets containing 70 % drug and 30 % polymer prepared by either direct compression (DC) or wet granulation (WG) were plotted in Fig. 28 for direct comparison. Both the preparation method and the polymer type had a strong effect on drug release. The slower release of wet granulated compared to directly compressed matrices, can be attributed to reduced porosity (Khan 2007).

With regard to the polymer type, the order of drug release from directly compressed tablets followed the tablet strength (Eudragit RS < Kollidon SR), as already discussed above, whereas, a different order can be read in case of wet granulated matrices (Kollidon SR < Eudragit RS < ethyl cellulose). Drug release from these matrices followed the permeability of the matrix carriers.

Fastest release was obtained with Kollidon SR, the most permeable carrier due to approximately 19 % of soluble material (polyvinylpyrrolidone). Eudragit RS is the second permeable carrier within the investigated polymers allowing water diffusion through hydrated quaternary ammonium groups in the polymer, making one in forty side chain residues. Ethyl cellulose exhibited slowest drug release, because it is itself impermeable for water.

Release durations of 10 – 16 h were thus obtained for caffeine at loadings of 70% w/w in dependence of the matrix polymer. Hence, flexible release profiles can be realized in formulation of matrices by choosing different polymers.

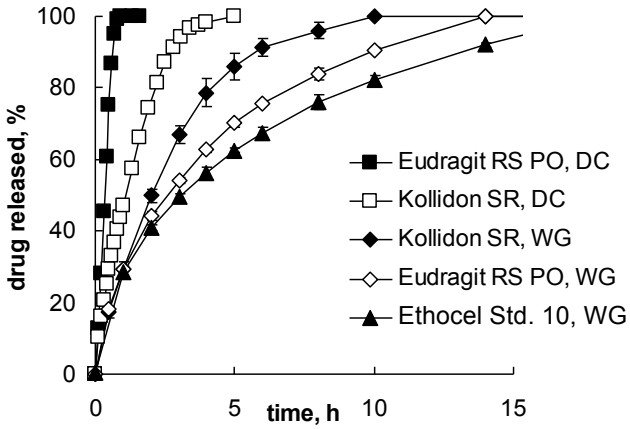

Fig. 28. Effect of matrix polymer and preparation method on caffeine release from 6 mm matrix tablets with drug/polymer (70/30).

Matrix dimensions

Finally, matrix dimensions were investigated as a common formulation tool. Matrix granules with diameters larger than 500 μm were studied regarding drug liberation alongside matrix compacts of 2 – 13 mm diameter (Fig. 29). A strong increase of release duration was observed with increasing matrix dimensions, due to the increased diffusion paths, resulting in 3 – 20 h profiles. Hence short diffusion paths (i.e. small matrices) should be selected for slightly and sparingly soluble drugs to counteract the solubility effect on drug release. In contrast, long diffusion paths (i.e. large matrices) would result in retardation of freely soluble drugs.

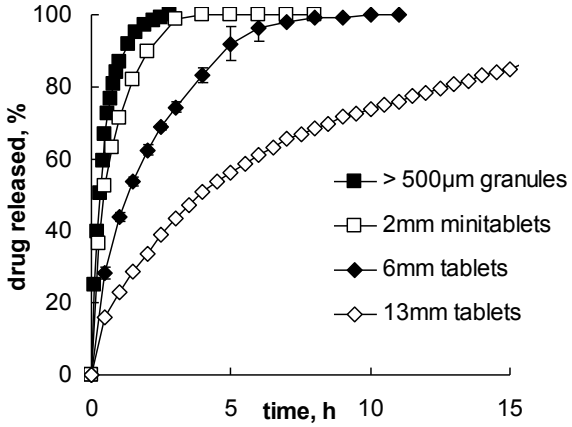

Fig. 29. Effect of tablet diameter on drug release from caffeine/ethyl cellulose (90/10) matrices.

The relationships of matrix surface area and drug solubility (as parameters with strong impact) and the release rate were determined pursuant to Ritger and Peppas and accordingly Higuchi (Fig. 30; Higuchi 1963, Ritger, Peppas 1987). Linearity was obtained for the matrix surface area allowing for estimation of drug release profiles within the linear range of the parameter. In case of the active's solubility, the release rate of the formulation of the freely soluble drug diprophylline deviated from the otherwise linear relationship obtained for the other drugs. A possible reason is the high solubility of the drug. After immersion in water, the drug will be fully dissolved and with the diffusion of the molecules out of the matrix the concentration within the matrix will decrease over time. A reduced gradient (reduced driving force for diffusion) and therefore a reduced release rate is the result.

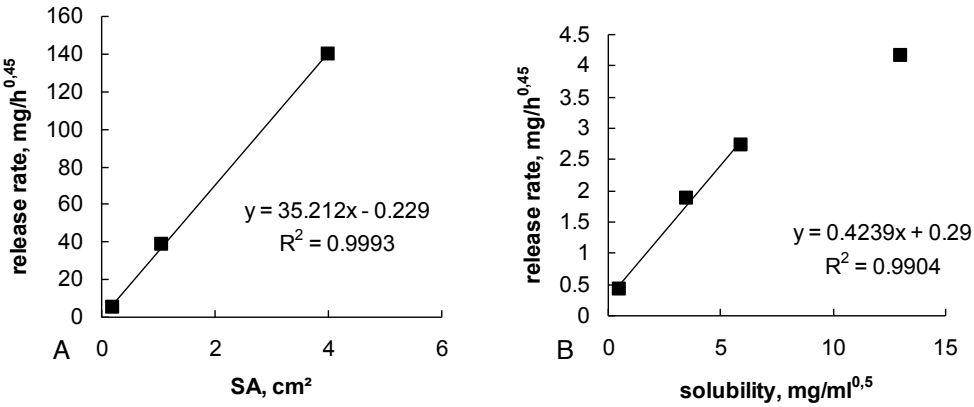

Fig. 30. Drug release rate vs. A) matrix' surface area (caffeine/ethyl cellulose 90/10), B) drug solubility (drug/Kollidon SR 50/50)

To summarize the obtained results, the time of 80% drug released from the obtained and estimated release profiles was plotted vs. the solubility of the drug (Fig. 31). Controlled release formulations could be manufactured for all drugs independent of their solubility. Slightly and sparingly soluble drugs that result themselves in retarded release due to their low dissolution rates should be best formulated as granules or minitablets, so that diffusion paths are short. Highest flexibility in formulation with regard to composition, matrix dimension and preparation method was determined for soluble drugs. The biggest challenge in controlled release matrix tablets is the formulation of freely soluble drugs. They needed the highest content of release retarding polymer and the largest dimensions.

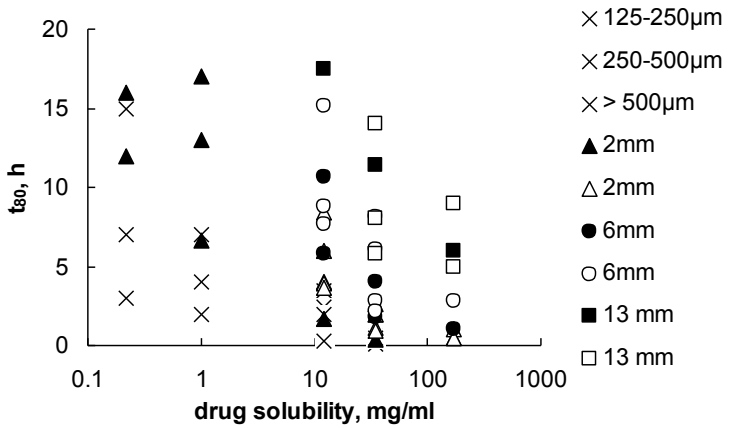

Fig. 31. Summary plot of t_{80} vs. solubility for matrices of different dimensions and compositions. Closed symbols represent direct compression, open symbols wet granulation as preparation method.

Conclusions

Matrix size, drug loading, preparation method and polymer type were identified as formulation parameters for controlled release matrices. Flexible release patterns can be realized for high dose drugs independent of their aqueous solubility.

The derived design space allows for straightforward selection of formulation parameters and thereby facilitates cost and time reduction in the formulation step of dosage form design.

Individual dosing and controlled release with matrix-minitablets for paediatric use

Background

To medicate the very heterogeneous group of children high flexibility and reliability of dosing is required alongside easy and convenient administration.

Minitablets present a drug delivery system, which combines this demand (Cox 1999, Lopes 2006). Further advantages are the formulation of controlled drug delivery systems and less susceptibility to stability problems compared to liquid or semi solid delivery systems. They have been investigated as dosage form that combines the physiological benefits of multiple units with the economic benefits of single units (Munday 1989, Sujja-areevath 1996).

Minitablets are defined as tablets with diameters smaller than 3 mm and with heights equal to their diameter resulting in approximately spherical shape (Fig. 32, Lennartz 1998). They are also referred to as ”solid drops“ to illustrate the ease of dosing and have been shown to be swallowed even by 2 year old children (Thomson 2009). Therefore, mini-matrix tablets are interesting candidates for pediatric drug delivery but have difficulties to sufficiently retard drug release of water-soluble compounds due to their high surface area and short diffusion pathways. Insoluble controlled release polymers and different methods for matrix preparation were investigated to overcome this challenge and to extend the applicability of this delivery technology to higher drug doses.

In this study a design space was envisaged including drugs of different solubilities, different matrix polymers and preparation methods.

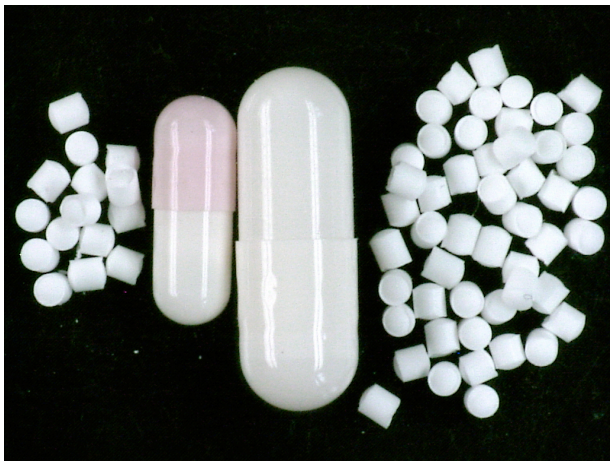

Fig. 32 Fixed dosing of 2 mm minitablets. Left capsule # 4 (15 minitablets, ~ 75 mg API), right capsule # 0 (50 minitablets, ~ 250 mg).

Materials and methods

Ethocel Std. 10 FP (The Dow chemical company, Midland, MI, USA), Kollidon SR, coarse theobromine and micronized caffeine, theophylline, diprophylline (BASF SE, Ludwigshafen, Germany), carbamazepine (F.I.S. - Fabbrica Italiana Sintetici S.p.A., Alto de Montevecchio, Italy), Aerosil 200 and Eudragit RS (Evonik Industries AG, Darmstadt, Germany), magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany), sodium carboxymethylcellulose (Clariant SE, Sulzbach am Taunus, Germany), and triethylcitrate (TEC; Merck KGaA, Darmstadt, Germany) were used as received.

Blends for tabletting

Polymer and drug powders were physically mixed in different ratios on a weight base to obtain 10 g of blend. In case of wet granulation these mixtures were wetted with isopropanol/water (88/12 w/w) to form granules and dried overnight.

Finally, 1 % w/w Aerosil and Mg stearate were added to the powder mixtures or the granules as lubricant and glidant.

Compaction

Matrix tablets were prepared by compressing the blends into tablets of different diameters with an equipped single punch tabletting machine (EK0, Korsch AG, Berlin, Germany) at a compression speed of 10 rpm and recording compression force (MGCplus, catman, HBM, Darmstadt, Germany). The tablets were further characterized regarding their dimensions and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany).

Hot melt extrusion

Hot melt extruded mini-matrices were prepared by Nutsawadee Apichatwatana, with physical mixtures of drug and plasticized polymer (10 % TEC based on polymer) in a one to one weight ratio. The blends were extruded with a conical co-rotating twin screw extruder (HAAKE Minilab Rheomex CTW5, Thermo Fischer Scientific GmbH, Dreieich, Germany) at 130 °C, with a screw speed of 20 rpm and a die diameter of 1.83 mm to obtain rods of 2 mm diameter. The matrices were cut manually into pieces of approximately 3 mm length.

Dissolution tests were performed using a USP paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), 900 mL phosphate buffer pH 6.8, at 50 rpm and 37 °C. Samples were taken at predetermined time points and analyzed spectrophotometrically (272, 290 and 295 nm, n=3).

Results and Discussion

As already discussed in Chapter 1, matrix tablets release the active compounds according to its aqueous solubility (Fig. 33). The previously identified formulation parameters were evaluated with regard to controlled release from matrix minitablets.

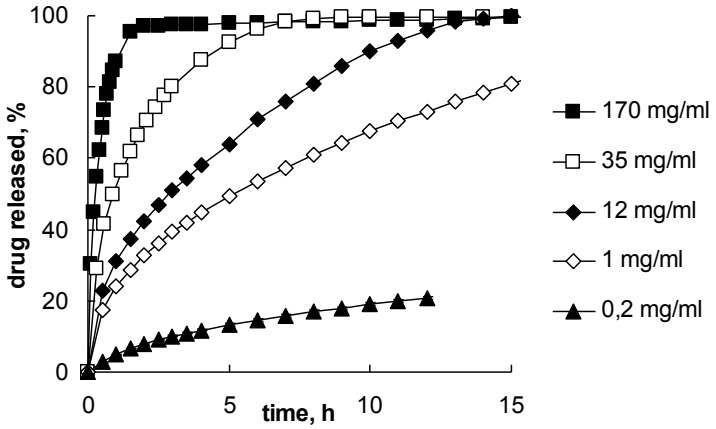

Fig. 33. Effect of aqueous solubility on drug release from 2 mm minitablets loaded with 70 % w/w drug and 30 % w/w ethyl cellulose.

The matrix size can be utilized to counteract solubility effects on drug release for sparingly soluble drugs such as carbamazepine (Fig. 34A). Granules of different diameters allow flexible release pattern, but formulated as regular minitablet the drug release would be too slow. Hence, minitablets that contain a disintegration agent, e.g. sodium carboxymethylcellulose, and break up into granules of proper sizes during dissolution make a suitable dosage form. In case of soluble drugs such as caffeine, rather larger tablets are needed to maintain controlled release (Fig. 34B). The swallowability of the tablet limits the size increase. For wet granulated minitablets with 70 % drug and 30 % ethyl cellulose a 6 h profile was obtained. With increasing the height of the minitablet or the diameter to 3 mm an increase in release duration would result, but children might not accept the tablets. Therefore, other approaches to retard the drug release further are necessary for soluble and freely soluble drugs.

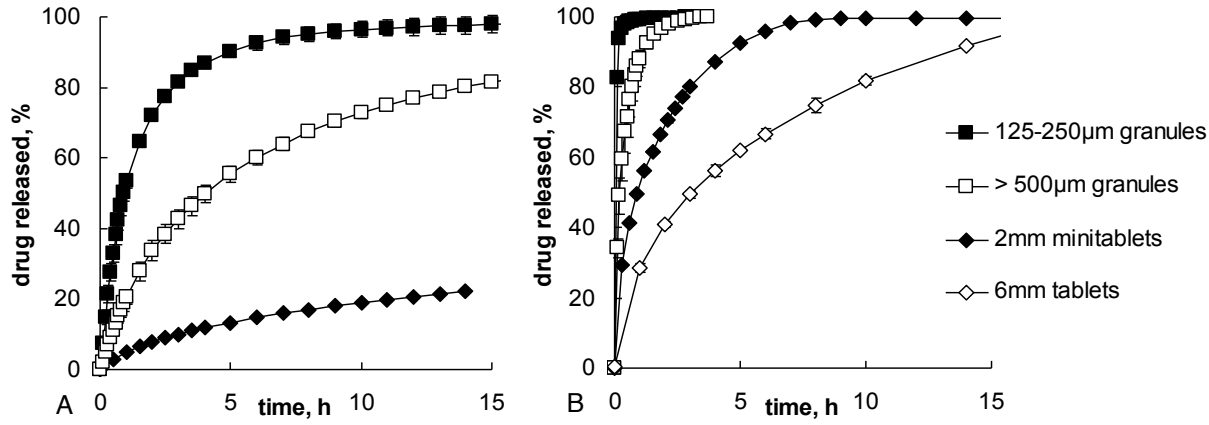

Fig. 34. Effect of matrix size on A) carbamazepine and B) caffeine release from matrices loaded with 70 % drug and 30 % ethyl cellulose.

Caffeine matrices with different compositions were formulated by direct compression and wet granulation. In both cases drug release decreased with increasing polymer content (Fig. 35), but at the same time the required amount of minitablets to administer a certain dose increased. For this reason, direct compression (Fig. 35A) failed to achieve extended release of highly dosed soluble to freely soluble drugs. In case of wet granulation the lower porosity caused stronger retardation (Fig. 35B). The lowest loading of 70 % drug resulted at least in a 6 h pattern for 2 mm minitablets, which would translate in a thrice-a-day administration. With the increased dimensions discussed above, extended release up to 16 h should be possible.

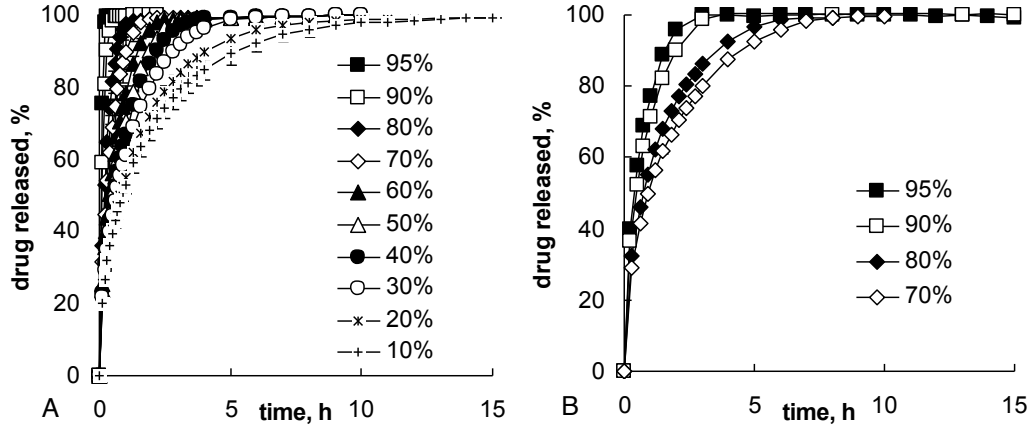

Fig. 35. Effect of drug loading on the caffeine release from 2 mm minitablets prepared by A) direct compression and B) wet granulation.

