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JARI PAJANDER

Prolonged Release Starch Acetate Matrix Tablets

Relationships Between Formulation Properties and *in vitro* Dissolution Behaviour

Doctoral dissertation

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ABSTRACT

A drug compound is most commonly introduced into the systemic plasma circulation by means of a solid oral dosage form due to convenience, robustness and ease of product handling. The utilisation of preparations that release their contents slowly in the gastrointestinal tract, i.e. prolonged release preparations, can reduce several undesired effects, such as unnecessarily frequent administration, unwanted side-effects or local irritation. However, the development of a well-designed prolonged drug release preparation is a challenging task.

The objective of the study was to find suitable methods to control the structure and subsequent drug release properties of hydrophobic starch acetate (ds 2.7) matrix tablets, and to relate the structural properties with the drug release behaviour. In addition, the functionality of an *in vitro* drug release test which is routinely used in order to ensure the consistency and safety of the preparation was evaluated.

The studies indicate that the structure of the matrix tablet can be controlled by altering the particle size fraction of matrix forming hydrophobic excipient or making the tablet more porous. When starch acetate (ds 2.7) powder with an adequately small particle size fraction is used, it can form a percolating network within the tablet. The consistence of a networking matrix in the tablet has a great significance. A networking matrix of the hydrophilic drug alone leads to immediate tablet disintegration and rapid drug release. Co-existing percolating networks of drug and excipient result in surface erosion and highly variable drug release. When the hydrophobic excipient is percolating, tablets maintain their shape and only crack during dissolution tests. Furthermore, when the tablet porosity of the studied SA particle size-hydrophilic drug (caffeine) combinations is increased over 20 %, the drug release determining feature changes from a relaxational component into a diffusional component.

In tablets where the networking matrix is composed of the hydrophobic excipient, the penetrating liquid weakens the internal bonds and initially this causes tablet expansion which is then transformed into cracking. The cracking increases the drug release rate, since the formation of a crack shortens the length of the diffusion path, increases the effective surface area and lowers the degree of tortuosity.

The structure of the tablet and parameters affecting it are crucial considering the drug release mechanism and rate. However, the properties of the drug compound, such as the water solubility and solubility rate, also contribute to the drug release mechanism and rate. However, in practice, the situations of the formation of the matrix and drug release can be extremely complicated and knowledge of maximum water solubility and dissolution rate do not describe this process adequately. The results indicate that although compound exhibits adequate maximum water solubility and solubility rate, other properties, such as the magnitude and location of hydrophilic and hydrophobic areas, can cause significant interactions with other excipients which might not be beneficial to drug release. These chemical molecular properties cannot be removed by means of traditional pharmaceutical processes and, thus the properties and nature of the drug compound in question need to be comprehensively characterized in order to fully understand and control the drug release process.

Finally, the results showed that USP paddle method produces relevant data describing the drug release of prolonged hydrophobic tablets if the preparation consists of an extremely water soluble compound with homogenous distribution within the matrix tablet. However, in the case of a less water soluble compound whose particle size distribution is wide and the consequent drug distribution is less homogenous, the *in vitro* test may not produce results which are meaningful. The obtained results showed that less water soluble compound clearly concentrated at the bottom edge of the tablet in contact with the dissolution vessel, although the poor hydrodynamic properties of the USP paddle method were considered to play a important part in this observation. Thus, the *in vitro* dissolution test should be chosen extremely carefully for prolonged release preparations or the existing test should be modified when the drug compound is not highly water soluble and the preparation is a hydrophobic polymer based matrix tablet.

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Kuopio, December 2009

Jari Pajander

ABBREVIATIONS

a_0	initial radial dimension of tablet
A	the total amount of drug present in the matrix per unit volume
AC	acyclovir
AP	allopurinol
ATR	attenuated total reflection
b_0	initial vertical dimension of tablet
C	concentration of solute
C_0	total amount of drug in a unit volume of the matrix
C_s	saturation solubility
CP	carrier payload
d_{mean}	mean particle size of the compound
ds	degree of substitution
D	diffusion coefficient
DSC	differential scanning calorimetry
D10%	The diameter when 10 % of particles are under the indicated size
D50%	The diameter when 50 % of particles are under the indicated size
D90%	The diameter when 90 % of particles are under the indicated size
ε	porosity of the matrix
$E_t\%$	percentage of expansion
FTIR	Fourier transform infrared
γ_s^D	dispersive component of the surface free energy
GI	gastrointestinal
h	thickness of the diffusion layer
H_{before}	height of the cylinder of the tablet before the dissolution test
H_t	height of the cylinder of the tablet after the dissolution test and freeze drying
HPLC	high performance liquid chromatography
IGC	inverse gas chromatography
IR	infrared
J	flux
k	square root release constant
k_a	erosion rate constant in the radial direction

k_b	erosion rate constant in the vertical direction
$k_{\text{diffusion}}$	diffusional constant
$k_{\text{relaxation}}$	relaxational constant
M	dissolved amount of drug at time point of t
M_t	amount of drug released at time t
M_∞	total amount of drug
MD	metronidazole
n	diffusional exponent
N	number of particles in the mixture
PC	paracetamol
PCA	principal component analysis
PEG	polyethylene glycol
PLS	partial least squares to latent structures
Q^2	prediction parameter
QSAR	quantitative structure-activity relationship
R^2	correlation coefficient
S	surface area of undissolved drug
SA	starch acetate
SC	salicylamide
SEM	scanning electron microscope
τ	tortuosity factor of the capillary system
t	time point
TF	theophylline
USP	United States Pharmacopoeia
UV	ultraviolet-visible
V	measured volume of the tablet
V_0	theoretical volume of the tablet
X	distance in the membrane

LIST OF THE ORIGINAL PUBLICATIONS

This doctoral dissertation is based on the following publications, referred to in the text by bolded Roman numerals **I-IV**. Some unpublished data are also presented in this thesis.

- I** van Veen B, Pajander J, Zuurman K, Lappalainen R, Poso A, Frijlink HW, Ketolainen J: The Effect of Powder Blend and Tablet Structure on Drug Release Mechanisms of Hydrophobic Starch Acetate Matrix Tablets. *European Journal of Pharmaceutics and Biopharmaceutics* 61: 149-157, 2005
- II** Pajander J, van Veen B, Korhonen O, Lappalainen R, Ketolainen J: Liquid Boundary Movements in Cylindrical and Convex Hydrophobic Matrix Tablets: Effects on Tablet Cracking and Drug Release. *European Journal of Pharmaceutics and Biopharmaceutics* 64: 167-172, 2006
- III** Pajander J, Korhonen O, Laamanen M, Ryyänänen EL, Grimsey I, van Veen B, Ketolainen J: Effect of Formulation Parameters and Drug-Polymer Interactions on Drug Release from Starch Acetate Matrix Tablets. *Journal of Pharmaceutical Sciences* 98: 3676-3690, 2009
- IV** Pajander J, Soikkeli AM, Korhonen O, Forbes RT, Ketolainen J: Drug Release Phenomena within a Hydrophobic Starch Acetate Matrix: FTIR Mapping of Tablets after *In Vitro* Dissolution Testing. *Journal of Pharmaceutical Sciences* 97: 3367-3378, 2008

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1 INTRODUCTION

When a drug is taken by a patient, the resulting biological effects, for example lowering of blood pressure, are produced via the interaction of the drug with specific receptors at the drug's site of action (Hillery 2001). Solid oral dosage forms, due to their robustness, ease of product handling and convenience, are most commonly used in order to introduce the drug into the systemic circulation (Rudnic and Kottke 1996, Venkatraman et al. 2000). However, if the patients' condition needs continuous medical treatment, a solid oral dosage form displaying an immediate drug release property is inconvenient and may even cause unwanted side-effects.

The unnecessarily frequent administration and other undesired features, such as side-effects or local irritation, can be avoided by utilisation of preparations that release their contents slowly into the gastrointestinal tract. These preparations are called using the term controlled release, but they are known by other names including slow release, extended release, sustained release and prolonged release (Alderborn 2007). However, all of the preparations given via the oral route should exhibit controlled release behaviour instead of random release and, therefore, within the context of this thesis, these slowly releasing preparations are designated with the term prolonged release. In addition to this, another clarification needs to be done in order to avoid possible confusion. Many handbooks refer to water non-dissolving polymers using the term hydrophobic, although they are not *per se* hydrophobic, i.e. repulsive to water. Therefore, within the context of this thesis the term hydrophobic, when used to describe excipients or matrix tablets, is used as a synonym for water non-dissolving, unless otherwise stated.

There are many different ways to achieve preparations having prolonged drug release properties, but the most common types are tablets (Lee and Robinson 1978, Rudnic and Kottke 1996, Venkatraman et al. 2000, Hayashi et al. 2005, Alderborn 2007). However, in particular the production of matrix tablets is not simple, since many different factors contribute to the final properties of the tablet preparation. The factors affecting the formation of the tablet are attributable to the physicochemical properties of the tablets' components, such as particle morphology and deformation properties, and processing, such as the mixing of the powder and compaction. In addition, the drug release mechanism and functionality of the prolonged release

preparation has to be optimized. This is most often performed routinely using *in vitro* dissolution tests, which are defined in the Pharmacopoeias.

In this thesis, the focus is on prolonged release hydrophobic matrix tablets, especially on the process and formulation parameters affecting their drug release properties during the *in vitro* dissolution test. To be more precise, the aim of the study was to identify methods to control the structure and subsequent drug release properties of hydrophobic starch acetate, with a degree of substitution 2.7, matrix tablets, relate the structural properties with the drug release behaviour, and, finally, to evaluate the functionality of *in vitro* drug release test. Therefore, in order to provide a more comprehensive presentation of the topic, the background of the study considers the following themes: oral administration, general principles and examples of prolonged drug delivery, *in vitro* dissolution tests, and tablet preparation, which includes the topics such as powder mixing and compaction. In addition, in the experimental section there are brief descriptions of analysing techniques, such as microcomputed tomography, Fourier transform infrared mapping and multivariate data analysis, which are rather new and unfamiliar in the field of pharmaceuticals.

2 BACKGROUND OF THE STUDY

2.1 Oral drug delivery

Drug treatment via the oral route is the most common and most convenient way to administer medications. Due to its non-invasive nature, it can be regarded as cost efficient, highly acceptable to patients and thus compliance enhancing. For that reason, the majority of the existing drug preparations are administered via oral route (Steele 2001, Qiu and Zhang 2000). In addition, it is likely that interest in the preparations given by mouth, i.e. systemic effects following the administration of preparation, such as tablet or capsule, and their development, will continue in the future.

The oral route is composed of parts, which are, in the order of appearance, the mouth, the stomach, the small intestine and the large intestine. Each part has one or more specific functions and therefore their properties differ vastly from each other. Thus, there are differences in the structure of tissue, such as surface area and extent of motility, chemical environment, such as range of pH and amount of moisture content, and biological activity, such as extent and diversity of enzymatic activity and microbiologic flora (Rowland and Tozer 1995, Guyton and Hall 2000a, Guyton and Hall 2000b, Lee and Yang 2001). In addition to mentioned, there are always inter- and intra-patient variations present.

In order to enter the general systemic circulation and evoke systemic effect after being taken by the oral route, a drug must dissolve from the preparation and pass from the gastrointestinal lumen, through the gut wall and through the liver (Rowland and Tozer 1995). However, this may not be a simple issue, since the characteristic structure and function of each part of the oral route can generate a rather hostile environment for the preparation and drug compound.

2.2 Prolonged oral drug delivery

The target of prolonged oral drug delivery is to produce preparations having increased therapeutic efficiency by reducing fluctuations in plasma concentrations, as well as increased patient compliance by reducing the administration to once or twice a day (Venkatraman et al. 2000).

One should consider the possibility of prolonged drug delivery if one or more of the following drug compound properties exist (Rowland and Tozer 1995, Jantzen and Robinson 1996, Qiu and Zhang 2000):

1. High water solubility
2. High permeability
3. Low effective dose
4. Wide therapeutic window
5. Poor physicochemical stability
6. Low first pass metabolism
7. Short half-life

Although prolonged oral drug delivery possesses significant benefits, they are not *per se* desirable solutions for drug delivery. According to Ballard (1978) there are some disadvantages associated with prolonged release attributable to various sources. The structure of prolonged release preparations is more delicate and can be more expensive than immediate release systems and therefore the unjustified utilization of such a preparation is a waste of resources. If drug compound has a specific absorption site, i.e. the upper part of small intestine, the prolonged drug release properties may not guarantee adequate absorption. Since drug loading of prolonged release preparation may be substantially high, the accidental or intentional collapse of the preparation can lead to acute poisoning. If the daily dose is high, i.e. from one to three grams, the physical size of the preparation may be too large to swallow. Finally, due to inter-individual variations in the function of GI tract an individual having a delayed gastrointestinal transit time may suffer from local irritation.

2.3 Types of prolonged oral delivery systems

Prolonged oral drug delivery systems can be classified into either single-unit or multiple-unit systems and their principle of drug release can be divided roughly into the following groups (Lee and Robinson 1978, Jantzen and Robinson 1996, Venkatraman et al. 2000, Hayashi et al. 2005, Alderborn 2007): dissolution-controlled, diffusion-controlled, ion exchange resins, osmotic controlled release and gastroretentive systems.

In dissolution-controlled prolonged preparations, the rate of dissolution of the drug or some other tablet ingredient in the GI juices is the release-controlling step (Alderborn 2007). Thus, a sparingly water soluble drug can be thought to be *per se* a dissolution-controlled preparation. Generally, the dissolution-controlled approach can be used with compounds having moderate to great and pH dependent solubility (Streubel et al. 2000, Alderborn 2007). Dissolution-controlled prolonged release properties can be achieved by incorporating the drug compound in a slowly dissolving or eroding carrier or coating, i.e. the drug release results as a dissolution or erosion of the carrier or coating, or the drug can be in a non-dissolving carrier, i.e. the drug release results when the penetrating liquid reaches and dissolves the drug compound (Venkatraman et al. 2000, Abdul and Poddar 2004, Alderborn 2007, Cao et al. 2007).

In diffusion-controlled systems, the release limiting process is the transport by diffusion of the dissolved drug in pores filled with surrounding liquid or in a solid phase, i.e. polymer (Alderborn 2007). This can be achieved by utilisation of an insoluble coating or a insoluble or swelling carrier (Abdul and Poddar 2004, Strübing et al. 2007, Siepmann et al. 2008). In the first case, the drug has to dissolve into coating and in the latter, the compound has to diffuse through a liquid filled material, i.e. pores or gel layer. This approach is suitable with compounds having a variety of solubilities and can achieve a uniform drug release rate; however the collapse of the diffusion restricting step might cause undesirably high drug release rates.

Ion-exchange resins consist of a cross-linked insoluble polymer backbone carrying ionisable functional groups, to which the drug is attached in an ionic form (Venkatraman et al. 2000, Anand et al. 2001, Pongjanyakul 2007). These groups are able to exchange the attached drug compound with ions from the surrounding liquid and subsequently the drug is released by diffusion (Florence and Attwood 1998). Ion-exchange resins provide uniform drug release and, in theory, their function in the GI tract is robust, since they are immune to enzymatic attack (Venkatraman et al. 2000, Anand et al. 2001). However, the pH and ionic strength varies between different parts of GI tract and there are always deviations between individuals. Therefore, the robustness of this system is questionable.

