FORMULATION DEVELOPMENT STRATEGIES FOR ORAL EXTENDED RELEASE DOSAGE FORMS

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TO MY FAMILY

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1. INTRODUCTION

1.1 EXTENDED RELEASE SOLID ORAL DOSAGE FORMS

Extended release (ER) dosage form is one of the drug products categorized under the term modified release dosage forms (FDA, 1997). It refers to products, which are formulated to make the drug available over an extended period after ingestion; thus, it allows a reduction in dosing frequency compared to a conventional type i.e. immediate release (IR) dosage form. Several advantages of ER products over IR ones have long been recognized (de Haan and Lerk, 1984; Krämer and Blume, 1994; Hoffman, 1998; Das and Das, 2003). ER solid oral dosage forms can be classified into two broad groups: (i) single unit dosage forms (e.g. tablets) and (ii) multiple unit dosage forms or multiparticulate pellet systems. The systems can be further subdivided into two concepts regarding to the design of dosage forms: (i) matrix systems and (ii) reservoir systems.

1.1.1 Single unit dosage forms

1.1.1.1 Matrix systems

Matrix or monolithic devices consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid. The devices can be prepared either by the compression of a polymer/drug mixture or by the dissolution or melting, resulted in the molecularly dispersed drug. The drug transport often results from a combination of several mechanisms included dissolution, diffusion, swelling and erosion.

a. Water-soluble matrix formers

Water-soluble or hydrophilic matrices are a well known type of ER oral dosage forms (Melia, 1991; Abrahamsson et al., 1998b; Siepmann and Peppas, 2001). While hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material, several others are also available; including (i) cellulose derivatives: hydroxypropyl cellulose (HPC), carboxymethylcellulose sodium (NaCMC), (ii) natural polymers: sodium alginate, carrageenan, chitosan and (iii) synthetic polymers: polymerized acrylic acid (Carbopol), polyvinyl alcohol (PVA), polyethylene oxide (PEO). It has been suggested, however, that

the term ‘swellable matrices’ is more appropriate as it better explains the characteristic of the systems (Colombo et al., 2000).

b. Water-insoluble matrix formers

Water-insoluble carrier materials include (i) lipid-base excipients: white wax, carnauba wax, glyceryl monostearate, hydrogenated vegetable oil, paraffin and (ii) polymer-based excipients: ethylcellulose (EC), cellulose acetate. In comparison to the hydrophilic matrices, the system has a greater physical stability, resulting in the less variable drug release and the lower incidence of ‘dose dumping’ in presence of food (Huang et al., 1994).

1.1.1.2 Reservoir systems

Reservoir systems are characterized by a drug-containing core surrounded by release-rate controlling polymer(s). The mechanism of the drug transport across the polymeric membrane has been extensively described by Lecomte (2004).

a. Coated tablets

An example of technology for ER coated tablet is MODAS (Multiporous Oral Drug Absorption System; Elan Corporation, Ireland). The tablet core consists of the mixture of active drug and other excipients, subsequently coated with a solution of water-insoluble polymers and water-soluble excipients. Upon exposure to aqueous media, the surrounded coating is transformed into a semi-permeable membrane through which the drug diffuses in a rate-limiting manner (Verma and Garg, 2001).

b. Osmotic pump systems

Osmotic device is a special type of the reservoir systems, where the release rate of the drug is controlled dynamically by an incorporated osmotic agent in the active drug core. The rigid surrounding semi-permeable membrane consists for example of cellulose acetate. The drug is released through a defined, laser drilled delivery orifice in the membrane (Verma et al., 2002).

1.1.2 Multiparticulate pellet systems

Several advantages of multiparticulate systems over the single unit ones have been well documented (Digenis, 1994; Steward, 1995; Bodmeier, 1997). Following a proper preparation method, the ER pellets are either filled into a capsule or are compressed into a tablet (Bodmeier, 1997).

1.1.2.1 Matrix systems

The matrix type of multiparticulate systems can be prepared by several techniques such as extrusion/spheronisation (Flament et al., 2004), spherical crystal agglomeration (Kachrimanis et al., 2000) and melt-solidification (Paradkar et al., 2003). Although, the production of multiparticulate matrix systems is considered to be easier than that of the reservoir systems, their extent of retardation is limited because of pellet geometry (Knoch, 1994).

1.1.2.2 Reservoir systems

Coated pellets as a mean to control drug delivery are widely used in the pharmaceutical industry, although the development and optimisation of the systems are rather complex (McGinity, 1997; Lecomte, 2004). Numerous aspects of the system performance have been investigated, for instance, the influence of formulation and coating technique (Nastruzzi et al., 2000; Ganesan et al., 2003; Pearnchob and Bodmeier, 2003; Lecomte et al., 2004), the effect of drug solubility and core material (Steiner and Bodmeier, 2007), the use of polymer blends (Lecomte, 2004), in vitro/in vivo evaluation (Li et al., 1995; Mohamad and Dashevsky, 2007; Cui et al., 2008) and the influence of release medium (Bodmeier et al., 1996).

1.2 DATA ANALYSIS

Data analysis is a process of collecting, modeling and transforming data with the goal of extracting useful information, facilitating conclusions and supporting decision making.

When the analysis involves a number of variables at a time (e.g. several drug properties), techniques such as multivariate statistics or data mining are generally applied.

1.2.1 Multivariate statistical approach

Multivariate statistics refer to any statistical technique that looks at interrelationships or pattern between several variables simultaneously. When the overall focus of analysis is mainly related to the practical and problem-specific use of the structure part rather than the random error part of data (i.e. noise), hypothesis testing and other statistical considerations, the term multivariate data analysis (MVA) is inferred (Esbensen et al., 2006).

The major objectives of the MVA include (i) data description, (ii) discrimination and classification and (iii) regression and prediction. Several MVA techniques are available, such as factor analysis (e.g. principal component analysis), discriminant analysis, logistic regression analysis and cluster analysis. The choice of technique depends on data analytical problems or the desired type of answer.

Principal component analysis (PCA)

PCA is a technique for simplifying data by reducing multidimensional data to lower dimensions while retaining as much as possible the variation of the data set (Jolliffe, 2002). It is a linear transformation that transforms the data to a new coordinate system, so called the principal components (PCs). The first few, i.e. lower-order, PCs are able to explain the largest structural variation of the original data set, whereas the higher-order ones are generally considered as less relevant and hence, being dropped from further analysis. It should be noted, however, that the lower-order PCs, such as PC1 and PC2, are not always the most relevant for some particular interpretation purposes because they are unable to reveal the targeted answer. Therefore, the use of the higher-order PCs, when they have the largest problem-specific information, is more appropriate in certain cases (Esbensen et al., 2006).

PCA can also be used to classify data. The method facilitates the classification of objects (e.g. drugs) considering conformity with the extracted model and variables (e.g. drug

properties) describing the objects (Esbensen et al., 2006). This classification can be interpreted through the map of samples so called score plots, the map of variables so called loading plots as well as the relationship between both plots. The interpretation can be further simplified by the rotation of PCs using, for example, varimax rotation (Kaiser, 1958). The rotation is performed so as to maximize the variance of factor loading by making high loadings higher and low ones lower for each factor.

The PCA technique has found application in many diverse fields such as environmental science (Soh and Abdullah, 2007), marketing (Petroni and Braglia, 2000), psychology (El Yazaji et al., 2002), food science (Cotroneo et al., 1990; Krauze and Zalewski, 1991; Muir et al., 1996) and pharmaceutical science (Tarvainen et al., 2001; Karalis et al., 2002; Tho et al., 2002).

1.2.2 Data mining approach

Data mining or Knowledge-Discovery in Databases (KDD) is the synthesis of several technologies, including data management, statistics, machine learning (which can include pattern recognition techniques) and visualization. The techniques are applied for extracting hidden knowledge and describing structural patterns in data as a tool for helping to explain and make predictions from the data. The entire process of data mining includes collection, abstraction and cleansing of the data, use of data mining tools to find patterns, validation and verification of the patterns, visualization of the developed models and refinement of the collection process.

Among several data mining modeling techniques, an appropriate one can be selected according to the problem type, for example classification, prediction and description. Many modeling tools are capable of generating models which at the same time solve classification task and provide an informative description of the model behind the data, i.e. descriptive task.

Decision tree induction

Decision tree induction is a well known and widely used data mining technique (Jong Woo et al., 2001; Slonim, 2002; Ordonez, 2006). It is a decision support tool that maps observations from a given dataset (e.g. drug properties) to possible consequences or target values (e.g. dosage form). Many popular algorithms, such as ID3 (Quinlan, 1986), C4.8 (Quinlan, 1992) or its open-source implementation J4.8 (Witten and Frank, 2005), are applied to the data for the construction of a classifier that is expressed as a tree. The generated model is used for classification and subsequently is applied for prediction. For example, the dosage form of drugs whose properties are known can be predicted from the decision tree model by following the set of classifiers (i.e. selected drug properties), starting at the root of the tree and moving through it until a leaf node, where the classification of the drug is provided (Fig. 1). Several advantages of decision tree model include; (i) useful for both classification and prediction tasks, (ii) simple to understand and interpret, (iii) requires little data preparation, (iv) handles both numerical and categorical data, (v) uses a white box model, (vi) possible to validate a model using statistical tests and (vii) robust and performs well with large data in a short time (Witten and Frank, 2005).

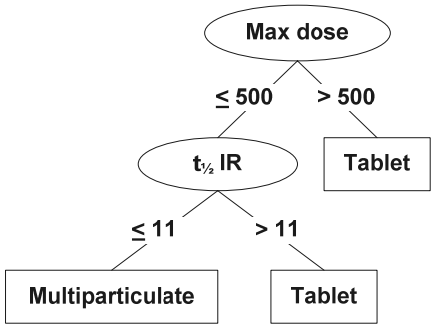


Fig. 1 Example of a decision tree model

1.3 IN VITRO PERFORMANCE OF ORAL ER FORMULATIONS

1.3.1 Dissolution testing

Dissolution testing is an official evaluation method for solid oral dosage forms. Several pharmacopeial standard dissolution media and apparatuses are well documented. The

method was initially developed for IR solid oral dosage form and then extended to modified release solid oral dosage forms as well as other novel/special dosage forms. Guidelines to dissolution testing for a range of novel dosage forms, such as chewable tablets, suppositories, transdermal patches, aerosols, implants and liposomes have been extensively discussed (Siewert et al., 2003; Azarmi et al., 2007).

The application of dissolution testing was conventionally known as a tool for ensuring batch to batch consistency. It is also an essential mean for deciding on a candidate formulation in product development. The tests should be sensitive enough to demonstrate any small variable in manufacturing of a product as well as the type and level of excipients used. Therefore, it is possible that an over-discriminatory test, although in vivo irrelevance, might be suitable for these purposes (Azarmi et al., 2007).

The value of dissolution test was later shifted to bioavailability prediction. Challenges in selecting the test conditions which reflect in vivo drug release have been of interested to many researchers (Uppoor, 2001; Gu et al., 2004; Royce et al., 2004). The tests may not be pharmacopeial standard, they should, however, be sensitive, reliable and discriminatory with regard to the in vivo drug release characteristics (Qureshi, 2006; Azarmi et al., 2007). The ultimate goal of the dissolution test is to predict the in vivo performance of products from in vitro test by a proper correlation, so called in vitro/in vivo correlation (IVIVC) (Emami, 2006). In certain cases, dissolution tests can be used for providing biowaivers for lower strengths of a product once the higher strength is approved. The waivers can also be granted to some categories of postapproval changes, based on the appropriate bioavailability/bioequivalence test procedure (FDA, 1997; FDA, 2000).

1.3.2 Biorelevant dissolution testing

1.3.2.1 Physiological properties of the gastrointestinal tract

Physiological conditions vary wildly along the gastrointestinal (GI) tract. Not to mention intersubject variability, various factors within an individual, such as disease states, physical activity level, stress level and food ingestion, considerably influence the GI conditions (Dressman et al., 1998). The effects of this variability on the performance of ER systems are

even more pronounced given that the dosage forms are designed to remain in the GI tract for the substantially longer period of time and transit through various conditions compared with IR systems. Inhomogeneous distribution of fluid in the small and large intestine (Schiller et al., 2005) is one of many factors that potentially contributes to the variability of drug release and absorption. Physiological properties in various GI compartments with and without effect of food are presented in Table 1 and Table 2.

Table 1 Physiology of the GI tract of healthy humans in fasted state

Location	Fluid volume (ml)	Transit time (h)	pH	Osmolality (mOsm/kg)	Buffer capacity (mmol/L·ΔpH)	Surface tension (mN/m)
Stomach	45[1]	1-2[2-3]	1.5-1.9[3-7]	98-140[4]	7-18[4]	42-46[4]
Duodenum	105[1]	3.6[3]	6.5[3]	178[4]	5.6[4]	32.3[4]
Jejunum			6.8[3]	271[8]	2.4[9]	28[9]
Ileum			7.2[3]	n/a	n/a	n/a
Colon	13[1]	7-20[2]	6.5[3]	n/a	n/a	n/a

Table 2 Physiology of the GI tract of healthy humans in fed state

Location	Fluid volume* (ml)	Transit time (h)	pH	Osmolality (mOsm/kg)	Buffer capacity (mmol/L·ΔpH)	Surface tension (mN/m)
Stomach	800-900[10]	1.4-4.0[3]	3-7[2, 4, #]	217-559[4, #]	14-28[4]	30-31[4]
Duodenum	900-1000[10]	3.8[3]	5.1-5.4[2]	390[4]	18-30[4]	28.1-28.8[4]
Jejunum			5.2-6.0[11]	n/a	14.6[9]	27[9]
Ileum			7.5[11]	n/a	n/a	n/a
Colon	n/a	n/a	5[2]	n/a	n/a	n/a

* including the volume of meal
# changed with time, see text
[1] Schiller et al. (2005)
[2] Dressman et al. (1998)
[3] Ibekwe et al. (2008)
[4] Kalantzi et al. (2006)
[5] Dressman et al. (1990)
[6] Evans et al. (1988)
[7] Vertzoni et al. (2005)
[8] Lindahl et al. (1997)
[9] Persson et al. (2005)
[10] Custodio et al. (2008)
[11] Hörter and Dressmann (2001)
n/a: information not available

Schiller et al. (2005) investigated the transit of non-disintegrating capsules in relation to the presence of fluid in the GI tract as well as the effect of meal. Instead of a continuous fluid compartment, four and six fluid-filled pockets were found discontinuously located in the small intestine in fasted and fed state, respectively. A solid dosage form was, therefore, not

at all time accessible to the fluid as found from the study that 27% and 90% of the capsules located in the small and larger intestine, respectively, were not in contact with the fluid pocket. Interestingly, the total fluid volume of the small intestine reduced at one hour after meal, where chyme had not yet presented, from 105 ml to 54 ml. This reduction was due to the gastro-ileocaecal reflex mechanism that caused the distal part of the small intestine pushing the remaining content, including the preceding dose of a dosage form, forward into the colon. This phenomenon, however, did not increase the total fluid in the colon because of the high water absorption capacity.

Gastric emptying time of a solid dosage form changes dramatically with the effect of co-administered food. One out of twelve capsules taken three hours before meal and all twelve capsules taken immediately after meal remained in the stomach for at least one hour, while in the fasted state, the majority of the capsules had left the stomach within one hour (Schiller et al., 2005). The total time for a dosage form to empty from the stomach in the fasted state depends on the size of the dosage form, i.e. the longer time is needed for the larger, as well as the motility cycle of the stomach which is two hours in average. The emptying for most non-disintegrating solid dosage forms with larger than one millimeter diameter occurred in the late phase II or phase III of the cycle (Dressman et al., 1998). Co-administered food even further altered the emptying time depending on the calorie content. Davis et al. (1984) and Velchik et al. (1989) reported that the higher the calories contained in the meal, the longer the gastric emptying time. A delay for several hours to empty a relatively large solid dosage form can also occur as the food will be first cleared from the stomach and return to the normal gastric motility cycle in the fasted state. The dosage form is then emptied under the phase III activity (Dressman et al., 1998). Unlike the gastric emptying, transit time in the small intestine in both fasted and fed states are not significantly different, regardless of the type of dosage forms (Dressman et al., 1998; Ibekwe et al., 2008).

pH and osmolality of the stomach and the upper small intestine is greatly influence by co-administered food. In healthy humans, their values for the stomach increased from pH 1.7/ 140 mOsm kg^{-1} up to pH 6.4/559 mOsm kg^{-1} within thirty minutes postprandially and then gradually decreased to pH 2.7/217 mOsm kg^{-1} after 3.5 hours. Composition and quantity of the meal significantly affected the time require to re-establish the fasting gastric pH more

than did the pH value of the meal. For example, two hours was required after a 651 mOsm/1000 kcal (pH 5.6) meal whereas only one hour was needed for a 540 mOsm/458 kcal meal (pH 6) (Kalantzi et al., 2006). As the average time for restoring the pH of the stomach was two to three hours (Dressman et al., 1998), dosage forms with pH-dependent controlled release, such as an enteric coated tablet, may fail to control the release when taken with or soon after meal. Recently, Jantratid et al. (2008) proposed the biorelevant dissolution media simulating the characteristic of the GI fluids in both fasted and fed states. As the postprandial conditions vary according to the time, the diverse compositions of the media for different states were presented accordingly.

Physiology of the colon has not much influence by co-administered food. As previously mentioned, the fluid volume of the colon was not significantly changed with meal induction (13 ± 12 ml vs. 11 ± 26 ml) because of the high water absorption capacity (Schiller et al., 2005). Unlike the stomach and the small intestine, the movement of luminal contents in the colon did not always occur longitudinally, but also laterally in order to assist the mixing of the contents and to facilitate absorption (Price et al., 1993). A food effect study with radiography revealed the remaining of some of the radio-opaque markers after 36 h at the ascending colon, whilst some of them taken only 12 h before the study were found at the end of the transverse colon (Dressman et al., 1998). The transit time of a dosage form was, therefore, considered as no effect of food intake. This is in agreement with a study by Edsbacker et al. (2002) which reported that delivery to the colon and ileum was independent of co-administered meal.

1.3.2.2 Effect of food on the bioavailability of drugs and dosage forms

The presence of food within the GI tract can significantly influence the bioavailability of drugs, both by the nature of food and the drug formulations. Factors deserving critical attention for predicting bioavailability under fed conditions are;

1. An increase in solubilisation capacity by higher concentrations of bile salts and fatty acids. This factor can alter the release profiles of lipophilic drugs (TenHoor et al., 1991; Kostewicz et al., 2002) or from dosage forms that drug released is controlled by hydrophilicity (Khan, 1996).

2. A prolonged gastric emptying time (increased GI-residence time), thus increasing the total time available for dissolution and improve the bioavailability (Marvola et al., 1989; Kenyon et al., 1995; Ishibashi et al., 1999; Fabre and Timmer, 2003). This factor, however, can also inversely affect acid labile drugs that would expose to the acidic environment of the stomach for a significantly longer period of time.
3. An elevation of the pH in the stomach altered the release pattern of pH-dependent controlling formulations as well as affected the dissolution rate of drugs with pH-dependent solubility (Marvola et al., 1989).
4. Changes in the physical and biochemical barrier function of the GI tract (Crison, 1999; Porter and Charman, 2001). The increased fluidity of the intestinal wall by lipid as well as the increased leakiness of tight junctions by high concentration of glucose can enhance the permeability of the small intestine (Crison, 1999).
5. Stimulation of intestinal lymphatic transport (Porter and Charman, 2001).

a. Drugs

Highly water soluble drugs

BCS Class I compounds, which are highly soluble across a wide range of pH values (Amidon et al., 1995), are unlikely to be affected by ingested food. However, a delay in gastric emptying may increase the time to peak drug concentrations (t_{max}). Simulated Gastric Fluid (SGF) and milk can be used as in vitro dissolution media to predict the performance of the drugs in vivo (Galia et al., 1998). Food components that alter mucosal enzymatic activity and/or P-glycoprotein activity are also expected to change the absorption of compounds of BCS Class III (high solubility - low permeability). It was also evident that co-administered food reduced the bioavailability of atenolol and sotalol, the very hydrophilic compounds. This was due to an interaction of the drugs with bile acid produced in the fed state (Welling, 1996).

Poorly water soluble drugs

In general, food intake results in an increase in both rate (C_{max}) and/or extent (AUC) of absorption because of the improved drug solubility. This higher solubility of drug was

attributed to the presence of fat content in the co-administered food as well as bile acid producing in the fed state. For BCS Class II compounds (low solubility - high permeability), an increase in absorption is expected when the product is administered with high fat meals. In vitro dissolution study in two media simulating the small intestinal contents in the fed (FeSSIF) and fasted (FaSSIF) states as well as the modified versions of the two (Wei and Löbenberg, 2006; Zoeller and Klein, 2007) can provide good information of the in vivo behaviour of weak basic and weak acid compounds, while FaSSIF is recommended for neutral compounds (Galia et al., 1998).

A review by Welling (1996) reported a number of drugs that co-administered food influenced their absorption. The author categorized the drugs with regard to the effect of food into four groups (Table 3); drugs whose absorption is decreased, delayed, increased and those in which food has no effect.

It can be noted from Table 3, however, that a drug could be categorized into more than one group according to the results obtained under various study conditions, such as single vs. multiple doses, light vs. heavy meals. Consequently, the effect of food on drug absorption could only be predicted partially from physicochemical point of view. A conclusive decision based solely on a single study was unwarranted. In addition, a very important factor pointed out by the author as well as by several researchers (Davis et al., 1984; Abrahamsson et al., 1998a; Halsas et al., 1999; Schug et al., 2002a; Schug et al., 2002b; Wei and Löbenberg, 2006) was that the effect of food on the bioavailability of a drug is more likely to be formulation/dosage form-dependent.

Table 3 Drugs whose absorption is affected by food[1]

Decreased	Delayed	Increased	Unaffected
Alendronate Sodium	Acetorphan	Alprazolam	Alpramlam
Ambenonium chloride	Albuterol	Amiodarone	Amlodipine
Atenolol	5- Aminosalicylic acid	Amocarzine	Bambuterol
Azithromycin	Aniracetam	Astemizole and	Bisoprolol and
Cefprozil	Beta-methyldigoxin	Pseudoephedrine	Hydrochlorothiazide
Ceftibuten	Cefaclor	Atovaquone	Brofaramine
Cicaprost	Cefdinir	Brofaromine	Bromocriptine
Ciprofloxacin	Cefprozil	Buflomedil	Carbamazepine
Didanosine	Diclofenac	Cefetamet pivoxil	Cardizem
Dideoxycytidine	Diltiazem	Cefuroxime	Cefetamet pivoxil
Doxazosin	Doxycycline	Clarithromycin	Cimetidine and
Flecainide	Erythromycin acistrate	Cyclosporine	Ranitidine
Hydralazine	Fadrozole	Danazol	Cyclosporine
Levodopa, Carbidopa	Famotidine	Diltiazem	Diazepam, Ethinyl
Metformin	Flurbiprofen	Encainide	estradiol,
Methotrexate	Fluvastatin	Felodipine	Norethindrone,
Naproxen	Fusidate sodium	Fenretinide	Propranolol
Navelbine	Hydroxychloroquine	Gepirone	Diazepam
Nitrendipine	Isosorbide-5-	ltraconazole	Fluvoxamine
Norfloxacin	mononitrate	ltraconazole and	Ibuprofen
Paracetamol	Lomefloxacin	Fluconazole	Levodopa
Phenytoin	Loracarbef	Levodopa	Methotrexate
Pravastatin	Methotrexate	5-Methoxypsoralen	Metoprolo1 succinate
Rufloxacin	Monofluorophosphate	Moclobemide	Morphine sulfate
Sotalol	Moricizine	Nifedipine	Mosapride citrate
Sulpiride	Nicorandil	Oxcarbazine	Moxonidine
Tacrine	Nifedipine	Oxybutinin	Nefiracetam
Tetracycline	Ofloxacin	Phenytoin	Paroxetine
Verapamil	Paracetamol	Progesterone	Piroximone
Zidovudine	Penciclovir	Repirinast	Procainamide
	(famciclovir prodrug)	Sparfloxacin	Pseudoephedrine and
	Rifabutin	Theophylline	Brompheniramine
	Salsalate	Ticlopidine	Rifabutin
	Terazocin	Tramadol	Sparfloxacin
	Terfenadine	Vanoxerine	Temafloxacin
	Theophylline	Vinpcetine	Theophylline
	Tiagabine	Zalospirone	Tiaprofenic acid
	Topiramate		Trimetazidine
	Trazodone		Verapamil
	Valproic Acid		
	Vigabatrin		
	Zalospirone		
	Zidovudine		

[1] Welling (1996)

b. Dosage forms

Immediate release dosage form (IR)

The prolonged gastric emptying and the reduced hydrodynamic flow under fed state led to a delay of t_{max}, while the AUC remained unaffected. Those effects depend, however, on formulation characteristics. Panchagnula et al. (2003) found that the tablet of rifampicin having the fast release (≥ 85% in 10 min) showed similar in vitro release profiles under fasted and fed conditions while the formulation with the slower release rate (≥ 75% in 45 min), though comply with the USP dissolution criteria, demonstrated the varied release profiles at different percentage of sunflower oil in SGF without pepsin and the reduced release rates at lower agitation intensities. A further retardation of the release can be caused by a slower tablet disintegration and drug dissolution through the formation of a protein film around the tablet (Abrahamsson et al., 2004). Complexation of food contents and bioadhesive materials such as polycarbophil, an excipient in bioadhesive tablet, can cause a decrease in both C_{max} and AUC (Hosny et al., 1994). However, a longer GI-residence time also allows a better site-specific absorption, resulting in an increase of AUC (Gouda et al., 1987).

Extended release dosage form (ER)

Multiparticulates

Multiparticulate pellet systems demonstrate less influence of co-administered food with regard to the gastric emptying/GI-residence time compared to single unit dosage forms (Davis et al., 1984). Pellets (size range 0.7-1.2 mm) were emptied from the stomach much faster (4-5.5 h) than that of an osmotic tablet (9 h) when administered shortly after a heavy meal (3600 kJ). While, following a light meal (1500 kJ), the gastric emptying times of both systems were approximately the same (~2 h). Co-administered food, especially with high caloric content, also allowed the higher degree of spreading of the pellets in comparison to that under fasted state. The delayed GI-residence time of pellets in the upper GI tract allows a longer time for dissolution and absorption, thereby increases bioavailability. The higher and earlier peak plasma concentration of verapamil and its main metabolite norverapamil

were more pronounced when multiparticulate pellets formulation was compared to the single-unit tablet, given that the in vitro release characteristics of both formulations were similar (Marvola et al., 1989). This increased bioavailability of ethylcellulose-coated verapamil hydrochloride pellets was attributed to the higher solubility of the drug at lower pH values, thus promoted the drug solubility and absorption.