Decreased porosity seems to be the key for further drug release retardation. Hence, hot melt extrusion was investigated as matrix preparation technique producing nearly zero porosity extrudates. Due to processibility issues, the maximum drug loading was limited to 50 %. At higher loadings an increased torque and an irregular surface (so-called shark-skin) hindered production.

Ethyl cellulose matrices prepared with the three different manufacturing techniques were investigated with regard to drug release (Fig. 36). The graph clearly illustrates the differences in porosity of the delivery systems. As ethyl cellulose is itself impermeable for water and drug can only diffuse through water-filled pores, entrapment of part of the drug particles in the polymer network formed by hot melt extrusion is likely. The addition of pore formers or the application of a slightly more permeable polymer are suggested for fine-adjustment of the matrix' porosity (compare Sato 1997).

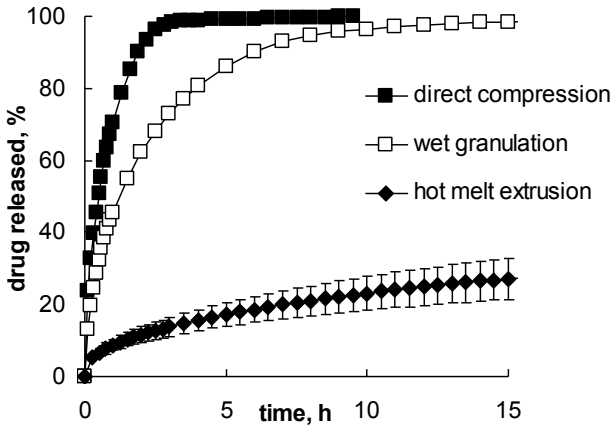

Fig. 36. Effect of preparation method on caffeine release from 2 mm ethyl cellulose minitablets.

Conclusion

To summarize the data, again a design space was formulated by plotting t_{80} of the obtained and estimated release profiles vs. drug solubility (Fig. 37). Flexible release patterns were obtained for highly dosed drugs with solubilities of 0.1 – 100 mg/ml. Key parameters were matrix dimensions, composition and preparation method. Wet granulation allowed highest flexibility with regard to matrix size and resulted in good release retardation.

For drugs with solubilities above 100 mg/ml, hot melt extrusion needs to be evaluated. Possible subjects are drug entrapment, permeability and porosity adjustment.

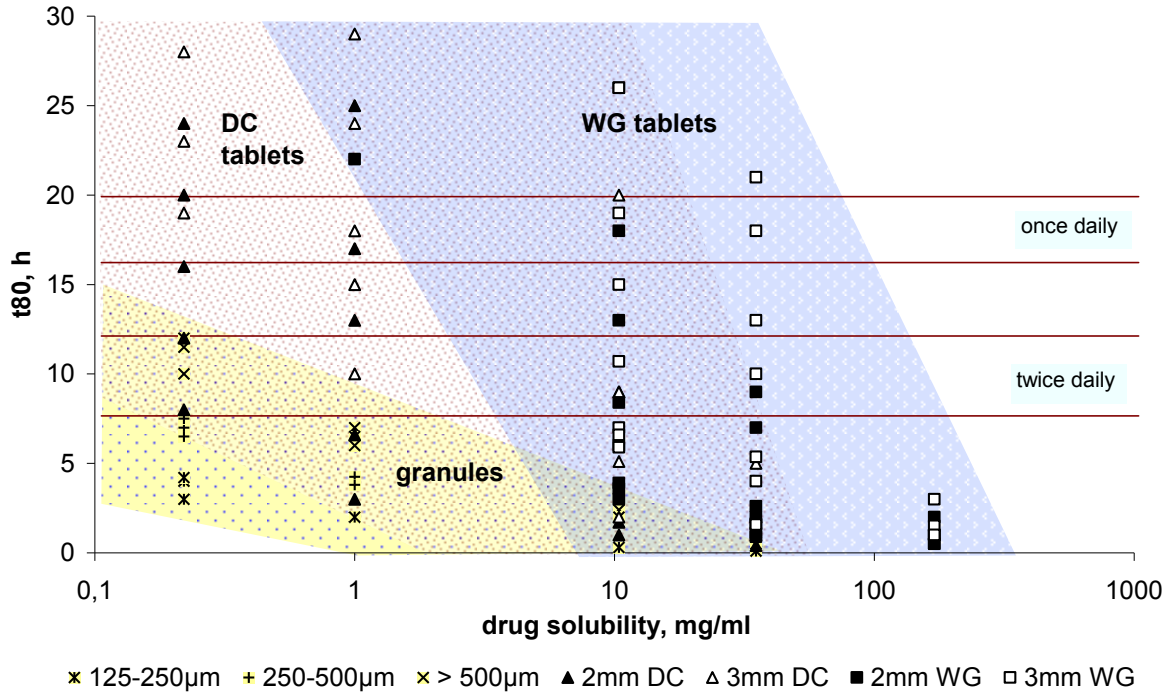

Fig. 37. Summary graph of release durations of matrices containing different drugs.

The effect of polymer properties on direct compression and drug release from insoluble matrix tablets

Background

Formulation and manufacturing of controlled release matrix tablets are well known and established processes that result in highly reproducible controlled drug delivery. Furthermore, the perpetual development of innovative functional excipients (entirely new substances as well as derivative synthesis, grafting or coprocessing of existing materials) and the evaluation of the drug delivery potential of these systems make matrix tablets an extremely interesting field of research (Colombo 2009).

Commonly used excipients for matrix preparation can be subdivided into water-soluble and water-insoluble carriers. Tablets prepared with the former dissolve or erode with time, dependent on their molecular weight and solution viscosity (Viridén 2009), whereas tablets made with the latter stay intact during drug release and are excreted as an empty scaffold (Barra 2000). Polymer properties affecting the integrity and drug release from insoluble matrices are not fully evaluated, yet. Typical examples of insoluble carriers are Kollidon SR (co-processed polyvinylacetate and polyvinylpyrrolidone, ratio 8:2), Eudragit RS (poly(meth)acrylate) and ethyl cellulose, which allow matrix preparation by direct compression, the simplest and most cost effective method for tablet manufacturing (Neau 1999, Leuenberger 1995, Kranz 2005, Caraballo 1996).

The concepts of percolation theory were evaluated for such matrices with regard to tabletting and drug release (Leuenberger 1987, Bonny and Leuenberger 1993). The percolation threshold of a component is the critical concentration necessary to form a coherent network and to dominate the properties of the whole system. In case of insoluble matrices important features are drug release retardation combined with matrix integrity, which can only be obtained if the percolation threshold of the polymer is exceeded. A bond percolation threshold, where particles of the same species are connected via weak interparticular bonds, and a site percolation threshold, discernible by measurable cohesion, can be distinguished (Leu and Leuenberger 1993). Below the percolation threshold, matrix tablets would erode (below site percolation) or even disintegrate (below bond percolation), resulting in fast liberation of the drug. Drug percolation thresholds have been estimated by the break of slope of the "tablet property ß", the slope of the Higuchi equation, vs. total porosity plot (Higuchi 1963, Bonny and Leuenberger 1991), but this approach could not predict the polymer percolation (Caraballo 1999). Significant matrix characteristics can be derived from the Higuchi equation, such as tablet dimensions and porosity, but it fails to describe polymer properties affecting drug release.

The objective of this study was the determination of the polymer percolation threshold and the identification and evaluation of polymer properties affecting processing and drug release. The results will enable knowledge-based formulation of insoluble matrix tablets and may contribute to the development of functional excipients.

Materials and methods

Materials

Ethocel Std. 10 and Std. 10 FP (The Dow chemical company, Midland, MI, USA), Kollidon SR, Kollidon 30 and micronized diprophylline (BASF SE, Ludwigshafen, Germany), Aerosil 200 and Eudragit RS (Evonik Industries AG, Darmstadt, Germany), and magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany) were used as received.

Characterization of polymer particles

The particle size distributions of the polymer powders were measured using laser diffractometry (LS 230, Beckman Coulter GmbH, Krefeld, Germany). Particle shape was analyzed microscopically (Zeiss Axioscope, Carl Zeiss Jena GmbH, Jena, Germany; magnification 10x). Flow properties were assessed by utilizing a tap densiometer (Erweka GmbH, Heusenstamm, Germany) and calculating the Hausner ratio. In addition the flow energy was determined with the PT4 Powder rheometer (Freeman technology, Tewkesbury, UK) at similar conditions reported by Lindberg (2004), but for a tip speed of 30mm/s.

Blends for tabletting

Different polymer powder fractions were prepared by sieve classification (100 μm, 125 μm, 250 μm, 315 μm, 425 μm and 500 μm; Analysette 3 PRO, Fritsch GmbH, Idar-Oberstein, Germany). The micronized model drug was granulated with PVP-solution (1 % w/w), dried overnight and classified to obtain different size fractions.

Polymer and drug powders were physically mixed in a 6:4 ratio w/w to obtain 10 g of blend. In case of wet granulation these mixtures were wetted with isopropanol/water (88/12 w/w) to form granules and dried overnight.

Finally, 1 % w/w Aerosil and Mg stearate were added to polymer powder alone, the powder mixtures or the granules as lubricant and glidant.

Compaction

Compaction behavior was evaluated by compressing the blends into 7 mm flat faceted tablets with an instrumented single punch tabletting machine (EK0, Korsch AG, Berlin, Germany) at a compression speed of 10 rpm. Compression force and upper and lower punch displacement were recorded during the compaction process (MGCplus, catman, HBM, Darmstadt, Germany). The net work of compaction, as well as elastic and plastic work was obtained by calculating the areas under the curve of the force-displacement diagrams of the upper punch (List 1985).

Tablet characterization

The tablets were further characterized regarding their dimensions and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany) allowing the comparison of different sized tablets by calculating the tensile strength of the tablets, σ_0, according to Fell and Newton (1970).

$$\sigma_0 = \frac{2P}{\pi D t}$$

P represents the force applied to form the tablet and *D* denotes the diameter and *t* the thickness of the tablet. The porosity of the compacts was derived from the ratio of apparent and true density.

To investigate the impact of thermal treatment, tablets containing Kollidon SR and Eudragit RS as matrix former were subjected to dry heat at 25 K above glass transition temperature of the polymer, whereas tablets of all matrix polymers were subjected to heat/humidity treatment at 60 °C/75 % RH for 24 h respectively (oven Heraeus T6060, Thermo Fischer Scientific GmbH, Dreieich, Germany).

Dissolution tests were performed using a USP paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), 900 ml phosphate buffer pH 6.8, at 50 rpm and 37 °C. Samples were taken at predetermined time points and analyzed spectrophotometrically at 272 nm.

Water uptake and weight loss were determined gravimetrically by weighting tablets in dry, wet and dried state (dried at 105 °C overnight, Heraeus T6000, Hanau, Germany) and swelling of tablets was measured macroscopically (IQ easy measure, INTEQ Informationstechnik GmbH, Berlin, Germany).

All measurements were performed in triplicate.

Scanning electron microscopy (gold sputtering, Hitachi S2700, Hitachi Kabushiki-gaisha, Tokyo, Japan) was used to investigate the breaking surfaces of polymeric tablets after diametrical hardness testing.

Results and discussion

Characterization of polymer particles

Direct compression of tablets requires good flowability and compactibility of the excipients to guarantee reproducibility of the process and product quality.

The flowability of a powder depends on material properties like the particle surface, size and shape (Lindberg 2004). Table 11 summarizes the properties of the polymers used in this study.

Table 11. Surface properties and particle size of the matrix polymers.

Polymer	Glass transition temperature [1]	Particle shape	Particle size, μm			Hausner ratio		Flow Energy, mJ	
			10 % <	50 %<	90 %<	Mean	SD	Mean	SD
Kollidon SR	35°C	Spherical	29.3	86.5	156.0	1.19	0.03	4.6	0.4
Eudragit RS	58°C	Irregular	28.8	94.4	175.8	1.33	0.02	11.0	0.4
Ethocel Std. 10	133°C	Irregular	60.4	277.4	522.0	1.25	0.00	21.1	4.1
Ethocel Std. 10 FP		Irregular agglomerates	6 – 10 [1]			1.33	0.05	n.d	

[1] product brochures of the manufacturers (Bühler 2008, Evonik 2012, Dow 2005)

Kollidon SR particles were spherical in shape, while the other polymers exhibited irregular shaped particles (Fig. 38). Only marginal differences could be seen between Kollidon SR and Eudragit RS regarding particle size, whereas ethyl cellulose particles of the standard grade were larger. The fine powder grade consisted of very small particles of approximately 10 μm according to the manufacturer but tended to agglomerate to clusters of up to 1 mm in diameter hindering accurate measurement by laser diffractometry.

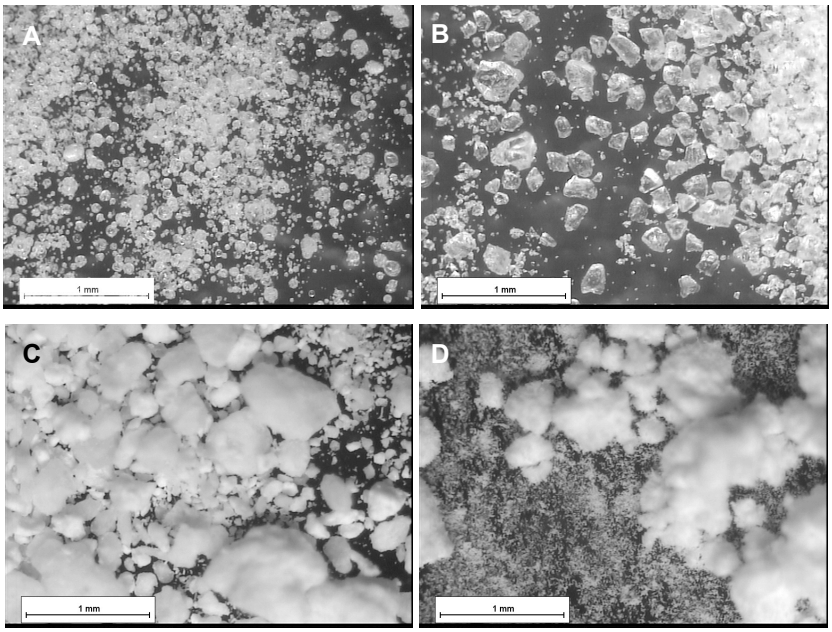

Fig. 38. Macroscopic pictures of A) Kollidon SR, B) Eudragit RS, C) Ethocel Std. 10 and D) Ethocel Std. 10 FP

Hence, highest flowability was expected for Kollidon SR amid the investigated polymers and confirmed by the lowest Hausner ratio and flow energy. Eudragit RS and ethyl cellulose exhibited little higher Hausner ratios and flow energies, indicating higher surface roughness of the particles. Therefore, powder flow through a vibrating funnel was determined, to ensure processibility. A differentiation of the materials was not obtained by this method, because all polymers showed comparable flow of approximately 5 g/s. Only the fine powder grade of ethyl cellulose differed. Here, powder flow was completely prevented by arching due to the higher surface area and subsequently higher cohesive forces and friction between particles. Hence, this material cannot be used without addition of any glidants.

The compactibility of the polymers followed the order: Eudragit RS < ethyl cellulose < Kollidon SR (Fig. 39A). From punch force-displacement curves the proportion of plastic and elastic work in total work of compaction was determined (Fig. 40).

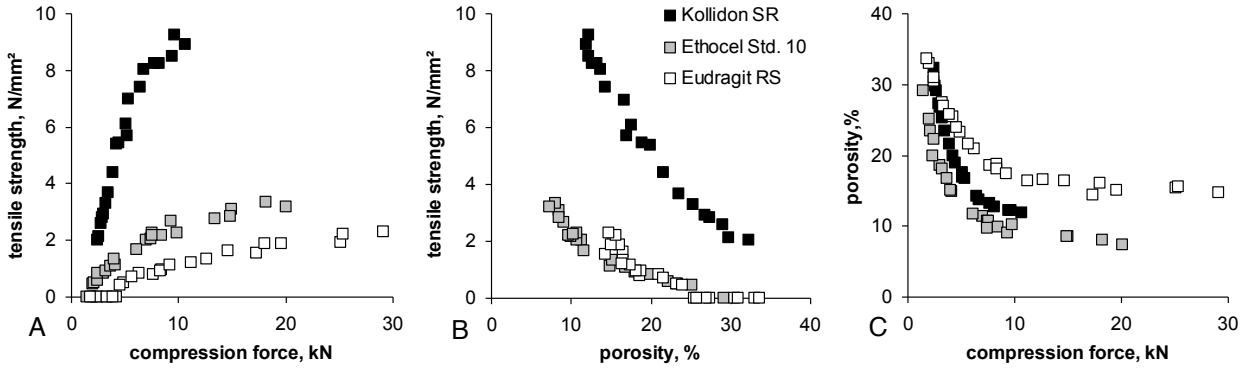

Fig. 39. Compactibility of matrix polymers: A) tensile strength in dependence of applied compression force; B) tensile strength in dependence of resulting porosity; C) resulting porosity in dependence of applied compression force.

With increasing compression forces the proportion of plastic work decreased and that of elastic work increased. The dominant densification mechanism was plastic deformation, confirming previous results obtained for Kollidon SR and ethyl cellulose (Reza 2003, Katikaneni 1995). The plasticity was almost similar for all polymers (slightly lower for ethyl cellulose) but the degree of elastic deformation differed, following the glass transition temperature of the polymers (Fig. 40, Table 11).