The function of osmotic controlled release preparation is based on the difference in osmotic pressure between two compartments which are separated using semipermeable membrane (Martin 1993a, Florence and Attwood 1998, Venkatraman et al. 2000, Verma et al. 2000, Verma et al. 2002). Basically, the osmotically active

core consisting of the drug compound or an excipient draws surrounding liquid into the preparation, creating a pressure which will force the drug compound to diffuse out from a specially designed orifice. The benefits of this system include achievement of uniform drug release, suitability for compounds having water solubility from moderate to extreme and a functionality regardless of the surrounding environment, i.e. changes in pH, ionic strength and microbiological activity (Verma et al. 2000, Lee and Yang 2001, Verma et al. 2002). However, due to their delicate structure, their functionality is sensitive to deviations in their manufacture and furthermore they may be considered to be expensive to mass produce (Verma et al. 2000).

The principle of gastroretentive systems is that the transit of the preparation from stomach to small intestine is delayed or prevented by altering the size or the density of the preparation (Moës 1993, Hou et al. 2003, Talukder and Fassihi 2004, Bardonnnet et al. 2006). These systems enable prolonged release in the upper part of GI tract and are useful not only for prolongation of drug release, but also especially suitable for drug compounds that are effective locally in the stomach, have poor solubility at the higher pH of small intestine or are unstable in the colon (Reddy and Murthy 2002, Bardonnnet et al. 2006). It is notable that gastroretentive systems are not suitable for compounds, which may cause gastric lesions or which are not stable in acidic conditions (Talukder and Fassihi 2004). Furthermore, the differences in transit properties, i.e. time and the size of the object, among individuals can result in unintentional loss of the preparation during gastric emptying and this can lead variations in drug release properties (Bardonnnet et al. 2006).

2.3.1 Matrix tablets

On the basis of the previous chapter, it can be concluded that the challenge for producing preparations with prolonged drug release properties can be met in a large variety of ways. However, the most common prolonged release system has been the matrix tablets because of their effectiveness, low cost and ease of manufacturing (Abdul and Poddar 2004). In matrix tablets, the drug compound is either dissolved molecularly or suspended physically as a particle mixture into the surrounding excipient (Martin 1993a, Hillery 2001, Alderborn 2007). In its simplest form the matrix tablet consists of a single-unit and can be referred to as monolithic. However, there are matrix tablets available with a multiple unit structure, i.e. they consist of two

or more parts, such as individual layers containing drug compound or excipient (Chidambaram et al. 1998, Qiu et al. 1998). In this thesis, the monolithic matrix tablets are the focus of interest and, therefore, the other types of matrix tablets are not discussed further in the following sections.

The easiest and, thus, most generally applied method to produce orally administerable prolonged release matrix tablets is the direct compression of a physical mixture consisting of drug compound, matrix forming polymer and, if needed, other excipients (Sánchez-Lafuente et al. 2002, Le Tien et al. 2003, Nabais et al. 2007, Abdelbary and Tadros 2008, Corti et al. 2008). Direct compression can provide not only economical but also technical benefits; stability and dissolution improvements for some drugs have been attributed to direct compression (Davies 2001). In cases where the existing powder lacks suitable properties prior to tableting, the powder can be processed. The typical processing methods are wet and dry granulation and extrusion, which are commonly done with powders, and melting, which is especially used with formulations containing waxes (Davies 2001, Tiwari et al. 2003, Kiortsis et al. 2005, Hayashi et al. 2005, Kuksal et al. 2006, Patel et al. 2006). However, direct compression of physical mixtures containing drug and excipient is convenient, and is the most widely used method to produce matrix tablets but the processing *per se* is complicated and thus the processes of granulation, extrusion and melting are not dealt within the context of this thesis.

2.3.1.1 Hydrophobic excipients for matrix tablets

The excipients, which have no dissolving or swelling properties and are used in the formation of hydrophobic matrix tablets, are generally waxes and polymers. Waxes are high molecular weight excipients without liquid components composed of hydrocarbons containing straight, branched or cyclic alkanes (Walters and Brain 2001). Waxes, such as carnauba wax, yellow wax, microcrystalline wax, and waxlike polymers, such as glycerides, can be used alone or with other excipients to produce prolonged release solid-dosage formulations (Yonezawa et al. 2002, Cao et al. 2007, Oladiran and Batchelor 2007, Rowe et al. 2009). When used as an additive, they can form complexes by combining with hydrophilic polymers resulting in the creation of in preparations having prolonged drug release properties (Hayashi et al. 2005, Abdelbary and Tadros 2008).

Polymers for prolonged release hydrophobic matrix tablets can be either natural or chemically modified natural materials, e.g. starch, cellulose and chitin, and their derivatives, or synthetic products, e.g. acrylate derivatives (Le Tien et al. 2003, Siepmann et al. 2008, Rowe et al. 2009). The originally swelling or dissolving polymers can be transformed into more hydrophobic derivatives by changing the degree of polymerisation, adding cross-linkages or introducing hydrophobic groups into the polymer backbone (Te Wierik et al. 1993, Raatikainen et al. 2002, Le Tien et al. 2003, Grassi and Grassi 2005, Nabais et al. 2007, Ching et al. 2008). The range of hydrophobic polymers for prolonged matrices is wide, but the most commonly used are polyethylene, polypropylene, polyvinyl chloride and polyvinyl acetate (Florence and Attwood 1998, Venktraman et al. 2000, Grassi and Grassi 2005, Rowe et al. 2009).

2.3.1.2 Starch acetate

Starch consists of two polysaccharides based on α -glucose: linear amylose and highly branched amylopectin (Young 1984, Rowe et al. 2009). The properties of starch are affected by its botanical source, but they all share common features: they are hygroscopic, insoluble in cold water, swellable up to 5–10 % at 37°C and soluble in hot water at temperatures above the gelatinization temperature. Starch is widely used as an excipient primarily in oral solid dosage formulation where it is utilized as a binder, diluent and disintegrant (Rowe et al. 2009).

Starch acetates are modified starches produced by mixing the native starch with acetic acid anhydride in the presence of a catalyst (Raatikainen et al. 2002, Pohja et al. 2004). The modification converts starch into more a hydrophobic derivative by replacing original hydroxyl groups by acetyl groups (Fig. 1) and the hydrophobicity increases proportionally as the degree of substitution (ds) increases from 0 up to 3.0. Starch acetate possesses a number of beneficial properties compared to unmodified starch. Its flowing properties are suitable for direct compression, it exhibits both plastic deformation and fragmentation under pressure, it has excellent binding properties when ds is greater than 1.19 and, finally, it produces tablets with sustained drug release properties when ds is greater than 2.1 (Korhonen et al. 2000, Korhonen et al. 2002, Raatikainen et al. 2002, Pohja et al. 2004).

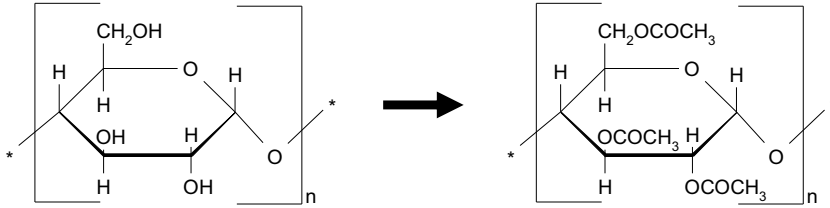


Figure 1. Starch acetate is produced by acetylating native starch monomer into fully acetylated (ds 3.0) starch acetate monomer.

2.3.2 Drug release from hydrophobic matrix tablet

The solid drug has to dissolve and diffuse out from the preparation in order to become systemically available. Thus, the concept of drug release, i.e. mass transfer from a hydrophobic matrix can be proposed to be based on two different phenomena: dissolution of solid and diffusion. However, since the tablets are complex systems and the drug release is very complicated, a knowledge of dissolution rate and diffusion is not sufficient to describe the situation of drug release in a comprehensive manner. This thesis concentrates on two main mechanisms for depicting the method of drug release from hydrophobic matrix tablets: drug release by diffusion and by erosion. Thus, in the following chapters, in addition to mass transfer, these main drug release mechanisms and the most common mathematical equations describing these phenomena are discussed.

2.3.2.1 Dissolution rate of solids

When a tablet or other solid drug form is introduced into a liquid, the drug begins to pass into solution from the intact solid. Noyes and Whitney (1897) have proposed an equation describing the rate at which a solid dissolves in a solvent

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C) \quad (1)$$

where M is the dissolved amount of drug at time point of t , D is the diffusion coefficient, S is the surface area of the dissolving solid, h is the thickness of the diffusion layer, C_s is the saturation solubility of the solid and C is the concentration of solute in bulk solution at time point of t . It has to be emphasized that the drug solubility alone is not a simple issue since it is dependent of the properties of drug molecule, such as polymorph forms, complexes and purity, and solvent properties, such as temperature, pH and consistency (Martin 1996b, Röst and Quist 2003).

2.3.2.2 Diffusion

Diffusion is defined as a process of mass transfer of individual molecules of a substance, brought about by random molecular motion and associated with a concentration gradient (Martin 1996a). Diffusion has been described by the Fick first law as follows:

$$J = -D \frac{dC}{dX} \quad (2)$$

where J is the flux, D is the diffusion coefficient of the drug in the membrane and dC/dX represents the rate of change in concentration C relative to distance X in the membrane.

2.3.2.3 Drug release by diffusion

There are two main drug release mechanisms from hydrophobic matrices: diffusion and erosion and their importance depends on the formulation and structure of the preparation (Steendam et al. 2000, Hayashi et al. 2005, Cao et al. 2007). The main difference in these mechanisms is that when the drug release occurs by diffusion, the drug release restricting matrix remains intact. Many authors have described diffusion from tablet preparations composed of both waxes and as well as from hydrophobic polymers (Pather et al. 1998, Steendam et al. 2000, Steendam et al. 2001, Reza et al. 2003). The schematic illustration of diffusion is presented in Figure 2 and the principles of the mechanism are as follows: when a tablet is immersed into a liquid environment, liquid starts to penetrate into the matrix through the pores. As the liquid

reaches the drug compound, it starts to dissolve and, finally, the dissolved drug molecule diffuses out through the liquid filled pores of the matrix.

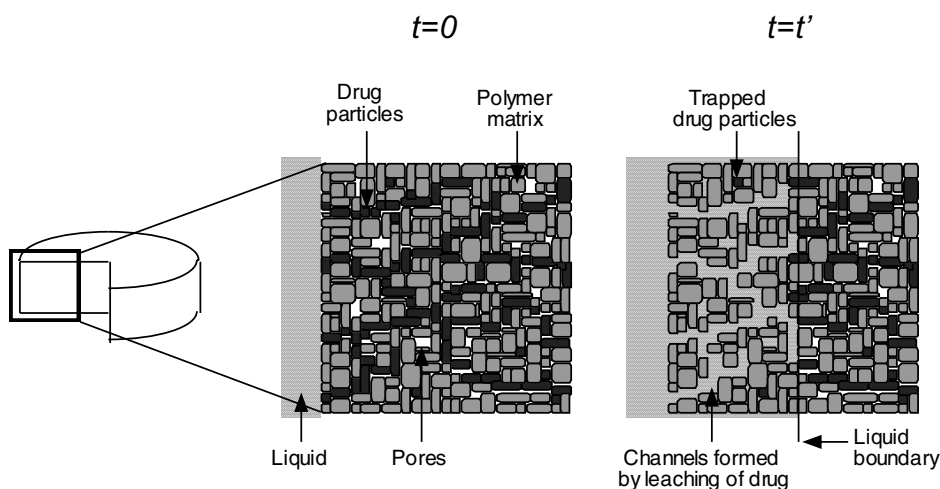


Figure 2. The schematic illustration of diffusion in a hydrophobic matrix tablet (modified from Steendam et al. 2000).

Higuchi (1963) has proposed that a drug release from hydrophobic matrices can be described by the equation

$$M_t = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t} \quad (3)$$

where M_t is the amount of drug released after time t per unit exposed area, D is the diffusivity of the drug in the permeating fluid, τ is the tortuosity factor of the capillary system, A is the total amount of drug present in the matrix per unit volume, C_s is the solubility of the drug in the permeating fluid and ε is the porosity of the matrix. When the drug release mechanism is diffusion-based the diffusion path grows as a function of time, which will affect the drug release rate i.e. it will decline as more and more drug is release. Therefore, the drug release rate occurs by square root kinetics, which is generally expressed as follows

$$\frac{M_t}{M_\infty} = kt^{1/2} \quad (4)$$

where M_t is the amount of drug released at time t and M_∞ is the total drug amount and k is a constant.

Although the Higuchi model has a high degree of approximation, it is widely used due to its simplicity (Siepmann and Peppas 2001, Grassi and Grassi 2005). However, there are many other empirical and semi-empirical release models describing drug release phenomena. In addition to the Higuchi model, widely used models with the best abilities to describe the phenomena are the zero-order model, the Weibull model and the Korsmeyer-Peppas model (Costa and Sousa Lobo 2001). However, the creation of empirical and semi-empirical models describing drug release may be time-consuming. Therefore, numerical methods, such as the finite difference and the finite element methods, have been introduced (Zhou and Wu 1997, Wu and Zhou 1998, Frenning et al. 2005).

2.3.2.4 Drug release by erosion

When drug release occurs by erosion, the preparation will gradually erode which will ultimately expose the solid drug for dissolution and diffusion. Erosion can result as a change in the matrix forming polymer backbone or dissolution of one or several components of the preparation. Changes in polymer backbone can be due to degradation, i.e. the polymer chains are cleaved to form oligomers and monomers chemically via hydrolysis or enzyme-catalysed hydrolysis, or erosion, i.e. the loss of material due to monomers and oligomers being released from the polymer (Göpferich 1996, Siepmann and Göpferich 2001, Grassi and Grassi 2005). Erosion of the preparation may result from either bulk (homogenous) or surface (heterogenous) erosion as shown in Figure 3.

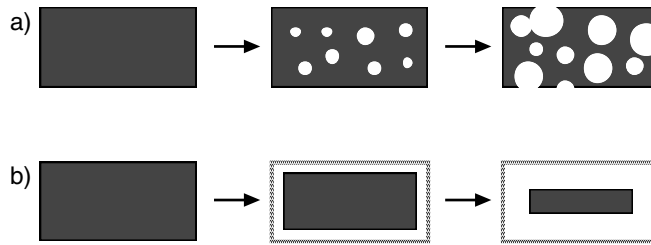


Figure 3. Schematic illustration of (a) bulk and (b) surface erosion (modified from Göpferich 1996, Siepmann and Göpferich 2001).

In bulk eroding preparations, polymers degrade and erode throughout the matrix since water diffusion into the matrix is substantially faster than the degradation of the polymer and thus the size of the preparation remains constant (Göpferich 1996, Grassi and Grassi 2005). In surface eroding preparations, the water penetration is slower than the polymer degradation which means that the preparations become smaller but keep their original geometric shape. (Siepmann and Göpferich 2001, Grassi and Grassi 2005). Both types of the erosion of the preparation have been reported to occur with hydrophobic polymer based matrices (Göpferich 1996, Te Wierik et al. 1997a, Tuovinen et al. 2002).

However, the reason for erosion of the hydrophobic polymer based tablets is not likely to be the degradation or erosion of the matrix forming polymer. Due to hydrophobic nature of the polymer, the water uptake and consequent hydrolysis of water-labile structures may be restricted (Grassi and Grassi 2005). A more probable reason for erosion is a reduction of the cohesiveness of the tablet due to dissolution of the drug compound or other excipient and subsequent cleavage of the binding forces between particles (Pather et al. 1998, Barra et al. 2000). In other words, prolonged drug release hydrophobic matrix tablets having erosion as release mechanism exhibit more often surface erosion than bulk erosion.

