RELEASE ADJUSTMENT OF DRUG COMBINATIONS WITH DIFFERENT DRUG SOLUBILITY

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1. Introduction

1.1 Drug combination

Combination therapy for the treatment of a disease generally refers to either the simultaneous administration of two or more pharmacologically active agents or to the combination of different types of therapy (e.g. chemotherapy and radiotherapy) (Greco and Vincent, 2009). Oral combination drug delivery systems have been proven to be highly beneficial and essential in the treatment of several diseases such as cancer, acquired immune deficiency syndrome (AIDS), tuberculosis, diabetes (Type 2), heart diseases, central nervous system (CNS) disorders, and for treating several other microbial infections (Mayer and Janoff, 2007). Combination therapy may be achieved by prescribing/administering separate drugs, or, where available, dosage forms that contain more than one active ingredient. A combination drug most commonly refers to a fixed-dose combination (FDCSs), which is a formulation including two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in certain respective fixed doses. FDCSs products are often claimed to make medicine-taking more convenient for patients taking multiple medication. The advantages of fixed combinations are:

i. increased convenience for physician and patient,
ii. improved compliance
iii. low cost including production, storage, transport, dispensing and other health system costs
iv. tested safety of the specific combination resulted, means that active ingredients used in the FDCSs are unlikely to exhibit adverse drug interactions with each other.

The disadvantages of fixed combinations are:

i. limitation on flexibility and individualization in dosing
ii. potential for inappropriate widening of the target population
iii. exposing patients to risks of additional ingredients
iv. encouraging imprecision in diagnosis
v. difficulty of determining which ingredient is causing side effect

1.1.1 Routes of drug combination delivery

1.1.1.1 Oral drug delivery

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and, most importantly, patient compliance. Oral dosage forms can be in the form of tablets, capsules and pellets. Pellets, in turn, can be filled in to hard gelatin capsules or compressed as tablets. Many studies on combination drug as tablet dosage forms have been published. The study on formulation and affecting variables with different novelty of finding on product formulation issues including disproportionate doses, different release kinetics or solubility, hygroscopicity or altered stability will be discussed.

Taupitz et al., (2013) improved the solubility and dissolution of two fixed dose combination formulations (FDCs) with opposite ionisation properties; a weak acid glimepiride and a weak base pioglitazone, while the second FDCs contained simvastatin and ezetimibe that are essentially non-ionised over the physiological pH range. The formulation approaches used were inclusion complex with hydroxypropyl-β-cyclodextrin (HP-b-CD), solid dispersion with Soluplus® (highly water soluble polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) and ternary inclusion complex with both HP-β-CD and Soluplus®. Alone or in combination, these effects resulted in an improved solubility and/or dissolution rate. In particular, the addition of highly water soluble polymers to binary CD inclusion complexes may increase the solubilising effects obtained with the CDs, based on reports that hydrophilic polymers can stabilize drug/CD complexes by the formation of so-called ternary complexes (Loftsson et al., 1994 and 1998). Even though simvastatin and ezetimibe both contain ionisable groups, they show essentially pH independent solubility characteristics across the gastrointestinal pH range. In vivo drug release of a ternary HP-β-CD : Soluplus® formulation containing a fixed dose combination of pioglitazone and glimepiride was much higher than that of Tandemact® and therefore is likely to result in a higher bioavailability of both drugs.

Release adjustment due to different solubility of drug in different pH as simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) was developed from C.R. formulations for concomitant delivery of combination drugs rifampicin and isoniazid with the technology that is cost effective, reproducible and, easy to manufacture and scale-up in an industry with minimum set-up/facility. A series of formulations with different release rates using hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) as

matrix tablet were developed. Rifampicin release decreased in SGF and increased in SIFsp in presence of Eudragit L100-55, due to pH-dependent solubility of the Eudragit, which is an anionic polymer based on methacrylic acid and methacrylic acid esters that dissolve above pH 5.5 by salt formation. In SGF, as the polymer was insoluble, it closed the pores available for the media infiltration in to the matrix. This caused the delay in the matrix hydration, swelling and ultimately erosion. Thus, the rifampicin release was slightly lower in presence of the Eudragit in SGF. When the release study was continued in SIFsp, the rifampicin release got enhanced because of the increased solubility and release of the Eudragit in SIFsp that resulted in the significant increase in the matrix porosity (Hiremath and Saha, 2008).

High differences in doses of combination drugs can easily be found at combination of antihistamines, antidiabetic or analgetics. It has been documented that combination therapy comprising antihistamine, such as loratadine, fexofenadine, and cetirizine, and a decongestant, such as pseudoephedrine hydrochloride and phenylephrine hydrochloride, is more effective in relieving the symptoms of allergic rhinitis than either component alone (Fallier and Redding, 1980; Sznitowska, 2004). Consequently, the combined immediate-release or modified-release products of antihistamine and decongestant are available in the market either in the form of single-unit tablets or multiple-unit capsules. Once-a-day modified-release products contain 10 mg of loratadine and 240 mg of pseudoephedrine, whereas twice-a-day products comprise 5 mg loratadine and 120 mg pseudoephedrine. The products are formulated in such a way that the entire loratadine and half of pseudoephedrine are intended for immediate release, while the balance of pseudephedrine is for prolonged/extended release.

Modified-release multiple-unit tablets of loratadine and pseudoephedrine hydrochloride with different release profiles were prepared from the immediate-release pellets comprising the above two drugs and prolonged-release pellets containing only pseudoephedrine hydrochloride (Zeeshan and Bukhari, 2010). The immediate-release pellets containing pseudoephedrine hydrochloride alone or in combination with loratadine were prepared using extrusion–spheronization method. The pellets of pseudoephedrine hydrochloride were coated to prolong the drug release up to 12 h. Both immediate and prolonged-release pellets were filled into hard gelatin capsule and also compressed into tablets using inert tableting granules of microcrystalline cellulose Ceolus KG-801. This layer might have served as the cushioning agents. Since immediate release pellets were

uncoated, hence they possess a relatively weaker mechanical strength than that of the coated pellets, which might have caused them to fragment easily during compression, thus forming the protective film for the coated pellets. The drug release profile of the multiple-unit tablets was found to be closely similar to that of the multiple-unit capsules, indicating that compression did not alter the release profiles of drugs. The findings of the present study suggest that multiple-unit tablet systems could be applied to deliver multiple drugs with different release profiles (Zeeshan and Bukhari, 2010).

Other example of disproportionate doses of drug found in combination of nicotinic acid (NA) and simvastatin (SIM) is possible to be prepared as developed by Zhao et al. High-dose sustained-release NA pellets coated with EC double polymer was combined with little-dose immediate release SIM milled suspension on NA pellets in a bottom-spray fluidized bed coater, respectively. The uncoated pellets were prepared by extrusion–spheronization and double ethylcellucose (EC) films. SIM was milled by wet grinding and then the milled suspension was layered on the coated pellets (Zhao et al., 2010). NA dissolution behavior was controlled by double EC coating to achieve sustained release and SIM was grinded with magnesium oxide to provide immediate release.

Combination of release profile from single drug

Many studied have been developed to modify the release of drugs from oral drug delivery system. By using multilayer tablet system, it makes possible to design desired release preparations of the same drug with an immediate release quantity in one layer and an extended release portion in the second, thus maintaining a prolonged blood level.

Conte et al. (1996) developed three layer Geomatrix® tablets which consists of a hydrophilic matrix core, containing the active ingredient, and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core (Figure 1). An extended release at a constant rate can easily be reached from the two-layer and particularly from the three-layer Geomatrix® systems, thus allowing administration once a day. On the other hand, if the device contains drugs of low solubility, the release rates obtained are generally too slow. In this case, to maintain the linearization of the dissolution profile while increasing the release rate, a different approach is proposed. A new barrier is designed whose protective effect (towards hydration + swelling/erosion + release) could be time-dependent, being maximal at the beginning and progressively diminishing during the dissolution process (Figure 2). During

dissolution, the swellable barrier swells and gels, but is not eroded, thus acting as a modulating membrane during the release process. The erodible barrier, instead, is progressively removed by the dissolution medium, exposing in time an increasing extent of the planar surface(s) of the core to interaction with the outer environment and to drug release. Both types of coatings are able to control drug release from the devices: the swellable barrier shows a stronger modulation efficiency and is more suitable to modify the delivery pattern of highly soluble drugs; the erodible barrier shows a time-dependent coating effect that provides better control of the dissolution profile of sparingly soluble drugs.

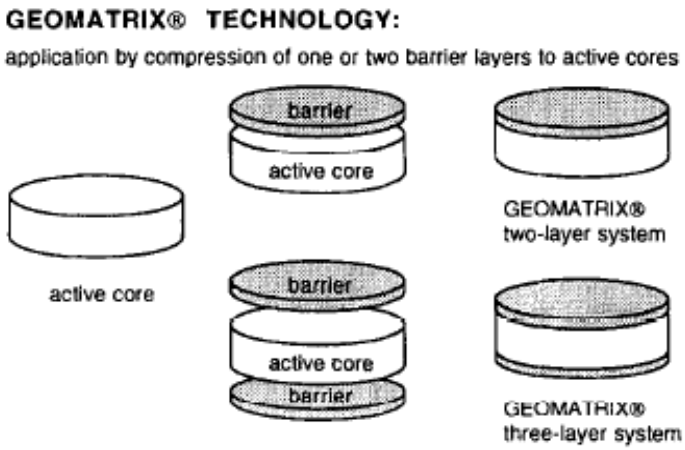


Figure 1. Geomatrix® Technology: two- and three-layer systems obtained by compression (Conte and Maggi, 1996)

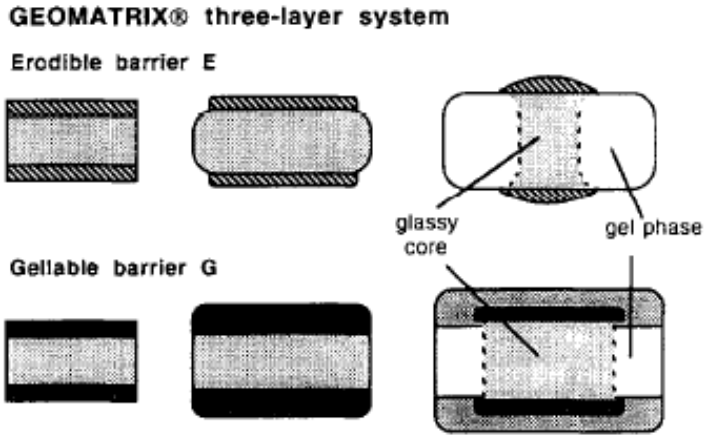


Figure 2. Swelling behaviour of the Geomatrix® three layer systems with the different types of barrier coatings: erodible or gellable (Conte and Maggi, 1996)

Multilayer tablet of isosorbid mononitrate with carbopol as matrix displayed sustained release (Efentakis and Peponaki, 2008). However three-layer tablet formulations

demonstrated lower drug release compared to matrix tablets. The structure of the tablets and weight/thickness of the barrier-layers considerably affected drug release and the release mechanisms. The barriers suppressed drug release causing a shift from Fickian (matrix tablet) to anomalous or erosion/relaxation release kinetics (three-layer tablet). The advantage of Carbopol three-layer tablet formulations is that a wide range of release profiles can easily be achieved through variation of tablet structure. In general, it appears that the barriers not only decrease the drug release from these systems, but also modulate the relative contribution of diffusion and polymer relaxation to drug release and therefore influence drug release mechanisms (Efentakis and Peponaki, 2008).

Multilayered matrix tablet technology also applied in formulation of guar gum three-layer matrix tablets with guar gum layers on both sides of the metoprolol tartrate (Krishnaiah, 2002). The three-layer matrix tablet with 75 mg of guar gum layers on both sides of formulation containing 50% of guar gum was found to provide the required release rate matching with the theoretical release rate constants calculated on the basis of pharmacokinetic properties of the drug.

Another technology for combining different release profile for single drug dosage form is PRODAS or Programmable Oral Drug Absorption System (Elan Corporation) which introduce a multiparticulate drug delivery technology that is based on the encapsulation of controlled-release mini tablets in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Mini tablets with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. These combinations may include immediate-release, delayed-release, and/or controlled-release mini tablets. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using mini tablets formulated with different active ingredients (Verma and Garg, 2001).

Furthermore, co-extruded dosage forms allow to modulate the release profile of a specific drug by incorporating drug in layers formulated with different thermoplastic polymers. Co-extrusion also offers the opportunity to formulate many either the same or different drugs in different layers, enabling their simultaneous administration. The design of co-extrusion a solid dosage form for oral application which provides dual release of a

single drug: a layer with immediate drug release to ensure a fast onset of action, in combination with a sustained release layer to sustain the activity of the drug over a longer period was studied. Diclofenac sodium (DS) was incorporated as model drug in the co-extruded formulation (Dierickx, 2013). Therefore, a core/coat dosage form was designed via co-extrusion to obtain a dual release rate of DS, the inner core providing sustained drug release (SR) and the outer (non-enteric) coat immediate drug release (IR). Core/coat dosage forms were developed using two different polymer combinations (ethylcellulose/ Soluplus® and polycaprolactone/ PEO). The two pairs of co-rotating screws each consisted of three mixing sections and a densification zone (the geometry of the screws is illustrated in Fig. 3). A co-extrusion was connected to both extruders. In the die, the two melts were combined to form two concentric layers, a core and a coat (Fig 4). The coat of all experimental co-extruded formulations rapidly dissolved (±20 min) in the dissolution medium, through which the DS release from the core was hardly obstructed. All formulations showed an initial burst released in 1 h, followed by a sustained DS release. The initial burst was mainly caused by the immediate release of the entire drug fraction in the coat, plus a small fraction already released from the core. The remaining DS fraction was sustained released from the core. Co-extrusion proved to be a promising technique to produce in a single step multilayer mini-matrices with dual drug release. Co-extruded formulations composed of polycaprolactone (core) and PEO/PEG (coat) were preferable because they allowed extrusion at a lower temperature and they provided better mechanical properties.

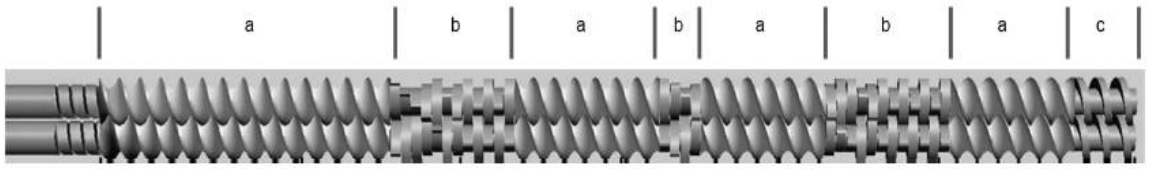


Figure 3. Configuration of the intermeshing co-rotating screws. Standard screw configuration with three kneading blocks: transport zone (a), mixing zone (b), and densification zone (c).

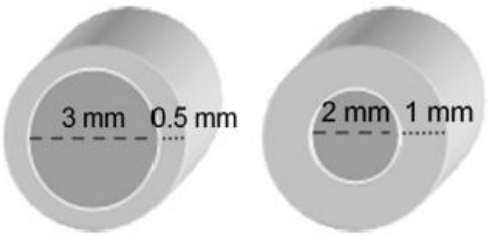


Figure 4. Different dimensions of co-extrusion die.

The combination of different release profile from the same drug in one dosage form was also developed by multilayer drug coated cores system (Lucy et al., 1992). The system used multilayer coated granules prepared by consecutively spraying aqueous solutions of diphenhydramine HCI, dissolved in methylcellulose (MC) of various viscosity grades, onto lactose granules in a fluidized bed. The in vitro drug release profiles of the coated product were shown to be a function of the polymer viscosity grade and the sequential order of application of the polymeric component layers on the lactose granules. Swelling of each component layer influenced drug diffusion to some extent, the overall release profiles were also modulated by the dissolution characteristics, particularly the particle size of the recrystallized drug that is embedded in the polymeric coat. This phenomenon reveals the concept of utilizing non-uniform initial viscosity distribution as a means to modify drug reIease in the design of drug delivery systems. The simplicity of the approach arises from the use of just a single type of polymer in the system and the rapid, efficient and reproducible production of the coated granules in a fluidized bed.

The possible release profile from combination of different release profile of the same drug within one dosage form designed by various multi-layer design are discussed in section below.

a. Quick/slow release profile

This system is characterized by an initial rapid release phase, followed by a period of constant slow release (Fig. 5). This is achieved by the application of immediate release layer to the conventional layered matrix tablet. This system can produce a rapid rise in plasma levels for those drugs that are needed to show appearance promptly for the therapeutic effect, followed by an extended release phase at a constant rate. Thus these quick/slow drug delivery systems demonstrated their versatility for those dosing regimens

where a simple constant rate of drug release does not entirely satisfy the therapeutic objective (Maggi, et al., 1992).

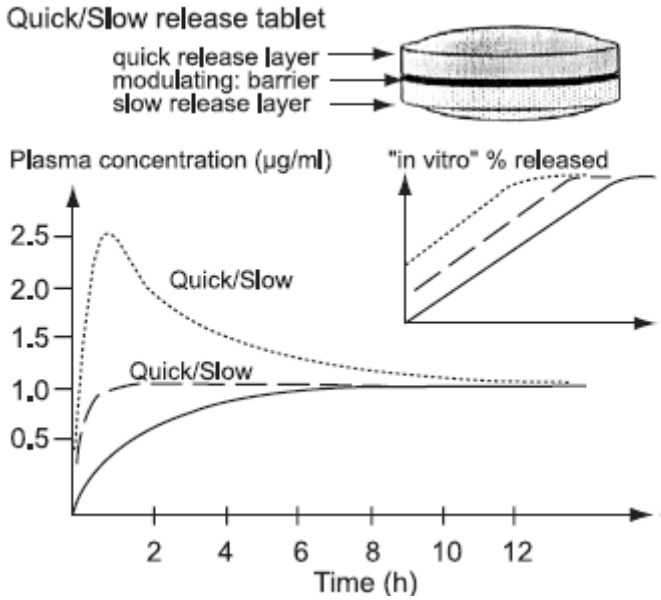


Fig. 5. Simulated plasma levels for different dose fractions combinations for a quick/slow geometric device (Conte et al., 2000)

b. Time-programmed release profile

To follow the circadian rhythm, a reasonable and generally accepted rationale is to have a delivery system capable of releasing drugs, in a pulsatile fashion rather than continuous, at predetermined time points and/or sites following suitable administration like oral (Yoshida et al., 1992; Lin et al., 1996). Press coating technique is one candidate for such a novel system that not only acts as a rate controlling system but also delivers the drug in the gut when it is required, which is in a time-controlled fashion. This technique has many advantages because no special coating solvents or equipments are needed for coating of tablets and manufacturing speed is also faster. The system consists of a core (either conventional or a modified release formulation), which is coated by compression with different polymeric barriers (presscoated systems) (Conte et al., 1993 and 1995; Rujivipat and Bodmeier, 2010) (Fig. 6). The outer shell may delay the penetration of fluid, thereby inducing a long lag time prior to the start of drug release. Once the solvent penetrates into the interior core tablet, the core tablet will dissolve and/or swell to break the outer shell resulting in rapid drug release (Fukui et al., 2000 and 2001; Lin et al., 2001). This delay in the start of release is not influenced by the core composition and only

depends on the shell formulation. Fig. 7 shows the dissolution profiles of core tablets and two types of press coated tablets (Fukui, 2000).

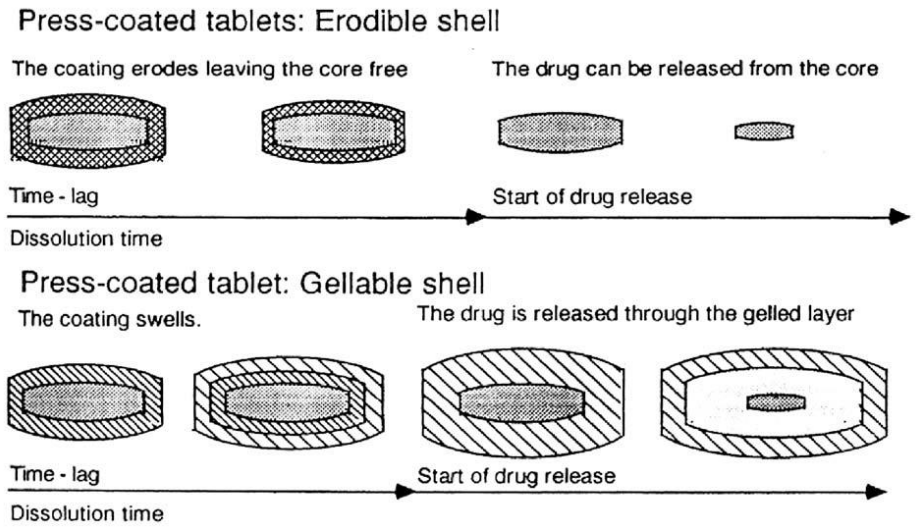


Figure. 6. Geometric press coated tablets for the delayed release of drugs (Conte et al., 2000).

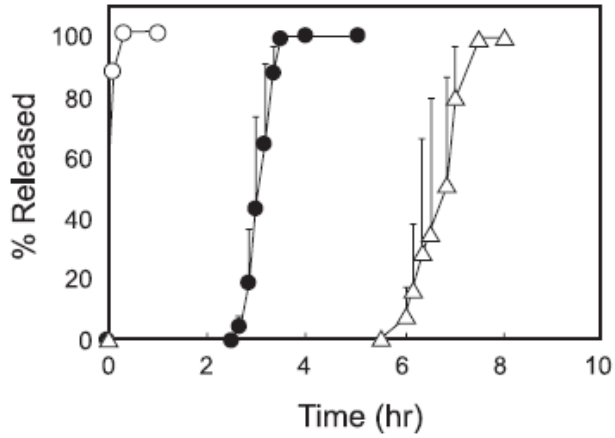


Figure. 7. Dissolution profile of Diltiazem hydrochloride from core tablet (o) and two types of press coated tablets (• and Δ) (Fukui, 2000)

c. Bimodal release profile

For many drugs, absorption is moderately slow in the stomach, rapid in the proximal intestine, and declining sharply in the distal segment of the intestine. The bimodal release system provides such a variable rate release. Bimodal release is characterized by an

initial rapid release, followed by a period of slow and constant release, and again a second phase of rapid drug release (i.e. sigmoidal release profile) (Abdul and Poddar, 2004). Such bimodal release system can offer two major advantages over other systems: (1) it produces rapid drug release during the initial and later phase to compensate for the relatively slow absorption in the stomach and large intestine; (2) it can be used to design programmed pulse release oral drug delivery systems for the therapeutic agents that perform more effectively when drug levels at the site of action undergo periodic changes. To obtain bimodal drug release patterns, hydroxypropylmethylcellulose based matrix tablets can be used (Shah et al., 1987 and 1989). Core-in-cup tablets design technology for this purpose was developed by Marvola et al., (Sirkia et al, 1994 and 1994b). Streubel et al. (2000) developed layered matrix tablets which showed that in bimodal delivery system an additional layer, i.e. fourth, containing initial dose rapidly disintegrates to produce quick onset of dissolution, promoting greater concentration gradient to compensate for poor absorpitivity in stomach (Fig. 8).

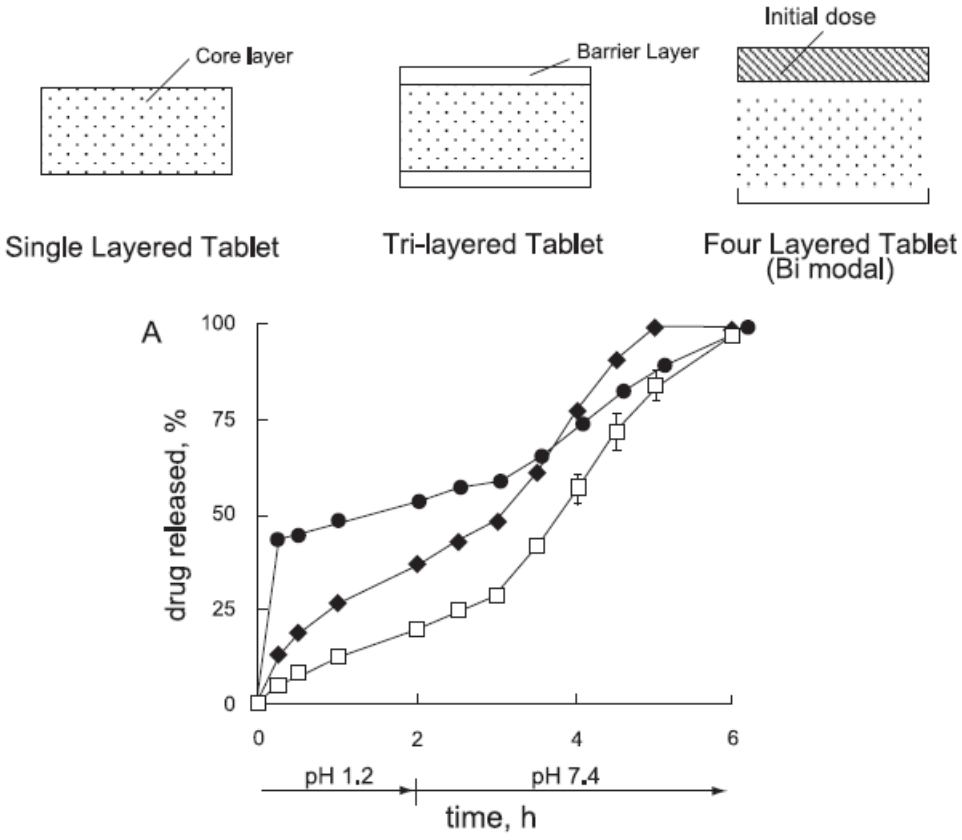


Figure. 8. Release profiles of theophylline from investigated tablets (•) Bimodal; (♦) Single layered tablet; (□) Tri-layered tablet (Streubel et al., 2000)

Combination of release profile from oral combination drug

Combining the same drug with different release profile in one dosage form can be designed by the same technology as described previously for single drug (the same drug in one dosage form). By using multilayer or bilayer tablet system, it makes possible to design extended release preparations with an immediate release quantity in one layer and an extended release portion in the second, thus maintaining a prolonged blood level. Similarly, in combination therapy as multilayer tablet, one drug can be administered for immediate release and another for sustained release as multilayer tablet, depends on required release of each drug.

A new multi-kinetics and site-specific oral antimalaria drug delivery system (MKSDDS), containing artesunate and clindamycin, based on the Dome Matrix® module assembly technology has been developed (Strusi, 2010). Due to morphological features, two modules can be assembled in two basic configurations, i.e. by inserting the convex base of the first module into the concave base of the second (stacked configuration), or by sticking the concave base of one module with the concave base of the other (void configuration). The void configuration showed gastro-retentive behavior in humans, due to the presence of an air chamber inside the two modules' assembly (Strusi et al., 2010 and 2008). The system comprises of four modules, i.e., two controlled release (CR) modules for delivery of 160 mg of clindamycin phosphate, one immediate release module containing 50 mg of artesunate and one immediate release module containing 80 mg of clindamycin phosphate. The clindamycin dose was formulated in modules exhibiting two different release kinetics: one immediate release (IR) and another prolonged release in gastro-retentive conditions for maximizing clindamycin absorption in the upper GI tract, in order to prevent adverse effects due to partial oral absorption. One module, referred as “male” (Fig. 9D), had the concave base lined, referred as “female” (Fig. 9C). Assembling the modules in this manner forms a ‘void’ configuration with floating properties. The ‘stacked’ configuration is formed by interlocking the male and female convex base modules with additional concave female modules (Fig. 9B and E). Finally, four modules were assembled to form the clindamycin artesunate multi-kinetics and site-specific delivery system: MKS_DDS. Specifically, two prolonged release clindamycin modules (CR), one male and one female, were interlocked on the concave bases, forming an assemblage in void configuration. Then, one immediate release clindamycin module (IRc) was stacked onto one of the convex bases of the void assemblage, and one immediate

release module of artesunate (IRa) to the second convex base (Fig. 9A). Clindamycin prolonged release modules (CR) were manufactured as swellable matrices. For their preparation, clindamycin phosphate and HPMC K100 M were kneaded with a 1:1 (v/v) ethanol–water solution of PVP K30 5% (w/v). For the artesunate immediate release module (IRa) preparation, the drug was mixed in Turbula® for 15min with micro crystalline cellulose, carboxymethyl starch, sodium dodecyl sulphate, talc and magnesium stearate. Female modules (Fig. 9B) having a thickness of 4.17±0.05 mm were tabletted with this mixture.

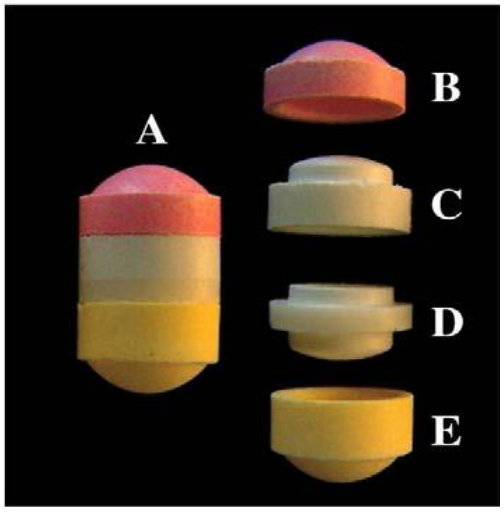


Figure. 9. (A) MKS_DDS DomeMatrix® assembled systemformalaria therapy: (B) immediate release module of artesunate; (C) and (D) female and male controlled release modules of clindamycin, forming the void configuration system; (E) clindamycin immediate release module (Strusi, 2010)

Kim et al., (2012) developed combination drug FCDs as tablet coated by drug suspension a new FDCS for once daily administration of glimepiride (GLM) and metformin HCl (MTF) by coating GLM-IR layer on MTF-ER core tablet. With this active film coating method, favored oral dosage forms can be prepared with a smaller tablet diameter than multi-layer coated tablets. Further, a film coating machine and tableting machine simply used without other specialized equipment, making this process more advantageous. MTF-ER tablets (total weight: 1000 mg) were prepared by the wet granulation method. GLM with excipients such as HPMC (4.5 cP), PEG 6000 and titanium oxide were prayed as coating suspension. When the HPMC matrix was swollen, a viscous hydrogel surrounding the matrix was established. This viscous hydrogel was thought to make GLM-IR layer stick on the core tablet and retard the release rate of GLM. When inert HPMC layer was introduced, it could prevent contact between the GLM-IR layer and the

core tablet. Although the inert mid-layer also contained HPMC, its much lower viscosity grade did not cause the decrease in release rate.

Formulation of bilayer tablets consisting of atorvastatin calcium (AT) as an immediate release layer and nicotinic acid (NA) as an extended release layer has been developed (Nirmal et al., 2008). The immediate release layer was prepared using super disintegrant croscarmellose sodium and extended release layer using hydroxypropylmethyl cellulose (HPMC K100M). Both drugs having different mechanism of action were combined to achieve the same goal. To maintain the environmental pH, calcium carbonate light was included. The MCC (Avicel PH 101 and super disintegrant croscarmellose sodium) in outer layer of tablet has the disintegration property when it comes in contact with the dissolution medium hence facilitates the tablet to erode. In the extended release layer of NA to control its release, high viscous polymer HPMC K100M was incorporated.

Another approaches to include different release profile of combination drug from oral pharmaceutical dosage form is by introducing co extrusion method. In co-extrusion, two or more materials are simultaneously processed via hot melt extrusion (HME) (Quintavalle, 2008; Vaz et al., 2003). This method offers additional opportunities to design innovative pharmaceutical dosage forms as multilayered devices can be manufactured, each layer having specific properties, for example. The production of oral drug delivery systems via co-extrusion offers the opportunity to combine different drugs with different release profiles, to modulate drug release (either by loading the different layers with different amounts of drug or by incorporating the drug in different matrices) and to enable the simultaneous administration of non-compatible drugs (formulated in separate layers). So far, there are no co-extruded dosage forms for oral use on the market and hardly any research has been done in this field (Vaz et al, 2003; Quintavalle et al., 2007; Losio et al., 2008). The biggest challenge of the co-extrusion process is to find good polymer combinations, taking into account the pharmaceutical aspects (e.g. good drug release characteristics) as well as some technical considerations (e.g. similar extrusion temperature, melt viscosity, adhesion between layers, etc.). Fixed-dose combination mini-tablets with good in vitro and in vivo performance were successfully developed by means of co-extrusion, using a combination of polycaprolactone and polyethylene oxide. Metoprolol tartrate (MPT) and hydrochlorothiazide (HCT) were incorporated as sustained and immediate release model drugs, respectively. Combination of polycaprolactone (core) and polyethylene oxide (coat) was selected for co-extrusion trials, taking into account their

drug release profiles and extrusion temperature (70^{o}C). This combination (containing 10% HCT in the coat and 45% MPT in the core) was successfully co-extruded (diameter core: 3 mm/thickness coat: 0.5 mm). According to the dissolution data, both test and reference formulation provided immediate release (less than 30 min) of HCT and sustained MPT release over 24 h (Dierickx, 2012).

Many product has been marketed as oral drug delivery combination drugs. Table **1** depicts the examples of some oral combination products on the US and worldwide market (WHO, 2009; Hughes, 2009). There are also many patent has been published concerning this. Recent combination formulation patents and patent publications summarized in Table 2.

1.1.1.2 Parenteral drug delivery

Microparticles

Combination of chosen injectable drug-delivery systems for the lipophilic steroidal drugs ethinyl estradiol (EE) and drospirenone (DRSP) as combination drug had been investigated as microparticles and organogels. The study was focused on in vitro release kinetics. Stability, drug content, morphology, and particle size were also investigated because these factors may influence drug release (Nippe and General, 2012). The morphology and release kinetics of DRSP PLGA microparticles indicated that DRSP is dispersed in the polymer. The in vitro release profiles correlated well with in vivo data. EE release from PLGA microparticles was faster than DRSP release; EE release is assumed to be primarily controlled by drug diffusion. The bursting of microcapsules accelerating the drug delivery was therefore delayed. The DRSP organogels system was not combinable with EE PBCA microcapsules due to immediate bursting of microcapsules. Both sedimentation and particle growth of DRSP microcrystals were decelerated in MCT organogels. EE PLGA microparticles incorporated into DRSP organogels released EE significantly slower than aqueous dispersions. The deceleration should mainly be caused by slowed drug diffusion.