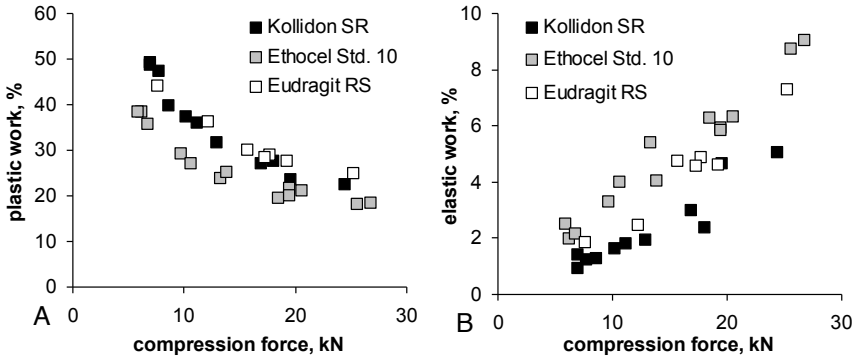

Fig. 40. Plastic and elastic work relative to the total work of compaction of matrix polymers in dependence of applied compression force.

The deformation behavior should generate a different compactibility order than the one observed, but diverse binding mechanisms need to be taken into account. The contribution of mechanical interlocking of the polymer particles is more likely for irregular particles and stronger the rougher the surface. This could explain the higher compactibility of ethyl cellulose particles which exhibited the highest surface roughness (Table 11).

The impact of particle size on compaction was analyzed by compressing different polymer size fractions into tablets (Fig. 41). No effect was seen for Kollidon SR, but the other polymers were sensitive to size effects (confirming previous results for ethyl cellulose, Katikaneni 1995). Generally, the polymer particle size affected the hardness of a tablet but not the required compaction force except for very large particles (ethyl cellulose > 500 μm). The size dependence of compactibility followed the order of Kollidon SR < Eudragit RS < ethyl cellulose, which was consistent with the flow energy and the glass transition temperature of the materials (Table 11). When comparing the particle size fractions to the bulk materials, the overall compactibility could be considered as the mean value of the individual compactibilities, so that the particle size could be used as formulation tool if poor matrix hardness and integrity is an issue.

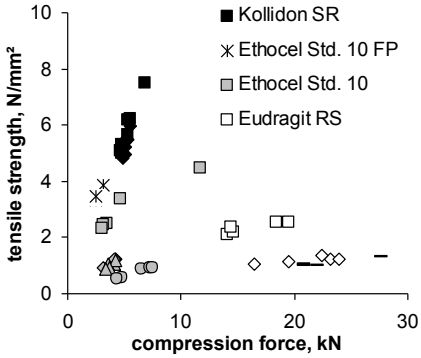

Fig. 41. Effect of particle size on the compactibility of polymers: < 125 μm (□), 125-250 μm (◇), 250-315 μm (△), 315-500 μm (○), > 500 μm (-). Tablets with fixed porosity of 16 % v/v.

Differences in matrix integrity could also be seen in SEM pictures of the surfaces of diametrically broken polymer tablets compressed with 20 kN (Fig. 42). Kollidon SR matrices appeared as a continuous dense mass with a clean break, whereas individual particles and pores could be clearly distinguished for Eudragit RS. Ethyl cellulose tablets had a rough breaking surface where cracks parted the aggregates formed during compaction. The pictures also stressed that tablets have to be considered as binary systems of solids and gas, often referred to as tablet porosity.

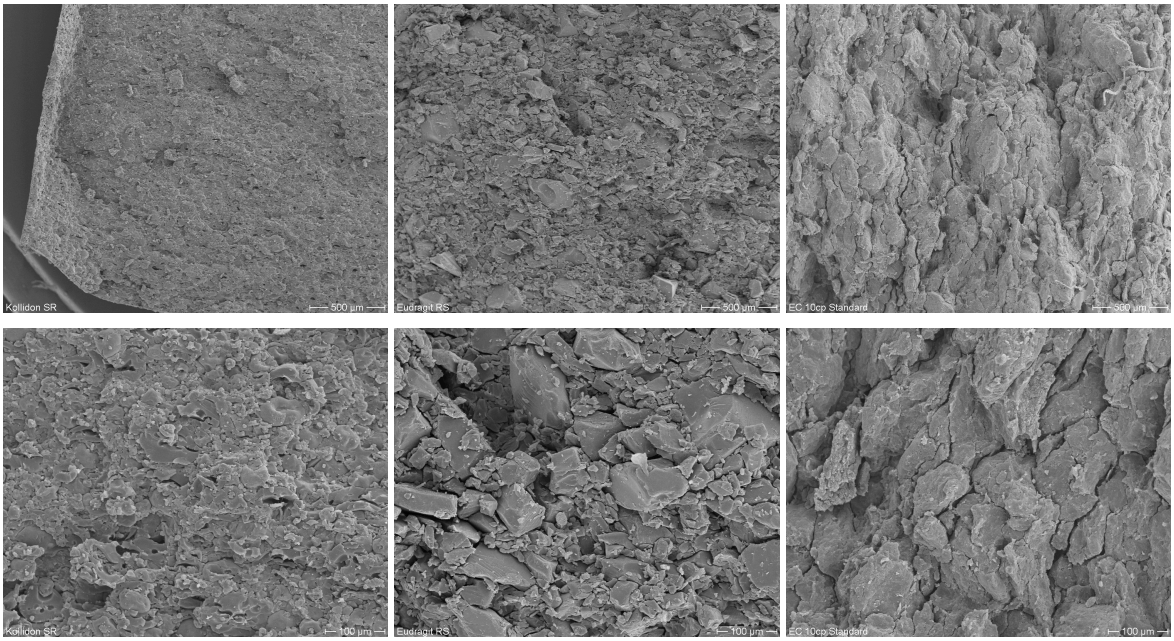

Fig. 42. SEM photographs of polymer compacts´ surfaces after diametrical breaking. Kollidon SR, Eudragit RS and ethyl cellulose (left to right), scalebars (500 μm in the top line and 100 μm in the bottom line) in the bottom right corner of each picture.

Tablets – binary systems (polymer and air)

The analysis of the compaction data regarding air content of the compacts revealed that a porosity of more than approximately 35 %, or a volume fraction of less than 65 % polymer, did not result in compacts similar for all polymers (Fig. 39B, 39C). At this air content the inter-particle binding was insufficient to maintain the geometric form of the tablet and as a result disintegration into smaller particle aggregates occurred. This critical concentration can be regarded as site percolation threshold of the polymer (Leu and Leuenberger 1993).

Lower air content resulted in stronger tablets (Fig. 39B). The tensile strength-porosity plot also confirmed the superior compactibility of Kollidon SR, but revealed that ethyl cellulose and Eudragit RS tablets exhibited similar hardness at the same air content. They only differed in the smallest achievable porosity, which was ~ 8 % and 15 % for ethyl cellulose and Eudragit RS, respectively. Application of higher compression forces did not result in denser tablets due to increasing elastic recovery (Fig. 39B).

Tablets - ternary systems (polymer, drug and air)

The drug used in this study, diprophylline, was micronized and thus exhibited poor flowability, but on the other hand acceptable compactibility.

Drug containing matrices were formulated with a polymer volume fraction of approximately 56%, which was close to the site percolation threshold of the polymer observed before. The surface area of the

tablets was controlled and the porosity was set to 16 % (84 % solids fraction) so that matrix integrity after compaction was given. The particle size effect on matrix hardness was verified for ternary systems of drug, polymer and air (data not shown), confirming the organization effect on compactibility (Barra 1999).

During drug release experiments the drug would dissolve leaving a polymer scaffold surrounding water filled pores. At the adjusted polymer volume fraction surface erosion was expected and every parameter changing the percolation threshold would have a recognizable impact on matrix integrity, resulting in either tablet disintegration or coherence. Hence the matrix system was very sensitive and identification of critical properties was facilitated.

Drug release – polymer type

Drug release of tablets prepared with identical organization, dimensions and porosity was plotted in Fig. 43. The fastest release profile was obtained for Eudragit RS, followed by ethyl cellulose and Kollidon SR. Percolation of the polymer could be assumed since no pronounced erosion of particles occurred from the matrix surface.

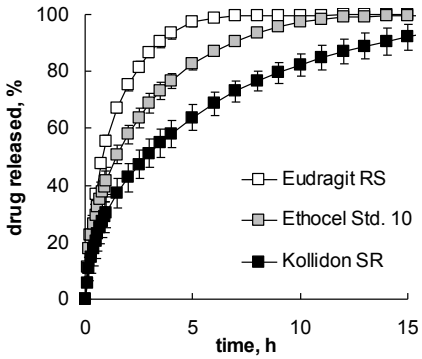

Fig. 43. Effect of polymer type on drug release from matrix tablets (drug particle size / polymer particle size ratio 425 μm / < 125 μm).

In previous studies a decreased glass transition temperature in presence of elevated humidity was reported for PVP and Kollidon SR (Oksanen 1990, Hauschild 2006). Therefore, the conversion of Kollidon SR from glassy to amorphous state was possible in wet state at 37 °C. The interaction between aqueous media and the polymers was investigated by studying water uptake and weight loss for drug free films and tablets (Fig. 44). Kollidon SR and Eudragit RS films as well as tablets showed high water uptake exceeding the pore volume calculated from their total porosities. The polymers have to swell to keep these amounts of water, indicating polymer mobility for both materials. Ethyl cellulose films took up negligible amounts of water confirming its suitability as moisture barrier, whereas the extent of water uptake in tablets was consistent with the filling of all pores.

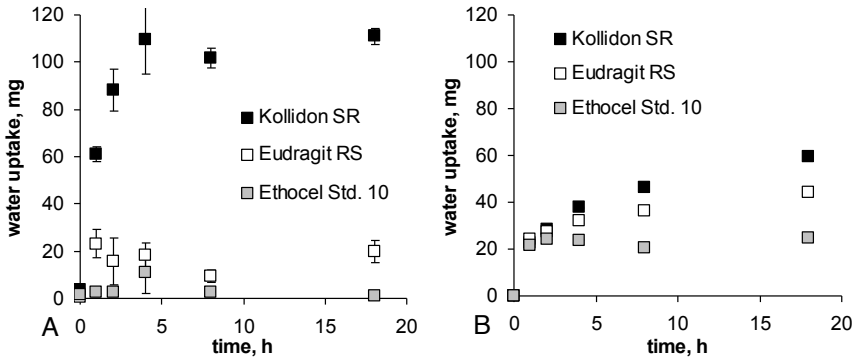

Fig. 44. Water uptake of A) polymer films and B) matrix tablets (16 % v/v porosity).

Weight loss after drying of Kollidon SR tablets was high compared to the insignificant amounts of the other polymers. It revealed that part of the povidone was leached from the matrices confirming previous results (Shao 2001). The diffusion of polymers is considerably slow compared to small drug molecules (Wesselingh 1993), so that supposedly more povidone dissolved than what diffused out. This is significantly changing the microenvironment inside the tablet. A povidone solution exhibits an increased viscosity compared to aqueous buffer solution (Bühler 2008), which will decrease general diffusivity. That means water penetration into the matrix, as well as drug diffusion out of the tablets, will be decreased.

The differences seen in drug release can be explained by these findings: When immersed in dissolution medium, Kollidon SR and Eudragit RS matrices swelled, increasing the surface area from which drug release occurred compared to ethyl cellulose matrices. But in case of Kollidon SR matrices the diffusion of drug out of the matrix was decelerated by the dissolution of povidone inside the matrix resulting in much slower release. This hypothesis could be confirmed with Eudragit RS matrices containing PVP in a similar ratio as Kollidon SR that exhibited almost equally retarded drug release (see 'The effect of polymer properties - Supplementary data').

Drug release – particle size of drug and polymer

The particle size dependence of compactibility found for binary systems was reflected in drug release studies from ternary structures (Fig. 45) and was governed by the glass transition temperature. On the one hand, for Kollidon SR only marginal differences could be seen. All matrices stayed intact during drug release, implying polymer fusion and percolation. Diprophylline liberation was retarded over 15 h independent of the particle sizes (Fig. 45A). On the other hand, the polymers Eudragit RS and ethyl cellulose showed particle size dependent profiles. For better comparison the drug/polymer size ratio was employed. At ratios < 1 the matrices disintegrated, whereas at ratios ≥ 1 integrity of the tablets was maintained (Fig. 45B and 45C). In case of Eudragit RS, overall drug release was very fast and

differences between matrices that stayed intact during drug release were insignificant. Whereas in case of ethyl cellulose, a higher ratio caused further retarded drug release. Consequently, strongest tablets and best retardation of drug could be achieved with the fine powder grade of the polymer, but manufacturing was challenging for flow and segregation issues.

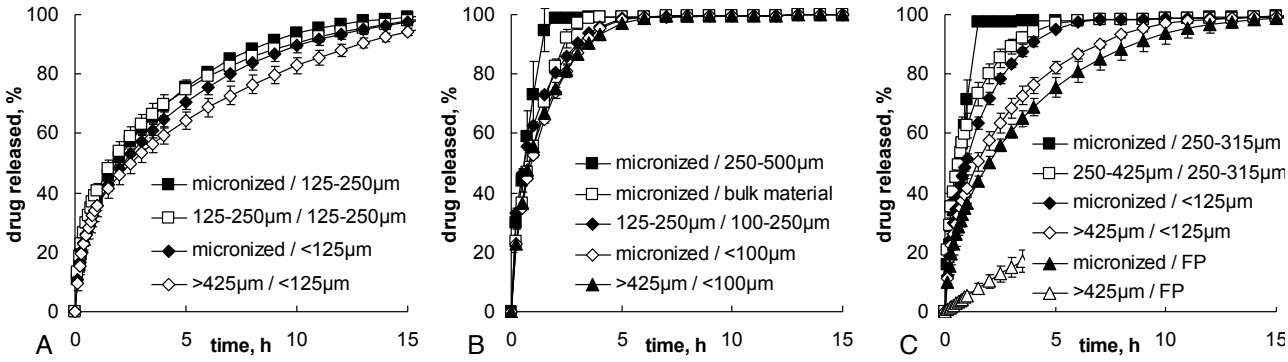

Fig. 45. Effect of drug particle size / polymer particle size ratio for different matrix polymers A) Kollidon SR; B) Eudragit RS; C) Ethocel Std. 10 .

The effect of drug and polymer particle size could be explained by a shift in the percolation threshold of each of the constituents with smaller particles percolating at lower concentrations (Caraballo 1996, Millán 1998, Barra 2000). Moreover, at similar porosities, the pore size and distribution differed according to the drug/polymer size ratio, changing the path length (tortuosity) for the diffusing molecules (Crowley 2004). The tortuosity was used as fitting parameter for the Higuchi model (Higuchi 1963), but with the knowledge of the size effect it can be replaced by a measurable feature.

Percolation threshold – wet state

From the drug release experiments differences in polymer percolation thresholds for the matrix carriers can be concluded. A critical concentration less than 55 % v/v polymer was observed for Kollidon SR, because fusion of the polymer in wet state caused coincidence of bond and site percolation, contributed to matrix integrity and diminished the particle size effect. The other two polymers differed only slightly in cohesion. The size dependent site polymer threshold of close to 65 % volume fraction observed for dry matrices could be confirmed.

Preparation method

Matrices were formulated by wet granulation, which is known to affect the flowability as well as the distribution of the polymer in the tablet blend. Therefore, bond as well as site percolation thresholds of the polymer might be reduced. The physical mixture of drug and polymer was wetted with organic solution to dissolve the polymer particles and form solid bridges after drying.

In case of Kollidon SR no difference between directly compressed and wet granulated matrices was expected due to fusion of the polymer during dissolution. But wet granulated matrices exhibited faster drug release than those prepared by direct compression (Fig. 46A). Similar results were observed after granulation with aqueous media (Riis 2007), which was attributed to a loss in polymer structure. Segregation of the co-processed polymers is likely due to different solubility in the granulation fluid. Clusters of povidone form that result in increased pore radii and therefore, decreased tortuosity after dissolution.

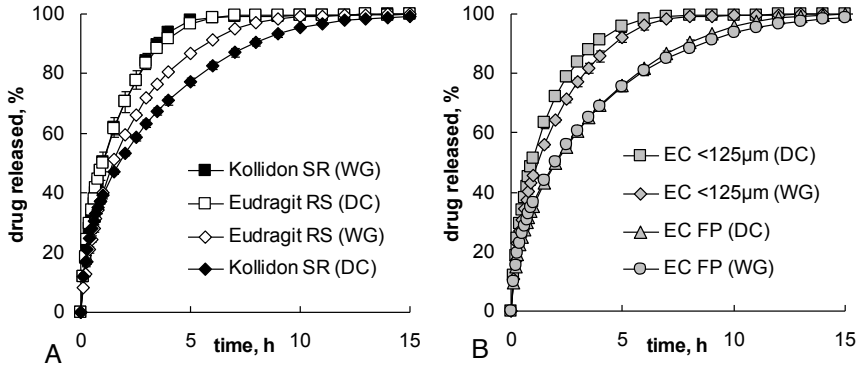

Fig. 46. Effect of preparation method on drug release from matrix tablets (polymers: A) Kollidon SR, Eudragit RS, B) Ethocel Std. 10 and Std. 10 FP).

Only little or no effects were seen for Eudragit RS and ethyl cellulose matrices, respectively (Fig. 46A, 46B). In contrast to literature (e.g. Khan 2007), the porosity of the tablets after compaction was kept constant. Furthermore, these polymers are known to form rather brittle films (Abbaspour 2007, Rekhi and Jambhekar 1995), thus the bondages that occurred due to dissolution and precipitation of the polymer particles in wet granulation might be broken by the compaction forces during tabletting.
Consequently, above the percolation threshold of the polymer, wet granulation alone cannot provide further drug release retardation for the polymers under investigation.