Similar to the single-unit systems, changes of pH in the GI tract by food altered the dissolution pattern of the pH-dependent dissolving particles (De Jaeghere et al., 2000). The premature release and precipitation in the stomach of captopril formulated as pH-sensitive matrix-type particles, thus decreased bioavailability, were attributed to the higher pH in the stomach under fed state.

Swellable matrix

An in vivo study on a hydrophilic matrix system showed significant variation in pharmacokinetic parameters when given with food (Dennis et al., 2000). The C_{max} and AUC of HPMC matrix tablets increased under fed conditions due to a greater tablet erosion rate, which induced by intense motility as well as physicochemical effects of food components and gastric secretions (Abrahamsson et al., 1998a). Swellable matrix tablet of the very low water soluble drugs, nifedipine and felodipine, were used in the investigation of this effect postprandially (Abrahamsson et al., 1999). Mechanical stress on the tablet, which adjusted by varying the agitation intensities of dissolution apparatus, was the key factor enhancing the rate of erosion corresponded to postprandial effect in vivo. Other factors investigated in vitro including the used of simulated fed conditions and the elevated osmolality or viscosity did not contribute to the higher erosion rate as the opposite effect, i.e. retarded erosion, to those found in vivo was observed. The role of the GI mechanical destructive forces in accelerating drug released under fed conditions has also been reported for acetaminophen matrix tablets in other study (Shameem et al., 1995).

A remarkably increase of the oral bioavailability of an erosive tablet nifedipine for once daily administration under fed state was explained as a pH-sensitive of the system (Schug et al., 2002a). This was due to pH-dependent in vitro release characteristics, which were observed when aqueous buffer solutions pH range 1-8 containing 1% SDS were used as

dissolution media. The tablet was robust with regard to the effect of agitation, osmotic pressure and different concentrations and types of surface active ingredients.

There are also contradicting reports showed, however, that the bioavailability of swelling matrix tablets was reduced under fed conditions. Halsas et al. (1999) reported the prolonged t_{max} and the decreased AUC of the HPMC press-coated tablet of ibuprofen when taken with meal. A stable HPMC is formed over the pH range 3-11. With a lower pH, e.g. under fasted conditions, a less stable gel around the tablet is formed and the formulation losses its integrity. The elevated pH and viscosity in the stomach in fed state let to a more mechanically stable HPMC gel resulting in the reduced drug release. Another study from Crevoisier et al. (2003) showed postprandial effect on the release of levodopa from a Geomatrix® tablet. Though the AUC was unaffected, the lower C_{max} and the longer t_{max} compared to those under fasted conditions were reported when the tablet was co-administered with food. The reduced absorption rate of levodopa was explained as the prolonged gastric emptying time.

Osmotic tablets

Co-administered food has less impact on osmotic systems compared with other ER systems. A drug releases independently from the GI environment. For example, the oral bioavailability of nifedipine-containing ER formulations were studied in healthy subjects (Schug et al., 2002a). The osmotically driven gastrointestinal therapeutic system (GITS) i.e. Adalat® OROS showed no significant effect of co-administered food on the nifedipine bioavailability after a high fat meal when compared to that observed under fasted state. The same study conditions were applied to an erosive matrix tablet, CORAL® (D.R. Drug Research S.R.L., Italy) and a mini-tablets-containing capsule, Nifedicron (Searle farmaceutici, Italy) (Schug et al., 2002b). Unlike the osmotic tablet, both generic products showed a strikingly increased bioavailability (matrix tablet: 186% for $AUC_{(0-24)}$ and 317% for C_{max}, mini-tablets: 136% for $AUC_{(0-24)}$ and 243% for C_{max}) under fed state due to dose dumping of these formulations. In addition, the erosion rate of the osmotic systems did not alter when co-administered with food as observed with the HPMC matrix tablets (Abrahamsson et al., 1998a). Many studies suggested the similar results that food had no effect on the clinical performance of osmotic systems (Lecaillon et al., 1985; van den Berg

et al., 1990; Gupta et al., 1995; Grundy and Foster, 1996), although the prolonged t_{max} could be observed because of a delayed gastric emptying (Davis et al., 1984; Modi et al., 2000).

1.3.2.3 Drug delivery systems independent of food intake

Not only have the osmotic pump systems demonstrated the drug released independently of co-administered food, some other formulation designs were reported the lack of food effect. For instant, an ER matrix tablet of nefazodone hydrochloride, an antidepressant drug which required a dose of 200-600 mg daily, has shown no effect of food intake (Dennis et al., 2000). The tablet composed of HPMC (the ratio of a 5 cps viscosity to a 100 cps viscosity was 1:2), sodium alginate and microcrystalline cellulose (MCC) as the main inactive ingredients. A mixture of the non-ionic gelling polymer, HPMC, and the ionic one, sodium alginate as well as the insoluble hydrophilic agent, MCC, which was incorporated into the formulation for encouraging water penetration into the dosage form but not causing the ready disintegration, were properly combined in a ratio that provided a pH-modulated erosion rate of the tablet. The release rates were faster at higher pH values in order to compensate the lower solubility of this basic drug with pH-dependent solubility (sparingly soluble as defined by USP, pK_a=6.4). The HPMC matrix tablet of the same drug showed effect of co-administered food by the increased bioavailability from 28 to 66%.

A patent has been issued on the ER formulation of Levetiracetam for once daily administration that showed no effect of food (Kshirsagar et al., 2008). The tablet composed of a core of the drug disperses in a high viscosity HPMC matrix (greater than 15 cps in a 2% w/w solution), then coated with the dispersion of ethylcellulose as a release rate controlling polymer and optionally with HPMC (low viscosity) as a pour former in the coating. The tablet comprised between 20% and 40% HPMC matrix, between 1% and 10% ethylcellulose and up to 5% of the pour former, per weight of the coated tablet. This formulation exhibited a mean $(AUC_{fasted})/(AUC_{fed})$ in human subjects of at least 0.80.

1.3.2.4 In vitro studies of food effect and the in vivo correlation

Biorelevant GI media, i.e. FaSSIF and FeSSIF were demonstrated as the potential in vitro dissolution media for poorly soluble drugs in order to predict the in vivo performance

especially with the effect of food on drug absorption (Nicolaides et al., 1999; Kostewicz et al., 2002). Aqueous buffer solutions with varying pH (range 2.5-6.5), concentration of bile salt and lecithin as well as the biorelevant GI media were used to evaluate the solubility and dissolution characteristics of the compounds. The higher concentration of bile salt and lecithin (combined with the lower pH, in case of weak bases) improved the solubility of the compounds, thus increased dissolution rate. The release of the drugs in FaSSIF and FeSSIF were much faster than those in water and Simulated Intestinal Fluid without pancreatin (SIF_{sp}) (Nicolaides et al., 1999). In addition, the calculation of dose to solubility ratios from the solubility data of the drugs in different media revealed the potential site for dissolution and absorption, based on fluid available in the particular regions of the GI tract (Kostewicz et al., 2002). The higher solubility and the faster dissolution rate in FaSSIF and FeSSIF were in agreement with the in vivo studies of these compounds that demonstrated the positive impact of co-administered food on the bioavailability. Dipyridamoles, one of the compounds studied, showed increased AUC and t_{max} when co-administered with food in healthy volunteers. It could, therefore, be explained as the improved drug solubility that caused by the high concentration of bile salt and lecithin together with the reduced pH during the prolonged GI residence time.

The updated versions of FaSSIF and FeSSIF, which more closely mimic the human physiological conditions under both fasted and fed states, were recently published (Jantratid et al., 2008). Based on the in vivo data available from human aspirates, FaSSIF-V2 was recommended as the medium to simulate preprandial conditions, while the three 'snapshot' media as well as the FeSSIF-V2 were recommended for the postprandial ones in the upper small intestine. These updated biorelevant media showed the better agreement with the in vivo bioavailability of glibenclamide in comparison to the results obtained from FaSSIF and FeSSIF (Janssen et al., 2008).

According to simulated stomach media, Vertzoni et al. (2005) suggested the use of FaSSGF as an in vitro dissolution medium in the fasted stomach for weakly basic compounds. The medium exhibited the better reflection of the in vivo release of GR253035X, a weak base, than the profiles obtained from SGF with sodium lauryl sulphate (SGF_{SLS}) or TritonX100 (SGF_{Triton}). With regard to the study of food effects on the drug released in the stomach,

FeSSGF or the combination of UHT-milk and aqueous buffer solutions in different ratios, depending on the digestion phases, were recommended (Jantratid et al., 2008).

Prior to the introduction of FaSSIF and FeSSIF, several in vitro studies of food effects were summarized in a review article by Khan (1996) as shown in Table 4. Those conditions included pre-treating the dosage forms with peanut oil (Maturu et al., 1986; El-Arini et al., 1989), the use of milk as dissolution medium (Macheras et al., 1989) and the addition of oil in dissolution media (El-Arini et al., 1990).

Table 4 In vitro studies of food-induced conditions[1]

Drug/dosage form	In vitro conditions	Results	Reference
Theophylline • matrix tablet • beads filled in capsule	Pre-treatment of the dosage form (or content) in peanut oil for 2 h prior to standard dissolution testing	The in vitro dissolution data correlated well with in vivo percent dissolved in humans after high fat breakfast	Maturu et al. 1986
Propranolol HCl • capsule	Pre-treatment of the dosage form content in peanut oil for 1 h at 37°C prior to standard dissolution testing	A significant decrease in dissolution rate of the drug was observed as a result of pre-treatment of the dosage form with peanut oil when compared with untreated dosage form	E1-Arini et al. 1989
Theophylline • matrix tablet • capsule	Milk with various levels of fat content (0.1%, 2.0%, 5.0% and 7.5%) was used as dissolution medium	A direct relationship was established between fat contents of milk and dissolution data with a good correlation between data obtained using 7.5% fat content milk and in vivo data obtained in humans after a high fat meal	Macheras et al. 1989
Theophylline • beads embedded in matrix tablet • beads filled in capsule	A dialysis cell containing the dosage form in a small volume of fluid is immersed in the dissolution medium in a dissolution vessel. The physiological conditions are simulated by adjusting the fluid of the dialysis cell	The method allowed testing of the extended release dosage forms under various food induced conditions	El-Arini et al. 1990

[1] modified from Khan (1996)

The study from Al-Behaisi et al. (2002) reported the use of milk, sunflower oil and sucrose as the favourable dietary components for in vitro dissolution studies under fed conditions (Table 5). Film-coated IR tablets of deramciclane, an acid-labile drug, were used in the study of food effects. The dissolution testing was performed with USP paddle method, at 100 rpm in 500 ml of the test media. The comparable tendencies of in vitro dissolution and in vivo studies in healthy male volunteers for cumulative AUC (AUC_{cum}) under fasted and fed states were demonstrated. Moreover, the ratio of $AUC_{cum,\ fed}/AUC_{cum,\ fasting}$ showed the

linear relationship between the in vitro dissolution time and the logarithmic in vivo blood sampling time (Fig. 2). It was also speculated that an increased pH under fed conditions improved the bioavailability by reducing the drug degradation.

Table 5 Compositions of artificial gastric juice and the dietary components added during the in vitro dissolution testing for simulated fasted and fed states[1]

Dietary components	Simulated fasting state: artificial gastric juice pH 1.2	Simulated fed state: dietary components added to artificial gastric juice, end-result pH 2.98
1 N HCl	94 ml	94 ml
NaCl	0.35 g	0.35 g
Glycine	0.5 g	0.5 g
Whole-milk powder	-	30 g
1% methylcellulose	-	450 ml
Sunflower oil	-	50 ml
Sucrose	-	65.5 g
H_2O	add 1 L	add 1 L

[1] modified from Al-Behaisi et al. (2002)

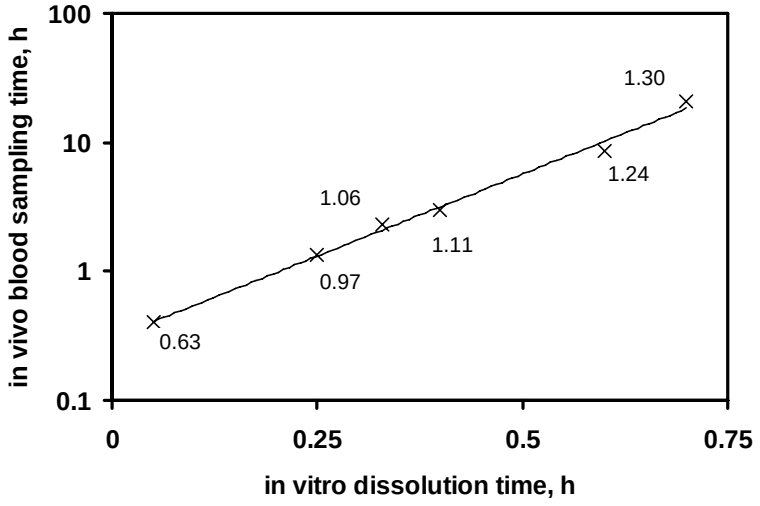


Fig. 2 Correlation between logarithmic in vivo blood sampling time and in vitro dissolution time assigned to equal AUC_{cum} ratio ($AUC_{cum,\ fed}/AUC_{cum,\ fasting}$). Modified from Al-Behaisi et al. (2002).

In vitro study of food effect on the bioavailability of rifampicin was carried out in the different concentration of sunflower oil (10-35%) in SGF without pepsin (Panchagnula et al., 2003). The USP Apparatus II at 30 and 50 rpm were used to simulate hydrodynamic stress under fed conditions, while the 75 rpm was used for fasted conditions. It was found

that, neither agitation intensities nor sunflower oil added influenced the release of the formulation that releases 90-100% rifampicin within 10 min in fasted state. The drug released from the slower released formulation (75-100% within 45 min), however, decreased with decreasing agitation rate. The profiles also varied with the addition of sunflower oil, though without a clear trend. In vivo data supported the effect of co-administered food on the bioavailability of rifampicin by the reduced C_{max} and the increased t_{max}, while AUC was unaffected. This was due to the decreased dissolution rate and the increased disintegration of the formulation when food was presented.

1.3.3 Drug release in the presence of alcohol

Co-administered alcoholic beverages with drugs may severely cause adverse consequence, particularly with formulations containing a narrow therapeutic index drugs or strong opioids. An unintended overdose of hydromorphone from once-daily ER pellets-containing-capsule (Palladone™) was reported as alcohol-drug interaction, leading to the voluntarily withdrawal of the product by its manufacturer from the US market (FDA, 2005a). The pharmacokinetic studies were subsequently performed in healthy subjects receiving 240 ml of high concentration of ethanol (40% v/v), equivalent to the one-third of a bottle of spirit, taken over five min immediately before Palladone™ dosing. The results revealed the fatally rise in hydromorphone plasma concentration with the average sixfold increase in C_{max} (maximum of 16-fold in one subject) and the 1.3-fold increase in AUC, in comparison to when taken with water. In vitro dissolution result of this product was reported by Walden et al. (2007), which correlated well with the in vivo data. Consequently, a regulatory decision framework has been develop in order to assess, thus minimise, the risk of ethanol-induced dose dumping for oral modified release formulations (Meyer and Hussain, 2005). Suitable in vitro tests are encouraged for new drug applications and currently marketed modified release products, since in vivo pharmacokinetic studies may post a risk to subjects. Recently, draft guidance for industry for several ER preparations has been issued with regard to additional dissolution testing in the presence of 5-40% ethanol in HCl for 2 h (FDA, 2007).

Attempts were made on designing in vitro conditions to evaluate the possible effects of concomitant alcoholic beverages on the release of various drug products (Table 6). Fadda et

al. (2008) studied the release of mesalazine from three marketed ER products, which aim for colonic targeting. 0.1 M HCl (pH 1.2) containing up to 40% v/v ethanol was used to simulate the gastric environment on ingestion of alcohol. This highest concentration of ethanol was expected to represent the most extreme conditions likely to be encountered in vivo (Walden et al., 2007). After pre-determined HCl/ethanol exposure times, successive pH transitions to simulate different regions of the GI tract were then performed. Dissolution profiles of Asacol® exhibited the highest variability (Fig. 3), while Pentasa® showed the most consistency when their releases were compared between different scenarios. It was found that, 40% ethanol led to the complete dose dumping of Pentasa® in most scenarios. The authors suggested that, the effect of alcohol on the release of drugs in vivo will be highly dependent on the kinetics of alcohol absorption and emptying, as the diverse release patterns for the same preparation were observed in different scenarios. The solubility of mesalazine was found to be independent of ethanol concentration, therefore, a complex interplay between the formulation, the release medium and the duration to its exposure was proposed. Moreover, no clear tendency, either as the form or extent, of alteration induced by ethanol was observed. This finding is consistent with those by Walden et al. (2007) where they found no clear correlation between the ethanol solubility of the ingredients and the ethanol susceptibility of several opioid formulations. Similarly, they suggested the occurrence of complex interactions between active and inactive ingredients and dosage form design. The authors claimed no risk of ethanol-induced dose dumping on various ER formulations of opiates employing different release technologies (Table 6), by utilising the in vitro dissolution tests over 2 h in standard aqueous dissolution media containing 4-40% v/v ethanol.

A 50% aspirin-loaded HPMC matrix tablet showed no dose dumping with regard to the effect of ethanol (Roberts et al., 2007). The kinetics and mechanism of aspirin released were, however, affected by the exposure to 40% v/v ethanol. The release of aspirin increased proportionally to the concentration of ethanol, because of the improved drug solubility. The polymer-alcohol interaction led to the initial fast release observed in the first 30 min as the polymer hydration rate was suppressed by the high concentration of ethanol. Similarly, Levina et al. (2007) reported no dose dumping of the HPMC matrix tablet containing felodipine, gliclazide or metformin hydrochloride when exposed to ethanol solutions. The release of metformin hydrochloride was slightly decreased in comparison to

the release in water, after exposed to the 40% v/v ethanol aqueous solution for 1 h. This was due to the reduced drug solubility (295 mg/ml in 40% v/v ethanol) compared with that in water (450 mg/ml). In contrast to the result obtained by Roberts et al. (2007), the three HPMC grades studied by Levina et al. (2007) exhibited consistent swelling and gel formation when exposed to hydro-alcoholic media. Koziara et al. (2006) also reported no dose dumping from OROS® system subjected to ethanol concentration up to 60%, although the drug released increased slightly. The permeability, the elasticity and the swelling of cellulose acetate membranes used for the osmotic system increased with increasing ethanol concentration.

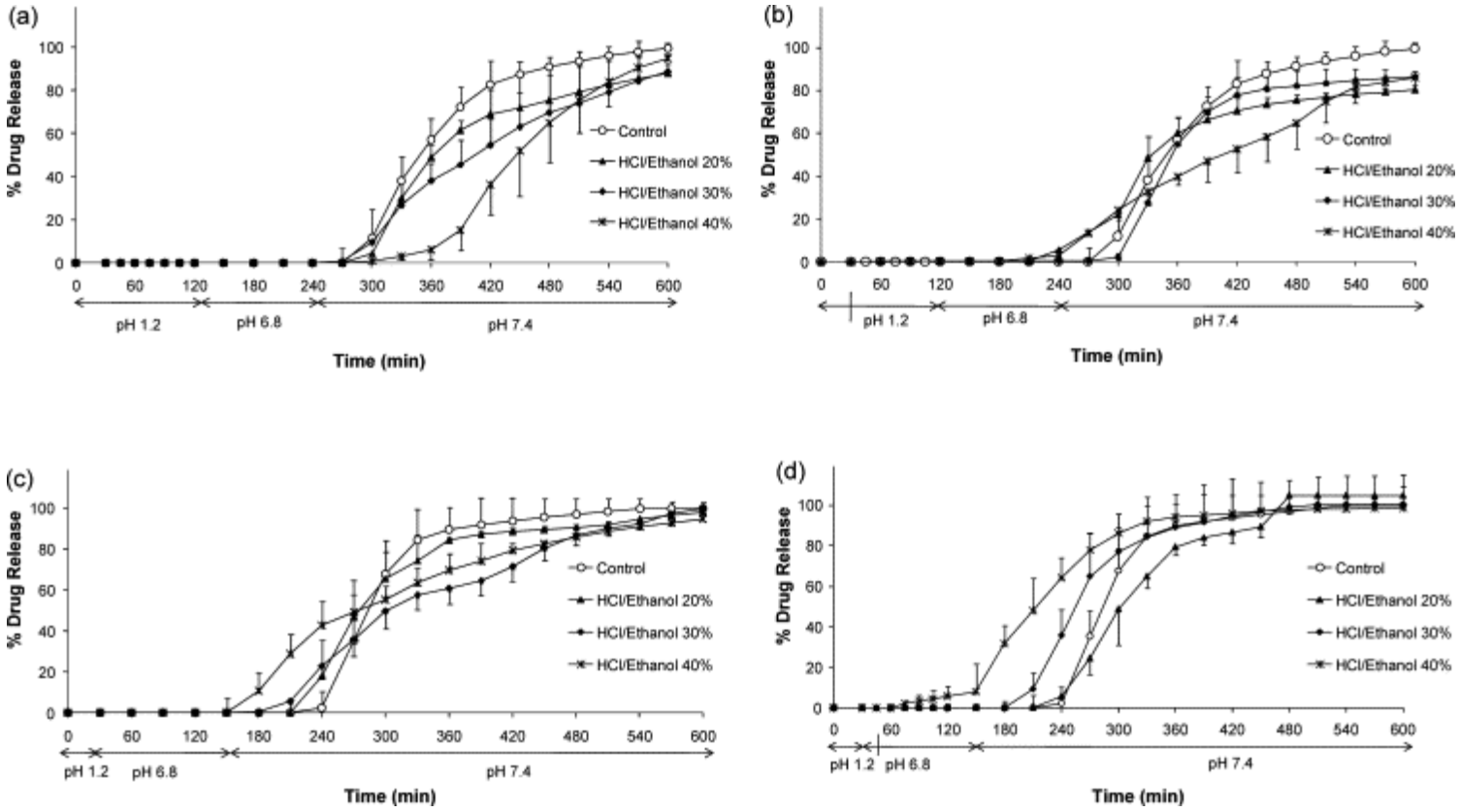


Fig. 3 Dissolution of Asacol tablets in (a) 0.1 M HCl with ethanol for 2 h followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer, (b) 0.1 M HCl with ethanol for 30 min followed by 0.1 M HCl with no ethanol for 90 min followed by pH 6.8 phosphate buffer for 2 h then by pH 7.4 phosphate buffer, (c) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h then pH 7.4 phosphate buffer and (d) 0.1 M HCl with ethanol for 30 min followed by pH 6.8 phosphate buffer for 2 h (first 15 min containing ethanol equivalent to half the concentration in acid) followed by pH 7.4 phosphate buffer. Dissolution profiles presented as mean (±S.D.) (Fadda et al., 2008).

Table 6 ER formulations and dissolution conditions to study the effect of ethanol

Active	Product	Technology/Excipients	Dissolution media and conditions (37°C)		Reference
Mesalazine	Salofalk®	Eudragit L coated tablet	0.1 M HCl, pH 1.2 with 0-40% v/v ethanol 0.05 M phosphate buffer, pH 6.8 and 7.4 USP Paddle 50 rpm, 1000 ml	*Scenario A*: HCl with/without ethanol (2 h) followed by pH 6.8 (2 h) then pH 7.4 *Scenario B*: HCl with/without ethanol (0.5 h) followed by HCl without ethanol (1.5 h) followed by pH 6.8 (2 h) then pH 7.4 *Scenario C*: HCl with/without ethanol (0.5 h) followed by pH 6.8 (2 h) then pH 7.4 *Scenario D*: HCl with/without ethanol (0.5 h) followed by pH 6.8 (2 h, first 15 min with/without half the concentration of ethanol in acid) then pH 7.4	Fadda et al. 2008
	Asacol®	Eudragit S coated tablet			
	Pentasa®	Compressed ethylcellulose (EC) coated granules			
Dihydrocodeine tartrate	DHC® Continus® 120 mg tablets*	CONTINUS® matrix control Hydroxyethylcellulose (HEC), cetostearyl alcohol	Phosphate buffer pH 6.5 Ph. Eur.[1] Paddle 100 rpm, 900 ml	Replace the appropriate volume of the aqueous media with the volumes of ethanol to obtain the ethanol concentration of 0-40% v/v 2 h dissolution time	Walden et al. 2007
Morphine sulphate	MST® Continus® 200 mg suspension*	Controlled (Ion exchange) release granules in sachets Cationic exchange resin, xanthan gum	Modified USP SGF (no pepsin)[2] pH 1.1 ± 0.05 Paddle 100 rpm, 900 ml		
	MST® Continus® 200 mg tablets*	CONTINUS® matrix control HEC, cetostearyl alcohol	Phosphate buffer pH 6.5 Ph. Eur.[1] Paddle 100 rpm, 900 ml		
	MXL® 200 mg capsules*	Matrix prolonged-release multiparticulates Hydrogenated vegetable oil, polyethylene glycol			
Oxycodone hydrochloride	OxyContin® 80 mg tablets*	ACROCONTIN® matrix control Ammoniomethacrylate polymer, glyceryl triacetate, povidone, stearyl alcohol	Modified USP SGF (no pepsin)[2] pH 1.2 ± 0.1 USP Basket 100 rpm, 900 ml		

Active	Product	Technology/Excipients	Dissolution media and conditions (37°C)		Reference
Hydromorphone hydrochloride	Palladone® SR 24 mg capsules*	Coated bead technology Microcrystalline cellulose, HPMC, EC, dibutyl sebacate	0.1% w/v sodium lauryl sulphate (SLS) solution Ph. Eur. Basket 150 rpm, 900 ml	Replace the appropriate volume of the aqueous media with the volumes of ethanol to obtain the ethanol concentration of 0-40% v/v 2 h dissolution time	Walden et al. 2007
Codeine base, Codeine sulphate	Codeine Contin® 100 mg tablets**	CONTINUS® matrix control HEC, cetostearyl alcohol	Purified, deionised water USP Basket 100 rpm, 500 ml		
Tramadol Hydrochloride	Zamadol® 24 h 400 mg tablets (once daily)***	Matrix prolonged-release tablet Hydrogenated vegetable oil	Phosphate buffer pH 6.5 Ph. Eur.[1] Paddle 100 rpm, 900 ml		
	Dromadol® SR 200 mg tablets (twice daily)****				
Aspirin	-	HPMC (Methocel® K4M) matrix tablet	Acetate buffer B.P. with 0-40% v/v ethanol B.P. Basket 50 rpm, 500 ml 6 h dissolution time		Roberts et al. 2007
Felodipine	-	HPMC (Methocel® K100LV CR) matrix tablet	0.1 M Phosphate buffer pH 6.5 USP with 1% w/v SLS USP Paddle 100 rpm, sinker, 500 ml	Replace the appropriate volume of the aqueous media with the volumes of ethanol to obtain the ethanol concentration of 0, 5 or 40% v/v 12 h dissolution time or hydro-alcoholic solutions for 1 h followed by the relevant non-alcoholic medium for 11 h	Levina et al. 2007
Gliclazide	-	HPMC (Methocel® K100LV CR) matrix tablet	Purified, deionised water USP Paddle 100 rpm, sinker, 900 ml		
Metformin hydrochloride	-	HPMC (Methocel® K100M CR) matrix tablet	Purified, deionised water USP Paddle 100 rpm, sinker, 1000 ml		

[1] For each litre dissolve in deionised water: 6.805 g potassium dihydrogen orthophosphate, 0.56 g sodium hydroxide. Purge with Helium; pH to 6.5 ± 0.05

[2] For each litre dissolve 2.0 g of sodium chloride in 500 ml of deionised water. Add 7.0 ml of concentrated hydrochloric acid, dissolve and make to 1 litre with deionised water. Purge with helium.