Table 1. Examples of some oral combination products

Brand	Generic Name	Indication	Innovator
Atripla®	Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate	Antiviral against HIV	Bristol-Myers Squib
Truvada	Emtricitabine and Tenofovir Disoproxil Fumarate	Antiviral against HIV	Gilead
Kaletra®	Lopinavir and Ritonavir	Antiviral against HIV	Abbott
Combivir®	Zidovudine and Lamivudine	Antiviral against HIV	GlaxoSmithKline (GSK)
Trizivir®	Abacavir Sulphate, Zidovudine and Lamivudine	Antiviral against HIV	GSK
Augmentin®	Amoxicillin and Clavulanate Potassium	Antibacterial	GSK
Bactrim®	Sulphamethoxazole and Trimethoprim	Antibacterial	Roche
Riamet®	Artemether and Lumefantrine	Antimalarial	Novartis
Activella®	Estradiol and Norethindrone Acetate	Hormone therapy	Novo Nordisk
Yasmin®Yaz®	Drospirenone and Ethinyl Estradiol	Hormone therapy	Bayer
Symbyax®	Olanzapine and Fluxetine HCl	Bipolar depression	Eli Lilly
Treximet®	Naproxen Sodium and Sumatriptan	Migrane	GSK
Stalevo	Carbidopa, Levodopa and Entacapone	Parkinson's disease	Novartis
Allegra-D®	Fexofenadine HCl and Pseudoephedrine HCl	Seasonal allergy	Sanofi-Aventis
Vytorin®	Simvastatin and Ezetimibe	Lipid/Cholesterol lowering	Merck
Co-Diovan®	Valsartan and Hydrocholorothiazide	Blood pressure control	Novartis
Exforge®	Amlodepine Besylate, Valsartan and Hydrocholorothiazide	Blood pressure control	Novartis
Lotrel®	Amlodepine Besylate, Benazepril HCl, Valsartan and Hydrocholorothiazide	Blood pressure control	Novartis
Caduet®	Amlodipine Besylate and Atorvastatin Calcium	Blood pressure control	Pfizer
Avandamet®	Rosiglitazone Maleate and Metformin HCl	Type 2 diabetes	GSK
Glucovance®	Glipizide and Metformin HCl	Type 2 diabetes	BMS
Janumet	Sitagliptin and Metformin HCl	Type 2 diabetes	Merck

Table 2. Summary of patents on combination drugs

Principles of APIs morphology	Novelty	Patent No (Reference)
Simple mixing of acetaminophen and tramadol with MCC and Povidone as binder, and matrix system Methocel K4M	Sustained release formulation contain Acetaminophen and tramadol which provide 25-60% total drug release in first hour, 50-90% release in first 4 hour and not less than 80% release in first 12 hour	US 7374781 B2 May 2008 (Zhang and Way, 2008)
Amlodipin as CR was wet granulated by carbomer 71G or Kollicoat SR30D or Eudragit RS PO and simvastatin as IR was wet granulated by MCC and mannitol . They were mixed and compress as press coated tablet or as multilayered tablet	Combination for chronotherapeutic and xenobiotics (simvastatin - Amlodipine). The formulation then compress to tablet using film coating layer, multilayer tablet or capsules.	US Patent No. 2008/0241240 A1 October 2008 (Kim et al., 2008)
Multilayer tablet comprising two external drug containing layers in stacked arrangement on opposite sides of matrix tablet, as a hard capsules or as osmotic tablet	Oral dosage form which provide a triple combination release of at least one active agent.	US Patent No 2008/0299197 A1 Dec 2008 (Toneguzzo et al., 2008)
Simple mixing, by wet granulation, then compressed into tablets Polymer: HPC-L and HPC-M with different ratio and different molecular weight	Slow release of Levodopa and Carbidopa by erosion or by diffusion controlled mechanism, depending on molecular weight of polymer	US Patent 2006/0159751 A1 (Gogia et al., 2006)
- Ramipril dispersed in disintegrating tablet as IR matrix - Hydrochlorothiazid in disintegrating tablet as IR Matrix - Telmisartan in dissolving IR matrix as Fast release Compressed into three layer tablet	Multilayer tablet of angiotensin II receptor antagonist Telmisartan and ACE inhibitor ramipril alone or together with diuretics Hydrochlorothiazide	US patent 2005/0186274 A1 (Kohlrausch, 2005)
- As osmotic tablet consist of bilayer core with first drug layer in laminar (staked) arrangement with second drug layer with external coat and passageways hole. The passage were laser drilled. - As bilayer tablets: first drug layer and second drug layer are coated by water erodible or water permeable polymer	Pharmaceutical composition and dosage form for the treatment of incontinence with oxybutynin and darifenacin with tolterodin L-tartrate as matrix tablet	US Patent No 2003/0185882 A1 October 2003, (Vergez and Riccci, 2003)
Ibuprofen and codeine were wet granulated separately, then compress into bilayer tablet (ibuprofen as as first layer and codein as second layer)	Multiphase (especially bilayered, optionally coated) tablet of narcotic analgesic (e.g. Codeine phosphate) and ibuprofen	US patent No 4.844.907, July 1989 (Elger et al., 1989)

Principles of APIs morphology	Novelty	Patent No (Reference)
Tablet core: Acetaminophen, Hydromorphone, Poly ethylen oxyd and PVP was wet granulated then compressed into tablets Coating layer: a. Interior wall: EC: HPC b. Exterior wall : Cellulose acetetat and ethylen oxyd and propylen oxyd Sparyed in coating pan. The mils were laser drilled	Combination products providing opioid hydromorphone with acetaminophen and ibuprofen with hydrogel polymer which exhibit osmotic tablet system	US Patent no. 6.245.357 Juni 2001, (Edgren et al., 2001)
1. - CR of flurbiprofen with Kollidon SR extruded by spheronizer then compressed into first layer tablet - CR or IR of thiocolchicoside or tizanidine extruded by spheronizer then compressed into tablet as second layer 2. multilayer tablet with same formulation with (1) but covered by coating layer Opadry 3. - CR with core for slow release drug (flurbiprofen) - coating layer comprising tizanidine as IR with HPMC 3 cp and PEG 8000 4. – core of drug (flurbiprofen) - Polymer coating to give CR of core Opadry - Coating layer comprising IR drug Thiocochicoside or tizanidine	Controlled release of flurbiprofen and muscle relaxant combination for oral administration as multilayer tablet, multicoated tablet and capsules. The solid dosage forms is bilayer tablet having flurbiprofen in phase I and thiocolchicoside or tizanidine in phase II	US patent 2009/ 0175938 A1 july 2009 (Cifter et al., 2009)
The polymer matrix of crosslinked polyvinyl alcohol. The drug maybe included in the same microspheres, or microspheres each with an individual pharmaceutical agent may be mixed together	Microspheres of a polymer matrix, having two different APIs active for killing tumor cells. The combination are doxorubicin with rapamycin, irinotecan with ibuprofen, ibuprofen with doxorubicin and irinotecan and doxorubicin.	US Patent 2011/0229572A1 Sep 2011 (Lewis et al., 2011)
Nanoparticulate meloxicam or salt or derivate in combination with multiparticulate hydrocodone	Nanoparticulate meloxicam composition in combination with multiparticulate modified release hydrocodone composition which delivers hydrocodone in bimodal or multimodal release.	US Patent 2008/0102121 A1 May 2008. (Devane et al., 2008)

Micelles

Novel drug combinations of cytotoxic agents of poly(ethylene glycol)-block-poly(ε-caprolactone) (PEG-b-PCL) micelles loaded with paclitaxel (cytotoxic agent), cyclopamine (hedgehog inhibitor), and gossypol (Bcl-2 inhibitor) as current treatment strategies for ovarian cancer was studied (Cho et al., 2013). Drug-loaded PEG-b-PCL micelles were prepared by a solvent evaporation technique as previously described by Cho et al., (2011). All three anticancer agents are poorly water-soluble, and PEG-b-PCL micelles can deliver all three together following multiple drug solubilization at 18 mg/mL, ca. 6.2 mg/mL for each anticancer agent, enabling in vivo toxicity and efficacy studies in xenograft models. Multi-drug loaded PEG-b-PCL micelles may potentially fulfill several major requirements for IP combination drug delivery including : biocompatibility, multiple drug solubilization, physical stability against drug precipitation, and sustained release (Cho et al., 2013).

In an attempt to develop multidrug vehicle as co-delivery of drug combination at a controlled ratio via the same vehicle to the cancer cells, Desale et al. (2013) studied co-incorporation of drug molecules used in the treatment of ovarian cancer with different physicochemical properties, such as hydrophilic cisplatin (cis-dichlorodiamminoplatinum (II), (CDDP) and hydrophobic paclitaxel (PTX) into triblock copolymers containing the blocks of ethylene glycol, glutamic acid and phenylalanine (PEG–PGlu–PPhe) micelles. These nanostructures were designed to have multicompartment morphology for drug loading and were cross-linked at an intermediate layer within the polymer micelles to ensure their prolonged stability upon systemic administration. Hydrophilic CDDP and hydrophobic PTX were loaded with high efficiency, exhibited differential release profiles and synergistic cytotoxic effect against ovarian cancer cells. Altogether, this study demonstrates a fundamental possibility for simultaneous delivery of chemotherapeutics and molecular targeting agents via single well-defined and structurally tunable polymeric nanocarrier.

Other study on development of poly(ethylene glycol)-block–poly(D,L lactic acid) (PEG-b–PLA) micelles to deliver multiple poorly water-soluble drugs has been investigated by Shin et al. (2013). PEG-b–PLA micellar systems that can simultaneouly deliver multiple anticancer agents, like Paclitaxel (PTX), etoposide (ETO), docetaxel (DCTX) by co solublizing them with 17-allylamino-17-demethyoxygeldanamycin (17-AAG) to generate safer, more stable formulations for potentially synergistic combination

chemotherapy had been successfully developed. Scematic presentation of single and multiple drug loaded micelles shown in Fig. 10. The solubility enhancement for all drugs in the MDM micelles was similar to the single drug micelles (SDMs). The presence of multiple drugs within PEG-b–PLA micelles did not adversely affect the apparent solubility enhancement of the individual drugs. Another promising find of this work is the ability of 17-AAG to maintain the stability of different hydrophobic drugs in the carrier system for 24 h.

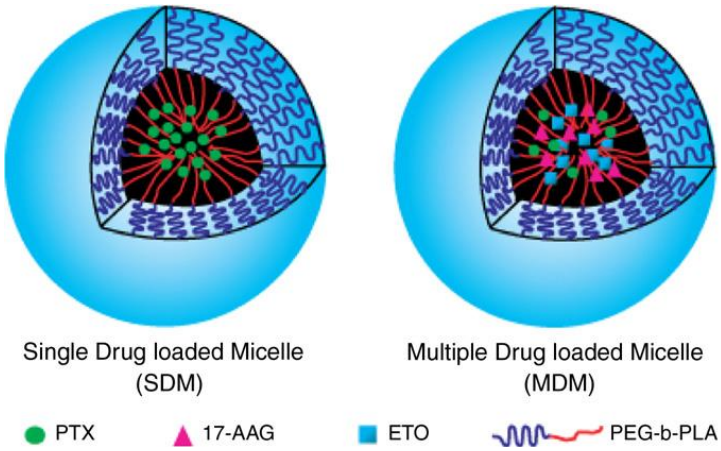


Figure 10. Schematic representation of single and multiple drug-loaded PEG-b–PLA micelles.

Liposomes

Celecoxib (Clx) and hyaluronate (HA) are both efficient in the treatment of osteoarthritis (OA), but in two different mechanisms, expected to have synergistic effect. The evaluation whether treatment with the drug combination was better than a single drug was studied by Dong et al. (2013) by developing Clx-loaded liposomes embedded in HA gel, then administered the liposomal Clx–HA combination via intra-articular injection. Clx-loaded liposomes showed high efficiency encapsulation (>99%). In vitro release studies demonstrated that the release of Clx from lipsosomes was delayed by the combination of HA with liposomes. Liposomes containing Clx were prepared by film technique. As a vehicle for liposomal Clx–HA combination, HA gel and liposome suspension were mixed 1:1 ratio on volume basis by a vortex mixer.

Hydrogels

Current local delivery strategies for neuroprotective strategies during the trauma of spinal cord injury (SCI) sometimes are inadequate: bolus delivery often results in rapid clearance due to cerebrospinal fluid flow in the intrathecal space. Drug delivery system that would provide sustained, local release of factors can be designed by delivery in which a drug loaded thermo-sensitive hydrogel which is injected intrathecally and remains localized at the site of injection, delivering the drug load to the spinal cord and then biodegrading. In this manner the hydrogel provides a platform for localized release over the life of the material. Fig. 11 shows that intrathecal injection bypasses the dura and arachnoid mater and limits convective drug redistribution from CSF flow, all barriers that negatively impact epidural delivery (Chvatal et al., 2008). High molecular weight blends of hyaluronan HA and methyl cellulose MC (HMW HAMC) which remain injectable and are stable for more than 28 days in vitro provides longer term release suitable for combination neuroregenerative and neuroprotective strategies. To achieve longer-term release profiles, we dispersed formulations of drug loaded poly(lactic-co-glycolic acid) (PLGA) nano- and microparticles in the HMW HAMC gel. Use of the drug delivery platform is demonstrated using six therapeutic molecules or models human basic fibroblast growth factor (FGF-2, N95 wt.%), 2,3-Dioxo-6-nitro- 1,2,3,4-tetrahydrobenzo[β]quinoxaline-7-sulfonamide disodium salt (sodium NBQX, N98 wt.%), α-Chymotrypsin (type II from bovine pancreas), human IgG, andN6,2'-O-dibutyryladenosine 3',5'-cyclicmonophosphate sodium salt (dbcAMP) and recombinant human epidermal growth factor (EGF). As an injectable drug delivery platform, the particle loaded hydrogels allow different drug formulations to be dispersed within the hydrogel to create a combination therapy while maintaining control of the resulting release profiles. Existing drug and particle formulations can be directly dispersed in the hydrogel without modification, and the combination of fast diffusion limited release from the dissolved phase and slow release of particle-borne drugs can be exploited such that release can be substantially decoupled from molecular weight (Baumann et al., 2009).

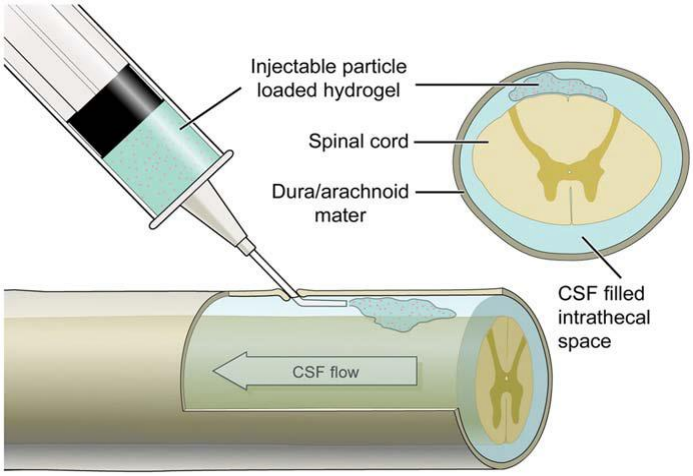


Figure. 11. An intrathecal drug delivery system. The composite hydrogel is injected intrathecally at the site of injury and remains localized between the arachnoid and piamater, releasing the drug load into the spinal cord (Baumann et al., 2009)

Another injectable hydrogels as a multi-drug delivery system using synthesized hyperbranched poly(amine-ester) (HPAE) macromers with different degrees of terminal C=C modification was developed by Zhang et al. (2010). The aqueous solutions of the macromers were fast transformed into hydrogel at body temperature with a low concentration (0.05 wt%) of ammonium persulfate (APS). Three different types of drugs, doxorubicin hydrochloride (Dox), 5-fluorouracil (5FU) and leucovorin calcium (LC), were used as model drugs. This system allows locally releasing single and/or combinations of anticancer drugs simultaneously by a controllable way. Behaviors of drug release can be controlled by the drug-loading methods or/and the C=C modification degree of macromers loaded with the drug molecules. The drug release period could be prolonged when the drug was loaded into the macromers with high content of C=C. Based on swelling and degradation tests, hydrogel with the formulation of 30 and 40 degree of substituted C=C was employed for combination delivery of three drugs and the drug delivery profile showed each drug could release independently in a controlled way. Moreover, good biocompatibility of these hydrogels was demonstrated against L929 and MCF7 cells. These results suggest that the HPAE hydrogels hold great potential for use as injectable systems for locally delivering single and/or multiple drugs in chemotherapy of cancer.

Implants

Not so many combination drug as implant for parenteral delivery has been marketed. Sulperazone® (sulbactam-cefoperazone 1:1) and Duocids® (sulbactam-ampicillin 1:1)-loaded poly(3-hydroxybutyrate-co-4-hydroxyvalerate), (P(3-HB-co-4-HB)) rods were reported as effective biodegradable implants to treat osteomyelitis. In this in vivo study, a hemolytic strain of *S. aureus* was directly delivered into the medullary cavity of rabbit tibiae. Surgery sites were almost completely healed at 6 weeks using these antibiotic-loaded P(3-HB-co-4-HB) intramedullary implants (Gursel et al., 2001). Other combination drug available on the market until now are dual drug loading as co-extruded dosage forms Nuvaring®, a contraceptive vaginal ring, and Implanon®, a contraceptive implant (Fischer, 2008)

Use of drug-polymer conjugates

Polymer–drug conjugates are drug delivery technologies in which a drug is covalently bound to a polymeric carrier, normally via a biodegradable linker. The term polymer–drug conjugates for combination therapy is a general phrase that encompasses at least four types of systems(Greco and Vicent, 2009), namely :

1) Type I: polymer–drug conjugate plus free drug.
   In this approach, a polymer–drug conjugate carrying a single drug is administered in combination with a low molecular weight drug or with another type of treatment (e.g. radiotherapy).
2) Type II: polymer–drug conjugate plus polymer–drug conjugate. Two polymer–drug conjugates, each carrying a single therapeutic agent, are administered in combination.
3) Type III: Single polymeric carrier carrying a combination of drugs. In this approach two or more drugs are attached to a single polymer carrier.
4) Type IV: polymer-directed enzyme prodrug therapy (PDEPT) and polymer enzyme liposome therapy (PELT). The fourth type of system encompasses the combination of a polymer–drug conjugate carrying a single therapeutic agent with a polymer–enzyme conjugate (PDEPT) or the combination of a liposomal system with a polymer–phospholipase conjugate (PELT). The polymer–enzyme conjugate is responsible for drug release following cleavage of the drug–polymer linker (in PDEPT) or disruption of the liposomal system (in PELT).

Another study on the use of pro drug for parenteral dosage form been developed by Thing et al. (2012). Intra-articular injection of naproxen and ropivacaine as a sustained drug delivery system was studied by combining the use of lipophilic solution with the prodrug approach in providing efficient and prolonged release of N,N-diethyl glycolamide ester of two drugs from an oil vehicle consisting of medium-chain triglycerides. The in vitro release study on phosphate buffer and 80% (v/v) synovial fluid at pH 7.4 was examined in two dialysis membrane-based release models. The ester prodrug exhibited high solubility in medium-chain triglyceride, a high partition coefficient and was rapidly converted to naproxen in synovial fluid. Compared to naproxen, the release of the prodrug from the oil was sustained. In synovial fluid, the reconversion to naproxen resulted in faster release compared to that observed using buffer. In both release models, the use of ropivacaine–prodrug combination provided concomitant release from the oil into synovial fluid with ropivacaine being released faster than naproxen.

1.1.1.3 Transdermal delivery system

As locally controlled drug delivery, combination products have already found applications in various areas of cardiovascular disease, diabetes, orthopedics, and cancer (Wu and Grainger, 2006). CardioTech International, Inc. (Woburn, MA, USA) just received FDA approval to market an antibiotic containing hydrogel wound and burn dressing intended for use in the management of partial and full-thickness wounds including venous stasis ulcers, diabetic ulcers, pressure sores, blisters, superficial wounds, abrasions, lacerations and donor sites. The wound contact surface comprises a hydrogel containing mixed antibiotic components including neomycin sulfate, bacimicin zinc and polymyxin B sulfate (10,000 Units). A second outer layer consists of a polymeric film. The combination of wound dressing with direct antibiotic release provides obvious advantages over traditional wound dressings in preventing bacterial infection.

A more recent clinical study confirmed excellent performance of pacemaker leads containing dexamethasone sodium phosphate and dexamethasone acetate (Singarayar et al., 2005). PLGA microspheres alone or PLGA microsphere/poly(vinyl alcohol) (PVA) hydrogel composites releasing dexamethasone have been implanted subcutaneously into rats and investigated in vitro and in vivo as a conjunctive therapy with implantable sensors. Dexamethasone release from PLGA microsphere/PVA hydrogel composites exhibited approximately zero-order kinetics. These composites demonstrated some in vivo capability

to modulate both acute and chronic inflammatory responses, and minimized fibrosis adjacent to the implants (Patil et al., 2004; Hickey et al., 2002). Such composite coating design provides some versatility for combination devices for altering drug dosing via microsphere loading into the hydrogel matrix, as well as through microsphere composition, and mixed microsphere-based dual drug administration.

1.1.1.4 Pulmonary delivery system

Stable and well-dispersible pulmonary fine powders composed of combination drugs with different water solubility, to facilitate concomitant release of corticosteroid budesonide and short acting β-agonist salbutamol sulphate and to improve the dissolution of the budesonide has been prepared by Raula et al. (2013). The budesonide nanosuspensions were prepared by a wet milling which were mixed then with salbutamol sulphate, mannitol (bulking material) and leucine (coating material) for the preparation of micron-sized particles by an aerosol flow reactor wherein leucine formed a rough coating layer on particle surface. The stable and intact particle assemblies showed excellent aerosolization performance. Combining the two formulation technologies enabled the encapsulation of drugs with different solubility into a single, intact particle. The leucine coating provided excellent aerosolization properties which allowed fine powder delivery from the inhaler without carrier particles. This study showed the feasibility of preparing powders for combination therapy that are utilized, for instance, in inhalation therapy.

Inhalable biodegradable microparticles containing isoniazid and rifampicin were prepared by a combination of solvent extraction and evaporation methods by Sharma et al. (2001). The extent of microparticle delivery *in vivo* was examined by flow-cytometry. Drug concentrations in the blood and in alveolar Mf were estimated by high-performance liquid chromatography after oral, vascular, intratracheal, and inhalation administration. Large numbers of particles could be delivered to the bronchiopulmonary system through a 2-min exposure to fluidized particles. The microspheres delivered by inhalation or intra tracheal instillation release significant amounts of drug almost instantaneously, so that appreciable amounts can be recovered from serum within the short sampling time. Conclusion from this work is that inhalable microparticles containing drugs offer promises of dose and dosing-frequency reduction, toxicity alleviation, and targeting Mf-resident persistent mycobacteria.

Another work from Taki et al. (2011) found that inhalation of salmeterol xinafoate (SX) and fluticasone propionate (FP) from a combination product produced superior clinical outcomes in comparison to the administration of 'similar' doses via separate single-active inhalers. The stage-by-stage deposition of drugs aerosolised from the single-active Accuhaler® products Serevent® (SX) and Flixotide® (FP) with the SX®FP combination product Seretide® Accuhaler® in vitro showed significant differences in drug deposition profiles were obtained following aerosolisation from the single-active versus combination products. Deposition on several next generation impactor (NGI) stages exceeded the acceptability limit of ± 15% set for inhaler bioequivalence testing. If these differences in local deposition are reflected in vivo, then these findings may explain the reported clinical improvements achieved with the combination products compared to similar doses delivered by separate single-active inhalers.

1.1.2 Stability issues

When combinations of drugs are used in one formulation, chemical incompatibility issues become one of the most important factors influencing drug stability. The instability of combination drugs is manifested in various forms that can be broadly classified into three groups: physical instability, which includes changes in physical appearance (e.g., colour, precipitation, hardness, etc.); chemical instability (variation in drug content and impurities); and functional instability (changes in the drug release pattern). The incompatibility interactions are often facilitated by the close contact between drugs and drugs or drugs and excipients. There are other factors such as the pH of the formulation microenvironment, temperature and moisture, all of which initiate and catalyse chemical reactions. Stability problems in combination products can be attributed to three types of interaction:

i. **Drug–drug chemical interaction:** two or more drugs interact directly, resulting in drug degradation and a number of impurities; for example, lisinopril combined with aspirin undergoes acetylation to generate acetyl lisinopril (Kumar et al., 2008) which could lead to a number of possible adverse events. Occasionally, combination drugs, which may not be interacting directly, exhibit incompatibility in the presence of certain formulation components; for example, the combination of rifampicin and

isoniazide is stable unless there is any excipient or agent that creates an acidic or alkaline environment.

ii. **Drug–excipient interaction**: a drug in a combination product has an excipient that is incompatible with other drugs; for example, telmisartan in a telmisartan-hydrochlorothiazide combination product needs the incorporation of an alkaline excipient. Hydrochlorothiazide, however, degrades in an alkaline environment (M. Nakatani *et al*., 2007)

Stability in solid state

Significant research has been conducted to understand the cause of drug instability issues. Various combination products of tubercular drugs are examples of drug–drug, as well as drug excipient interaction.

Ranitidine chloride has very poor stability because of high moisture absorption and is discolored by light while aspirin (acetyl salicylic acid) can be easily hydrolyzed into salicylic acid and acetic acid. In order to study how to prepare single-layer combination tablet containing incompatible active ingredients, aspirin and ranitidine hydrochloride were selected as model drugs because of the serious interaction between them (Wang et al., 2003). Aspirin powders without any additives were granulated with hydroxypropyl methyl cellulose (HPMC) water solution as a binder using a Wurster coating apparatus. On the other hand, ranitidine hydrochloride was coated with Aquacoat (ethyl cellulose aqueous dispersion) after preliminary granulation with the Wurster coating apparatus. The aspirin granules and coated ranitidine hydrochloride particles were compressed into tablets with suitable excipients. The combination tablets showed good dissolution, content uniformity and improved stability of active ingredients. With granulation and coating, it is possible to prepare combination tablets by a common compressing method which do not show incompatibility between the main active ingredients (Wang et al., 2003).

Stable fixed dose combination tablet for a model dipeptidyl peptidase IV (DPP-IV) inhibitor and metformin hydrochloride as moisture- sensitive drug substances has been developed by Burke et al., (2013) by investigation on a drug layered pellet containing the DPP-IV inhibitor, which was further coated with various seal coats and moisture barriers then compressed into a tablet with granulated metformin hydrochloride. The DPP-IV inhibitor was particularly challenging to formulate due to its significant chemical instability and moisture sensitivity. The investigations revealed that the drug layered

pellets compressed into a fixed dose combination tablet yielded a unique stability enhancement. The stability was highly dependent on the final tablet water content and could be further improved by the addition of moisture barrier coatings. While the exact mechanism of stability enhancement has not been elucidated at a molecular level, the pellet coating process is able to reduce cyclization of the nitrile and amine group on the molecule. The stability enhancement of drug layered pellets goes beyond a simple reduction in moisture and preventing direct physical contact with other tablet components and suggests that the DDP-IV inhibitor molecule adopts a more favorable conformation which reduces degradation.

Although anti-tuberculosis (TB) FDCSs are associated with many advantages, marketed anti-TB FDCSs containing two, three, and four drugs of rifampicin (R) isoniazide (H), pyrazinamide (Z) and ethambutol HCl (E) underwent extensive physical and chemical changes during storage under accelerated stability testing conditions, resulting in generation of isonicotinyl hydrazone (HYD) as the major degradation product (Bhutani et al., 2004). HYD as a result of the interaction of the imine group of rifampicin and the amino group of isoniazid is slow in a solid state, it increases exponentially in the presence of acid and other tubercular drugs, such as ethambutol hydrochloride and pyrazinamide. Another important finding was that other co-drugs present in the formulations could catalyze the reaction between rifampicin and isoniazide to form HYD (Bhutani et al., 2004). This was evident from much higher loss of R and H from formulations containing RHZ, RHE, and RHZE, as compared to the formulations containing RH only (Singh et al., 2001 and 2003; Sankar, 2003; Bhutani et al., 2004 ; 2004b and 2005).

Tablet containing isoniazid and ethambutol was found to gain moisture when exposed to accelerated stability test conditions of 40^{o}C/75% relative humidity (RH) (Bhutani et al., 2004). It was considered that the instability was linked to the hygroscopic nature of ethambutol (Singh et al., 2002) and moisture gain by the formulation through the pinholes in the packaging material. It suggests that the combination of drugs contained in the formulation and their relative ratio is so critical that even small moisture ingress can result in the transfer of drugs from the tablet to the inside surface of the strip pockets. The tentative solution lies in use of barrier packaging free from any defects, along with film coating of the tablets with moisture-resistant polymers. The catalytic role of pyrazinamide and ethambutol hydrochloride. It is postulated that pyrazinamide and ethambutol

hydrochloride exhibit catalytic role through involvement of intra-molecular proton transfer during reaction between rifampicin with isoniazid, which is conceived to occur through a base-catalyzed transhydrazone formation process entailing a tetrahedral mechanism (Bhutani et al., 2005).

Stabilities of metronidazole, tetracycline HCl and famotidine and their combinations in solid and liquid states were studied as part of preformulation by Wu and Fassihi (2005) in the development of a combination drug delivery system. Metronidazole is relatively stable with little degradation in liquid phase. The results from the solubility study indicate that both metronidazole and tetracycline HCl showed good solubilities at low pH. Tetracycline HCl in the dry state is stable when stored at room temperature. Enhanced temperature associated humidity effect was responsible for the instabilities of tetracycline HCl and famotidine to different extents. Elevated temperature accelerated the degradation of all the drugs in liquid phase but light exposure was not a factor for the degradation. No potential incompatibility between the drugs under storage conditions was observed in the development of a new multi-drug delivery tablet. Degradation rate of drug stored in liquid phase was particularly by hydrolysis. In general, in solid state and well-protected storage conditions combinations of metronidazole and tetracycline HCl, famotidine along with bismuth subcitrate does not present any major problem in the development of a new multi-drug delivery system.

Stability in liquid state

Multiple-agent infusions of drug admixtures represent a unique approach to combination chemotherapy. The most common cause of incompatibility between drugs in liquis state is a shift in the pH of formulation as a result of admixing. The consequence of a pH shift may be either a change in chemical stability or precipitation of one or more drugs. Admixing may also cause a direct reaction between two drugs, producing a new substance of unknown qualities, or a drug-adjuvant reaction that results in chemical incompatibility. The most common physical change that lowers potency is precipitation of the drug. In some cases, degradation products may also precipitate. Crystallization results in an observable loss of drug in the final infusion. A drug is maintained in solution as long as its concentration remains below its saturation solubility, which is a function of temperature. Environmental factors such as temperature, pH, light, air, and the type of

container used can affect the stability of the final solution. The most important factor affecting drug stability is pH, which can have a dramatic effect on the stability of labile drugs (Williams, 1990). Because most drugs are either weak acids or bases, their water solubility in the final solution is controlled by their respective ionization constants (pKa), the final pH of the infusion, and the concentration of the nonionized drug at this pH. If the final pH of the infusion increases the amount of nonionized drug and this concentration exceeds the drug's maximal aqueous solubility, precipitation (or crystallization) is likely to occur. (Williams and Lokich, 1992). It is possible to predict drug-infusion fluid or drug-drug incompatibilities due to changes in pH, provided that the pH range for optimal stability of the drug is known. In most cases, the incompatibility or instability of a drug in an infusion is due to pH shifts, not to drug-drug interactions. The second most important factor that can influence the rate of degradation and substance stability is temperature. An increase of 10~ in the storage temperature can enhance chemical degradation by a factor of 2-5.

Most diluents are thought to be inert in their capacity to react chemically with antineoplastic drug in infusion, yet dextrose is capable of reacting with antineoplastic drugs that possess a free amino group (e.g., Neomycin). The aldose form of dextrose can react with the free amino group to form a Schiff base, which can rearrange to form a stable product (the Maillard reaction).

1.2 Coated pellets as controlled release drug delivery systems

Coated pellets are frequently used for oral controlled release drug delivery and offered numerous advantages over single unit dosage forms. (Ozturk et al, 1990; Fukumori, 1997; Ghebre-Sellassie, 1997; McGinity, 1997; Muschert et al, 2009). The multiparticulates (pellets) spread uniformly throughout the gastrointestinal tract. High local drug concentrations and the risk of toxicity due to locally restricted tablets can be avoided. Premature drug release from enterically coated dosage forms in the stomach, potentially resulting in the degradation of the drug or irritation of the gastric mucosa, can be reduced with coated pellets because of a more rapid transit time when compared to enterically coated tablets. The better distribution of multiparticulates along the GI-tract could improve the bioavailability, which potentially could result in a reduction in drug dose and side effects. Inter- and intra-individual variations in bioavailability-caused for example by food effects-are reduced (Bodmeier, 1997). Compared to coated tablets and

capsules they avoid the all-or nothing effect of single unit dosage forms (Digenis, 1994; Karrout et al., 2009).

Pellets loaded with different drugs as combination drug can be blended and formulated in a single dosage form. This allows the administration of two or more types of drugs that may or not be chemically compatible, at the same or different sites within the gastro-intestinal tract. Furthermore, pellets with different release rates from the same drug can be combined in a single unit dosage form in order to achieve the desired drug release profile.

1.2.1 EC : HPC polymer blends for controlled release pellets coatings

Polymeric film coatings are frequently used to control drug release from solid pharmaceutical dosage forms (Ghebre-Sellassie, 1994; Cole, et al., 1995; McGinity, 1997). Polymers suitable for this fall into two groups: those based on natural polymers and those based on synthetic polymers. To obtain a particular desired release profile, different formulation and processing parameters can be varied, such as the coating level, type of polymer and type and amount of added plasticizer (Frohoff-Hülsmann et al., 1999; Okarter, 2000; Shao, et al., 2002). By using blends of two types of polymers, the resulting film coating properties can effectively be altered (Fig. 12), and broad ranges of drug release patterns be provided (Lecomte, et al., 2003).

Figure. 12. Schematic presentation of the strategy to use polymer blends as coating materials for controlled drug delivery systems (Siepmann et al., 2008)

Different types of classification schemes can be used for polymer blends, based for instance on the chemical structure, thermal properties, miscibility or solubility of the macromolecules. The polymer blend systems are classified according to their solubility along the gastro-intestinal-tract (GIT), distinguishing: (i) polymers that are insoluble throughout the GIT (GIT insoluble polymers), (ii) polymers that are soluble throughout the

GIT (GIT-soluble polymers), (iii) enteric polymers, and (iv) enzymatically degradable polymers (Siepmann et al., 2008).

Ethylcellulose is a semi-synthetic, frequently used GIT-insoluble polymer in controlled drug delivery systems. It is generally considered non-toxic, non-allergenic and stable under physiological conditions. Its water-insoluble and pH-independent properties have made ethylcellulose one of the most important polymers for controlled-release applications, moisture protection or taste masking purposes (Marucci, et al. 2009). Pure EC exhibits a very low water permeability; only ~1/10 of celluloseacetate (Lindstedt et al. 1989).

However, if applied as a film coating material, ethylcellulose perfectly formed membranes result in very low drug release rates because is poorly permeable for most drugs (Lecomte et al., 2003). To overcome this restriction, water-soluble polymers can be added to ethylcellulose coatings. For example, polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP) and hydrophilic cellulose ethers, such as hydroxypropyl methylcellulose (HPMC) have been proposed (McGinity, 1997; Nesbitt, 1994; Tang, et al., 2000 Rohera and Parikh, 2002). Upon contact with aqueous media, these additives hydrate and potentially leach out from the polymeric membranes, resulting in more permeable films and increased drug release rates.

Hydroxypropyl methylcellulose (HPMC) is the most commonly used water-soluble polymer, and the release mechanism from pellets coated with EC:HPMC films with different polymer ratios has been extensively studied (Lindsted et al., 1989; Hjärstam and Hjertberg. 1998; Marucci et al., 2009). However, it must be pointed out that when using aqueous dispersions of ethylcellulose for film coating (e.g., Aquacoat® ECD or Surelease®), the coating formulations can flocculate and sedimentation can occur upon addition of HPMC (Wong and Bodmeier, 1994). This can be attributed to a destabilization of the colloidal ethylcellulose dispersion by the presence of dissolved HPMC chains. Furthermore, Sakellariou et al. showed that HPMC is incompatible with ethylcellulose, resulting in inhomogeneous films (Sakellariou et al, 1986; Sakellariou and Rowe, 1995). Even films prepared from organic polymer solutions (where the degree of polymer chain interpenetration is much higher than in systems prepared from aqueous dispersions) are inhomogeneous: HPMC-rich domains are dispersed within an ethylcellulose- rich matrix (Sakellariou et al., 1988; Sakellariou and Rowe, 1995).

Hydroxypropyl cellulose (HPC) is another attractive water-soluble polymer as it has low toxicity and easily forms films. The structure of films made of EC and HPC has been studied by Sakellariou et al. (Sakellariou, et al., 1986; 1988; 1995). The release rate from coated formulations increased with higher percentages of HPC in the film (Thombre, et al., 1994; Umprayn, 1999). During drug release, changes take place in the composition and structure of coating films composed of polymer blends due to leaching of the water soluble polymer. Marucci et al. found that EC/HPC-LF films containing 20–30% HPC-LF were semi-permeable to the compound at the beginning of the release experiments. However, films with 30% HPC-LF became permeable during the release due to HPC-LF leaching. The release mechanism depended on the amount of HPC-LF initially present in the film and changed from osmotic pumping to diffusion as the amount of HPC-LF increased the release mechanism at different ratios (Marucci et al, 2009).

1.2.2 Release from coated pellets by diffusion through aqueous pores

In pellet coated by polymer blends film coating, the film is not homogeneous and continuous, but punctuated with pores. These pores filled with solution when the dosage form comes in contact with an aqueous medium, and thereby facilitate the diffusion of the drug, The transport mechanism in these pores can range from pure molecular diffusion to convection, depending on the pore size. Pores, and sometimes even cracks, can occur as a result of processing conditions under which coalescence of the pseudolatex particles is incomplete or defects are produced. In this case, the permeability coefficient, P, is given by:

$$P_p = \frac{D_p \epsilon_p}{\tau_p}$$

K is unity, as there is no partitioning between the channels and the aqueous environment in the bulk, ϵ_p is the volume fraction of the aqueous channels and τ_p is the tortuosity of the aqueous channels. Relevant studies in the literature indicate that this mechanism is often accompanied by other mechanisms (Vidmar et al., 1982; Benita and Donbrow, 1982; Hoffman, 1986). The most usual combination is diffusion through the continuous polymer phase in parallel with diffusion through aqueous channels.

For films made of ethylcellulose (a water-insoluble polymer) and hydroxypropyl cellulose (a water soluble polymer), we have previously shown for water soluble drugs that below the critical concentration the release mechanism is mainly osmotic pumping

(Marucci et al., 2009, 2010), while above it the diffusional contribution becomes increasingly more significant (Marucci et al., 2009). A sigmoid release profile, showing a lag phase with an initially slow release rate followed by a gradual increase in the release rate, has been observed in many cases. During the lag phase the solvent crosses the coating, mass accumulates inside the formulation and a hydrostatic pressure builds up (Marucci et al., 2008 and 2009). In systems where cracks are not developed in the coating due to the pressure build-up, the length of the lag phase depends on the time required for the water-soluble polymer to leach out, creating a pore system that connects the inside of the formulation with the release medium (Marucci et al., 2009).

1.3 Pellets compressed as matrix tablet

1.3.1 Release mechanism from matrix tablet

Owing to the rapid "gelification" of the polymers forming them, hydrophilic matrices in contact with water become hydrated instead of disintegrating. This hydration, due to the increase in size of the polymer molecules as a consequence of the entry of solvent, leads to the formation of a zone in which the polymer passes from the crystalline state to a "rubbery" state known as a gel layer (Maderuelo et al., 2011). The solvent continues to penetrate the tablet and the gel layer. The thickness of the gel layer increases as more and more water enters the system. At the same time, the surface-most polymer chains, which become hydrated earlier than the others, gradually relax until they lose consistency, after which matrix erosion begins. A polymer concentration gradient is formed in the tablet, starting at a high concentration in the more or less dry core and declining through the gel layer towards the gel layer surface. At the surface of the gel layer, the polymer concentration is assumed to correspond to the critical polymer concentration, C_{crit}. Below this concentration, the polymer chains can no longer withstand the shear forces surrounding the gel and therefore detach from the matrix (Ju et al., 1995; Veriden, 2011; Colombo, et al., 1995, Colombo, et al., 1996; Siepmann and Peppas, 2001).

Penetration of the medium into the matrix is accompanied by the formation of a series of fronts (Fig. 13), which later disappear along the process of matrix dissolution (Maderuelo, 2011):

A. The swelling front:

With the entry of water into the matrix, the polymer passes from the crystalline state to a hydrated or gelified state. This front is thus seen separating the crystalline state (glassy region) from the hydrated or gelified one (rubbery region).

- The rubbery zone is characterized by being the one into which more solvent has entered and hence the Tg of the polymer is lower than the experimental temperature.
- The glassy region is the one into which the least solvent has entered and hence its Tg is higher than the experimental temperature.

B. The erosion front or dissolution front:

This separates the gelified zone from the matrix of the solvent.

C. Diffusion front (solid drug–drug solution boundary):

This is located between the swelling and erosion fronts and it separates the zone of the gelified matrix containing the drug dissolved in the medium from the zone of the matrix containing the undissolved solid drug

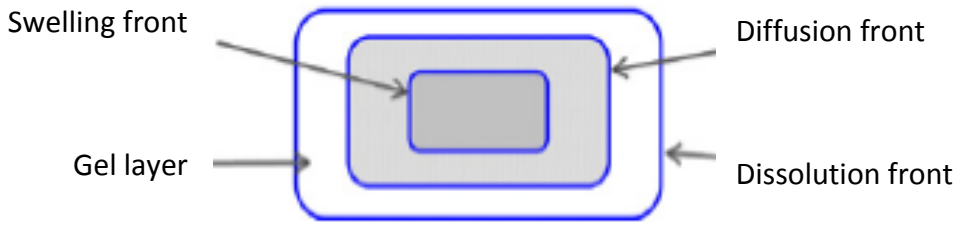


Figure 13. Scheme of the hydrophilic matrix after entry of the dissolution medium

The position of the diffusion front is dependent on the solubility of the drug molecule, where the front of a more-soluble drug has been shown to lie closer to the swelling front of the tablet when compared to a less-soluble drug (Bettini et al., 2001).