Thermal treatment

Improved contact between the polymer particles, decreased porosity and increased tortuosity of the matrices due to thermal treatment of tablets after compaction was reported in the literature (Shao 2001, Azarmi 2005). Because of the high T_g of ethyl cellulose, the required temperature exceeded 150 °C. Hence, tablets with this carrier were not treated. The effect of thermal treatment of Kollidon SR and Eudragit RS tablets on tablet hardness is shown in Table 12.

Table 12. Effect of preparation method and thermal treatment on tablet hardness.

Polymer	Hardness of tablets, N			
	Direct compression		Wet granulation	
	After compaction	Thermally treated	After compaction	Thermally treated
Kollidon SR	110	160 (44 °C) 192 (64 °C)	110	160 (64 °C)
Eudragit RS	70	140 (63 °C) 155 (83 °C)	70	110 (83 °C)

Breaking strength of the tablets was considerably higher after thermal treatment, promoting polymer fusion due to increased mobility. A change in dimensions and therefore porosity of the tablets was not observed, but redistribution of the pores is possible. Drug release from thermally treated tablets was not affected in case of Kollidon SR tablets, suggesting that polymer mobility is higher in the wet state (during dissolution testing) than in the dry state (during thermal treatment, Fig. 47A). However, Eudragit RS matrices showed slightly decreased release after thermal treatment of directly compressed tablets and an even stronger effect on wet granulated tablets, which can be explained by regeneration of the solid bridges obtained during wet granulation (Fig. 47B).

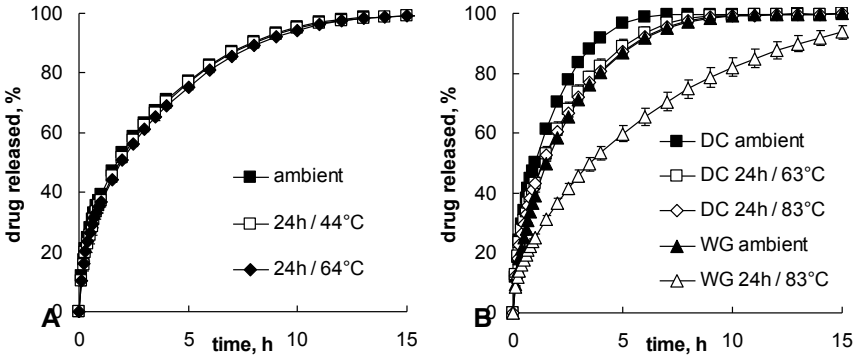

Fig. 47. Effect of thermal treatment on drug release from A) Kollidon SR and B) Eudragit RS matrices.

Matrix tablets of all polymers were subjected to a combination of heat and humidity treatment for 24h (Fig. 48). Kollidon SR matrices showed the strongest retardation of drug release after heat/humidity treatment. The effect is not caused by the elevated temperature, which can be concluded from the thermal treatment. It results from the sensitivity to humidity, which reduces the T_g of the polymer but is insufficient to cause polymer segregation seen in wet granulation. Theoretically, this can be utilized as formulation tool but special moisture protections must be considered for storage of matrix tablets containing Kollidon SR as carrier.

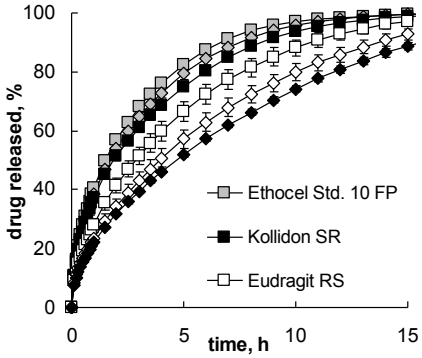

Fig. 48. Effect of heat humidity on drug release from matrix tablets: ambient (□), 24h at 60 °C / 75 % RH (◇).

On the other hand, for Eudragit RS matrices only a small decrease of drug release could be observed, which was attributed to further fusion of the polymer particles, whereas drug release was only marginally affected in case of ethyl cellulose. Its low affinity to water and its high T_g result in very stable tablets at various conditions.

Conclusions

Insoluble matrix polymers were evaluated with regard to drug release affecting properties. The key parameter was the glass transition temperature of the polymers. It governed other characteristics such as compactibility, matrix integrity during processing and drug release (polymer percolation threshold), permeability of the matrix for medium and drug, the particle size effect on drug release and sensitivity against influences from temperature and humidity. Hence, its effect on drug release is complex.
Incorporation of drug release affecting properties into mathematical models would be another step to comprehensive prediction of drug release from insoluble matrix tablets.

Supplementary Data

In both, 'Matrix systems for controlled delivery of high drug doses' and 'The effect of polymer properties…', a comparison between directly compressed and wet granulated Kollidon SR matrix tablets was made. For matrices with 70 % caffeine as model drug, release was faster from directly compressed tablets due to higher porosity (see 'Matrix systems for controlled delivery of high drug doses'). On the other hand, when porosity of the final tablet was controlled, wet granulated matrices of 40 % diprophylline exhibited faster release than directly compressed ones ('The effect of polymer properties…'). That was explained by separation of the co-processed polymer material and formation of PVP clusters.

These results were confirmed by investigations over the range of possible compositions (Fig. 49). At low drug loadings wet granulated matrices showed faster release than those prepared by direct compression. With increasing drug content this difference disappeared and above a critical composition wet granulated matrices released the drug slower than directly compressed ones. Percolation of Kollidon SR is probably the key parameter, because the threshold coincides with the critical composition. Above the percolation threshold of the polymer, factors like porosity and tortuosity affect drug release. The hypothesized cluster formation of PVP will not change the total porosity but results in increased pore sizes and therefore, decreased tortuosity of the matrix.

Below the percolation threshold, tablets erode during dissolution testing. The rate of erosion determines the release profile and is itself influenced by the distribution of the polymer. As previously mentioned, a better distribution is achieved during wet granulation. This facilitates in turn the compression of the granules and therefore lower porosities can be obtained.

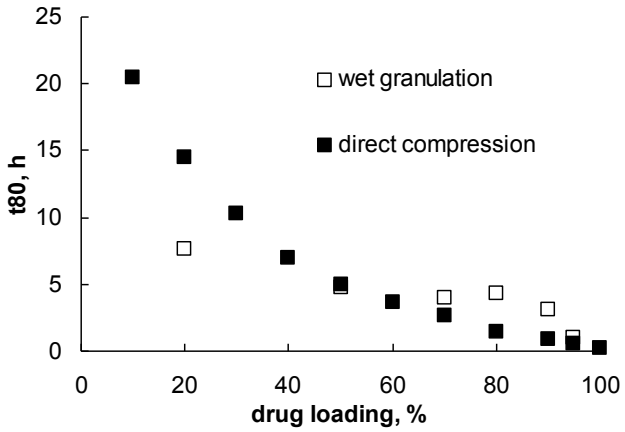

Fig. 49. Effect of preparation method on caffeine release from matrix tablets with different composition.

An improved compression was similarly the purpose of the following studies. Dry binders were added to Eudragit RS and ethyl cellulose to enhance their release retardation potential. In 'The effect of polymer properties…' a lower compactibility was determined for these polymers compared to Kollidon SR, which consists of the flexible PVAc and PVP, itself used as dry binder.

After addition of comparable amounts of PVP to Eudragit RS (20 % w/w based on polymer) matrix tablets were prepared and tensile strength and drug release determined (Fig. 50). In this concentration, PVP had no effect on tablet hardness but significantly reduced the erosion rate and therefore drug release. Due to its solubility the matrices still eroded. This lead to the assumption, that insoluble binder might exhibit preferable properties.

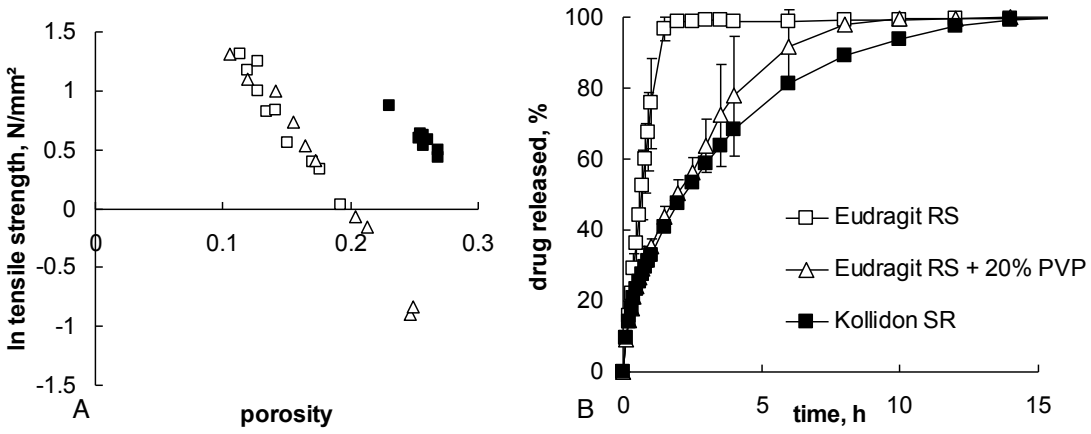

Fig. 50. Effect of PVP addition on A) tensile strength and B) caffeine release of Eudragit RS matrix tablets (Drug/excipient 50/50).

This approach was evaluated with ethyl cellulose as matrix polymer. 10 and 20 % of MCC or dicalcium phosphate (w/w, based on the polymer) were mixed into the powder blend and compressed. The hardness of the tablets increased more than twofold compared to binder-free formulations (45 N vs. > 105 N), confirming the suitability of these substances.

Drug release experiments revealed different behaviors of the binders (Fig. 51). While MCC swelled, causing the matrix to erode at 20 % content and therefore accelerated drug release, dicalcium phosphate slowed down the release independent of the concentration. Thus, MCC did not suit the binding purpose, whereas dicalcium phosphate exhibited potential. Similar results were obtained for wet granulated matrices. Hence, the suitability of dicalcium phosphate as functional additive to matrix formulations should be further evaluated.

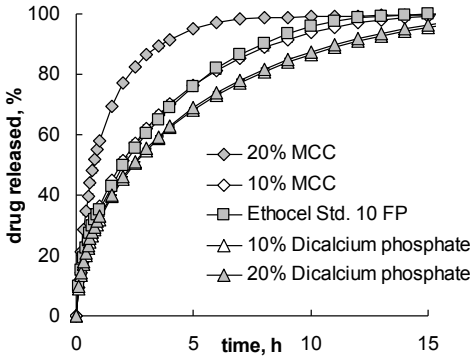

Fig. 51. Effect of binder addition on diprophylline release from ethyl cellulose matrices (drug/excipient 40/60).

Dissolution testing of extended release insoluble matrices

Background

Dissolution testing of extended release drug delivery systems has two major aims. First, it is used for quality control during development stage (Jorgensen 1998), ideally confirming the robustness of the formulation. Valuable information about risks, such as dose dumping, food effects and interaction of drug substance with other components are gained (FIP guidelines 1997). And thereby, screening and selection of suitable formulations is facilitated during formulation development (Khan 1996). Furthermore, dissolution testing can also be of importance in evaluation of changes in production site or manufacturing process.

The second aim is reliable prediction of the in vivo performance of a dosage form, so-called in vitro-in vivo correlation (IVIVC). Suggestions with regard to test conditions can be found in the FIP guidelines for dissolution testing of solid oral products (1997).

Key parameters are apparatus, media, volume, and agitation rate selection. Physiological conditions should form the rationale for all parameters but strict mimicking of the gastrointestinal environment is not recommended.

Buffers are usually utilized to simulate different sites of the gastrointestinal tract. Additives such as surfactants, enzymes or salts may be considered in specific cases and need to be justified. The agitation of the dissolution medium was restricted to 50 – 150 rpm for paddle and basket method to ensure thorough mixing (Mauger 2003) alongside discriminative character (Hamlin 1962, Shah 2006). The effect of simultaneous food intake has been studied by incubation with peanut oil (Maturu 1986, El-Arini 1989) or milk as dissolution fluid (Macheras 1989). Usually, best IVIVCs were obtained for extended release delivery systems that were unaffected by media selection.

With regard to controlled release systems extensive dissolution testing is encouraged to ensure control of the release rate through the delivery system, instead of through variation of test conditions.

Studies on the effect of dissolution media and agitation rate are rather rare on insoluble matrix tablets. For Kollidon SR no effect of pH on drug release was measured (Cailly-Dufestel 2009, Siepmann 2010, Wang 2006). And Eudragit RS matrices did not show sensitivity to the agitation rate of the dissolution tester (Billa 1998).

As drug release from matrix systems is diffusion controlled, the solubility of the drug can also be altered by the medium pH. Hence, drugs with pH-dependent solubility exhibit release profiles dependent on the pH of the dissolution medium (Draganoiu 2003, Kranz 2005, Riis 2007). To single out the effect on matrix excipients, active compounds with pH-independent solubility have to be incorporated.

The purpose of this study was to evaluate the sensitivity of matrix tablet formulations on dissolution media and mechanical stress.

Materials and methods

Ethocel Std. 10 FP (The Dow chemical company, Midland, MI, USA), Kollidon SR, caffeine, diprophylline micronized (BASF SE, Ludwigshafen, Germany), Aerosil 200 and Eudragit RS (Evonik Industries AG, Darmstadt, Germany), and magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany) were used as received.

Blends for tabletting

Drug and polymer powders were physically mixed in a fixed ratio (40/60) on a weight base to obtain 10 g of blend. In case of wet granulation these mixtures were wetted with isopropanol/water (88/12 w/w) to form granules and dried overnight.

Finally, 1 % w/w Aerosil and Mg stearate were added to the powder mixtures or the granules as lubricant and glidant.

Compaction

Matrix tablets were prepared by compressing the blends into tablets of 7 mm diameter with an equipped single punch tabletting machine (EK0, Korsch AG, Berlin, Germany) at a compression speed of 10 rpm and recording compression force (MGCplus, catman, HBM, Darmstadt, Germany). The tablets were further characterized regarding their dimensions and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany).

Dissolution tests were performed using a USP paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany). If not otherwise stated, standard parameters were: 900 ml phosphate buffer pH 6.8, at 50 rpm and 37 °C. Samples were taken at predetermined time points and analyzed spectrophotometrically (290 nm, n=3).

The effect of media pH was studied in different USP buffer formulations, such as 0.1 M HCl (pH 1), acetate buffer (pH 4.5) and 0.05 M phosphate buffer (pH 6.8) and distilled water. Sodium chloride was added to level the osmolarity of the buffers and water.

The “food effect” was determined with a modified method according to US 2004/0121015 A1. 25 g of the “50 % hydrolyzed model oil” (composition Table 13) were mixed with 475 g of pH 6.5 PBS buffer with additional 1 % w/w Tween 80 for 5 min at 4000 rpm (Ultra Turrax T25, IKA®-Werke GmbH & Co. KG, Staufen, Germany). 50 ml of emulsion or PBS buffer with 1 % w/w Tween 80 as reference were filled into closable plastic containers and equilibrated at 37 °C. Tablets were weighed and placed in baskets. The baskets were placed into the containers and incubated at 37 °C and 80 rpm in a horizontal shaker for 2 h (incubation shaker GFL 3033, GFL Gesellschaft für Labortechnik mbH, Burgwedel, Germany). After 2 h, tablets were rinsed with PBS buffer and subsequently dissolution tested (see above).

Table 13. Composition of 50 % hydrolyzed model oil.

Ingredient	Amount, %
Olive oil	38
Glycerol monooleat	15
Oleic acid	23
Tripalmitin	9
Glycerol monostearate	4
Palmitic acid	5
Tributyrin	3
Butyric acid	2
Lecithin	1

All measurements were performed in triplicate.

Results and discussion

With the passage through the GI-tract, the dosage form encounters different environments. Variable parameters are the pH, the ionic strength, the fat content of the gastro-intestinal fluids and the mechanical forces of the peristalsis.

In contrast to coated systems, where counter ion effects (on Eudragit RS films, Wagner 2002) and osmolarity effects (for Eudragit RS or ethyl cellulose coated systems, Kallai 2010, Muschert 2009) were observed, drug release from insoluble matrices was unaffected by pH and osmolarity of the dissolution medium (Fig. 52). These results suggest that porosity and tortuosity are not affected by the pH, the buffer species and the differences in osmotic pressure inside and outside the matrix. Hence, the diffusion coefficient of the active remains the same.

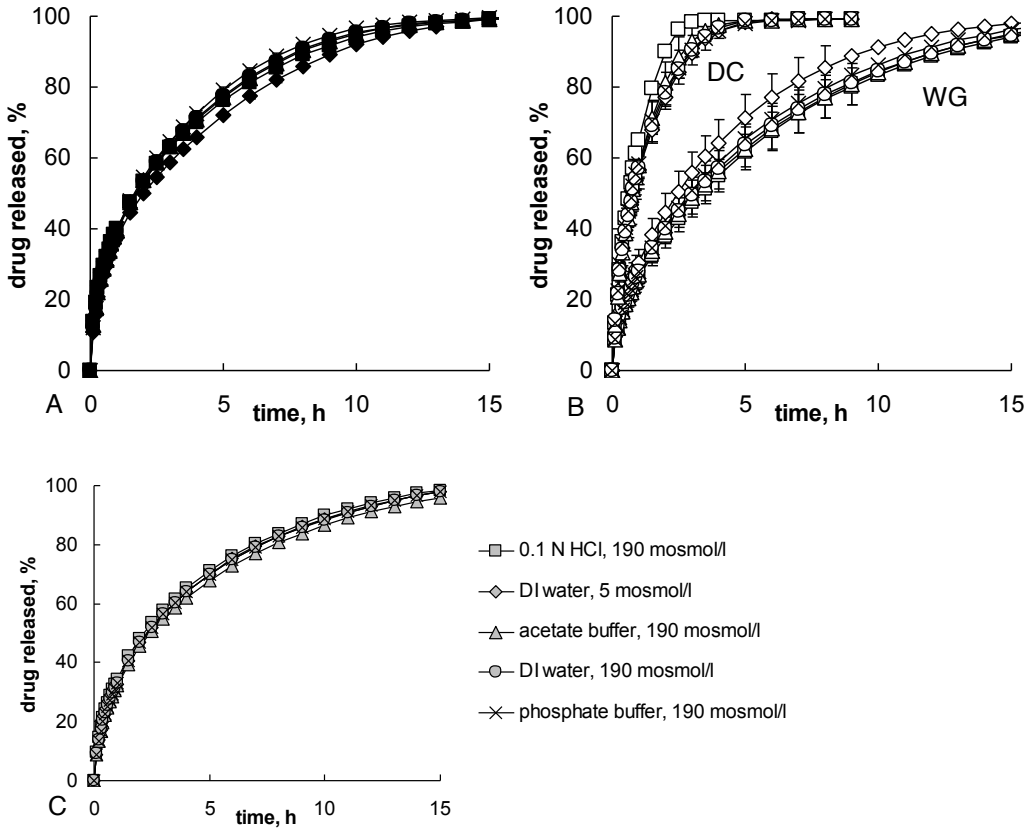

Fig. 52. Effect of pH and osmolarity of the dissolution medium on diprophylline release from matrix tablets. A) Kollidon SR, B) Eudragit RS (direct compression and wet granulation) and C) ethyl cellulose (with 10 % dicalcium phosphate).