Katzhendler et al. (1997) have derived the following equation for drug release from erodible tablets:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_a t}{C_0 a_0} \right)^2 \left(1 - \frac{2k_b t}{C_0 b_0} \right) \quad (5)$$

where M_t is the amount of drug released at time t and M_∞ is the total drug amount, C_0 is total amount of drug in a unit volume of the matrix, a_0 and b_0 are the initial radial and vertical dimensions of the tablet, k_a and k_b represent the erosion rate constant in the radial and vertical directions. Erosion can theoretically produce zero-order drug release kinetics, i.e. the drug release rate is constant as a function of time, which can be generally expressed using the following equation

$$\frac{M_t}{M_\infty} = kt \quad (6)$$

where M_t is the amount of drug released at time t and M_∞ is the total drug amount and k is a constant. However, the true zero-order drug release kinetics can be achieved only if the following conditions are fulfilled: the drug diffusion is slow within the polymer matrix compared to the rate of erosion, surface erosion occurs and the surface area does not change with time (Jantzen and Robinson 1996). Since there are strict limitations for zero-order release and there are many factors related to the drug compound and polymer, which can affect these properties, the kinetics of eroding tablets may be difficult to control and, furthermore, it seems that eroding tablets often exhibit apparent zero-order kinetics.

2.3.2.5 Drug release by erosion and diffusion

The drug release mechanism can be often classified into diffusion or erosion since the dominant mechanism will overshadow other processes. However, in practice the mechanism can change as a function of time, be parallel and even promote each other (Jantzen and Robinson 1996, Göpferich 1997, Te Wierik et al. 1997b, Zuleger and Lippold 2001). Thus, modeling and controlling of the drug release mechanism and rate using approaches based strictly on either diffusion or erosion theories is not always satisfactory.

In attempts to describe the release behaviour of tablets showing a combination of Fickian diffusion and Case II relaxation, i.e. the influence of polymer relaxation on molecules' movement in the matrix, Ritger and Peppas (1987) and Peppas and Sahlin (1989) derived an equation depicting diffusion and relaxation mechanisms as the limiting factors of controlled drug release:

$$\frac{M_t}{M_\infty} = k_{diffusion} t^n + k_{relaxation} t^{2n} \quad (7)$$

where M_t is the amount of drug released at time t , M_∞ is the total drug amount, $k_{diffusion}$ is the diffusional constant, $k_{relaxation}$ relaxational constant and, thus, the first term on the right-hand side of the expression represents the Fickian contribution and the second term the Case II relaxation contribution to the fractional drug release. The purely Fickian diffusion exponent n and the relaxation exponent, which is two times the factor n , depend on the aspect ratio between tablet diameter and height. These exponents for cylindrical tablets derived from studies by Ritger and Peppas (1987) have been reported to have values of 0.45 and 0.89 for the diffusional and relaxational exponent, respectively.

2.4 *In vitro* dissolution tests

The drug release mechanism and rate of the preparation have to be determined in order to ensure both consistency and safety of the product. European (2007) and United States (2009) Pharmacopoeias contain definitions of *in vitro* dissolution tests, which provide information on release mechanism and kinetics. The principle of the *in vitro* dissolution test is to imitate the general conditions in the human body, which is commonly achieved by utilization of an appropriate medium, hydrodynamic conditions and adjusting the temperature to 37 °C. There are four different *in vitro* dissolution tests for solid dosage forms which, in the order given by the Pharmacopoeias, are basket apparatus, paddle apparatus, reciprocating cylinder and flow-through cell. All these apparatuses can be used to investigate the functionality of prolonged release preparations, but the first two are the most widely used as formulation development tools and quality control tests (Qureshi and McGilveray 1999, Azarmi et al. 2007, Gray et al. 2009). Thus, the focus of interest in this thesis will be on the basket and paddle methods.

In vitro dissolution tests are standardised by the Pharmacopoeias in order to improve their reproducibility: the materials and dimensions of vessels, baskets and paddles, location of sampling and procedure of de-aeration are strictly defined. Nonetheless, it has been reported that dissolution tests performed with equipment in

accordance with the Pharmacopoeias can produce data with unacceptable variations (Cox et al. 1982, Qureshi and McGilveray 1999, Tanaka et al. 2005, Deng et al. 2008, Bai and Armenante 2009). This is a problem and, thus, the relevance and reliability of the dissolution tests with prolonged preparations is recognized as being problematic (Qureshi and McGilveray 1999). Despite the evidence of the variance among results, there have been extensive studies which have concluded that *in vitro* tests yield reproducible data and they can even simulate *in vivo* situations under certain conditions (Siewert et al. 2002, Scholz et al. 2003, Crail et al. 2004, Azarmi et al. 2007).

Although some parameters are well defined, the Pharmacopoeias leave some freedom for the choice of the apparatus, time points for sampling, the amount, composition and temperature of the dissolution medium, and stirring speed, since their optimal properties are considered to be dependent on the physicochemical characteristics of the dosage form. However, all of these variables have an impact on the results. The nature and the effect of these variables are presented in more detail in Table 1. Thus, the optional parameters of *in vitro* test need to be chosen carefully.

Table 1. The nature and effect of method variables in drug release behaviour of prolonged release preparation during *in vitro* dissolution test.

Method variable	Nature of the effect of the method variable	Reference
Basket apparatus	Tablet is immersed into a basket and medium can flow rather freely and homogeneously over all surfaces of the tablet. There are high velocity regions at the sides of the basket. The basket method produces data with less extensive variability than the paddle method, but disintegrating dosage forms may be ejected through the basket and pass into a low velocity zone.	D'Arcy et al. 2006, Deng et al. 2008, Morihara et al. 2002, Tandt et al. 1994
Paddle apparatus	Tablet is immersed at the bottom of the vessel and medium can flow at the top planar surface and at the edges of the tablet, but not at the lower surface. Paddle apparatus has highly non-uniform hydrodynamic pattern: high velocity regions at the bottom edge of vessel and dead zone directly under the paddle, responsible for a coning effect, i.e. formation of loosely aggregated particles. Paddle apparatus produces higher release rates than basket apparatus, but is very sensitive to the location of the tablet during the test.	Bai et al. 2007, Bai et al. 2008, Bai and Armenante 2009, Baxter et al. 2005, D'Arcy et al. 2005, Gray et al. 2009, Healy et al. 2002, Morihara et al. 2002, Qureshi and Shabnam 2001, Wu et al. 2004
Materials	Inert materials, such as glass or plastic, should be used. However, some compounds may undergo interactions with these materials.	Cox et al. 1982
Sampling time	The time points of sampling should produce adequate conditions for continuous monitoring. Sampling time points at the beginning of the test (< 1 minute) may be too early, due to unbalanced conditions inside the dissolution vessel and lead to unwanted variation.	McCarthy et al. 2004, Siewert et al. 2002
Medium	Amount of medium should be sufficient enough in order to obtain sink conditions, i.e. the concentration of solute is considerably less than the maximum solubility. 900 ml is typically adequate, but smaller amounts, such as 500 ml, may be used in order to achieve similar results. However, a reduction of medium volume may result in deviations in hydrodynamic pattern and lower drug release rates, especially if geometrically smaller vessels are used. Typically the medium is a buffer solution with a pH of 6.8, imitating the conditions of the intestine. Moreover, the Pharmacopoeias state that one can use buffers containing different pHs, surfactants and enzymatic activities in order to better mimic the conditions present in the GI tract. These alterations are connected with degree of ionization of the compound, degradation and erosion process of the preparation, and ultimately may affect the drug release rate. Lately, more physiologically adapted and biorelevant dissolution media have been developed in order to improve the <i>in vitro</i> – <i>in vivo</i> correlation.	Azarmi et al. 2007, Crail et al. 2004, Gray et al. 2009, Lozano et al. 1994, Martin 1993a, Nikolić et al. 1992, Röst and Quist 2003, Scholz et al. 2003

Table 1. The nature and effect of method variables in drug release behaviour of prolonged release preparation during *in vitro* dissolution test (cont.).

Method variable	Nature of the effect of the method variable	References
Medium	Increase in temperature increases the maximum solubility and diffusion coefficient and, thus, dissolution rate. However, the impact of this feature has been reported to be small or even insignificant.	
Stirring	The purpose of stirring is to remove the drug-saturated layer from around the preparation and to replace it with fresh medium. The same stirring speed produces almost similar hydrodynamic velocities in basket and paddle apparatuses. Greater stirring produces higher drug release rates, but does not achieve greater homogeneity in the hydrodynamic pattern. Inadequate stirring can not only cause reduced drug release rates, but also a non-uniform drug accumulation inside the matrix tablet.	Baxter et al. 2005, Baxter et al. 2006, Gray et al. 2009, D'Arcy et al. 2006, Nikolić et al. 1992, Scholz et al. 2003, Wu et al. 2004, Zhou and Wu 1997

Despite the fact that the existing *in vitro* dissolution tests are considered to produce adequate data, several groups have made a number of attempts to improve the robustness and reproducibility of these tests. The problems associated with high variability in the results can be traced to the variable flow-dynamics and poor mixing and stirring (Qureshi and Shabnam 2001). Thus, most often the improvement attempts consist of geometrical alterations of one or several parts, such as the impeller and the vessel, which are responsible on the hydrodynamic conditions and which on the dissolution rate of the preparation is strongly dependent (McCarthy et al. 2004, Wu et al. 2004, D'Arcy et al. 2005, Bai et al. 2007). Therefore, the role of the impeller is crucial and it has been shown that the shape, diameter and area of the paddle and even small changes in the location of the regular paddle can be used to produce hydrodynamically favorable conditions for drug dissolution (Röst and Quist 2003, Wu et al. 2004, Baxter et al. 2006, Bai and Armenante 2009). In addition, the design of a paddle was taken a step further when a specially curveshaped spindle was introduced (Qureshi and Shabnam 2001, Qureshi 2004). This novel paddle enabled more biorelevant characterization for prolonged release preparations by providing more efficient mixing and preventing the formation of loosely aggregated particles under the impeller resulting from the disintegration of the preparation, which is known as the coning effect, a common problem encountered with the paddle method (Gao et al. 2009). The modifications of basket method have not been so intensively investigated

(Gray et al. 2009), but Crist and Spisak (2005) reported that a basket attachment with smooth surface and mesh containing fewer openings and larger wire could result in lower release rates.

The vessel is the other feature which strongly affects the hydrodynamic pattern. Studies have shown that the 200 ml vessel produces lower drug release rates than the regular vessel and longitudinal type sinkers lead to higher drug release rates and less variable results than lateral sinkers (Soltero et al. 1989, Crail et al. 2004). However, with an adequate stirring setup the 200 ml vessel may produce comparable results to that achieved by the 1000 ml vessel (Crail et al. 2004). The coning effect has been also prevented by geometrical alterations of the vessel. This has been achieved by utilization of an inverted cone molded into bottom, known as the commercially available PEAK vessel, or a metal strip at the bottom of a regular vessel (Qureshi and Shabnam 2001, Mirza et al. 2005, Baxter et al. 2006, Gray et al. 2009).

2.5 Structural properties of matrix affecting drug release

On basis of previous chapter, it can be concluded that the drug release rate can be affected by the choice of the *in vitro* dissolution test parameters. However, the drug release from hydrophobic matrix tablets is mostly dependent on structural properties of the preparation. These properties consist of the composition of the surface of the tablet, porosity, tortuosity of the capillary network, drug loading, percolating network, tablet hardness and geometry. An overview of the effect of each property, and the basic methods to control them, has been gathered in Table 2. Some properties, e.g. drug loading, are rather easy to control by simply increasing the amount of drug in the original powder formulation, but the other properties, such as percolating network, porosity and tablet hardness, are dependent on many factors, i.e. particulate interactions, the mechanical properties of the material and compression, and thus their control is complicated.

Table 2. The properties of hydrophobic matrix tablet, and their general controlling methods, affecting the drug release rate and mechanism.

Property	Effect on drug release	Method of control	Reference
Porosity	Increase of porosity and decrease of tortuosity, i.e. changes in relative density, enhances liquid penetration and increases subsequent tablet disintegration and/or diffusion out from the matrix.	Porosity can be controlled by the compaction process, but the mechanical properties of materials and composition mixture also make a contribution.	Te Wierik et al. 1997b, Te Wierik et al. 1997a, Barra et al. 2000, Sinka et al. 2009, Steendam et al. 2000
Drug loading	Increase in drug loading can result in higher drug release rate and change the mechanism. Core centered drug loading can produce zero-order kinetics.	Degree of drug loading can be affected simply by increasing or decreasing the amount of drug in the original powder formulation.	Te Wierik et al. 1997a, Pather et al. 1998, Wu and Zhou 1998, Neau et al. 1999, Grassi and Grassi 2005
Percolating network	Consisting of a very soluble compound, i.e. drug, the drug release rate may increase and the mechanism may be erosion, whereas if it is a hydrophobic polymer this will restrict drug release rate; it produces release by diffusion.	The consistency of the percolating network and the subsequent drug release mechanism can be affected by altering the particle size fractions of drug compound or matrix forming agent.	Barra et al. 2000, Grassi and Grassi 2005, Röst and Quist 2003, Te Wierik et al. 1997b
Surface properties	Hydrophobic, i.e. repulsive to water, surface has a low wettability and this will hinder water penetration into tablet, diminishing the drug release rate. A surface containing a large amount of drug may increase drug release rate due to the burst effect.	The surface properties are strongly linked with the structure of the tablet, such as the consistency of percolating network, but the utilisation of excipients, such as hydrophobic lubricants, can have crucial impact on this property.	Dürig and Fassih 1997, Rippi et al. 1998, Barra et al. 2000, Huang and Brazier 2001
Tablet hardness	Tablets with low tensile strength have a faster dissolution rate, which may be due to increased erosion or enhanced liquid penetration, since the decrease of porosity is proportional to the increase of tensile strength.	Tablet hardness is basically controlled by the compaction process. However, the situation is not so simple, because the properties of the compressed material and excipients, such as lubricants, have significant importance.	Rudnik and Kottke 1996, Pather et al. 1998, Steendam et al. 2000, Tye et al. 2005
Tablet geometry	Increase of the ratio of surface area for drug to diffuse increases the drug release. Geometrically different tablets may exhibit variations in density and pore structure, which may alter the drug release properties.	The geometry of the tablet preparation can be affected simply by using punches and dies with different geometries.	Kim 1995, Te Wierik et al. 1997a, Zhou and Wu 1997, Siepmann et al. 2000, Wu et al. 2004, Zuleger and Lippold 2001, Djemai et al. 2006, Sinka et al. 2006

2.6 Process and formulation properties affecting the formation of a matrix tablet

If one can control the factors determining the formation of the matrix tablet this will enable the achievement of desired drug release mechanism and rate, i.e. they are dependent on the properties of the tablet. The factors affecting the formation of the tablet are related to the powder, i.e. the interparticulate forces formed between the particles during the mixing responsible of the powder organization, and tableting, i.e. the forces and compaction speeds utilized for particle arrangement and volume reduction leading to formation of the tablet. For this reason, the following chapters will deal with parameters affecting the organisation of the powder blend and the compaction process.

2.6.1 Organisation of the powder

Formulations for pharmaceutical preparations seldom consist of one ingredient only, especially when one tries to achieve prolonged release properties, other excipients are needed. If the preparation contains more than one component, mixing will need to be done prior to tableting. A theory of mixing and types of mixes has been well defined by several authors (Staniforth 1987, Davies 2001, Venables and Wells 2001, Twitchell 2007). Mixing can be defined as a unit operation that is intended to treat two or more components, initially in an unmixed or partially mixed state, so that each unit of the components lies as nearly as possible in contact with a unit of each of the other component. This ideal situation can be regarded as perfect mix. However, a random mix, which can be defined as a mix where the probability of selecting a particular type of particle is the same at all positions in the mix, is much more probable in practice. Furthermore, when one considers an ordered mix, the particles are not independent of each other and a degree of order is detected in the mix. An ordered mix is often due to adhesion of small particles on the surfaces of large particles and can produce greater homogeneity than a random mix.