*Marketed in the UK by Napp Pharmaceuticals Limited.

**Marketed in Canada by Purdue Pharma Inc.

***Marketed in the UK by Meda Pharmaceuticals.

****Marketed in the UK by Teva Pharma.

1.3.4 Dissolution conditions for ER dosage forms

Standard conditions for dissolution testing (apparatuses, media compositions and volume, agitation rates, and temperatures) for various ER formulations are readily available in the official monographs. Often, those compendial dissolution tests are 'too general' because the diversity of technologies in formulation designs are utilized; thus, there are variety of product characteristics that dictate the test parameters (Jorgensen and Bhagwat, 1998). Several dissolution studies of ER products and various methods recommended by the FDA, see for example FDA (2005b), suggested the modifications of the existing dissolution tests in order to achieve a more reproducible and more realistic situation in vivo (Grundy et al., 1997; Dürig and Fassihi, 2000; Morita et al., 2003; Mu et al., 2003; Missaghi and Fassihi, 2005). The major considerations of the modifications include (i) dissolution testing equipment and (ii) physiological conditions, such as gastric emptying/intestinal transit time, variable pH, mechanical destructive forces, metabolism and food effects.

1.3.4.1 Dissolution testing for water-soluble matrix system

In spite of its popularity, the physicochemical characteristics of water-soluble matrix tablets, such as the formation of a highly viscous mass when fully hydrated, are subject to the difficulty of using compendial dissolution test methods. The large variation of drug released from each matrix tablet is caused by the unpredictable sticking and/or floating of the tablet to different positions within a dissolution vessel (Dürig and Fassihi, 2000). This random stickiness occurred either immediately at the bottom of the vessel or following a certain time of floating due to the reduction in tablet density once released. The varied release profiles of such tablets was attributed to the different limitation of the tablet surface that exposed to the release medium as well as an inconsistent hydrodynamic conditions which rely on the position of the sticking tablets. Moreover, the sampling process could be obstructed once the tablet stuck on the sampling filter. To overcome these difficulties, Dürig and Fassihi (2000) suggested the addition of a double ring mesh to the dissolution vessel of the USP apparatus II (Fig. 4). This setting was able to produce a more reliable release. The double mesh device created a space, to which the tablet will be placed. This method allowed full tablet surface exposure as expected to be the behavior of the tablets in vivo. It also

prevented the floating and did not restrict the tablets from swelling, as observed by the using of USP apparatus I (basket) or a wire helix sinker (Pillay and Fassihi, 1998; USP 29, 2006).

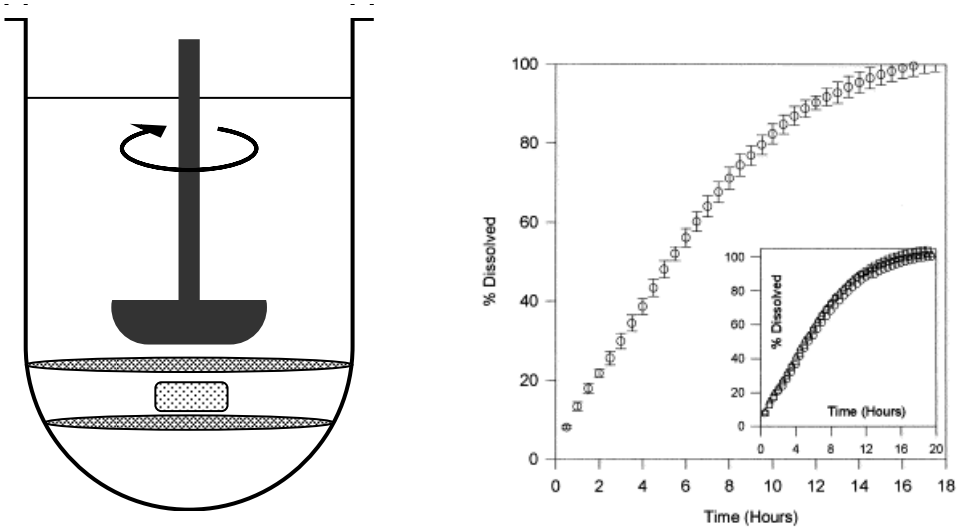


Fig. 4 Schematic showing the modification of apparatus II by inclusion of a double ring device and the release profiles representing the less variable of the individual tablets in the inset (Dürig and Fassihi, 2000).

The modification of testing conditions such as hydrodynamic mechanical stress and pH were suggested to provide the discriminatory dissolution tests for water-soluble matrix tablets. Abrahamsson et al. (1999) investigated prandial effects on the erosion rate, and hence the drug release from HPMC matrix tablets. The increased agitation was the only factor influenced the erosion of tablets in accordance with the in vivo food effects. Therefore, the USP apparatus II operated at 50 and 100 rpm was proposed as a discriminatory test. The significant of hydrodynamic conditions on the release of water-soluble matrix tablets were confirmed by Missaghi and Fassihi (2005). They evaluated the effect of hydrodynamics and the choice of a dissolution method on dimenhydrinate release from HPMC matrix tablets. The release rate was in the following order: apparatus III at 8 dpm > compendial apparatus II at 100 rpm > modified apparatus II (paddle over mesh) at 100 rpm > apparatus III at 5 dpm > modified apparatus II at 50 rpm > compendial apparatus II at 50 rpm > apparatus I at 100 rpm > apparatus I at 50 rpm. Full surface exposure of the tablets in the dissolution media was suggested to provide the more realistic conditions.

pH dependence of drug release from matrix tablets has been reported in the literature. The release of 6-*N*-Cyclohexyl-2′-*O*-methyladenosine sesquihydrate, a weak base with a pK_a of 3.01, was pH-dependent when formulated into a HPMC matrix tablet. This pH dependence of the drug release was not found when the drug was formulated into an osmotic tablet or EC-coated pellets (Royce et al., 2004). The effect of pH on the release of Nifedipine from a water-soluble matrix tablet was also reported (Schug et al., 2002a). While the drug release from the osmotic tablet (Adalat® OROS) was unaffected by the change of pH, the release from the matrix tablet was in the following order: pH 6.8 > pH 8.0 > pH 4.5 > pH 1.0. As a result, a discriminatory dissolution test for a water-soluble matrix tablet should include the effect of pH on the drug release.

1.3.4.2 Dissolution testing for osmotic system

The drug release from the osmotic system usually followed zero-order fashion. As reported by several researchers, the system was robust to environmental conditions. Hence, there is no specific dissolution apparatus or testing conditions recommended. As from experimental experience, however, the release of drugs from the osmotic tablets was in some cases inconsistent. This was due to the opening of the laser drill was blocked by the vessel wall. The inconsistency of the drug release was more pronounced when the drug was poorly soluble and the agitation rate was slow, since the drug was release as a suspension and accumulated at the delivery orifice. This retarded apparent release was the slower drug dissolution once released, and not the slower drug release (Wen and Park, 2010). Therefore, the appropriate dissolution media for the osmotic system should provide sink condition for the drug. The dissolution should also be rapid and complete, so the dissolution rate can be a surrogate for drug release.

1.3.4.3 Dissolution testing for multiparticulate pellet system

USP apparatus III (reciprocating cylinder) is considered as the first line apparatus in product development of controlled release products and especially the pellets (Joshi et al., 2008). The advantage of the system is the ability to mimic the changes of media, including pH gradient, buffer concentration, ionic strengths and mechanical forces of the GI tract, as it allows the dissolution tube to move between the successive rows of vessels containing

different media. The apparatus also offers sound hydrodynamic conditions, compared to that of the USP apparatus I or II. Jantratid et al. (2009) reported the successful of predicting food effect on the diclofenac release from modified release pellets by the application of the USP apparatus III and biorelevant dissolution media. Other studies have shown that the apparatus III was an attractive system for the dissolution testing of multiparticulate pellet system (Joshi et al., 2008; Chevalier et al., 2009).

1.4 OBJECTIVES

The purposes of this work were:

1.4.1 to examine the performance of commercially available bioequivalent products in vitro by performing release studies in various dissolution conditions and to evaluate the discriminating ability of those test conditions. Compendial dissolution methods with minor modification that mimic conditions in vivo were used to evaluate the performance of two pentoxifylline BE products and three verapamil hydrochloride bioequivalent products.

1.4.2 to investigate the effect of sodium dodecyl sulphate on the releases of drugs from different ER solid oral dosage forms. The release of poorly soluble drug and the drug formulated with ionic excipients are also explored. The influence of sodium dodecyl sulphate will be discussed mainly on formulation aspects.

1.4.3 to understand the relationships between the properties of drugs and their available ER dosage forms and to establish a guide for ER technology selection by the application of principal component analysis. The classification of single- vs. multiple-unit dosage form and the carrier systems of matrix tablets were examined. Significant properties distinguishing the dosage forms and matrix types were investigated

2. MATERIALS AND METHODS

2.1 MATERIALS

2.1.1 Drugs

Verapamil hydrochloride (HCl) (Knoll AG, Ludwigshafen, Germany), diltiazem HCl, carbamazepine (CBZ) (BASF AG, Ludwigshafen, Germany), pentoxifylline (Sigma-Aldrich Chemie GmbH, Steinheim, Germany).

2.1.2 Drug products

Thirteen commercially available extended release (ER) solid oral dosage form products were purchased from retail drugstores in Germany and the USA. Their compositions (Table 7), the pharmacokinetic data of bioequivalent products (pentoxifylline and verapamil HCl, Table 8) and the physicochemical properties of the drugs (Table 9) were collected from literature.

2.1.3 Buffer components

Hydrochloric acid (Carl Roth GmbH, Karlsruhe, Germany), sodium chloride (Carl Roth GmbH, Karlsruhe, Germany), potassium dihydrogen phosphate (Carl Roth GmbH, Karlsruhe, Germany), sodium hydroxide (Carl Roth GmbH, Karlsruhe, Germany), sodium acetate trihydrate (Carl Roth GmbH, Karlsruhe, Germany), glacial acetic acid (Carl Roth GmbH, Karlsruhe, Germany), sodium dihydrogen phosphate monohydrate (Merck KGaA, Darmstadt, Germany) and sodium dodecyl sulphate (SDS) (Carl Roth GmbH, Karlsruhe, Germany), polyoxyethylene sorbitan monooleate (Tween 80) (Carl Roth GmbH, Karlsruhe, Germany) and sorbitan monooleate (Span 80) (Merck Schuchardt OHG, Hohenbrunn, Germany). All chemicals and reagents were of analytical grade and were used as received.

Table 7 Composition of ER formulations (extended release polymers in bold)

Active	Type	Name	Company	Excipients
Verapamil HCl 120 mg	Matrix tablet	Isoptin	Abbott	**Sodium alginate, HPMC**, Microcrystalline Cellulose (MCC), Povidone K30, Mg stearate, [Film coating: HPMC, Montanglycol wax, Macrogol 400, Macrogol 6000, Talc]
	Coated pellets	VeraHexal	Hexal	**Ethylcellulose, Eudragit® L100-55**, Sucrose, Corn starch, Mg stearate, Povidone K30, Talc, Triethyl citrate, TiO_2
	Coated pellets	Verelan	Elan Drug	**Shellac,** Fumaric acid, Sucrose, Povidone, Talc, Titatium dioxide (TiO_2), Methylparaben, Propylparaben, Silicon dioxide, Sodium dodecyl sulphate (SDS)
	Osmotic tablet	Covera-HS[1]	G.D. Searle LLC	**Cellulose acetate**, HEC, HPMC, Hydroxypropyl cellulose, Butylated hydroxytoluene, Lactose, Mg stearate, Polyethylene glycol (PEG), Polyethylene oxide, Polysorbate 80, Povidone, Sodium chloride, TiO_2
Diltiazem HCl 180 mg	Matrix tablet	Dilzem retard	Pfizer	**HEC, HPMC**, Lactose monohydrate, Macrogol 6000, Mg stearate, Hydrogenated castor oil, Stearic acid, Simeticon, Talc, TiO_2
	Coated pellets	Diltiazem-ratiopharm	Ratiopharm	**Ethylcellulose**, Sucrose, Corn starch, Cetyl alcohol, SDS, Povidone K30, Talc, Dibutyl decandioat, TiO_2
	Coated pellets	Dilzem uno	Pfizer	**Eudragit® RS and RL**, Sucrose, Corn starch, Fumaric acid, Povidone K30, Propylene glycol, Talc, TiO_2
Pentoxifylline 400 mg	Matrix tablet	Trental	Sanofi Aventis	**HEC 4000 mPa·s**, Povidone K25, Macrogol 8000, HPMC 5 mPa·s, Mg stearate, TiO_2, Talc
	Matrix tablet	Rentylin	Amdipharm	**Eudragit® RS and RL**, Eudragit® E, Povidone K25, Macrogol 6000, Mg stearate, TiO_2
Carbamazepine 200 mg	Matrix tablet	Tegretal	Novartis	**Eudragit® NE 30D, Aquacoat ECD** (Ethylcellulose, Cetyl alcohol and SDS), Colloidal silicon dioxide, Mg stearate, Talc, MCC, Carboxymethylcellulose sodium [Film coating: HPMC, Macrogolglycerol hydroxystearate, Talc]
	Matrix tablet	Espa-lepsin	Esparma	**Eudragit® RS, Eudragit® L 100-55**, Triacetin, Talc, MCC, Crospovidone, Colloidal silicon dioxide, Mg stearate, Sorbic acid, Sodium hydroxide, SDS, Polysorbate 80
	Coated pellets	Carbatrol[2]	Shire	Citric acid, Colloidal silicon dioxide, Lactose monohydrate, MCC, PEG, Povidone, SDS, Talc, Triethyl citrate
	Osmotic tablet	Tegretol-XR	Novartis	**Cellulose acetate**, Dextrates, Iron oxide, Mg stearate, Mannitol, PEG, SDS, TiO_2

[1] 180 mg

[2] tree types of pellet: 25%-IR, 40%-ER and 35%-enteric coated

Table 8 Pharmacokinetic parameters of bioequivalent products

(a) Pentoxifylline: 600 mg, single dose[1]

	HEC matrix tablet (Trental)	Eudragit RS/RL matrix tablet (Rentylin)
C_{max} (µg/ml)	111.8 ± 57.1	116.1 ± 65.7
t_{max} (h)	2.1 ± 1.1	1.4 ± 0.9
AUC (h-µg/ml)	637.7 ± 282.0	583.0 ± 331.7

(b) Verapamil HCl: 240 mg per day for 5 days[1]

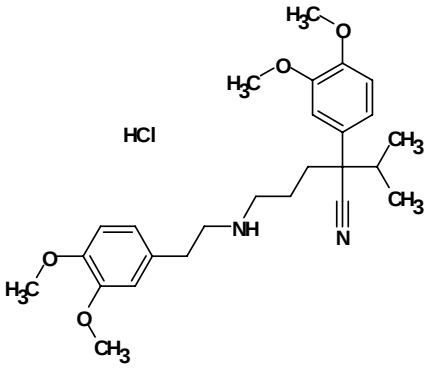
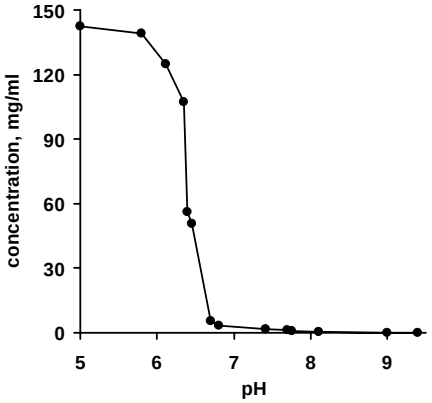
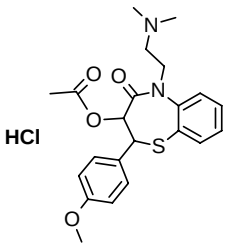
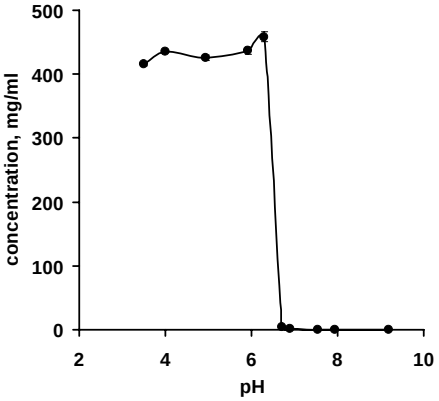
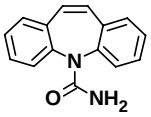
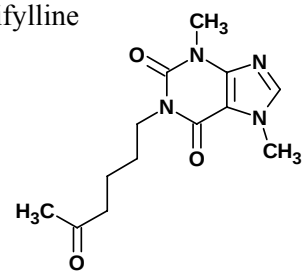
	Sodium alginate/HPMC matrix tablet (Isoptin)	EC/Eudragit L100-55 coated pellets (VeraHexal)
C_{max} (ng/ml)	191.8 ± 134.2	163.1 ± 63.2
t_{max} (h)	5.5 ± 2.5	5.1 ± 1.2
AUC (h-ng/ml)	2043.6 ± 1106.3	1943.1 ± 846.1

(c) Verapamil HCl: 240 mg, single dose[2]

	Sodium alginate/HPMC matrix tablet (Isoptin)	Shellac/Fumaric acid coated pellets (Verelan)
C_{max} (ng/ml)	171.0 ± 78.2	114.3 ± 33.9
t_{max} (h)	5.0 ± 2.0	7.3 ± 1.6
AUC (h-ng/ml)	1670.9 ± 909.3	1675.0 ± 518.1
$t_{1/2}$ (h)	6.2 ± 1.4	9.2 ± 2.1
Peak-to-24 h trough ratio	10.1 ± 4.1	3.8 ± 2.8

[1]Fachinformation Online Database
[2]Devane et al. (1990)

Table 9 Physicochemical properties of drugs

Drug	Solubility
Verapamil HCl 	 pH-solubility profile of verapamil HCl (water, 37 °C), reproduced from Streubel et al. (2000)
Diltiazem HCl 	 pH-solubility profile of diltiazem HCl (water, room temperature)
Carbamazepine 	0.22 mg/ml (water, 37 °C) 0.51 mg/ml (water, 0.25% SDS, 37 °C)
Pentoxifylline 	191 mg/ml (water, 37 °C) (El-Gazayerly, 2003)

2.2 EXPERIMENTAL METHODS

2.2.1 Drug solubility determinations

Diltiazem HCl

Solubility measurements of diltiazem HCl were conducted in the pH range from 3.5 to 9.0 at room temperature (*n*=2). An excess amount of drug was added to 100 ml deionized water. The sample was stirred at 500 rpm with magnetic stirrer. After 1 h stirring time at each pH step (modified with 1 N sodium hydroxide), 5 ml samples were repeatedly taken and centrifuged (DIGIFUGE GL, Heraeus-Christ GmbH, Osterode) at 4500 rpm for 30 min. The drug concentration in the supernatant was determined spectrophotometrically at 260 nm and the final pH value was measured (pH-Meter CG711, Schott-Geräte GmbH, Hofheim, Germany).

Carbamazepine

An excess amount of drug was added to deionized water containing 0–1% w/v sodium dodecyl sulphate (*n*=2). After equilibrium was reached (24 h, horizontal shaking, 37 °C) the drug concentration in the supernatant was determined spectrophotometrically at 312 nm (HP8453, Hewlett-Packard, Waldbronn, Germany).

2.2.2 In vitro drug release studies

In vitro drug release was determined using the USP rotating paddle method (900 ml medium; 10-150 rpm; 37 °C; *n*=2-3) (VanKel 7010 or VanKel 7025, Varian Inc., NC, USA) equipped with an online UV-visible spectrophotometer (Cary 50 Tablet, Varian Inc. NC, USA). At predetermined time intervals, samples were automatically withdrawn and assayed spectrophotometrically at 278 nm for verapamil HCl, 260 nm for diltiazem HCl, 312 nm for carbamazepine and 295 nm for pentoxifylline.

The dissolution media were prepared according to the USP XXVI as followed: simulated gastric fluid without enzyme pH 1.2, simulated intestinal fluid without enzyme pH 6.8, acetate buffer pH 4.5 and simulated intestinal fluid without enzyme pH 6.8. Osmolality of the media (Semi-Micro Osmometer K-7400, Knauer GmbH, Berlin, Germany) was adjusted with sodium chloride. The dissolution media for the lower surface tension of 30-48 mN/m

(detachable ring method, Digital-Tensiometer K 10 ST, Krüss GmbH, Hamburg, Germany), which are close to that of the human GI fluid (33 mN/m) (Pedersen et al., 2000; Kalantzi et al., 2006), were prepared by the addition of 0.25% w/v and 0.50% w/v sodium dodecyl sulphate, 0.25% w/v Tween 80 or 0.05% w/v Span 80 into sodium phosphate buffer solution pH 6.8 (one litre contained 6.9 g sodium dihydrogen phosphate monohydrate and 0.89 g sodium hydroxide). The sodium dodecyl sulphate concentration of 0.25% was according to the recommendation of the International Pharmaceutical Federation (FIP) guidelines, 1997. It was also the lowest sodium dodecyl sulphate concentration above the critical micelle concentration that provided sink condition for carbamazepine products (200 mg).

2.2.3 Comparison of release profiles

Similarity factor (f_2) was applied to compare the difference between percent drug released per unit time for a pair of drug products. It is defined as followed (Moore and Flanner, 1996):

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

where n is the number of dissolution sample times, and R_t and T_t are the mean percent drug dissolved at each time point t for the reference and test products, respectively. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar (FDA, 1997). A robust formulation within the scope of this study refers to a product that releases its drug similarly in various dissolution conditions.

2.3 THEORETICAL METHODS

Nomenclature

IR	Immediate release
ER	Extended release
Mw[a]	Molecular weight
LogP[a]	Logarithm of the ratio of the concentrations of the un-ionized compound between octanol and water
H-bond donors[b]	Number of the hydrogen bond donor (OH and NH) of a compound
H-bond acceptors[b]	Number of the hydrogen bond acceptor (N and O) of a compound
PSA[b]	Summation of polar surface area of all polar fragments (A°)
Max dose	Maximum dose strength of a product (mg)
Do	Dose number
$t_{1/2}$ IR	Elimination half-life of a drug as IR formulation (h)
$t_{1/2}$ ER	Elimination half-life of a drug as ER formulation (h)
$t_{1/2}$ ratio	Ratio of $t_{1/2}$ ER to $t_{1/2}$ IR
t_{max} IR	Time to peak plasma concentration of a drug as IR formulation (h)
t_{max} ER	Time to peak plasma concentration of a drug as ER formulation (h)
t_{max} ratio	Ratio of t_{max} ER to t_{max} IR

[a]NCBI (1993)
[b]Calculated through Molinspiration Property Calculation Service (http://www.molinspiration.com) using the JME molecular editor

2.3.1 Data set

145 samples (85 tablets and 60 reservoir-typed multiparticulate pellet systems) of commercially available ER solid oral dosage form products were include in the classification of single- vs. multiple-unit dosage forms, while 62 matrix tablets were used in the classification of matrix carrier systems. The formulation compositions and the drug properties were retrospectively collected from readily available literature and various databases. The physicochemical, biopharmaceutical and pharmacokinetic properties included in the classification of dosage forms and the matrix carrier systems are: Mw, pKa,

LogP, H-bond donors, H-bond acceptors, PSA (°A), Solubility (mg/ml), Max dose (mg), Dose number (Do), $t_{1/2}$ IR (h), $t_{1/2}$ ER (h), $t_{1/2}$ ratio, t_{max} IR (h), t_{max} ER (h) and t_{max} ratio

2.3.2 Calculation of dose number

The dimensionless dose number (Do) is the ratio of drug concentration in the administered volume (250 ml) to the saturation solubility of the drug in water (Oh et al., 1993). Eq. 1 was used to calculate the Do:

$$Do = \frac{dose(mg)/250ml}{solubility(mg/ml)} \qquad \text{(Eq. 1)}$$

A drug with Do less than or equal to one is defined as a highly soluble drug.

2.3.3 Statistical analysis

To ensure the normal distribution of input data, square root transformation or logarithmic transformation was applied to the variables (i.e. drug properties) which have non-normal distributed values. A standard score (Z-score) was then calculated for each (transformed) variable by Eq. 2:

$$z = \frac{x - \mu}{\sigma} \qquad \text{(Eq. 2)}$$

where x is a raw score to be standardized, μ is the mean of the population and σ is the standard deviation of the population. This standardization was performed so that each variable was mean-centered with a standard deviation of one, hence contributed equally to the analysis regardless of their respective values. The Z-scores of all variables were used as input data for PCA, which was carried out using JMP® 8.0 (SAS Institute Inc., Cary, NC).

3. RESULTS AND DISCUSSION

3.1 In vitro performance and dissolution robustness of bioequivalent extended release solid oral dosage forms

3.1.1 Introduction

Bioequivalence (BE) is defined by the Food and Drug Administration (FDA) (2003) as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." Under certain circumstances indicated in the regulatory guidance (FDA, 2003), an in vitro approach, i.e. dissolution test, can replace in vivo studies for BE assessment.