Furthermore, incubation with phosphate buffer or an emulsion, containing partially hydrolyzed model oil, did not alter the release profiles (Fig. 53). Equal amounts of drug were released into the emulsion and the buffer during incubation or dissolution testing.

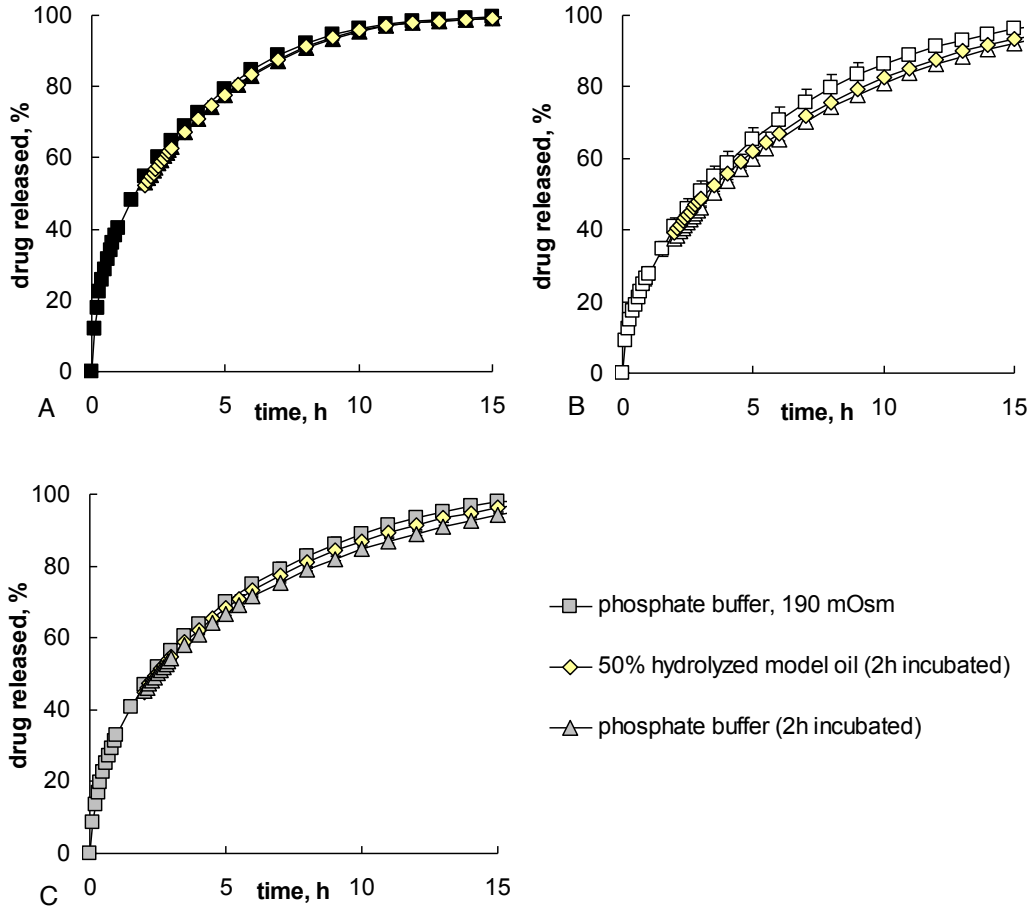

Fig. 53. Effect of incubation with 50 % hydrolyzed model oil or phosphate buffer on diprophylline release from insoluble matrix tablets. A) Kollidon SR, B) Eudragit RS and C) ethyl cellulose.

Hence, insoluble matrix tablets form robust systems with release profiles independent of dissolution medium selection. A reliable in vitro-in vivo correlation is assumed.

A manipulation of the microenvironment in order to achieve pH-independent release of drugs with pH-dependent solubility has been shown for weak acids and bases (Kranz 2005, Riis 2007), thus, decreasing the sensitivity to dissolution media for those systems as well.

With regard to mechanical stress, two systems have to be distinguished: eroding and non-eroding matrices. For eroding matrices the drug release is dependent on the erosion rate, which is in turn dependent on the dissolution rate of the solutes. These systems showed faster release profiles at higher agitation rates (Fig. 54A). A possible explanation is the thinner stagnant layer around the dissolving particles at higher agitation rates with subsequently shorter diffusion pathways and faster dissolution.

On the other hand, non-eroding matrices released the drug independent of the agitation rate (Fig. 54B). The mechanical forces do not reach the insides of the tablet and therefore the system is not affected.

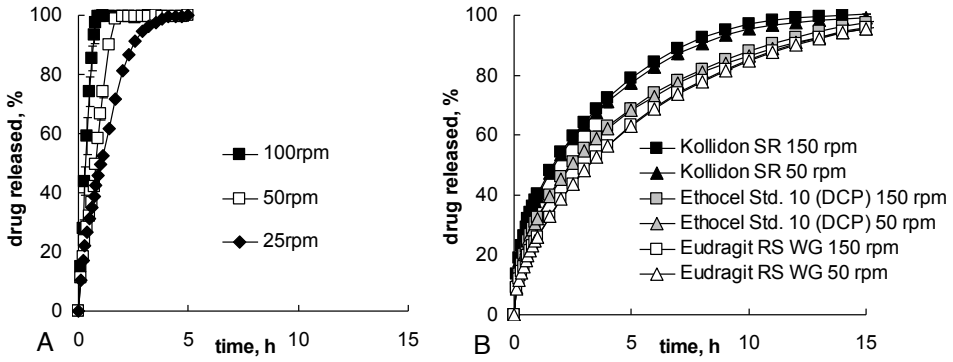

Fig. 54. Effect of agitation rate on drug release from insoluble matrix tablets. A) eroding matrix (Caffeine/ Eudragit RS 50/50), B) non-eroding matrix (diprophylline/polymer 40/60).

Conclusions

Non-eroding insoluble matrix tablets were not sensitive to variations in dissolution test conditions, comprising parameters like pH, buffer species, ionic strength, fat content of the medium and agitation rate. Their in vivo performance should be analyzed to fully evaluate these systems with regard to reliability of sustained drug delivery to the human body.

Predictability of drug release from directly compressed water-insoluble polymeric matrix tablets

Background

Mathematical modelling of drug release has two major aims: the elucidation of underlying mechanisms and the simulation of drug release and therefore the reduction of the number of experiments required during formulation development (Siepmann 2008).

Mechanistic models for matrix systems with diffusion-controlled drug release are based on Fick´s second law of diffusion (Crank 1975).

$$\frac{\partial c}{\partial t} = \frac{1}{r} \cdot \left\{ \frac{\partial}{\partial r}\left(rD \frac{\partial c}{\partial r} \right) + \frac{\partial}{\partial \theta}\left(\frac{D}{r} \cdot \frac{\partial c}{\partial \theta} \right) + \frac{\partial}{\partial z}\left(rD \frac{\partial c}{\partial z} \right) \right\} \quad \text{(Eq. 1)}$$

where c is the concentration of the diffusing compound with diffusion coefficient D, t represents the time, and r, θ and z are the three spatial directions.

For its solution, two special cases have to be distinguished: monolithic dispersions and monolithic solutions (Siepmann 2012).

Monolithic dispersions contain the drug dispersed in the matrix and upon contact with dissolution medium an excess of drug cannot be rapidly dissolved by the penetrating dissolution medium, so that dissolved and dispersed drug coexist in the wetted areas of the tablet. Drug release from this type of matrix can be described by the Higuchi-model, initially developed for homogeneous ointments and extended to granular matrices (Higuchi 1961, 1963):

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s) C_s t} \quad \text{(Eq. 2)}$$

where Q is the release rate per unit surface area, D is the diffusion coefficient of the drug in the permeating fluid, ε is the porosity and τ the tortuosity of the matrix, A is the amount of drug per unit volume, C_s is the solubility of the drug in the permeating fluid and t is the time.

Its simplicity often tempted researchers to apply this equation to matrix tablets. However, two conditions have to be met: First, drug diffusion is restricted to one direction only; valid systems comprise ointment films, transdermal patches or films for oral delivery (Siepmann 2011). And second, the drug loading exceeds the solubility in the matrix. As long as solid drug is present, the concentration gradient and therefore the diffusion coefficient remain constant.

Monolithic solutions contain the drug molecularly dispersed or in quantities the penetrating dissolution fluid quickly dissolves, so that the dissolution front moves in parallel with the penetration front. A modification has been proposed to extend the Higuchi model to monolithic solutions (Bunge 1998). An

error of 0.5 % compared to a numeric solution of Fick's second law of diffusion has been postulated. However, the restriction to one-dimensional diffusion remained.
Another solution of Fick's second law describing drug release from cylindrical monolithic solutions considering axial as well as radial diffusion has been developed (Vergnaud 1993):

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D_{app} t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \cdot \exp\left(-\frac{(2p+1)^2 \cdot \pi^2}{H^2} \cdot D_{app} t\right) \quad \text{(Eq. 3)}$$

where M_t/M_∞ is the cumulative drug release, n and p are real numbers, q_n are the roots of the Bessel function of the first kind of zero order ($J_0(q_n) = 0$), D is the apparent diffusion coefficient of the drug in the matrix, t is the time and R and H represent the radius and the height of the tablet, respectively.
This model has been applied to Gelucire matrices (Aïnaoui 2000) and Kollidon SR tablets (Siepmann 2010). With known apparent diffusion coefficient, drug release from tablets of different initial dimensions can be predicted due to the low degree of swelling and hence the constant dimensions of the systems (Shao 2001). However, the apparent diffusion coefficient has not been evaluated in detail, which limits the predictability of drug release profiles.

The objective of this study was to better understand the processes governing drug diffusion from water-insoluble polymeric matrix tablets and to evaluate parameters influencing the apparent diffusion coefficient and to develop a mathematical model with high predictive power. For this purpose, a spray-dried copolymer of polyvinyl acetate (PVAc) and polyvinyl pyrrolidone (PVP) in a ratio of 8:2 (Kollidon SR) was chosen as matrix carrier due to its excellent flow and compression behavior and its drug release retarding effect (Bühler 2008, Hauschild 2006, Strübing 2008).

Materials and methods

Materials

Metoprolol tartrate (Moehs, Barcelona, Spain), propranolol hydrochloride, Kollidon SR (spray dried PVAc 80 %, PVP 19 %, 0.8 % sodium laurylsulfate and 0.6 % silica, lot no. 81969968E0), PVP (Kollidon 30) and micronized theophylline, caffeine, and diprophylline (BASF SE, Ludwigshafen, Germany), pentoxifylline (Sigma Aldrich Chemie GmbH, Munich, Germany), Aerosil 200 (Evonik Industries AG, Darmstadt, Germany), and magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany) were used as received.

Tablet formulation and preparation

Kollidon SR and drug powders were physically mixed in a mortar with a pestle and 1 % w/w Aerosil and Mg stearate each were blended to the powder mixtures as glidant and lubricant.

Tablets were prepared by compressing the powder mixture with an instrumented single punch tabletting machine (EK0, Korsch AG, Berlin, Germany) recording compression force during the compaction process (MGCplus, catman, HBM, Darmstadt, Germany). The tablets were characterized with regard to their dimension and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany). The porosity was calculated from the ratio of apparent density and true density of the tablets.

Drug release

Dissolution tests were performed using a USP paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), 900 mL phosphate buffer pH 6.8 at 50 rpm and 37 °C. Samples were taken at predetermined time points and analyzed spectrophotometrically (at 272, 290 and or 295 nm, n=3).

Mass loss studies

The mass loss of Kollidon SR matrices after dissolution testing was determined gravimetrically. Dry tablets were weighed to determine the initial dry mass (m_{ini}). After dissolution testing, the wet tablets were dried in an oven (Heraeus T6060, Thermo Fischer Scientific GmbH, Dreieich, Germany) at 105 °C overnight and weighed again (m_{final}). The mass loss was calculated by

$$\text{mass loss } \% = \frac{m_{ini} - m_{final}}{m_{final}} \cdot 100 \qquad \text{(Eq. 4)}$$

Solubility determination

An excess of drug powder was added to PVP solutions in phosphate buffer pH 6.8 (0 %, 10 % and 20 % w/w) and conditioned at 37 °C and 80 rpm (incubation shaker GFL 3033, GFL Gesellschaft für Labortechnik mbH, Burgwedel, Germany) for 48 h. The concentration of the drug in the supernatant was measured spectrophotometrically (at 272 nm, n=3).

Results and discussion

Kollidon SR matrices containing water-soluble drugs can be categorized as monolithic solutions. The drug release kinetics obeyed Fick's second law of diffusion (Eq. 3), which facilitated modelling the effect of matrix dimensions on drug release (Siepmann 2010). Formulation parameters affecting the apparent diffusion coefficient of the drug (*D*), however, were not considered.

In the present study, the matrix dimensions were kept constant in order to facilitate the evaluation of factors influencing the apparent diffusion coefficient. Previous work (e.g. Higuchi 1963, Bunge 1998, Shao 2001, Kranz 2006) indicated the importance of parameters such as porosity, drug loading, tortuosity and drug solubility for the drug release from water-insoluble matrices. Therefore, the correlations of these parameters to the apparent diffusion coefficient were investigated in this study.

Initial porosity

The porosity of a solid body describes its pore volume in relation to its total volume. Tablets are solid dosage forms that contain considerable amounts of air depending on the degree of compaction. Generally, this initially present porosity decreases with increasing compression force during tabletting.

As expected, the drug release increased with increasing initial porosity of the tablets (Fig. 55A). The air trapped inside the tablets was displaced or dissolved by the dissolution medium, creating water-filled pores and the release of dissolved drug molecules occurred by diffusion through these pores. The apparent diffusion coefficient increased with higher initial porosity according to the Higuchi equation (Eq. 2). A non-linear correlation was obtained (Fig. 55B).

Drug loading

The drug release increased with increasing drug loading (Fig. 56A), this being in accordance with previous results (Reza 2003). As the dissolution medium enters the matrix, drug particles are dissolved and the volume occupied by the drug will be replaced by its solution over time. Hence, the pore volume for diffusing molecules increases by the drug volume over time in addition to the initial porosity. Correspondingly, a higher drug loading resulted in a higher apparent diffusion coefficient (Fig. 56B).

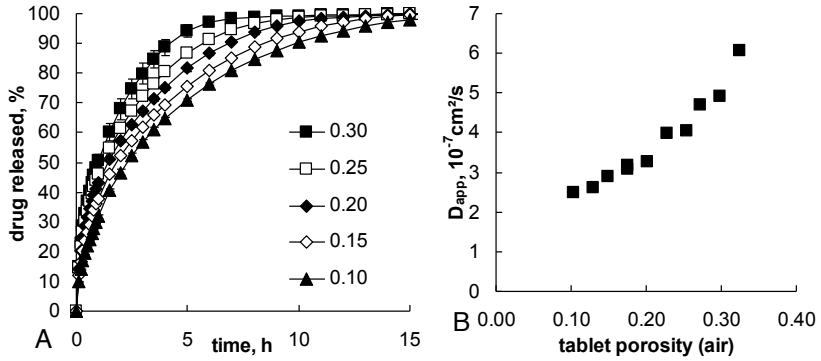

Fig. 55. Effect of initial porosity (v/v) on drug release from Kollidon SR tablets A) diprophylline, drug / polymer weight ratio 40/60, B) apparent diffusion coefficient vs. initial porosity.

Besides the drug, other solid soluble components of the matrix can be dissolved by the dissolution medium, thus increasing the porosity of the matrix (Strübing 2008). Approximately 19 % of Kollidon SR is the water-soluble PVP. Hence, about 19 % of the matrix-forming polymer volume dissolves and generates additional pores, i.e. channels for drug diffusion.

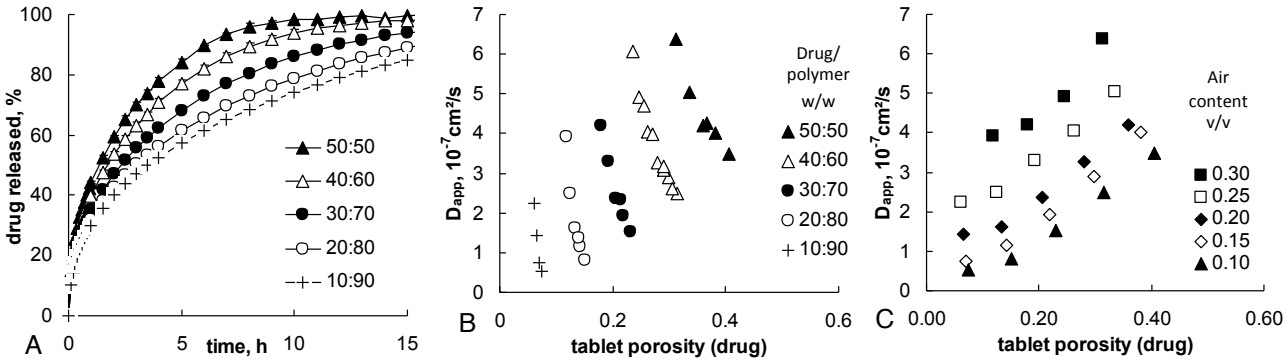

Fig. 56. Effect of drug / polymer weight ratio on diprophylline release from Kollidon SR matrix tablets A) drug released vs. time (20 % initial porosity), B) apparent diffusion coefficient vs. tablet porosity (drug), legend represents drug / polymer weight ratio, C) apparent diffusion coefficient vs. tablet porosity (drug), legend represents initial porosity.