The structure of the tablet is clearly dependent on the organization of the powder blend, which is the consequence of the interactions of its components (Nyström and Karehill 1996, Barra et al. 1999). Thus, it is crucial that one can control the mixing process and the particulate interactions responsible for the organisation. Interparticulate attractions can be divided into cohesion and adhesion: the first is the attraction between particles of the same material and the latter between different

materials (Führer 1996, Zeng et al. 2001a). Furthermore, the particulate interactions within a powder is a summation value of a number of concurrently acting forces or mechanisms, which are van der Waals, electrostatic, capillary forces and mechanical interlocking (Podczeck et al. 1997, Zeng et al. 2001a). Van der Waals forces are the major forces between uncharged solid particles; they are of an electrostatic nature, but are involved in interactions only over limited range (Führer 1996, Zeng et al. 2001a). Electrostatic charging, in most cases triboelectrostatic charging, is very common in pharmaceutical systems and is responsible for interactions over long distances by electrification: when two surfaces make contact, the transfer of electrons can occur resulting in surfaces with opposite charges after their separation (Führer 1996, Rowley 2001). Capillary forces occur when condensed moisture create an interaction by evoking liquid bridge formation between particles (Padmadasastra et al. 1994). Finally, mechanical interlocking occurs where adhesion is provided by interparticulate hooking of rough and irregular particles (Alderborn 2007).

The relative contribution of each individual force and mechanism to the overall interparticulate force is a function of the physicochemical and morphological properties of the interacting particles and the mixing process conditions, such as particle size, particle density, particle rigidity, particle shape, crystal form, surface area, surface energy, moisture content and relative humidity, and electrostatic properties (Führer 1996, Zeng et al. 2001b). An overview of the particle properties and process conditions affecting the organisation of the powder blend during mixing is presented in Table 3. Table 3 reveals that the organisation of the powder is a complicated process, since there are many simultaneous forces and mechanisms participating, many of them with multiple functions. This can be clarified with a short example: an increase in the moisture content decreases the triboelectrification by surface contamination, which will result in a decline of the adhesion (Eilbeck et al. 2000, Rowley 2001). However, the increase in relative humidity will promote the liquid bridging and, as a consequence, increase the adhesive forces (Padmadasastra et al. 1994, Shimada et al. 2003, Murtomaa et al. 2004). Thus, the role of moisture is ambivalent.

Table 3. The properties of particles affecting the organization of the powder during the mixing.

Property	Effect	Reference
Particle size	Small particles tend to fall into the void spaces between larger particles and, therefore, a nearly or completely identical particle size distribution prevents segregation during mixing if no other adhesion promoting factors are present. If the particle size difference is adequate, the small particles tend to adhere onto the surface of the larger ones producing an ordered mix. Small particles have a great surface area, i.e. area taking part in the interparticulate attraction, and thus, due to lower gravitational forces, they are more easily exposed to electrostatic interactions.	Barra et al. 1998, Führer 1996, Mäki et al. 2007, Nikolakakis et al. 2002, Nyström and Karehill 1996, Patel et al. 2006, Rudnic and Kottke 1996, Twitchell 2007, Venables and Wells 2001
Particle density	The more dense particles tend to move downwards due to gravitational force. This phenomenon occurs even if the particles are of the same size.	Staniforth 1981, Twitchell 2007, Venables and Wells 2001, Wadke and Jacobson 1980
Particle rigidity	Rigid particles tend to have a lower adhesive force than deformable particles due to their smaller contact surface area.	Feng 2001, Shimada et al. 2003, Zeng et al. 2001b
Particle shape	Spherical particles are more easily mixed than irregular ones, which have a smaller contact surface area. However, the segregation of the irregular and rough particles may be prevented due to increased changes for mechanical interlocking. Furthermore, rough particles have extremely high values of electrostatic charge at the sharp corners and edges; whereas spherical particles have homogenously distributed values and therefore less active adhesion sites. Finally, the surface energy is dependent of the shape of particle.	Führer 1996, Grimsey et al. 2002, Nyström and Karehill 1996, Staniforth 1987, Swaminathan and Kildsig 2000, Twitchell 2007, Venables and Wells 2001, Wong and Pilpel 1990
Crystal form	A change in the crystal form may influence the adhesion affinity between particles. This takes place because the amorphous form and different crystal forms can exhibit different physicochemical properties, such as morphology, surface energy, hygroscopicity and density.	Grimsey et al. 2002, Harjunen et al. 2002, Murtomaa et al. 2004, Song and de Villiers 2004, Zeng et al. 2000, Zeng et al. 2001b
Surface area	Greater contact surface area decreases segregation by increasing cohesive effects. In addition, this increases the potential for particulate interactions which arise from the properties of the surface, such as surface energy, moisture uptake and electrical properties.	Feng 2001, Twitchell 2007, Venables and Wells 2001
Surface energy	Particles with a great surface energy have a high tendency to interact with other compounds, such as water and other particles. In the dry state, the interaction is due to van der Waals forces i.e. the interaction is likely to occur when the difference in surface energy of the particles is great. Surface energy is sensitive to contamination.	Barra et al. 1999, Grimsey et al. 2002, Nikolakakis et al. 2002, Podczek et al. 1997, Zeng et al. 2001a

Table 3. The properties of particles affecting the organization of the powder during the mixing (cont.).

Property	Effect	References
Moisture content and relative humidity	The probability of capillary forces increases as a function of relative humidity and is likely to predominate when it reaches >60 %. Adhesion due to moisture content occurs with hygroscopic and hydrophilic compounds which have the ability to undergo hydrogen bonding. An increase in the moisture content may lower the surface energetics and electrostatic properties of the powder surface.	Eilbeck et al. 2000, Murtomaa et al. 2004, Nikolakakis et al. 2002, Padmadisastra et al. 1994, Podczek et al. 1997, Price et al. 2002, Sunkersett et al. 2001, Zeng et al. 2001b
Electrostatic properties	Opposite electrostatic charges promote adhesion. A change in the charge-inducing material can produce electrostatic charges of different magnitudes. Electrostatic charge is not stable: it is sensitive to surface contamination and pharmaceutical excipients have low resistivity and therefore lose any electrostatic charge through earth leakage relatively quickly.	Eilbeck et al. 2000, Mäki et al. 2007, Rowley 2001, Staniforth 1987, Staniforth and Reese 1982
Mixing time	Mixing is an equilibrium event. If continued, segregation occurs due to differences in particle size, shape or density.	Davies 2001, Twitchell 2007, Venables and Wells 2001

2.6.2 Compaction

Tablets are prepared by forcing particles into close proximity to each other by powder compaction, which transforms the particles into a porous, coherent compact form with a defined shape (Nyström and Karehill 1996, Alderborn 2007). The compression of the powder and the consequent tablet formation may involve the following processes: particle rearrangement, elastic deformation of particles, plastic deformation or fragmentation of particles and finally formation of interparticulate bonds (Nyström and Karehill 1996, Rudnic and Kottke 1996, Davies 2001). Initially, the powder bed becomes rearranged in order to achieve closer packing. Due to the densification, the arrangement becomes more difficult and deformation of particles at points of contact begins. This may result in reversible elastic deformation or irreversible plastic deformation. If the applied force is greater than the fracture strength, the deformation will reach its limits and the particles fragment into smaller ones. Eventually, the surfaces of the particles become reduced by bonding and consolidation. When compressing dry solid particles, the bonding formation, i.e. the strength keeping the tablet intact, is due to the sum of intermolecular forces, solid bridges and mechanical interlocking (Alderborn 1996, Nyström and Karehill 1996,

Patel et al. 2006, Alderborn 2007). The intermolecular forces are van der Waals forces, electrostatic forces and hydrogen bonding. Solid bridges can be regarded as contact at an atomic level between adjacent surfaces in the compact material, and mechanical interlocking is due to interparticulate hooking of rough surfaces.

Although material may undergo a combination of different deformation mechanisms during compaction, the powders are classified based on the dominating mechanical properties such as elastic, plastic or fragmentation (Nyström and Karehill 1996, Hiestand 1997, Patel et al. 2006, Alderborn 2007). Elastic and plastic deformations are time independent and the degree of deformation is related to the applied stress. Elastic materials tend to regain their original shape as the stress is removed and because of these post compaction strength changes, they are not desirable binders. In contrast, plastic materials, which undergo permanent changes, exhibit better binding properties and have a good ability for solid bridging. Materials, which undergo deformation by fragmentation, will create a number of smaller particles which results in a large number of interparticulate contact points when fracture strength is achieved and therefore these materials are not so sensitive for load dependent changes and less prone to undergoing postcompaction strength changes. In addition, there are two deformation mechanisms which deviate from the above: reversible viscoelastic and permanent viscous deformation, which are dependent of applied stress and the time of loading (Nyström et al. 1996, Alderborn 2007). In general, pharmaceutical materials tend to undergo a combination of elastic and plastic deformation (Davies 2001).

The type of deformation and the formation of the tablet depend not only on the physical properties of the materials but also on the rate and magnitude of the applied force and the duration of the locally induced stress, which can be controlled by means of compaction parameters (Steendam et al. 2001, Patel et al. 2006). An overview of the compaction parameters and their impact on the properties of the final tablet is presented in Table 4.

Table 4. The impact of compaction parameters on formation of tablet.

Property	Effect	Reference
Compaction force	Generally, higher compaction force produces harder tablets. Compaction force has significant importance with materials having elastic, plastic and fragmentation deforming properties. High compaction force decreases the effects of particle size and shape, and, after a certain threshold, compaction force does not affect the tensile strength of brittle materials, but increases the magnitude of solid bridging with plastically deforming materials.	Alderborn 2007, Fukunaka et al. 2005, Nyström and Karehill 1996, Rudnic and Kottke 1996, Sun and Grant 2001a
Compaction speed	The effect of compaction speed is different for each formulation, but, in general, changes in compaction speed have no significant effect with time independent deforming materials. However, viscoelastic materials with plastic deformation produce stronger tablets with lower speeds and if the material can undergo two deforming mechanisms, e.g. elastic/fragmentation or elastic/plastic deformation, with the first becoming predominant as the compaction speed is increased.	Davies 2001, Haware et al. 2009, Katikaneni et al. 1995, Marshall et al. 1993, Roberts and Rowe 1985, Roberts and Rowe 1986, Patel et al. 2006, Sinka et al. 2009, Tye et al. 2005
Compaction profile	A double-sided compaction produces stronger tablets. Furthermore, the single compaction generates an uneven densification of the powder bed during compaction, which may result in differences in density and pore structure compared to tablets produced by double-sided compaction. However, this may not be a significant problem in practice.	Busignies et al. 2006, Davies 2001, Ellison et al. 2008, Muñoz-Ruiz et al. 1997, Patel et al. 2006
Tablet ejection	The compacted tablet may adhere to the die wall and subsequent ejection may disrupt the tablet's structure, which can affect the drug release. Thus, the ejection speed and force may affect the magnitude of friction between powder and die during ejection. The ejection enables an elastic recovery in the radial direction and disruption of structure, if material has elastic and fragmentation deformation properties.	Davies 2001, Djemai and Sinka 2006, Doelker and Massuelle 2004, Korhonen et al. 2005, Sinka et al. 2004b, Sinka et al. 2009, Takeuchi et al. 2004, Wang et al. 2004
Geometry of tooling	The various shaped punches generate different degree of densification of the powder bed during compaction, and subsequently on the density distribution of the final tablet, which may result in different physical and drug release properties despite the equal surface area ratio. However, it has been reported that if compaction forces are kept equal, the tensile strength of the tablets will not vary. A low height/diameter ratio is desirable to minimize friction between powder and die.	Davies et al. 2007, Djemai and Sinka 2006, Rudnic and Kottke 1996, Sinka et al. 2004a, Sinka et al. 2009

2.6.3 Properties of powder affecting the compaction

The compaction parameters and the deformation characteristics are not solely responsible of the properties and drug release behaviour of the tablet. In general, the discussion attributed with the properties of the powder and tablet strength is concentrated to the impact of original particle size and shape (Alderborn 1996). However, since the tablet strength is known to be directly proportional to the surface adhesiveness, when the particles have the same order of elasticity and plasticity, the properties of the powder affecting the strength of the tablet bonding are mostly of the same origin as those involved in particulate attraction during powder mixing, which was dealt with in previous chapter (Li et al. 2004). Table 5 presents an overview of particle and powder properties affecting to the outcome of the tablet.

Although the parameters presented in Table 5 have undeniable significance in the formation of a matrix tablet and its consequent drug release properties, the concept of tablet generation is complicated. Firstly, even small additions of excipients, such as lubricants, may have a crucial impact on the behaviour of the powder under compression and, thus, on the drug release properties of the final tablet (Dürig and Fassihi 1997, Pather et al. 1998, Steendam et al. 2000). Secondly, many parameters may have simultaneous effects. This can be exemplified by the following example dealing with the moisture content of powder, which can have an ambivalent role in tablet formation and on the drug release properties. Steendam et al. (2000) reported that the moisture content of matrix forming polymer, amylopectin, prior to tableting and a defined compression force were essential in order to achieve reproducible and constant prolonged drug release properties. However, in the case of methyl methacrylate-hydroxypropylstarch copolymers, the moisture content of compressed powder could alter the drug release of water-soluble drug by inducing its rapid dissolution, promoting the weakness of the matrix structure and hence improving its partial disintegration (Bravo-Osuna et al. 2008). Thus, the details in Table 5 are best regarded as a rough guideline of general trends.

Table 5. Powder properties influencing the formation of the tablet.

Property	Effect	Reference
Particle size	In general, small particles, which have an increased bonding surface area, yield stronger tablets and more homogenous distribution of pores. Furthermore, small particles may dominate the bonding due to the formation of a percolating network. Large particles tend to fragment and therefore a change in the particle size fraction may alter the deformation properties of the materials having tendency towards fragmentation and plastic deformation.	Alderborn 1996, Fukunaka et al. 2005, Haware et al. 2009, Li et al. 2004, Nyström and Karehill 1996, Patel et al. 2006, Roberts and Rowe 1986, Sun and Grant 2001a, Twitchell 2007
Particle shape	Generally, more irregular and rough particles yield stronger tablets, but fragmentation deforming materials are less sensitive to the original particle shape. It is notable that different crystal forms exhibit various crystal habits and shapes, but the differences in tableability are not due to shape but form.	Alderborn 1996, Fukunaka et al. 2005, Nyström and Karehill 1996, Patel et al. 2006
Crystal form	Different crystal forms may exhibit different compaction characteristics due to varying physical properties. It has been reported that more stable forms produce weaker bonds and polymorphs having slip planes, corresponding to greater plasticity in the crystal structure produce harder tablets. Generally, amorphous forms exhibit plastic deformation and thus degree of crystallisation may affect the deformation properties.	Feng and Grant 2006, Hiestand 1997, Nyström and Karehill 1996, Patel et al. 2006, Sinka et al. 2009, Sun and Grant 2001a, Sun and Grant 2001b, Sun and Grant 2001c, Wadke and Jacobson 1980
Surface area	High surface area confers more possibilities for interactions responsible for bonding and thus it can be used to affect the drug release properties of the preparation.	Fukunaka et al. 2005, Te Wierik et al. 1997b
Surface energy	The surface energy of particles may produce harder tablets with brittle materials when bonding is due to interparticulate attraction and, thus, this effect is less significant with plastically deforming materials.	Fichtner et al. 2008, Li et al. 2004
Moisture content	Moisture content, due to capillary forces or facilitation of solid bridging by acting as a surface-restructuring medium, can increase the tensile strength. In contrast, moisture content may act as lubricant by decreasing the tablet strength and the density variation within the tablet, and surface energy, which decrease the friction between the tablet and the die.	Steendam et al. 2000, Patel et al. 2006, Wadke and Jacobson 1980

2.6.4 Compaction of binary mixtures

The properties affecting compaction of powder, such as deformation, are often determined using only a single material due to simplify the evaluation. However, pharmaceutical preparations seldom consist of only one ingredient and, thus, some insight into the behaviour of the binary mixtures will be provided.