The selection of appropriate dissolution media, apparatus and test parameters which reflect in vivo drug release is challenging (Uppoor, 2001; Gu et al., 2004; Royce et al., 2004). The ultimate goal of the dissolution test is to predict the in vivo performance of products from in vitro test by a proper in vitro/in vivo correlation (IVIVC) (Emami, 2006). The tests may not be pharmacopeial standard, however, they should be sensitive, reliable and discriminatory with regard to the in vivo drug released characteristics (Qureshi, 2006; Azarmi et al., 2007).

Physiological conditions vary considerably along the gastrointestinal (GI) tract. Various factors within an individual as well as the influence of co-administered food significantly influence the GI conditions (Dressman et al., 1998). Those aspects, among other things, include the changes of pH, osmolality, agitation and mechanical destructive forces, and surface tension. The variation of these parameters can be critical for the performance of extended release (ER) systems, given that the dosage forms are designed to remain in the GI tract over a longer period and transit through various conditions. Therefore, a robust ER formulation which demonstrates a reliable performance over a wide range of the GI conditions is highly desirable.

Efforts have been made to simulate biorelevant dissolution media (Galia et al., 1998; Al-Behaisi et al., 2002; Sunesen et al., 2005; Jantratid et al., 2008). Although, they were used successfully to establish IVIVC (Nicolaides et al., 1999; Dressman and Reppas, 2000; Wei

and Löbenberg, 2006), the application of these media is less likely to be a standard practice because they are expensive and less stable. Since the compositions of the biorelevant media are complex, it is difficult to understand the influences of an individual factor on dosage form performance. The present study simulated various dissolution conditions, which ER dosage forms would encounter in vivo. The pharmacopeial standard buffer solutions were properly adjusted to meet those conditions.

The objective of this study was to examine the in vitro release patterns of BE products of pentoxifylline and verapamil hydrochloride, which are commercially available as ER formulations. There release profiles were expected to be similar once tested in discriminatory dissolution conditions. Factors affecting the release were also investigated.

3.1.2 Results and discussion

Upon contact with release media, the dissolution characteristics of each drug product vary from one to the other. This variation depends on several factors such as the physicochemical properties of drugs (e.g. solubility), type of dosage forms/technologies, formulation compositions as well as test conditions. Discriminatory dissolution test should be used to evaluate the drug release as it represents the product performance in vivo. Compendial dissolution methods with minor modification that mimic conditions in vivo were used to evaluate the performance of two drugs, pentoxifylline (Trental and Rentylin) and verapamil HCl (Isoptin, VeraHexal and Verelan).

3.1.2.1 Pentoxifylline

In vitro performance of bioequivalent pentoxifylline products

The release of pentoxifylline (Fig. 5-7) and the characteristic of the tablets (Fig. 8) of water-soluble, hydroxyethyl cellulose (HEC) (Trental) and water-insoluble, poly(ethyl acrylate, methyl methacrylate) trimethylammonioethyl methacrylate chloride (Eudragit RS/RL) (Rentylin) matrix formers are presented. After 24 h release, the remaining of the HEC matrix tablet was a small gel mass (Fig. 8a), while the Eudragit RS/RL matrix was intact but soft and fell apart when touched (Fig. 8b).

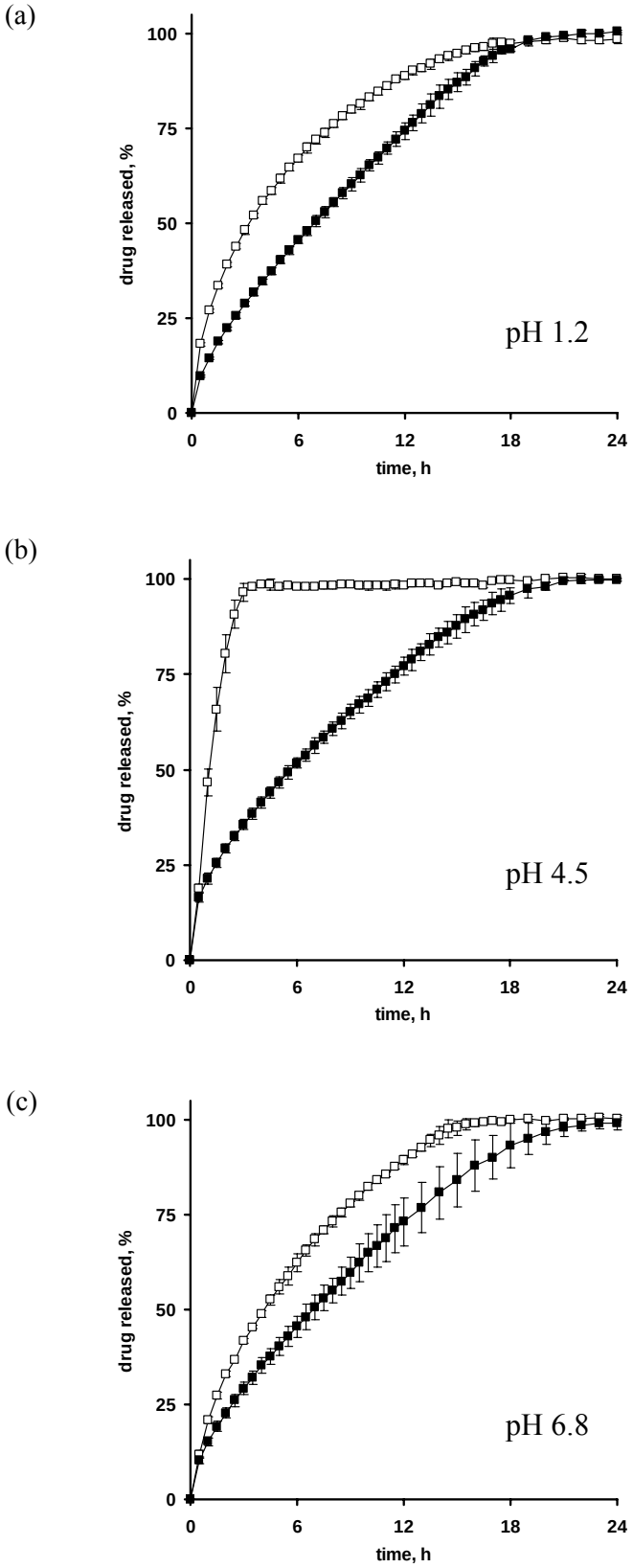


Fig. 5 Pentoxifylline release from two bioequivalent products as a function of pH: (■) HEC tablets (Trental) and (□) Eudragit RS/RL tablets (Rentylin).

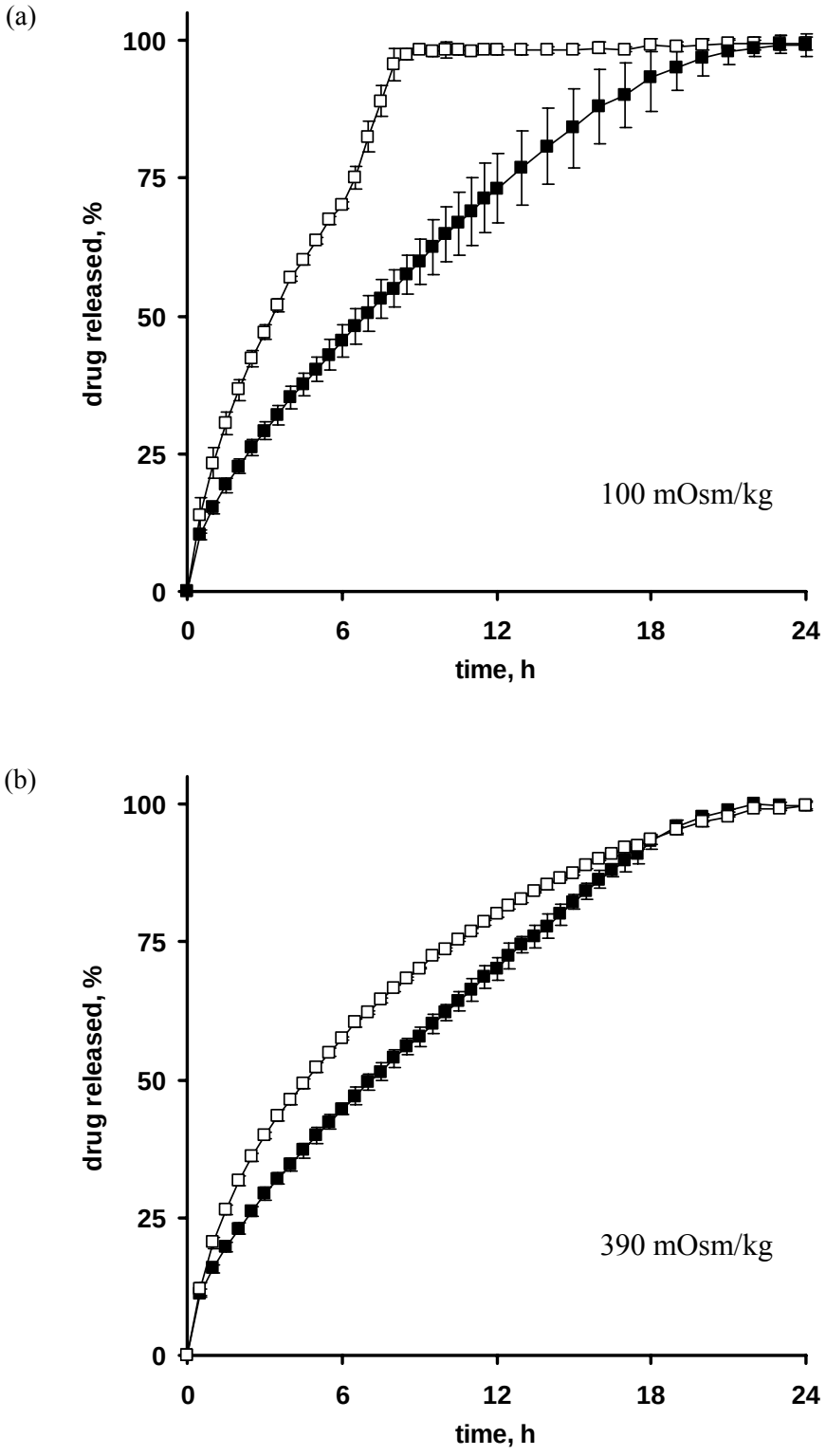


Fig. 6 Pentoxifylline release from two bioequivalent products as a function of osmolality: (■) HEC tablets (Trental) and (□) Eudragit RS/RL tablets (Rentylin).

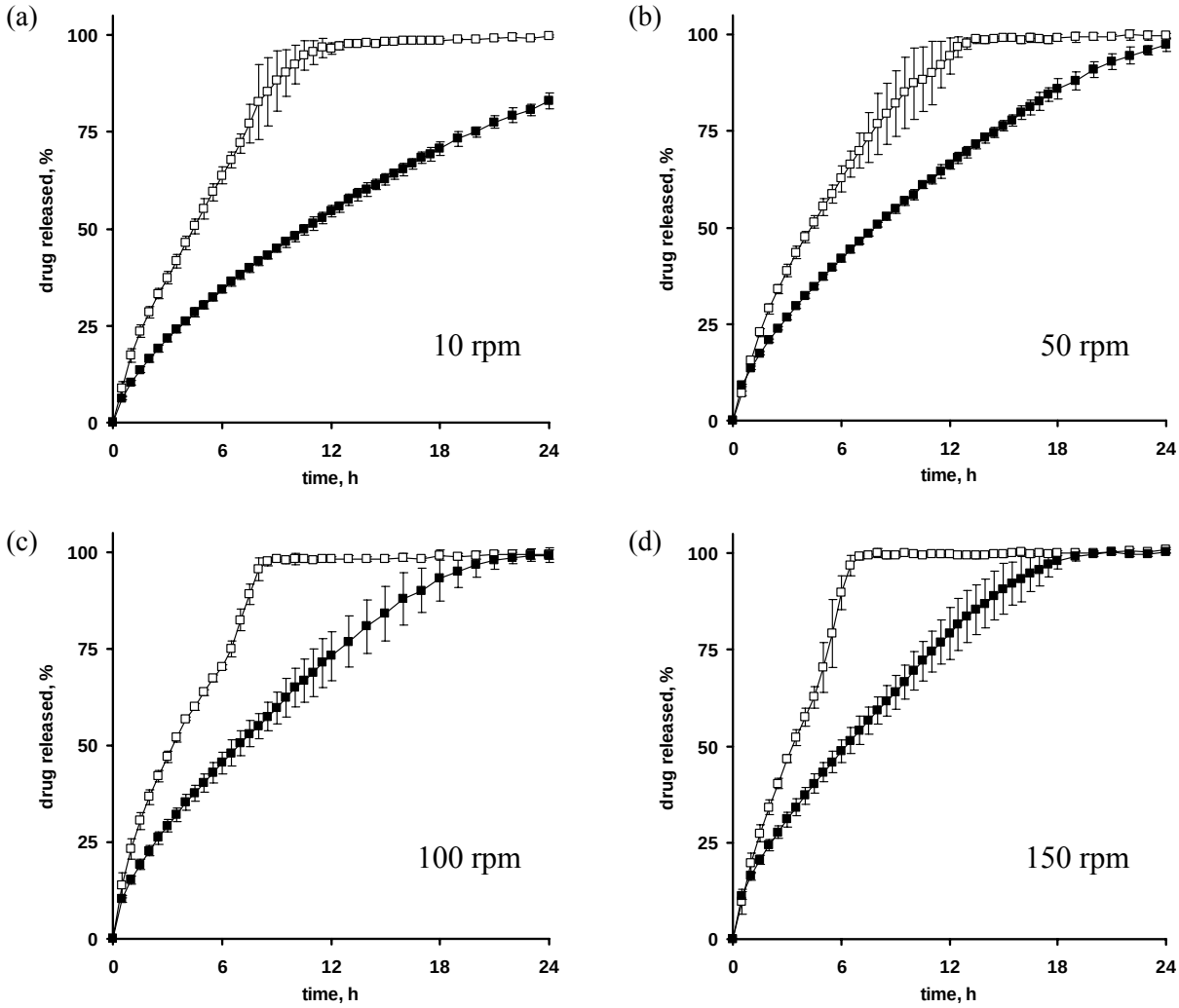


Fig. 7 Pentoxifylline release from two bioequivalent products as a function of agitation rate: (■) HEC tablets (Trental) and (□) Eudragit RS/RL tablets (Rentylin).

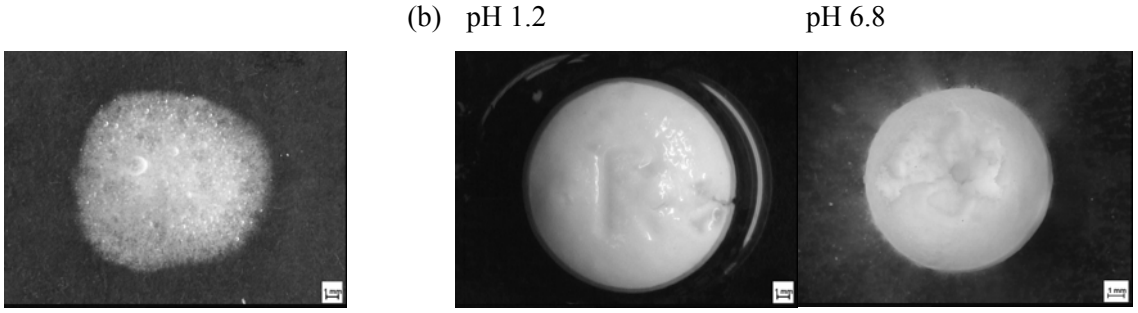


Fig. 8 Microscopic pictures of pentoxifylline (a) HEC and (b) Eudragit RS/RL matrix tablets after 24 h release in pH 1.2 and pH 6.8. The characteristic of the HEC tablets in both pH media were similar.

Pentoxifylline release from the HEC matrix tablet was significantly slower (f_2 < 50, Table 10) under all test conditions when compared to Eudragit RS/RL tablets (Fig. 5-7). The most comparable profiles, although f_2 is 48.6 (Table 10), was seen when the osmolality of the dissolution medium was 390 mOsm/kg (Fig. 6b). Both products had extended dissolution profiles with 50% release times in pH 6.8 ($t_{50\%}$) of approximately 7 h and 3 h for the HEC- and the Eudragit RS/RL matrix tablets, respectively. The extended in vitro profile was confirmed in vivo where the HEC matrix had the longer t_{max} of 2.1 h compared with 1.4 h for the Eudragit RS/RL one (Table 8a). It could be assumed from their t_{max} values that the release from both tablets in vivo was much faster than those in vitro, particularly in the case of the less mechanically stable HEC matrix. This rapid release could be caused by the stronger mechanical destructive force of the GI tract, thereby accelerating the drug release.

Table 10 Similarity factor (f_2) calculated from mean dissolution data of BE pentoxifylline matrix tablets in various dissolution conditions

Dissolution condition	f_2 value HEC vs. Eudragit RS/RL matrix tablets
pH 1.2	36.0
pH 4.5	19.6
pH 6.8	41.0
100 mOsm/kg	33.0
390 mOsm/kg	48.6
10 rpm	28.5
50 rpm	35.5
100 rpm	33.0
150 rpm	33.8

Robustness of pentoxifylline ER products

The drug release from the HEC matrix tablet was robust to changes in pH and osmolality, but varied with agitation rate (Fig. 9). However, only the release at 10 rpm was considered different from the others (f_2 = 48.8, 42.7 and 37.4: at 10 rpm vs. 50, 100 and 150 rpm, respectively). The f_2 values of all other comparison pairs ranged between 50 and 100 (Table 11a).

Although a pH-independent drug release is expected from the Eudragit RS/RL matrix tablet, Fig. 9 (top) shows the fastest release of pentoxifylline in pH 4.5, followed by release in pH 1.2 and pH 6.8; however, the release in the latter two pH media were similar (f_2 = 65.0, Table 11b). This variation was caused by the effect of anionic buffer species, which have different selectivity coefficient (chloride > phosphate > acetate) (Bodmeier et al., 1996). The drug release in different pH composed of those buffer species, therefore, demonstrated different release profiles. The anionic interaction between the fixed groups and the counterions was also contributed to the decreased drug release in the medium with higher osmolality. The pentoxifylline release from the Eudragit RS/RL matrix tablet in 390 mOsm/kg (as in fed state) (Kalantzi et al., 2006) decreased significantly (f_2 = 46.2) when compared to that in 100 mOsm/kg (Fig. 9, middle). This was due to the greater amount of chloride ions in the media of the higher osmolality and thus, the stronger chloride ion effect. A lower degree of polymer hydration, swelling and drug released were then expected.

The effect of agitation rates on the drug release from the Eudragit RS/RL matrix (Fig. 9, bottom) was less pronounced than that of the HEC tablets. This could be explained by the higher physical stability of the water-insoluble matrix former (Huang et al., 1994).

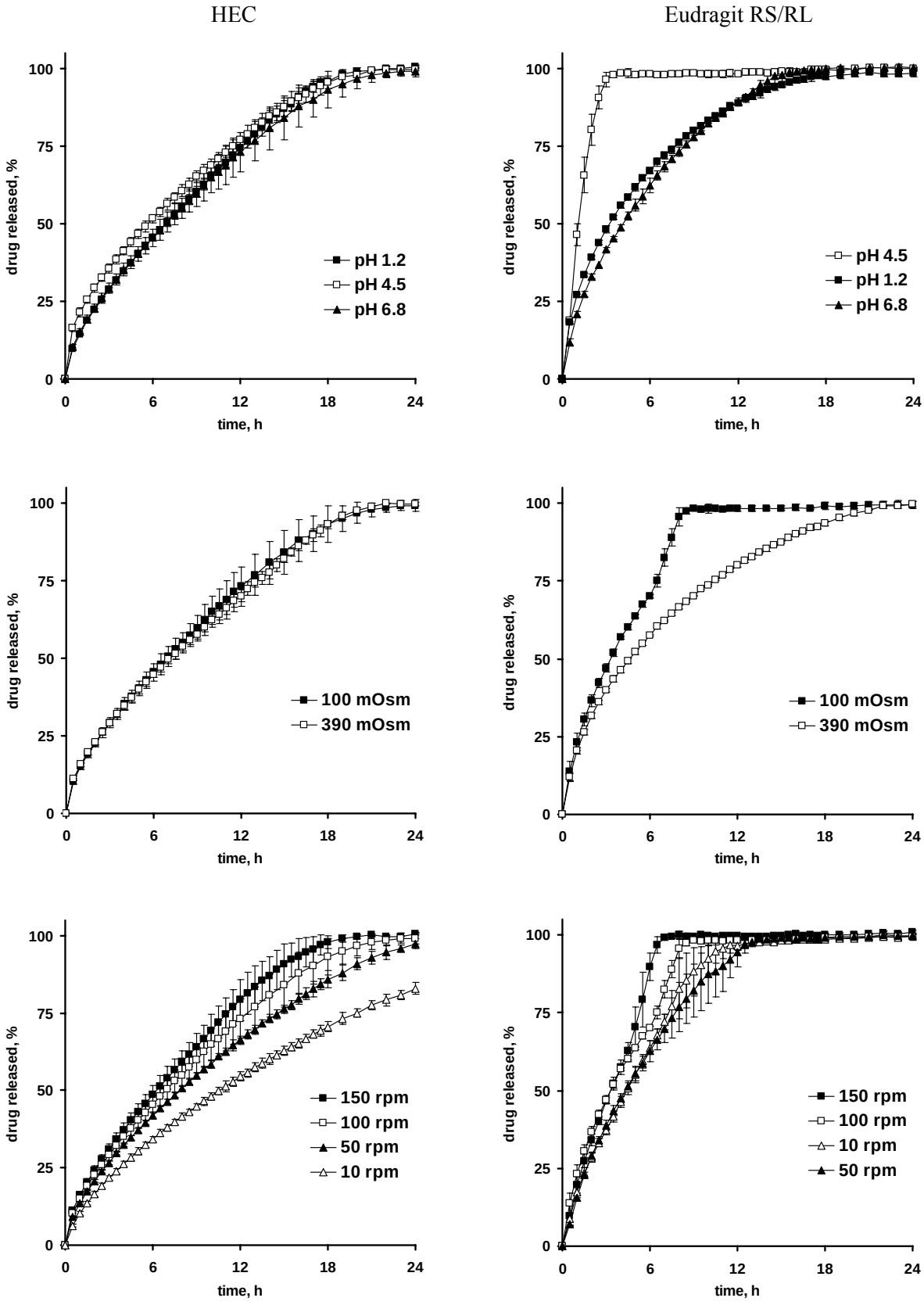


Fig. 9 Pentoxifylline released from HEC and Eudragit RS/RL matrix tablets; effect of pH at 100 rpm (top), osmolality at 100 rpm/pH 6.8 (middle) and agitation rate in pH 6.8 (bottom).

Table 11 Similarity factor (f_2)* calculated from mean dissolution data of pentoxifylline matrix tablets in various dissolution conditions

(a) HEC matrix

Test / Reference	pH 4.5	pH 6.8	390 mOsm/kg	50 rpm	100 rpm	150 rpm
Effect of pH at 100 rpm						
pH 1.2	**63.7**	**92.6**	-	-	-	-
pH 4.5	-	**62.7**	-	-	-	-
Effect of osmolality at 100 rpm/pH 6.8						
100 mOsm/kg	-	-	**85.3**	-	-	-
Effect of agitation rate in pH 6.8						
10 rpm	-	-	-	48.8	42.7	37.4
50 rpm	-	-	-	-	**65.0**	**52.3**
100 rpm	-	-	-	-	-	**69.8**

(b) Eudragit RS/RL matrix

Test / Reference	pH 4.5	pH 6.8	390 mOsm/kg	50 rpm	100 rpm	150 rpm
Effect of pH at 100 rpm						
pH 1.2	24.4	**65.0**	-	-	-	-
pH 4.5	-	20.8	-	-	-	-
Effect of osmolality at 100 rpm/pH 6.8						
100 mOsm/kg	-	-	46.2	-	-	-
Effect of agitation rate in pH 6.8						
10 rpm	-	-	-	**76.3**	**52.9**	45.1
50 rpm	-	-	-	-	**51.7**	45.2
100 rpm	-	-	-	-	-	**56.8**

*__bold__: the releases were similar

3.1.2.2 Verapamil HCl

In vitro performance of bioequivalent verapamil HCl products

Fig. 10-12 and Table 12 show the release and the similarity factor of verapamil HCl from there bioequivalent ER products (Isoptin, VeraHexal and Verelan) in various pH media, osmolalities and agitation rates. In most test conditions, the matrix tablet released faster than did the pellets, where the shellac/fumaric acid coated ones exhibited the slowest release. The more similar release profiles between the matrix tablet and the EC/Eudragit L100-55 coated pellets, when compared to shellac/fumaric acid coated pellets, was also demonstrated in the more comparable pharmacokinetic parameters (Table 8b). While the extent of absorption (AUC) of the matrix tablet and the shellac/fumaric acid coated pellets were similar, the slow release profile of the latter was confirmed in vivo by the lower C_{max} of 114.3 ng/ml and the longer t_{max} of 7.3 h compared to the tablet (171 ng/ml and 5 h, respectively) (Table 8c). It can be noted that the drug release from shellac/fumaric acid coated pellets was incomplete within 24 h in all studied conditions, except when 0.25% w/v sodium dodecyl sulphate was added into the dissolution medium (Fig. 10c). This release profile was very similar to the release obtained using rotating basket method at 75 rpm, pH 3.0, which was suggested by the FDA (2005b) and has been reported previously (Devane et al., 1990). It can be speculated that, the GI physiological conditions accelerate the release of pellets to a much faster rate than that observed in vitro. This could be attributed to the effect of the lower surface tension. Accordingly, the addition of 0.25% w/v sodium dodecyl sulphate to the media recommended in the compendial dissolution test conditions, i.e. paddle method, 50 rpm, pH 1.2 and 6.8 (USP XXVI) could provide the better dissolution conditions, as it mimics those in vivo.