Total porosity

The initial porosity and the porosity resulting from the dissolution of drug particles and other soluble components contribute to the "total porosity" of matrix-type drug delivery systems (Bonny and Leuenberger 1991). Plotting the sum of the individual porosities as total porosity against the apparent diffusion coefficient indicated a general mathematical relationship between both variables (Fig. 57), which was not clearly seen from the plots of the individual porosities based on drug (Fig. 56B) and air (Fig. 56C) before. The data set was fitted to a cumulative normal distribution (Eq. 3), with ε_{mean} and σ denoting the mean and the standard deviation of the normal distribution, and D_{aq} and D_p representing the diffusion coefficient of the drug in aqueous pores and pore-free polymer, respectively.

$$D_{app} = D_p + D_{aq} \int_0^1 \left(\frac{1}{\sigma\sqrt{2\pi}} \cdot e^{-\frac{(\varepsilon-\varepsilon_{mean})^2}{2\sigma^2}} \right) d(\varepsilon) \qquad \text{(Eq. 5)}$$

It was reasonable to assume a sigmoidal character for the relationship between porosity and apparent diffusion coefficient, since the apparent diffusion coefficient would range between the diffusion coefficients of drug molecules in the pore-free polymer ($D_p \geq D_{polymer} \sim 10^{-9}$ cm²/s, Wesselingh 1993) and the diffusion coefficient in aqueous medium ($D_{aq} \leq D_{water} \sim 10^{-4}$ cm²/s). Moreover, the sigmoidal character accounts for the probabilistic nature of pore formation and drug/polymer percolation (Hastedt 1990).

A drug diffusion coefficient in air-free Kollidon SR of $D_p = 0.25 \cdot 10^{-7}$ cm²/s was obtained applying equation 5, which was higher than the values reported in the literature, since Kollidon SR itself provides pores for diffusion by leaching PVP.

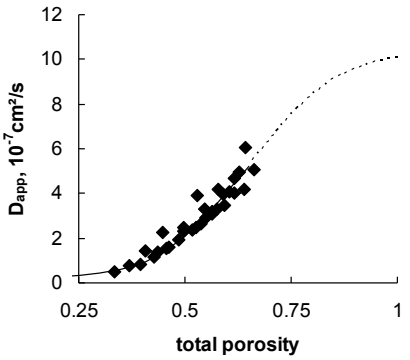

Fig. 57. Apparent diffusion coefficient vs. total porosity (air, drug, PVP) of the matrix.

The normal distribution was characterized by a mean ε_{mean} of 0.65 (or 65 %) and a standard deviation σ of 0.165. Mass loss of drug-containing tablets revealed a value for the critical polymer concentration of Kollidon SR, which compared well with ε_{mean} (Table 14). For total porosities of more than 64 % v/v the mass loss exceeded the total content of soluble compounds, indicating a loss of insoluble polymer due to tablet erosion. Therefore, the percolation threshold of the polymer (Leu and Leuenberger 1993, Brohede 2007) was between 64 - 68 % v/v total porosity. The derived percolation threshold (ε_{pp}) thus coincided with the turning point of the normal distribution (65%), indicating the change of the system from diffusion- to erosion-controlled drug release.

The sigmoidal correlation between apparent diffusion coefficient and total porosity (Fig. 57) was lost beyond the percolation threshold of the polymer. This was attributed to uncontrolled changes of the matrix dimensions impeding the applicability of equation 3. The correlation of total porosity and apparent diffusion coefficient is thus valid for non-eroding matrices only.

Table 14. Initial content of soluble compounds and mass loss after release from formulations with different total porosities (model drug: diprophylline, loading: 10-60 % w/w, initial porosity: 10-30 % v/v).

Total porosity, % v/v	Drug loading, % w/w	Soluble compounds (Drug, PVP and Aerosil), % w/w	Mass loss, % w/w
48	10	30	26
52	30	46	40
59	50	62	58
64	50	62	58
68	50	62	64
70	60	69	72

Tortuosity

The tortuosity of a matrix system is closely related to its porosity (Frenning 2011). Its effect on drug release, however, was negligible for the investigated matrices, since parameters affecting the tortuosity (e.g. polymer particle size) were kept constant (Crowley 2004).

Solubility

Different D_{aq} were obtained for the model drugs diprophylline, caffeine and theophylline, which was in line with the influence of drug solubility on drug release from Kollidon SR matrices (Fig. 58A). An increased solubility increases the release of the drug molecules due to the higher concentration gradient between medium inside the tablet and the bulk medium. A logarithmic correlation between D_{aq} and the drug solubility (expressed as w/w ratio, Fig. 58B) provided a better fit (R^2 = 0.9921) than a square root relation (R^2 = 0.9388).

$D_{aq}=m \cdot ln\ (C_S)+n$ (Eq. 6)

with m = 3.1714 · 10^{-7} cm²/s and n = 15.79 · 10^{-7} cm²/s

Implementing this relationship into equation 5 enabled the calculation of the apparent diffusion coefficients of the investigated formulations. The plot of calculated vs. experimentally determined diffusion coefficients exhibits good agreement for the entire data set (R^2 = 0.935; Fig. 59).

$$D_{app} = D_p + 3.17 \cdot 10^{-7}\,\frac{cm^2}{s} \cdot (\ln(C_S) + 4.98) \int_0^1 \left(\frac{1}{\sigma\sqrt{2\pi}} \cdot e^{-\frac{(\varepsilon-\varepsilon_{pp})^2}{2\sigma^2}} \right) d(\varepsilon) \qquad \text{(Eq. 7)}$$

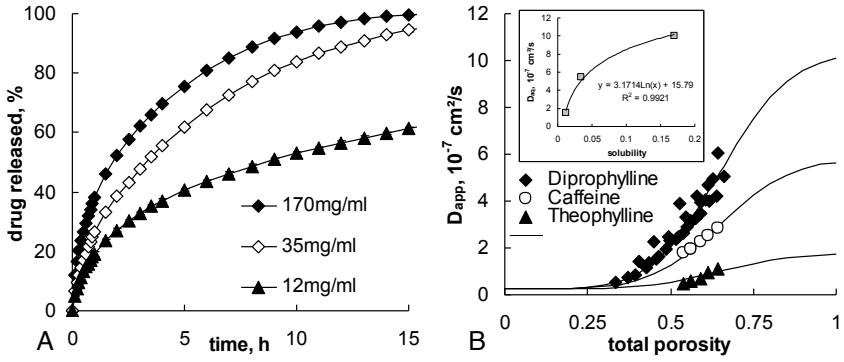

Fig. 58. Effect of drug solubility on drug release from Kollidon SR matrices A) Drug loading = 40 % w/w, initial porosity = 15 % v/v, B) apparent diffusion coefficient vs. total porosity, (indentation: derived D_{aq} vs. solubility of the drug).

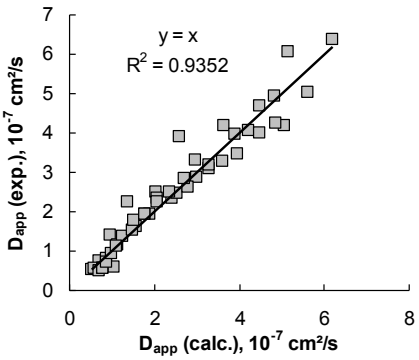

Fig. 59. Experimentally determined apparent diffusion coefficient vs. calculated apparent diffusion coefficient.

Independent experiments

The derived mathematical model was challenged by independent experiments. Three different formulations (Table 15) containing model drugs with solubilities within (pentoxifylline), slightly above (propranolol hydrochloride) and much above (metoprolol tartrate) the range used for model development were employed in order to verify the empirical approach.

In all cases, good agreement was obtained for the release predictions and the independent experiments with similarity factors $f_2 > 50$ (Table 15, Fig. 60). These results confirmed that the key parameters affecting the drug release from Kollidon SR matrices have been adequately addressed in the mathematical model. It further demonstrated that the developed model is broadly applicable to drugs of different solubilities.

Table 15. Tablet formulations of independent experiments.

Model drug	Solubility, mg/ml	Drug loading, % w/w	Tablet diameter / height, mm	Initial porosity	Similarity factor[1]
Pentoxifylline	112	50	7 / 3.5	0.20	56.98
Propranolol HCl	200	40	9 / 2.3	0.15	55.44
Metoprolol tartrate	1000	25	9 / 4.75	0.20	75.17

[1] according to Moore and Flanner 1996

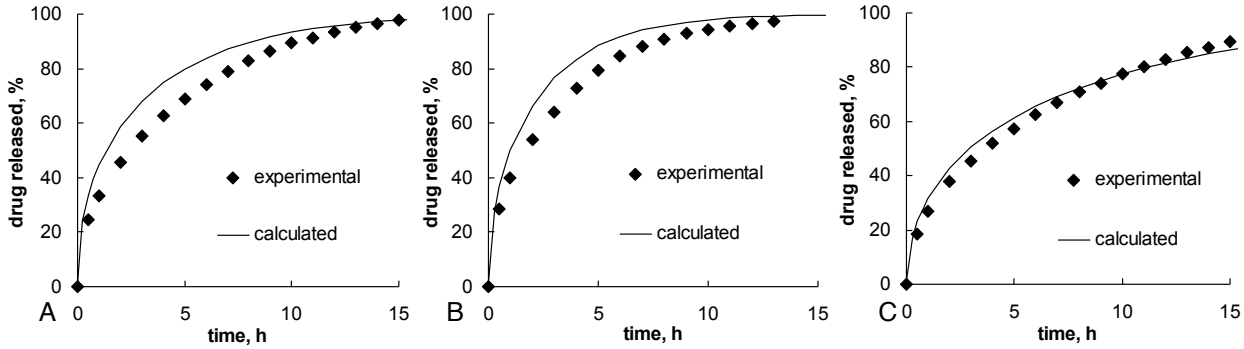

Fig. 60. Theoretical prediction (line) and independent experimental verification (symbol) of A) pentoxifylline, B) propranolol HCl and C) metoprolol tartrate release from Kollidon SR matrices.

Conclusions

Parameters affecting drug release, such as initial tablet porosity, drug loading and drug solubility, were correlated to the apparent diffusion coefficient derived from an established analytical solution of Fick's second law of diffusion. The developed empirical model allows prediction of drug release from non-eroding Kollidon SR matrices for drugs within a wide range of solubilities (10 - 1000 mg/ml). It is based on initial properties of the matrix and its components. Therefore, formulation development can be managed with a minimum of experiments, saving time and costs.

Mathematical model for directly-compressed multi-component matrix tablets

Background

The simplest and most cost effective way to produce controlled release matrix tablets is direct compression of physical blends of drug and release controlling matrix former. The key parameters, affecting drug release from compacts of those binary blends, have been elucidated (e.g. Katikaneni 1995, Neau 1999, Azarmi 2002, Kranz 2006).

Kollidon SR combines required properties for a directly compressible matrix polymer, such as adequate binding and flow, pH-independent and retarded drug release (Bühler 2008, Draganoiu 2003, Kranz 2005).

Recently a mathematical model for the drug release from Kollidon SR matrices has been developed (see Predictability of drug release) based on Fick's second law of diffusion (Eq. 1, Vergnaud 1993) which facilitates prediction of the drug release pattern by expressing the apparent diffusivity of the drug through relevant formulation parameters (Eq. 2):

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D_{app} t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \cdot \exp\left(-\frac{(2p+1)^2 \cdot \pi^2}{H^2} \cdot D_{app} t\right) \qquad \text{(Eq. 1)}$$

where M_t/M_∞ is the cumulative drug release, n and p are real numbers, q_n are the roots of the Bessel function of the first kind of zero order ($J_0(q_n) = 0$), R and H represent the radius and the height of the tablet, respectively, t is the time and D_{app} is the apparent diffusion coefficient of the drug in the matrix. It can be described as

$$D_{app} = D_p + 3.17 \cdot 10^{-7} \frac{cm^2}{s} \cdot (\ln(C_s) + 4.98) \cdot \int_0^1 \frac{1}{\sigma\sqrt{2\pi}} \cdot e^{-\frac{(\varepsilon - \varepsilon pp)^2}{2\sigma^2}} \, d(\varepsilon) \qquad \text{(Eq. 2)}$$

with D_p expressing the diffusivity of drugs in polyvinyl acetate = 0.25 · 10^{-7} cm²/s, C_s denoting the solubility of the drug in the dissolution medium, ε representing the total porosity and ε_{pp} the polymer percolation threshold and σ is the standard deviation of the cumulative normal distribution describing D in dependence of ε (σ = 0.165). This model allows accurate description and prediction of drug release from Kollidon SR matrices.

However, marketed products usually contain a wide variety of different excipients in addition to the release retarding agent. Especially fillers are used in large quantities to dilute the active material, giving the tablet its weight and shape. Hence, their impact on drug release is of interest in the formulation of pharmaceutical dosage forms.

Generally, a drug release accelerating effect has been reported for increasing filler contents when the filler replaced part of the release retarding polymer and a polymer content dependent behavior was assumed (e.g. Shao 2001, Draganoiu 2003, Billa 1998). The results of studies on filler type are rather controversial. Kranz et al. found strong effects of the filler type (Kranz 2005), whereas, Ford et al. showed filler type–independent acceleration of drug release below a critical excipient to polymer ratio of 1:1. At a higher ratio (3:1) the properties of the fillers became evident in the release profiles (Ford 1987).

Materials such as lactose, microcrystalline cellulose and calcium phosphate are commonly used as fillers in direct compression due to their excellent flow and binding properties (Haware 2009, Jivraj 2000). These excipients differ in their aqueous solubility, affecting the micro-environmental conditions and therefore potentially the drug's solubility and diffusivity (e.g. Streubel 2000, Riis 2007, Güres 2011).

The objective of this study was to evaluate whether drug release from Kollidon SR matrix tablets containing drug and common fillers follow the mathematical model developed to predict drug release from drug matrix tablets (see Predictability of drug release).

Materials and methods

Materials

Kollidon SR and micronized diprophylline (BASF SE, Ludwigshafen, Germany), Aerosil 200 (Evonik Industries AG, Darmstadt, Germany), magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany), microcrystalline cellulose (Avicel PH102, FMC BioPolymer, Philadelphia, PA, USA), sodium chloride (Carl Roth GmbH & Co.KG, Karlsruhe, Germany), dicalcium phosphate anhydrous (Merck KGaA, Darmstadt, Germany), low viscosity HPMC (Methocel E5, Colorcon Limited, Dartford Kent, UK), and lactose (Flowlac, Molkerei Meggle Wasserburg GmbH & Co. KG, Wasserburg, Germany) were used as received.

Tablet formulation and preparation

Polymer, excipients and drug powders were physically mixed and 1 % w/w Aerosil and Mg stearate each were added to the powder mixtures as lubricant and glidant.

Tablets were prepared by compressing the blends with an instrumented single punch tabletting machine (EK0, Korsch AG, Berlin, Germany) and recording compression force during the compaction process (MGCplus, catman, HBM, Darmstadt, Germany). The tablets were further characterized regarding their dimensions and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany). The porosity was calculated from the ratio of apparent density and true density of the tablets.

The dimensions of the standard formulation were fixed to 7 mm in diameter and 2.9 mm in height and an initial porosity 15 % v/v was targeted, if not otherwise mentioned.

Drug release

Dissolution tests were performed using USP paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), 900 ml phosphate buffer pH 6.8, at 50 rpm and 37 °C. Samples were taken at predetermined time points and analyzed spectrophotometrically (272, 290 nm, n=3).

Mass loss studies

The mass loss of Kollidon SR matrices after drug release was determined gravimetrically. Dry tablets were weighed to determine the initial dry mass (m_{ini}). The wet tablets were dried in an oven after drug release testing (Heraeus T6060, Thermo Fischer Scientific GmbH, Dreieich, Germany) at 105 °C overnight and weighed again (m_{final}). The mass loss was calculated as follows:

$$mass\ loss\ (\%) = \frac{m_{ini} - m_{final}}{m_{final}} \cdot 100 \qquad \text{(Eq. 3)}$$

Results and discussion

Binary (drug and excipient) and ternary blends (drug, polymer and excipients) were prepared and compressed to assess the impact of the materials on processing and drug release alone and in combination with the release-retarding polymer (Table 16). If incorporated, the concentration of the polymer was kept above its percolation threshold to ensure matrix integrity during release studies (see Predictability of drug release). For better comparison the volumetric content of the polymer is given, as well.