The binary mixtures can be categorised into three different types, based on their densification properties: ductile-ductile, ductile-brittle and brittle-brittle (Fell 1996, Majuru and Wurster 1997, Wurster et al. 1999). Many authors have observed simple relationships between a mechanical property, such as consolidation behaviour, yield pressure or crushing strength, with the mass fraction of the components of the binary mixture (Leuenberger 1982, Riepma et al. 1990, Fell 1996, Majuru and Wurster 1997, Wurster et al. 1999, Mohammed et al. 2006, Tatavarti et al. 2008). These relationships have been especially relevant if the conditions are favourable, e.g. when both of the mixture components consolidate by the same mechanism or the mixture consists mostly of a single well compactable excipient and one or several poorly compactable components (Majuru and Wurster 1997, Kuentz and Leuenberger 2000, Mohammed et al. 2006).

However, the situation is usually far more complex. The conditions of the powder are not always favourable and there have been examples reported, where the mechanical property, e.g. tensile strength of the tablet, does not follow the mass fraction of the components of the mixture (Vromans and Lerk 1988, Garr and Rubinstein 1991, van Veen et al. 2000). Van Veen et al. (2002) and Wu et al. (2008) have reported that even a small amount of starch can reduce the tensile strength of the sodium chloride tablets, indicating that instead of the mass fraction of the mixture components, the volume fraction of the component is more significant. In contrast, other studies by Olsson et al. (1998) and Mattsson and Nyström (2000) emphasized that the addition of polyethylene glycols (PEGs) can elevate the tensile strength of tablets having a greater fraction of sodium chloride, sodium bicarbonate or calcium carbonate. The authors deduced that during compaction, the rigid and coarse material became fragmented and even a small amount of the relatively ductile material, PEG, was sufficient to fill the interparticulate voids, resulting in a creation of strong tablets. Thus, it has been concluded that the behaviour of the binary mixtures under compaction is a very complex issue and simple theoretical approaches based on studies with only single compound are likely to be grossly misleading (Fell 1996).

3 AIMS OF THE STUDY

The general objective of this study was to find suitable methods to control the structure and subsequent drug release properties of hydrophobic starch acetate (ds 2.7) matrix tablets, to relate the structural properties with drug release behaviour, and, finally, to evaluate the functionality of *in vitro* drug release test. The specific aims were as follows:

1. To investigate the effects of drug-exciient interactions in a powder blend and to determine how this influence the tablet structure and, consequently, the drug release mechanism
2. To determine the impact on drug release behaviour of structural changes in a tablet caused by crack formation
3. To determine the effect of formulation based parameters and drug compound related properties on the drug release rate and to specify the most dominating features
4. To evaluate the functionality and reliability of USP II paddle method by visualisation of the diffusion of two physicochemically different drug compounds from a hydrophobic matrix tablet

4 EXPERIMENTAL

4.1 Materials

4.1.1 Starch acetate (I-IV)

Potato starch acetate (SA) with a degree of substitution 2.7 (Polymer Corex Oy Ltd., Kuopio, Finland) was used as the matrix forming polymer. Starch acetate was sieved through vibration sieves (Type 3D, Retsch, Germany) into 5 different particle size fractions: < 53 μm , 53–149 μm , 149–297 μm , 297–420 μm and 420–710 μm (I, III) or solely through a 710 μm sieve in order to remove larger aggregates (II, IV).

4.1.2 Model drugs (I-IV)

Anhydrous caffeine (I, II, IV), allopurinol (III), metronidazole (III) and salicylamide (III) were all obtained from Sigma-Aldrich (Chemie Steinheim, Germany). Acyclovir (III) was obtained from Recordati Industria Chimica E Farmaceutica (Milano, Italy), anhydrous theophylline (III) from Oriola (Espoo, Finland), paracetamol (III) from Orion Pharma (Espoo, Finland) and riboflavin sodium phosphate (IV) Fluka Chemika (Steinheim, Germany). Model drugs were usually used as received. However, anhydrous caffeine was sieved through a 710 μm sieve in order to separate aggregates (II, IV) and anhydrous theophylline (III) and salicylamide (III) (Sigma-Aldrich Chemie, Steinheim, Germany) were ground in a mortar in order to reduce their particle sizes. All drugs fulfilled the quality requirements of Ph.Eur.

4.1.3 Other chemicals (I-IV)

Magnesium stearate powder (Orion Pharma, Espoo, Finland) (I-IV) and phenolred (II) (Merck, Darmstadt, Germany) were used as received. Chemicals for the preparation of dissolution mediums (I, II) and inverse gas chromatography (III) were obtained from commercial suppliers and used as received. All materials were at least

of analytical grade and, in the case of inverse gas chromatography, HPLC grade or equivalent.

4.2 Methods

4.2.1 Compound characterisation (I, III, IV)

The particle size distributions of drug compounds and sieved starch acetate fractions (I, III, IV) were measured by laser diffraction (Mastersizer2000, Malvern Instruments Inc., Southborough, MA, USA) using the dry measurement option (Scirocco2000). The particle density of drug compounds and SA fractions was measured by a pycnometer (MVP-1, Quantachrome, Syosset, NY, USA), using helium as the measuring gas. The morphology of SA particles was examined by scanning electron microscopy (SEM)-photographs (I), which were taken with a JEOL JSM-35 SEM (JEOL, Tokyo, Japan). The specific surface areas of drug compounds and SA fractions were determined (BET Flowsorb 2300 II (86-089), Micromeritics Instrument Corp., USA) (III).

4.2.1.1 Maximum water solubility, dissolution rate and moisture uptake (III)

Maximum water solubility of drug compounds was studied by making saturated solutions in purified water as the medium (5 UV, Elix, pro-gard 2, Millipore S.A.S., Molsheim, France) which were kept at 37 °C and shaken at a frequency of 75 strokes/min (Grant OLS200, Cambridge, UK) for 68 hours. The solutions were filtered (0.45 µm) to remove non dissolved drug particles and the concentrations were determined by UV-spectrophotometry (Genesys 10UV, Thermo Spectronic, Rochester, USA). The specific wavelengths used are listed in the original paper (III).

The dissolution rates of the pure drug compounds were determined by the USP basket method, using purified water as the medium (900 ml, 37 °C, 50 rpm). Approximately 200 mg of drug compound was placed into a bag, which was made of a net with a gap diameter of 15 µm. Three bags containing the drug compound were tested individually. The samples were taken from the dissolution bath at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 17, 20, 30, 40, 50 and 60 min. The concentrations were determined by UV-spectrophotometry as stated in the original paper (III). When the

dissolved amount of drug was plotted as a function of time, the slope of the best fit straight line was considered as the dissolution rate.

The moisture uptake of the drug compounds was examined by keeping the samples in a desiccator for 24 hours at a relative humidity of 100 %. The absorbed moisture content of untreated and treated samples was measured by Karl-Fischer titration (Mettler DL 35, Greifensee, Switzerland). The percentage of moisture uptake was calculated by comparing the moisture content of original and treated samples.

4.2.1.2 pH of the solution and degree of ionization (III)

The pH of the solutions or, in the case of non-dissolving SA, suspension containing each of the compounds was measured (Methorm 744, Methorm Ltd., Herisau, Switzerland). The theoretical amount of ionized form of drug compound in presence of SA was calculated for weak molecular acids using the Henderson-Hasselbalch equations as follows (Eq. 8):

$$\%Ionized = \frac{100}{(1 + \text{anti} \log(pK_a - pH))} \quad (8)$$

and for weak molecular bases (Eq. 9):

$$\%Ionized = \frac{100}{(1 + \text{anti} \log(pH - pK_a))} \quad (9)$$

4.2.1.3 Inverse gas chromatography (III)

The dispersive component of the surface free energy (γ_s^D) of the drug compounds was determined by inverse gas chromatography (IGC) (Auto System Gas Chromatograph, Perkin Elmer Instruments, Norwalk, USA). The columns used in IGC were short glass U-shaped tubes. The hydroxyl groups of glass were deactivated by silanation using a 5% (w/V) solution of dimethyldichlorosilane in toluene in order to prevent these moieties from reacting with probe gases. After standing for 48 h at room temperature, the column was then washed with toluene followed by methanol and it was then dried.

The deactivated empty column was filled with approximately 2 g of compound and plugged with silanated glass wool. The filled column was stabilised by flowing a carrier gas, nitrogen, using approximately 10 ml·min⁻¹ as the flow rate, for 48 h at 30 °C. An infinite dilution of probe gas was injected into the column to obtain a retention time between 30 min and 50 min. Non-polar probe gases used were hexane, pentane, octane and nonane, respectively. The values of γ_s^D of drug compounds were calculated from the retention times of the probe gasses, determined by a flame ionisation detector. The calculated value of γ_s^D was the average of eight individual measurements.

4.2.1.4 Differential scanning calorimetry (IV)

Modulated temperature differential scanning calorimeter (DSC823^o, Mettler Toledo GmbH, Analytical, Schneezenbach, Switzerland) was used in order to determine possible polymorphic changes of caffeine and riboflavin. Temperature and enthalpy calibration were carried out with water, indium, zinc and lead. The measurements were made in duplicate using a heating rate of 10 °C/min and temperature scale of 25–300 °C for riboflavin and of 25–280 °C for caffeine. Samples weighing 4–6 mg were crimped in 50 µl aluminium pans with holes. A similar empty pan was always used as a reference. All runs were performed under an atmosphere of dry nitrogen (50 ml/min).

4.2.2 Powder mixture preparation (I-IV)

The powder mixtures were prepared on volume basis and they contained 78 % starch acetate and 22 % drug compound (**I**, **II**, **III**, **IV**) or 80 % starch acetate and 20 % drug compound (**IV**). The powders were mixed in a high shear impeller mixer (MCM1201EU, Bosch, Stuttgart, Germany) at a mixing time of 4 minutes (**I**) or manually in a geometric series using a card in a mortar with a mixing time of 4 min (**II**, **III**, **IV**). The homogeneities of the mixtures were then tested. The mixing time was extended gradually, in 2 min steps, the maximum being 8 min, if the desired homogeneity was not achieved earlier (**II**, **III**, **IV**).

4.2.3 Tablet compaction (I-IV)

Tablets were compacted with a compaction simulator (PCS-1, Puuman Ltd., Kuopio, Finland) to produce cylindrical tablets with a diameter of 13 mm (I-IV), the weights of tablets being 500 mg. The powder was poured into the die and overflowing powder was gently collected into die, which was manually prelubricated with magnesium stearate using a brush. A sine wave compaction profile was used for the upper punch, while the lower punch was kept stationary. The compaction properties of the powder were variable as different drug compound or particle size fractions of SA were used. Therefore, a wide range of amplitudes was applied in order to generate different compaction pressures. The compaction pressures with the respective tablet porosities are described in more detail in the original papers (I-IV). The average compaction speed was $4 \text{ mm}\cdot\text{s}^{-1}$ and the ejection time was always 1.8 s. After compaction, the tablets were stored over silica for at least 14 hours before any further procedures, such as the dissolution test. In addition, tablets of SA having different particle size fractions and caffeine were also compacted and treated in a similar way as described above (I).

4.2.4 Tablet characterisation (I-IV)

The porosity of the tablet was determined by mercury intrusion porosimetry (I) (Micromeritics, Model Autopore 9220, Norcross, GA, USA). Sufficient amounts of tablets were used for each particle size distribution and porosity in order to obtain a sufficient change of mercury in the penetrometers, and thus an accurate measurement. The pressures applied in the low-pressure and high-pressure domains were from 7 to 171 kPa and 0.2–370 MPa, respectively. These pressures correspond to pore sizes ranging from 220 to $0.004 \mu\text{m}$. The contact angle of mercury with starch acetate and caffeine was assumed to be 140° and the surface tension of mercury $480 \text{ mN}\cdot\text{m}^{-1}$. Otherwise the porosity (ε) was determined on volume basis as follows (II, III, IV) (Eq. 10):

$$\varepsilon = 100\% \times \left(1 - \frac{V_0}{V} \right) \quad (10)$$

where V_0 is the theoretical volume of the tablet, based on the mass of the tablet and the densities of the tablet composites, and V is the measured volume of the tablet, which is based on the dimensions of the tablet.

The fracture/yield strength of the single materials and sieve fractions were analyzed from their densification profiles according to Heckel (1961) (I). Scanning electron microscopy (SEM)-photographs were taken of the surface and the cross-sections of both room temperature stored and freeze-dried tablets after 6 hours of dissolution testing in order to confirm that freeze drying had not altered the morphology of the tablets (II).

4.2.4.1 X-ray computed microtomography (unpublished)

The X-ray computed microtomography is based on the different absorption coefficients for X-rays in different materials, such as tissues. This technique was originally devised for medical imaging: it has been routinely applied to the non-destructive analysis of bone structures in the clinics, e.g. after fractures (Stock 1999, Neues and Epple 2008). The development of powerful but miniaturised X-ray sources has resulted in a technique called X-ray computed microtomography, the principle of which has been described by many authors (Farber et al. 2003, Yang and Fu 2004, Neues and Epple 2008, Zeitler and Gladden 2008). Data for one slice in the xy plane are acquired at different angles. The object is moved in the z-direction and the process is repeated until the area of interest has been covered. The three-dimensional image is obtained by stacking the corresponding slices on top of each other and the subsequent reconstructing of the data using mathematical algorithms. The utilization of X-ray computed microtomography in the field of pharmaceuticals has barely started, but in recent years some successful experiments have investigated compaction of the powder, density variations within a tablet and void formation during dissolution (Sinka et al. 2004a, Busignies et al. 2006, Fu et al. 2006, Karakosta et al. 2006, Zeitler and Gladden 2008).

The structure of the tablet was determined by computed microtomography measurements (Skyscan 1172 X-ray Micrograph, Skyscan N.V., Aartselaar, Belgium). The tablets were placed on a rotary turntable with their radius in the horizontal direction. The data was collected using 100 kV voltages, 0.5 mm thick aluminium filter and by rotating the tablet 0–360°. The angular increment used in these scans was

0.68° and at each angle, ten radiographic images were averaged. The pixel size achieved with this setup was approximately 22.5 µm.

4.2.5 *In vitro* dissolution testing (I-IV)

Drug release from tablets was determined by the USP II paddle method (AT6 and AT7, Sotax, Basel, Switzerland) at 75 rpm. The dissolution medium (900 ml, 37 ± 0.5 °C) was phosphate buffer (pH 6.8) (**I, II**) or purified water (**III, IV**). Detailed information about sampling times is given in the original papers. The concentrations of drug samples taken were determined by UV-spectrophotometry (Genesys 10UV, Thermo Spectronic, Rochester, USA) at wavelengths given in the original papers (**I-IV**).

4.2.6 Freeze drying and tablet processing (II, IV)

Three tablets were taken out from the dissolution vessel at each measurement time point, directly frozen at -70 °C and then freeze dried (ModulyoD, Thermo Savant, Rochester, USA) to remove the dissolution liquid by sublimation. It was assumed that freezing of tablets at -70 °C would stop almost instantaneously the movement of liquid in the tablet.

After the freeze drying the tablets were cut axially into two pieces (Isomet Low Speed Saw, Buehler, Lake Bluff, USA) using a 0.3 mm thick diamond blade.