1.3.2 Critical factors in drug release from hydrophilic matrices

Drug solubility

Drug solubility affects the release rate (Gao et al., 1996). In general, water-soluble drugs tend to follow a release mechanism based on diffusion through the gel layer, while water-insoluble drugs do so mainly through a mechanism of erosion (Tahara et al., 1995).

The release of water soluble moieties will typically follow first order release kinetics. Thus the high solubility of some drugs in water leads to rapid release, and the burst effect appears. This involves a very rapid initial release of an amount of drug in a short period of time as soon as it enters into contact with the medium before it starts to be released at the desired rate (Huang and Brazel, 2001). Subsequently, a more-soluble drug will diffuse out of the gel, while a less-soluble drug will be controlled more by the rate of polymer erosion and therefore exhibit time independent or zero-order release kinetics (Ranga Rao et al., 1990; Ford et al., 1987; Vazquez et al., 1992; Colombo et al., 1996, 1999). Hence, the release mechanism and the release rate have for example been shown to depend on the solubility and properties of the drug (Bettini et al., 2001; Fu et al., 2004), the area from which the drug can diffuse (Ford et al., 1985; Velasco et al., 1999) and the drug concentration gradient formed in the gel (Colombo et al., 1999; Siepmann and Peppas, 2000).

The release rate of a drug in the presence of another one that is water-soluble may be altered. The incorporation of some water-soluble drugs leads to a slower rate of drug release (Mitchell et al., 1993). This is the case of acetaminophen in HPMC matrices to which pseudoephedrine has been incorporated. The latter alters the hydration characteristics of the HPMC, leading to a slower release rate.

Drug particle size

For some authors, the effect of particle size on the release rate from HPMC matrices can only be considered important in cases where the percentage of polymer is low. In these cases, the porosity of the matrix increases considerably, increasing the release rate (Li et al., 2005). In the case of highly water-soluble drugs, drug particle size affected the rate of release because the actual drug form channels that cross the gel layer with the consequent increase of the porosity of the system. The higher the percentage of drug incorporated into the matrix, the greater the porosity. In these cases, the higher the drug particle size, the larger the size of the pores formed (Kim, 1999; Kim, and Fassihi, 1997). If the drug is only sparingly water-soluble, the main release mechanism will be erosion. In this case larger drug particle sizes will elicit a greater degree of erosion (Ford et al., 1987). Studies carried out with Rifampicin, which is only sparingly soluble in water, to compare matrices with different drug particle sizes have shown that in general decreases in particle size give rise to slower release rates (Hiremath and Saha, 2008). The authors attributed this

phenomenon to the rapid formation of gel and to the fact that in the formulation with the smaller particle size the greater surface area of the particles present at the surface of the matrix hinders slower releases in the first hours. In formulations with smaller particle sizes, this effect of the increase in the surface area of the particles contrasts with the fact that they in turn allow an increase in the density of the polymer since they decrease the porosity of the system and its tortuosity increases.

Viscosity and blend of polymer

By using polymer combinations, formulators may be able to develop sustained-release drug dosage forms with better performance than is shown by the individual polymer components. Various polymer blends have been studied in order to achieve the desired release kinetics. The pores of high-viscosity hypromellose block up quickly and inhibit further liquid uptake (Wan et al., 1991). This in turn leads to the formation of a turbid gel, which resists dilution and erosion, subsequently resulting in slower drug diffusion and release rates (Wan et al., 1991; Gao et al., 1996; Talukdar et al., 1996). Drugs that are charged or possess long side-chains are less mobile because of interaction with the gel. This increases the time taken for such drugs to diffuse through the gel structure. One proposed advantage of using a high-viscosity polymer is that, because of the rapid hydration and formation of a gel, it is likely to prevent dose dumping.

The molecular weight of the polymer is directly related to gel strength and is of great importance in drug release since it is decisive for the passage of water through the gel layer during swelling. For hydrophilic matrices, gel strength is what determines the erosion capacity of the polymer, such that the higher the molecular weight of the polymer, the greater the degree of swelling and the lower its ability to erode. This characteristic, together with the solubility of the drug incorporated into the polymer matrix, will govern the release mechanism.

1.4 Approaches for preparing drug combination as matrix drug delivery system

Preparation of combination drug as matrix drug delivery system in this present study were conducted by these methods; (i) direct compression by simple mixing, (ii) wet granulation and (iii) compressed pellet. These technological operations are used to propose a new approach which does not require the modification of the existing formulation nor the use of additional costly technological operations in combining highly and poorly soluble drug as combination drug as matrix tablet delivery system.

Direct compression

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required. The drug and the excipients are mixed homogeneously and compressed into tablets. Although this method provides many advantages, there are some limitations of the process. The compressibility and flow properties of materials are required in this method. The difference in particle size of powder components of the formulation can affect a segregation of the powder mixture (Cooper and Rees, 1972), resulting in the high variation of tablet properties (weight variation, hardness and friability) and the homogeneity of the mixture for low drug content formulation. This is one factor which can directly affect drug release from tablets (Velasco et al., 1999).

Wet granulation

Granulation may be defined as a size enlargement process which converts fine or coarse particles into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity. Wet granulation involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. The wet mass is dried and then sized to obtained granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during subsequent drying which leads to the formation of agglomerates. Primarily granules are prepared to improve flow and compression characteristics of the blend.

High shear mixture has been widely used in pharmaceutical industries for blending and granulation. The large lumps was cut into smaller fragments thus increases the binder distribution into the blend. The binder liquid is added by pouring, pumping or spraying from the top. Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed. The material processed by fluid bed granulation are finer, free flowing and homogeneous. Wet stage granulating allows for denser products. Disadvantages of this method are cleaning process which is labor-intensive and time consuming.

Compressed pellets

Compaction of pellets is a challenging area. Only a few multiple unit containing tablet products are available, such as Beloc® ZOK (Sandberg, et al., 1988), Antra® MUPS and Prevacid® SoluTabTM (Shimizu, 2001). The aim of most studies on the compaction of pellets is to convert a multiple unit dosage form into a single unit dosage form containing the multiparticulates, with this single unit dosage form having the same properties, in particular drug release properties, as the individual multiparticulates (Bodmeier, 1997). Importantly, the drug release should not be affected by the compaction process. With reservoir-type coated-pellet dosage forms, the polymeric coating must be able to withstand the compaction force. It may deform but should not rupture, since, for example, the existence of crack in the coating may have undesirable effects on the drug release properties of that subunit. The type and amount of coating agent, the size of subunits, selection of external additives, and the rate and magnitude of pressure applied must be considered carefully to maintain the desired drug release properties of that subunit. Schematic design of multiple-unit pellet system (MUPS) tablets shown in Fig. 14.

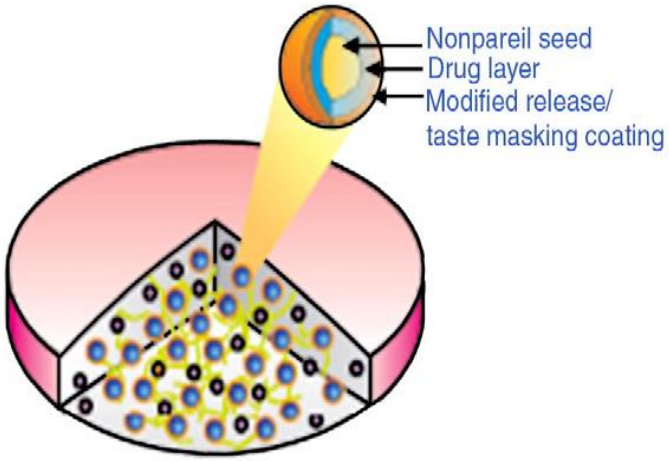


Figure 14. Schematic representation of multiple-unit pellet system (MUPS) comprising of coated pellets

Some key variables could affect the compaction and performance of coated pellets (reservoir-type drug delivery systems) including the type and amount of polymer coating and the proper selection of pellet core and tableting excipients. The polymeric particles have to be mechanically deformable to form films under specified conditions. This is achieved at a softening temperature which corresponds to a sharp increase in

polymer chains mobility hence viscous flow, which eliminates the boundaries between adjacent polymer particles to coalescence completely (Yang and Ghebre-Sellassie, 1990; Okhamafe and York, 1988; Porter, 1989). Thus, the mechanical properties of the polymeric film and its response to stresses of different types must be studied in order to investigate its suitability for the coating of pellets to be compressed. Ethylcellulose films cast from the plasticized pseudolatexes, Aquacoat® and Surelease®, were very brittle and weak with low values for puncture strength and elongation (<5%) (Bodmeier and Paeratakul, 1994). Most studies on the compaction of pellets coated with ethylcellulose revealed a damage to the coating with a loss of the sustained release properties. This is not surprising because of the weak mechanical properties of ethylcellulose. Coatings prepared from organic solution were mechanically stronger than coatings prepared from the pseudolatexes (Bodmeier and Paeratakul, 1994). An increase in coating level, however, caused a decrease in tensile strength, a reduction in the yield pressure of the pellets and an increase in the elastic recovery upon ejection. Increasing the coating level reduced the pressure necessary to obtain the same in-die porosity, indicating an easier compressibility of the coated pellets (Maganti and Celik, 1994). If the coating level was increased, binder concentration got increased that led to greater binder–binder than binder–substrate bonding responsible for tensile strength. The ability of the pellets to deform, both plastically or elastically, increased with increasing coating level.

As described above, without sufficient flexibility of the film, the coating could rupture during. Besides the coating, the bead core also will affect the compaction behavior of the coated pellets. The bead core should also have some degree of elasticity, which can accommodate changes in shape and deformation during tableting. It should deform and recover after compression without damage to the coating (Bodmeier, 1997). Drug release from small, coated pellets to be less affected by compaction, than larger ones (Ragnarsson et al., 1987; Haslam et al., 1998).

Various tableting excipients have to be added to assist the compaction of coated pellets. Theoretically, 29% of excipient are needed to fill the void space between densely packed spheres (Bodmeier, 1997). The excipients are used to fill the void space between the pellets to be compressed and act as cushioning agent to absorb compression forces. The filler materials are used for separation of individual pellets to prevent direct contact of pellets (e.g. polymer-coated pellets that tend to fuse with each other during compression) by forming a layer around the pellets. Besides their compaction properties, the excipients

have to result in a uniform blend with the coated pellets, avoiding segregation and therefore weight variation and poor drug content uniformity of the resulting tablets. The variation in weight and drug content uniformity was minimized when using higher pellet concentrations or larger particle size fractions (e.g. granules) of the inert excipients. It was found that, at 30% w/w pellet concentration, granules of Avicel have to be added in order to achieve sufficient drug content uniformity (Bodmeier, 1997). At a lower pellet content, the excipients act as cushions while the pellets deform to a larger extent at a higher pellet content. The fillers had very little effect on the drug release at low pellet content (< 10%). In addition, the coated pellets could be prepared with a smaller size in order to approach the particle size of the inert excipients. Smaller pellets would also improve the content uniformity of low dose drugs. However, particle size is an important factor affecting the drug release and, in general, thicker coatings have to be applied to smaller pellets in order to obtain the same drug release profiles when compared to larger pellets.

1.5 Objectives

The purposes of this work were:

1. to modulate the release of two drugs of different solubility as drug combination in extended release matrix tablets and evaluate the critical factors influencing their release such as polymer blend ratio, particle size of granules and method of granulation
2. to modulate the release of two drugs of different solubility in drug combination as pellets within matrix tablets system by introducing ethylcellulose coated pellets within HPMC matrix tablet for controlled release drug delivery, and evaluate the critical factors influencing their release such as HPC content, coating level of film coating, polymer blend ratio of matrix and particle size of carbamazepine
3. to control the release of two drugs of different drug solubility from multilayered pellets coated with ethylcellulose-HPC blends and study the factors affecting release such as drug solubility and drug loading
4. to study the effect of HPC as porogen on drug release from ethylcellulose coated single layer pellets and extend the application of the findings to more complex systems (multilayer pellets) as drug combination. The contribution of other common formulation variables such as coating level was also studied.

2. Materials and methods

2.1 Materials

Propranolol HCl, caffeine anhydrous, carbamazepine, diprophylline and theophylline (BASF AG; Ludwigshafen, Germany), hydroxypropyl methylcellulose (HPMC, Methocel® E5, Methocel® K15M Premium CR, Methocel® K4M Premium CR and Methocel® K100LV Premium CR, Colorcon, Orpington, UK), ethylcellulose (EC, Ethocel® standard 10 cP FP premium grade and Ethocel® standard 10cP, premium grade, Colorcon, Kent, UK), Eudragit®RS (Evonik Industries AG, Darmstadt, Germany), hydroxypropylcellulose (HPC, Klucel® JF Pharm and Klucel® LF Pharm, Ashland Aqualon, Wilmington, USA), Non-pareils core (Suglets® sugar spheres NF; 355-425µm and 710-850µm, NP Pharma S.A., Bazainville, France), Polyvinylacetate/ polyvinylpyrrolidone (Kollidon® SR, BASF AG, Ludwigshafen, Germany), magnesium stearate (Herwe Chemisch-technische Erzeugnisse GmbH, Sinsheim-Dühren, Germany), direct compressible lactose (FlowLac® 100, Meggle GmbH, Wasserburg, Germany) were used as received.

2.2 Methods

2.2.1 Release adjustment of combination drug with different drug solubility from matrix tablet system

2.2.1.1 Tablet preparation

a. Direct compression

Single drug tablets were prepared by blending propranolol HCl or carbamazepine powder (40% w/w of tablet), polymer (30% w/w of tablet) and lactose (up to 600mg tablet) for 20g of batch size and blended in a turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min., followed by the addition of magnesium stearate (1% w/w of tablet) and further mixing for 5 min. A single punch tableting machine (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany) was equipped with 13 mm flat faced punches to compress tablets of 600 ± 5 mg. The hardness was kept constant (50 ± 5 N for Kollidon®SR and 70± 5 N for HPMC and Ethylcellulose) and was measured with a hardness tester (Erweka GmbH, Heusenstamm, Germany).

Combination tablets were prepared by blending propranolol HCl and carbamazepine (each 20% w/w of tablet), polymer (30-40% w/w of tablet) and lactose (up to 600mg tablet) for 20g of batch size and blended in a turbula mixer (Willy A.

Bachofen AG, Basel, Switzerland) for 10 min., followed by the addition of magnesium stearate (1% w/w of tablet) and further mixing for 5 min. Tablet compression were performed in a single punch tableting machine (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany) with 13 mm flat faced punches for 600 ± 5 mg tablets. The hardness was kept constant (50 ± 5 N for Kollidon®SR and 70± 5 N for HPMC and Ethylcellulose) and was measured with a hardness tester (Erweka GmbH, Heusenstamm, Germany).

Combination tablets using polymer blend as matrices were prepared by blending propranolol HCl and carbamazepine (each 20% w/w of tablet), polymer (30% w/w of tablet) and lactose (up to 600mg tablet) for 20g of batch size and blended in a turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min., followed by the addition of magnesium stearate (1% w/w of tablet) and further mixing for 5 min. Polymer blend as matrices were ethylcellulose : Methocel®K15M (2:3) or ethylcellulose : Methocel®K15M : Methocel®K100LV (2:1.5:1.5). The tablets were compressed in a single punch tableting machine (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany) with 13 mm flat faced punches 600 ± 5 mg tablets. The hardness was kept constant 70± 5 N and was measured with a hardness tester (Erweka GmbH, Heusenstamm, Germany).

b. Wet granulation by shear mixed method

Propranolol HCl and ethylcellulose (1:1) were blended in a turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 5 min. The powder blend was transferred into a mortar and isopropyl alcohol was added with constant mixing. The wet mass was then passed through a 1 mm sieve and the resulting granules were dried for 24 h in oven at 40^{o}C. The granules were classified by sieves of 200, 425 and 800 µm. Granules (40% w/w of tablet) containing propranolol HCl 20 % w/w of tablet, carbamazepine (20 % w/w of tablet), HPMC polymer (30 % w/w of tablet) and lactose (up to 600mg tablet) were prepared for 20 g batch size and blended in a turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min., followed by the addition of magnesium stearate (1% w/w of tablet) and further mixing for 5 min. A single punch tableting machine (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany) was equipped with 13 mm flat faced punches to compress tablets of 600 ± 5 mg. The hardness was kept constant (70±

5 N) and was measured with a hardness tester (Erweka GmbH, Heusenstamm, Germany).

c. Wet granulation by fluid bed granulation method

Propranolol HCl powder was granulated with ethylcellulose 10 cPFP in isopropyl alcohol : water mixture (88:12 w/w) solution (10% w/w solid content) in a fluidized bed coater (Mini Glatt®, Glatt, GmbH, Binzen, Germany) with ratio drug to polymer 1:1. The coating condition were; batch size: 40g, nozzle diameter = 0.5 mm, air flow: 0.05 bar, spray pressure: 0.2 bar, product temperature= 40 ± 2 °C, spray rate 0.8 - 1.2 g/min, final drying at 40°C for 10 min. The granules were passed through standard sieves of 425 and 800 µm. Granules (40% w/w of tablet) containing propranolol HCl 20 % w/w of tablet, carbamazepine (20 % w/w of tablet), HPMC polymer (30 % w/w of tablet) and lactose (up to 600mg tablet) were prepared for 20 g batch size and blended in a turbula mixer (Willy A. Bachofen AG, Basel, Switzerland). A single punch tableting machine (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany) was equipped with 13 mm flat faced punches to compress tablets of 600 ± 5 mg. The hardness was kept constant (70± 5 N) and was measured with a hardness tester (Erweka GmbH, Heusenstamm, Germany).

2.2.1.2. Drug release and tablet erosion study

The release studies were performed in a paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), 100 rpm, 37°C, 900 ml, phosphate buffer pH 6.8, n = 3. At predetermined time, samples were taken and drug release were measured by UV spectrophotometer with diode arrays (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at wavelengths 227 and 285nm. The t_{80} were defined as the times in hour of 80% drug released.

Tablets for erosion study were weighed (w_i) and subjected to release study. At predetermined time points (t) the samples were removed and placed in an aluminum can. The remaining tablets were then dried in a vacuum oven at 50°C until constant weight (w_t). The percentage matrix erosion (*E*) at time, *t*, was calculated by:

$$\text{Matrix erosion } (\%) = (\text{Wi} - \text{Wt})/Wi * 100$$

2.2.2 Release adjustment of drug combination with different drug solubility from coated pellets within matrix tablet system

2.2.2.1 Tablet preparation

a. Direct compression

Method of direct compression described in section 2.2.1.1. a.

b. Pellet compression

Pellet preparation

Propranolol HCl was layered onto non-pareil cores (355-425 μm). Drug layering solutions were prepared using isopropyl alcohol : water 70:30 w/w as a solvent (7% w/w solid content). Methocel®E5 (20 % w/w based on propranolol HCl weight) was used as a binder to achieve 40 % w/w weight gain (based on initial weight of cores). Layering was performed in a fluidized bed coater (Aeromatic Strea-I, Binzen, Germany). The layering conditions were: batch size = 900 g, product temperature = 40 ± 2°C, air flow = 60-70 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 6-10 g/min, final drying for 15 min.

Drug-layered cores were coated with ethylcellulose containing 0-20% w/w Hydroxypropylcellulose (HPC) in isopropyl alcohol : water (88:12 % w/w) solution (7% w/w solid content) in a fluidized bed coater (Mini Glatt®, Glatt, GmbH, Binzen, Germany) to 5–20 % w/w coating level. The coating condition were: batch size = 80 g, nozzle diameter = 0.5 mm, air flow = 0.2 bar, spray pressure = 0.9 bar, product temperature = 40 ± 2°C, spray rate = 0.5-1 g/min final drying at 40°C for 10 min.

Compression of pellets

Coated pellets containing 17.5 % propranolol HCl w/w of tablet (48.13% w/w pellets for 600 mg tablet) were mixed with 17.5% carbamazepine (w/w of tablet), HPMC (30% w/w of tablet) and lactose (up to 600mg) up to for 20g batch size mixed in a turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min followed by the addition of magnesium stearate (**1 %** w/w of tablet) and further mixing for 5 min. The mixture was then compressed into a 13 mm flat-faced tablet (600 ± 5 mg) by a single punch press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany). The hardness was kept constant (70 ± 5 N) and was measured with a hardness tester (Erweka, Heusenstamm, Germany).

2.2.2.2 Drug release, tablet erosion and pellet release study

The drug release and tablet erosion studies were described in section 2.2.1.2. Pellet released were determined according to matrix erosion. Instead of weighing the remaining tablets, the pellets were counted initially (pellet content in the tablet, P_i) and after sampling (pellet released to the medium, P_t). The pellets liberation at time *t*, was calculated by:

$$\text{Pellet release } (\%) = \frac{(Pi - Pt)}{Pi} * 100$$

2.2.2.3 Similarity factor

The release similarity was evaluated by using f_2 similarity factor, f_2 = 50-100 means the release was similar (Moore and Flanner et al.; 1996; Polli et al., 1997).

$$f_2 = 50 * \log \{[1+ (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} * 100\}$$

where f_2 is similarity factor, n is the number of observations, R_t is percentage of drug dissolved from reference formulation (R_1), and T_t is percentage of drug dissolved from test formulation (R_2)

2.2.3 Release of drug combinations with different drug solubility from multilayered pellet systems

2.2.3.1 Preparation of pellets

Drug combination as single layer pellets

Propranolol HCl and carbamazepine as model drugs with different solubility were mixed as drug layering suspension (10% w/w solid content) in isopropanol:water 70:30 w/w containing 20% w/w Methocel®E5(20 % w/w based on propranolol HCl weight) as the binder to achieve 15% weight gain of each drug (based on initial weight of cores) in a fluidized bed coater (Aeromatic Strea-I, Binzen, Germany). Layering conditions shown in Table 3.

Table 3. Process parameters for the drug layering of pellets

Parameter	D_1 layer		D_2 layer
	Propranolol HCl (solution)	Caffeine, carbamazepine, diprophylline, theophylline (dispersion)	caffeine carbamazepine theophylline (dispersion)
batch size, g	900	500	500
inlet air temperature, °C	50 - 55	40 -45	40 - 45
product temperature, °C	40 ± 2	35 ± 2	35 ± 2
air flow, m³/h	60-70	60-70	60-70
spray rate, g/min	4-10	6-12	6-12
nozzle diameter, mm	1.2	1.2	1.2
Final drying, min	15	15	15

Drug loaded cores were coated with 10% w/w coating level ethylcellulose containing 20-40% w/w HPC solution in isopropanol: water 88:12 w/w (7% solid content) in a fluidized bed coater Mini Glatt® (Glatt, GmbH, Binzen, Germany). Coating conditions described in Table 4.

Table 4. Process parameters for the coating of drug layered pellets

Parameter	Single layer	Multilayer	
		C_1	C_2
batch size, g	80	500	80
inlet air temperature, °C	48-55	50 - 55	48 - 55
product temperature, °C	40 ± 2	40 ± 2	40 ± 2
air flow, m³/h	0.2	60 - 70	0.2
Spray pressure, bar	0.9	1.2	0.9
spray rate, g/min	0.5 - 1	5-10	0.5 - 1
nozzle diameter, mm	0.5	1.2	0.5
Final drying, min	15	15	15

Drug combination as multilayer pellets with different drug solubility

Drug combination pellets were prepared based on solubility ratio shown in Table 5. Model drug of D_1 were layered onto non pareil core under layering process conditions described in Table 3. D_1 pellets cores were coated with ethylcellulose containing HPC (20-35% w/w) in isopropranol : water 88:12 w/w solution (7% w/w solid content) in a fluidized bed coater to achieve coating levels of 10% w/w as first coating (C_1). The coating conditions described in Table 4. Either theophylline, carbamazepine or caffeine as second drug layer (D_2) were layered onto coated D_1 pellets, with the same amount of D_1. Layering dispersion of D_2 (10% w/w solid content) were isopropanol: water 88:12 w/w (theophylline and caffeine anhydrous) or only water (carbamazepine), containing HPMC (Methocel®E5, 20 % w/w based on propranolol HCl weight) as the binder. Layering process were performed in fluidized bed coater using coating condition described in Table 3. Multilayer drug-loaded cores were coated with ethylcellulose containing HPC (25-40% w/w) as second coating C_2 in isoprapanol: water solution 88:12 w/w (7% w/w solid content) to achieve coating level of 5-20% (w/w). Coating process were conducted in a fluidized bed coater under the predetermined coating conditions described in Table 4. Schematic presentation of multilayer pellet containing two drugs with different solubility is illustrated in Figure 15.

Table 5. Drug combination as multilayer pellets based on solubility ratio

	First drug, D_1 (solubility, mg/ml)	second drug, D_2 (solubility, mg/ml)	Solubility ratio of D_1/D_2
1	theophylline (10)	propranolol HCl (250)	0.04
2	propranolol HCl (250)	diprophylline (170)	1.47
3	propranolol HCl (250)	caffeine (35)	7.14
4	propranolol HCl (250)	theophylline(10)	25
5	caffeine (35)	carbamazepine (0.2)	175
6	diprophylline (170)	carbamazepine (0.2)	850
7	propranolol HCl (250)	carbamazepine (0.2)	1250

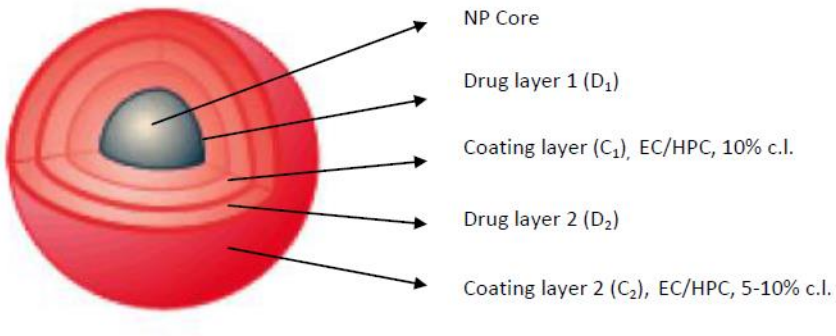


Figure 15. Schematic presentation (not up to scale) of multilayer pellet containing two drugs with different solubility as drug combination

2.2.3.2 Drug release study

Drug release were studied in a paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), (100 rpm, 37^{o}C, 900 ml, phosphate buffer pH 6.8, n = 3). Drug releases were measured by UV spectrophotometer with diode arrays (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at wavelengths 285; 290; 273; 211/272; 273/285; 232/273; 227/285; 230/272; and 229/267 depending on combination drug to be measured. The t_{80} were defined as the times in hour of 80% drug released.

2.2.3.3 Study on drug loading effect

Drug loading effect was studied by applying different drug loading of propranolol HCl and carbamazepine as combination drug to give ratio as shown in Table 6. Other parameters such as HPC content and coating level in each coating were kept constant. First and second coating (C_1 and C_2) had coating level of 10% w/w. HPC content for first coating (C_1) were 20% w/w, while that of C_2 were 30% w/w.

Table 6. Drug loading ratio of propranolol HCl – carbamazepine as multilayer pellets

Drug loading (DL)	**Propranolol HCl loading (%)**	**Carbamazepine loading (%)**	**DL D_1/ DL D_2**
5 – 35	5	35	0.14
15 – 25	15	25	0.60
15 – 15	15	15	1.00
25 – 15	25	15	1.67
35 - 5	35	5	7.00

2.2.3.4 Apparent permeability of coating

Since the permeability of the drugs is proportional with diffusion properties and its thickness, simplified equation was used to quantify the effect of formulation on drug release and assumed as apparent permeability of film coating. Apparent permeability of coating was calculated as follow:

$$\text{Apparent permeability} = \frac{\text{HPC content x surface area}}{\text{coating level}}$$

2.2.4 Quantification of the effect of porogen on release from single and multilayer ethylcellulose-coated pellets as combination drug

2.2.4.1 Preparation of coated pellets

Conventional EC/HPC coated single drug pellets

Propranolol HCl, caffeine and carbamazepine were used as drug models for single layer pellets. Drug layering solution of propranolol HCl was prepared in isopropyl alcohol:water 70:30 w/w containing Methocel®E5 20% w/w of drug (7% w/w solid content) as the binder to achieve 15% weight gain (based on initial weight of cores). Caffeine and carbamazepine layering dispersion were prepared in isopropyl alcohol : water solution (88:12 w/w) containing Methocel®E5 20% w/w of drug (7% w/w solid content) as the binder to achieve 15% weight gain (based on initial weight of cores). Layering processes were performed in a fluidized bed coater (Aeromatic Strea-I, Binzen, Germany). Layering conditions were shown in Table 3 with final drying for 15 min.

Drug loaded cores were coated with organic ethylcellulose solutions (in 88:12 isopropyl alcohol:water, 7% solid content) containing 0-40 % HPC in a fluidized bed coater Mini Glatt® (Glatt, GmbH, Binzen, Germany) to coating level of approximately 1-4 mg/cm^2. The coating condition were; batch size: 80g, nozzle diameter = 0.5 mm, air flow: 0.2 bar, spray pressure: 0.9 bar, product temperature= 40 ± 2°C, spray rate 0.5-1 g/min, final drying at 40°C for 10 min.

EC/HPC coated multilayer pellets

Propranolol HCl layered cores as first drug layer (D_1) from aforementioned pellets were coated with ethylcellulose containing 20% w/w HPC (7% w/w solid content) in a

fluidized bed coater (Aeromatic Strea-I, Binzen, Germany) to achieve coating levels of 2.14 mg/cm^2 as first coating (C_1). The coating conditions were: batch size = 500 g, product temperature = 40±2°C, air flow = 60-70 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 5-10 g/min, final drying for 15 min. Either carbamazepine or caffeine as second drug (D_2) were dispersed in isopropyl alcohol : water 88:12 w/w containing Methocel®E5 20% w/w of drug as binder (10% w/w solid content) and layered onto coated D_1 pellets in fluidized bed coater (Aeromatic Strea-I, Binzen, Germany). The amount of D_2 (15% weight gain based on initial weight of NP cores) was the same as D_1. The coating conditions were: batch size = 500 g, product temperature = 35±2°C, air flow = 60-70 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 8-12 g/min, final drying for 15 min. Multilayer drug-loaded cores were coated with ethylcellulose containing HPC (0-40% w/w) in isopropyl alcohol : water 88:12 w/w as second coating C_2, in a fluidized bed coater to a coating level of approximately 2-4 mg/cm^2. The coating condition were the same with those for single drug pellets (Table 4). Schematic presentation of multilayer pellets containing two drugs with different DRUG solubility is illustrated in Figure 15.

2.2.4.2 Drug release study

Drug release was studied in a paddle apparatus (VK 7010, Agilent Technologies Deutschland GmbH, Böblingen, Germany), (100 rpm, 37^{o}C, 900 ml, phosphate buffer pH 6.8, n = 3). Drug release was measured UV spectrophotometrically (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at wavelengths 227/285 for propranolol HCl- carbamazepine combination and 230/272 for propranolol HCl- caffeine.

3. Results and discussions

3.1 Release adjustment of combination drug with different drug solubility from matrix tablet system

3.1.1 Introduction

Various diseases such as cancer, acquired immune deficiency syndrome (AIDS), tuberculosis, diabetes (Type 2), heart diseases, or central nervous system (CNS) disorders require medical treatment with more than one drug. Drug combination therapy for the treatment of a disease offers some advantages including increased convenience for physician and patient, improved compliance and low cost of production, storage and transport. One of the manufacturing challenges regarding product formulation issues of drug combination could be due to the different solubility of the drugs which will give different release profile. Several publications have reported the effect of drug solubility on the release from hydrophilic, monolithic matrices. Higher drug solubility generally leads to faster release because of their high diffusional driving force. As drug solubility declined, there was an increased contribution of erosion on drug release from hydrophilic matrix systems (Viriden, 2011b; Zuleger, 2002; Ford et al., 1987; Zueleger and Lippold, 2001).

Many different formulation approaches are known to obtain extended release delivery systems. Matrices are considered as the simplest and cheapest systems in formulation of sustained release dosage forms. One approach suitable to obtain extended release combination products are matrix tablets based on either water-soluble/swellable or water-insoluble polymers (Zeeshan and Bukhari, 2010). Formulating matrix systems for drugs with different solubilities is challenging because the release mechanism is strongly dependent on the drug's solubility (Viriden et al., 2011; Ranga et al., 1990; Ranga et al., 1988). With water-soluble/hydrophilic matrix tablets, highly soluble drugs are predominantly released by diffusion, whereas poorly soluble drugs are released by erosion. Although there are many studies on the effect of solubility of drug on release from matrix tablets (Viriden et al., 2011a; Tahara et al., 1996; Ranga et al., 1990; Zuleger, 2002), only few studies have evaluated drug combinations with regard to drug solubility differences. The study on combination of rifampicin and isoniazid was studied by Hiremath et al. (2008) using hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and hydroxypropylcellulose (HPC), by simple direct compression. The results did not show flexible release modulation of the two drugs with regards to their solubility difference.

Studies focusing on release adjustment of drugs of different solubility as drug combination in matrix tablets has not been investigated in detail. The objective of this study is therefore to modulate the release of two drugs of different solubility as drug combination in extended release matrix tablets. Critical factors influencing their release such as polymer blend ratio, particle size of granules and method of granulation were evaluated.

3.1.2 Results and discussions

3.1.2.1 Direct compression

Due to ease and simplicity in manufacturing, first preparations of drug combination with drugs of different solubilities were performed by direct compression method. Ethylcellulose 10 cPFP (EC, Ethocel®) and Kollidon®SR were selected as water-insoluble polymers whereas hydroxypropylmethyl cellulose (HPMC, Methocel® K15M) was selected as hydrophilic erodible matrix system.

As expected, by direct compression method, propranolol HCl was released faster than carbamazepine because of its higher solubility and therefore faster dissolution. The release of propranolol HCl from HPMC tablets was extended (t_{80}% was approx. 12 hour) due to rapid gel formation on the surface, (Fig. 16 A). The gel layer acts as a diffusion barrier for both water and drug molecules (Maderuelo et al., 2011). Propranolol HCl was rapidly released from ethylcellulose and Kollidon®SR tablets due to fast erosion/disintegration of the tablet (Fig. 16).

At 30% polymer content and 40% drug loading, release of propranolol HCl either from single drug or combination tablets with carbamazepine did not change, irrespective of type of polymer matrix used. The release of the slightly soluble carbamazepine as single drug tablet was extended from both hydrophilic and hydrophobic polymers due to low solubility and dissolution rate of the drug and therefore reduced erosion rates of the matrices. Carbamazepine was released faster from the combination tablets because of the presence of the more hydrophilic propranolol HCl and faster tablet disintegration. (Fig. 16 B and C).

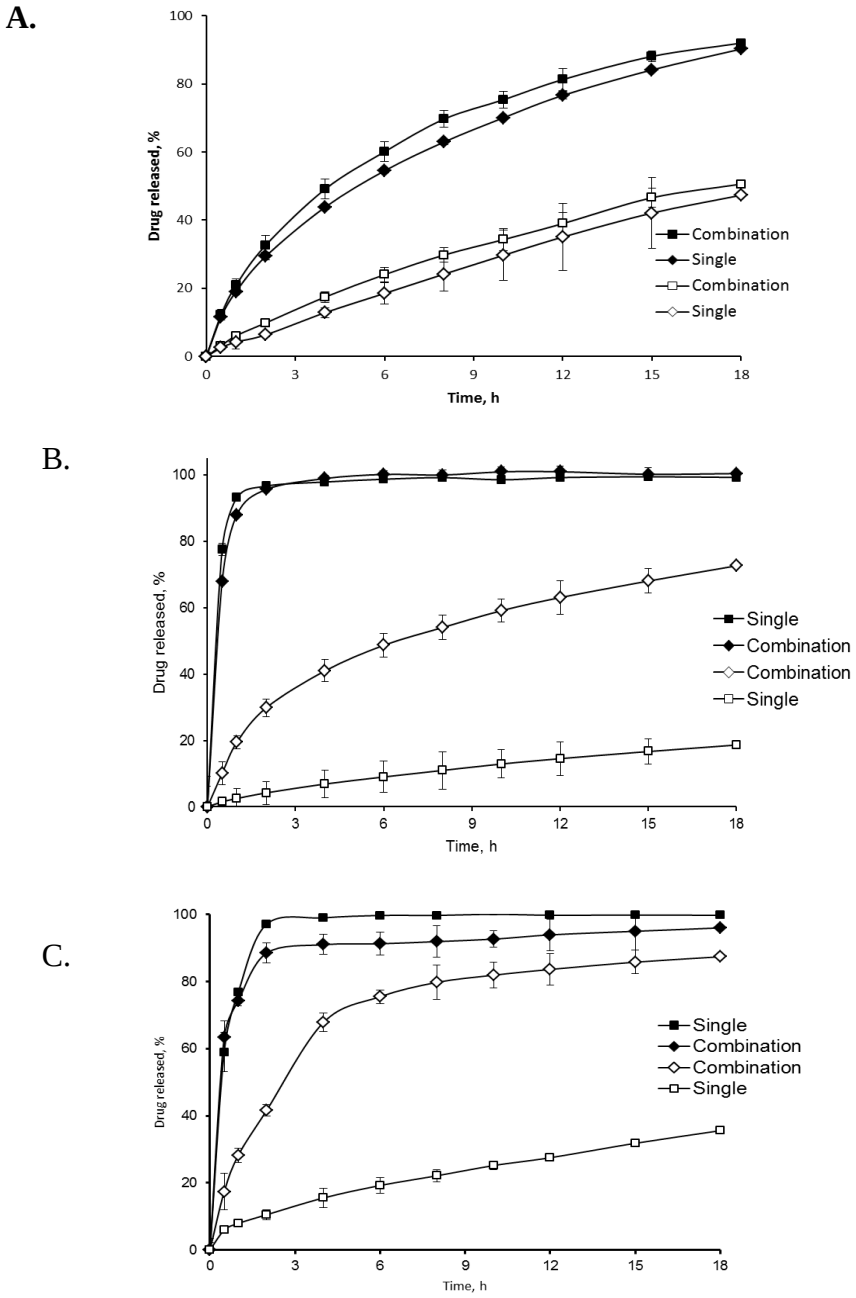
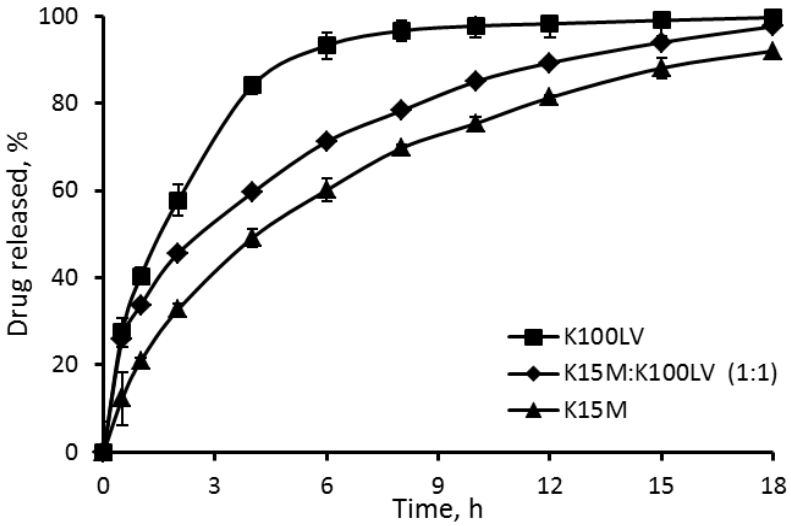


Figure 16. Release of propranolol HCl (closed symbol) and carbamazepine (open symbol) as single drug (40% loading, 30% polymer) or drug combination (20% of each drug , 30% polymer) from A) HPMC (Methocel ®K15M, B) Ethylcellulose (EC) 10 cPFP and C) Kollidon®SR matrix tablets prepared by direct compression

One approach for release adjustment could be the matrix erosion adjustment with polymer blends. Therefore, tablets containing blends of hydrophilic HPMC polymers were evaluated (Fig. 17). Release of propranolol HCl and carbamazepine increased when

Methocel® K15M : K100LV (1:1) blend was used, and exhibited fast release with only Methocel® K100LV (Fig. 17). Erosion studies on tablets with Methocel®K15M (Fig 18 A) and K100LV (Fig 18 B) confirmed that faster erosion from lower molecular weight HPMC (Methocel®K100LV) as matrix resulted in faster release of drugs compared to those from high molecular weight grade (Methocel®K15M).