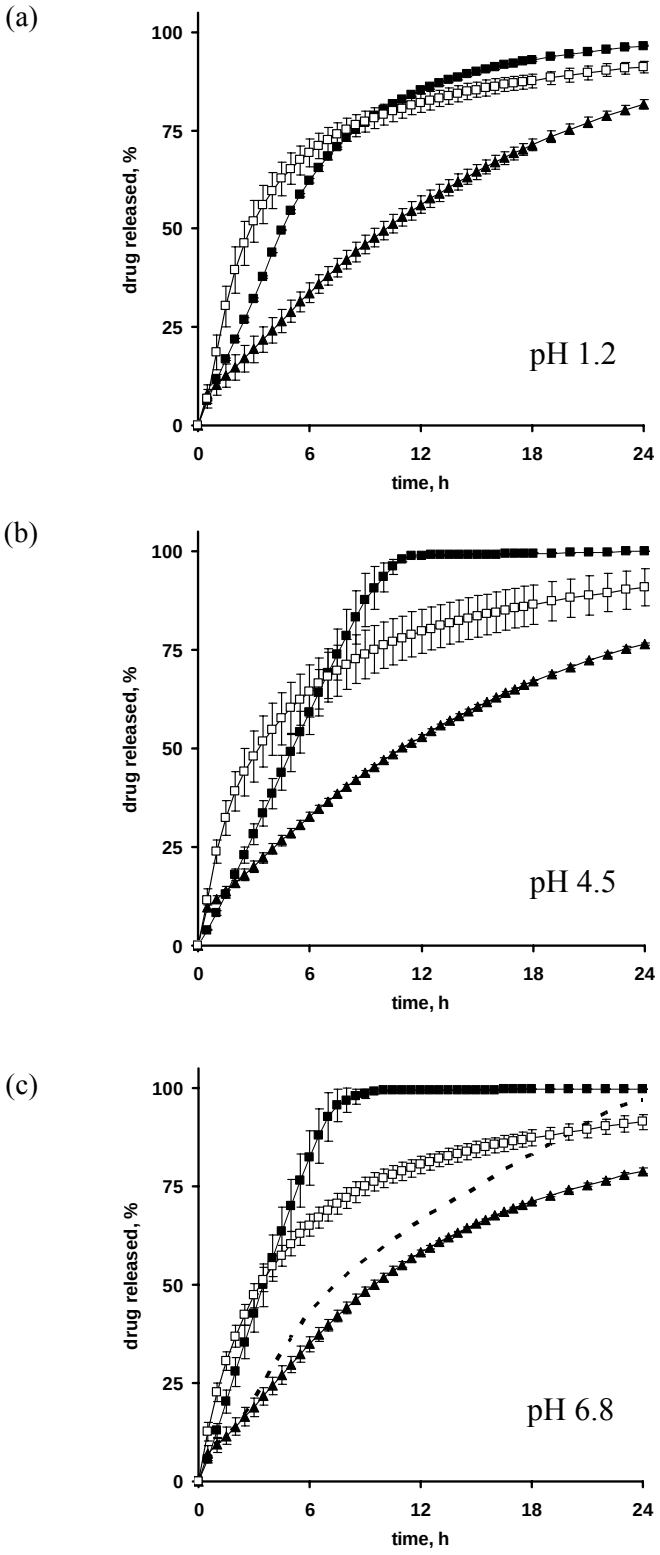


Fig. 10 Verapamil HCl release from three bioequivalent products as a function of pH: (■) sodium alginate/HPMC matrix tablet (Isoptin), (□) EC/Eudragit L100-55 coated pellets (VeraHexal), (▬) shellac/fumaric acid coated pellets (Verelan), with 0.25% w/v sodium dodecyl sulphate and (▲) Verelan without sodium dodecyl sulphate.

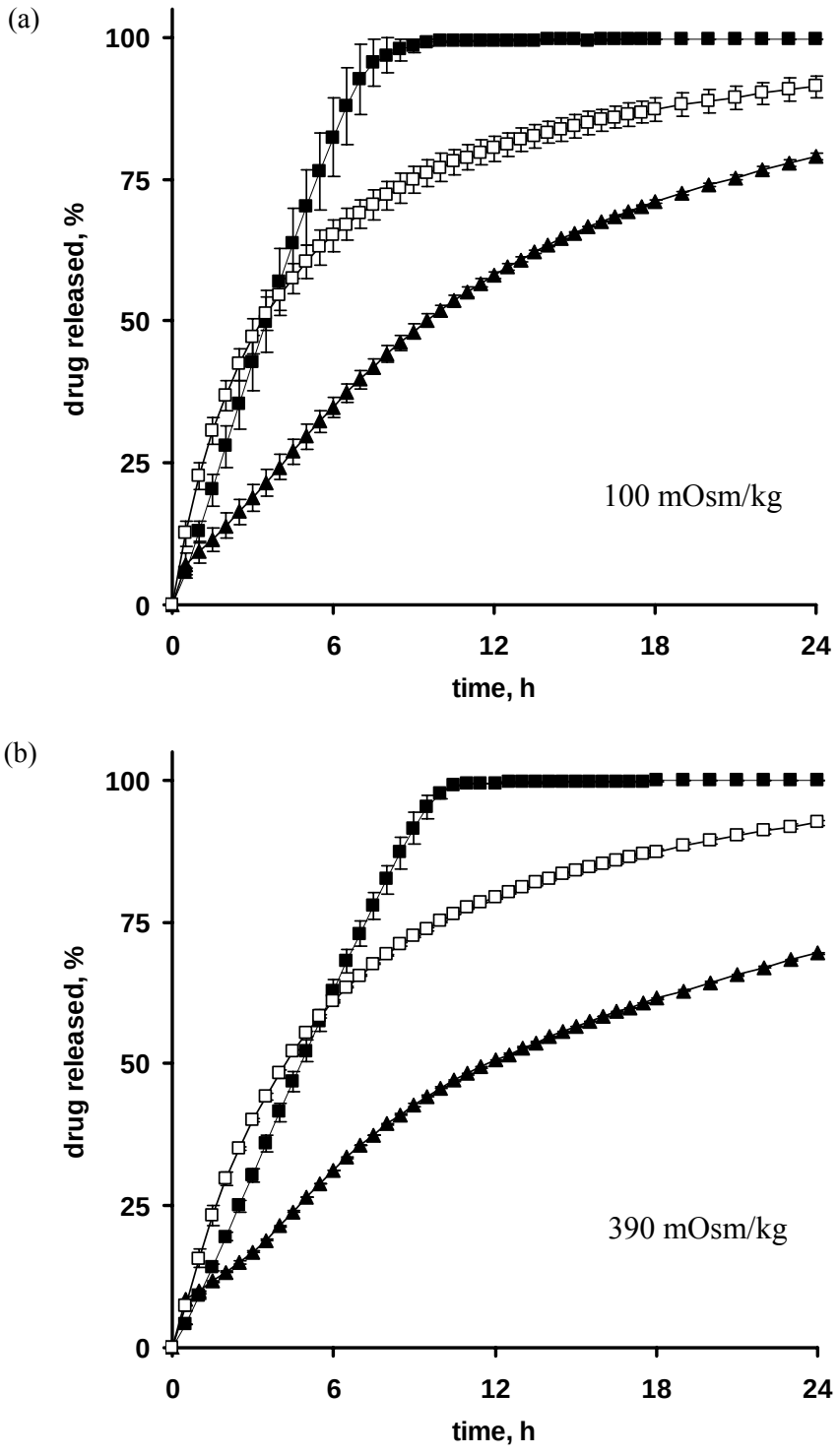


Fig. 11 Verapamil HCl release from three bioequivalent products as a function of osmolality: (■) sodium alginate/HPMC matrix tablet (Isoptin), (□) EC/Eudragit L100-55 coated pellets (VeraHexal) and (▲)shellac/fumaric acid coated pellets (Verelan).

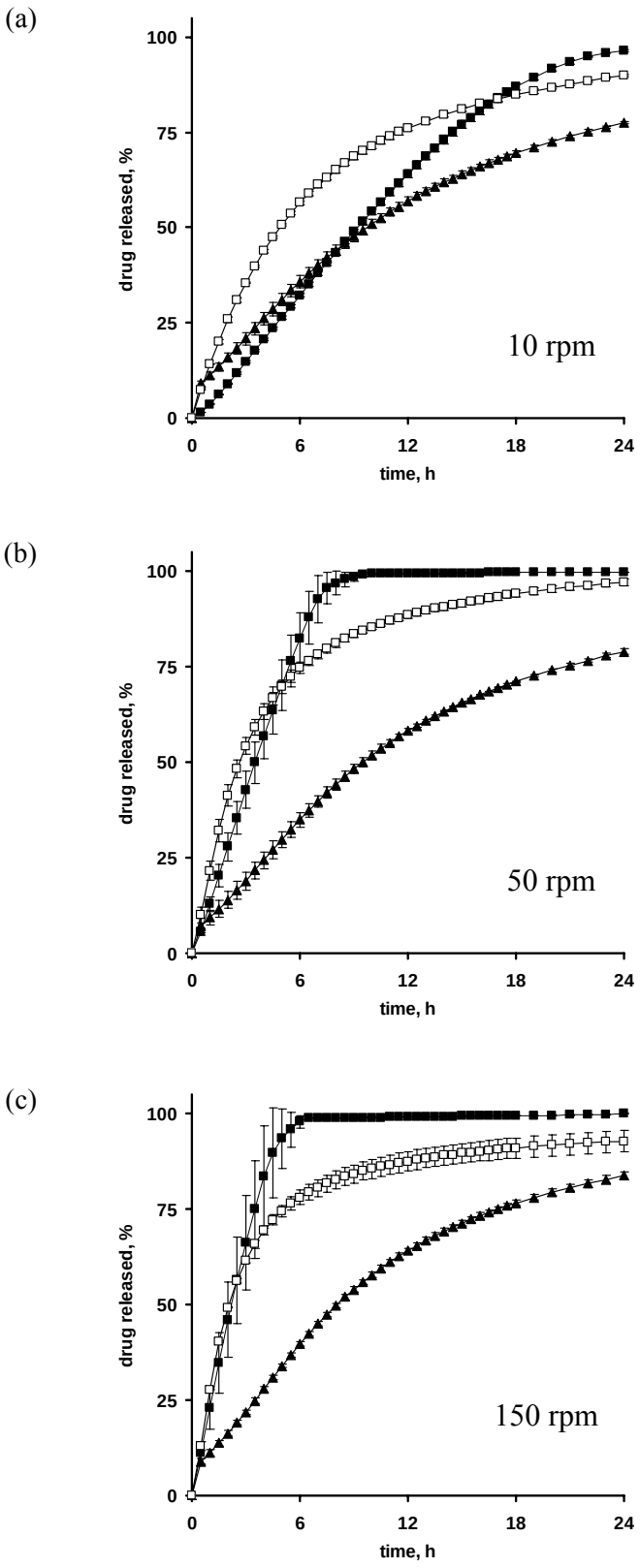


Fig. 12 Verapamil HCl release from three bioequivalent products as a function of agitation rate: (■) sodium alginate/HPMC matrix tablet (Isoptin), (□) EC/Eudragit L100-55 coated pellets (VeraHexal) and (▲)shellac/fumaric acid coated pellets (Verelan).

Table 12 Similarity factor (f_2) calculated from mean dissolution data of BE verapamil HCl products in various dissolution conditions

Dissolution condition	f_2 value*		
	Sodium alginate/HPMC matrix tablet vs. EC/Eudragit L100-55 coated pellets	Sodium alginate/HPMC matrix tablet vs. Shellac/fumaric acid coated pellets	EC/Eudragit L100-55 coated pellets vs. Shellac/fumaric acid coated pellets
pH 1.2	**50.2**	30.2	27.3
pH 4.5	43.3	30.6	28.8
pH 6.8	48.7	25.2	30.7
100 mOsm/kg	48.7	25.2	30.7
390 mOsm/kg	**53.5**	28.6	28.7
10 rpm	37.6	**52.6**	37.7
50 rpm	**52.2**	25.2	23.3
150 rpm	**52.9**	20.3	23.6

***bold**: the releases were similar

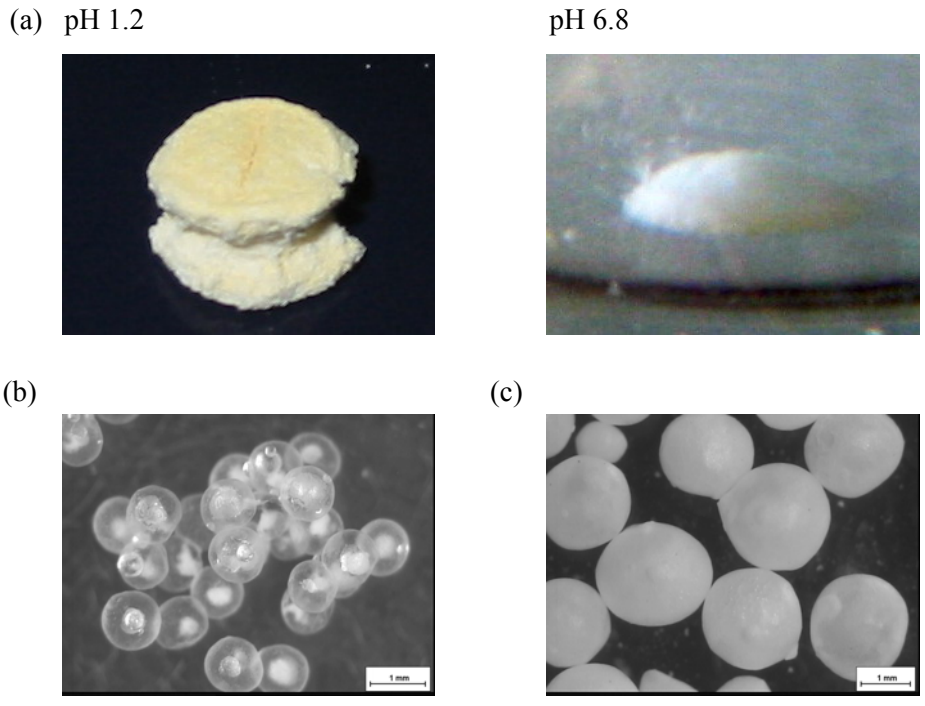


Fig. 13 Macroscopic picture of verapamil HCl (a) sodium alginate/HPMC matrix tablet in pH 1.2 and pH 6.8 at 2 - 24 h, and microscopic picture of verapamil HCl (b) EC/Eudragit L 100-55 coated pellets in pH 6.8 at 24 h and (c) shellac/fumaric acid coated pellets in pH 6.8 at 24 h

Robustness of verapamil HCl ER products

Sodium alginate and HPMC were used to control the release of verapamil HCl, a weakly basic drug with pH-dependent solubility (Table 9). Sodium alginate (pKa = 3.2) retarded the drug release in the pH lower than its pKa by swelling and forming a rigid matrix, whereas it dissolved and eroded in a higher pH and hence, facilitating the drug release (Fig. 13a). The slight overcompensation for drug solubility was exhibited in Fig. 14a (top), where the release was in the following order: pH 6.8 > pH 4.5 > pH 1.2. Fig. 14a (middle) shows a decreased drug release in the higher osmolality (f_2 = 42.7, Table 13a). This slower drug release could be caused by the effect of common salt, as the medium of 390 mOsm/kg contained the higher amount of sodium chloride.

With regard to the effect of agitation intensity, the drug released similarly at above 100 rpm (Fig. 14a, bottom). This was due to the erosion rate reached its maximum. The release at 50 rpm and 10 rpm was significantly slower (Table 13a).

The coated pellet formulations of verapamil HCl offered robust release profiles in different pH media and osmolality. Fig. 14b and 14c show the release from pellets coated by EC/Eudragit L100-55 and shellac/fumaric acid, respectively. Eudragit L100-55 and shellac are enteric polymers which dissolve at pH above 5.5 and 6.9, respectively. The low solubility of verapamil HCl and, thus the slower drug released, in a higher pH is then able to compensate when these pH-sensitive polymers are incorporated into the matrix. Fig. 14b and 14c (top) and Table 13b and 13c demonstrate the drug release as 'unaffected' by varying pH, including at pH 7.5 for shellac coated ones. In addition, acidic excipients such as enteric polymers (e.g. Eudragit L100-55) as well as organic acids (e.g. fumaric acid) can lower the micro-environmental pH of the formulation and, hence improve drug solubility (Streubel et al., 2000). The dissolution medium of 390 mOsm/kg slightly reduced the drug release when compared with that of 100 mOsm/kg (Fig 14b and 14c, middle), but they were considered similar according to the f_2 values (Table 13b and 13c).

The drug release from the EC/Eudragit L100-55 coated pellets at 50 and 150 rpm were significantly faster than that at 10 rpm (Fig. 14b, bottom) (f_2 = 39.8: at 10 vs. 50 rpm). The release from the shellac/fumaric acid coated pellets, on the other hand, remained unaffected

from the agitation rate (Fig. 14c, bottom). The similar release profiles in pH 7.5, despite the varying agitation intensity, were also observed (data not shown).

Table 13 Similarity factor (f_2)* calculated from mean dissolution data of verapamil HCl products in various dissolution conditions

(a) Sodium alginate/HPMC matrix tablet

Reference \ Test	pH 4.5	pH 6.8	390 mOsm/kg	50 rpm	100 rpm	150 rpm
Effect of pH at 100 rpm						
pH 1.2	**65.2**	**51.6**	-	-	-	-
pH 4.5	-	45.8	-	-	-	-
Effect of osmolality at 100 rpm/pH 6.8						
100 mOsm/kg	-	-	42.7	-	-	-
Effect of agitation rate in pH 6.8						
10 rpm	-	-	-	23.2	17.7	16.9
50 rpm	-	-	-	-	36.6	34.7
100 rpm	-	-	-	-	-	**85.0**

(b) EC/Eudragit L 100-55 coated pellets

Reference \ Test	pH 4.5	pH 6.8	390 mOsm/kg	50 rpm	150 rpm
Effect of pH at 100 rpm					
pH 1.2	**71.6**	**73.4**	-	-	-
pH 4.5	-	**92.6**	-	-	-
Effect of osmolality at 100 rpm/pH 6.8					
100 mOsm/kg	-	-	**69.3**	-	-
Effect of agitation rate in pH 6.8					
10 rpm	-	-	-	39.8	34.9
50 rpm	-	-	-	-	**65.7**

(c) Shellac/fumaric acid coated pellets

Test / Reference	pH 4.5	pH 6.8	pH 7.5	390 mOsm/kg	50 rpm	100 rpm	150 rpm
Effect of pH at 100 rpm							
pH 1.2	**74.6**	**87.1**	**55.0**	-	-	-	-
pH 4.5	-	**70.7**	**50.9**	-	-	-	-
pH 6.8	-	-	**57.6**	-	-	-	-
Effect of osmolality at 100 rpm/pH 6.8							
100 mOsm/kg	-	-	-	**58.0**	-	-	-
Effect of agitation rate in pH 6.8							
10 rpm	-	-	-	-	**88.4**	**69.7**	**61.7**
50 rpm	-	-	-	-	-	**72.1**	**64.5**
100 rpm	-	-	-	-	-	-	**82.8**

***bold**: the releases were similar

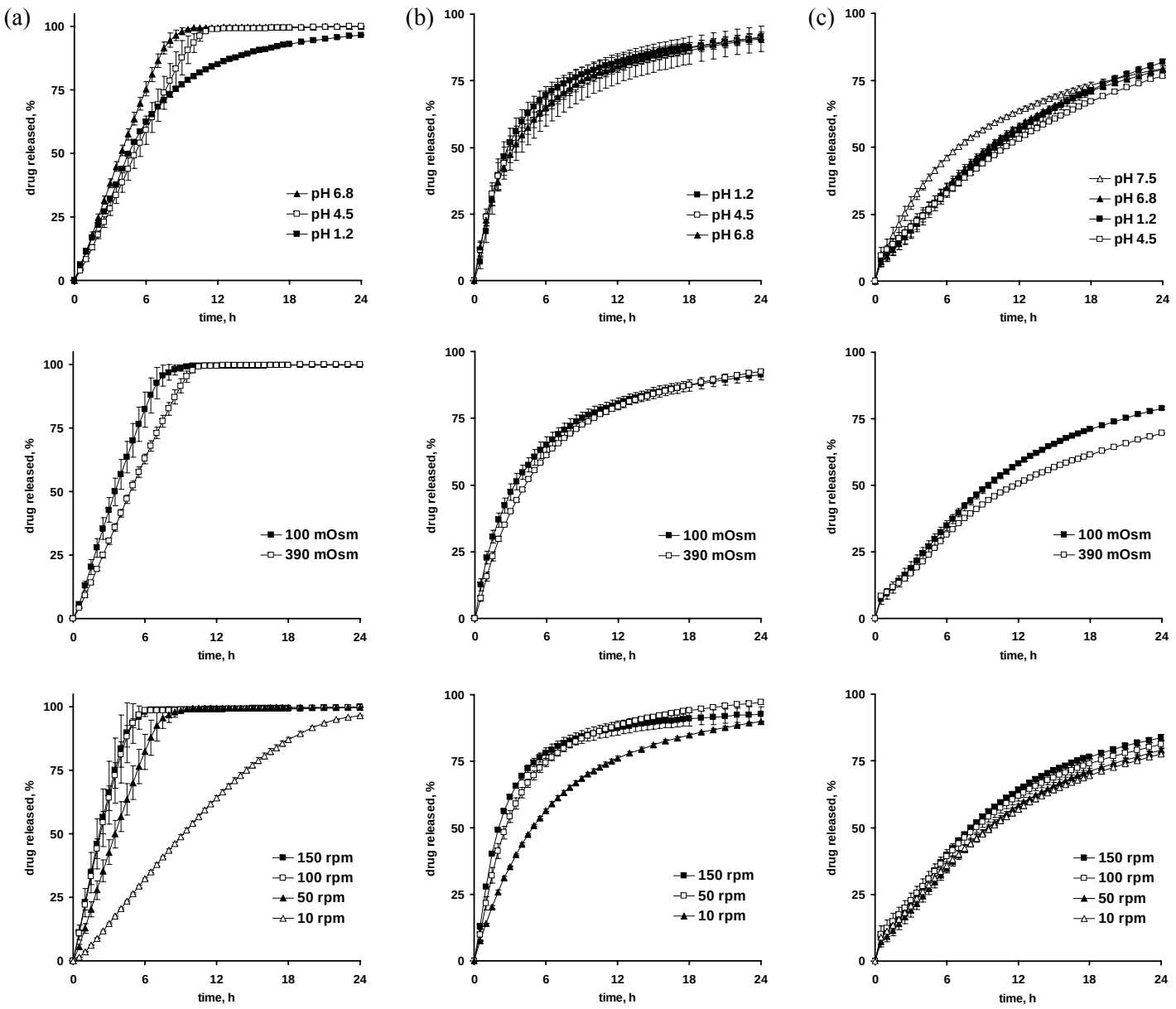


Fig. 14 Verapamil HCl released from (a) sodium alginate/HPMC matrix tablets (Isoptin), (b) EC/Eudragit L 100-55 coated pellets (VeraHexal) and (c) shellac/fumaric acid coated pellets (Verelan); effect of pH at 50 rpm (top), osmolality at 50 rpm/pH 6.8 (middle) and agitation rate in pH 6.8 (bottom).

3.1.3 Conclusion

The drug products are bioequivalent when their active ingredients in pharmaceutical equivalents or pharmaceutical alternatives are available at the site of action with similar rate and extent when administered at the same molar dose under similar conditions. A discriminatory dissolution test should be able to demonstrate the similarity between bioequivalent products as well as the dissimilarity between bioinequivalent products. The objective of this study was to observe the performance of commercially available bioequivalent products in vitro by performing release studies in various dissolution conditions and to evaluate the discriminating ability of those test conditions. The release profiles of bioequivalent products were different in most test conditions. HEC matrix tablets of pentoxifylline (Trental) released slower than Eudragit RS/RL tablets (Rentylin). This could be due to the less mechanical stress in vitro as compared to the condition in vivo. The release of verapamil HCl was in the following order: sodium alginate/HPMC matrix tablets (Isoptin) > EC/Eudragit L 100-55 coated pellets (VeraHexal)> shellac/fumaric acid coated pellets (Verelan). The latter was the most robust formulation. The difference of bioequivalent verapamil HCl releases could be attributed to the high surface tension in vitro, which led to the decreased drug release. Compendial in vitro dissolution methods used in this study were not discriminating because they were unable to reflect the in vivo behaviour of the products. The results of robustness test indicated potential factors influencing the in vitro releases of both drugs. The simulation of in vivo osmolality, such as the addition of sodium chloride into the standard dissolution media, and/or the optimization of mechanical destructive force, by adjusting the agitation intensity or the addition of glass beads, should be further investigated to obtain the discriminatory dissolution test for pentoxifylline ER tablets. Likewise, the decreased mechanical destructive force and surface tension should be considered for the dissolution studies of verapamil HCl ER products.

3.2 Effect of sodium dodecyl sulphate on the in vitro dissolution of extended release solid oral dosage forms

3.2.1 Introduction

Many factors influence in vitro drug dissolution. They include physicochemical properties of the drug (e.g. solubility, particle size and crystalline forms), formulation characteristics (e. g. types of dosage form, excipients and manufacturing parameters) and dissolution testing (e.g. volume, pH, surface tension, ionic strength and viscosity of the dissolution medium, hydrodynamic conditions and types of apparatus). Meaningful dissolution tests recognized by both regulatory agencies and pharmaceutical industries are those with discriminatory power and physiological relevance. Setting up such specifications is challenging, especially when dealing with poorly soluble drugs.

To overcome the drug solubility issue, the addition of surfactants into the dissolution media, has been recommended (FDA, 2005b). Many researchers start with sodium dodecyl sulphate (SDS) due to its excellent solubilizing capacity. An increase in drug release by the addition of SDS was reported in many studies. Most of them dealt with its effect on physicochemical properties of the drugs (Rohrs, 2001; Alkhamis et al., 2003; Balakrishnan et al., 2004; Park and Choi, 2006). Only few discussed the effect on formulation characteristics. For example, Marchais et al. (2003) reported the negative impact of SDS on the release of carbamazepine from cross-linked hard gelatin capsules. Similarly, the drug release is slower because the solubility of the gelatin capsule shell is reduce when SDS was added in the dissolution medium at pH less than 5 (Zhao et al., 2004). This was caused by the formation of a less-soluble precipitate from the interaction between SDS and gelatin. A better in vitro/in vivo relationship of felodipine extended release (ER) matrix tablet was found with SDS in the dissolution medium, as compared to polyoxyethylene 20 sorbitan monooleate (Tween) and cetyltrimethylammonium bromide (CTAB) (Abrahamsson et al., 1994). The physicochemical interactions between the matrix forming agent and the surfactants were thought to play an important role on the drug release rate.