4.2.7 Calculation of molecular descriptors (III)

For molecule description calculations, two different molecular modelling software packages were used (Material Studio version 4.2, Accelrys, San Diego, CA, USA, and VolSurf version 4.1.4.3, Molecular Discovery, Middlesex, UK). Molecule structures were first sketched using the Material Studio software package. Sketched structures were minimized using the Forcite toolbox with the COMPASS force field and force field assigned charges. A smart minimization algorithm was used with following convergence tolerances: energy 10e⁻⁴ kcal/mol, force 5e⁻³ kcal/mol/Å, and displacement 10e⁻⁵ Å. A first set of molecular descriptors was calculated using the Material Studio QSAR toolbox. In addition, VolSurf descriptors were calculated using

the default calculation settings. The procedure described above yielded 158 molecular descriptors for each molecule. It was essential to use different software packages and force fields since the molecular descriptor based approach to explain drug release is novel and there wasn't any prior information on which software package, descriptors, or force fields would yield the best data for the purpose in question.

4.2.8 Multivariate data analysis (III)

Traditionally in the field of chemometrics, which can be defined as the acquisition of the data and the extraction of useful information from that data, the nature of analysis method has been univariate, i.e. one signal is proportional to the concentration of the analyte (Deming 1986, Forina et al. 2007). However, the information available has clearly increased in recent years due to more and more efficient measurement techniques and computational resources and thus the emphasis of the chemometrics has been transferred from classical univariate into multivariate analyses (Olivieri 2008). Basically, instead of the determination of the analyte from complicated spectroscopy data, the multivariate data analyses can be exploited in situations when there are complex data matrices to be interpreted or their relationships clarified. Thus, in the field of pharmaceuticals, where the relationships of composition of the formulation, powder mixing and compaction, and tablet formation and subsequent drug release mechanism and rate are the focus of interest, the multivariate analysis methods, such as principal component analysis (PCA) and its regression extension partial least squares to latent structures (PLS), has been utilized (Adams et al. 2001, Gabrielsson et al. 2002, Korhonen et al. 2005, Gabrielsson et al. 2006, Haware et al. 2009). The objective of PCA is to describe the variation in the data matrix, X, with a minimum of variables (Gabrielsson et al. 2002). In addition, PLS takes a step forward and it is a method of modelling two data matrices, X (variables) and Y (observations) and to establish the relationship between them (Wold et al. 2001).

Due to the complex nature of the data, i.e. the large number of formulations and properties of drug compounds, the PLS was used as a regression extension of PCA (SIMCA-P, Version 11.0, Umetrics AB, Umeå, Sweden). In this case, the X-matrix consists of explanatory variables, i.e. formulation and powder blend parameters, and both the measured and the modelled drug properties. The Y-matrix (observations)

consists of the various percentages of the released amount of drug at given time points. Data was pre-treated using unit variance scaling and mean centering in order to normalize the weight of each variable in the model. Then, the observations were divided into a training set and a test set by excluding approximately every second observation. The training set was used to evaluate the validity of model. The sizes of training and test sets were 141 and 121 observations, respectively.

The models were generated from three different observation sets: time points from 0 - 45 min, 60 - 1200 min, and 0 - 1200 min, which covered all the measurement points. In model building, insignificant variables can be detected according to the coefficient and variable importance plots. The other models were created by temporarily eliminating variables by choosing them on the basis of the coefficient plot, and the other models by choosing them on the basis of the variance important plot. If the value of prediction parameter (Q^2) was seen to have subsequently increased without the newly removed variable, it was then permanently removed. This procedure was repeated until the Q^2 parameter did not improve or change any longer. The possible strong outliers were determined by *Hotelling's T²* diagnosis at the 95% confidence level.

4.2.9 Fourier transform infrared spectroscopy, mapping and data processing (IV)

Infrared (IR) spectroscopy is based on the absorption of IR light by molecular vibration when the frequencies of light and vibration coincide, and it has been routinely used as an identification assay (Bugay and Findlay 2001, Barth and Zscherp 2002). Although the basis of the Fourier transform infrared (FTIR) imaging was developed as early as in 1949, due to rapid developments in this technique, this method has become increasingly popular in recent years (Wetzel and LeVine 1999, Bugay and Findlay 2001). This method for obtaining non-invasive information usually from the surface of the sample is often attributed with the term imaging, although there are three different approaches for the data acquisition: point mapping, line imaging and focal plane array (Levin and Bhargava 2005, Gendrin et al. 2008). In point mapping, a spectrum is measured at one position, after which the sample moves to the next measurement point on the grid, where the measurement occurs, until the desired area is scanned. Line imaging resembles point mapping, but instead of several

individual measurement points, the spectrum is collected continuously as a line. Focal plane array consists of several thousand elements forming a matrix of pixels, which enables the acquisition of thousands of spectra at the same time. FTIR spectroscopy is suitable for various situations in the field of pharmaceuticals, since it can distinguish not only different compounds, but it is also sensitive enough to determine even small changes, such as different polymorphic forms (Barth and Zscherp 2002). Thus, FTIR with imaging options is suitable for use in solid dosage form studies and it has been so far utilized for evaluating homogeneity, stability and lately even drug release behaviour issues (Markovich et al. 1997, El-Hagrasy et al. 2001, Coutts-Lendon et al. 2003, Kazarian and Chan 2003, Lee and Lin 2004).

In order to obtain the characteristic peaks of the model compounds, i.e. anhydrous caffeine, riboflavin sodium salt and SA, the spectra of pure compounds were determined by the attenuated total reflectance (ATR) (Nicolet 8700 FT-IR, Thermo Nicolet, Madison, USA) using a diamond crystal and wavenumbers from 2000 cm^{-1} up to 600 cm^{-1} . Resolution was 1.0 cm^{-1} and the number of measurements was 64.

Fourier transform infrared mapping of the cross-section surfaces of the tablets removed from the dissolution bath was performed by ATR (Spectrum Spotlight, PerkinElmer, Beaconsfield, UK) using a germanium crystal. The wavenumbers used ranged from 2000 cm^{-1} up to 600 cm^{-1} with a resolution of 1 cm^{-1} with the size of one pixel being $100\times 100\text{ }\mu\text{m}^2$. The number of scans was four since this produced spectra with practically no noise. The measurements were carried at a temperature of $22\text{ }^{\circ}\text{C}$ and the area contained 6 pixels in the radial and approximately 30 pixels in the axial direction, as presented in Figure 4.

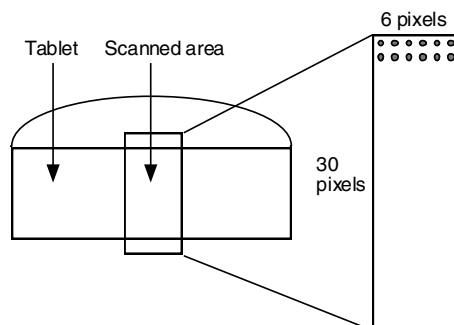


Figure 4. Schematic showing the scanned region of the tablet.

The interpretation of spectra may be difficult, since there are overlapping bands, shifting baselines and other artifacts, which are due to rough surfaces of the sample, optical effects, and detector noise (Bhargava and Levin 2001, Levin and Bhargava 2005, Gendrin et al. 2008). Therefore, in this case, the second derivative of the spectra was obtained and the band of the characteristic peak of the compound in question was used in the image generation. This procedure eliminated the effect of baseline shifting and allowed more sensitivity in selecting peaks from the complex absorption, but, however, it did increase the noise (Stuart 2004, Gendrin et al. 2008). The data processing and image generation for analysis were done with Spotlight Software (version 1.0.1, PerkinElmer Instruments LCC, Shelton, USA).

5 RESULTS AND DISCUSSION

5.1 Powder and mixture characterisation (I)

The starch acetate particle size fractions consisted of particles having fairly round shapes and smooth surfaces (Fig 5a). The powder characteristics are presented in Table 6. The density of starch acetate particle decreased with increasing particle size. A cross-section of a starch acetate particle shows large holes inside the particle (Fig. 5b). These encapsulations are inaccessible to helium gas intrusion during pycnometry measurements and are responsible for the lower measured particle densities compared to that of milled starch acetate (Table 6). The measured density of milled starch acetate can be regarded as a more accurate estimation of the true material density, and this is used in the further calculations. As for most drugs, the particle size of caffeine is small compared to most SA particle size fractions.

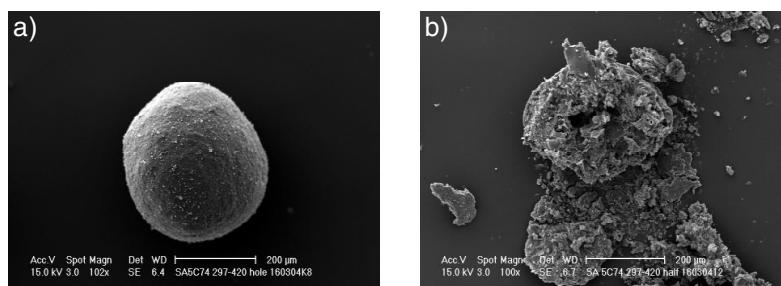


Figure 5. SEM photographs of starch acetate: (a) an intact 297-420 μm SA particle and (b) cross-section of a 297-420 μm SA particle.

Table 6. Physical characteristics of starch acetate sieve fractions, caffeine and their mixtures.

Material	Sieve fraction (μm)	Pycnometric particle density (g/cm^3)	Volume mean particle size (μm)	Fracture strength ^a (MPa.)	Carrier payload SA/Caffeine
starch acetate	< 53	1.341	11	63 ^b	0.06
	53-149	1.341	110	48	0.59
	149-297	1.367	265	47	1.44
	297-420	1.324	396	50	2.09
	420-710	1.311	542	53	2.83
	milled	1.425			
caffeine	-	1.404	11	90 ^b	

^a Fracture strength was calculated as an average value in the range of the compaction pressures used.

^b viscoelastic densification.

As pointed out in the review of the literature (chapter 2.5.1), depending on differences in particle size, surface morphology and surface energy, powder mixtures can have different organisations. Thus, if one cannot determine the surface energy, it can be assumed that the micronised drug particles adhere onto the larger SA particles forming an ordered mix (Barra et al. 1998). However, when the smallest SA fraction is used, a random type mixture is obtained.

Although Barra et al. (1998, 1999) noted that the increase in the difference in particle size causes the more frequent interaction, the interaction frequency cannot take into account the total amount of drug and carrier particles in a blend, especially when all carrier surfaces are completely occupied. In the calculation of the coverage of carrier particles by all drug particles, the following assumptions made by Dickhoff et al. (2003) were applied: firstly, all particles of each compound are spherical and monodisperse with a diameter that equals the volume mean particle size obtained by laser diffraction measurements; secondly, the projection of each drug particle on the carrier surface is a square with a side that has the same length as the diameter of the particle.

Since the particles of SA fulfill these assumptions, the carrier payload (CP), i.e. the ratio between the total projection surface area of drug particles and the total outer particle surface area of SA, can be calculated as follows:

$$CP = \frac{d_{mean,drugparticle}^2 N_{drugparticle}}{\pi d_{mean,SA}^2 N_{SA}} \quad (11)$$

where d_{mean} is the mean particle size of the compound and N is the number of particles in the mixture. It is notable that the utilization of CP does not automatically give exact knowledge of the organization of the powder, since there are strict requirements for properties of the powder components, as described above. However, despite the restrictions, CP can still be thought to give an adequate estimation of the organization of the powder mixture. Table 6 gives the calculated carrier payloads for the different SA particle size fractions and caffeine. Although a mixture containing the smallest particle size fraction of SA is to be considered as a non-interactive mixture, the carrier payload is still a good indicator of SA surface occupation within this mixture. A

carrier payload exceeding 1 indicates that the complete outer particle surface area of SA is covered by caffeine particles with no free SA surface area available.

SA deforms partially by fragmentation and plastically, and has lower fracture strength than viscoelastically deforming caffeine (Table 6). Therefore, in all particle size fractions, SA particles fracture at an earlier stage during compaction than caffeine particles, which can be used in order to estimate the structure of the tablet. When the powder is compressed, the unoccupied surfaces of SA, in powders having *CP* lower than 1, have possibilities to bond with each other and establish a continuous network, i.e. percolate. In contrast, with powders having greater value of *CP*, a higher densification is necessary to overcome the SA-drug bonding and obtain SA-SA bindings.

5.2 Pore size distribution in tablets compressed from blends (I)

Tablets compressed from binary mixtures can be regarded as three-component particulate systems containing not only excipient and drug but air, which is considered as porosity. As discussed in the review of the literature (chapter 2.4), the porosity plays important role in drug release behaviour of the matrix preparation. Tablets from each SA fractions containing caffeine were compacted to achieve porosities 12, 15, 20, 22 and 25 %. The calculated porosities corresponded to mercury intrusion measurements, which confirmed that all pores were interconnected and formed a percolating network. Furthermore, the initial particle size distribution of a blend determines the pore size distribution between particles in a tablet structure. However, for brittle materials, particle fragmentation will partially eliminate the effect of particle size over a certain particle size range. Since SA exhibits fragmentation, no large differences were found between the pore size distributions of different SA particle size fractions at equal tablet porosities.

The walls of the pores can consist of different materials: only drug, excipient as well as drug, or only excipient. The consistency of pores is important, since the capillary force is related to the contact angle between the medium and pore wall material and, thus, the pore wall material determines the medium penetration rate. The pore wall construction depends on the particle packing in the tablet structure and it can consist only of drug particles when the drug particles form a percolating network throughout the tablet. To determine whether or not a drug percolating matrix existed in a tablet

structure, the pore size distributions of tablets compressed from SA/caffeine blends were compared with the pore size distribution of tablets compressed from pure SA and caffeine at equal porosities. Tablets compressed from pure caffeine showed particular pore sizes between the caffeine particles for each tablet porosity and no similar pores were found in tablets compressed from pure SA particles, as can be seen from Figure 6a. When caffeine particles are not able to form pores between themselves, no extra pores of similar size can be seen from tablets compressed from blends (Fig. 6a). In other tablets, especially when the value of CP is greater than 1, extra pores were found and these had the same size as those in caffeine tablets, which is an indication of the existence of a caffeine matrix in tablet (Fig. 6b). Caffeine matrices could be distinguished in tablets compressed from SA particle size fraction 53-149 μm with tablet porosities of 20 % and higher, and in tablets prepared from the three largest SA fractions with porosities of 15 % and higher.

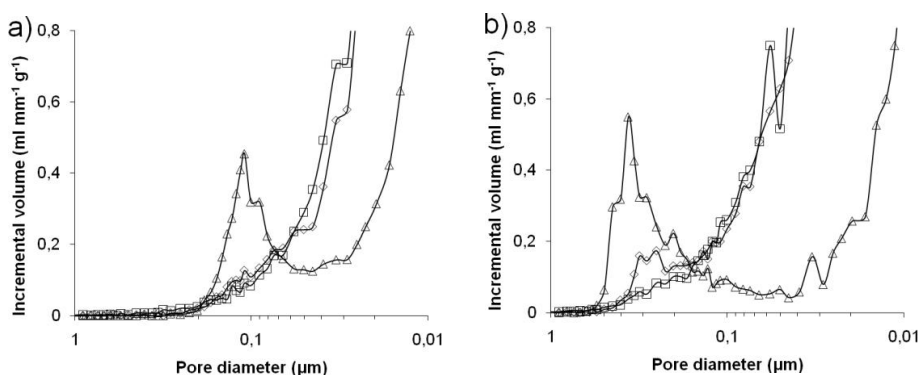


Figure 6. Pore size distributions of tablets, measured with mercury intrusion porosimetry, consisting of (\diamond) 80% 149-297 μm SA and 20% caffeine, (\square) 100% 149-297 μm SA and (Δ) 100% caffeine with equal tablet porosities of (a) 12% and (b) 22%.