A.



B.

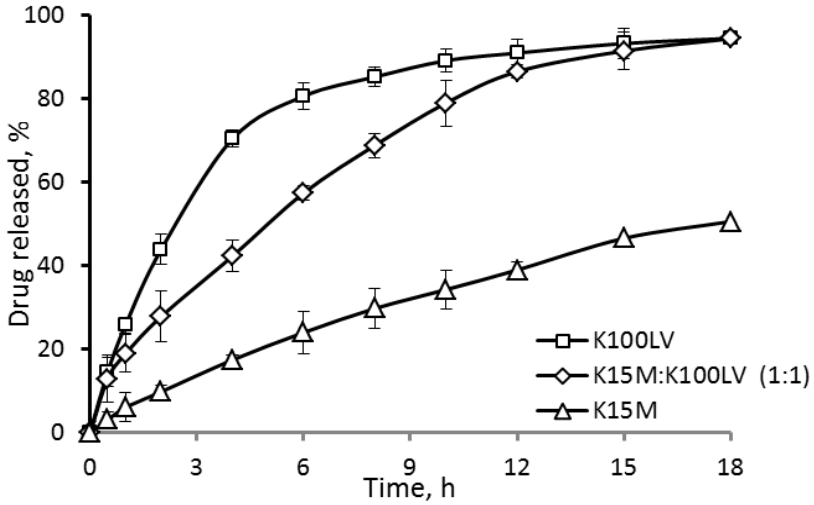
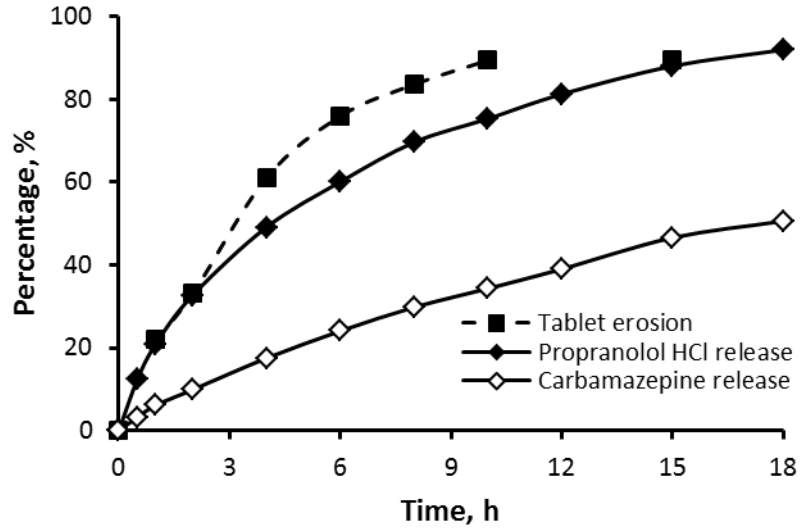


Figure 17. Release of A) propranolol HCl, and B) carbamazepine from drug combination (20% of each drug loading) with 30% w/w Methocel® as matrix former by direct compression

A.



B.

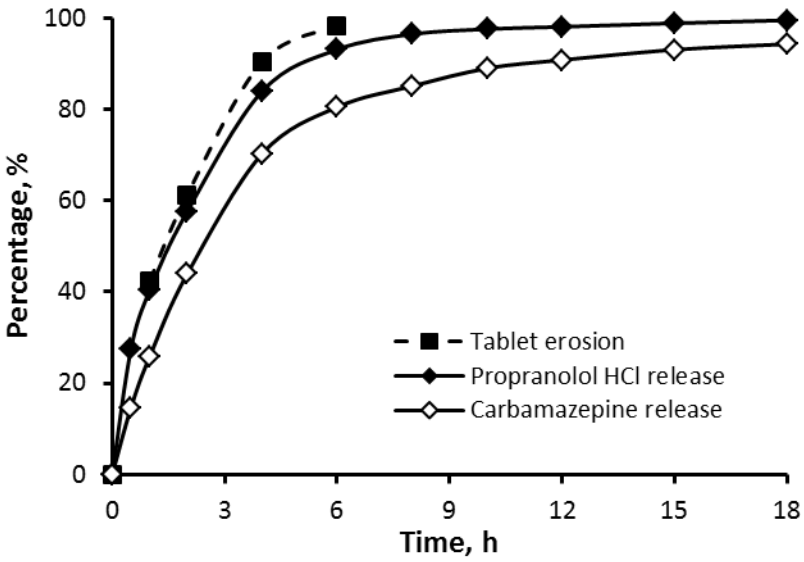


Figure 18. Erosion and release of propranolol HCl (closed symbol) and carbamazepine (open symbol) from drug combination using A) Methocel® K15M, and B) Methocel®K100LV as matrix former for direct compression

Investigating the amount of ethylcelllulose in the matrix showed that slower release of propranolol HCl in drug combination tablet could not be adjusted by simply increasing the polymer level since it simultaneously decreased the carbamazepine release (Fig. 19).

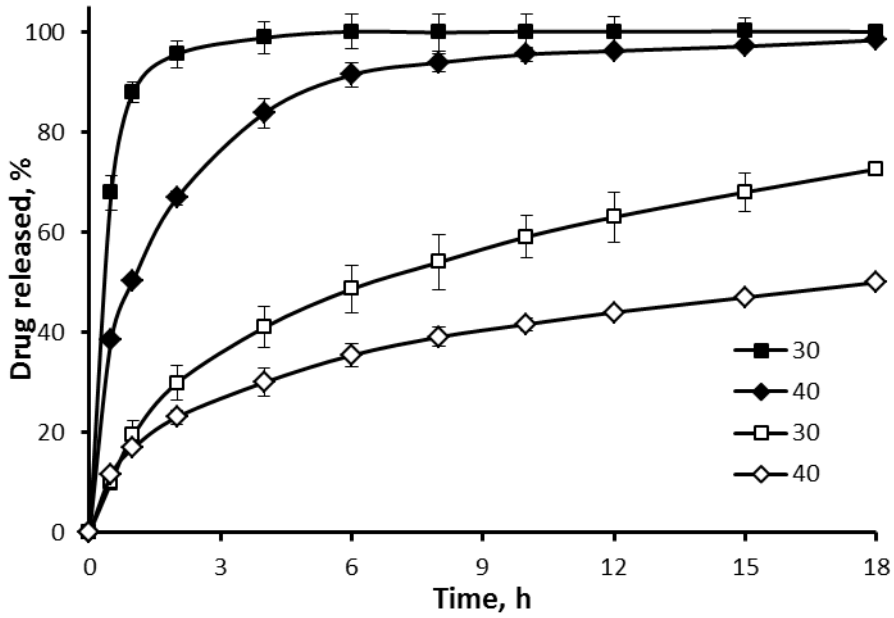


Figure 19. Release of propranolol HCl (closed symbol) and carbamazepine (open symbol) with different polymer level (%) of Ethylcellulose 10 cP FP as water-insoluble polymer matrix for direct compression

Release adjustment of combination drug with different solubility can be performed by either reducing the propranolol HCl release or enhancing the carbamazepine release. The first approach was performed by using Ethylcellulose:HPMC blends as matrix former for direct compression, due to its formulation simplicity. Propranolol HCl release was slower with Ethylcellulose:Methocel®K15M (2:3) blend in comparison with only ethylcellulose (Fig. 20 A). The decrease in propranolol HCl release was attributed to an additional barrier for drug diffusion caused by the insoluble ethylcellulose particles present in the HPMC gel layer. This is in line with a previously published study (Badshah et al., 2010). The release of carbamazepine, being mainly controlled by erosion, became slower in the presence of HPMC in etylcellulose matrix (Fig. 20 B) due to slower erosion. Further addition of low molecular weight HPMC into the polymer matrix led to increased erosion of the tablets and hence a faster drug release.

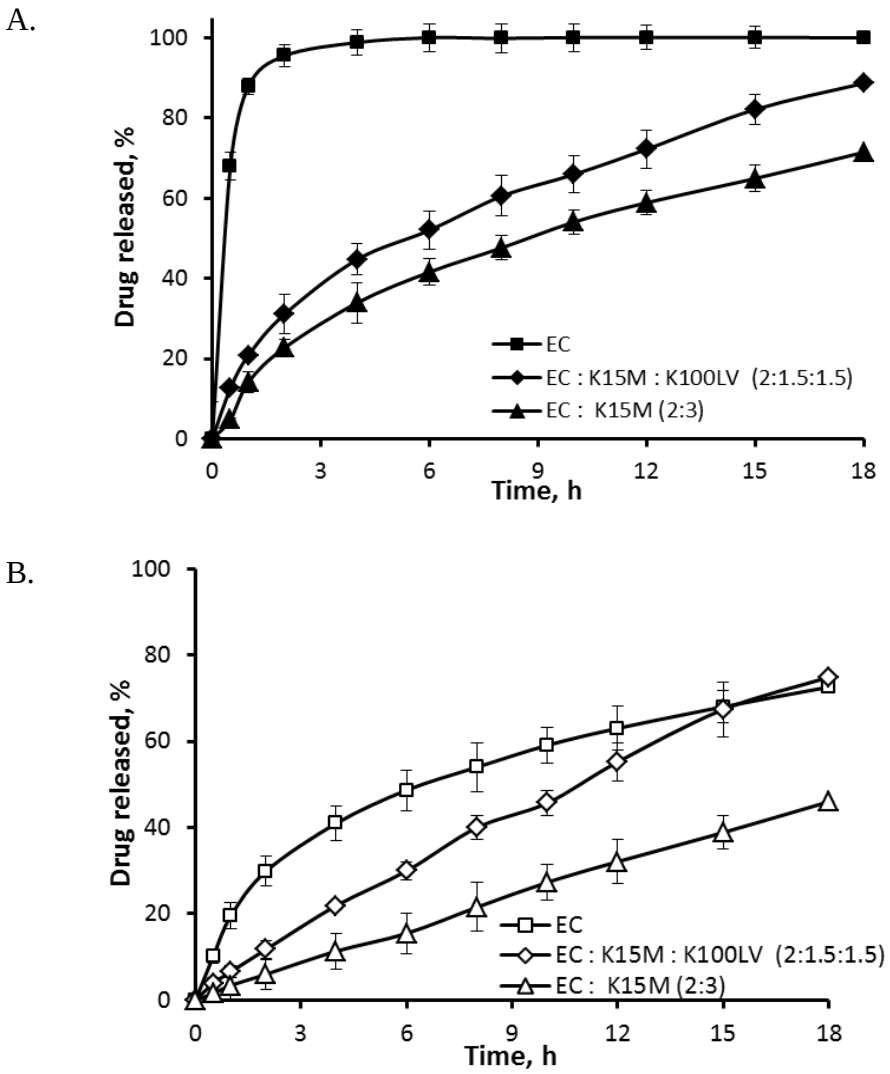


Figure 20. Release of A) propranolol HCl and B) carbamazepine from drug combination tablet using blend of hydrophilic HPMC and water insoluble ethylcellulose polymer matrix for direct compression method

3.1.2.2 Wet granulation of propranolol HCl

In order to provide an additional diffusion barrier, propranolol HCl powder was granulated with release-retarding polymers to form drug granules with reduced drug release. Two polymers, high molecular weight HPMC (Methocel®K15M) and ethylcellulose 10 cPFP were used as examples for hydrophilic and water-insoluble polymers. Propranolol HCl granulated in Methocel®K15M released faster when it was compressed with ethylcellulose as polymer matrix compared to those compressed with HPMC only (Fig. 21 A). Ethylcellulose as water insoluble polymer matrix could not provide release retardation of propranolol HCl granules. Hydrophilic polymer (HPMC) as

matrix for propranolol HCl granulated in HPMC provide strong release retardation of propranolol HCl with very slow release of carbamazepine due to high polymer content of HPMC in tablets and hence a thicker gel layer for diffusion path.

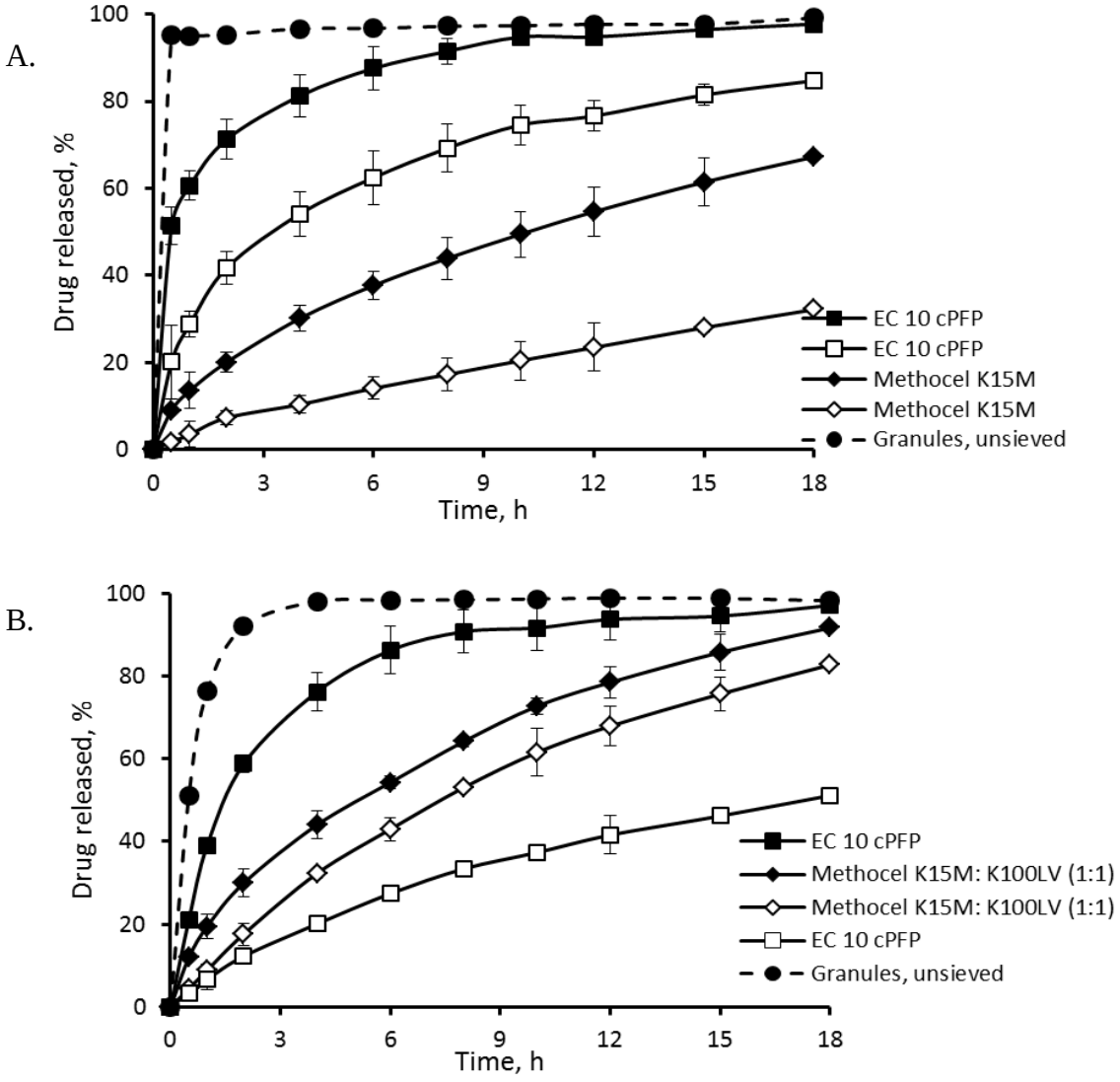


Figure 21. Release of propranolol HCl (closed symbol) and carbamazepine (open symbol) with granulated propranolol HCl in A) Methocel®K15M (2:3) and B) Ethylcellulose 10 cPFP (1:1) with different type of polymer as matrix

Furthermore, release of propranolol HCl granulated with ethylcellulose 10 cPFP prior to compression using HPMC matrix was slower than those compressed in ethylcellulose matrix (Fig. 21 B) due to rapid gel formation retarding the release. Carbamazepine release from this matrix was retarded due to slower erosion. Interestingly, release of poorly soluble drug carbamazepine was enhanced when HPMC polymer matrix

was used, probably because of solubilization of the drug (Fig. 21 B). With regard to release adjustment of two drugs of different solubility, this approach enable to give similar release of highly and poorly soluble drug in matrix tablet system.

Effect of propranolol HCl granule size

Using hydrophobic polymer matrices (ethylcellulose and Kollidon®SR), increasing the particle size of the granules decreased both propranolol HCl and carbamazepine release (Fig. 22 A and C). This was associated with slower erosion of the tablet. Larger granules have a small surface area (Itiola and Pilpel, 1986). Large propranolol granules in matrix tablet provided small surface area for diffusion within the tablet and therefore a slower release.

Furthermore, smaller granules exhibit larger surface area to volume ratio (Mullarney and Leyva, 2009). Larger area of propranolol HCl granules resulted in higher water penetration therefore faster erosion which led to faster release of carbamazepine. Erosion study on tablets with different sized propranolol HCl granules with ethylcellulose as polymer matrix showed that smaller granules promoted faster erosion, which confirms the faster drug release (Fig. 23). The coating effect of ethylcellulose on propranolol HCl during granulation could be another explanation for the slower release from larger granules.

Slower release of drug from tablet with larger propranolol HCl granules within the hydrophilic polymer matrix probably attributed to fast gel layer formation (Fig. 24). Release of propranolol HCl from hydrophilic polymer was extended (80% release after 14.5 h) when compared with release from its original granules (unsieved).

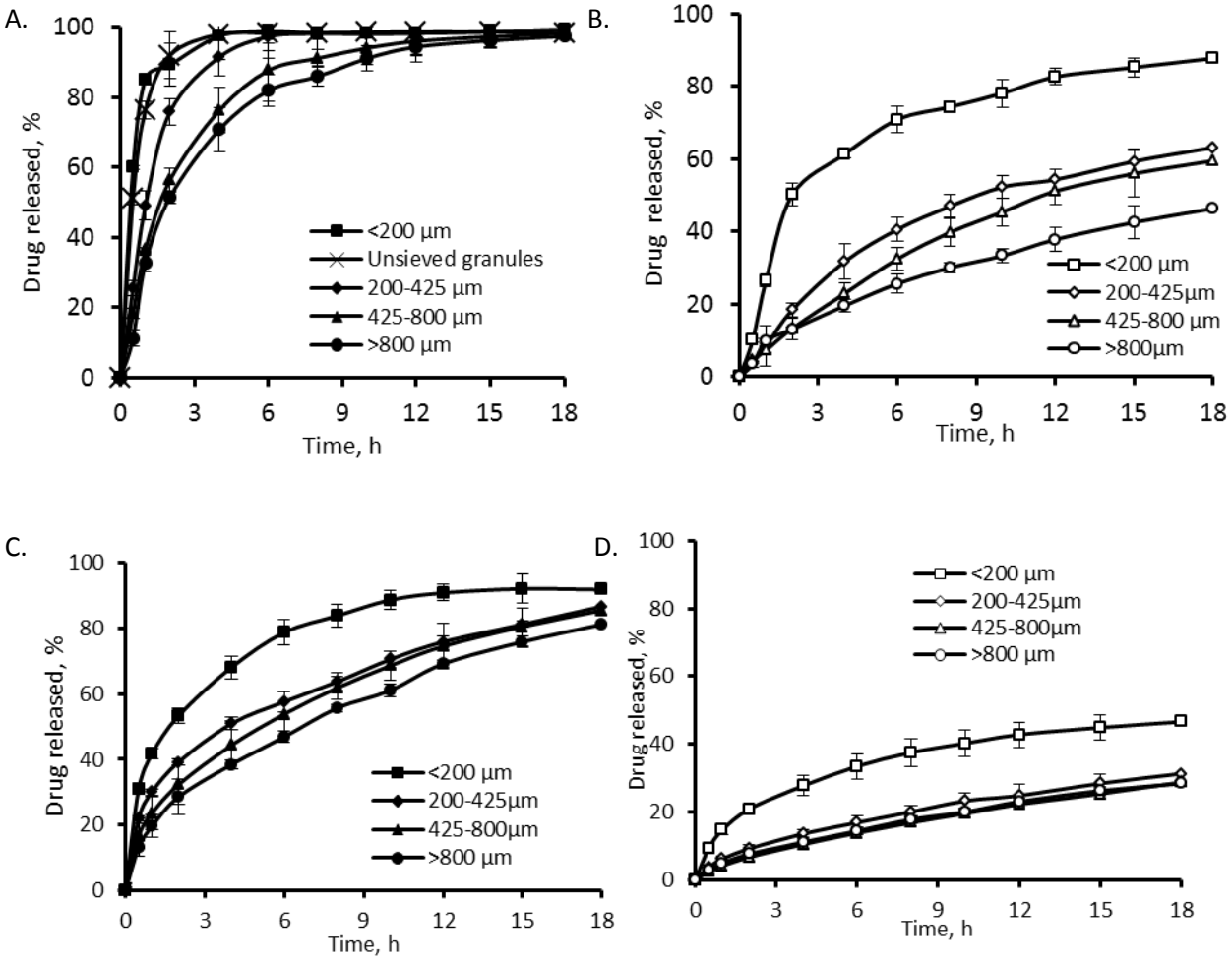


Figure 22. Effect of granule size on release of propranolol HCl (A and C) and carbamazepine (B and D) from drug combination with propranolol HCl : ethylcellulose 10cP granules using ethylcellulose 10 cPFP (A and B) and Kollidon®SR (C and D) as hydrophobic polymer matrix

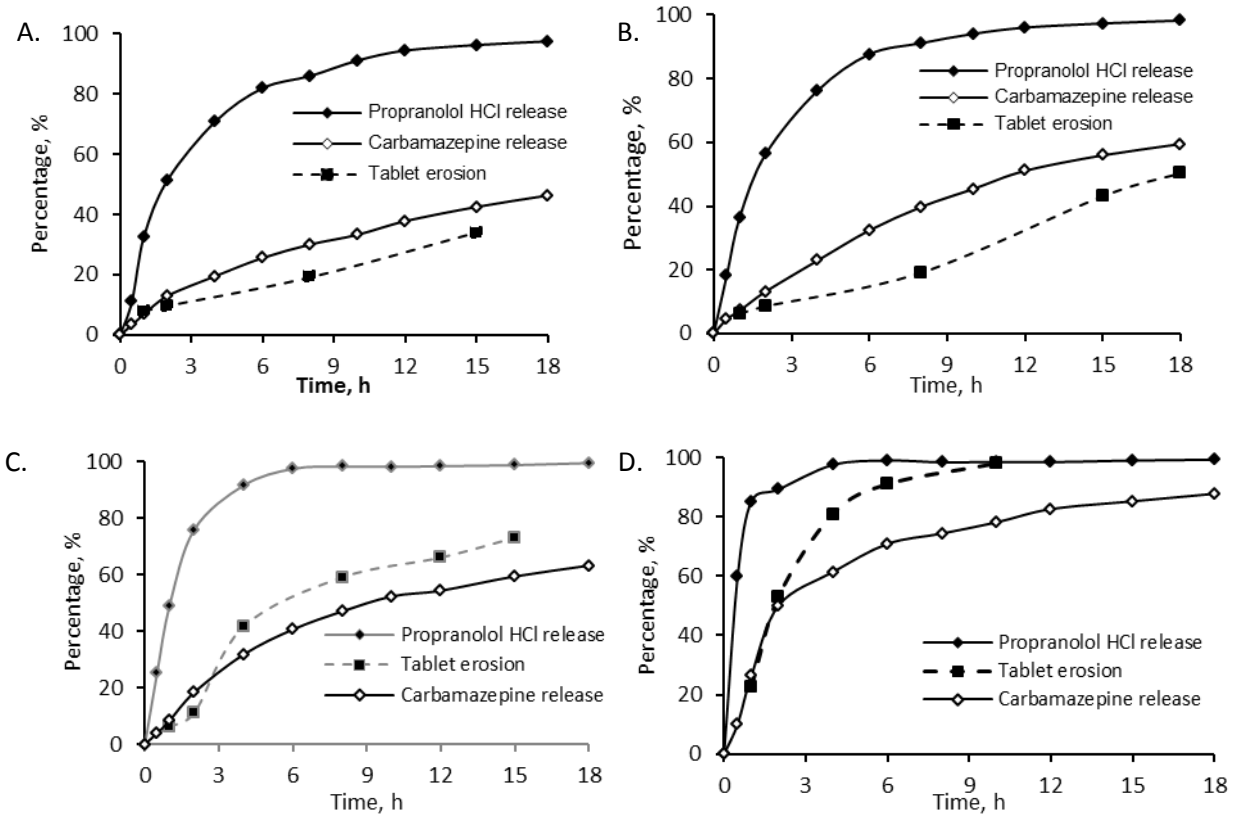


Figure 23. Erosion and release of combination drug with propranolol HCl : EC 10cP granules at A) >800µm , B) 425-800µm , C) 200-425µm and, D) <200 µm granule size, using 30% w/w ethylcellulose 10 cPFP as matrix

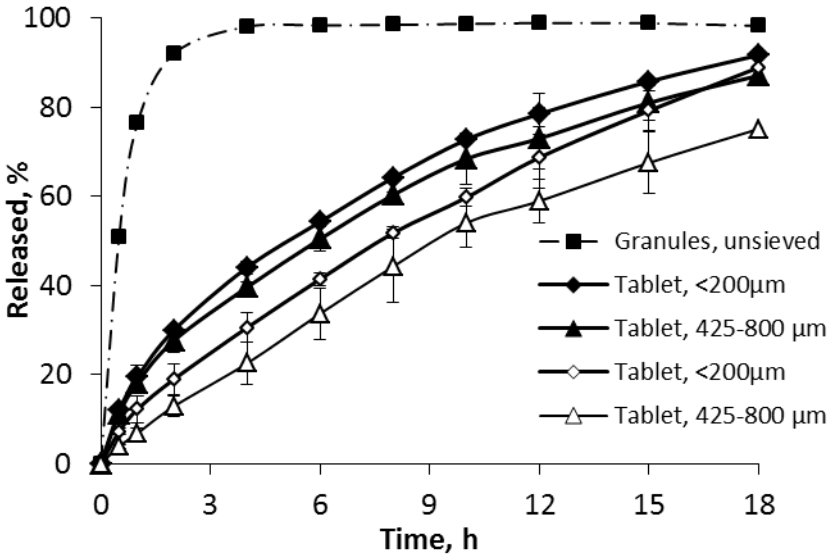


Figure 24. Effect of granule size on release of propranolol HCl (closed symbol) and carbamazepine (open symbol) from drug combination with propranolol HCl granules using Methocel®K15M: K100LV (1:1) blend as polymer matrix

Drug release from insoluble but permeable polymer Eudragit®RS revealed that the presence of the highly soluble drug propranolol HCl granules in the formulation with 30% w/w polymer content exhibited very fast release of both propranolol HCl and carbamazepine (Fig. 25) which was associated with the fast disintegration of the tablet (less than one hour). The study also showed independent effect of granule size on drug release. Slower drug release was observed by inclusion of ethylcellulose into the Eudragit®RS matrix tablets (Fig. 25). The presence of from the water-insoluble ethylcellulose in the matrix led to less hydration and hence slower erosion of and release from the tablets. However, polymer blend ratio had no pronounced effect on the release.

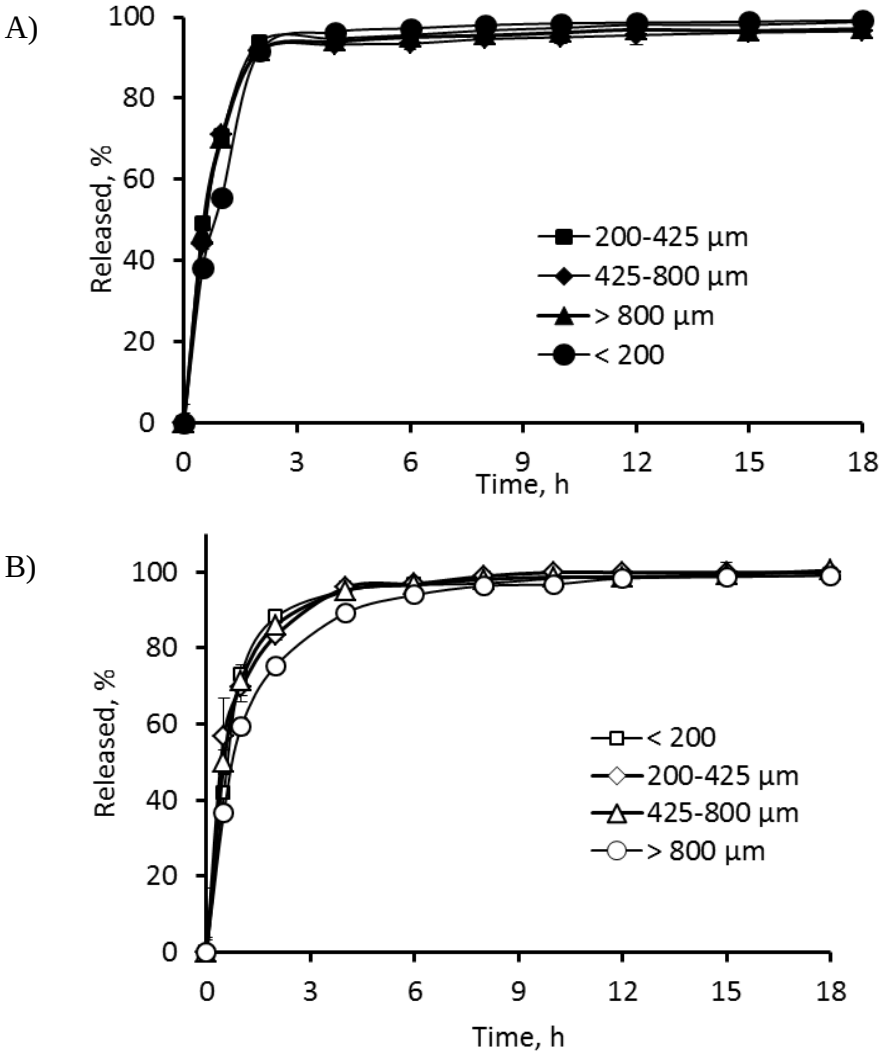


Figure 25. Release of A) propranolol HCl and B) carbamazepine with different granule size of propranolol HCl: ethylcellulose granules using 30% w/w Eudragit RS as insoluble permeable polymer matrix

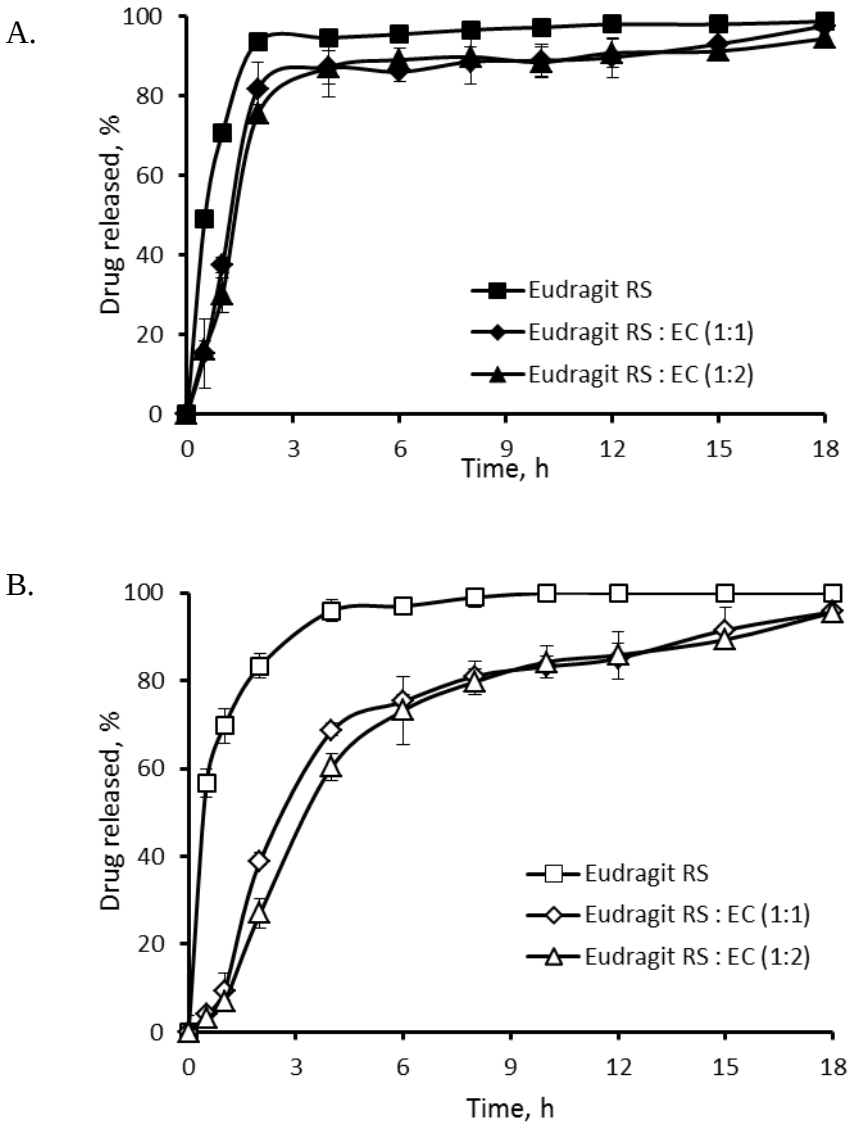


Figure 26. Release of A) propranolol HCl and B) carbamazepine from combination tablet with propranolol HCl: EC granules (200 – 425 µm) using 30% w/w polymer blends of Eudragit RS: Ethylcellulose as matrix

Tablets using ethylcellulose and Kollidon®SR remained intact close to 8 h, and after 18 h a small tablet erosion was observed (Fig. 27, A and B). At the end of dissolution study the ethylcellulose matrix was a soft tablet which easily can be crushed whereas Kollidon®SR had a tough and rubbery texture. Eudragit®RS as matrix led to complete disintegration in less than one hour, whereas after inclusion of ethylcellulose, the tablets remained intact for more than 2 hours. Further immersion in dissolution media revealed a hydrated layer which lead to lamination and complete disintegration after 4 h (Fig 27, C). Visual observation on HPMC matrix tablets indicated that at the beginning of the study, the matrix appeared did not swell like most HPMC matrices, a gel mass was not easily

observed. The hydrated layer was not viscous but adhesive in nature in the beginning. After more than 8 h, the tablets were eroded and at the end of dissolution study, the remaining tablet was in form of soft and thin viscous gel mass (Fig. 27, D).