The objective of this study was to investigate the effect of SDS on the release of drugs from commercially available ER solid oral dosage forms. The release of poorly soluble drug and

the drug formulated with ionic excipients are also explored. The influence of SDS will be discussed mainly on formulation aspects. 0.25% w/v SDS in pH 6.8 was used in this study as a standard concentration, as it lowered the surface tension of dissolution media to 33 mN/m which is similar to that in vivo (Pedersen et al., 2000; Kalantzi et al., 2006). In addition, this is a minimum concentration that increases the solubility of carbamazepine (Table 8) so that sink condition can be maintained.

3.2.2 Results and discussion

The addition of surfactants, such as sodium dodecyl sulphate, into dissolution media have been recommended by several researchers and the regulatory agencies (Shah et al., 1989; Galia et al., 1998; FDA, 2005b; USP 29, 2006). The goal was to lower surface tension of the release media, so that to mimic the condition in vivo. Types and concentrations of surfactants are especially important in this simulated in vitro condition, as they influence the drug release. The physicochemical properties of the drugs and excipients as well as the dosage forms play a role on the drug release with the presence of surfactants. This study investigated the effect of sodium dodecyl sulphate on the releases of drugs from different ER dosage forms including: matrix tablets, coated pellets and osmotic tablets.

3.2.2.1 Effect of sodium dodecyl sulphate on drug release from ER dosage forms

The release profiles of verapamil HCl from four ER products are presented in Fig. 15. While the release of drug from sodium alginate/HPMC matrix tablet (Isoptin, Fig. 15a) and that from osmotic tablet (Covera-HS, Fig. 15d) were not influenced by the addition of 0.25% w/v sodium dodecyl sulphate (Table 14), the releases from coated pellets formulations (VeraHexal, Fig. 15b and Verelan, Fig. 15c) were faster when sodium dodecyl sulphate was added. This is similar to the release of diltiazem HCl ER products (Fig. 16); the effect of sodium dodecyl sulphate was only seen with the release of coated pellets (Diltiazem-ratiopharm, Fig. 16b and Dilzem uno, Fig. 16c). Although, the f_2 values of the releases of verapamil HCl and diltiazem HCl from shellac/fumaric acid coated pellets and Eudragit RS/RL coated pellets, respectively, indicated the similarity (Table 14), the effect of the addition of sodium dodecyl sulphate into the dissolution media was more pronounced when compared with that on the drug releases from matrix tablet formulations.

The solubility of weakly basic drugs such as verapamil HCl and diltiazem HCl are pH-dependent. At pH 6.8, which is close to their pKa (8.6 for verapamil HCl (Kasim et al., 2004) and 7.7 for diltiazem HCl (Reza et al., 2003)) the drug solubility decreased dramatically (Table 9). With this low solubility, the drug release from matrix tablets was primarily caused by the erosion of the polymer matrix. Therefore, the improved wettability resulting from the decreased surface tension did not have much effect on the drug release from this matrix system. Likewise, the more water accessible did not accelerate the release of verapamil HCl from osmotic tablet. Although, the drug incorporated in the osmotic system releases by osmotic pressure generated by water penetrates into the tablet (Fig. 17), it is eventually the permeability of the semi-permeable, rigid membrane that controls the water penetration rate and in turn the drug released (Wen and Park, 2010).

With regard to the release of drugs from coated pellets, it is generally controlled by a combination of two or more processes (Lecomte, 2004). For example, a drug is released by convection through water-filled channels and, in parallel, diffuses through the polymeric membrane. In contrast to the semi-permeable membrane of the osmotic tablets, the water-filled channels were created by hydrostatic pressure developed within the pellet core or by the leaching of water soluble components, e.g. sugar, into the bulk fluid. The more water accessible to the pellets as a result of the increased wettability is, therefore, contributes to the faster drug release.

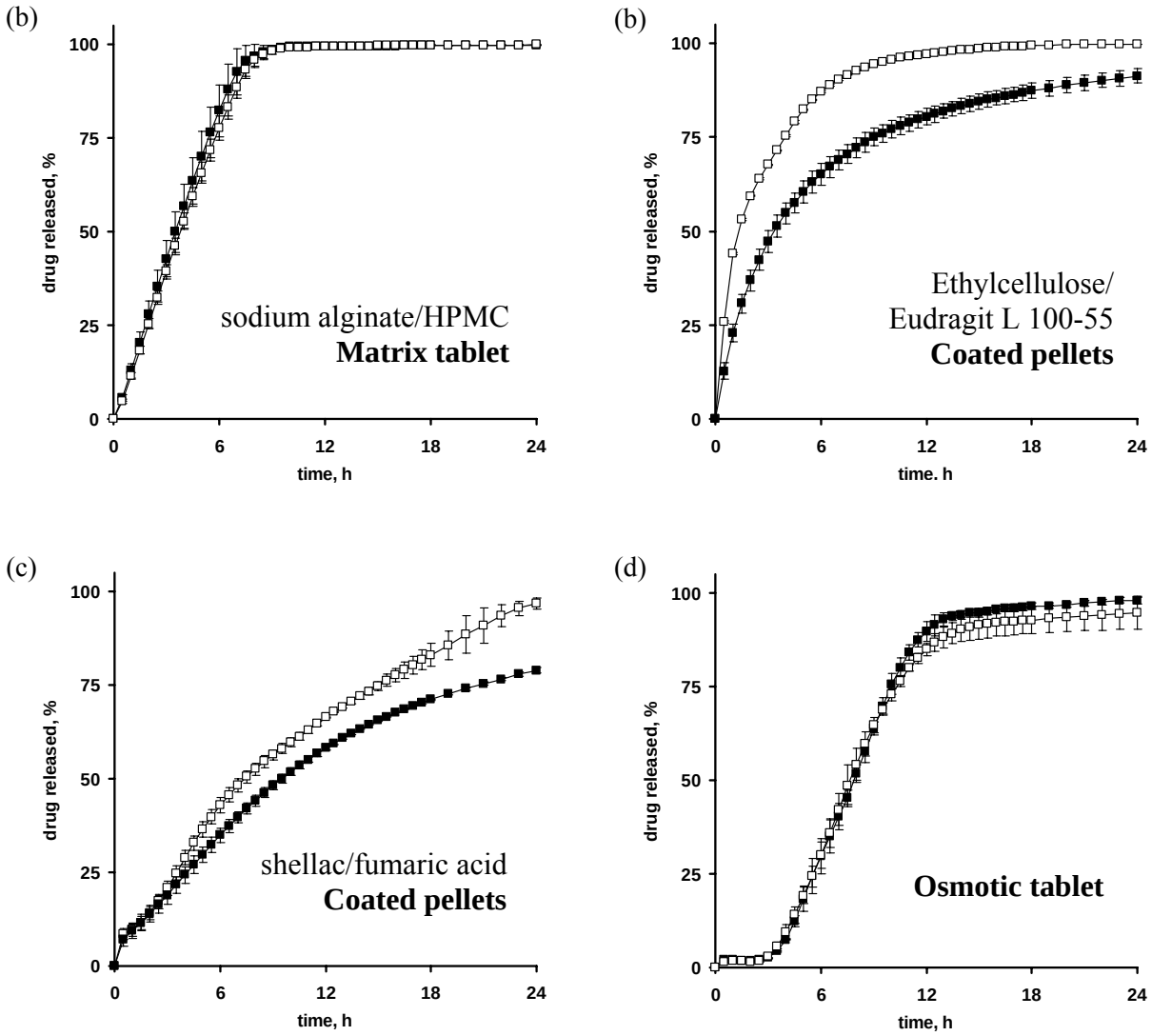


Fig. 15 Verapamil HCl released from different ER products; effect of (■) 0% and (□) 0.25% w/v sodium dodecyl sulphate at 50 rpm/pH 6.8.

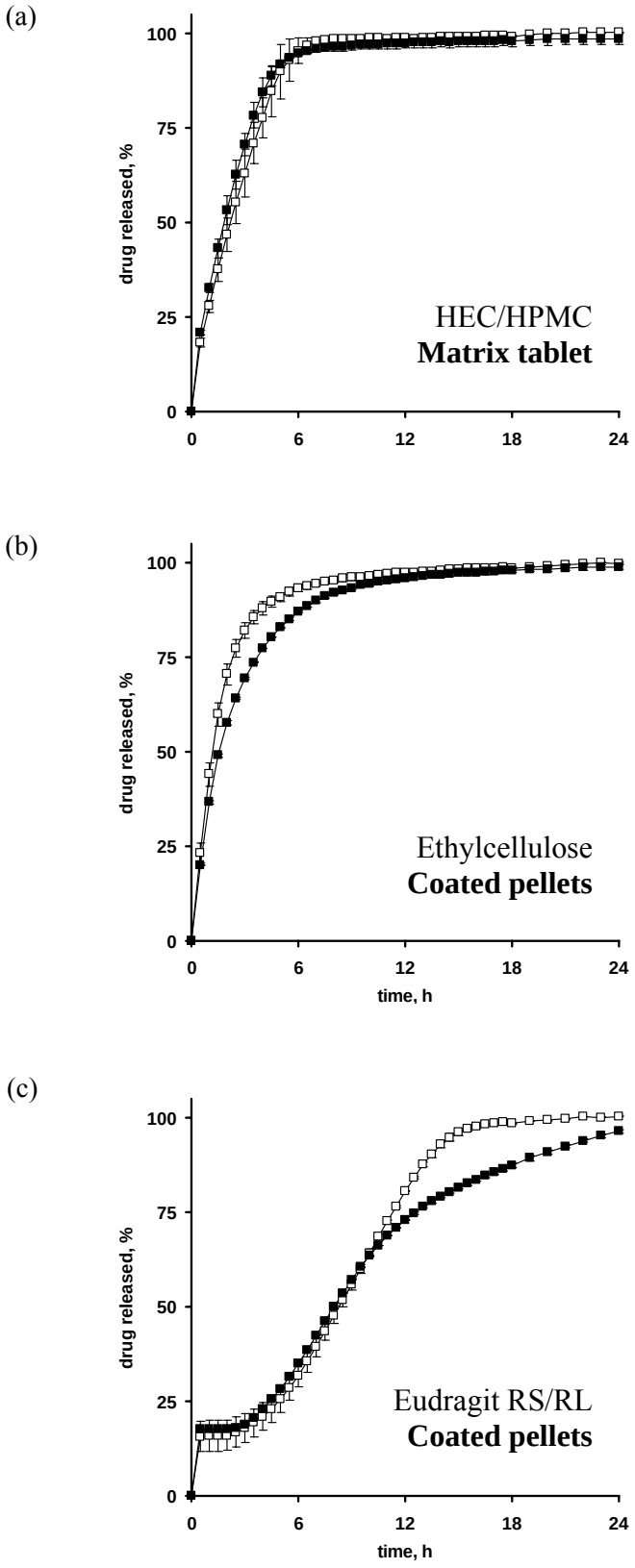


Fig. 16 Diltiazem HCl released from different ER products; effect of (■) 0% and (□) 0.25% w/v sodium dodecyl sulphate at 100 rpm/pH 6.8.

Table 14 Similarity factor (f_2)* calculated from mean dissolution data of drugs in buffer solution pH 6.8 with 0% and 0.25% w/v sodium dodecyl sulphate (SDS).

Dosage form		f_2 value Drug released in 0% vs. 0.25% w/v SDS			
		Verapamil HCl	Diltiazem HCl	Pentoxifylline	Carbamazepine
Matrix tablet	Sodium alginate / HPMC	**71.5**	-	-	-
	HEC / HPMC	-	**60.6**	-	-
	HEC	-	-	**95.9**	-
	Eudragit RS / RL	-	-	35.5	-
	Eudragit NE 30D / Aquacoat ECD	-	-	-	25.0
	Eudragit RS / L 100-55	-	-	-	25.9
Coated pellets	Ethylcellulose / Eudragit L 100-55	33.9	-	-	-
	Shellac / fumaric acid	**54.1**	-	-	-
	Ethylcellulose	-	48.1	-	-
	Eudragit RS / RL	-	**69.2**	-	-
	mix	-	-	-	19.8
Osmotic tablet		**81.9**	-		38.3

***bold**: the releases were similar

(a)

(b)

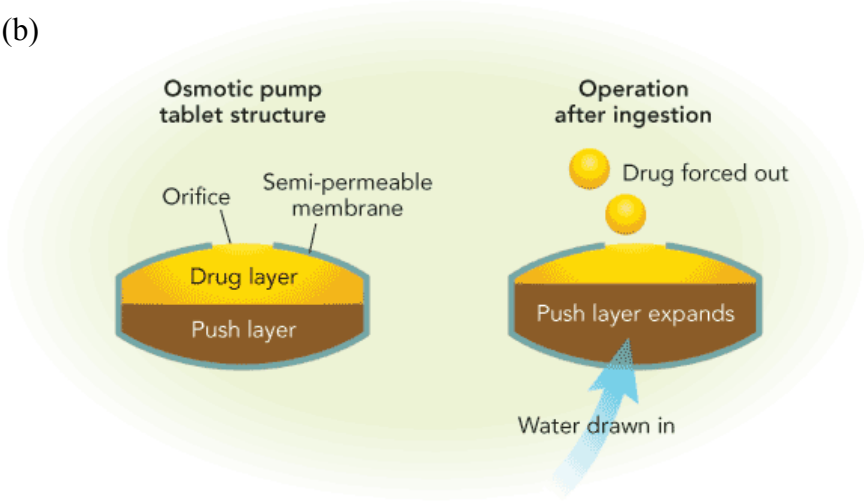


Fig. 17 (a) microscopic picture of a cross-section of verapamil HCl osmotic tablet (Covera-HS) and (b) structure of a bilayer core osmotic tablet (OptoIQ, 2007)

3.2.2.2 Effect of sodium dodecyl sulphate on the release of poorly soluble drug

Carbamazepine is a poorly soluble drug. Its solubility in water at 37 °C is 0.22 mg/ml. With the dosage strength of 200 mg used in this study, sink conditions were not achieved when the dissolution test was performed in the standard 900 ml dissolution medium. As a result, the carbamazepine released from all test products (except for the osmotic tablet) at 24 h reached only 75% when there was no sodium dodecyl sulphate added into the dissolution media (Fig. 18a – 18c).

The osmotic delivery system of carbamazepine (Tegretol-XR) is a swelling-monolithic core type (Fig. 19). Though, it is the simplest approach of an osmotic delivery system for poorly soluble drug, the limitation of this single layer swelling core is the incomplete drug release (Wen and Park, 2010). Fig. 18d shows the release profiles of carbamazepine from the osmotic tablets, where the maximum drug release was lower than those of other formulations.

The solubility of carbamazepine in 0.25% w/v sodium dodecyl sulphate increased significantly to 0.51 mg/ml (37 °C). This improved solubility led to the much faster drug release, irrespective of the dosage forms (Fig. 18, Table 14). Despite maintaining the sink condition, a plateau of about 80% drug release was still observed in the case of the osmotic tablet (Fig. 18d). Other conditions in vivo (e.g. mechanical destructive force) should heavily contribute to the release of carbamazepine from the osmotic tablet, because Carbatrol (Fig. 18c) and Tegretol-XR (Fig. 18d) are bioequivalent (Stevens et al., 1998).

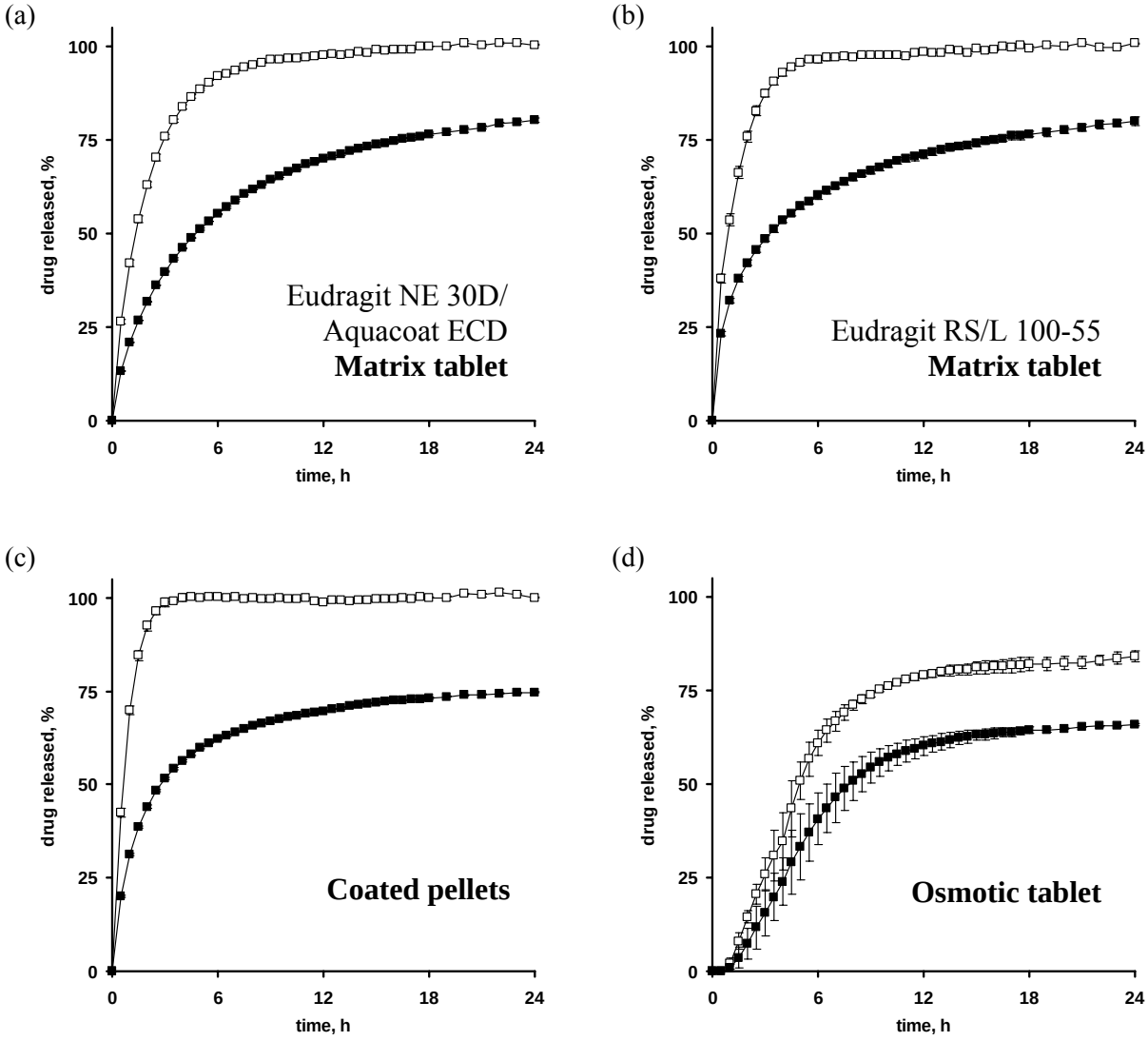


Fig. 18 Carbamazepine released from different ER products; effect of (■) 0% and (□) 0.25% w/v sodium dodecyl sulphate at 100 rpm/pH 6.8.

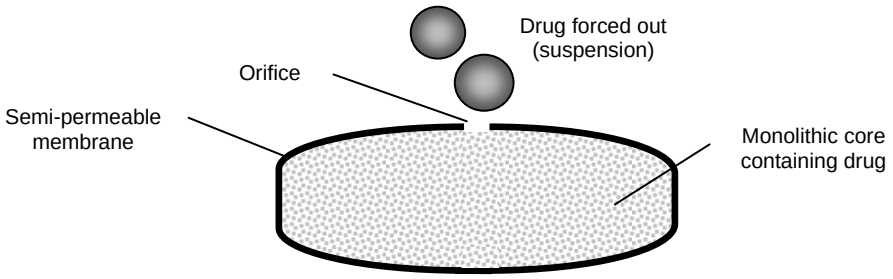


Fig. 19 Structure of a swelling-monolithic core osmotic tablet. Modified from Wen and Park (2010).

3.2.2.3 Effect of sodium dodecyl sulphate on the release of pentoxifylline from matrix tablets of ionic and nonionic excipients

The characteristic of the tablets and the release of pentoxifylline from hydroxyethyl cellulose (HEC) (Trental) and poly(ethyl acrylate, methyl methacrylate) trimethylammonioethyl methacrylate chloride (Eudragit RS/RL) (Rentylin) matrix formers are presented in Fig. 20 and 21, respectively. The remaining of the HEC matrix tablet after 24 h release was a small gel mass (Fig. 20a), while granules were observed from the Eudragit RS/RL matrices in the release media containing surfactants (Fig. 20b).

The drug release from the HEC matrix tablet was robust to the addition of sodium dodecyl sulphate (Fig. 21a, Table 14), whereas, it decreased significantly in the case of Eudragit RS/RL ones (Fig 21b). The release in 0.25% and 0.50% w/v sodium dodecyl sulphate (33 mN/m) were similar (Table 15), but they were much slower than those in the media containing 0.25% w/v Tween 80 (48 mN/m) and 0.05% w/v Span 80 (30 mN/m), which are nonionic surfactants. The drug release in the presence of the latter two surfactants was also comparable to that in medium without surfactant (69 mN/m). As a result, the reduced drug release in the sodium dodecyl sulphate solutions was attributed to the cationic/anionic interaction between the Eudragit polymers and sodium dodecyl sulphate, and not the change of surface tensions.

(a) (b)

Fig. 20 Microscopic picture of pentoxifylline (a) HEC and (b) Eudragit RS/RL matrix tablets after 24 h release in pH 6.8 with surfactant.

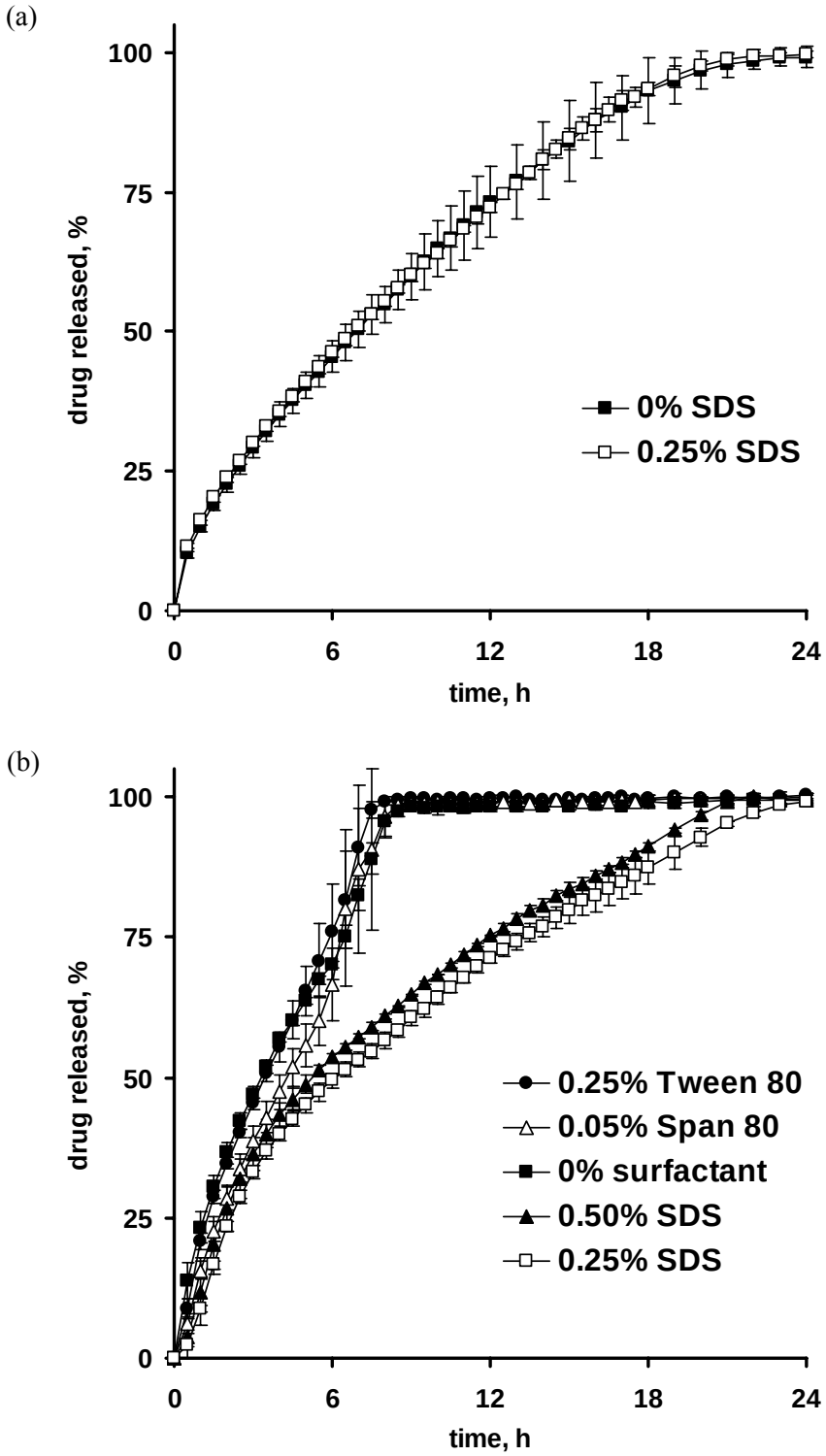


Fig. 21 Pentoxifylline released from (a) HEC and (b) Eudragit RS/RL matrix tablets; effect of surfactant at 100 rpm/pH 6.8.

Table 15 Similarity factor (f_2)* calculated from mean dissolution data of Eudragit RS/RL matrix tablets of pentoxifylline in buffer solution pH 6.8 with various concentrations of surfactants.