Table 16 Composition of the powder mixtures for tablet preparation (% w/w).

substances	DPP	Kollidon SR w/w / v/v	NaCl	lactose	HPMC E5	MCC	dicalcium phosphate
Binary blends	10	90 / 63	-	-	-	-	-
	30	70 / 51	-	-	-	-	-
	40	60 / 45	-	-	-	-	-
	50	50 / 38	-	-	-	-	-
	30	-	70	-	-	-	-
	30	-	-	70	-	-	-
	30	-	-	-	70	-	-
	30	-	-	-	-	70	-
	30	-	-	-	-	-	70
Ternary blends	30	60 / 47	10	-	-	-	-
	30	60 / 45	-	10	-	-	-
	30	60 / 44	-	-	10	-	-
	30	60 / 45	-	-	-	10	-
	30	60 / 49	-	-	-	-	10
	30	50 / 41	20	-	-	-	-
	30	50 / 38	-	20	-	-	-
	30	50 / 37	-	-	20	-	-
	30	50 / 38	-	-	-	20	-
	30	50 / 44	-	-	-	-	20
	10	50 / 38	-	40	-	-	-
	10	50 / 36	-	-	40	-	-
	10	50 / 37	-	-	-	40	-
	10	50 / 40	-	-	-	-	40

Tabletting

All powder blends resulted in tablets with a tensile strength of at least 1 N/mm², which implies sufficient hardness for handling and packaging. The excipients differed in their binding capacities, which can be concluded from the tablet tensile strength of binary and ternary blends (Fig. 61). Weaker tablets were obtained with the soluble fillers sodium chloride, lactose and HPMC compared to the release-retarding polymer Kollidon SR. While tablets with the insoluble fillers dicalcium phosphate and microcrystalline cellulose showed similar strength, though the targeted initial porosity of 15 % v/v could not be achieved for dicalcium phosphate. Hence, the compactibility of dicalcium phosphate exceeds that of Kollidon SR. The impact of the fillers on tablet hardness in ternary blends increased with increasing filler content.

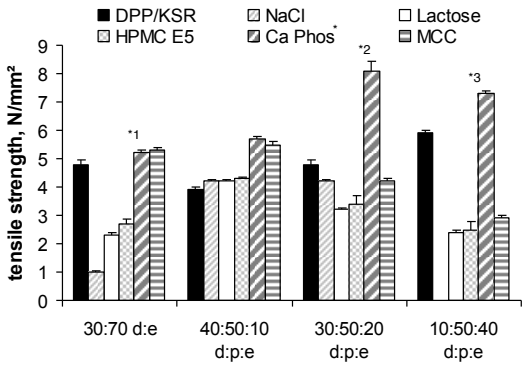

Fig. 61 Tensile strength of matrix tablets composed of drug (d), Kollidon SR (p), filler (e) in different ratios (*deviation of initial porosity: *1 24 %, *2 18 %, *3 19 %).

Drug release

Drug-excipient blends

The effect of the excipients on drug release was investigated with formulations containing 30 % w/w diprophylline and 70 % w/w excipients. Thus, percolation of the excipients was ensured, resulting in matrix property domination (Leuenberger 1987).

Tablets containing the water-soluble compounds sodium chloride and lactose dissolved rapidly leading to immediate drug release of the drug, whereas a four hours profile was obtained for HPMC (Fig. 62A). Swelling and gradual dissolution over time was observed for the hydrophilic polymer. The drug was trapped and diffusion was slowed down in the viscous gel.

The water-insoluble MCC also swelled rapidly resulting in tablet disintegration and hence in immediate drug release. On the other hand, dicalcium phosphate, formed intact matrices and retarded the drug release for approximately four hours (Fig. 62B). The insoluble salt built up a porous network, where the drug had to diffuse through.

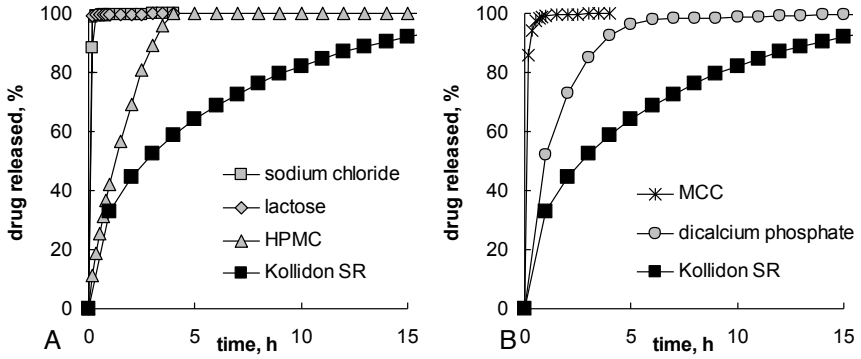

Fig. 62. Drug release from matrices containing 30 % diprophylline and 70 % A) soluble and B) insoluble excipients compared to Kollidon SR.

However, none of the excipients under investigation retarded the drug release as Kollidon SR. Less than 60 % of the drug was liberated within four hours. Upon contact with dissolution medium fluid is imbibed, causing the drug as well as the soluble polymer fraction (PVP) to dissolve and creating a viscous microenvironment for the solutes to diffuse through (Shao 2001). The increased viscosity decreases drug diffusivity in the water-filled pores. Simultaneously, the humidity causes phase transition of the polymer to the amorphous state, hence allowing for polymer mobility and fusion (Hauschild 2006), which has an impact on matrix porosity (Billa 1998).

Ternary mixtures

Incorporating fillers into drug-Kollidon SR matrix tablets (30 % drug loading) increased the drug release rate. At 10 % w/w excipient level the release pattern corresponded to a drug loading of 40 % of binary drug/Kollidon SR matrices and at 20 % to a drug loading of 50 % w/w (Fig. 63 and Fig. 64). The effect was independent of the excipient type suggesting that the increase in drug release is primarily resulting from the reduction of the most retarding formulation ingredient - Kollidon SR.

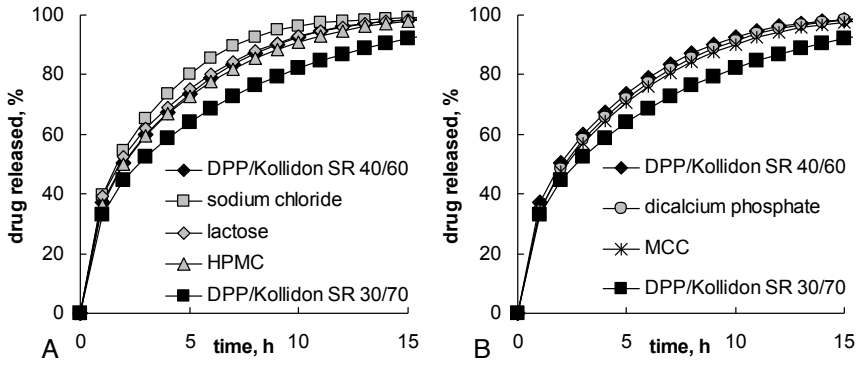

Fig. 63. Drug release from matrices containing 10 % w/w A) soluble and B) insoluble excipients.

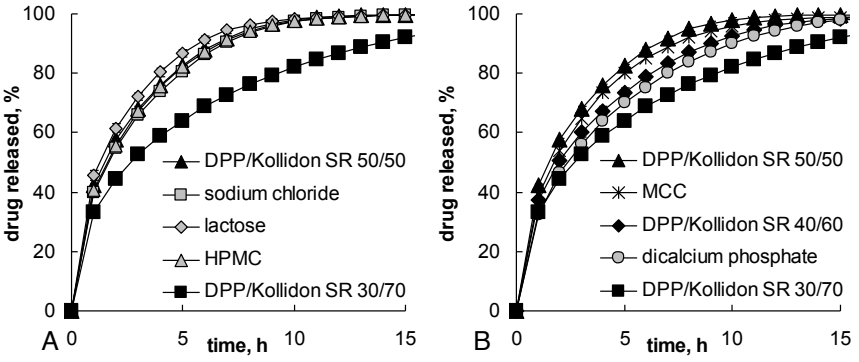

Fig. 64. Drug release from matrices containing 20 % w/w A) soluble and B) insoluble excipients.

Increasing the excipient level to 40 % w/w resulted in filler type-dependent release profiles (Fig. 65). For the soluble excipients lactose and HPMC no significant differences could be seen between formulations with drug/polymer/excipient ratios of 30/50/20 and 10/50/40 (Fig. 65A and 65B), where the polymer content was the same. Similarly MCC increased the release profiles as the MCC content increased (Fig. 65C), whereas drug release decreased with dicalcium phosphate (Fig. 65D).

For better comparison, the differences in porosity and polymer volume are pointed out.

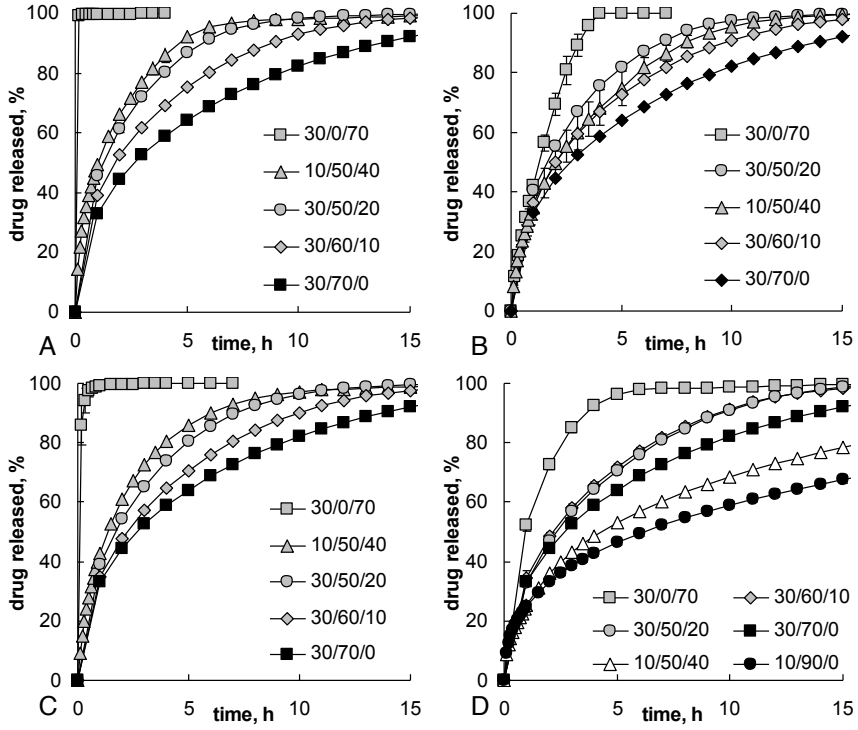

Fig. 65. Effect of matrix composition (drug/polymer/filler ratios w/w) for tablets containing A) lactose, B) HPMC, C) MCC or D) dicalcium phosphate.

Mass loss studies of the tablets after release indicated matrix integrity of all ternary formulations, except for tablets containing 40 % w/w MCC (Table 17). The result of this formulation exceeded the solutes content, being a sign for matrix erosion and the swelling force exerted on the matrix by this disintegrant.

Table 17 Initial content of soluble compounds and mass loss after release.

	Content of soluble compounds/mass loss, % w/w at excipient content of		
Excipient	10 % w/w	20 % w/w	40 % w/w
Sodium chloride	52/52	60/57	n.d.
Lactose	52/48	60/58	60/58
HPMC	52/46	60/56	60/49
Dicalcium phosphate	42/40	40/36	20/15
MCC	42/39	40/38	20/27

The drug release profiles of ternary blends are a result of the combined impact of polymer and filler. Thus, the filler's properties are of great importance to the formulator of matrix tablets similarly to the polymer's properties.

Hence, for Kollidon SR matrices two filler species have to be distinguished (compare Fig. 62):

Fillers without release retardation potential (sodium chloride, lactose and MCC) and

Fillers with release retardation potential (HPMC, dicalcium phosphate)

According to this distinction, applicability of the previously developed mathematical model for filler-free tablets, equation 2, has been evaluated.

In case 1, the experiments indicate, that drug release was mainly dependent on the Kollidon SR content. Hence, the mathematical model can as well be written as:

$$D_{app} = D_p + 3.17 \cdot 10^{-7} \frac{cm^2}{s} \cdot (\ln(C_s) + 4.98) \cdot \int_0^1 \frac{1}{\sigma\sqrt{2\pi}} \cdot e^{-\frac{(V_{ppt}-V_p)^2}{2\sigma^2}} \, d(V) \qquad \text{(Eq. 4)}$$

where V_{ppt} and V_p denote the polymer percolation threshold and, the polymer volume fraction, respectively.

To evaluate the predictability of equations 2 and 4 the drug release from Kollidon SR matrices containing fillers was calculated and compared to the actual experiments. Good agreement (f_2 – factor > 50, Moore 1996) could be found for all formulations employing equation 4 (Table 18). For MCC equation 2 resulted in poorer similarity (e.g. 40 % MCC: f_2 = 19 vs.83 with equation 4, Fig. 66A), confirming appropriateness to replace the total porosities by polymer volume fractions.

Table 18 Model verification for matrices containing 10 % and 20 % w/w of different excipients-

Excipient	f_2 similarity factor at excipient content of		
	10 % w/w	20 % w/w	40 % w/w
Sodium chloride	60	77	n.d.
Lactose	84	84	73
HPMC	76	69	54
Dicalcium phosphate*	65 (45)	70 (44)	45 (35)
MCC *	73 (50)	69 (39)	83 (19)

* f_2 factors in brackets for predictions made with equation 2

In case of fillers with release retardation potential additional experimentation is required to determine the excipient effect on drug release.

HPMC already exhibited matrix formation in binary mixtures. In ternary blends the mass loss data of HPMC containing matrices indicate HPMC retention in the tablets. Nevertheless, the increase of microenvironmental viscosity by HPMC only marginally slowed down the release profile (Fig. 65B)

suggesting that diffusion through the insoluble polyvinyl acetate is the release rate-limiting step. Therefore, also HPMC corresponds to case 1 and equation 4 is applicable. On the other hand, there is no big difference between viscosities of HPMC E5- and PVP-solutions of equivalent concentrations. Hence, an effect on drug release by incorporation of a water-soluble polymer of higher viscosity is not excluded.

Dicalcium phosphate retarded the release in binary as well as in ternary blends. At low concentrations (< 20 % w/w) equation 4 predicts drug release reasonably well, but neither equations 2 nor 4 are adequate to describe drug release from dicalcium phosphate containing matrices at higher concentrations (f_2 factor 45.0 vs. 34.8; Fig. 66C).

Applicability of the developed model is limited to fillers that have no impact on drug release in ternary blends, since it describes drug diffusion through polyvinyl acetate, only.

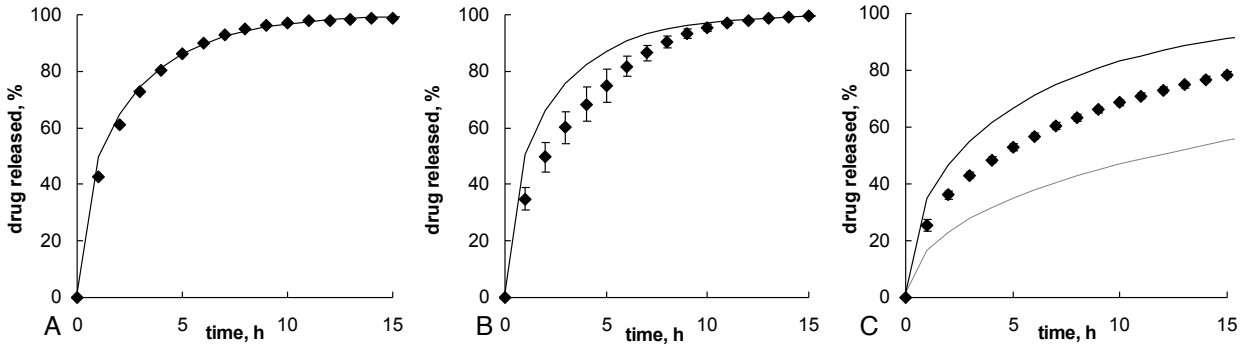

Fig. 66. Theoretical prediction (solid line = polymer based porosity; dashed line = total porosity) and independent experiment (symbol) of diprophylline release from Kollidon SR matrices containing drug / polymer / excipient in a ratio of 10/50/40; excipient: A) MCC, B) HPMC and C) dicalcium phosphate.

Conclusions

The validity of the presented mathematical model with minor modification has been confirmed for multi-component formulations containing a variety of commonly used fillers and binders. Even the applicability to formulations containing several excipients is assumed, as long as the polymer content exceeds its percolation threshold and the added materials do not affect drug diffusivity. This significantly extends the practical benefit the model can offer, since real-life formulations are covered by the equation, facilitating the quality-by-design approach.

Acknowledgements

We would like to thank Susana Alexandra Afonso da Silva Henriques for her technical assistance.

Summary

In this work, controlled release matrix formulations with insoluble polymers (Ethocel Std. 10, Eudragit RS and Kollidon SR) were evaluated regarding their manufacturing and release affecting properties.

To achieve controlled drug release over 6 - 24 h, parameters such as drug loading, matrix dimensions, and the preparation method were investigated. Drug release from matrix tablets occurs as a function of their aqueous solubility. Formulation parameters such as matrix size and drug loading were varied in order to counter-act the drug solubility effect on release. An increasing matrix size decreased, and an increasing drug loading increased the release rate, which facilitated flexible release patterns for all drugs.
The type of the release retarding polymer and the preparation method also affected the drug release by influencing mainly the porosity of the final matrices.
The combination of all parameters into a design space indicated the broad applicability of polymer matrices for the flexible (6 - 24 h) high dose (> 500 mg) delivery of drugs with solubilities ranging from 0.1 – 170 mg/ml.

Mini-matrix tablets (≤ 3 mm diameter) are interesting candidates for pediatric drug delivery but have difficulties to sufficiently retard drug release of water-soluble compounds due to their high surface area and short diffusion pathways.
Minitablets were prepared by direct compression, wet granulation or hot melt extrusion of plasticizer containing drug/polymer mixtures. Disintegrating minitablets were formulated by adding a superdisintegrant into the granule-mixture prior to compression.
Drug/Kollidon SR blends showed a superior compressibility, which was a limiting factor for Carbamazepine, in case of direct compression. Again, decreasing the drug loading decreased the release, but also decreased the tablet dose. Increasing the surface area/volume ratio of the matrix increased the release, while wet granulation resulted in better polymer percolation and therefore stronger retardation of drugs. The best retardation was obtained with tablets prepared by wet granulation using ethyl cellulose as polymer. Hot melt extrusion failed to provide high dosed matrix systems due to processing issues.
Wet granulated mini-matrices offered flexible release patterns for water-soluble drugs even at high loadings. This is advantageous for the treatment of small infants, where a decreased dose volume can improve patient compliance.
Employing the above-mentioned parameters controlled drug delivery over 6 - 24 h is achievable for drugs with a solubility of ≤ 0.1 mg/ml – 100 mg/ml. An individually adjusted dose ranging from several up to 1000 mg can be administered.