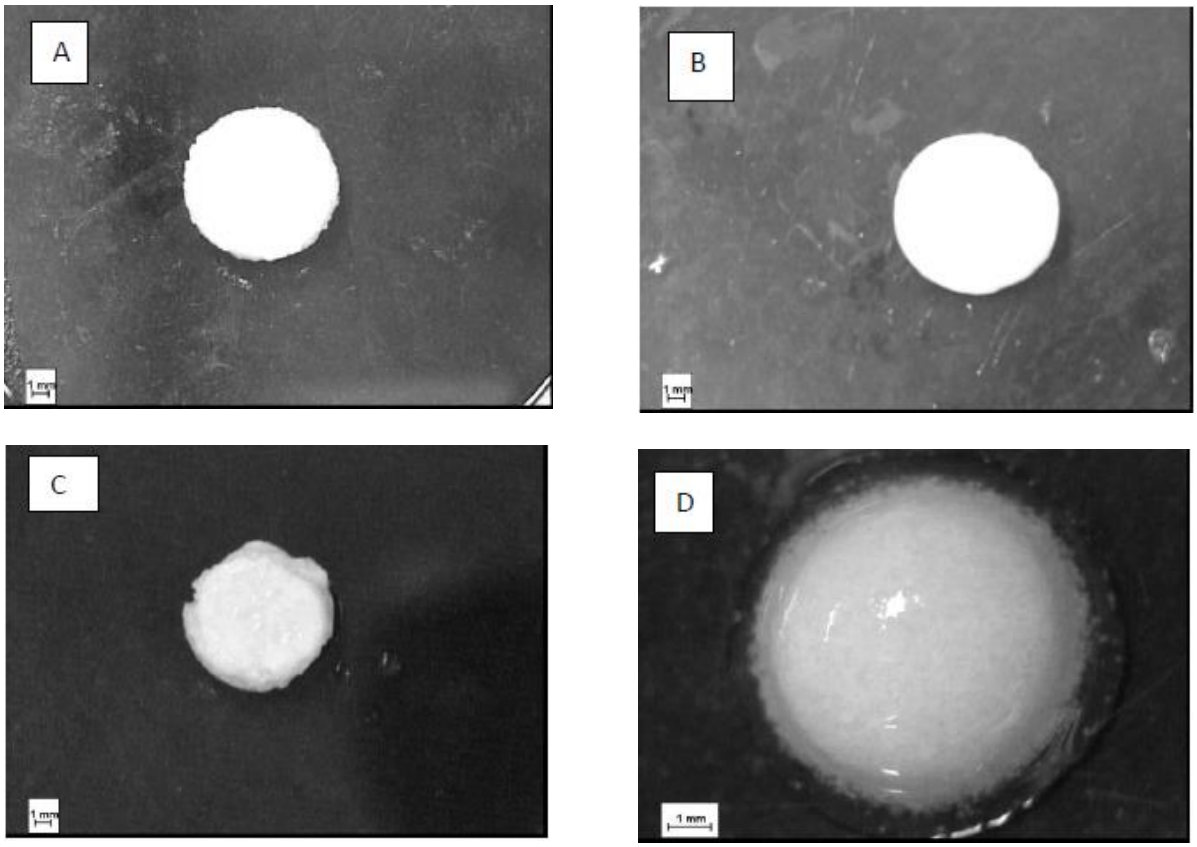


Figure 27. Combination tablet using propranolol HCl granules with A) Ethylcellulose 10cPFP B) Kollidon®SR, C) Eudragit®RS :Ethylcellulose (1:1) and D) Methocel®K15M as polymer matrix; after 18h (A and B), 2 h (C) and 6h (D) in release medium

Adjustment of erosion rate

Since the water-insoluble polymer matrices (ethylcellulose and Kollidon®SR) as well as insoluble permeable matrix (Eudragit®RS) did not provide flexibility in adjusting drug release, further studies focused on hydrophilic HPMC. Approach on release adjustment can be by increasing erosion rate of tablets. Erosion as predominant release mechanism of poorly soluble drug (Maderuelo, 2011) was dependent on polymer molecular weight of HPMC matrices; the rate of polymer erosion increased with a decrease in polymer molecular weight (Reynold et al., 1998). Namely, by using low molecular HPMC (Methocel®K100LV), release of both propranolol HCl and carbamazepine

increased (Fig. 28, A) due to faster erosion. Medium molecular weight HPMC (Methocel®K4M) exhibited a slower release of propranolol and carbamazepine and was similar to the higher molecular weight Methocel® K15M (Fig. 28, A).

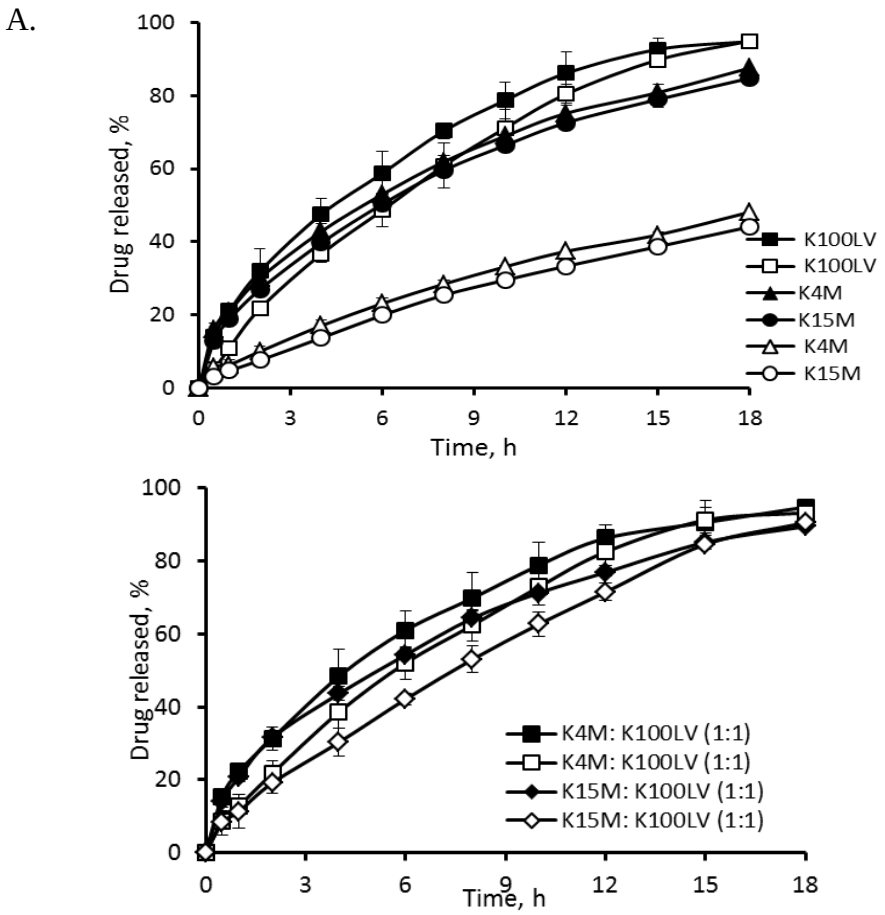


Figure 28. Release of propranolol HCl (closed symbol) and carbamazepine (open symbol) from drug combination with propranolol HCl granules using 30% w/w A) different type of Methocel® and B) polymer blend of Methocel® as polymer matrix

The use of polymer blends of HPMC as polymer matrices has been extensively studied. Polymer blends of Methocel®K15M: K100LV or Methocel®K4M: K100LV exhibited increased release of carbamazepine which was closer to propranolol HCl release (Fig. 28, B). Blending Methocel® K15M : K100LV (1:1) resulted in more intact tablets compared to K4M : K100LV (1:1). Methocel®K15M : K100LV (1:1) played a major role in controlling drug release of carbamazepine, not only due to its fast surface erosion but also in maintaining the matrix during dissolution test.

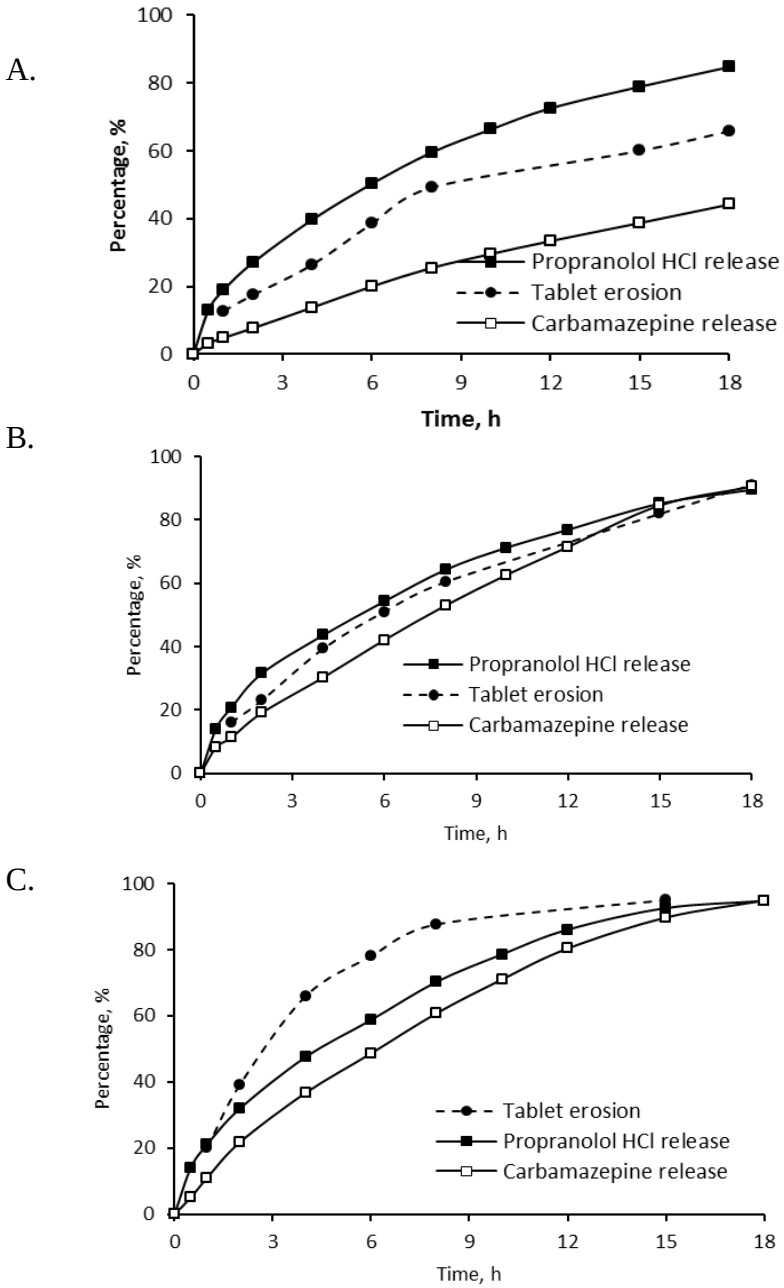


Figure 29. Erosion and release of propranolol HCl (closed symbol) and carbamazepine (open symbol) from drug combination with propranolol HCl granules (200 – 800 µm), using 30% w/w A) Methocel ® K15M, B) polymer blend of Methocel ® K15M : K100LV (1:1) and C) Methocel® K100LV as matrix

Erosion studies of tablets with Methocel®K15M: K100LV (1:1) blend compared with a single polymer matrix (Methocel®K15M) confirmed that the faster release was attributed to faster erosion (Fig. 29, A and B).

Erosion rate can also be adjusted by the presence of soluble fillers in the matrix, which promote higher matrix hydration and hence weaker gel formation. The effect of

lactose filler on release of drug from HPMC matrix was evaluated. Release from Methocel®K4M with lactose was faster than K15M which was attributed to faster erosion (Fig. 30). The effect of soluble filler was more pronounced on carbamazepine release (Fig. 30 B), which was associated with higher erosion as predominant release mechanism.

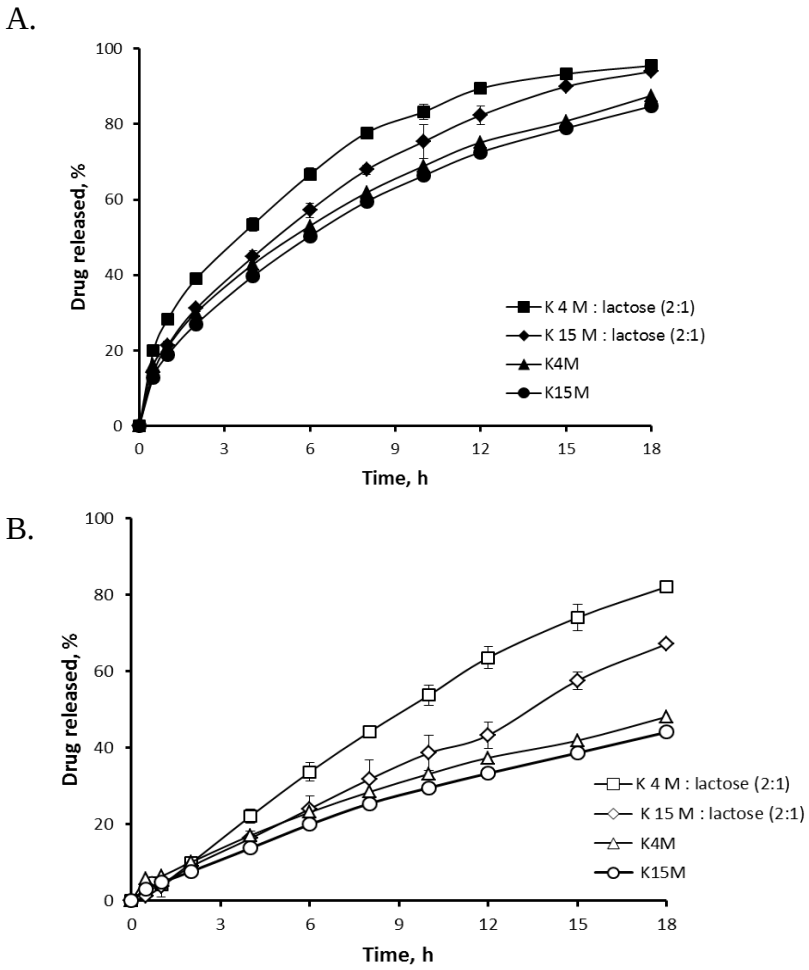


Figure 30. Release of A) propranolol HCl and B) carbamazepine from drug combination with propranolol HCl granules using blends of Methocel®K15M : lactose as soluble filler as matrix

Different method of granulation

Due to high solubility, release of propranolol HCl showed burst effect and fast release. In order to obtain more uniform coating of particles, the approach to provide an additional diffusion barrier by granulation method of propranolol HCl in ethylcellulose can also be conducted by wet granulation in fluid bed granulator. Release of propranolol HCl from matrix tablet was extended (less than 80% release after more than 18 h, using

Methocel®K15M) (Fig. 31). Poor water penetration which was hindered due to hydrophobic nature of EC as coating layer of propranolol particles probably was the reason for slow release of carbamazepine. Blend of HPMC as matrix resulted in faster release of propranolol HCl and carbamazepine due to faster erosion. By using Methocel®K100LV, due to high erosion of tablet surface, the formulation completely disintegrated during dissolution test.

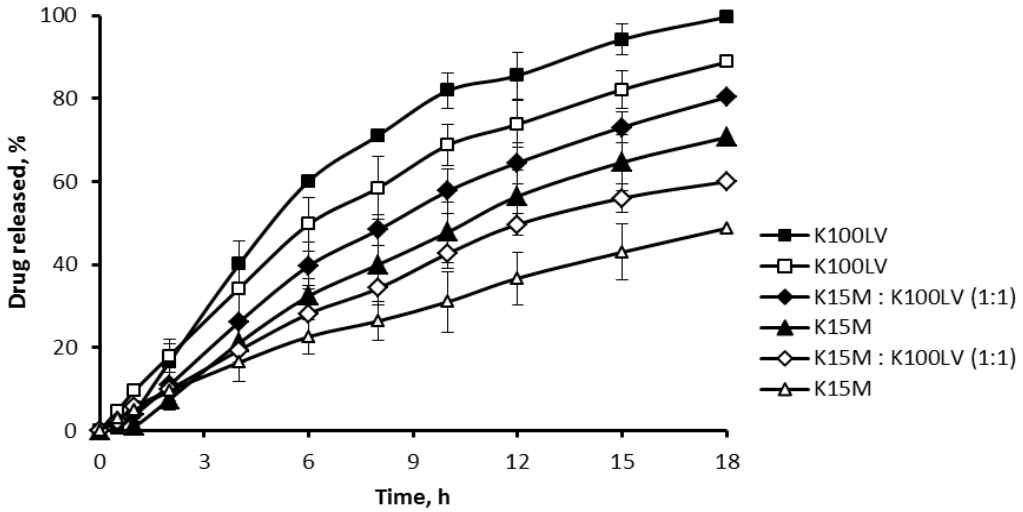


Figure 31. Release of propranolol HCl (closed symbol) and carbamazepine (open symbols) using propranolol HCl : EC (1:1) granules prepared by fluid bed granulation method using different type of Methocel® as outer matrix

To conclude the release retardation of propranolol HCl as combination drug from matrix tablet system, three different methods of tablet preparation were compared (Fig. 32). Granulation of propranolol HCl prepared by fluid bed granulation retarded propranolol HCl release better than shear mixed granulation method due to a more homogeneous coating of the particles. Compression of the granules with other excipients following shear granulation exhibited almost the same propranolol HCl release as with direct compression. The more bulky powder for direct compression compared with denser materials for granulation method should also be considered. Fluid bed granulation method prior to compression as matrix tablet provided highest retardation of propranolol HCl (80% released after more than 18 h).

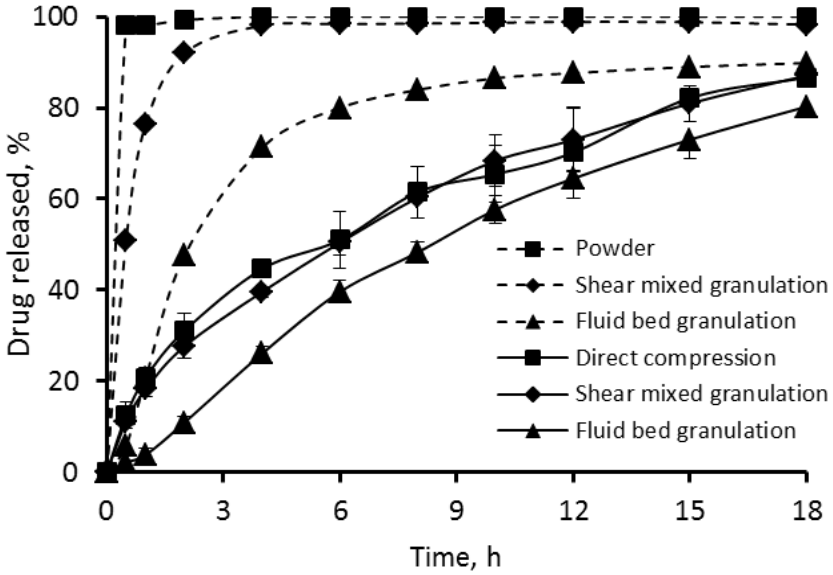


Figure 32. Release retardation of propranolol HCl from combination drug as matrix tablets (continues line) using propranolol HCl granules (425-800 µm) prepared by different method compared with original powder and granules (dash line)

Release of carbamazepine as model of poorly soluble drug in Methocel®K15M : K100Lv (1:1) matrix was also affected by method of granulation of propranolol HCl (Fig. 33). Wet granulation of propranolol HCl resulted in higher release of carbamazepine which probably could be attributed to higher water penetration due to some uncoated propranolol HCl in the matrix and hence higher erosion. Fluid bed granulation which homogeneously coated propranolol HCl particles with hydrophobic ethylcellulose promoted less water uptake and therefore slower carbamazepine release due to slower erosion.

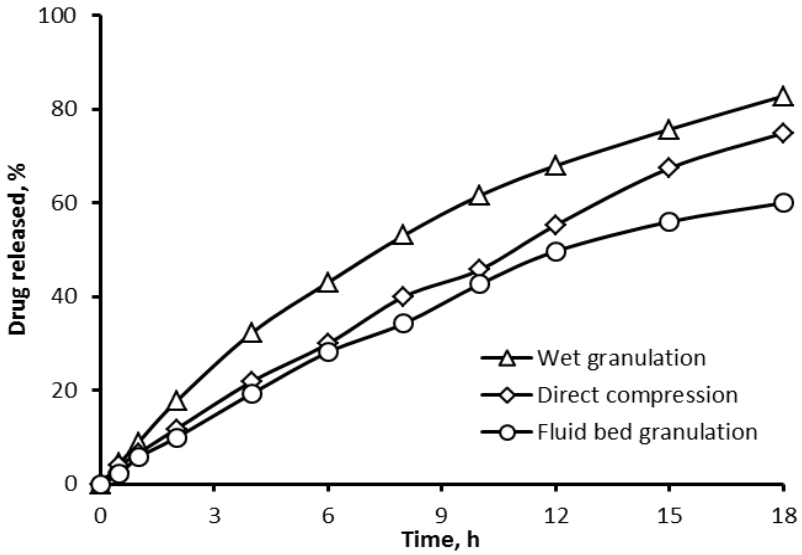


Figure 33. Release of carbamazepine from combination drug using propranolol HCl granules as matrix tablets prepared by different method with Methocel®K15M : K100LV (1:1) as polymer matrix

3.1.3 Conclusions

With direct compression method, irrespective of type of polymers, the release of propranolol HCl was much faster than carbamazepine due to solubility differences. The increase in release was attributed to the increase in tablet erosion. Release adjustment with the direct compression method was obtained by inclusion of ethylcellulose into HPMC matrices. Slower release of propranolol HCl was attributed to increase in total polymer loading with the presence of the water-insoluble ethylcellulose in the gel layer .

In order to provide an additional diffusion barrier, propranolol HCl powder was granulated to form drug granules with reduced drug release prior to compression with carbamazepine and other excipients as matrix tablet. The increase in particle size of granules resulted in a decrease in both propranolol HCl and carbamazepine release. Large granules have a smaller surface area and therefore slower release, whereas smaller granules provide larger surface area thus higher water penetration and faster erosion. The coating effect of ethylcellulose on propranolol HCl during granulation could be another explanation for slower release from larger granules. More homogeneous coating of propranolol HCl particle by fluid bed granulation resulted in better retardation of propranolol release either as granule or after compression into matrix tablet.

Release adjustment can be conducted by controlling the erosion rate of the matrix which enables a faster release. Blending of HPMC matrices with lower molecular HPMC or lactose increased the erosion rate and resulted in a faster drug release. The effect of soluble filler blended with polymer matrices was more pronounced on carbamazepine release which associated with higher erosion.

3.2 Release adjustment of drug combination with different drug solubility from coated pellets within matrix tablet system

3.2.1 Introduction

Many studies regarding dosage form for drug combination had been published. Oral dosage forms for combination therapy can be in the form of tablets, capsules and pellets. Pellets, in turn, can be filled in to hard gelatin capsules or compressed into tablets. Multiparticulates (pellets) systems are suitable for a combination of incompatible drugs or when different release rates of drug are needed from the same dosage forms. Mainde and Vahile (2009) patented combination tablet of enteric coated pellets rabeprazole sodium, and granules comprising aceclofenac and paracetamol, which were further compressed into bilayer tablets to give different release profiles. A cored tablet wherein the aspirin forms the core, and statin plus buffering agent are present in a surrounding coat layer, was prepared to give different release profiles (Ullah and Jain, 2001). The study on drug combination as compressed pellet system with different release profiles of loratadine and pseudoephedrine HCl as combination drugs was performed by mixing pellets and granules having different release profile and compressed into tablet (Zeeshan and Bukhari, 2010).

Polymeric film coatings are frequently used to control drug release from solid pharmaceutical dosage forms (Ghebre-Sellassie, 1994; Cole, et al., 1995; McGinity, 1997). Water insoluble ethylcellulose have proven to be suitable coating materials as a highly suitable polymer for controlled release pellet coatings which can be used as polymer blend with water soluble cellulose derivates such as hydroxypropyl methylcellulose (HPMC) or hydroxypropyl cellulose (HPC) as pore-forming agents (Marucci et al., 2009; Sakellariou and Rowe, 1995).

To obtain a particular, desired release profile from different solubility of drugs in combination drug, different formulation and processing parameters can be varied. Polymeric coated reservoir pellet system had been extensively employed to retard highly soluble drugs to give a controlled release. Regarding release of highly soluble drugs when combined with poorly soluble one as drug combination in one dosage form, retardation can be performed by providing additional barrier for diffusion compared with that for poorly soluble drug. Extensive study on factor influencing the system has not been studied yet. Therefore the objective of the study was to modulate the release of two drugs of different

solubility in drug combination as pellets within matrix tablets system by introducing ethylcellulose coated pellets within HPMC matrix tablet for controlled release drug delivery. Furthermore, critical factors influencing their release such as HPC content, coating level of film coating, polymer blend ratio of matrix and particle size of carbamazepine were evaluated.

3.2.2 Results and discussions

With regard to simplicity and ease of manufacturing, as first approach, combination drug as matrix tablet was prepared by direct compression method. Using ethylcellulose as water insoluble polymer matrix, propranolol HCl showed fast release whereas carbamazepine was extended (70% released after 18 h) due to difference in solubility (Fig 34). The release of propranolol HCl was extended (t_{80}% was approx. 12 hour) when HPMC polymer matrix was used, due to rapid gel formation on the surface. Accordingly, carbamazepine release was extended into slower release (48% release after 18 h).

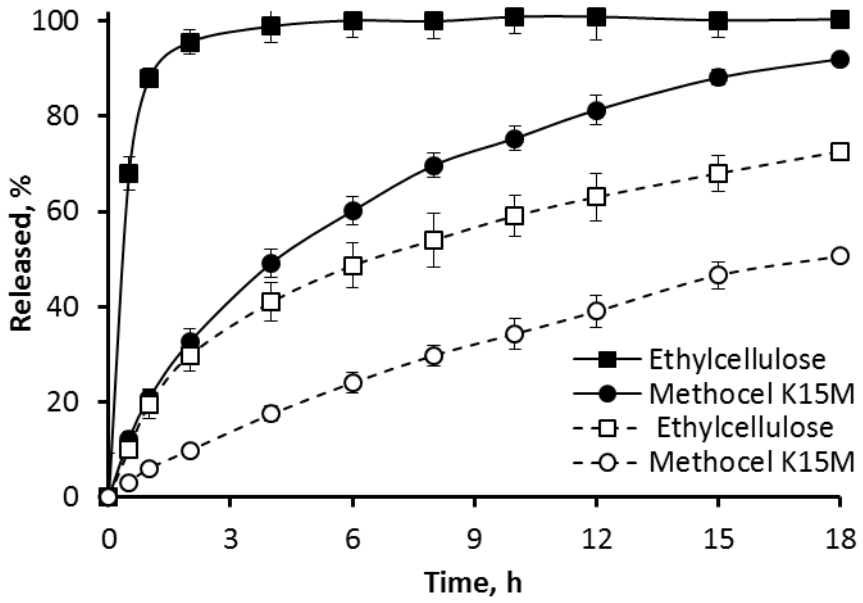


Figure 34. Release of propranolol HCl (closed symbols) and carbamazepine (open symbols) as drug combination (20% of each drug loading, 30% polymer) from different polymer matrix tablets by direct compression method

Release adjustment can be performed either by retardation of propranolol HCl or enhancement of carbamazepine release. Retardation of propranolol HCl was performed by layering propranolol HCl onto non-pareils followed by coating with ethylcellulose. These

pellets were compressed together with carbamazepine powder into HPMC tablets. Using this approach, an almost similar release of propranolol HCl and carbamazepine (f_2 factor = 68.29) was obtained. Typical sigmoidal release of highly soluble drug (as shown by uncompressed pellets) was improved into linear release (Fig. 35). Release of propranolol HCl from coated pellets within the matrix was retarded by the ethylcellulose coating and the HPMC.

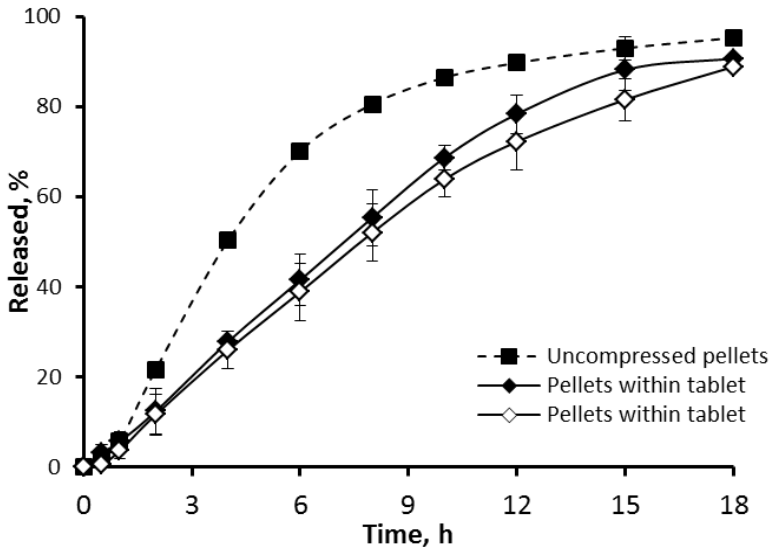


Figure 35. Release profile of propranolol HCl (closed symbol) and carbamazepine (open symbol) from uncompressed pellets and pellets within tablet with Methocel® K15M : K 100LV (1:1) as polymer matrix

At the beginning of the release study, the matrix appeared not to swell like mostly HPMC matrices, a gel mass was not viscous but adhesive in nature. Following tablet erosion, pellets are release from the matrix gradually (Fig. 36).

For the flexible adjustment of drug release, mechanisms of release should be decoupled. The adjustment of propranolol HCl release is possible by controlling permeability of film coating. Erosion rate of matrix is variable to be adjusted for both propranolol HCl and carbamazepine releases. By simply varying the polymer:polymer blend ratio, the resulting film coating properties can effectively be altered (Siepmann, 2008). Increase in hydroxylpropylcellulose (HPC) content in ethylcellulose coating resulted in increase of propranolol HCl release either from uncompressed pellets or pellets within matrix after compression (Fig. 37) due to increase of coating permeability. The release of carbamazepine was independent of HPC content on film coating of pellets.

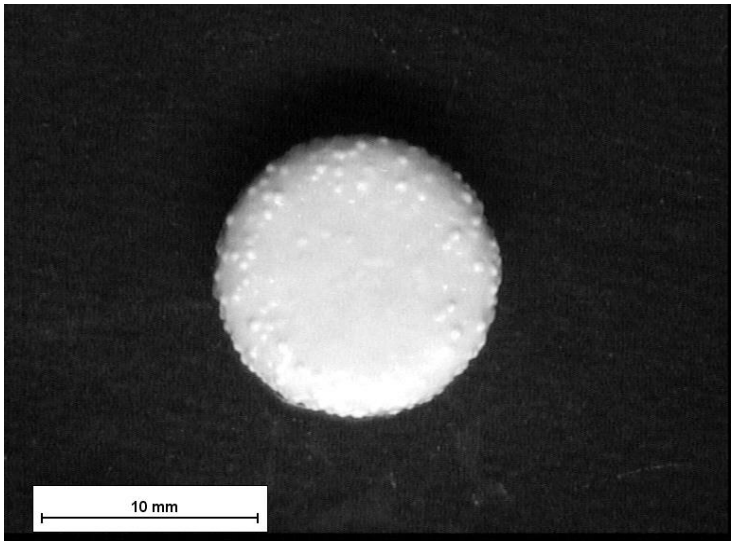


Figure 36. Propranolol HCl pellets within matrix tablet with Methocel® K15M : K 100LV (1:1) as polymer matrix after 1h in release medium

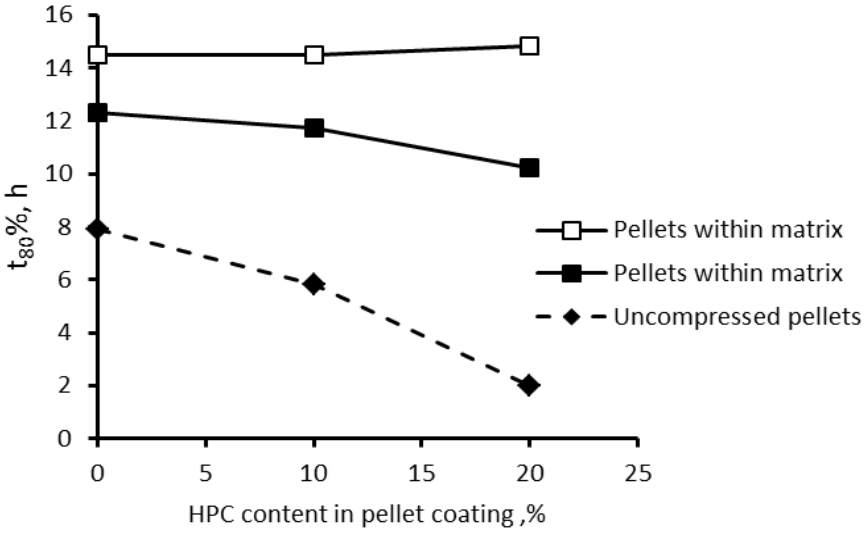


Figure 37. Effect of HPC content of pellet coating on release of carbamazepine (open symbol) and propranolol HCl (closed symbol) from uncompressed pellets and pellets within matrix (10% w/w coating level, Methocel® K15M : K 100LV (1:1) as polymer matrix)

The film permeability can be increased by either incorporating a pore former or reducing the film thickness and thereby the diffusion path length. As expected, propranolol HCl release decreased with increasing coating level of propranolol HCl pellets (Fig. 38). Coating level of pellets influenced the release of propranolol HCl either as pellets (uncompressed) or after compression into tablet (Fig. 38). Decrease in propranolol HCl

release after compression was attributed to an addition of diffusional barrier from matrix HPMC. Surprisingly, release of pellets with 20% coating level was almost unchanged after compression. The hypothesis that the damaged coating as possible reason for this was not proved as the ruptured coating of pellets after compression (Fig. 39) was found only in a small portion of pellets (less than 10%). The ruptured film coating caused by compaction probably only from outermost pellets of the tablets. It can be concluded that at higher coating level, reduced release of propranolol HCl after compression was predominantly associated to an additional diffusion barrier of HPMC matrix.

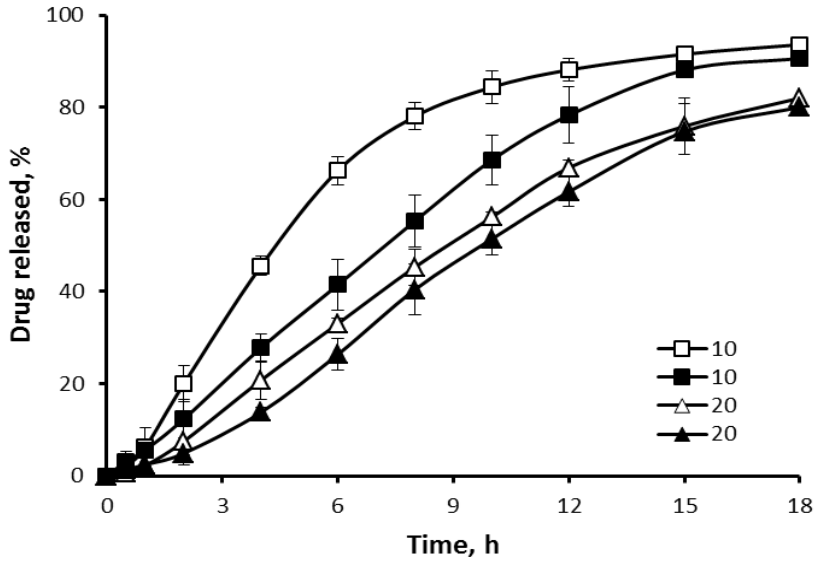


Figure 38. Release of propranolol HCl from uncompressed pellets (open symbol) and after compression (closed symbol) at different coating level of pellet coating (% w/w)

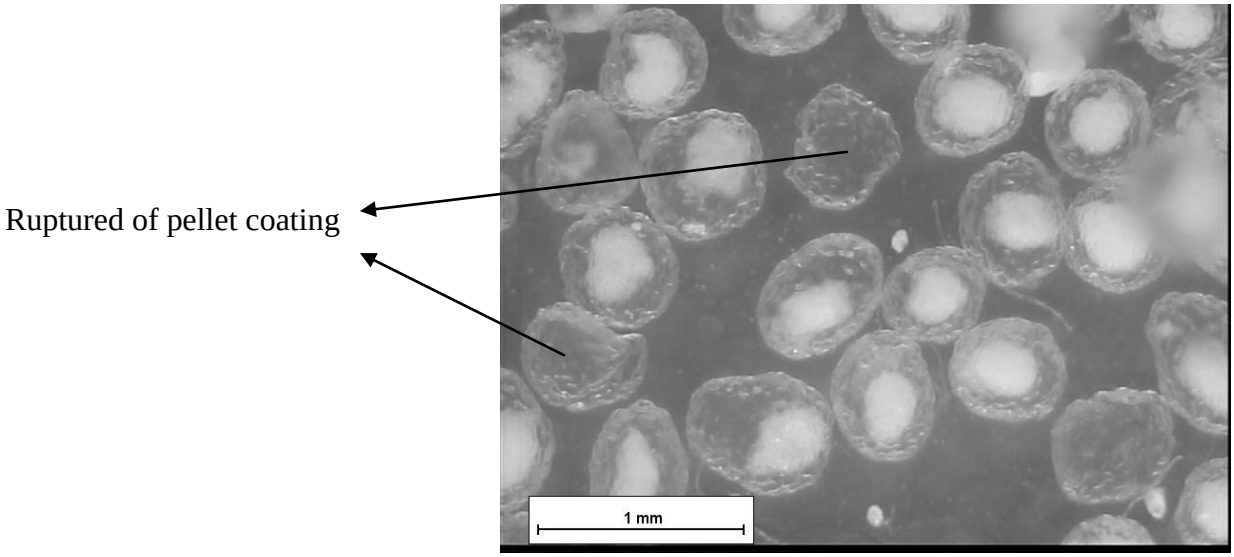


Figure 39. Macroscopic picture of propranolol HCl pellets released from matrix tablet after 18h in release medium

Theoretically, 29 % (w/w) of excipient are needed to fill the void space between densely packed spheres (Bodmeier, 1997). In this study, the outer matrix of the tablet made of 30% w/w HPMC, 17.5 % w/w carbamazepine and 5.7% w/w lactose as excipients enable the pellets to withstand the compression force, as microscopic pictures showed only a very small fraction of ruptured pellets after compression process.

The permeability of the film coating might change the release profile of the drug incorporated into the pellets without affecting the release of the drug in the outer matrix formulation. As expected, propranolol HCl release decreased with increasing coating level of propranolol HCl pellets without remarkable effect of the carbamazepine release (Fig. 40). This knowledge facilitates formulation of combination products of drugs of different solubilities. After drug release of the soluble drug can be adjusted by its permeability of the coating, release of poorly soluble drug can be adjusted by increasing erosion rate of matrix, as predominant mechanism for release of poorly soluble drugs.