Test / Reference	0.25% SDS	0.50% SDS	0.25% Tween 80	0.05% Span 80
0% surfactant	35.5	39.8	**69.7**	**55.9**
0.25% SDS	-	**70.3**	35.2	42.0
0.50% SDS	-	-	39.0	46.7
0.25% Tween 80	-	-	-	**57.2**

***bold**: the releases were similar

3.2.3 Conclusion

The goal of adding surfactants into dissolution media was to mimic the condition in vivo by lowering surface tension. The drug release in this simulated media is, however, influenced by the type of surfactant. In addition, the physicochemical properties of drugs, excipients and the dosage forms also contribute to the release pattern. The purpose of this study was to investigate the effect of sodium dodecyl sulphate on the releases of drugs from different ER dosage forms. The matrix tablets of verapamil HCl and diltiazem HCl were robust to the addition of sodium dodecyl sulphate. Their release patterns were unchanged because the improved wettability did not have much effect on the erosion rate of the polymer. In contrast, this increased water accessibility facilitated the release from coated pellets, as could be seen from the release of both drugs. There was no effect of sodium dodecyl sulphate on the drug release from osmotic tablet because the rate of water penetration into the tablet, which controlled by the semi-permeable membrane, was unchanged. The significantly increase solubility of carbamazepine outperformed the effect of sodium dodecyl sulphate on the drug release from different types of dosage form. Therefore, all formulations of carbamazepine show the considerably increase drug release when sodium dodecyl sulphate was added. Another concern of adding ionic surfactant into dissolution medium is the cationic/anionic interaction between the surfactant and the drug or other excipients. Pentoxifylline released from matrix tablets composed of HEC, a nonionic matrix former, were unaffected by the addition of sodium dodecyl sulphate, an anionic surfactant. On the contrary, the decreased drug release was observed when the matrix former was Eudragit RS/RL, a cationic polymer. Despite the dissolution was performed in the similar

surface tension as of sodium dodecyl sulphate solution, the decreased drug release was not seen when Tween 80 or Span 80, the nonionic surfactants, were added. In conclusion, the effect of sodium dodecyl sulphate on drug release could be attributed to many formulation factors. Although the use of sodium dodecyl sulphate is recommended for dissolution studies of several products, the contributions of those factors as for example reported in this study should not be disregarded.

3.3 Evaluation of drug properties for the selection of extended release solid oral dosage form: Application of principal component analysis

3.3.1 Introduction

Success of an extended release (ER) formulation depends not only on the performance of the formulation, but also the suitability of the chosen dosage form. Cost and effort are greatly required throughout the development and assessment processes; it is therefore, even more sensible to identify whether the selected delivery system would possibly be the most promising achievement. Several research studies have been focused on novel delivery technologies (see, for example, (McGinity, 1997; Flament et al., 2004; Kshirsagar et al., 2008; Tiwari and Rajabi-Siahboomi, 2008). There were, however, only few reports suggesting the selection of a particular delivery system for a particular drug (Lipper, 1999; Thombre, 2005). The understanding of the relationship between properties of drug such as solubility, maximum dose strength and elimination half-life, and the dosage form selection, is essential for identifying the most promising formulation development. In order to understand this relationship and to establish a guide for ER technology selection, a multivariate data analysis approach, namely, principal component analysis (PCA) was employed.

PCA is a technique for simplifying data by reducing multidimensional data to lower dimensions while retaining as much as possible the variation of the data set (Jolliffe, 2002). It is a linear transformation that transforms the data to a new coordinate system, so called the principal components (PCs). The first few, i.e. lower-order, PCs are able to explain the largest structural variation of the original data set, whereas the higher-order ones are generally considered as less relevant and hence, being dropped from further analysis. It should be noted, however, that the lower-order PCs, such as PC1 and PC2, are not always the most relevant for some particular interpretation purposes because they may not reveal the targeted answer. Therefore, the use of the higher-order PCs, when they have the largest problem-specific information, is more appropriate in certain cases (Esbensen et al., 2006).

PCA can also be used to classify data. The method facilitates the classification of objects (e.g. drugs) considering conformity with the extracted model and variables (e.g. drug

properties) describing the objects (Esbensen et al., 2006). This classification can be interpreted through the map of samples so called score plots, the map of variables so called loading plots as well as the relationship between both plots. The interpretation can be further simplified by the rotation of PCs using, for example, varimax rotation (Kaiser, 1958). The rotation is performed so as to maximize the variance of factor loading by making high loadings higher and low ones lower for each factor.

The PCA technique has found application in many diverse fields such as environmental science (Soh and Abdullah, 2007), marketing (Petroni and Braglia, 2000), psychology (El Yazaji et al., 2002), food science (Cotroneo et al., 1990; Krauze and Zalewski, 1991; Muir et al., 1996) and pharmaceutical science (Tarvainen et al., 2001; Karalis et al., 2002; Tho et al., 2002). The present study explored the relationships between properties of drugs and their available ER dosage forms. The classification of single- vs. multiple-unit dosage form and the carrier systems of matrix tablets were examined. Significant properties distinguishing the dosage forms/matrix types and the guideline for ER system selections were investigated.

3.3.2 Results and discussion

Many different types of ER solid oral dosage forms exist. These include among others reservoir or matrix systems, osmotic systems and specialized drug delivery systems, such as pulsatile and gastroretentive drug delivery systems. The investigation of successful marketed ER products could provide a valuable clue for formulation scientists to select a system over another one for a particular drug. In this respect, the correlation of drugs properties and their available dosage forms was examined.

3.3.2.1 Classification of single- vs. multiple-unit dosage form

The 59 percent of the collected samples were classified as ‘tablet’, while 41 percent were multiparticulate pellet systems (will be referred to as ‘multiparticulate’). Within the tablet group, 43 percent were matrix tablets, 13 percent were osmotic and 3 percent were coated ones. Various drug properties and their value distribution were presented in Table 16 and

Fig. 22. Most properties of tablet and multiparticulate groups showed the values overlay to each other.

Table 16 Mean values and ranges of variables: Tablet vs. Multiparticulate systems

Variables	**Tablet; n = 85**		**Multiparticulate; n = 60**	
Mw	287.08	(41.99 - 484.63)	310.25	(144.21 - 591.74)
pKa	7.55	(0.00 - 13.94)	7.85	(0.00 - 13.94)
LogP	2.14	(-5.03 - 5.69)	2.46	(-1.03 - 5.82)
H-bond donors	1.93	(0 - 10)	2.30	(0 - 10)
H-bond acceptors	5.39	(0 - 14)	6.17	(1 - 14)
PSA (°A)	58.27	(0.00 - 130.15)	64.27	(3.24 - 134.23)
Solubility (mg/ml)	163.24	(0.001 - 2000)	165.68	(0.01 - 2000)
Max dose (mg)	221.59	(0.40 - 1000)	150.30	(0.25 - 500)
Dose number (Do)	5.60	(0.0001 - 160.16)	4.70	(0.00001 - 100.00)
$t_{1/2}$ IR (h)	7.46	(0.75 - 23.00)	6.19	(0.03 - 26.90)
$t_{1/2}$ ER (h)	10.96	(2.30 - 24.00)	9.85	(1.64 - 37.00)
$t_{1/2}$ ratio	2.13	(0.77 - 10.00)	15.42	(0.97 - 533.33)
t_{max} IR (h)	1.88	(0.50 - 6.30)	1.99	(0.50 - 6.30)
t_{max} ER (h)	6.39	(1.40 - 25.70)	5.46	(2.04 - 13.30)
t_{max} ratio	4.30	(1.06 - 24.00)	3.58	(1.00 - 9.36)

Contributing drug properties and pattern

PCA was used to identify the significance of drug properties for dosage form selection. The interpretation of variance is straightforward given that scores and loadings are orthogonal. Fig. 23a illustrated the score plot of PC1 vs. PC2 for 125 samples and 10 properties. The samples presented in the lower part of the plot had the highest values of maximum dose strength, while those occurring in the upper part reached the lowest values. According to sample distribution, there were two subgroups of 'tablet'. The first group (1) exhibited the samples with elimination half-life of their drugs as immediate release (IR) formulation ($t_{1/2}$ IR) greater than 11 h, all of which too showed LogP above 1.8. There was, however, an exception for four multiparticulate samples i.e. amitriptyline hydrochloride, clonidine hydrochloride, dextromethorphan hydrobromide and fluvoxamine maleate. Insight into the specific reason for these samples having similar properties to tablets requires further investigation. The second group of tablets (2) formed among those with maximum dose

strength greater than 500 mg, corresponding with the positions of the properties in the loading plot (Fig. 23b). Samples positioned outer the two ellipses formed no separated groups.

Although the half-life of greater than 10 h is, in general, sufficiently long for a drug to be self-sustaining (Thombre, 2005), ER formulations may be required when the drug has C_{max}-related side effects. In such cases, tablet formulations appeared to be the dosage form of choice. This could be due to the lower C_{max} produced by tablets as compared with multiparticulates (Hovi et al., 1983; Anon, 1995). Dose limitation was also evident for multiparticulate systems. The maximum dose strength of not-more-than-500 mg was observed for all multiparticulate samples. This limitation was attributed to the proportionally higher need for excipients in the formulations (Bussemer et al., 2001). A very high drug loading of a multiparticulate system thus requires a large capacity beyond an acceptable capsule size.

Table 17 Multivariate analysis of drug properties: PCA with varimax rotation on ER products

Drug properties	Correlation of scores on the extracted components[1]	
	PC1	PC2
LogP	**0.794**	0.186
$t_{1/2}$ IR	**0.665**	-0.061
t_{max} IR	0.600	-0.093
H-bond acceptors	-0.525	0.642
PSA	-0.494	**0.691**
H-bond donors	-0.433	0.163
Max dose	-0.401	-0.503
Mw	0.309	**0.790**
pKa	0.180	-0.287
Do	-0.056	0.441
Variance explained by component, after rotation	24.3	21.2

[1]bolded values thought to be important

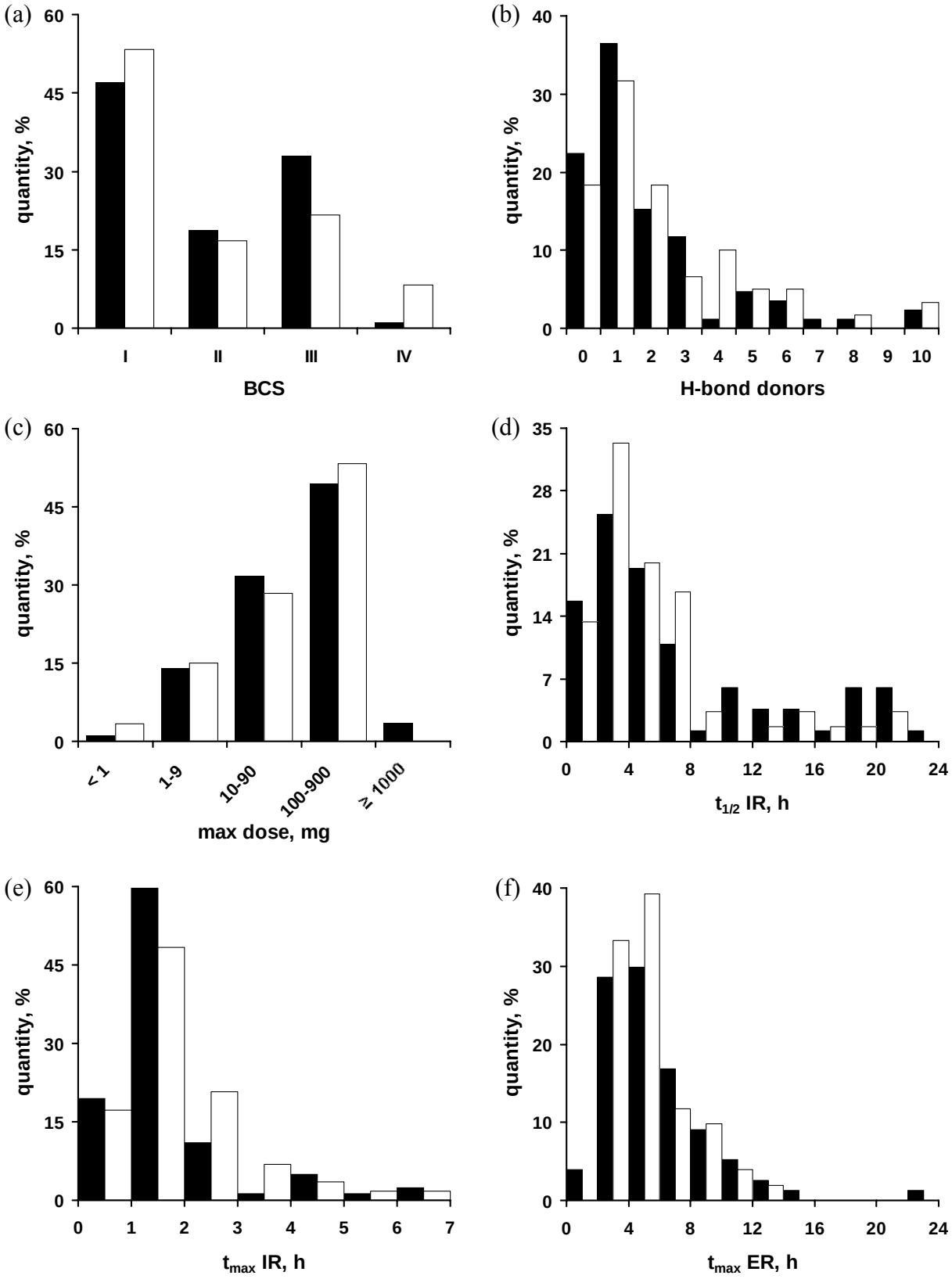


Fig. 22 Data distribution of selected variables used in the classification of (■) tablet and (□) multiparticulate

After identifying the distribution of samples, the variables were rotated using varimax rotation to form the new set of score and loading. Fig. 23c and 23d showed score and loading plots after varimax rotation of the same data set, respectively. Distribution of the samples and the drug properties were better aligned on the PCs axes. All samples belonged to the group (1) were in the positive region of PC1 and those of the group (2) were in the negative region of both PCs. This new data distribution yielded the stronger correlation between the samples/variables and the PCs.

The significance of individual properties in classifying the type of dosage forms based on the values of PCs could be identified from the loading plots. The two or three initial PCs usually explained the majority of data variability. A strong association was found when a variable has the large value of, for example, PC1 and the relatively low (close to zero) of PC2. Table 17 and Fig. 23d represented the correlation scores of each drug properties on the extracted components. LogP and $t_{1/2}$ IR were strongly associated with PC1, while Mw and PSA were with PC2. However, the latter two could not be used to discriminate the type of dosage forms when the score plot (Fig. 23c) and loading plot (Fig. 23d) from the same data set were evaluated together.

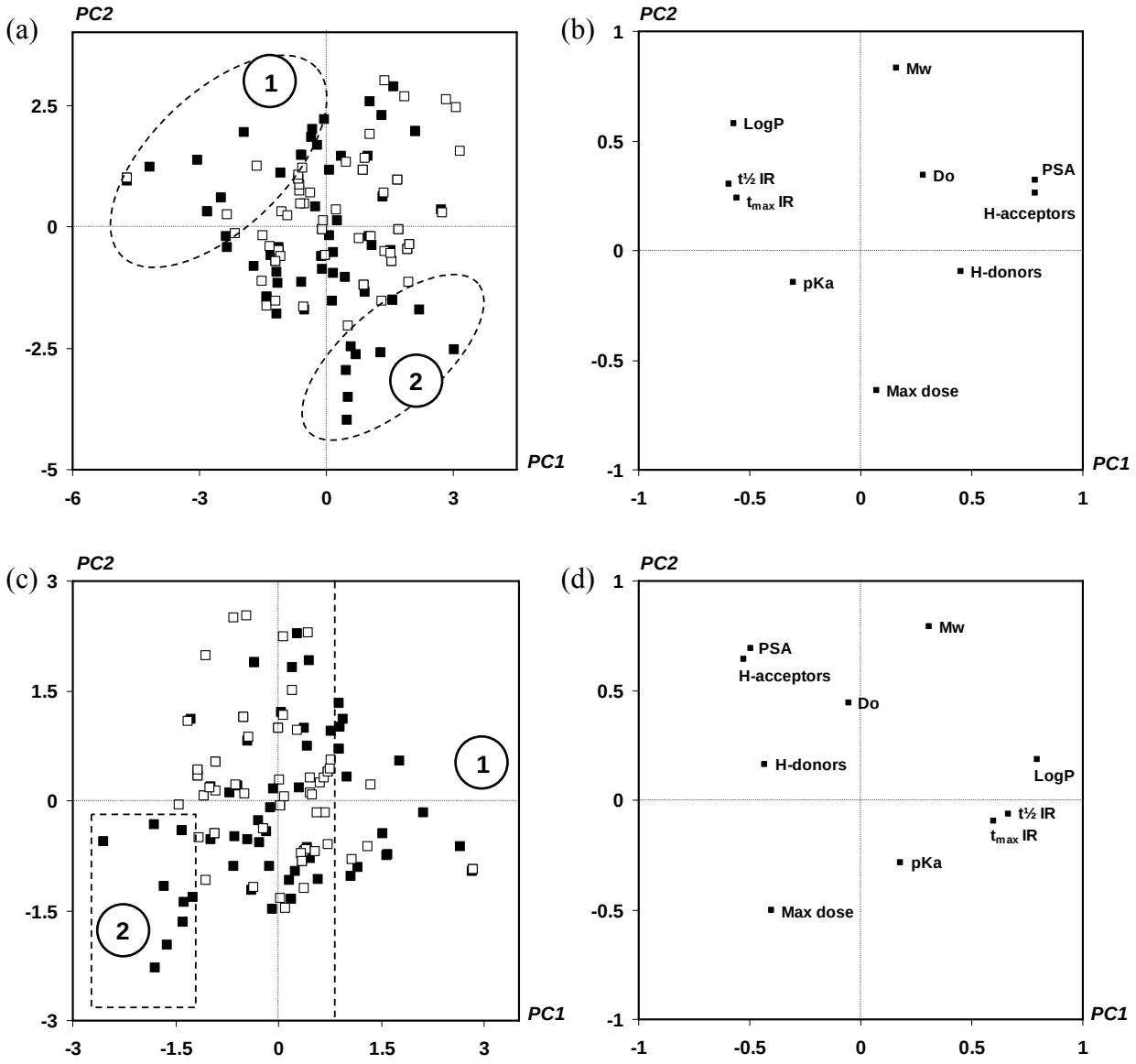


Fig. 23 Score plots (left column) and loading plots (right column) of PC1 vs. PC2, (a-b) before and (c-d) after varimax rotation of 125 ER samples and 10 properties, explaining 45.5% of the total variance; (■) tablet and (□) multiparticulate. Group (1) and (2) showed the accumulation of tablet samples.

Application of PCA model

Although the maximum dose strength (>500 mg) or the $t_{1/2}$ IR (>11 h) played more significant roles for a drug to be formulated as a single unit dosage form, other properties included in this study also involved to the distribution of samples and hence, contributed to

the classification. The values of PCs that define the location of both tablet groups can be used for the prediction of tablet. As read out directly from Fig. 23c, the position of the groups are (1) PC1 $\geq$ 0.80 and (2) PC1 $\leq$ -1.20 and PC2 $\leq$ -0.25. Therefore, tablet is recommended for a drug that has the PC scores fall within those ranges, or else it can be formulated as either system. For a given drug with known properties, PC scores are determined by the following equations:

$$\begin{aligned} PC1 = {} & 0.196(LogP) + 0.045(t_{1/2}\ IR) + 0.218(t_{max}\ IR) - 0.056(H\text{-bond acceptors}) \\ & - 0.005(PSA) - 0.073(H\text{-bond donors}) - 0.001(Max\ dose) + 0.002(Mw) \\ & + 0.022(pKa) + 0.004(Do) - 0.935 \end{aligned} \quad \text{(Eq. 3)}$$

$$\begin{aligned} PC2 = {} & 0.08(LogP) + 0.002(t_{1/2}\ IR) - 0.005(t_{max}\ IR) + 0.086(H\text{-bond acceptors}) \\ & + 0.01(PSA) + 0.022(H\text{-bond donors}) - 0.001(Max\ dose) + 0.004(Mw) \\ & - 0.048(pKa) + 0.161(Do) - 2.063 \end{aligned} \quad \text{(Eq. 4)}$$

where the drug properties are substituted by their values.

3.3.2.2 Classification of matrix tablets: hydrophilic-, lipophilic- and mix carrier systems

Among ER solid oral drug products, monolithic matrix systems especially those composed of hydrophilic polymeric materials are the most common (Skinner et al., 2002; Tiwari and Rajabi-Siahboomi, 2008). Cellulose ethers such as hydroxypropylmethylcellulose (HPMC) and hydroxyethylcellulose (HEC) are widely employed as the water soluble, swellable matrices, whereas those composed for example of ethylcellulose (EC) and acrylic polymers are for hydrophobic ones. Within the studied data set, 51 percent of the matrix tablets were comprised of hydrophilic carrier, while 31 percent were lipophilic one. The rest, 18 percent, were the mixture of both carrier systems. Table 18 and Fig. 24 showed the drug properties and the distribution of variables used in the study.

Table 18 Mean values and ranges of variables for matrix tablets

Variables	Hydrophilic matrix; n = 32		Lipophilic matrix; n = 19		Mix systems; n = 11	
Mw	296.86	(41.99 - 454.60)	273.15	(74.55 - 484.63)	276.41	(144.21 - 389.45)
pKa	7.28	(1.00 - 13.70)	6.84	(0.00 - 13.94)	7.72	(3.61 - 9.67)
LogP	2.26	(-5.03 - 5.69)	1.61	(-4.51 - 4.55)	1.99	(-1.03 - 5.19)
H-bond donors	1.82	(0 - 7)	1.35	(0 - 10)	2.67	(0 - 8)
H-bond acceptors	5.38	(0 - 11)	5.29	(1 - 12)	6.08	(2 - 14)
PSA (°A)	59.97	(0.00 - 130.15)	55.05	(0.00 - 128.58)	53.84	(6.48 - 111.85)
Solubility (mg/ml)	131.95	(0.001 - 2000)	100.15	(0.03 - 400)	218.74	(0.01 - 1000)
Max dose (mg)	193.78	(0.40 - 1000)	296.79	(4.00 - 1000)	285.42	(10.00 - 800)
Dose number (Do)	4.60	(0.0002 - 65.31)	1.45	(0.0001 - 21.82)	18.95	(0.0004 - 160.16)
$t_{1/2}$ IR (h)	7.07	(0.75 - 21.00)	7.41	(0.75 - 20.00)	6.17	(1.70 - 20.40)
$t_{1/2}$ ER (h)	10.09	(2.30 - 24.00)	11.98	(6.50 - 20.30)	9.29	(3.00 - 20.40)
$t_{1/2}$ ratio	1.80	(0.83 - 3.89)	3.95	(1.00 - 10.00)	1.69	(1.00 - 2.59)
t_{max} IR (h)	1.80	(0.50 - 6.30)	1.93	(1.00 - 4.50)	1.83	(1.00 - 4.83)
t_{max} ER (h)	5.23	(2.25 - 12.00)	5.47	(1.40 - 12.00)	5.04	(2.40 - 9.67)
t_{max} ratio	3.73	(1.25 - 10.60)	3.16	(1.17 - 6.84)	2.94	(1.86 - 6.45)

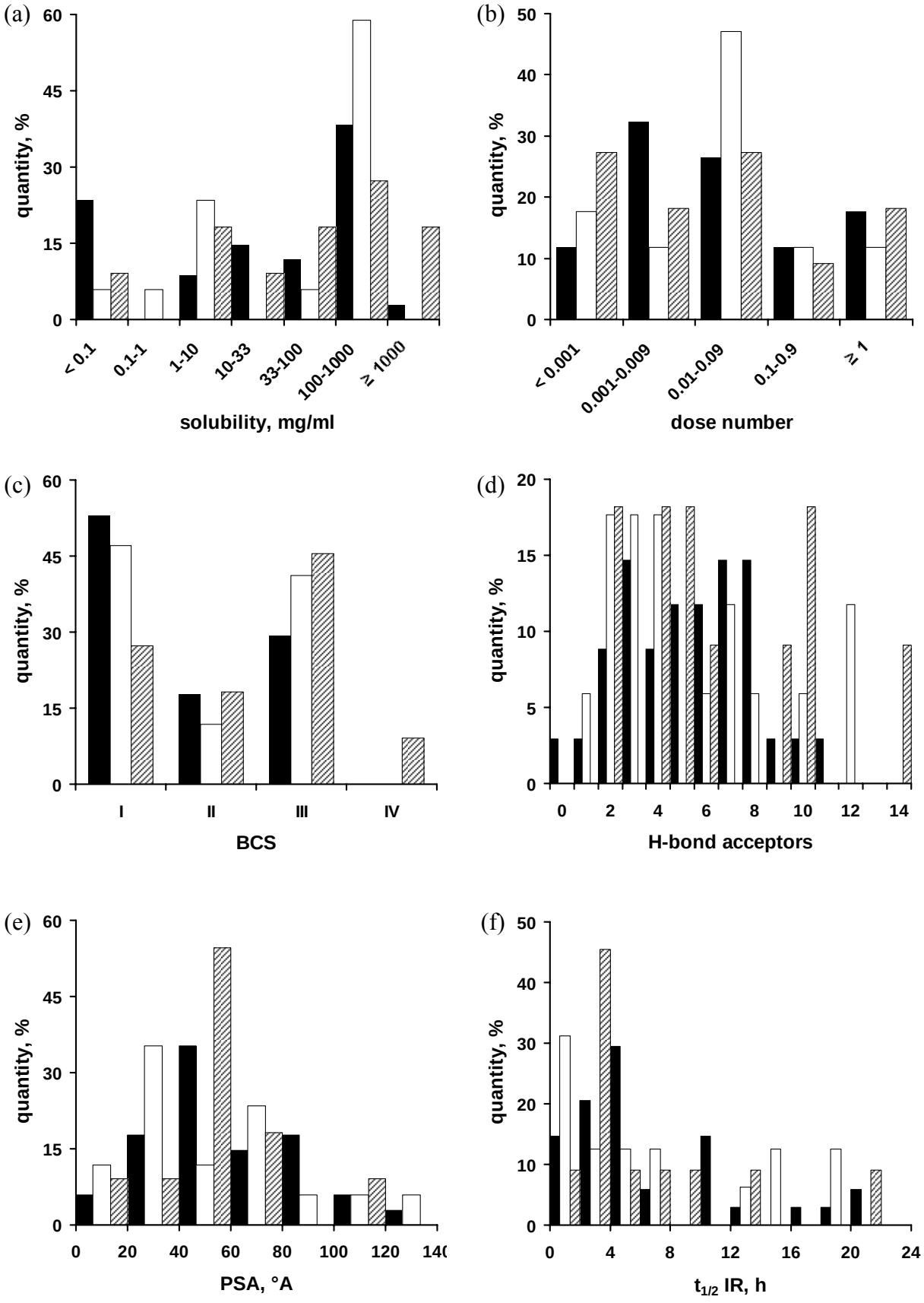


Fig. 24 Data distribution of selected variables used in the classification of (■) hydrophilic-, (□) lipophilic- and (▨) mix matrix systems

Contributing drug properties and pattern

The score plot of 58 matrix tablets and the loading plot of their contributed variables were presented in Fig. 25a and Fig. 25b, respectively. The samples located in the negative region of PC1 had the lowest solubility or the highest dose number when compared with the matrices in the positive region. The majority of samples located on the left side (group 1) of the dashed line (PC1 = -0.75) were hydrophilic matrices, whereas those on the right side (group 2) were the samples of all matrix types. Due to this distribution pattern, properties of drugs which were highly correlated with PC1 were responsible for the classification of matrix systems. Table 19 listed the correlation values of the drug properties on the extracted components. The scores on the first component were correlated highly with solubility (r = 0.871) and dose number (r = -0.759).