Moreover, insoluble polymeric matrix tablets prepared by direct compression were evaluated regarding the matrix carrier properties affecting processing and drug release. Percolation theory was applied to estimate the limitations of the system concerning matrix integrity.
Kollidon SR, Eudragit RS and Ethocel Std. 10 were characterized, formulated into tablets and compared regarding their properties in dry and wet state.
A similar percolation threshold of 65 % v/v was found for the polymers in dry state for simple binary systems of polymer and air. Below that critical concentration cohesion of the polymer particles was too weak to maintain the tablet shape. However, differences were observed regarding densification behavior and matrix tensile strength (Eudragit RS < ethyl cellulose < Kollidon SR). Key parameters influencing compactibility were the surface properties and the glass transition temperature, affecting polymer elasticity and particle size dependent binding. Kollidon SR showed the lowest elasticity and high tablet strength irrespective of the particle size, whereas the tensile strength of Eudragit RS and ethyl cellulose tablets increased with decreasing particle size. The sensitivity to heat/humidity treatment of matrices after compaction was also affected by the glass transition temperature of the polymers resulting in hardening of the tablets in case of Kollidon SR and Eudragit RS, while there was no impact on ethyl cellulose tablets.
The important properties observed in dry state also governed the matrix characteristics in wet state and therefore drug release. Again the glass transition temperature strongly affected matrix properties like integrity, tortuosity and permeability resulting in release retardation in the same order of the polymers as observed for matrix tensile strength. The polymer percolation threshold of 65 % v/v was confirmed, only Kollidon SR exhibited a reduced threshold due to fusion of the polymer particles during dissolution testing.
A percolation threshold of this polymer of 32 – 36 % v/v, corresponding to a total porosity (porosity of the completely leached matrix) of 64 – 68 % v/v, was found.

Matrices containing Kollidon SR, Eudragit RS and ethyl cellulose were further subjected to different dissolution conditions mimicking the transit through the GI tract in fasted and fed state. Parameters such as pH, buffer species, ionic strength and fat content of the medium and agitation rate had no effect on drug release from non-eroding tablets.

The strongest release retardation and the lowest percolation threshold make Kollidon SR the most effective functional polymer in direct compression of controlled release matrices within the substances investigated.
Kollidon SR matrix tablets with various porosities (10 - 30 % v/v) and containing model drugs (theophylline, caffeine and diprophylline, C_S = 10 – 170 mg/ml) in different amounts (A = 10 – 90 % w/w) were prepared.
Drug release from the matrices was fitted to a solution of Fick's second law of diffusion for cylindrical bodies published by Vergnaud in 1993. Changes of apparent diffusivity as a function of total porosity and drug solubility were observed. The derived mathematical model was verified with independent

experiments applying pentoxifyllin, propranolol hydrochloride and metoprolol tartrate (C_S = 100 – 1000 mg/ml) as drug models. Good agreement was obtained in all cases, further broadening the applicability of the mathematical model to a solubility range of 10 - 1000 mg/ml.
The developed model gives further insights into drug release mechanisms, predicts drug release from Kollidon SR matrix tablets with adequate accuracy and can therefore efficiently reduce the cost-intensive experimental trials during formulation.

In a next step, the effect of fillers on the predictability of drug release from directly compressed multi-component matrix tablets was evaluated.
Commonly used fillers and binders, such as lactose, dicalcium phosphate, hydroxypropylmethylcellulose, sodium chloride and microcrystalline cellulose, were formulated with diprophylline and Kollidon SR as matrix-former and investigated regarding processing and drug release. Predictions based on the developed equation were compared with experimental data to challenge the validity of the employed diffusion model.
Increasing the excipient content in drug-Kollidon SR matrix tablets increased the drug release rate at low contents (≤ 20 % w/w). The effect was independent of the excipient type suggesting that the effect resulted from the reduction of the Kollidon SR content. The drug release profile agreed well with the prediction by the diffusion model irrespective of the solubility of the used excipient if the insoluble polymer volume fraction in the matrices was considered instead of the previously suggested total matrix porosity. At higher contents (≥ 20 % w/w) drug release varied according to the release retarding properties of the excipient. The applicability of the model was shown for lactose, sodium chloride, HPMC and microcrystalline cellulose independent of their content and for low contents of dicalcium phosphate.
Rearrangement of the diffusion model for simple drug-polymer blends extends its applicability to ternary tablet blends containing up to 40 % excipient and hence to real-life situations with multi-component tablet formulations, facilitating quality-by-design of new pharmaceutical products.

Zusammenfassung

Ziel dieser Arbeit war die Bewertung von Matrixformulierungen mit kontrollierter Freisetzung hinsichtlich ihrer Herstellung und Eigenschaften, die die Arzneistofffreisetzung beeinflussen. Unlösliche Polymere wie Ethocel Std. 10, Eudragit RS und Kollidon SR bildeten dabei die Matrix.

Parameter, wie die Arzneistoffbeladung, die Abmaße der Tablette sowie ihre Herstellungsmethode wurden untersucht um kontrollierte Arzneistofffliberation über 6 – 24 h zu erreichen. Die Freisetzung von Arzneistoffen aus Matrixtabletten folgt einer Funktion ihrer Löslichkeit in wässrigen Medien. Die Maße der Tablette und die Arzneistoffbeladung wurden als Formulierungsparameter variiert um dem Löslichkeitseffekt auf die Freisetzung entgegenzuwirken. Mit größeren Dimensionen verlangsamte und mit höheren Beladungen beschleunigte sich die Freisetzungsrate. So konnten flexible Freisetzungsprofile für alle Arzneistoffe erreicht werden.
Auch die Art des eingesetzten funktionellen Polymers und die Herstellungsmethode steuerten die Arzneistofffreisetzung, hauptsächlich durch Beeinflussung der Porosität der Matrix.
Die Verknüpfung aller Parameter in einen Formulierungsraum konnte die breite Anwendbarkeit von Polymermatrices als flexible (6 – 24 h), hoch dosierte (> 500 mg) Arzneiform für Arzneistoffe mit Löslichkeiten von 0,1 – 170 mg/ml zeigen.

Mini-Matrixtabletten, mit Durchmessern ≤ 3 mm, sind interessante Arzneiformen für die Arzneistoffversorgung von Kindern. Allerdings ist die Verzögerung der Freisetzung von wasserlöslichen Arzneistoffen durch die große Oberfläche und die kurzen Diffusionswege eher schwierig.
Minitabletten wurden durch Direktverpressung, Feuchtgranulierung oder Schmelzextrusion von Weichmacher enthaltenden Arzneistoff/Polymer-Mischungen hergestellt. Zerfallende Minitabletten wurden durch Zugabe von Sprengstoffen zur Granulat-Mischung und darauf folgender Verpressung formuliert.
Arzneistoff/Kollidon SR-Gemische zeigten herausragende Verpressbarkeit, die besonders wichtig bei schlecht verpressbaren Arzneistoffen wie Carbamazepin in der Direktverpressung ist. Auch bei Minitabletten bewirkte eine reduzierte Arzneistoffbeladung eine langsamere Freisetzung, allerdings verringerte sich damit auch die Tablettendosierung. Ein erhöhtes Oberflächen/Volumen-Verhältnis der Matrix beschleunigte die Freisetzung, während Feuchtgranulierung eine verbesserte Polymerperkolation und damit eine langsamere Freisetzung nach sich zog. Die beste Retardierung wurde mit feuchtgranulierten Matrices erreicht, die Ethylcellulose als Polymer enthielten. Die Schmelzextrusion konnte nicht als Alternative genutzt werden. Die Ursache dafür waren Probleme bei der Herstellung hochdosierter Matrices.

Feuchtgranulierte Minitabletten boten flexible Freisetzungsprofile für wasserlösliche Arzneistoffe, auch bei hohen Beladungen. Dies wirkt sich vorteilhaft auf die Behandlung von kleinen Kindern aus, da ein verringertes Dosisvolumen die Compliance verbessern kann.
Fügt man die oben beschriebenen Parameter zusammen, kann kontrollierte Arzneistoffversorgung über 6 – 24 h mit Arzneistoffen erreicht werden, deren Löslichkeit zwischen 0,1 und 100 mg/ml beträgt. Eine individuell abgemessene Dosis von einigen bis hin zu 1000 Milligramm kann verabreicht werden.

Weiterhin beschäftigte sich die Arbeit mit der Bewertung von durch Direktverpressung hergestellten, unlöslichen Matrixtabletten hinsichtlich der Eigenschaften der Trägermaterialien und ihrem Einfluss auf die Herstellung und auf die Arzneistofffreisetzung. Die Perkolationstheorie wurde angewendet um die Grenzen des Systems bezüglich des Zusammenhalts der Matrix abzuschätzen.
Gebräuchliche unlösliche Polymere, wie Kollidon SR, Eudragit RS und Ethocel Std. 10 wurden charakterisiert, Matrixtabletten formuliert und ihre Eigenschaften in trockener und wässriger Umgebung verglichen.
Eine gemeinsame Perkolationsschwelle von 65 Volumenprozent des Polymers wurde für einfache binäre Gemische aus Polymer und Luft in trockener Umgebung ermittelt. Unterhalb dieser kritischen Konzentration war die Kohäsion der Polymerpartikel zu schwach um die Tablettenform aufrecht zu erhalten. Andererseits wurden Unterschiede zwischen den Polymeren in ihrem Verdichtungsverhalten und in der Tablettenhärte beobachtet (Eudragit RS < Ethylcellulose < Kollidon SR). Die wichtigsten Parameter mit Einfluss auf die Kompaktierbarkeit waren die Oberflächeneigenschaften und die Glasübergangstemperatur, die selbst Einfluss auf die Polymerelastizität und partikelgrößen-abhängige Bindung hat. Die geringste Elastizität und hohe Tablettenhärte - unabhängig von der eingesetzten Partikelgröße - wurde für Kollidon SR beobachtet, während die Tablettenhärte von Eudragit RS- und Ethylcellulosetabletten mit Zunahme der Partikelgröße abnahm. Die Sensibilität gegenüber Hitze- und Feuchtigkeitsbehandlung der Matrixtabletten direkt nach der Kompaktierung wurde auch durch die Glasübergangstemperatur der Polymere beeinflusst. Im Falle von Kollidon SR und Eudragit RS nahm die Härte der Tabletten durch die Behandlung zu, während kein Einfluss auf Etylcellulosetabletten gemessen werden konnte.
Die in trockener Umgebung beobachteten Eigenschaften bestimmten auch die Matrixcharakteristiken in wässriger Umgebung und damit die Arzneistofffreisetzung. Die Glasübergangstemperatur hatte einen großen Einfluss auf Integrität, Tortuosität und Permeabilität, was wiederum in einer Verlangsamung der Freisetzung resultierte, die die gleiche Rangfolge der Polymere aufwies, wie die Tablettenhärte. Die allgemeine Perkolationsschwelle von 65 Volumenprozent wurde bestätigt, nur Kollidon SR zeigte eine reduzierte Schwelle durch Verschmelzen der Polymerpartikel im Freisetzungsmedium.
Die Perkolationsschwelle dieses Polymers lag zwischen 32 - 36 Volumenprozent, was einer absoluten Porosität von 64 - 68 Volumenprozent entspricht.

Kollidon SR, Eudragit RS oder Ethylcellulose enthaltende Matrixtabletten wurden im weiteren Verlauf verschienen Freisetzungsmedien ausgesetzt um die Bedingungen im GI-Trakt vor und nach Nahrungseinnahme zu simulieren. Faktoren wie der pH-Wert, die Puffersalze, die Ionenstärke und der Fettgehalt des Mediums sowie die Rührgeschwindigkeit zeigten keinen Effekt auf die Freisetzung aus nicht-erodierenden Tabletten.

Die stärkste Freisetzungsverzögerung und die kleinste Perkolationsschwelle zeichnen Kollidon SR als effektivstes funktionales Polymer innerhalb der untersuchten Substanzen aus.
Kollidon SR Matrixtabletten mit unterschiedlichen Porositäten (10-30% v/v) und Arzneistoffen (Theophyllin, Koffein und Diprophyllin, C_S = 10-170 mg/ml) in verschiedenen Beladungen (A = 10-90% v/v) wurden hergestellt. Die Freisetzung des Arzneistoffs wurde mit einer mathematischen Lösung des zweiten Fick'schen Diffusionsgesetzes für zylindrische Körper (veröffentlicht durch Vergnaud 1993) abgeglichen, und die Änderung der scheinbaren Diffusivität konnte in Abhängigkeit der absoluten Porosität und der Arzneistofflöslichkeit dargestellt werden. Das daraus resultierende mathematische Modell wurde mit unabhängigen Experimenten, unter Verwendung von Pentoxiphyllin, Propranololhydrochlorid und Metoprololtartrat (C_S = 100-1000 mg/ml) als Modellarzneistoffen, bestätigt. Gute Übereinstimmung zwischen Vorhersage und Experiment konnte in allen Fällen gezeigt und damit die Anwendbarkeit des Modells auf eine Arzneistofflöslichkeit von 10 - 1000 mg/ml erweitert werden.
Das entwickelte Modell erlaubt tiefere Einblicke in die Freisetzungsmechanismen, ermöglicht die Vorhersage der Arzneistofffreisetzung aus Kollidon SR Matrixtabletten mit adäquater Genauigkeit und kann somit die Anzahl kostenintensiver Probeläufe während der Formulierungsphase der Arzneiformherstellung effektiv reduzieren.

In einem nächsten Schritt wurde die Wirkung gebräuchlicher Füll- und Bindemittel auf die Arzneistofffreisetzung untersucht.
Laktose, Hypromellose, mikrokristalline Cellulose, Natriumchlorid und Dicalziumphosphat wurden mit dem Arzneistoff Diprophyllin und Kollidon SR als Matrixpolymer in unterschiedlichen Verhältnissen formuliert und hinsichtlich Tablettierbarkeit, Arzneistofffreisetzung und Gewichtsverlust untersucht. Die mithilfe der entwickelten Gleichung gemachte Vorhersage der Freisetzung wurde mit den experimentellen Daten verglichen um die Gültigkeit des Modells zu bestätigen.
Eine Erhöhung des Füllstoffgehaltes in Arzneistoff-Kollidon SR Matrixtabletten führte zu identischer Beschleunigung der Freisetzungsrate für kleine Anteile (bis zu 20 Gewichtsprozent). Der Effekt war unabhängig von der Art des eingesetzten Füllstoffs, was ein vom Gehalt des Kollidon SR abhängiges Verhalten deutlich macht. Das Ersetzen der absoluten Porosität in der mathematischen Gleichung durch den Polymergehalt ermöglichte den Einsatz des Modells unabhängig von der Löslichkeit und Art des eingesetzten Füllstoffs. Die vorhergesagten Freisetzungsprofile stimmten mit den experimentell ermittelten überein.

Bei höheren Füllstoffanteilen (mehr als 20 Volumenprozent) konnten, je nach Verzögerungsvermögen des Füllstoffs, Unterschiede in den Freisetzungsprofilen erkannt werden. Anwendbarkeit des mathematischen Modells konnte für Natriumchlorid, Lactose, mikrokristalline Cellulose und Hypromellose unabhängig von Gehalt und für kleine Anteile von Dicalziumphosphat gezeigt werden.
Zusammenfassend konnte die Änderung des entwickelten Models für einfache Gemische aus Arzneistoff und polymeren Matrixbildner die Anwendbarkeit auf ternäre Gemische mit Füllstoffanteilen bis zu 40 Massenprozent erweitern. Dadurch werden reale Formulierungen mit Vielstoffgemischen abgedeckt und die Entwicklung von neuen pharmazeutischen Produkten auf dem Gebiet der Matrixtabletten maßgeblich vereinfacht.

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List of publications

Original research articles

(1) **J. Grund,** M. Körber, R. Bodmeier; The effect of polymer properties on direct compression and drug release from insoluble matrix tablets. (manuscript in preparation)

(2) **J. Grund,** M. Körber, R. Bodmeier; Predictability of drug release from water-insoluble polymeric matrix tablets. Eur. J. Pharm. Biopharm. (submitted manuscript)

(3) **J. Grund,** M. Körber, R. Bodmeier; Mathematical modelling of drug release from multi-component matrix tablets. (manuscript in preparation)

Oral presentation

(4) **J. Herrmann,** M. Körber, R. Bodmeier; Individual dosing and controlled drug delivery with matrix-minitablets for paediatric use, 2nd Conference of the European Paediatric Formulation Initiative, Berlin, Germany, 2010

Poster presentations

(1) **J. Herrmann,** M. Körber, R. Bodmeier; Individual dosing and controlled drug delivery with matrix-minitablets for paediatric use, 2nd Conference of the European Paediatric Formulation Initiative, Berlin, Germany, # 13, 2010

(2) **J. Herrmann,** M. Körber, R. Bodmeier; Water insoluble polymers as drug carriers in directly compressed matrix systems, Biannual Meeting of the GDCh-Division Macromolecular Chemistry and Polydays 2010 , Berlin, Germany, # PolCDR 14, 2010

(3) **J. Herrmann,** M. Körber, R. Bodmeier; High dose matrix systems for controlled drug delivery, FIP Pharmaceutical Sciences 2010 World Congress in Association with the AAPS Annual Meeting and Exposition, New Orleans, USA, # SA8116 and T2175, 2010

(4) **J. Herrmann,** N. Apichatwatana, M. Körber, R. Bodmeier; Insoluble polymer mini-matrices as controlled drug delivery systems for high loadings of highly water-soluble drugs prepared by tabletting or hot melt extrusion, FIP Pharmaceutical Sciences 2010 World Congress in Association with the AAPS Annual Meeting and Exposition, New Orleans, USA, # SU9119 and R6213, 2010

Curriculum Vitae

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