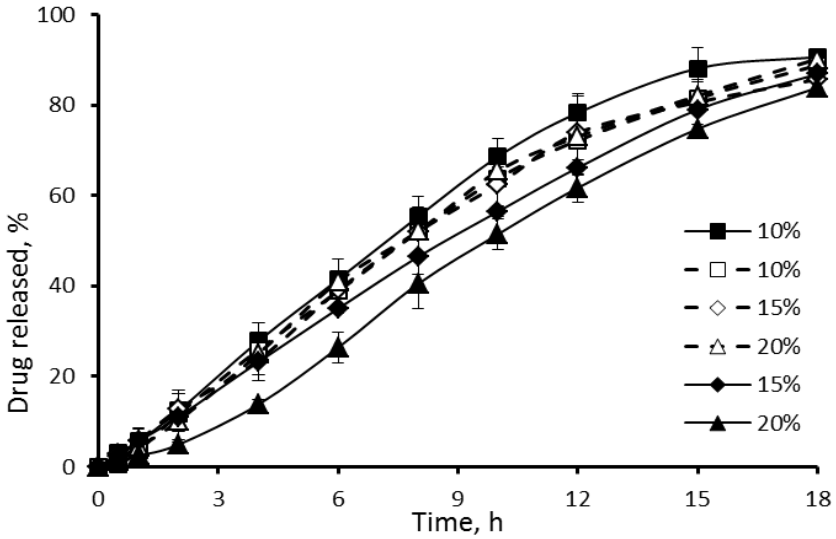


Figure 40. Independent effect of pellet coating level on release of carbamazepine from compressed pellets with Methocel® K15M : K 100LV (1:1) as polymer matrix

Erosion as predominant release mechanism of poorly soluble drug (Maderuelo, 2011); shown to be dependent on polymer molecular weight of HPMC matrices; the rate of polymer erosion increases with a decrease in polymer molecular weight (Reynold et al., 1998). Increasing low molecular weight of HPMC (Methocel®K100LV) content as polymer matrix resulted in increased release of carbamazepine (Fig. 41) due to faster erosion. Accordingly, propranolol HCl release was increase which attributed to increase in pellet released from the matrix, hence faster drug release. It can be concluded that propranolol HCl release was affected not only by film coating permeability of pellets in accordance with diffusion but also by erosion of matrix, which promote more propranolol HCl pellets released into medium (Fig.42 and 43).

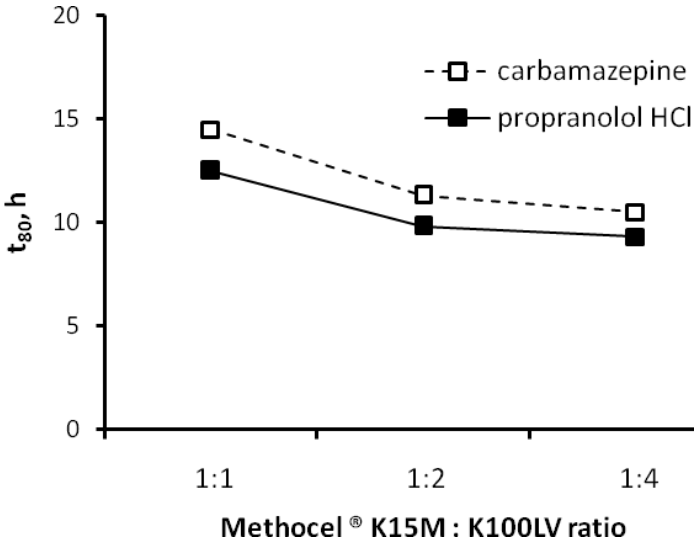


Figure 41. Effect of different ratio of Methocel® K15M : K100LV blends as polymer matrix on release of drug from compressed propranolol HCl coated pellets (ethylcellulose 10% w/w coating level)

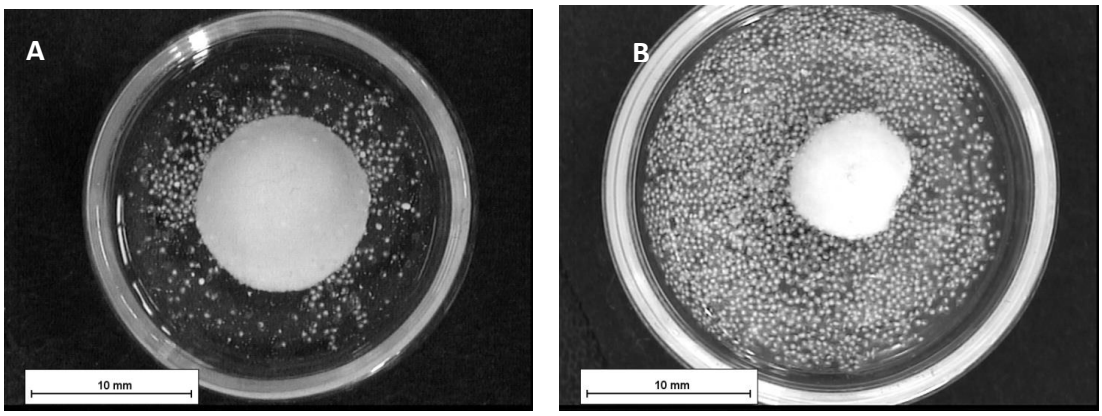


Figure 42. Combination tablet prepared by compression pellet method after A) 6 hour and B) 18 hour dissolution time with Methocel® K15M : K100LV (1:1) as polymer matrix

Erosion and pellet release study confirmed that carbamazepine particles and propranolol HCl pellets are released out of the matrix according the tablet erosion (Fig 43).

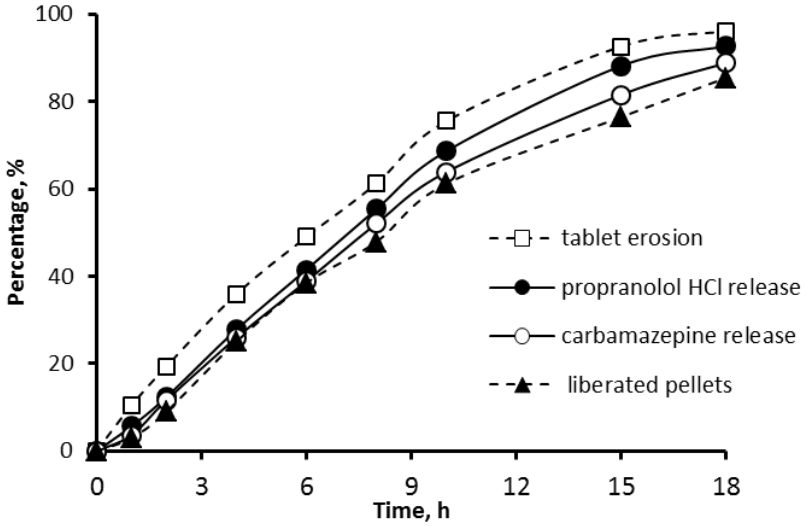


Figure 43. Relatioship between drug release with pellets release or erosion study from drug combination tablet with Methocel® K15M : K 100LV (1:1) as polymer matrix

The erosion was also controlled by the particles size of carbamazepine (Fig. 44). Small particle sizes result in the absence of a percolating carbamazepine network, through which pores run, which may facilitate rapid medium penetration into the tablet. The absence of a continuous pore matrix results in a reduction in the liquid penetration rate, therefore slower drug release of carbamazepine.

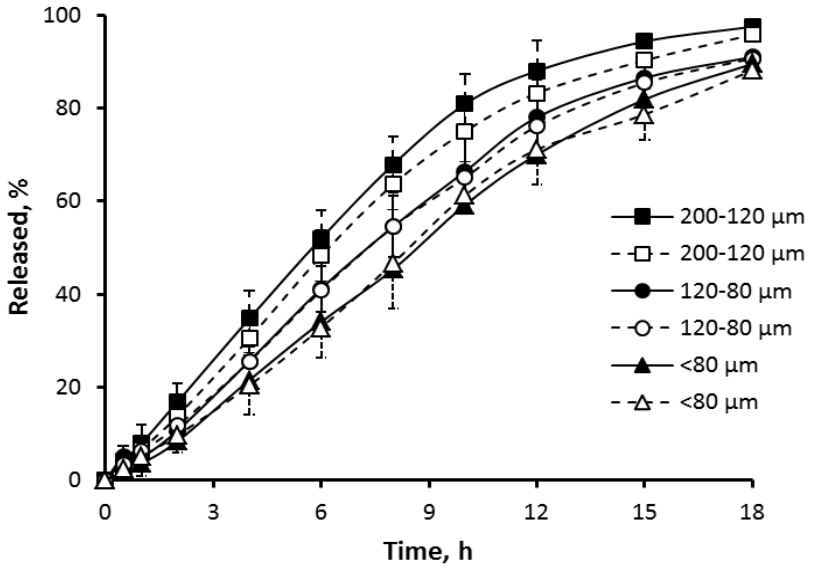


Figure 44. Release of propranolol HCl (closed symbol) and carbamazepine (open symbol) from compressed propranolol HCl pellets with Methocel® K15M : K 100LV (1:2) as polymer matrix and different particle size (µm) of carbamazepine

Slower erosion of tablet resulted in less pellets released from the matrix, hence slower release of propranolol HCl (Fig. 44). The result was in agreement with erosion and pellet release study (Fig. 43). It can be concluded that adjustment of release as coated pellets in matrix tablet can also performed by employing different particle size of carbamazepine which will affect erosion of tablet, therefore change the release. As release erosion increase/decrease, not only carbamazepine release will increase/decrease but also propranolol HCl.

3.2.3 Conclusions

Release adjustment of drug combination of different drug solubility as matrix tablet should be performed by employing more release barrier to propranolol HCl as model of highly soluble drug than that to carbamazepine as poorly soluble one. The release became similar when propranolol HCl pellet was introduced as ethylcellulose coated pellet and compressed as matrix tablet with carbamazepine mixed with other excipients in the matrix.

The adjustment on permeability of the film coating (including coating level of propranolol HCl pellets and HPC content as pore former), affected the release of propranolol HCl from the pellets without remarkable effect on the release of carbamazepine in the outer matrix formulation. In contrast, by adjusting erosion rate using different HPMC blend as matrix and different particle size of carbamazepine not only the release of carbamazepine which was affected but also propranolol HCl which associated with more pellets release from the matrix. In summary, compression of propranolol HCl pellets and carbamazepine in outer matrix, was the effective method to enable linear and almost the same (f_2 factor >50) and adjustable release of propranolol and carbamazepine as drug combination.

3.3 Release of drug combinations with different drug solubility from multilayered pellet systems

3.3.1 Introduction

In the past three decades, pellets as multiple unit drug system have gained increasing attention due to numerous advantages over single unit drug delivery system (Bechgaard and Nielsen 1978; Ghebre-Sellassie 1989; Roy and Shahiwala 2009). Although similar drug release profiles can be obtained with both dosage forms, multiple unit dosage forms offer several advantages. Pellets are less dependent on gastric emptying rate, have a lower tendency for local irritation and have a reduced risk of dose dumping (Muschert et al., 2009). Premature drug release from enterically coated dosage forms in the stomach, potentially resulting in the degradation of the drug or irritation of the gastric mucosa, can be reduced with coated pellets because of a more rapid transit time when compared to enterically coated tablets (Bodmeier, 1997).

In combination therapy, the drugs are either administered separately, or, where available, dosage forms that contain more than one active ingredients. Multilayer tablets can be designed for such a purpose, but expensive and specialized tableting machine is necessary. Pellet system comprising coated pellets with certain releases become an alternative. Mostly, they are marketed as a mixture of coated pellets of different drugs with different coating filled in hard gelatin capsules. Until now, some studies have been published concerning this area. Nicotinic acid sustained-release pellets combined with immediate release simvastatin was prepared by the double ethylcellulose coating as multilayer pellets (Zhao et al., 2010). Pellets with different release profiles can be incorporated within one dosage form, thus allowing a greater flexibility during formulation development (Ghebre-Sellassie 1989; Anschütz 2009), and offers many advantages including reduced amount of excipient thus higher drug loading and lower unit cost. However, an extensive study concerning multilayer coated pellets for drug combination containing different drug solubility and study on drug release adjustment from such a system hasn't been published yet.

In order to obtain a particular desired release from ethylcellulose coated pellets, different formulation and coating parameters can be varied, such as the type and amount of added pore former or plastisizer and coating level. With regard to drug release adjustment, ethylcellulose as a highly suitable polymer for controlled release pellet coatings can be

used as polymer blend with water soluble cellulose derivates such as hydroxypropyl methylcellulose (HPMC) or hydroxypropyl cellulose (HPC) as pore-forming agents (Marucci et al., 2009; Hjartstam et al., 1998, Sakellariou and Rowe, 1995b). The permeability of ethylcellulose and HPC film coating depends on the ratio between the two polymers (Marucci et al., 2009 and 2010). The release adjustment study by elaborating the effect of HPC content and coating thickness on release of propranolol HCl and carbamazepine from multilayer EC coated pellet were investigated. The objective of the study was to control the release of two drugs of different drug solubility from multilayered pellets coated with ethylcellulose : HPC blends. Factors affecting release such as drug loading and drug solubility were also studied.

3.3.2 Results and discussion

Release study

In a first approach and as reference, dissolution profiles of combination drug with different drug solubility propranolol HCl and carbamazepine were determined from single layer pellets. Propranolol HCl released faster than carbamazepine for all of HPC content as pore former (Fig. 45), due to higher solubility (propranolol HCl = 250 mg/mL, carbamazepine = 0.2 mg/mL) therefore higher diffusional driving force. Fast release of highly soluble drugs from coated pellet could be also due to steeper concentration gradient and an increased osmotic pressure difference over the membrane (Ragnarsson et al., 1992). By increasing HPC content in film coating from 20% to 40% w/w, the release of carbamazepine as poorly soluble drug was increased (Fig. 45). Accordingly, propranolol HCl as model of highly soluble drug released very fast to immediate release (100% drug released at less than 2 h). It can be concluded that the release profile of different drug with different solubility could not be adjusted by using conventional polymeric coating system (as drug blend in single layer coating). Therefore, multilayered pellet providing different coating for different drug according to their solubility were investigated further.

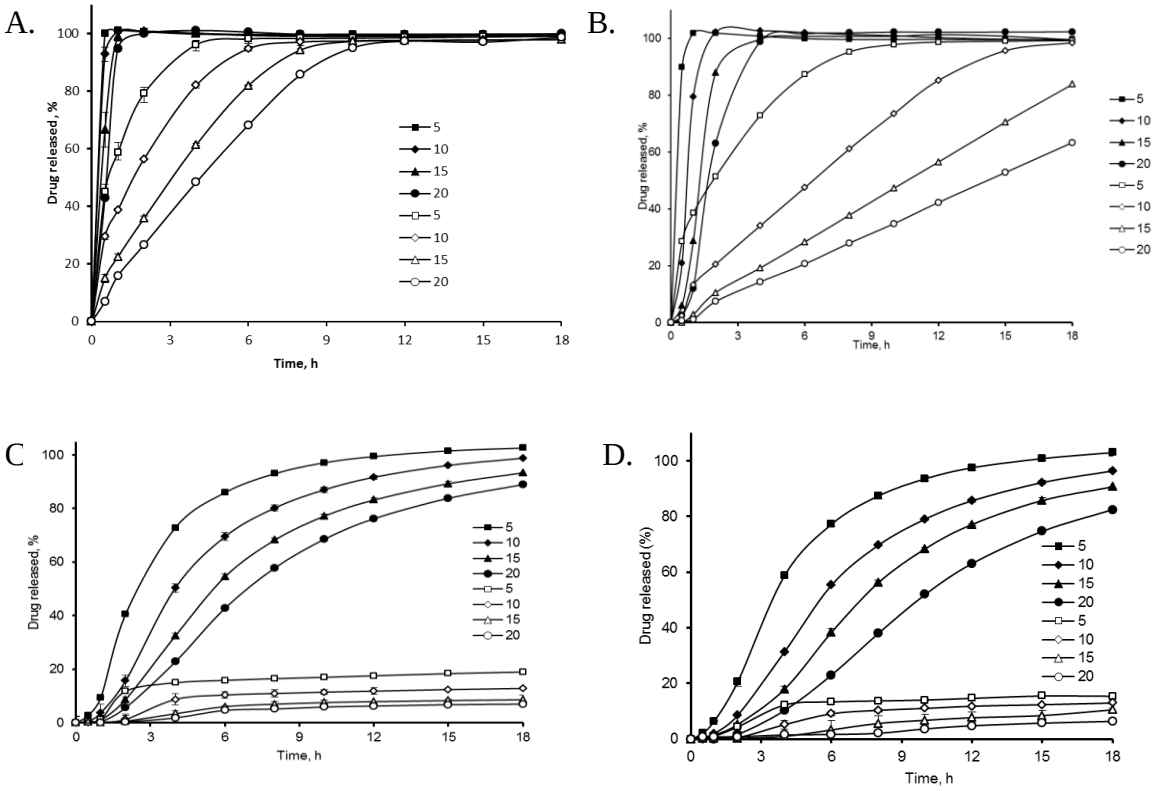


Figure 45. Release profile of propranolol HCl (closed symbol) and carbamazepine (open symbol) from combination drug as single layer ethylcellulose coated pellets with A) 40% B) 30% C) 20% and D) 10% w/w HPC content as pore former and coating level 5-20% w/w

Further study was focused on multilayered pellet system, which provided more diffusion barrier for highly soluble drug and more permeable coating for poorly soluble one. Compared with capsules comprising mixed different coated pellets with different drug release profile, multilayer system offer some benefits such as high drug loading and less materials. The multilayer system could be designed as follows: first drug (D_1) having higher solubility which is layered onto the neutral core (e.g. sugar) followed by first coating (C_1). Further, the second drug (D_2) having lower solubility is layered and consecutively coated with second coating (C_2). Release of first drug having higher solubility is controlled by both C_1 and C_2 coating whereas when first coating has low permeability, the release of second drug having lower solubility (D_2) is controlled only by C_2. In order to describe/predict behavior of such system, few assumption/simplification could be done. Namely, 1) release of first drug controlled by both C_1 and C_2 coating and

not affected by the drug layer D_2, 2) release of second drug occurred irrespective of the first drug (no partition of second drug towards the first drug layer occurs). Since the permeability of the drugs proportional to diffusion properties and its thickness, as tools to adjust drug release of both drugs the effect of amount of pore former (HPC JF) and the coating level for both coatings C_1 and C_2 were investigated.

Release of carbamazepine as model of poorly soluble drug could be adjusted to be faster, the same or slower than propranolol HCl as model of highly soluble drug (Fig. 46). At low permeable first coating (C_1 EC:HPC 80: 20 % w/w), release of propranolol HCl as first drug is almost independent of second coating (C_2) due to more dominant effect of C_1 for diffusion control and proved that lower permeability coating is the rate limiting of release.

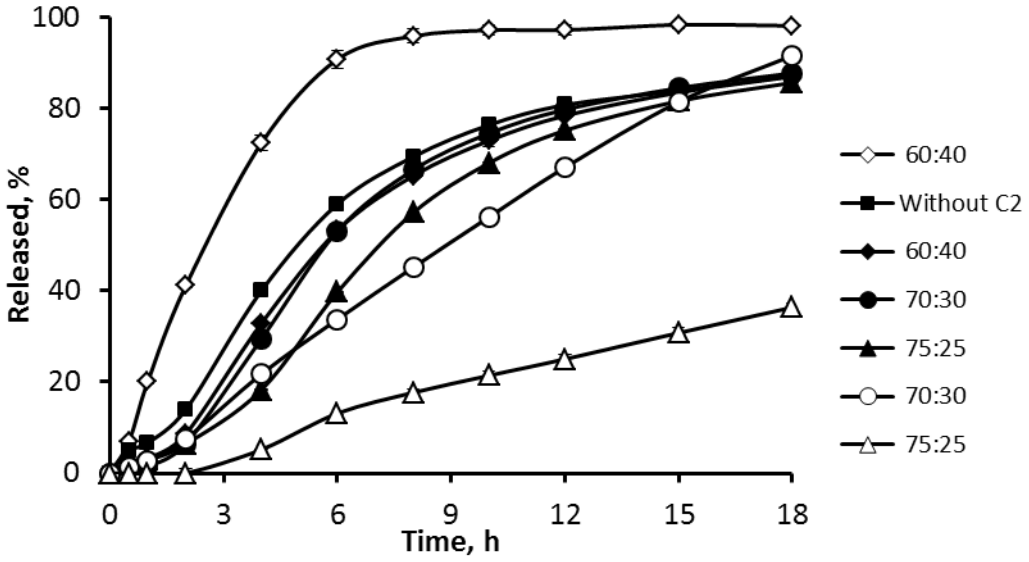


Figure 46. Release profiles of propranolol HCl (closed symbol) and carbamazepine (open symbol) as single drug pellet (without D_2 and C_2), and drug combination from multilayer coated pellets with different EC:HPC ratio in C_2 (C_1 EC:HPC 80:20, 10% coating level)

The release mechanism depends on the nature of the coating film and is mainly osmotic pumping for a semi-permeable film and mainly diffusion for a porous film (Marucci et al., 2010). Due to high permeability of C_2, propranolol HCl and carbamazepine as multilayer, pellets after dissolution study were swollen and no ruptures were visible (Fig. 47), confirming that the release mechanism was mostly by diffusion through the pores. This hypothesis was also supported by macroscopic picture of pellets

coated by low permeability coating EC:HPC 90:10 which show convection after 2 hour in release medium (Fig 48). The convective pulse was attributed to high osmotic pressure pellets due to less diffusion of dissolved drug out of the pellets. The result is in agreement with the study from Marucci et al. on films made of ethylcellulose (EC) and HPC which stated that for water soluble drugs, below the critical concentration the release mechanism is mainly osmotic pumping (Marucci et al., 2009 and 2010), while above it the diffusional contribution becomes increasingly more significant (Marucci et al., 2009).

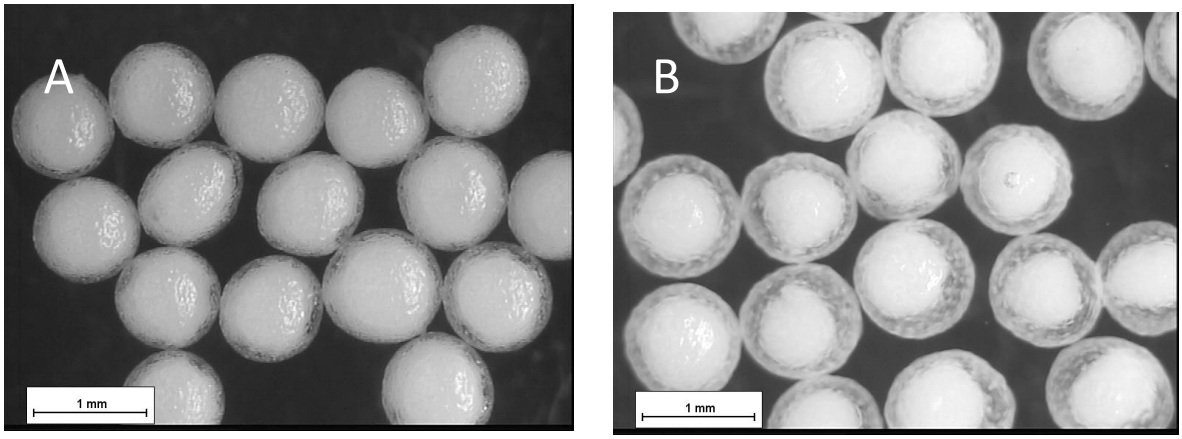


Figure 47. Macroscopic pictures from multilayer propranolol HCl – carbamazepine (C_1 EC:HPC 80:20, C_2 EC:HPC 70:30, 10% w/w coating level of C_1 and C_2) after A) 6 h and B) 18 h in release medium

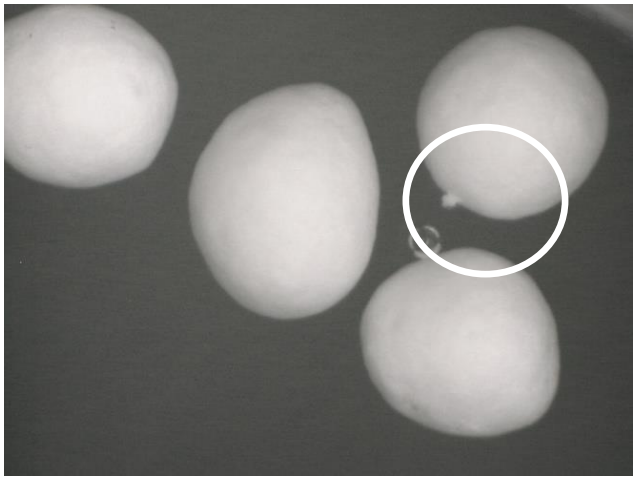


Figure 48. Convective release caused by osmotic pumping from multilayer pellet propranolol HCl – carbamazepine (C_1 EC:HPC 80:20, C_2 EC:HPC 90:10, 10% w/w coating level of C_1 and C_2) after 2 h in release medium

In order to obtain a particular desired release from ethylcellulose coated pellets in this system, different formulation and processing parameters can be varied, such as the type and amount of pore former and coating level. Applicability maps to improve flexibility in the formulation and to achieve variety of possible release (expressed as $t_{80\%}$) for drug 1 (D_1) and drug 2 (D_2) were prepared (Figs. 49 and 50). One approach was to use different HPC amounts in C_1 and C_2, while coating level of both coatings were kept at 10% w/w. HPC amounts for coating C_1 and C_2 could be read from the applicability map for particular $t_{80\%}$ values. On the Fig. 49, area A represents formulations for faster release of propranolol HCl, whereas area B is formulation for faster release of carbamazepine. Faster release of carbamazepine was attributed to higher permeability of the second coating (C_2) due to higher content of HPC. By using this worksheet, the formulation for pellets having propranolol HCl and carbamazepine released at the same time could be predicted as well (Fig 49, C).

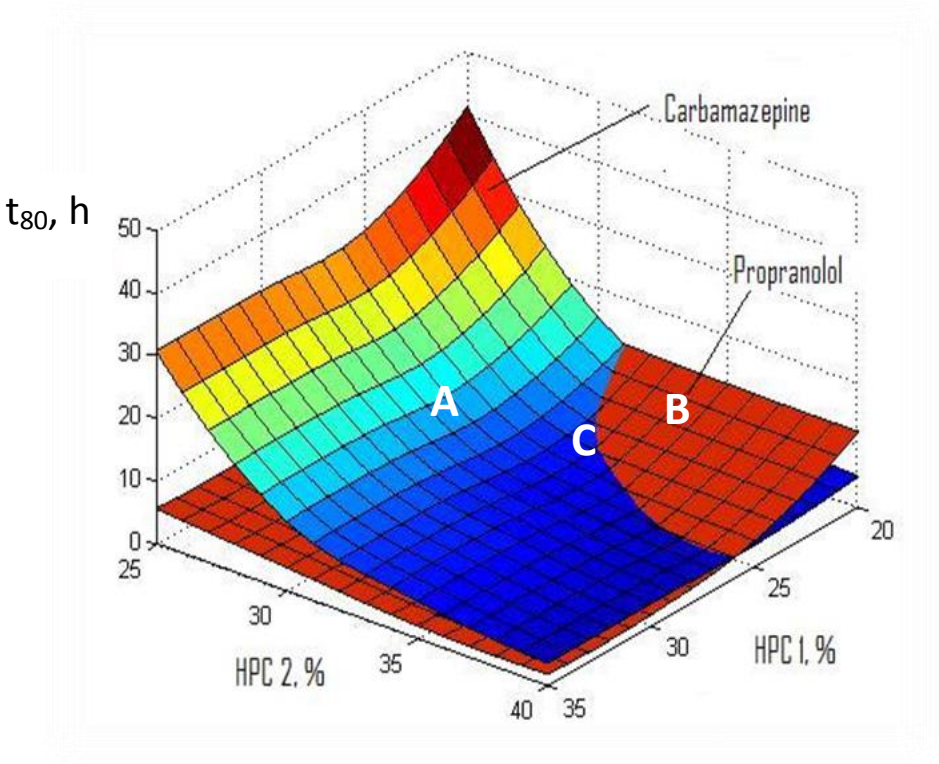


Figure 49. Applicability map for multilayered pellets system with particular release of propranolol HCl and carbamazepine by various HPC content in C_1 and C_2 (coating level at C_1 and C_2 10% w/w)

Next approach was performed by using the same film coating at C_1. Based on obtained applicability map, at C_1 20% HPC at 10% coating level, increase in coating level and HPC content of C_2 only have small effect on propranolol HCl release. Possible

explanation could be attributed to high drug solubility of propranolol HCl, for which release mechanism is less controlled by coating properties, but mostly by drug solubility. From Fig 50, area A represents formulations for faster release of propranolol HCl, area B for faster release of carbamazepine and C when propranolol HCl and carbamazepine were released in the same time. In summary, the obtained prediction sheet elaborating coating parameter affecting the releases enable to be used as applicability map to correlate formulation parameter such as HPC content and coating level for desired drug release of drug combination propranolol HCl and carbamazepine as models of combination drug with different solubilities from multilayer pellet system.

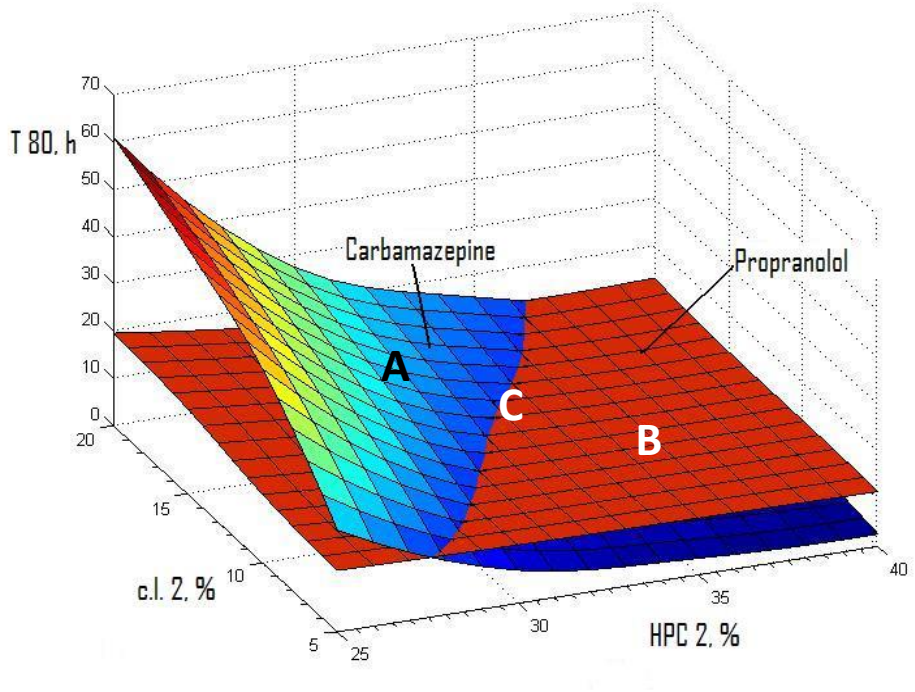


Figure 50. Applicability map for multilayered pellets system with particular release of propranolol HCl and carbamazepine using the same C_1 (EC: HPC 80:20, 10% w/w coating level)

Effect of drug solubility

In order to generalize the approach of multilayer pellets system, the experimental data set was extended to other combinations drugs. As comparison, the effect of solubility on release of drug from pellets with single drug as single layer pellet were studied. A power law distribution between drug release (presented as t_{80}) and drug solubility was found when single drug pellets coated with EC:HPC 70:30 and 75:25 (Fig. 51 A). According the previously studies, the release increased with increased drug solubility for

the same coatings (Ragnarsson et al., 1992; Neau et al., 1999; Sriamornsak and Kennedy, 2007). This was usually attributed to increased osmotic pressure resulted in higher tensile stress on the coating (Ragnarsson et al., 1992; Schultz and Kleinebudde, 1997) and consequently increased permeability of dissolved drug molecules (Hjärtstam et al., 1990). The plotted logarithmic of release rate (as $t_{80\%}$) of single drug coated by EC:HPC 70:30 and 75:25 pellets vs log drug solubility in exhibited linear relationship (Fig. 51B). In comparison with different coating, from Fig. 51 it can be concluded that for different permeability of coating, the relationship were the same with shifted value of asymptotes.

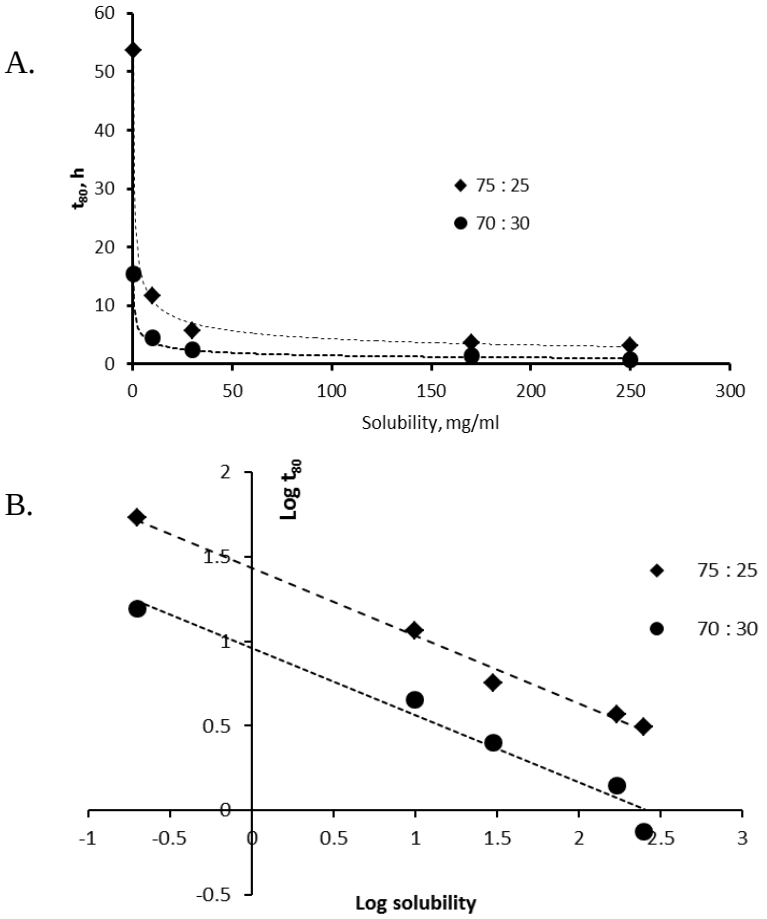
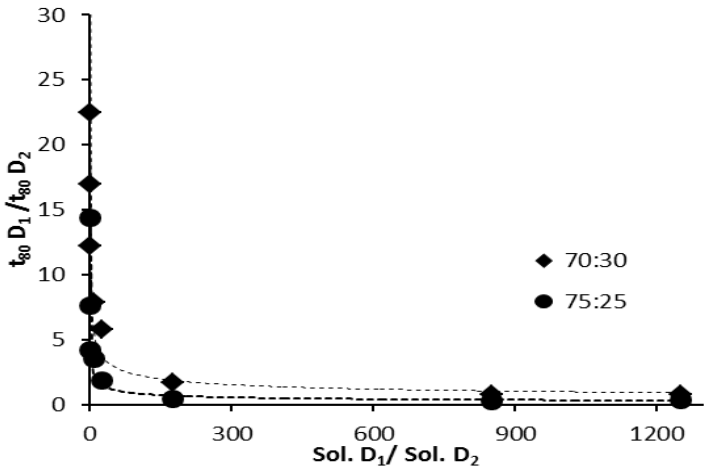


Figure 51. Relationship between release and solubility from single drug as single layer pellets A) as power law distribution and B) double logarithmic value at different coating (EC:HPC 70:30 and 75:25, 10% w/w coating level). The dashed lines represent the fit to power law distribution or linear trendlines.

Interestingly, when logarithmic value of release ratio ($t_{80\%}$ D_1/ $t_{80\%}$ D_2) from combination drug with different solubility coated with EC:HPC 80:20 as C_1 and 70:30 or 75:25 as C_2 (10% coating level C_1 and C_2) plotted against logarithmic value of solubility

ratio of D_1/D_2, linear relationship was also obtained with R^2 value 0.966, showing power law distribution (Fig. 52). Calculation of solubility ratio of each drug combination was shown in Table 5.

A.



B.

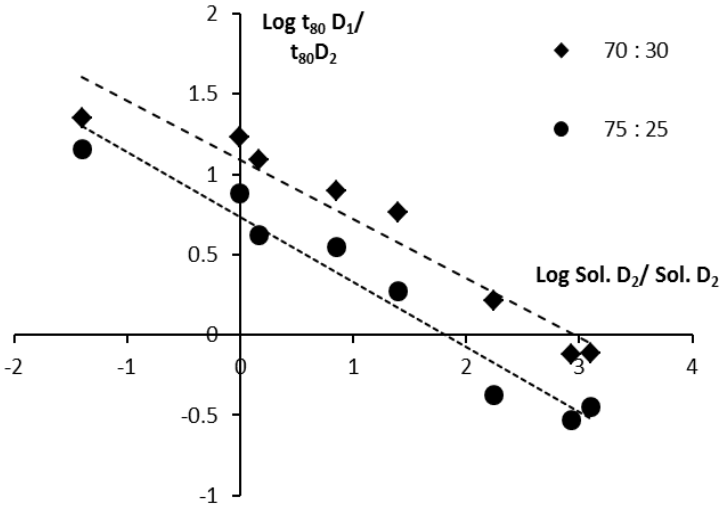


Figure 52.Relationship between release ratio and solubility ratio from multilayer pellets A) as power law distribution and B) double logarithmic value (C_1 EC:HPC 80:20, C_2 EC:HPC 70:30 or 75:25, 10% w/w coating level of C_1 and C_2). The dashed lines represent the fit to power law distribution or linear trendlines.