5.3 Relation between tablet behaviour and drug release (I)

Tablets compressed from the different mixtures showed variable behaviours during dissolution tests. The characteristic changes in physical appearance during dissolution could be classified into three different groups: appearance of cracks, surface erosion, and rapid tablet disintegration. The physical appearances of tablets, which were strong

enough to be removed from the dissolution bath after 24 h dissolution test, are presented in Figure 7a and a corresponding scheme classifying the same phenomena is presented in Figure 7b. As an example of the effect of different tablet behaviour during *in vitro* dissolution test on drug release, the drug release profiles of tablets compressed of SA/caffeine blends containing SA particle size fraction of 149-297 μm and with different porosities are presented in Figure 8.

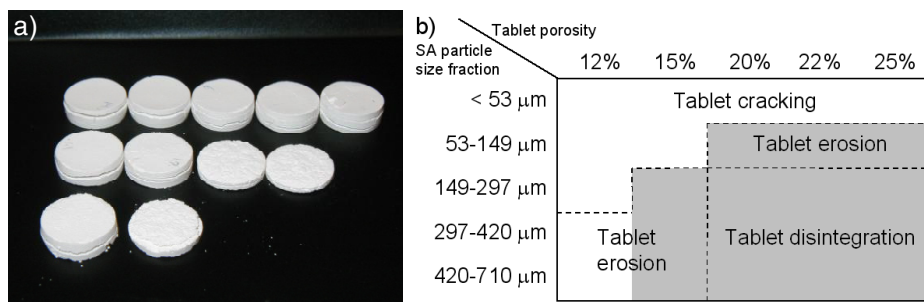


Figure 7. (a) Tablet shapes after the 24 hour dissolution test. SA particle size fractions: upper row <math>< 53 \mu\text{m}</math>, middle row 53-149 $\mu\text{m}</math> and lower row 149-297 $\mu\text{m}</math>. Other tablets were too weak to be recovered from the dissolution vessels.$$

(b) Schematic representation of different tablet behaviours during drug dissolution tests: tablet cracking, tablet erosion and tablet disintegration. Variables are the initial tablet porosity (x-axis) and SA particle size fraction (y-axis). The grey background indicates the presence of a caffeine matrix in the tablet, as detected by mercury intrusion porosimetry.

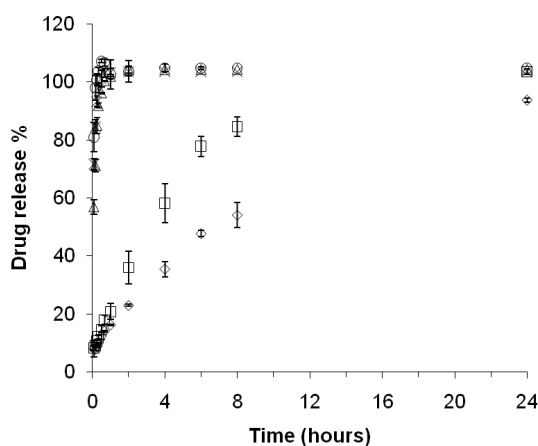


Figure 8. Percentage of caffeine released from tablets compressed from 149-297 μm SA as a function of time. Initial tablet porosities are 12% (\diamond), 15% (\square), 20% (Δ), 22% (\times) and 25% (\circ). Standard deviations are given as error bars ($n=3$).

By investigating Figures 7 and 8, it can be concluded that tablets exhibiting strong prolonged release properties maintain their shape and show only formation of cracks, and have low variation in the drug release rates. This is typical for those tablets that contain only a SA matrix in the structure. In contrast, a tablet containing a caffeine matrix (according to mercury porosimetry), which is indicated by the grey area in Figure 7b, allows rapid penetration of water into the tablet, which in the case where only a caffeine matrix exists results in rapid disintegration of the tablet. When a caffeine matrix coexists with a percolating SA matrix, surface erosion is observed, which results also in prolonged drug release properties but with more variation in drug release rates. Overall, the results from the range of tablets where mercury porosimetry detected the existence of a caffeine matrix are in a good agreement with the observed tablet behaviour during dissolution tests. Thus, the SA matrix prediction by *CP* is strengthened by the absence of tablet disintegration, i.e. tablets stay intact and exhibit crack formation or show slow erosion.

5.4 Liquid penetration into matrix tablet (II)

The formation of cracks is typical with tablets having a percolating network that consists of SA. The same phenomenon has been observed with another hydrophobic polymer, amylopectin (Steendam et al. 2000). The formation of cracks alters the structure of the tablet, which undoubtedly has an effect on the drug release properties. Thus, the formation of cracks was studied in more detail. Since the formation of the crack occurs during the *in vitro* dissolution test, it can be assumed that it is a result of liquid penetration, so the liquid penetration was determined using cylindrical tablets compressed from SA/caffeine blend into a porosity of 12 %, containing a colour indicator.

The radial and axial liquid boundary movements in tablet are shown in Figure 9. Data points are shown only up to 360 min, because the tablets had become completely wetted at 480 min. The radial movement in the tablets followed first order kinetics up to 120 min, after which there was an abrupt, but constant, increase in the movement and then it started to proceed linearly as a function of time. The axial liquid boundary movement followed also first order kinetics up to 120 min, subsequently it also started to proceed linearly as a function of time. The sudden acceleration observed in radial liquid boundary movement may well be associated with the changes occurring in the tablet structure in the radial direction.

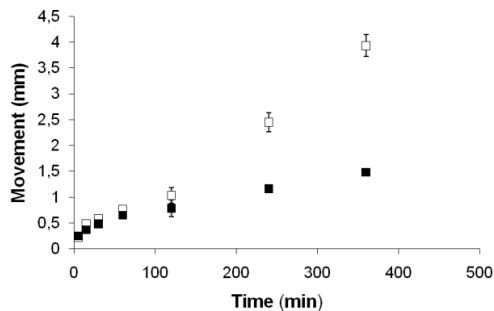


Figure 9. The axial (■) and radial (□) liquid boundary movements in cylindrical tablets as a function of time. Standard deviations are given as error bars ($n=3$).

5.5 Tablet geometry changes and crack formation (I, II and unpublished)

As the liquid boundary proceeds inside the tablet, it starts to expand mainly in an axial direction due to water absorption. This phenomenon is recognized as tablet expansion. As the expansion proceeds, the solid structures of the tablet start to disintegrate and visible cracks are generated in the radial side of the tablets. This phenomenon is known as cracking. The tablets examined here showed expansion and cracking during the dissolution process, but the expansion of matrix in the radial direction was insignificant.

The extent of the expansion and consequently, crack formation can be measured using the percent of expansion ($E_t\%$) which is calculated as follows:

$$E_t\% = \frac{H_t}{H_{before}} \times 100\% \quad (12)$$

where H_t is the height of the cylinder measured of the edge of the tablet after the dissolution test and freeze drying and H_{before} is the height of the cylinder of the tablet before the dissolution test. The percent of expansion for the cylindrical tablets as a function of time is shown in Figure 10.

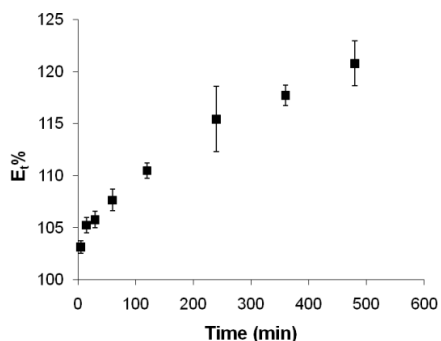


Figure 10. The percentage of expansion for cylindrical tablets as a function of time. Standard deviations are given as error bars ($n=3$).

It can be seen from Figure 10 that the tablets started to expand almost immediately, when immersed into the dissolution medium. However, the first visible cracks in the middle of the faces of the cylinder of the tablets became apparent after 2 hours as the $E_t\%$ reached approximately 110 %. This phenomenon can also be seen in the liquid boundary movement: there was an abrupt change in the radial liquid boundary movement speed at 2 hours (Fig. 9). Thus, it can be concluded that the structure of the tablet changes dramatically as the expansion proceeds up to an $E_t\%$ of 110 %.

Although the expansion had reached its apparent maximum within 8 hours (results not shown), the geometry changes within the tablet were not over. This was examined by X-ray computed microtomography with tablets at time points of 0, 4, 8, 14 and 24 h. The images generated by this method are presented in Figure 11 and quantitative information derived from the same data is presented in Table 7. While investigating Figure 11 and Table 7, some sources of deviation have to be discussed. Firstly, the resolution of method was approximately 22.5 μm and therefore, the smallest structures, such as pores, were not detected. Thus, in Table 7, the tablet at time point of 0 h seems to have a porosity of 0 %, although when calculated on the basis of equation (10), which produces almost identical results as accurate mercury intrusion porosimetry in chapter 5.2, the result was approximately 13 %. Secondly, although the method is able to define areas having different densities, such as matrix and drug compounds, in this particular case, the densities of tablet components were too close to each other and therefore, only air resulting from dissolution, expansion and

cracking could be confidently detected. Thirdly, the tablets tend to curve at the edges due to expansion and cracking (as shown in original paper II in Fig. 4a). This curved area was not taken into the analysis when Table 7 was generated, since it would have been time consuming and produced inaccurate data. Therefore, the data, especially at time points of 14 and 24 h, may not be accurate in terms of porosity, but still be a good estimation of the structure of the tablet at given time points.

By investigating Figure 11, it can be seen that as dissolution proceeds as a function of time, the pores are generated within the matrix. The diameter of a pore (diameter of approximately 10 pixels being equivalent to 225 μm) corresponds with the largest drug particles, since according to laser diffraction measurements, the diameter of 10 % of all drug particles were larger than 215 μm . Therefore, it can be assumed that the visible pores in the X-ray computed microtomography images were generated due to drug particle dissolution. In addition to formation of pores and cracks, there are small cavities or tunnels present. They might be due to the dissolution of small particles between the matrix forming agent as at the time point of 4 h, or an extension or preliminary stage of crack as especially at time points of 8, 14 and 24 h, where they extend even into the middle of the tablet. Finally, some tunnels, at the interface where pores change into solid tablet, seem to be slightly wider, entrapping an area having the same size as the pore. These might be drug particles in the middle of the dissolution process.

Table 7. The quantitative information of cylindrical tablets' geometry changes during dissolution test on basis of X-ray computed micro tomography.

Parameter	Time point (h)				
	0	4	8	14	24
Total tablet volume (mm^3)	306.9	412.2	413.3	420.9	420.9
Number of pores	0	2391	2922	3115	4486
Pore surface area (mm^2)	0	609.8	980.4	1392.8	1574.2
Pore separation (mm)	-	2.1103	1.4968	1.1165	0.89076
Volume of pores (mm^3)	0	18.6	35.0	50.2	50.1
Total porosity %	0	4.5	8.5	11.9	11.9

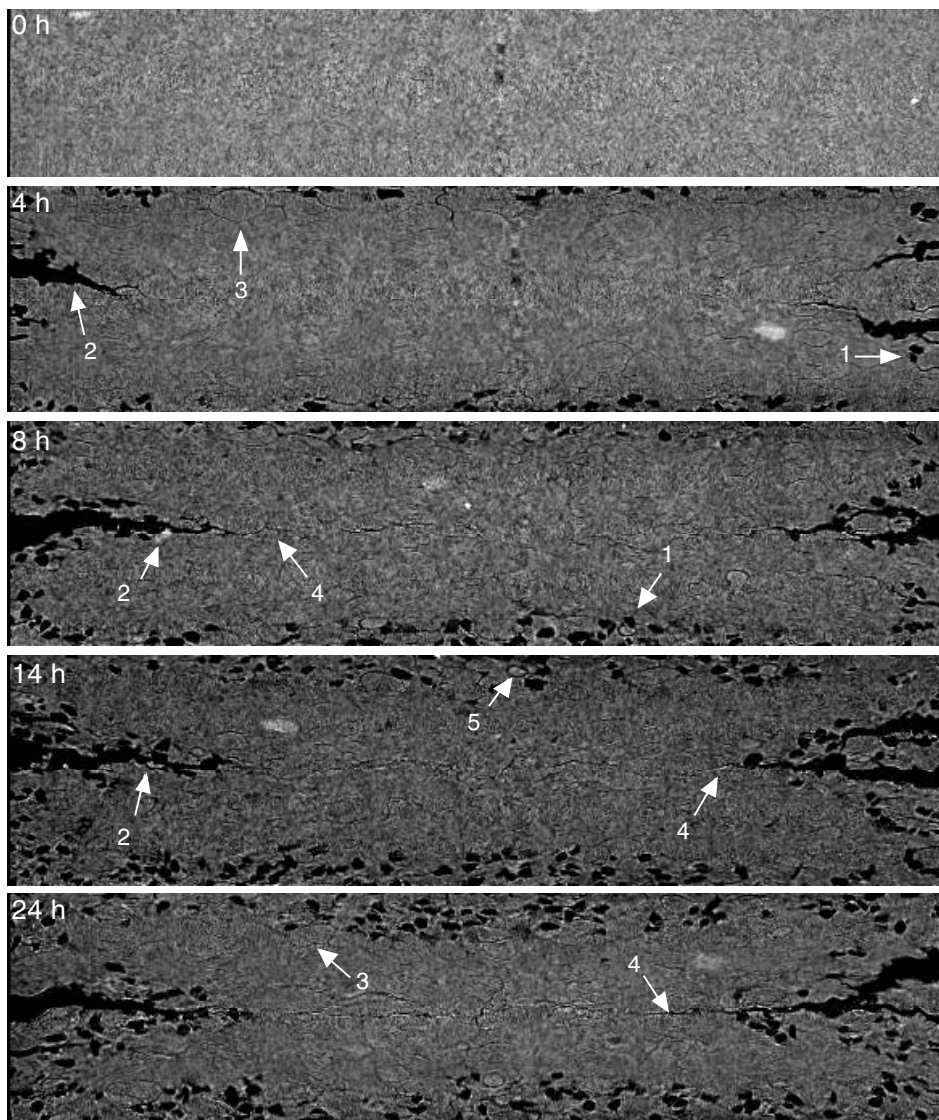


Figure 11. The X-ray computed micro tomography cross sections of cylindrical tablets. The density is presented as a function of color: less dense parts, such as air, are black and more dense areas are lighter. 1. Pore. 2. Crack. 3. Tunnel due to dissolution of small particles between matrix forming agent. 4. Tunnel as an extension of crack. 5. Partly dissolved drug particle.

The information in Table 7 supports the findings that the changes of tablet were not over although the expansion has reached its maximum. As the dissolution of drug compound, expansion and cracking proceeds, the total volume of tablet expands.

Furthermore, the number of individual pores, volume of pores, pore surface area, total porosity and pore separation, which can be regarded as the parameter describing the distance of the pores, all increase. Thus, it can be concluded on the basis of Table 7 that although tablet volume at time points of 14 and 24 h seems to be equal, the number of pores is greater and they are situated more closely than in tablets of earlier time points, which can be regarded as proof of structural changes.

The reason for expansion and crack formation can be sought from the compression and consequent internal structure of the tablets. Tablets are complex systems, which consist of inter (between drug and matrix compound particles) and intra (between two matrix compound particles) particulate bonds, where the energy generated during the compression is stored (van der Voort Maarschalk et al. 1996). The penetrating solvent molecules occupy the positions between the molecules and drug compound particles which reduce the secondary inter- and intra-molecular bonding forces (Narasimhan 2001, Callister 2000). SA, that has a d_s value as high as 2.7, is virtually in an amorphous and glassy state (Korhonen et al. 2000). Therefore, during the dissolution process, the interaction with water may lower the glass transition temperature of the starch acetate and the polymer transforms from a glassy, rigid configuration into rubbery state with an increase in elastic energy. Thus, because of these two processes, the stored energy generated during compaction is released and this is reflected as expansion, which ultimately leads to cracking (Callister 2000)

5.6 Effect of crack behaviour on drug release (I, II and unpublished)

On basis of the equation (3) and the results shown in chapter 5.3, it can be stated, that drug release is controlled by the tablet's structural properties, such as porosity and tortuosity of the capillary system. These properties are altered as the dissolution proceeds and the geometry of the tablet changes. Thus, it can be concluded that the crack formation can have a great impact on drug release behaviour.