Table 19 Multivariate analysis of drug properties: PCA with varimax rotation on matrix tablets

Drug properties	Correlation of scores on the extracted components[1]	
	PC1	PC2
Solubility	**0.871**	-0.185
Do	**-0.759**	0.055
pKa	0.615	0.092
PSA	-0.568	-0.631
Mw	-0.541	0.104
LogP	-0.368	**0.705**
H-acceptors	-0.237	**-0.680**
Max dose	0.144	-0.281
$t_{1/2}$IR	-0.065	**0.796**
Variance explained by component, after rotation	28.3	23.6

[1]bolded values thought to be important

The limited solubility of a drug was found to be the key parameter for identifying the matrix type. The studied drugs whose solubility values are the least or dose numbers are greater than one (i.e. poorly soluble) were presented in Table 20. Among those belonged to group (1), all of them are practically insoluble according to the USP. Nonetheless, alprazolam and indapamide are highly soluble with regard to their dose numbers. It was unlikely for a poorly soluble drug to be formulated as a lipophilic matrix system because an incomplete drug release from the dosage from was expected. The penetration of aqueous media through

the lipophilic matrix was restricted, resulted in the deficient drug dissolved and subsequently diffused through the matrix. Clearly, this effect was more pronounced when the high amount of such drugs were incorporated into the dosage forms. Hydrophilic matrix carrier, on the contrary, was a system of choice for a drug with poor aqueous solubility. The polymers underwent desirable hydration, swelling as well as erosion, which predominantly contributed to the release of poorly soluble drugs (Tahara et al., 1996; Kim, 1998). These characteristics also facilitated the penetration of aqueous media through the dosage form, thus the accelerated drug dissolution and release.

Table 20 Poorly soluble drugs

Drug	Matrix type	Solubility (mg/ml)*	Solubility**	Max dose (mg)	Dose number	PC1
Felodipine	hydrophilic	0.001[a]	pi	10	40.00	-2.56
Bezafibrate	mix	0.010[b]	pi	400	160.16	-2.09
Nifedipine	hydrophilic	0.010[c]	pi	90	36.00	-2.46
Mizolastine	lipophilic	0.013[d]	pi	10	3.08	-1.99
Nisoldipine	hydrophilic	0.025[e]	pi	40	6.50	-2.14
Glipizide	hydrophilic	0.037[f]	pi	10	1.08	-2.06
Alprazolam	hydrophilic	0.045[g]	pi	3	0.92	-1.51
Ibuprofen	hydrophilic	0.049[f]	pi	800	65.31	-0.90
Gliclazide	hydrophilic	0.055[h]	pi	80	5.82	-1.44
Indapamide	hydrophilic	0.075[f]	pi	1.5	0.08	-1.09
Carbamazepine	lipophilic	0.113[i]	vss	600	21.82	-0.22
Valproic acid	lipophilic, mix	1.300[b]	ss	500	1.54	-0.19

*water solubility at room temperature unless otherwise specified
**USP 29; pi: practically insoluble, vss: very slightly soluble, ss: slightly soluble
[a]Scholz et al. (2002), 37 °C
[b]Kasim et al. (2004)
[c]Abrahamsson et al. (1998a)
[d]Chariot et al. (2000)
[e]NLM (1994)
[f]Wishart et al. (2008)
[g]Williams et al. (2001)
[h]Alkhamis et al. (2003), 37 °C
[i]experimental

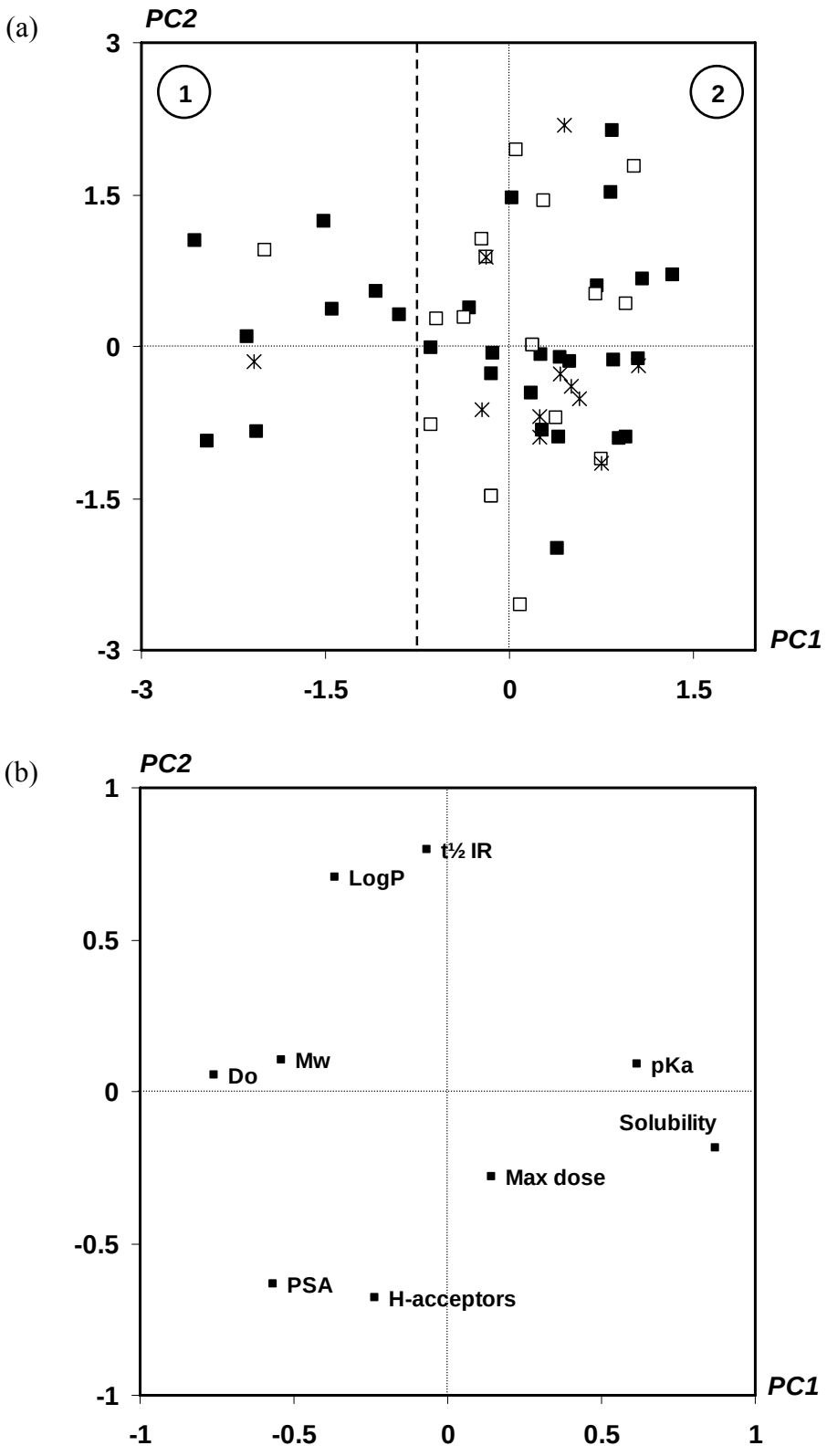


Fig. 25 (a) Score plot and (b) loading plot of PC1 vs. PC2 after varimax rotation of 58 matrix tablet samples and 9 properties, explaining 51.9% of the total variance; (■) hydrophilic-, (□) lipophilic- and (✳) mix matrix systems. The majority of samples in group (1) were hydrophilic matrices.

Application of PCA model

Similar to the classification of single- vs. multiple-unit dosage forms, the values of PC1 that define the location of the samples can be used for the suggestion of the matrix type. As mentioned earlier, the dashed line in Fig. 25a clearly divided the group of the hydrophilic matrices from the non-separated ones. Therefore, hydrophilic matrix is recommended for a drug that has the PC1 score less than -0.75, or otherwise it can be formulated as either system. For a given drug with known properties, PC1 are determined by the following equation:

$$\begin{aligned} PC1 = {} & 0.223\text{Log(Solubility)} - 0.191\text{Log(Do)} + 0.083(\text{pKa}) - 0.008(\text{PSA}) \\ & - 0.002(\text{Mw}) - 0.067(\text{LogP}) - 0.031(\text{H-bond acceptors}) \\ & + 0.006(\text{Max dose})^{1/2} - 0.019(t_{1/2}\ \text{IR})^{1/2} + 0.175 \end{aligned} \qquad \text{(Eq. 5)}$$

where the drug properties are substituted by their values.

3.3.3 Conclusion

While the maximum dose strength and the $t_{1/2}$ IR of a drug were the most significant properties for the classification of single- vs. multiple-unit dosage form, the solubility was a key parameter for the selection of the matrix type. The single unit dosage form was recommended when the dose strength was greater than 500 mg or when the $t_{1/2}$ IR was longer than 11 h. The hydrophilic matrix tablet was suggested when the aqueous solubility of a drug was practically insoluble. Despite these factors, PC scores calculated by Eq. 3-5 offered the better classification of the dosage form and the matrix type, since all relevant drug properties were employed.

The PCA technique provided possibility to classify type of the ER systems with respect to their correspondence with the extracted model. The location of the samples depends on the values of various variables, which were described in the new co-ordinate system. The PCA model for the dosage form selection created from a quality data set would be beneficial to formulation scientists in dosage form design, thus facilitate the successful of formulation development.

4. SUMMARY

4.1 In vitro performance and dissolution robustness of bioequivalent extended release solid oral dosage forms

The drug products are bioequivalent (BE) when their active ingredients in pharmaceutical equivalents or pharmaceutical alternatives are available at the site of action with similar rate and extent when administered at the same molar dose under similar conditions. A discriminatory in vitro dissolution test should be able to demonstrate the similarity between BE products as well as the dissimilarity between bioinequivalent products. The objective of this study was to examine the performance of commercially available BE products in vitro by performing release studies in various dissolution conditions and to evaluate the discriminating ability of those test conditions. Compendial dissolution methods with minor modification that mimic conditions in vivo were used to evaluate the performance of two pentoxifylline BE products and three verapamil hydrochloride (HCl) BE products.

Upon contact with release media, the release profiles of the BE products were different in most test conditions. Pentoxifylline released slower from hydroxyethyl cellulose (HEC) matrix tablets when compared to that from Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) (Eudragit RS/RL) tablets. The less mechanical stress that the tablets encountered in vitro was responsible for the dissimilarity of the two products. The release of verapamil HCl was in the following order: sodium alginate/hydroxypropyl methylcellulose (HPMC) matrix tablets > ethylcellulose (EC)/ Poly(methacylic acid-co-ethyl acrylate) 1:1 (Eudragit L 100-55) coated pellets > shellac/fumaric acid coated pellets. The latter was the most robust formulation. The difference of BE verapamil HCl releases could be attributed to the high surface tension in vitro, which led to the decreased drug release. Compendial in vitro dissolution methods used in this study were not discriminating because they were unable to reflect the in vivo behaviour of the products. The results of robustness test indicated potential factors influencing the in vitro releases of both drugs. The simulation of in vivo osmolality, such as the addition of sodium chloride into the standard dissolution media, and/or the optimization of mechanical destructive force, by adjusting the agitation intensity or the addition of glass beads, should be further investigated to obtain the discriminatory dissolution tests for pentoxifylline extended release (ER) tablets. Likewise, the decreased mechanical destructive

force and surface tension should be considered for the dissolution studies of verapamil HCl ER products.

4.2 Effect of sodium dodecyl sulphate on the in vitro dissolution of extended release solid oral dosage forms

The goal of adding surfactants into dissolution media was to mimic the condition in vivo by lowering surface tension. The drug release in this simulated media is, however, influenced by the type of surfactant. In addition, the physicochemical properties of drugs, excipients and the dosage forms also contribute to the release pattern. The purpose of this study was to investigate the effect of sodium dodecyl sulphate (SDS) on the releases of drugs from different ER dosage forms. The matrix tablets of verapamil HCl and diltiazem HCl were robust to the addition of SDS. Their release patterns were unchanged because the availability of water resulting from the lower surface tension did not have much effect on the erosion rate of the polymer matrix. In contrast, this increase water availability facilitated the release from coated pellets, as could be seen from the release of both drugs. There was no effect of SDS on the drug release from osmotic tablet because the rate of water penetration into the tablet, which controlled by the semi-permeable membrane, was unchanged. The significantly increase solubility of carbamazepine (CBZ) outperformed the effect of SDS on the drug release from different types of dosage form. Therefore, all formulations of CBZ show the considerably increase drug release when SDS was added. Another concern of adding ionic surfactant into dissolution medium is the cationic/anionic interaction between the surfactant and the drug or other excipients. Pentoxifylline released from matrix tablets composed of HEC, a nonionic matrix former, were unaffected by the addition of SDS, an anionic surfactant. On the contrary, the decreased drug release was observed when the matrix former was Eudragit RS/RL, a cationic polymer. Despite the dissolution was performed in the similar surface tension as of SDS solution, the decreased drug release was not seen when the nonionic surfactants, Tween 80 or Span 80, were added. In conclusion, the effect of SDS on drug release could be attributed to many formulation factors. Although the use of SDS is recommended for dissolution studies of several products, the contributions of those factors as for example reported in this study should not be disregarded.

4.3 Evaluation of drug properties for the selection of extended release solid oral dosage form: Application of principal component analysis

Success of an ER formulation depends not only on the performance of the formulation, but also the suitability of the chosen dosage form. The investigation of successful marketed ER products could provide a valuable clue for formulation scientists to select a system over another one for a particular drug. The objective of this study was: (1) to understand the relationships between properties of drugs; such as solubility, maximum dose strength and elimination half-life; and their available ER dosage forms, and (2) to establish a guide for ER technology selection by the application of principal component analysis (PCA). The classification of single- vs. multiple-unit dosage form and the carrier systems of matrix tablets were examined. Significant properties distinguishing the dosage forms and matrix types were investigated

While the maximum dose strength of a product and the elimination half-life of a drug as immediate release formulation ($t_{1/2}$ IR) were the most significant properties for the classification of single- vs. multiple-unit dosage form, the solubility was a key parameter for the selection of the matrix type. The single unit dosage form was recommended when the dose strength was greater than 500 mg or when the $t_{1/2}$ IR was longer than 11 h. The hydrophilic matrix tablet was suggested when the aqueous solubility of a drug was practically insoluble. Despite these factors, principal component scores calculated by Eq. 3-5 offered the better classification of the dosage form and the matrix type, since all relevant drug properties were employed.

The PCA technique provided a possibility to classify type of the ER systems with respect to their correspondence with the extracted model. The location of the samples depends on the values of various variables, which were described in the new co-ordinate system. The PCA model for the dosage form selection created from a quality data set would be beneficial to formulation scientists in dosage form design, thus facilitate the successful of formulation development.

5. ZUSAMMENFASSUNG

5.1 In-vitro-Performance und Robustheit der Freisetzung von bioäquivalenten, retardiert freisetzenden, festen oralen Arzneiformen

Arzneimittel sind bioäquivalent, wenn ihre Wirkstoffe in pharmazeutischen Äquivalenten oder pharmazeutischen Alternativen am Wirkort mit ähnlicher Geschwindigkeit und in ähnlichem Ausmaß verfügbar sind, wenn sie in der gleichen molaren Dosis und unter ähnlichen Bedingungen appliziert werden. Ein diskriminierender In-vitro-Freisetzungstest sollte in der Lage sein die Ähnlichkeit zwischen bioäquivalenten Arzneimittel zu zeigen ebenso wie den Unterschied zwischen bioinäquivalenten Arzneimitteln. Ziel dieser Studie war es, die Performance kommerziell verfügbarer, bioäquivalenter Arzneimittel in vitro mittels der Durchführung von Freisetzungsstudien unter verschiedenen Freisetzungsbedingungen zu untersuchen und die Unterscheidungsfähigkeit dieser Testbedingungen zu bewerten. Es wurden leicht modifizierte Arzneibuch-Freisetzungsmethoden benutzt, welche die In-vivo-Bedingungen imitieren, um die Performance von zwei bioäquivalenten Pentoxifyllin-Produkten und drei bioäquivalenten Verapamilhydrochlorid (HCl)-Produkten zu evaluieren.

Nach Kontakt mit dem Freigabemedium, waren die Freisetzungsprofile der bioäquivalenten Produkte bei den meisten Testbedingungen unterschiedlich. Pentoxifyllin wurde langsamer aus Hydroxyethylcellulose (HEC)-Matrixtabletten freigesetzt als aus Poly(ethylacrylat-co-methyl-methacrylat-co-trimethylammonioethylmethacrylatchlorid) (Eudragit RS/RL)-Tabletten. Die geringere mechanische Belastung, welcher die Tabletten in vitro ausgesetzt waren, war für den Unterschied zwischen den beiden Produkten verantwortlich. Die Freisetzung von Verapamil-HCl geschah in der Reihenfolge: Natriumalginat/Hydroxypropyl methylcellulose (HPMC)-Matrixtabletten > Ethylcellulose (EC)/ Poly(methacylsäure-co-ethylacrylat) 1:1 (Eudragit L 100-55)-überzogene Pellets > Schellack/Fumarsäure-überzogene Pellets. Letztere war die robusteste Formulierung. Der Unterschied in der Freisetzung der bioäquivalenten Verapamil-HCl-Produkte konnte der hohen Oberflächenspannung in vitro zugeschrieben werden, welche zur verminderten Arzneistofffreisetzung führte. Die in dieser Studie verwendeten Arzneibuch-Freisetzungsmethoden waren nicht diskriminierend, weil sie das In-vivo-Verhalten der Arzneimittel nicht widerspiegeln konnten. Die Ergebnisse des Robustheits-Tests wiesen auf

potentielle Faktoren hin, welche die In-vitro-Freisetzung beider Arzneistoffe beeinflussen. Die Simulation der In-vivo-Osmolalität, wie zum Beispiel die Zugabe von Natriumchlorid zum Standardfreisetzungsmedium, und/oder die Optimierung der mechanischen Zerstörungskraft durch Anpassung der Bewegungsintensität oder die Zugabe von Glaskugeln, sollte weiter untersucht werden, um diskriminierende Freisetzungstests für Pentoxifyllin-Retardtabletten zu erhalten. Desgleichen sollten die verminderte mechanische Zerstörungskraft und die Oberflächenspannung für die Freisetzungsstudien von Verapamil-HCl-Retardprodukten berücksichtigt werden.

5.2 Einfluss von Natriumdodecylsulfat auf die In-vitro-Freisetzung von retardiert freisetzenden, festen, oralen Arzneiformen

Das Ziel der Zugabe von oberflächenaktiven Substanzen zum Freisetzungsmedium war es, die Bedingungen in vivo durch das Absenken der Oberflächenspannung zu imitieren. Die Arzneistofffreigabe in dieses nachgeahmte Medium wird jedoch von der Art des Netzmittels beeinflusst. Zusätzlich tragen auch noch die physico-chemischen Eigenschaften der Arzneistoffe, der Hilfsstoffe und der Arzneiformen zum Freisetzungsprofil bei. Die Zielsetzung dieser Studie war es den Einfluss von Natriumdodecylsulfat (SDS) auf die Freisetzung von Arzneistoffen aus verschiedenen Retardarzneiformen zu untersuchen. Die Verapamil-HCl- und die Diltiazem-HCl-Matrixtabletten waren robust bei Zugabe von SDS. Ihre Freisetzungsprofile waren unverändert, weil die aus der niedrigeren Oberflächenspannung resultierende Verfügbarkeit von Wasser keine große Auswirkung auf die Erosionsgeschwindigkeit der Polymermatrix hatte. Im Gegensatz dazu förderte diese gestiegene Verfügbarkeit von Wasser die Freisetzung beider Arzneistoffe aus überzogenen Pellets. Es gab keinen Effekt von SDS auf die Freisetzung aus osmotischen Tabletten, weil die Geschwindigkeit der Wasser-Penetration in die Tablette, welche durch die semipermeable Membran kontrolliert wird, unverändert blieb. Der signifikante Anstieg der Löslichkeit von Carbamazepin (CBZ) übertraf den Effekt von SDS auf die Arzneistofffreisetzung verschiedener Arzneiformen. Deshalb zeigten alle CBZ-Formulierungen einen wesentlichen Anstieg der Arzneistofffreisetzung bei SDS-Anwesenheit. Bei der Zugabe von ionischen Tensiden zum Freisetzungsmedium ist zudem die mögliche kationische/anionische Wechselwirkung zwischen Tensid und Arzneistoff oder anderen Hilfsstoffen zu berücksichtigen. Die Pentoxifyllin-Freisetzung aus

Matrixtabletten bestehend aus dem nichtionischen Matrixbildner HEC wurde durch die Zugabe des anionischen Tensids SDS nicht beeinflusst. Hingegen wurde eine verminderte Arzneistofffreisetzung beobachtet, wenn der Matrixbildner das kationische Polymer Eudragit RS/RL war. Trotzdem die Freisetzungstests bei ähnlicher Oberflächenspannung wie der der SDS-Lösung durchgeführt wurden, war diese verminderte Arzneistofffreisetzung nicht beobachtbar, wenn die nichtionischen Tenside Tween 80 oder Span 80 zugesetzt wurden. Schließlich konnte der Einfluss von SDS auf die Arzneistofffreisetzung vielen Formulierungsparametern zugeschrieben werden. Obwohl die Verwendung von SDS für die Freisetzungsstudien verschiedener Produkte empfohlen wird, sollte die Kontribution dieser Parameter, wie sie zum Beispiel in dieser Untersuchung dargestellt wurden, nicht unberücksichtigt bleiben.

5.3 Bewertung der Arzneistoffeigenschaften in Hinblick auf die Auswahl geeigneter fester oraler Darreichungsformen mit verlängerter Wirkstofffreisetzung: Anwendung der Hauptkomponentenanalyse

Der Erfolg einer Formulierung mit verlängerter Wirkstofffreigabe hängt nicht nur von den Eigenschaften der Formulierung selbst, sondern auch von der gewählten Darreichungsform ab. Die Untersuchung von bereits auf dem Markt erhältlichen Produkten könnte daher wertvolle Hinweise für die Auswahl der geeignetsten Darreichungsform für einen bestimmten Arzneistoff liefern. Die Zielstellungen dieser Arbeit waren: (1) Die Abhängigkeiten zwischen bestimmten Eigenschaften eines Arzneistoffs (z.B. Löslichkeit, maximaler therapeutischer Einzeldosis und Eliminationshalbwertszeit) und dessen bereits verfügbaren Darreichungsformen mit verlängerter Wirkstofffreisetzung zu verstehen. (2) Durch Anwendung der Hauptkomponentenanalyse („principal component analysis“, PCA) eine Entscheidungshilfe für die Auswahl der geeignetsten Technologie zur Erzielung der gewünschten verlängerten Wirkstofffreisetzung zu entwickeln. Dabei wurden Einzeldosis- und Mehrdosissysteme, sowie der Einfluss verschiedener Tablettenmatrizes unter besonderer Betrachtung ihrer wichtigsten Eigenschaften untersucht.

Während die Arzneistoffdosis und die Eliminationshalbwertszeit des Arzneistoffs die wichtigsten Eigenschaften für die Auswahl zwischen Einzeldosis- und Mehrdosissystem waren, wurde die Löslichkeit des Arzneistoffs als wichtigster Parameter für die Auswahl des

Matrixtyps identifiziert. Einzeldosissysteme wurden vor allem dann empfohlen, wenn die Einzeldosis über 500 mg lag oder die Eliminationshalbwertszeit 11 h überschritt. Eine hydrophile Tablettenmatrix wurde dann empfohlen, wenn die Wasserlöslichkeit des Arzneistoffs sehr schlecht war. Ungeachtet dieser Aussagen, lieferte die PCA eine noch bessere Möglichkeit zur Auswahl der Darreichungsform und des Matrixtyps, da alle relevanten Arzneistoffeigenschaften berücksichtigt wurden.

Auf Basis des erstellten Modells und seiner Variablen konnten die untersuchten Proben in ein Koordinatensystem eingeordnet werden. Dieses kann nun dazu dienen, eine wahrscheinlich erfolgreiche Formulierungsstrategie für einen beliebigen Arzneistoff zu ermitteln.

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7. PUBLICATIONS & PRESENTATIONS RESULTING FROM THIS WORK

7.1 Publications

Raiwa, A. and Bodmeier, R. In vitro performance and dissolution robustness of bioequivalent extended release solid oral dosage forms. in preparation.

Raiwa, A. and Bodmeier, R. Effect of sodium dodecyl sulphate on the in vitro dissolution of extended release solid oral dosage forms. in preparation.

Raiwa, A. and Bodmeier, R. Evaluation of drug properties for the selection of extended release solid oral dosage form: Application of principal component analysis. in preparation.

Raiwa, A. and Bodmeier, R. Effect of co-administered food on different dosage forms. in preparation.

7.2 Presentations

Raiwa, A. and Bodmeier, R. Evaluation of molecular descriptors for the selection of extended release dosage form. *Proceedings of the 2006 AAPS Annual Meeting and Exposition, AAPS*, San Antonio, TX, USA, 29 October - 2 November 2006.

Raiwa, A. and Bodmeier, R. Comparison of the in-vitro dissolution profiles of commercially available verapamil hydrochloride extended release formulations in various release media. *Proceedings of the 2007 AAPS Annual Meeting and Exposition, AAPS*, San Diego, CA, USA, 11 - 15 November 2007.

Raiwa, A. and Bodmeier, R. Multiparticulates or single units: Evaluation of drugs properties for the selection of extended release dosage forms. *Proceedings of the 2007 AAPS Annual Meeting and Exposition, AAPS*, San Diego, CA, USA, 11 - 15 November 2007.

Raiwa, A. and Bodmeier, R. Evaluation of drug properties for the selection of extended release dosage form: Application of principal component analysis. *Proceedings of the 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology,* Barcelona, Spain, 7-10 April 2008.

8. CURRICULUM VITAE

For reasons of data protection,

the curriculum vitae is not included in the online version