Since the permeability of the drugs is proportional with diffusion properties and its thickness, simplified equation was used to quantify the effect of formulation on drug release and assumed as apparent permeability of film coating, which was calculated by

equation shown in section 2.2.3.4. Release of drug from multilayer pellets was a result from complex process which include drug dissolution rate and drug permeability of each film coating (C_1 and C_2). Based on assumption that at low permeable coating of C_1 (HPC 20%) the release of D_2 was only affected by permeability of second coating (C_2), the plotted apparent permeability vs release after normalized by its solubility (Fig. 53) can be described as following equation :

$$y = 566.66x^{-1.227} \qquad \text{Eq. 1}$$

y = apparent permeability of C_2

x = release of drug (t_{80}) normalized by solubility

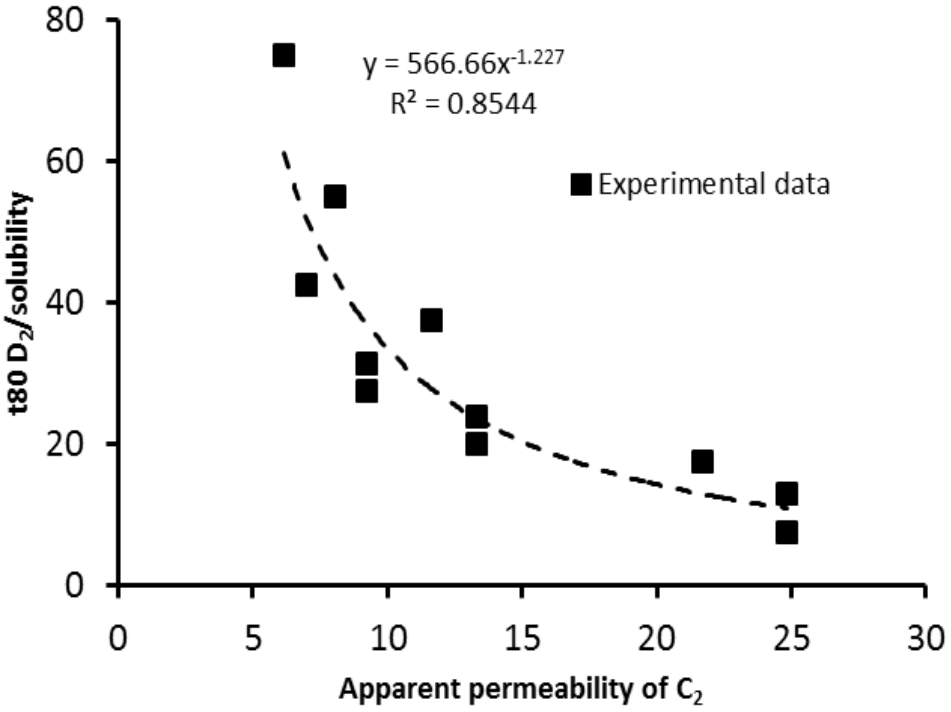


Figure 53. Effect of apparent permeability of C_2 on release of D_2 normalized by its solubility values from multilayer pellets (D_1 propranolol HCl, D_2 carbamazepine, C_1 EC:HPC 80:20, 10% coating level of C_1 and C_2). The dashed lines represent the fit to power law distribution trendlines.

One approach to formulate coating system with certain releases of two drugs as multilayer pellets can be predicted by following steps:

- Determination the desired release (as $t_{80\%}$) of drugs (D_1 and D_2) normalized by its solubility
- Based on Fig. 53 and Eq. 1, calculated apparent permeability for second coating (C_2) of D_2 can be determined
- With assumption that release of D_1 was affected either by C_1 and C_2, required apparent permeability of first coating (C_1) can be predicted by using the obtained curve (Fig. 53) and applicability map (Fig. 54).

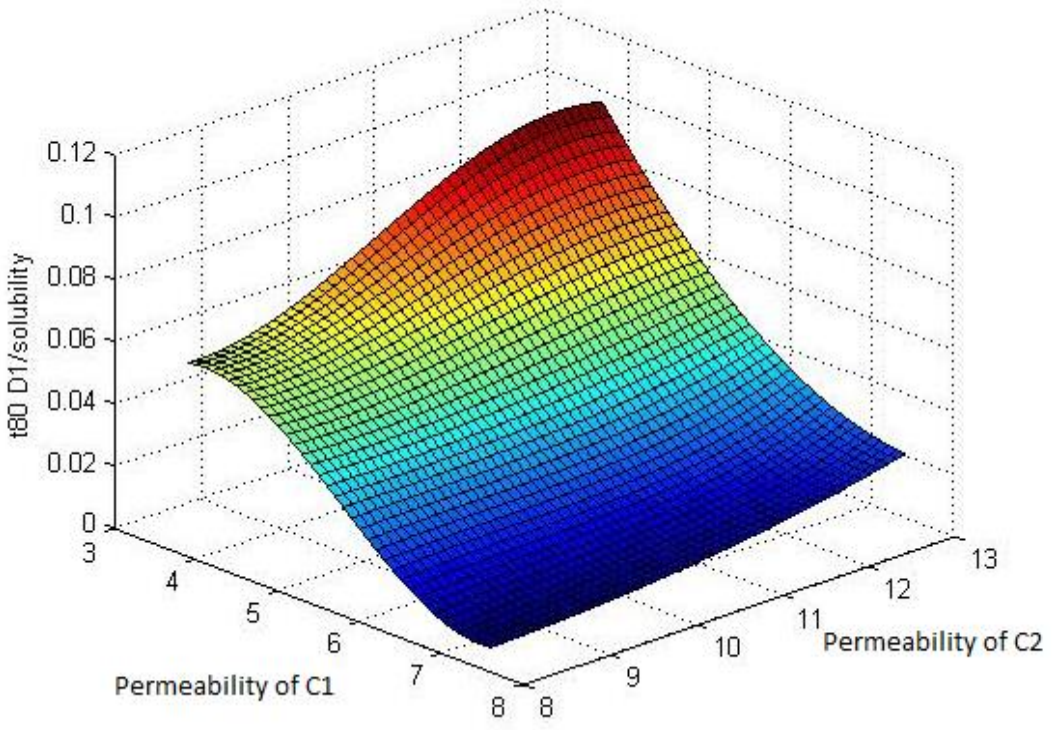


Figure 54. Applicability map of D_1 release normalized by its solubility values with apparent permeability of both coating 1 (C_1) and coating 2 (C_2)

To describe formulation of multilayer pellets, coating formulation of C_1 and C_2 can be elaborated. However, the formulations which can be performed are generally restricted. For instance, too low and too high coating levels must be avoided to prevent accidental film rupturing (and subsequent dose dumping) and too long processing times. Based on Eq. 1, Fig 53 and Fig. 54 the proposed formulation can be explained as follows:

- Select HPC content according to D_2. *Reasonable range : 0-40%*
- Calculate coating level C_2 using apparent permeability value of C_2 (from curve). *Reasonable range: 5-20%*

- By keeping the same HPC , calculate coating level C_1 using apparent permeability value of C_1 (from sheet).
- If not in preferable range the calculation can be changed using different HPC_2 content

Effect of drug loading

To study the effect of drug loading on release of drugs from multilayered pellets, calculation of drug loading ratio of each drug combination shown in Table 6. Increase in drug loading of propranolol HCl resulted in slower release (Fig 55, A) due to the decreased in surface area/volume ratio (8.161 cm^{-1} for 5% DL and 7.097 $cm^{-1}$for 35% DL). The result is in agreement with previously published study (Ueda, et al., 1994). Release of propranolol HCl from multilayered pellet was not affected by carbamazepine's drug loading, except for very low loading of propranolol (5-35% drug loading, Fig 55, A). Carbamazepine was strongly affected by drug loading, either by drug loading of carbamazepine itself or propranolol HCl as first drug. Increase of drug loading led to decrease in carbamazepine release due to changes in diffusion path (Fig. 55, B).

When expressed as drug loading ratio in multilayer pellets, increase in loading dose ratio (D_2/D_2), lead to increase in propranolol HCl release, and accordingly, decrease in carbamazepine release. At certain point, the release are the same (drug loading ratio = 1.58). Above that value, propranolol HCl released slower than carbamazepine (Fig. 56).

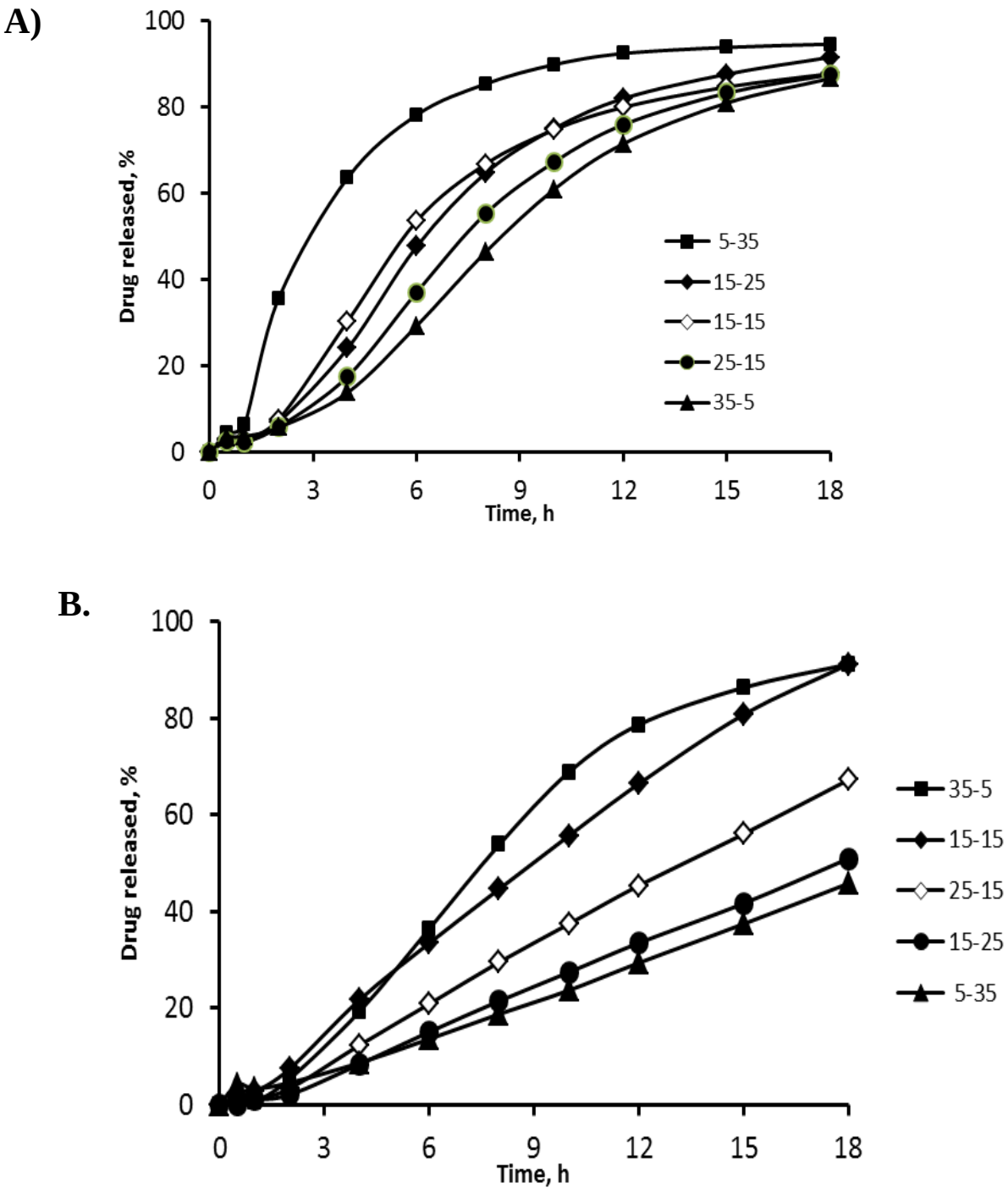


Figure 55. Effect of different drug loading of propranolol HCl – carbamazepine on release of A) propranolol HCl and B) carbamazepine from multilayer pellets (C_1 EC: HPC 80:20, C_2 EC: HPC 70:30, 10% coating level of C_1 and C_2)

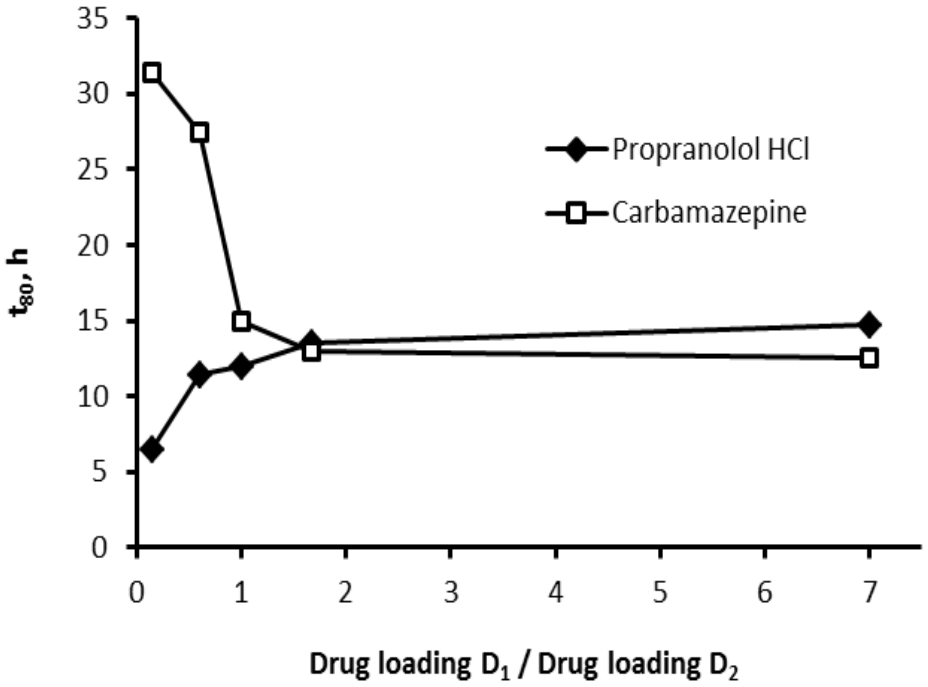


Figure. 56. Effect of drug loading ratio of propranolol (D_1) and carbamazepine (D_2) on release (as t_{80}) from multilayer pellets (C_1 EC: HPC 80:20, C_2 EC: HPC 70:30, 10% coating level of C_1 and C_2)

3.3.3 Conclusions

By employing multilayer pellet system, the release of two drugs of different solubility can be adjusted to give one drug released faster over the other or both are released in the same time by using obtained applicability map. Relationship between release of drug vs solubility either from single drug or multilayer with drug combination showed power law distribution. Using different permeability of coating, the relationship were the same with shifted value of asymptotes. The obtained applicability map can be used to design coating formulation of particular combination drug with different solubility owing desired released.

Decrease in loading dose of carbamazepine (D_2), expressed as higher drug loading ratio, lead to increase in release (lower $t_{80\%}$) of carbamazepine due to higher surface area/dose ratio of carbamazepine. Accordingly, increase in drug loading of propranolol HCl (D_1), expressed as higher drug loading ratio resulted in slower release of propranolol HCl (higher $t_{80\%}$) due to decrease in surface area.

3.4 Quantification of the effect of porogen on release from single and multilayer ethylcellulose-coated pellets as combination drug

3.4.1 Introduction

Despite their increasing popularity, only few drug combinations are formulated as pellet dosage form. Mostly, in marketed products, pellets containing one drug are blended with batches containing the other drug and filled in hard gelatin capsules. Pellets with different release profiles can be incorporated within one dosage form, offering many advantages including a greater flexibility during formulation development, reduced amount of excipient thus higher drug loading and lower unit cost (Ghebre-Sellassie 1989; Anschütz 2009).

Coated pellets are frequently used for oral controlled drug delivery (Ozturk et al., 1990; Fukumori, 1997; McGinity, 1997; Muschert et al., 2009). Compared to coated tablets and capsules they avoid the all-or nothing effect of single unit dosage forms and provide less variable transit times within the gastro intestinal tract (Digenis, 1994; Karrout et al., 2009). Release of the drugs from coated pellets were adjusted by applying different permeability of film coating.

Ethyl cellulose (EC) is a commonly used film-forming agent, because it has good film-forming properties and is generally regarded as nontoxic and non-allergenic (Marucci et al., 2009; Hjartstam et al., 1998). Membranes made of pure ethylcellulose are water insoluble with good mechanical properties, but have poor water permeability. In order to modify the release from these films, different ratios of water soluble pore-forming agents, such as hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) were added (Marucci et al., 2009; Hjartstam et al., 1998, Sakellariou and Rowe, 1995b). HPC has low toxicity and has good film-forming properties (Marucci et al., 2009). Films composed of ethylcellulode and HPC have been studied with regard to both structure and permeability. Effect of HPC as pore former in conventional coated pellets has been extensively study, however, the study on content of HPC affecting the release from ethylcellulose coated multilayer pellets with combination drugs of different solubility has not been done yet.

A number of studies have been devoted to mathematically describe the diffusional drug release from controlled release products. Different models have been developed to describe the drug release from coated multiparticulates (Siepmann, 2012; Frenning et al.,

2003; Haddish-Berhane et al., 2006; Muschert et al., 2009 ; Marucci et al., 2008). Drug release models can be classified as empirical models or mechanistic models. An empirical approach is based on the experimental behaviour of the system studied. No physical mechanisms are considered in the description of the problem. These kinds of models can often mimic the behaviour of the actual system very well, especially if an appropriate number of parameters are included in the model. However, these models serve the same purpose as any mathematical polynomial with sufficient properties to fit the experimental data (Kaunisto et al., 2011).

The objective of the present paper was to study the effect of HPC as porogen on drug release from ethylcellulose coated single layer pellets and extend the application of the findings to more complex systems (multilayer pellets) as drug combination. The contribution of other common formulation variables such as coating level was also studied.

3.4.2 Results and discussions

A number of studies have been devoted to mathematically describe the diffusional drug release from controlled release products and different models have been developed to describe the drug release. However in most cases only dimensional differences can be predicted, whereas effects from formulation variables are often neglected and summarized in an apparent diffusivity *D* (Siepmann 2012).

3.4.2.1 Conventional EC/HPC coated single drug pellets

Porogen content

A film coating with pore former can be regarded as a heterogeneous binary system, and as function of their relative volume ratio. One or both components constitute a percolating cluster, generating a continuous phase through the film. Percolation of the pore former, or better of the pores in the wetted film coating, is associated with a significant increase in water and drug molecule diffusivity. Hydrophilic polymers such as HPMC and HPC are commonly incorporated as porogens into impermeable ethylcellulose film coatings to accelerate the drug release from coated dosage forms by increasing the porosity of the diffusion barrier (Marucci et al., 2009; Hjartstam et al., 1998, Sakellariou and Rowe, 1988 and 1995).

Accordingly, propranolol HCl release could be accelerated upon incorporation of HPC (Fig. 57). The accelerating effect was low for HPC contents below 20%, whereas a marked increase of the release was obtained between 20 and 30%.

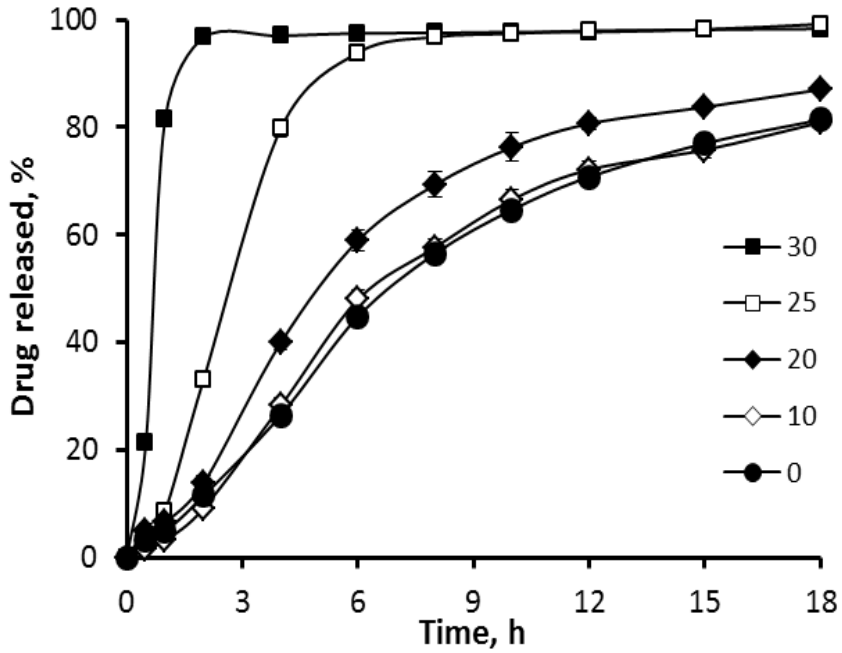


Figure 57. Effect of HPC content (% w/w) as pore former on release profile of propranolol HCl from conventional ethylcellulose coated drug (single layer) pellets

Plotting the drug release (expressed as $t_{80\%}$) of the individual formulations vs. the corresponding HPC content of the film coatings revealed a sigmoidal pattern (Fig. 58), reasonably well represented by a cumulative distribution normal:

$$f(x) = \int_{-x}^{x} N(\mu,\sigma)\, dx \qquad \text{Equation 2}$$

This behavior is in perfect agreement with the probabilistic nature of distribution phenomena of pores according to the percolation theory. According to percolation theory, a cluster is defined as a group of neighboring occupied sites in the lattice and is considered infinite or percolating when it extends from one side to the rest of the sides of the lattice to percolates the whole system (Stauffer and Aharony, 1992). A film coating with pore former can be regarded as a heterogeneous binary system, and as function of their relative

volume ratio, one or both components constitute a percolating cluster, generating a continuous phase through the film.

The extremes of the distribution reflect the highest as well as the lowest achievable $t_{80\%}$ at 0% and 100% HPC content, the latter approximating immediate release ($t_{80\%}$ = 0 h). The correlation indicated in Fig. 58 can therefore be described by the following equation:

$$f(t_x) = t_{x\,max} * \int_0^{HPC} N(\mu, \sigma)\, dHPC$$

Equation 3

t_x = time to release x % drug (h)
$t_{x\,max}$ = maximum time to release x % drug (0 % HPC) (h)
HPC = amount of HPC in coating (% w/w)
μ = mean value of pore-former content (% w/w)
σ = standard deviation (SD) of the curve (% w/w)

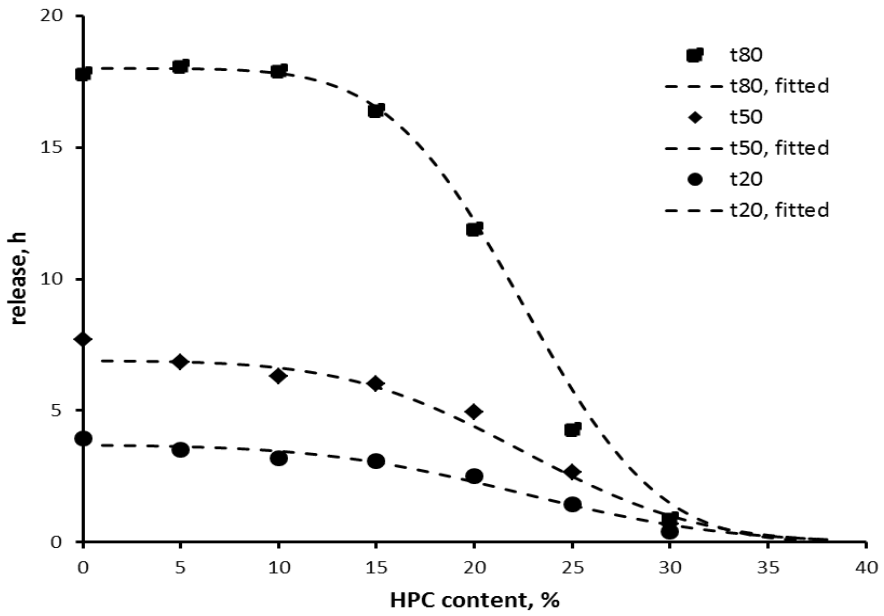


Figure 58. Effect of HPC content as pore former on release of propranolol HCl from EC coated pellets at different release time points. The dashed lines represent the fitted value to cumulative normal distribution functions

Plotting the times to release different proportions of drug ($t_{80\%}$, $t_{50\%}$ and $t_{20\%}$) showed that the distribution function of the model is valid for the entire profile in the release phase for the mean values are the same (22.5 % w/w, Fig. 58). Increase in standard

deviation values (5.4%; 7.15 and 8.2% of $t_{80\%}$, $t_{50\%}$ and $t_{20\%}$ respectively) were due to lower $t_{80\%max}$ of each curve.

Hence, the mathematical model to describe the effects of HPC content on propranolol HCl release (as $t_{80\%}$) from conventional pellets can be written as follows:

$$f\,(t_{80\%}) = 18 * [1 - \int_0^{HPC} N(22.5, 5.4)\,]\,dHPC$$

Equation 4

Coating level

The release (expressed as $t_{80\%}$) plotted as a function of coating level showed linear correlation (Fig. 59). Increasing the coating level resulted in decreased release of propranolol HCl due to higher thickness of the coating and therefore lower water inflow and higher amount of solid drug to dissolve (Marucci et al., 2008).

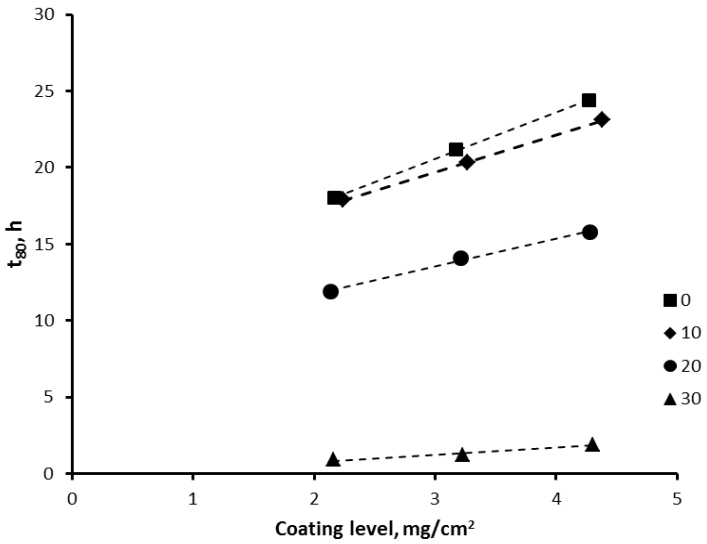


Figure 59. Effect of coating level on release of propranolol HCl from conventional EC coated pellets with 0-30% HPC content as pore former. The dashed lines represent the fit to linear trendlines.

Plotting drug release vs. HPC content for different coating levels revealed the same sigmoidal relationship (identical mean and standard deviation, Fig. 60). Hence, drug release of different coating level using different HPC content can be predicted, connecting both relationships.

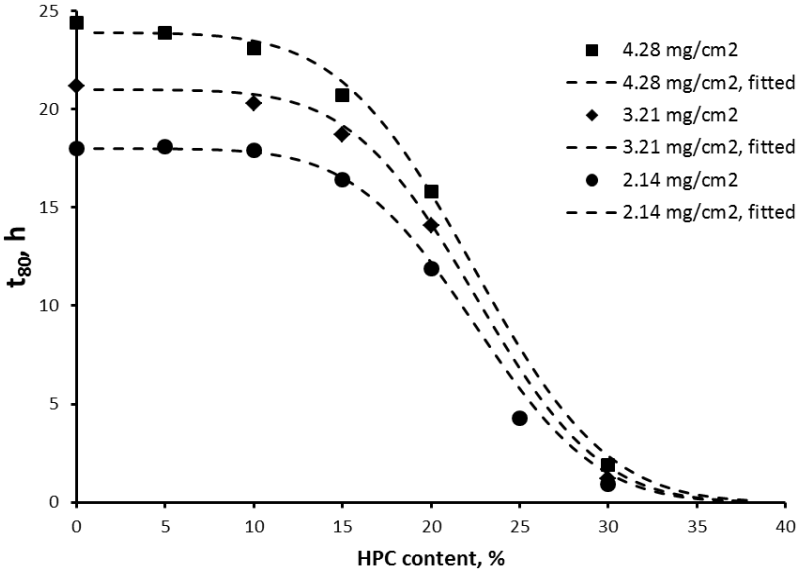


Figure 60. Effect of HPC content as pore former on release of propranolol HCl from EC coated pellets at different coating level. The dashed lines represent the fitted value to cumulative normal distribution functions.

3.4.2.2 EC/HPC coated multilayer pellets

The quantitative basis of the findings was extended to more complex systems (multilayer system) as drug combination containing two drugs of different drug solubility. The drug with the higher solubility was coated with less permeable coating and consecutively layered with the less soluble drug which coated with highly permeable coating to allow release profile adjustment according to the solubility.

Release of propranolol HCl as highly soluble drug

At HPC content >15% w/w, release of propranolol HCl from single layer were the same with those from multilayer pellets (Fig. 61), while at lower HPC content, release from multilayer pellets were slower due to more barrier of film coating resulting higher release retardation. Hence, a $t_{80\%\ max}$, mean and standard deviation value of 19.3%; 21.5% and 5.6% respectively were obtained for propranolol HCl release from multilayer pellets (D_2 carbamazepine, C_2 25-40% HPC, coating level < 3.21 mg/cm^2).

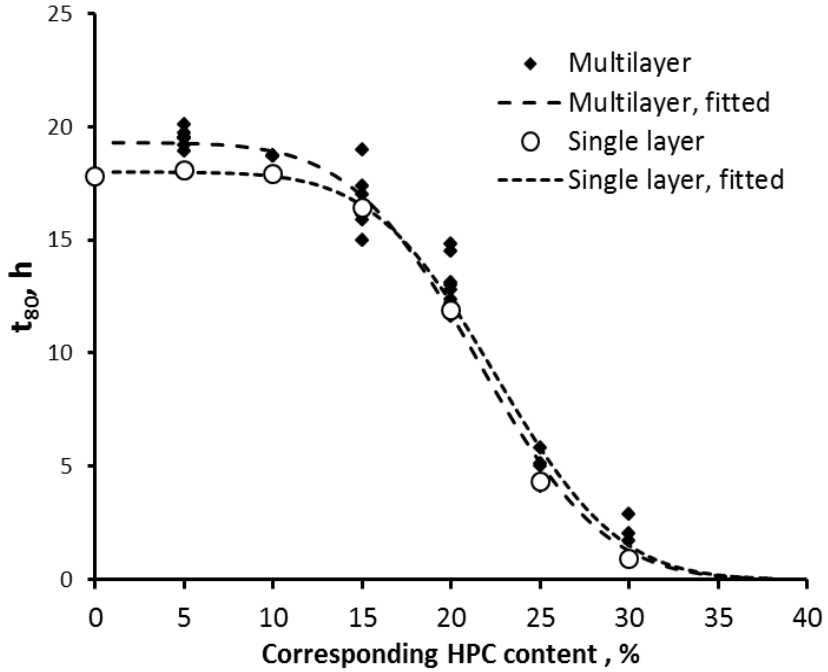


Figure 61. Effect of HPC content as pore former on release of propranolol HCl from single layer pellet (open symbol, coating level ±2.14 mg/cm^2) and multilayer pellets (closed symbol, D_1 propranolol HCl, D_2 carbamazepine, C_2 25-40% HPC, coating level of C_1 and C_2 < 3.21 mg/cm^2). The dashed lines represent the fitted value to cumulative normal distribution functions.

According to the apparent film coating permeability, three different conditions have to be distinguished:

- Permeability of C_1<C_2:

  Drug release is dominated by C_1. The contribution of C_2 to $t_{80\%}$ is small ($t_{80\%}$ (C_1)> $t_{80\%}$ (C_2), Fig. 62, A). The resultant $t_{80\%}$ is composed of the individual t_{80}s of the single layers, described as follows:

$$t_{80\%\ multilayer} = t_{80\%\ C1} + t_{80\%\ C2} \qquad \text{Equation 5}$$

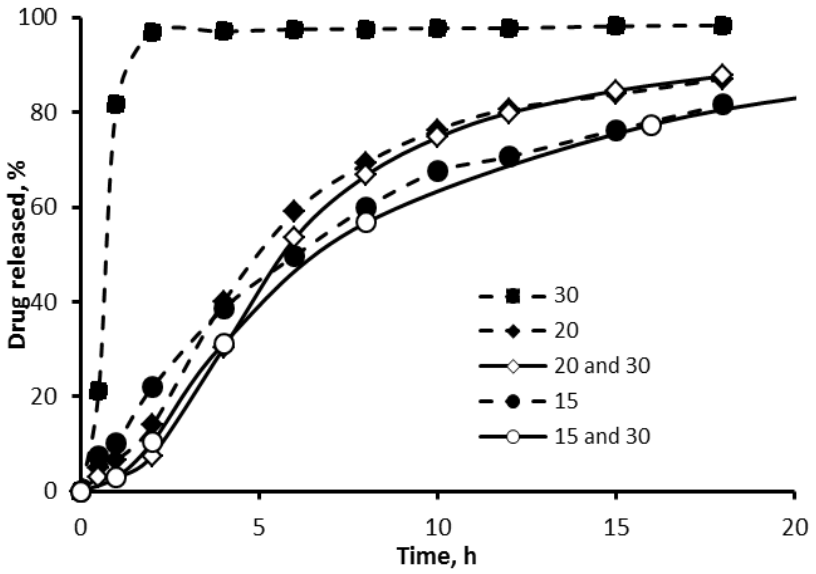
  By introducing Equation 3, the release from multilayer (ML) pellets can be described by following equation 6:

$$f(t_{80\%})_{ML} = [t_{80\%\ max} * \left(1 - \int_0^{HPC} N(\mu,\sigma)\right)\ dHPC]_{C1} + [t_{80\%\ max} * \left(1 - \int_0^{HPC} N(\mu,\sigma)\right)\ dHPC]_{C2}$$

- Permeability of $C_1 > C_2$:

  In this case, the kinetic and profile of release entirely changed (Figure 62, B). Higher permeability of first coating resulted in fast release of propranolol HCl after a prolonged lag time. Probably dissolution medium accumulated in the core and caused higher amounts of drug to dissolve (Marucci, 2008). Therefore, a steeper concentration gradient for drug diffusion was built and propranolol HCl was released faster from multilayer than single layer pellets with the same coating permeability (Fig. 62, B).

A)



B)

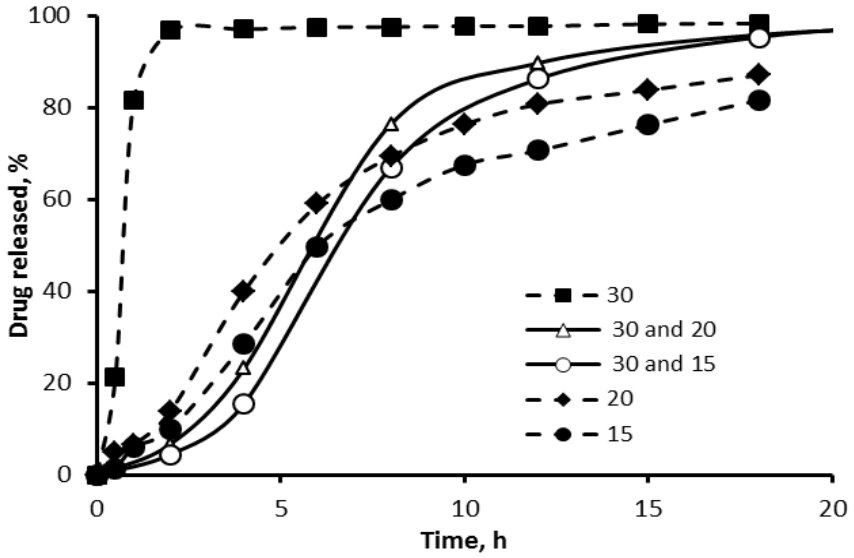


Figure 62. Effect of HPC content as pore former on release of propranolol HCl from single pellets (dashed lines) and multilayer pellets (continuous lines) comprising D_1 propranolol HCl and D_2 carbamazepine. A) $C_1 < C_2$ and B) $C_1 > C_2$ at coating level C_1 2.04± 0.06 mg/cm^2 and C_2 2.41± 0.05 mg/cm^2

In some cases, both layers of coatings contribute to drug release retardation from multilayer pellets. Besides an increased coating thickness also a decreased surface area to volume ratio compared to single layer pellets has to be considered for the outer coating. The resultant release from multilayer can be predicted by simple addition of $t_{80\%}$ of each single layer pellets (Eq. 6, Table 7).

Table 7. Propranolol HCl release (as $t_{80\%}$) from ethylcellulose coated single and multilayer pellets experimental and calculated values

		experimental	calculation	Data base of calculation		
HPC/coating level in C_1	HPC/coating level in C_2	$t_{80\%}$	($t_{80\%}$ C_1 + $t_{80\%}$ C_2)	$t_{80\%}$ C_1	$t_{80\%}$ C_2*	$t_{80\%}$ C_1 / $t_{80\%}$ C_2
25/10	25/10	6.05	8.71	4.30	4.41	0.98
	30/15	6.00	6.31	4.30	2.01	2.14
	30/20	6.90	6.79	4.30	2.49	1.73
	35/15	5.15	4.62	4.30	0.32	13.43
	35/20	5.60	4.79	4.30	0.49	8.78
20/10	25/15	18.05	18.93	12.05	6.88	1.75
	25/20	19.50	20.15	12.05	8.10	1.48
	30/15	14.05	14.04	12.05	1.99	6.05
	30/20	14.50	14.42	12.05	2.37	5.08
	35/15	12.20	12.33	12.05	0.28	43.04
	35/20	12.80	12.53	12.05	0.48	25.10

*) corrected calculation by coating thickness as multilayer pellets

With regard to release adjustment for combination of drugs with different solubility, apparent permeability of coating should be simplified into the conditions where release of first drug can be quantified based on permeability of each coating layer such as permeability in $C_1<C_2$ or $C_1=C_2$, release independent of drug layer D_2, and do not influence the release of D_2.

Propranolol HCl (D_1) pellets were also over-coated with caffeine (D_2) to evaluate the effect of second drug type on its release. Similar profiles of propranolol HCl release were obtained, thus implying independence of the type of second drug (Fig. 63).

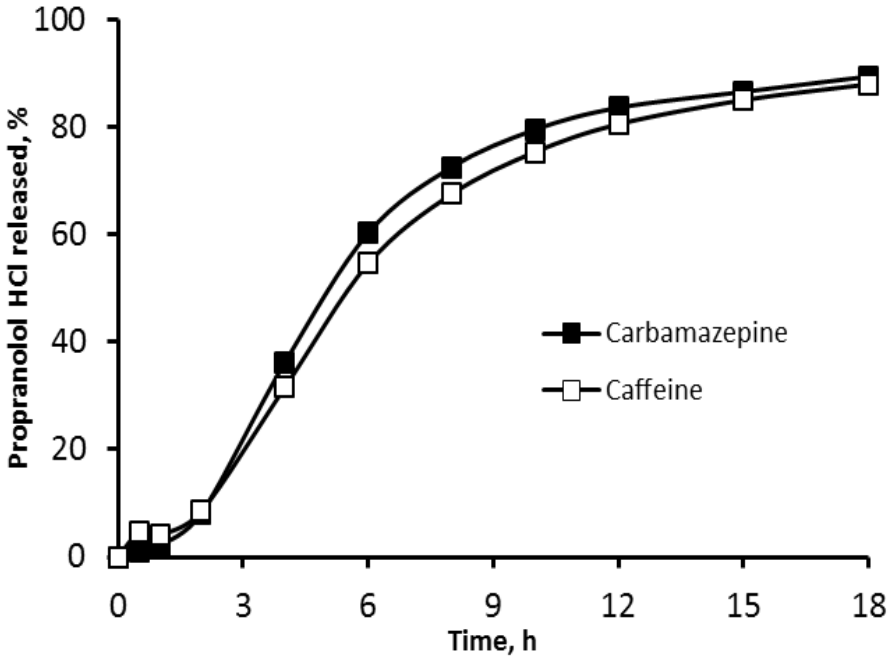


Figure 63. Drug release of propranolol HCl from multilayer pellets (C_1 20% HPC, C_2 30% HPC, 2.40 mg/cm^2 coating level) with different second drug layer (D_2)

Release of carbamazepine as poorly soluble drug model

Carbamazepine release from single and multilayer pellet are the same (Fig. 64). The increase of core diameter once carbamazepine applied onto propranolol HCl coated pellet as D_2 did not affect the release. In comparison with effect on propranolol HCl release as model of highly soluble drug (as D_1), plotted carbamazepine release vs. HPC content showed the same sigmoidal relationship (Fig. 65). Considering that the distribution function of the model is valid for the entire profile in the release phase (Fig. 58), due to low solubility, carbamazepine release can be represented as $t_{60\%}$. Values of $t_{60\%\ max}$, mean and standard deviation of 71%; 18% and 9.4%, respectively was obtained. High value of $t_{60\%\ max}$ was attributed to low solubility of drug.

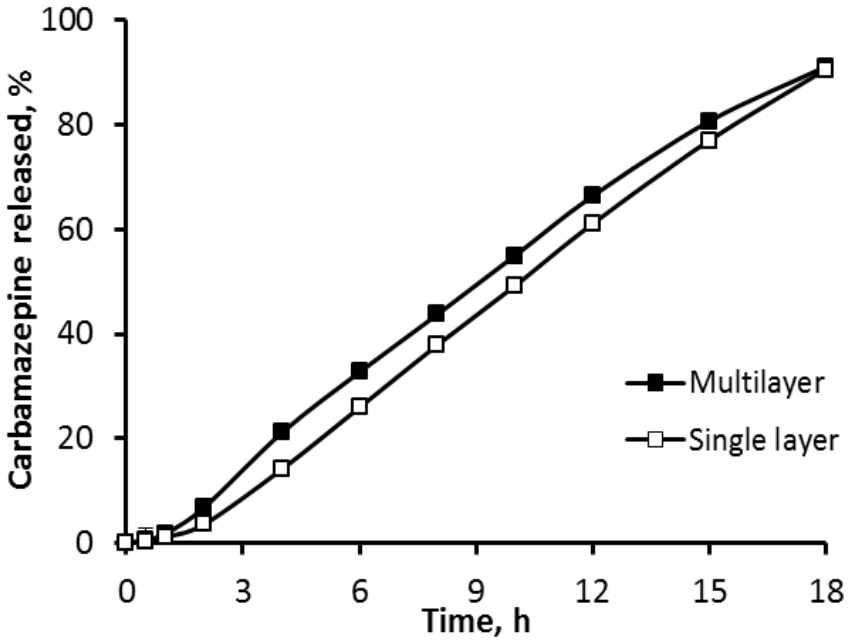


Figure 64. Drug release of carbamazepine from single layer (30% HPC, 2.13 mg/cm^2 coating level) and multilayer pellets (C_1 20% HPC, C_2 30% HPC, 2.42 mg/cm^2 coating level)

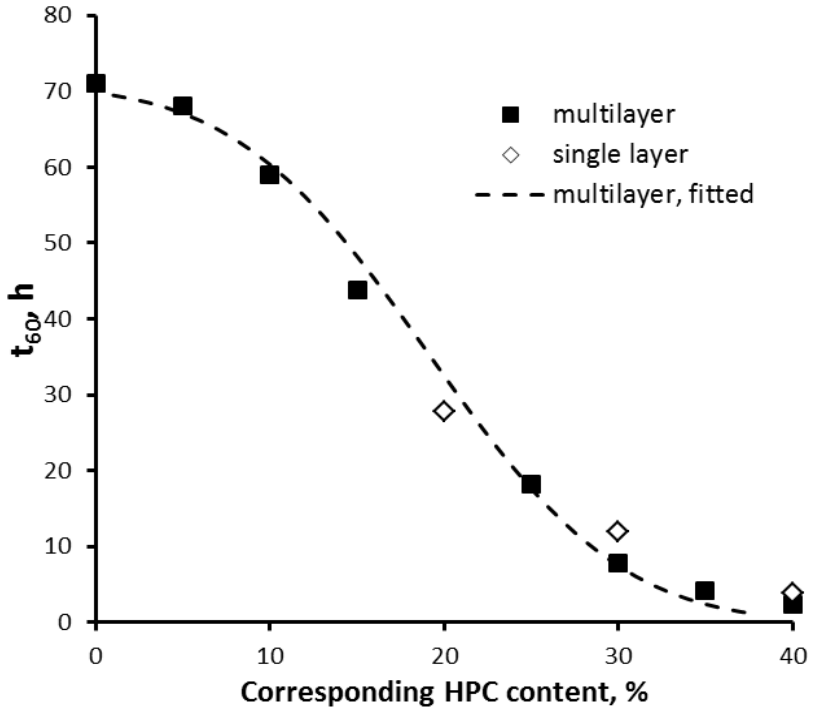


Figure 65. Effect of HPC content as pore former on release of carbamazepine from single layer (30% HPC, 2.13 mg/cm^2 coating level) and multilayer pellets as D_2 (D_1 propranolol HCl, C_1 20% HPC, coating level C_2 2.42 mg/cm^2). The dashed lines represent the fitted value to cumulative normal distribution functions.

3.4.3 Conclusions

Drug release acceleration of ethycellulose : HPC coated pellets in dependence of HPC content as porogen and exhibited a sigmoidal pattern reasonably well represented by a cumulative normal distribution function. The distribution function of the model is valid for the entire profile in the release for their mean values are the same. By connecting linear relationship of different coating levels, drug release of pellet using different HPC content at different coating level can be predicted.

The basis of the findings can be applied to multilayer pellet system either for first drug (high solubility) or second drug layer (low solubility) indicating the feasibility to extend the mathematical model to predict effect of HPC as porogen in more complex systems or to drugs of different physico-chemical properties.

Supplementary data

The feasibility of the model was extended to be applied on different drug type as second drug from multilayer pellet system, therefore release model of caffeine was also developed. Plotting drug release of caffeine vs. HPC content either as single layer or multilayer layer pellets (D_1 propranolol HCl, C_1 20% HPC, coating level C_1 2.04 mg/cm^2) revealed sigmoidal relationship (Fig. 66).

The value of $t_{80\%\ max}$, mean and standard deviation of 17.5%; 18.9% and 5.7% respectively were obtained for caffeine release from single layer pellets and 22.5%; 18% and 8% respectively from multilayer pellets (D_1 propranolol HCl, C_1 20% HPC, coating level of C_1 and C_2 < 3.21 mg/cm^2).

Release of caffeine from multilayer pellets at lower HPC content were slower than that from single drug pellets (Fig. 66). The possible explanation for this retardation is the seal coating effect of inner layer pellets. Pellet core of caffeine as single drug pellet was NP sugar which is highly osmotic agent while those of caffeine as multilayer drug combination pellets were EC/HPC 80/20 coated propranolol HCl pellets. With seal coating effect of EC/HPC film, release of caffeine from multilayer pellets were slower due to lower osmotic pressure gradient inside the pellets. The same release of caffeine from single and multilayer pellets at higher amount (>15% w/w) of HPC (Fig. 66), was attributed to dominating effect of diffusion in C_2 due to high content of HPC as porogen.

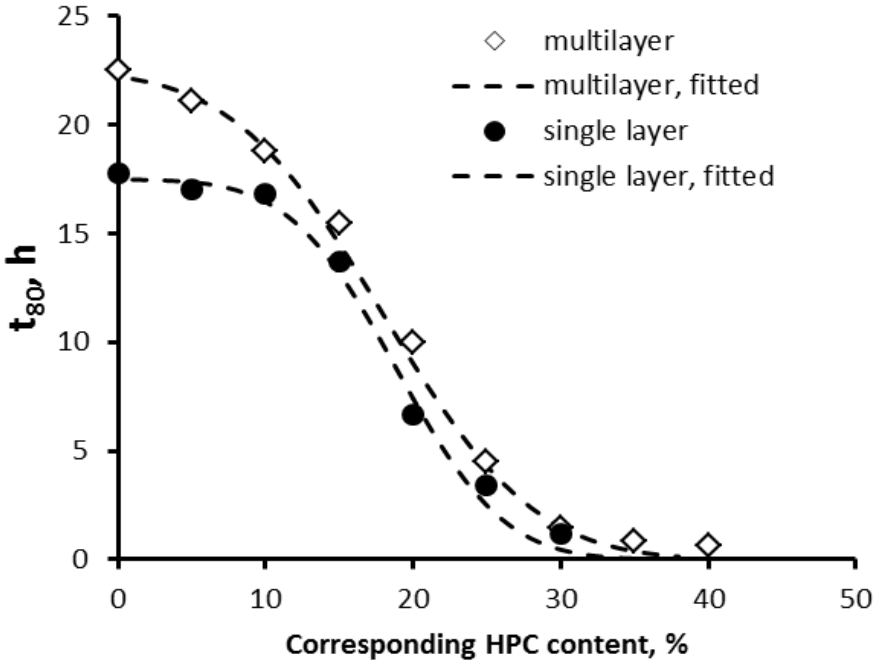


Figure 66. Effect of HPC content as pore former on release of caffeine from single layer pellet (closed symbol, coating level ±2.04 mg/cm^2) and multilayer pellets (open symbol, D_1 propranolol HCl, C_1 20% HPC; coating level of C_1 and C_2 < 3.21 mg/cm^2). The dashed lines represent the fitted value to cumulative normal distribution functions.

Type of pore-former

Basic finding on release prediction using HPC JF as porogen can be successfully applied for prediction of release using different type of HPC. Plotted release of caffeine as D_2 vs HPC content using HPC LF as lower viscosity of HPC revealed sigmoidal relationship as well as from HPC JF (Fig. 67). The value of $t_{80\%\ max}$, mean and standard deviation of 22.5%; 18% and 7.7% respectively were obtained for caffeine release from multilayer pellets using HPC JF and 18.5%; 18.7% and 7.6% respectively when HPC LF was used (D_1 propranolol HCl, C_1 20% HPC, coating level of C_1 2.11 mg/cm^2).

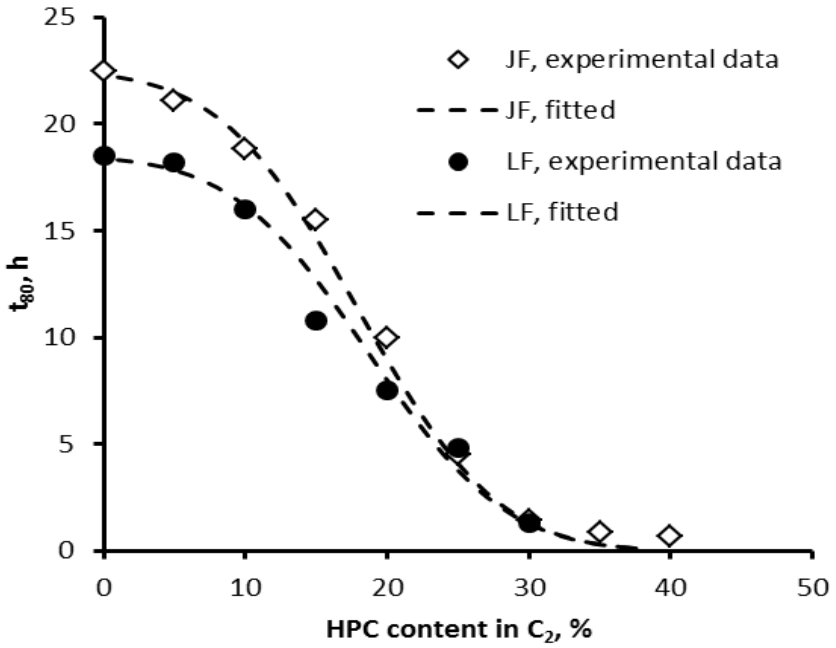


Figure 67. Effect of HPC content as pore former on release of caffeine from multilayer pellets using different type of HPC (D_1 propranolol HCl, C_1 20% HPC, coating level of C_1 2.11 mg/cm^2). The dashed lines represent the fitted value to cumulative normal distribution functions.

The increase on release from pellet coated with EC/HPC LF was due to lower viscosity value, resulted in faster leaching of HPC once the pellets introduced to the media. Viscosity of HPC used in this experiment at 5% w/w water shown in the table:

Table 8. Viscosity of different type of HPC

Type	Viscosities (cPs)*
JF Pharm	150-400
LF Pharm	75-150

*) Klucel Product and Technical information, 2001

The shift of release model only existed at HPC content lower than 25% (Fig. 67). However, possible explanation for this is that the film of both type of coating at above 25% HPC content were more dominant due to highly permeability of coating associated with high content of HPC. The amount of HPC was more dominating for diffusion on release of caffeine than viscosity of HPC. At lower content, viscosity of HPC still have an effect, hence caffeine from pellets with lower viscosity of HPC released faster.

4. Summary

4.1 Release adjustment of drug combination with different drug solubility from matrix tablet systems

Formulation issues of drug combination in one dosage form could be due to different solubility of drug which will give different release profile. Higher solubility of the drug generally leads to faster release because of their high diffusional driving force, while that of poorly soluble drug is fully controlled by erosion since it is the predominant release mechanism.

The objective of present study is therefore to adjust the release of two drugs of different solubility in drug combination as matrix tablets for controlled release drug delivery.

Employing direct compression method, irrespective to type of polymers, release of propranolol HCl was much faster than carbamazepine due to solubility differences. The modified method of simple mixing of EC with HPMC, followed by direct compression method, resulted in slower release of propranolol HCl. This retardation was attributed to increase in total polymer loading after the presence of EC. Slower release of propranolol HCl was attributed to increase in total polymer loading after the presence of EC, and the presence of hydrophobic property of ethylcellulose in the gel layer.

In order to provide an additional diffusion barrier, propranolol HCl powder was granulated to form drug granules with reduced drug release prior compression with carbamazepine and other excipients as matrix tablet. The increase in particle size of granules resulted in a decrease in both propranolol HCl and carbamazepine release. Large granules have small surface area therefore slower release, whereas smaller granule provide larger surface area thus higher water penetration and faster erosion. Coating effect of ethylcellulose on propranolol HCl during granulation could be another explanation for slower release from larger granules.

To provide more homogeneous coating of propranolol HCl particle, granulation process was performed in fluid bed granulator. This method of granulation resulted in better retardation of propranolol release either as granule or after compression into matrix tablets. In comparison with conventional wet granulation by shear mixed method, release of carbamazepine from tablet with granulated propranolol HCl using fluid bed granulator were slower. Conventional method of granulation of propranolol HCl enable to provide higher water penetration due to some uncoated propranolol HCl in the matrix hence higher

erosion. Fluid bed granulation which homogeneously coated propranolol HCl particles with hydrophobic ethylcellulose promoted less water uptake and therefore slower carbamazepine release due to slower erosion.

Release adjustment from matrix tablet system can be conducted by controlling the erosion rate of the matrix which enables to provide faster release. Blending of HPMC matrices with lower molecular weight HPMC increased erosion rate hence faster drug release. Either Methocel®K15M: K100LV or Methocel®K4M: K100LV polymer blend exhibited increased release of carbamazepine to be closer to propranolol HCl. Blends of Methocel® K15M : K100LV (1:1), resulted in more intact tablets.

The effect of soluble filler blended with polymer matrices promote higher matrix hydration hence weaker gel formation. The effect of lactose filler on release showed that release from Methocel®K4M after lactose inclusion were faster than K15M which attributed to faster erosion. Effect of soluble filler were more pronounced on carbamazepine release which associated with higher tablet erosion, as predominant release mechanism for poorly soluble drug.

4.2 Release adjustment of drug combination with different drug solubility from coated pellets within matrix tablet system

The objective of present study is therefore to adjust the release of two drugs of different solubility from coated pellets within matrix tablet system.

Using direct compression method and ethylcellulose as water insoluble polymer matrix, propranolol HCl showed fast release whereas carbamazepine was extended due to difference in solubility. The release of propranolol HCl was extended when HPMC polymer matrix was used, whereas carbamazepine extended to low release due to rapid gel formation on the surface.

Retardation of propranolol HCl performed by layering propranolol HCl onto non-pareils followed by coating with ethylcellulose prior to compression together with carbamazepine powder into HPMC tablets resulted in an almost similar release of propranolol HCl and carbamazepine (f_2 factor = 68.29). Typical sigmoidal release of highly soluble drug (as shown by uncompressed pellets) was improved into linear release. Fast release of highly soluble drug propranolol HCl (from direct compression method)

disappeared due to more controlled release of barrier system by film coating Release of propranolol HCl from coated pellets within the matrix was retarded by the ethylcellulose coating and the HPMC.

The adjustment on permeability of the film coating (including coating level and HPC content as pore former of propranolol HCl pellets), changed the release profile of propranolol HCl without remarkable effect of the carbamazepine release. In contrast, by adjusting erosion rate using different HPMC blends as matrix and different particle size of carbamazepine, not only the release of carbamazepine which was affected but also propranolol HCl which associated with more pellets released from the matrix.

Erosion and pellet release study confirmed that carbamazepine particles and propranolol HCl pellets are released out of the matrix according the tablet erosion.

The outer matrix and excipients of the tablet from the study enable the pellets to withstand the compression force, as microscopic pictures showed only a very small fraction of ruptured pellets after compression process.

In summary, compression of propranolol HCl pellets and carbamazepine in outer matrix, was the effective method to enable linear and almost the same (f_2 factor >50) and adjustable release of propranolol and carbamazepine as drug combination.

4.3 Release adjustment of drug combinations with different drug solubility from multilayered pellet systems

The objective of the study was to control the release of two drugs of different solubilities using propranolol HCl and carbamazepine as model of highly and poorly soluble drugs from multilayered pellets coated with ethylcellulose : HPC blends.

The release profile of drugs with different solubility could not be adjusted by using conventional polymeric coating system (as drug blend with a single layer coating). Therefore, drug with high solubility (D_1) was coated by less permeable coating (C_1) consecutively layered with low soluble drug (D_2) and coated with more permeable coating (C_2). The permeability of first and second coating were adjusted with the HPC content and coating level.

Propranolol HCl from single layer pellets released faster than carbamazepine for all of HPC content as pore former. By employing multilayer pellet system, the release of two drugs of different solubility can be adjusted to give one drug released faster over the other or both are released with the same profile.

Applicability maps to improve flexibility in the formulaon and to achieve variety of possible release (expressed as $t_{80\%}$) for drug 1 and drug 2 were prepared. Formulation to provide pellets with faster release of propranolol HCl, faster release of carbamazepine or both of drug are released in the same time had been developed from the applicability map for particular t_{80} values.

A power law distribution between drug release (presented as t_{80}) and drug solubility was found either for single drug coated pellets or combination drug with different solubility as multilayered pellets. In comparison with different coating system, it can be concluded that for different permeability of coating, the relationship were the same with shifted value of asymptotes.

Release of propranolol HCl from multilyered pellet was not affected by carbamazepine's drug loading. Carbamazepine was strongly affected by drug loading, to which higher drug loading resulted in slower release, either by drug loading of carbamazepine itself or drug loading of propranolol HCl as first drug. Decrease in loading dose of carbamazepine (D_2), expressed as higher drug loading ratio (D_1/D_2), led to increase in release (lower t_{80}) due to higher surface area/dose ratio of carbamazeine. Accordingly, increase in drug loading of propranolol HCl (D_1) resulted in slower propranolol HCl release (higher t_{80}) due to decrease in surface area. At certain point, the release are the same (drug loading ratio = 1.58). Above that value, propranolol HCl released slower than carbamazepine

4.4 Quantification of the effect of porogen on release from single and multilayer ethylcellulose-coated pellets as combination drug

In order to modify the release from ethyl cellulose (EC) film, different ratios of water soluble pore-forming agents, such as hydroxypropyl cellulose (HPC) and hydroxy propyl methyl cellulose (HPMC) are added into formulation. The permeability of a

membrane produced of ethylcellulose and HPC blends depends on HPC content as the pore former.

The objective of the present paper was to study the effect of HPC as porogen on drug release from EC coated single layer pellets on a quantitative basis and extend the application of the findings to more complex systems (multilayer pellets) with regard to drug combination.

The contribution of other common formulation variables such as coating level was also studied.

EC : HPC coated single layer pellets showed important change in the release profiles between 20 and 25% (w/w) of HPC content. Above the critical area of HPC content, the drug release is clearly faster. However, below this point, the profiles changed only little when the HPC content was varied, and typical profiles of controlled release systems were obtained.

Plotting the drug release (expressed as $t_{80\%}$) of the individual formulations vs. the corresponding HPC content of the film coatings revealed a sigmoidal pattern which reasonably well represented by a cumulative normal distribution. The distribution function of the model is valid for the entire profile in the release phase for the mean values are the same (22.5 % w/w).

Plotted drug release vs. HPC content for different coating levels revealed the same sigmoidal relationship (identical mean and SD). Hence, drug release of different coating level using different HPC content can be predicted, connecting both relationships.

Propranolol HCl (D_1) pellets were also over-coated with caffeine (D_2) to evaluate the effect of second drug type on its release. Similar profiles of propranolol HCl release were obtained, thus implying independence of the type of second drug

The quantitative basis of the findings from single layer system can be applied to multilayer pellet system either for first drug (high solubility) or second drug layer (low solubility) indicating the feasibility to extend the mathematical model to more complex systems or to drugs of different physico-chemical properties.

5. Zusammenfassung

5.1 Modifizierung der Freisetzung von Wirkstoffkombinationen mit unterschiedlicher Löslichkeit aus Matrixsystemen

Formulierungsprobleme bei Kombinationen von Wirkstoffen in einer Arzneiform können verursacht sein durch unterschiedliche Löslichkeit der Arzneistoffe und dadurch bedingte Unterschiede in den Freisetzungsprofilen. Höhere Löslichkeit führt im Allgemeinen zu schnellerer Freisetzung aufgrund der hohen Antriebskraft für die Diffusion. Die Freisetzung schwer löslicher Wirkstoffe ist hingegen vollständig durch die Matrixerosion kontrolliert, da dies der dominierende Freisetzungsmechanismus ist.

Das Ziel der vorliegenden Arbeit war es daher, die Freisetzung von zwei Wirkstoffen zu modifizieren, welche als Kombination in einer Retardmatrixtablette vorliegen.

Bei der Verwendung der Direkttablettierungsmethode war, unabhängig vom verwendeten Polymertyp, die Freisetzung von Propranolol HCl deutlich schneller als die von Carbamazepin aufgrund ihrer Löslichkeitsunterschiede. Die veränderte Methode, bei der EC und HPMC gemischt wurden, gefolgt von Direktverpressung, führte zu einer langsameren Freisetzung von Propranolol HCl. Diese Retardierung kann dem erhöhten Gesamtpolymergehalt nach dem Zusatz von EC zugeschrieben werden. Die langsamere Freisetzung von Propranolol HCl wurde dem erhöhten totalen Polymeranteil nach der Zugabe von EC zugeordnet und den hydrophoben Eigenschaften der Ethylcellulose in der Gelschicht.

Um eine zusätzliche Diffusionsbarriere zu erhalten wurde das Propranolol HCl–Pulver granuliert um Granulatkörner mit reduzierter Wirkstofffreisetzung herzustellen. Diese wurden dann mit Carbamazepin und anderen Hilfsstoffen zu Matrixtabletten verpresst. Eine Erhöhung der Partikelgröße der Granulate führte zu einer langsameren Freisetzung sowohl für Propranolol HCl, als auch für Carbamazepin. Grosse Granulatkörner haben eine kleinere Oberfläche und dadurch eine langsamere Freisetzung, während kleine Granulatkörner eine größere Oberfläche besitzen, wodurch mehr Wasser eindringt und die Erosion beschleunigt ist. Ein Beschichtungseffekt des Propranolol HCls durch Ethylcellulose während des Granulierens könnte eine weitere Erklärung sein für die langsamere Freisetzung der größeren Granulatkörner.

Um eine homogenere Beschichtung der Propranolol HCl-Partikel zu erzielen, wurde der Granulierprozess im Wirbelschichtgranulierer durchgeführt. Diese

Granuliermethode führte zu einer besseren Retardierung der Propranololfreisetzung, sowohl als Granulat, als auch nach dem Verpressen zu Matrixtabletten. Im Vergleich zur konventionellen Granuliermethode im Schnellmischgranulierer war die Freisetzung von Carbamazepin aus Tabletten mit Propranolol HCl, welches in der Wirbelschicht granuliert wurde, langsamer. Die konventionelle Methode der Granulierung von Propranolol HCl erlaubte ein schnelleres Eindringen des Wassers, da ein Teil des Propranolol HCl in der Matrix unbeschichtet war. Dadurch war auch die Erosion beschleunigt. Die Wirbelschichtgranulierung, welche die Propranolol HCl-Partikel homogen mit hydrophober Ethylcellulose überzog, führte zu einer reduzierten Wasseraufnahme und dadurch zu einer langsameren Freisetzung von Carbamapein aufgrund der langsameren Erosion.

Die Freisetzung aus dem Matrixtablettensystem kann angepasst werden durch eine Kontrolle der Erosionsrate der Matrix, welche zu einer schnelleren Freisetzung führt. Beimischung von HPMC mit niedrigem Molekulargewicht zu den HPMC-Matrices erhöhte die Erosionsrate und beschleunigte somit die Wirkstofffreisetzung. Sowohl Mischungen von Methocel®K15M: K100LV als auch Methocel®K4M: K100LV führten zu einer erhöhten Freisetzungsrate von Carbamazepin, welche dadurch derjenigen von Propranolol HCl ähnlicher wurde. Mischungen von Methocel® K15M : K100LV (1:1) ergaben intaktere Tabletten.

Das Beimischen von löslichen Füllstoffen zu den Polymermatrices verstärkte die Hydratation der Matrix und reduzierte dadurch die Festigkeit des Gels. Der Effekt von Laktose als Füllstoff auf die Freisetzung zeigte, dass die Freisetzung aus Methocel®K4M nach der Zugabe von Laktose schneller war als aus K15M was der schnelleren Erosion zugeschrieben wurde. Die löslichen Füllstoffe hatten einen stärkeren Einfluss auf die Freisetzung von Carbamazepin, da sie die Erosion beschleunigten, und dies der dominierende Freisetzungsmechanismus für schwer lösliche Wirkstoffe ist.

5.2 Modifizierung der Freisetzung von Wirkstoffkombinationen mit Wirkstoffen unterschiedlicher Löslichkeit aus überzogenen Pellets in Matrixtabletten

Das Ziel der vorliegenden Arbeit war es daher, die Freisetzung von zwei Wirkstoffen zu modifizieren, von Wirkstoffkombinationen mit Wirkstoffen unterschiedlicher Löslichkeit aus überzogenen Pellets in Matrixtabletten.

Bei der Direktverpressungsmethode mit Ethylcellulose als wasserunlösliche Matrixpolymer war, aufgrund der unterschiedlichen Löslichkeiten, die Freisetzung von Propranolol HCl schnell, während diejenige von Carbamazepin retardiert war. Die Freisetzung von Propranolol HCl wurde verlangsamt durch die Verwendung von als HPMC als Polymermatrix. Durch die schnelle Gelbildung an der Oberfläche wurde aber auch die Freisetzung von Carbamazepin sehr niedrig.

Die Ratardierung von Propranolol HCl durch das Auftragen von Propranolol HCl auf Non-Pareils und anschließendem Überziehen mit EC, gefolgt von Verpressung zusammen mit Carbamazepinpulver und HPMC ergab eine ähnliche Freisetzung für Propranolol HCl und Carbamazepin (f_2-Faktor = 68.29). Die typische sigmoidale Freisetzung stark löslicher Wirkstoffe (wie aufgeführt bei unverpressten Pellets) wurde verbessert hin zu einer linearen Freisetzung. Die schnelle Freisetzung des leicht löslichen Wirkstoffs Propranolol HCl (bei der Direktverpressungsmethode) verschwand wegen der stärkeren Freisetzungskontrolle durch die Barriere des Filmüberzugs. Die Freisetzung von Propranolol HCl aus überzogenen Pellets innerhalb der Matrix wurde verzögert durch den Ethylcellulose-Überzug und HPMC.

Die Anpassung der Permeabilität der Filmüberzüge (inklusive des Überzugslevels und des HPC-Gehaltes als Porenbildner der Propranolol HCl-Pellets), veränderte das Freisetzungsprofil von Propranolol HCl ohne merklichen Effekt auf die Carbamezepinfreisetzung. Im Gegensatz dazu, beeinflusste die Anpassung der Erosionsrate durch die Verwendung unterschiedlicher HPMC-Matrixmischungen und verschiedener Partikelgrößen von Carbamazepin nicht nur die Freisetzung von Carbamazepin, sondern auch diejenige von Propanolol HCl, was einer verstärkten Freisetzung von Pellets aus der Matrix zugeordnet wurde.

Die Erosions- und Pelletfreisetzungsstudie bestätigte, dass Carbamazepinpartikel und Propanolol HCL-Pellets entsprechend der Tablettenerosion aus der Matrix freigesetzt wurden.

Die äußere Matrix und die Hilfsstoffe der Tablette der Studie ermöglichten den Pellets den Verpressungskräften standzuhalten. So ist auf Mikroskopbildern nur ein kleiner Teil aufgerissener Pellets zu sehen nach dem Verpressen.

Zusammenfassend kann gesagt werden, dass die Verpressung von Propranolol HCl-Pellets und Carbamazepin in der äußeren Matrix eine effektive Methode war, um eine

lineare, fast gleiche (f_2 Faktor >50) und anpassbare Freisetzung zu erhalten von Propanolol und Carbamazepin als Wirkstoffkombination.

5.3 Modifizierung der Freisetzung von Wirkstoffkombinationen mit Wirkstoffen unterschiedlicher Löslichkeit aus Mehrschichtpelletsystemen

Das Ziel dieser Studie war die gezielte Kontrolle der Freisetzung von zwei Wirkstoffen mit unterschiedlicher Löslichkeit aus mehrschichtigen Pellets mit ethylcellulose:HPC-Mischungen als Überzug. Propranolol HCl und Carbamazepin wurden als Modellarzneistoffe mit hoher respektive niedriger Löslichkeit verwendet.

Das Freisetzungsprofil verschiedener Wirkstoffe mit unterschiedlicher Löslichkeit kann unter Verwendung konventioneller Polymerüberzugssysteme (als Wirkstoffmischung mit einem Einschichtüberzug) nicht angepasst werden. Dazu wurden die mit leicht löslichem Wirkstoff (D_1) beschichteten Pellets mit einem schwerpermeablen Film (C_1) überzogen, gefolgt von einer Schicht mit schwer löslichem Wirkstoff (D_2) und einem leicht permeablen Überzug (C_2). Die Permeabilität der Filme wurde über den HPC-Gehalt und die Filmdicke angepasst.

Bei allen HPC-Anteilen im Film war die Freisetzung von Propranolol HCl aus Einzelwirkstoffpellets schneller als diejenige von Carbamazepin. Durch das Verwenden eines mehrschichtigen Pelletsystems konnte die Freisetzung so kontrolliert werden, dass entweder ein Wirkstoff schneller freigesetzt wird als der andere oder dass beide das gleiche Profil aufwiesen.

Graphische Darstellungen der Anwendbarkeit wurden erstellt zur Verbesserung der Flexibilität in der Formulierung und um eine Vielfalt an möglichen Freisetzungen (ausgedrückt als $t_{80\%}$ -Wert) für Wirkstoff 1 und Wirkstoff 2 zu erhalten. Formulierungen, die eine schnellere Freisetzung von Propranolol HCl oder eine schnellere Freisetzung von Carbamazepin aufweisen oder beide Wirkstoffe gleichzeitig freisetzen, konnten anhand des Anwendbarkeitsdiagramm für spezifische t_{80} -Werte entwickelt werden.

Die Abhängigkeit der Wirkstofffreisetzung (dargestellt als $t_{80\%}$ -Wert) von der Löslichkeit folgt dem Potenzgesetz sowohl für überzogene Pellets mit einem Wirkstoff, als

auch für Wirkstoffkombinationen mit Wirkstoffen unterschiedlicher Löslichkeit in Mehrschichtpellets. Aus dem Vergleich der verschiedenen Überzugssysteme kann man schließen, dass für unterschiedliche Permeabilitäten des Überzugs die gleiche Abhängigkeit gilt mit verschobenen Werten für die Asymptote.Die Freisetzung von Propranolol HCl war nicht abhängig vom Carbamazepingehalt der Pellets. Die Carbamazepinfreisetzung wurde jedoch stark beeinflusst sowohl von der Carbamazapinbeladung wie auch von der Propranolol HCl-Menge in der inneren Wirkstoffschicht, wobei eine höhere Beladung zu einer langsameren Freisetzung führte. Eine geringere Beladung mit Carbamazepin (D_2), ausgedrückt als höheres Wirkstoffbeladungsverhältnis (D_1/D_2), führte zu einer schnelleren Freisetzung (tieferer t_{80}-Wert) bedingt durch das größere Verhältnis von Oberfläche/Dosis. Analog führte eine höhere Propranlolbeladung zu einer langsameren Freisetzung von Propranolol (höherer t_{80}-Wert) durch die Abnahme der Oberfläche. An einem gewissen Punkt sind die Freisetzungen gleich (Wirkstoffbeladungsverhältnis = 1.58). Oberhalb dieses Wertes ist die Propranolol HCl-Freisetzung langsamer als diejenige von Carbamazepin.

5.4 Quantifizierung des Porenbildnereffektes auf die Freisetzung aus Einzelwirkstoffpellets und Mehrschichtpellets mit Wirkstoffkombinationen mit Ethylcelluloseüberzug

Um die Wirkstofffreisetzung durch Ethylcellulose Filme zu modifizieren, werden wasserlösliche Porenbildner wie Hydroxypropylcellulose (HPC) und Hydroxypropyl methylcellulose (HPMC) in verschiedenen Anteilen in der Formulierung verwendet. Die Permeabilität eines Ethylcellulosefilms mit HPC als Porenbildner hängt vom HPC Gehalt ab.

Das Ziel dieses Artikels war die quantitative Untersuchung des Effektes von HPC als Porenbildner auf die Wirkstofffreisetzung aus Einzelwirkstoffpellets mit Ethylcelluloseüberzug und die Anwendung der Ergebnisse auf komplexere Systeme (mehrschichtige Pellets) mit Hinblick auf Wirkstoffkombinationen. Auch der Einfluss anderer üblicher Formulierungsparameter, wie die Überzugsdicke, wurde untersucht.

Pellets mit EC:HPC-Überzug zeigten entscheidende Änderungen im Freisetzungsprofil bei HPC-Anteilen zwischen 20 und 25 % (w/w). Oberhalb dieses kritischen Bereichs des HPC-Gehaltes war die Freisetzung deutlich schneller. Unterhalb

dieser Schwelle waren die Freisetzungsraten konstanter und die Profile entsprachen denjenigen typischer Retardsyeme.

Das Auftragen der Wirkstofffreisetzung (ausgedrückt als $t_{80\%}$ -Wert) der einzelnen Formulierungen gegen den jeweiligen HPC-Gehalt des Filmüberzugs zeigte eine sigmoidale Abhängigkeit, die mit angemessener Genauigkeit durch eine kumulative Normalverteilung ausgedrückt werden kann. Die Verteilungsfunktion des Models ist für das gesamte Profil in der Freisetzungsphase gültig, da die Mittelwerte gleich sind (22,5 % w/w).

Die Auftragung der Wirkstofffreisetzung gegen den HPC-Gehalt für verschiedene Überzugslevels zeigte die gleiche sigmoidale Abhängigkeit (gleicher Mittelwert und SD). Somit kann, durch die Verbindung der beiden Abhängigkeiten, die Wirkstofffreisetzung für verschiedene Überzugslevels und HPC-Gehalte vorhergesagt werden.

Propranolol HCl (D_1)-Pellets wurden auch mit Koffein überzogen (D_2) um den Effekt des Typs des zweiten Wirkstoffs auf die Freisetzung zu untersuchen. Die Freisetzungsprofile für Propranolol HCl waren ähnlich, was bedeutet, dass die Freisetzung nicht von der Art des zweiten Wirkstoffs abhängt.

Die quantitativen Ergebnisse für die Einzelwirkstoffpellets lassen sich auf Mehrschichtpellets anwenden, sowohl auf den Wirkstoff in der ersten Schicht (hohe Löslichkeit), als auch auf den Wirkstoff in der zweiten Schicht (tiefe Löslichkeit). Dies zeigt die Machbarkeit einer Ausdehnung des mathematischen Modells auf komplexere Systeme oder auf Wirkstoffe mit unterschiedlichen phsikalisch-chemischen Eigenschaften.

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7. Publications

7.1 Publications

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Chaerunisaa A.Y. , Bodmeier R., Release adjustment of combination drug with different drug solubility from matrix tablet system. In preparation.

Chaerunisaa A.Y. , Dashevskiy A., Bodmeier R., Release adjustment of drug combinations with different drug solubility from coated pellets within matrix tablet systems. In preparation.

Chaerunisaa A.Y. , Dashevskiy A., Bodmeier R., Release of drug combinations with different drug solubility from multilayered pellets systems. In preparation.

7.2 Presentations

Chaerunisaa A.Y. , Körber M., Bodmeier R., Drug release prediction for pellets coated with ethylcellulose films containing a water- soluble polymer as pore-former, AAPS Annual Meeting and Exposition, November, 2013, the Henry B. Gonzalez Convention Center in San Antonio, TX, USA

Chaerunisaa A.Y. , Dashevskiy A., Bodmeier R., Release adjustment of drug combinations with different drug solubility from multilayered pellet systems, AAPS Annual Meeting and Exposition, November, 2013, the Henry B. Gonzalez Convention Center in San Antonio, TX, USA

Chaerunisaa A.Y. , Dashevskiy A., Bodmeier R., Release adjustment of a drug combination formulated in erodible hydrophilic matrix tablets, 41st Annual Meeting & Exposition of the Controlled Release Society, July 13-16, 2014, the Hilton Chicago, Chicago, Illinois, USA (Abstract submitted)

8. Curriculum Vitae

For reasons of data protection,
the curriculum vitae is not included in the online version