The plot (and equation in the figure legend) describing the fraction of released caffeine as a function of the percent of the expansion is presented in Figure 12. A linear correlation was obtained between the cracking and the release of caffeine with cylindrical tablets over the experiment, i.e. up to 8 hours (time points are not shown in the Fig. 12). The linearity could be due to continual crack formation promoting the drug release. The rate of drug release decreases as the cracking reaches its maximum,

this being reflected in a lack of correlation at 24 hours (time point is not shown in the Fig. 12). The diffusion path for the drug compound does not any longer shorten as radically after the crack formation has reached its maximum, although there is a generation of tunnels according to the data in Figure 11.

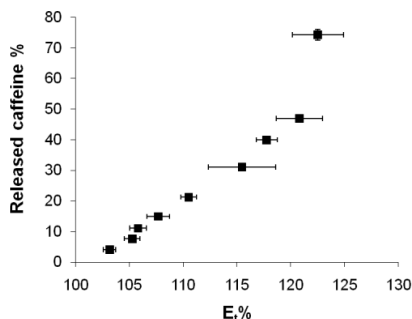


Figure 12. The fraction of released caffeine as a function of percent of expansion. The equation for describing the drug release as a function of expansion percentage at time scale of 0–480 min ($y = 2.4104x - 244.95$) has a correlation coefficient (R^2) of 0.9945. Standard deviations are given as error bars ($n=3$).

The effect of expansion and crack formation on drug release is a chain reaction. The tablets start to expand due to polymer relaxation as the liquid penetrates into the matrix. Cracks continue to be generated until the expansion proceeds up to the point where E_t is 110 %. Crack formation shortens the length of the diffusion path and decreases the total tortuosity. This promotes drug release and the liquid can penetrate deeper into the matrix. It seems that the structure of tablets change dramatically as the cracking proceeds.

5.7 Drug release kinetics from tablets with continuous porous networks (I)

The caffeine release profiles up to 60% from porous SA tablets depicting cracking and erosion with porosities higher than 10% were fitted by Equation (7). The diffusional and relaxational drug release rate coefficients are represented in Figure 13a and 13b, respectively, as a function of the initial tablet porosity. Although the diffusional and relaxational coefficients cannot be compared directly due to the different exponents of the units, the comparison between Figure 13a and 13b depicts some pronounced alterations. For tablet porosities lower than 20%, the difference in

caffeine release is primarily the result of changes in $k_{relaxation}$ (Fig. 13b). When the tablet porosity exceeds 20%, $k_{diffusion}$ plays a more important role in the changes of the caffeine release rate (Fig. 13a). As they are parallel processes, water penetration and drug diffusion at higher tablet porosities predominate over the contribution made by the relaxational release mechanism.

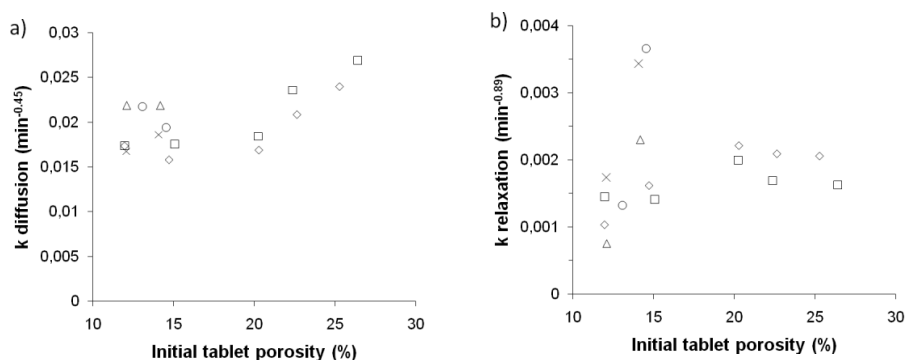


Figure 13. (a) $k_{diffusion}$ and (b) $k_{relaxation}$ of caffeine released from SA tablets as a function of initial tablet porosity. SA particle size fractions are $< 53 \mu\text{m}$ (\diamond), $53-149 \mu\text{m}$ (\square), $149-297 \mu\text{m}$ (Δ), $297-420 \mu\text{m}$ (\times) and $420-710 \mu\text{m}$ (\circ).

5.8 Characteristics of model compounds (III)

The characteristics of the compounds used in determining the most important formulation parameters and drug compound properties considering the drug release rate from hydrophobic matrix tablet are presented in Table 8. The drug particles seem to display almost identical physical properties, which are crucial according to Noyes and Whitney's definition of solubility as stated in Equation (1). However, acyclovir and salicylamide stand out as exceptions. Acyclovir has a small mean particle size and a large specific surface area, whereas salicylamide has a slightly larger particle size and a small specific surface area. According to the behaviour of drug particles used in this study, maximum water solubility seems to correlate well with the dissolution rate (results not shown). However, the anhydrous form of theophylline is an exception: it has a greater dissolution rate compared to the maximum water solubility and it exhibits higher percentage of water uptake. These findings might result in faster drug release. It is notable that all the compounds are practically unionized in the presence of SA (pH of SA suspension was 6.89). In conclusion, the water solubility and

dissolution rates of all the compounds, and, consequently, the predicted order of drug release according to Higuchi (1963), from greatest to lowest are as follows: paracetamol, theophylline and metronidazole, salicylamide, acyclovir and allopurinol.

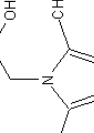

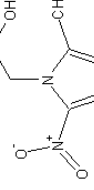
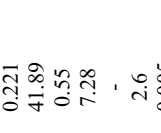
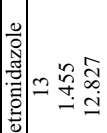

5.9 Powder organisation and tablet structure (III)

Small drug particles can adhere on the surface of SA particles, if certain conditions are fulfilled, as dealt in the review of the literature. Results indicate that SA has great surface energy due to the fact that it absorbs probe gases during inverse gas chromatography measurements and, more importantly, the mean particle size of the matrix compound for every size fraction used is substantially larger than those of the drug substances. Thus, the drug particles adhere onto the surface of SA and the arrangement of the powder blend and, consequently, the predicted theoretical structure of the tablet can be described by using *CP* as discussed earlier in chapter 5.1.

The calculated *CP* values of powder mixtures containing each drug compound and different particle size fractions of SA are presented in Table 9. As before, in powders having *CP* lower than 1, the SA particles have possibilities to bond with each other and establish a continuous network. It is notable that when the value of *CP* is approximately 1 or higher, the formation of percolating matrices are highly dependent on the deformation properties of the SA and the drug compound in question and, therefore, on the compaction pressure used. However, this was not taken directly into account, since *CP* has been shown to provide a good estimation of the structure of the tablet. In addition, the properties affecting the structure of the tablet, i.e. particle size fraction of the SA and the porosity the tablets, were standardized, and the variance caused by compaction pressure was included in the subsequent analyses.

By investigating Table 9, it can be concluded that the drug release controlling matrix of SA is generated with SA fractions of < 53 μm and 53-149 μm . Acyclovir stands out again as an exception: a *CP* value of 0.98 with SA fraction of 53-149 μm is close to the critical value of 1, but release is theoretically controlled by a single matrix of SA. Salicylamide is another exception: *CP* value of 1.05 with a SA fraction of 149-297 μm indicates that the tablets likely consist of two matrices and drug release might still be partially controlled by the SA matrix. However, when SA fractions of 297-420 μm and 420-710 μm are used with salicylamide, on the basis of *CP*, the drug release controlling SA matrix should not be present.

Table 8. Physicochemical properties of drug particles and molecular structures of compounds.

Property	Acyclovir	Allopurinol	Metronidazole	Paracetamol	Salicylamide	Theophylline
Volume mean particle size (μm)	8	15	13	14	19	14
Pycnometric particle density (g/cm^3)	1.517	1.640	1.455	1.240	1.338	1.485
Water solubility (mg/ml) ^a	2.089	0.915	12.827	19.761	3.339	9.386
Dissolution rate (mg/min) ^a	0.452	0.197	1.900	3.784	0.871	3.760
Specific surface area (m^2/g)	2.849	0.486	0.221	0.440	0.125	0.372
γ_s (mJ/m^2)	52.69	55.94	41.89	60.37	44.32	49.94
Water uptake (%)	0.11	0.33	0.55	0.01	0.09	2.61
pH of solution	6.80	6.85	7.28	5.7	6.02	5.9
pKa (acid) ^b	9.2	9.4	-	9.5	8.2	8.6
pKa (base) ^b	2.3	-	2.6	-	-	-
Percentage of ionised form ^c	0.49 ^d 0.003 ^e	0.31	0.005	0.25	4.90	1.95
Molecular structure						

^aDetermined at 37°C.^bData from Moffat et al. (2006).^cCalculated in presence of SA at pH of 6.89.^dAcid.^eBase.**Table 9.** Calculated values of carrier payload of SA and drug compound mixtures.

Sieve fraction (μm)	Acyclovir	Allopurinol	Metronidazole	Paracetamol	Salicylamide	Theophylline
< 53	0.12	0.07	0.08	0.10	0.05	0.10
53 – 149	0.98	0.53	0.61	0.70	0.42	0.70
149 – 297	2.45	1.32	1.53	1.62	1.05	1.62
297 – 420	3.81	2.06	2.38	2.51	1.63	2.51
420 – 710	4.87	2.63	3.03	3.29	2.08	3.29

5.10 Tablet behaviour and drug release (III)

The percentage of released amount of drug as a function of time is presented in Figure 14. In general, an increase in porosity and particle size fraction of the matrix compound used both enhance the drug release, as expected. This can be seen clearly with allopurinol, metronidazole, paracetamol and theophylline. The drug release behaviour of these tablets when a percolating matrix of SA is formed or when the porosity, using SA fraction of 149-297 μm , is 12 %, seems to follow the water solubility of the drug compounds. The unexpected higher released amounts of allopurinol and metronidazole might be due to homogeneity problems, leading to the variance in drug loading while mixing powders.

Interestingly, tablets containing acyclovir, which has quite a low water solubility and dissolution rate, displayed prolonged release properties only when SA fractions of < 53 μm or 53-149 μm were used. Even a decrease of porosity down to 12 % with the SA particle size fraction of 149-297 μm did not result in sustained release properties as with other compounds. Another anomalously behaving compound was salicylamide. Salicylamide tablets seemed to exhibit prolonged release in all of the formulations used despite the better water solubility and dissolution rate than acyclovir. In addition, the results were identical even if drug release promoting structures of the tablet, i.e. the utilization of SA fractions of 297-420 μm and 420-710 μm , were used (Table 9). On basis of the characteristics of these compounds, this behaviour is unexpected and indicates that there could be some underlying interactions between salicylamide and SA affecting the drug release, which are much more complex than can be obtained from knowledge of solubility and dissolution rate of the drug compound or the structure of the matrix as Higuchi (1963) has proposed.

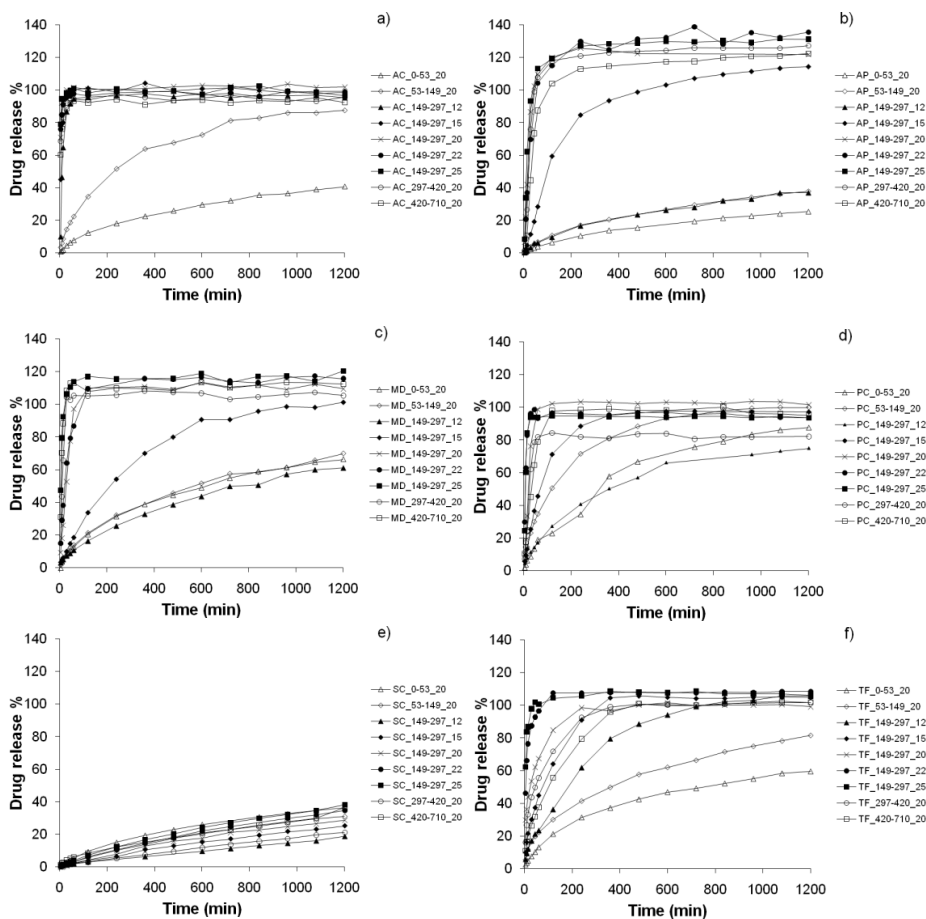


Figure 14. Drug release profiles of (a) acyclovir (AC), (b) allopurinol (AP), (c) metrodindazole (MD), (d) paracetamol (PC), (e) salicylamide (SC) and (f) theophylline (TF) as a function of time. The formulation in question, i.e. the porosity and particle size fraction of SA, is indicated on the right side of the figure. The standard deviation bars were left out for the sake of clarity ($n=3-6$).

5.11 PLS analysis of drug release properties of the tablets (III)

The multivariate analysis was used in order to determine, whether the formulation parameters of drug compound properties were the most important features determining the drug release rate. The best PLS was achieved by using five principal components and observations from all the dissolution test time points. The variable exclusion was conducted on the basis of a coefficient plot and this resulted in a model having parameters $R^2(X)$ of 0.86, $R^2(Y)$ of 0.69 and Q^2 of 0.65. In addition, the R^2 value at the time point of 480 min was improved from 0.74 to 0.80 when the

functionality of the model was tested, i.e. the test set was used instead of the training set. This was probably due to the rather large training set which results in a wider variance. Three observations were detected as outliers, which were three individual acyclovir containing tablets with SA fraction of 420-710 μm . These observations can be considered as extreme values and, therefore, this was accepted. In conclusion, the developed model can be regarded as satisfactory and it was used in the analysis.

The time point of 480 min was chosen for use in the subsequent experiments since it was one of the best modelled individual time points and it also represents well the median of the time points (Fig. 15). The order and magnitude of the important variables did not vary significantly even if other well modelled time points were used. The importance and extent of variables which remained after the creation of the model on the drug release at time point of 480 min are presented in the coefficient plot (Fig. 16). The interpretation of designations used in the coefficient plot is presented in Appendix 1. The height of the bar of the variable indicates its importance, i.e. the higher the bar, the more important the variable. Furthermore, variables with positive values correlate positively with the drug release and vice versa.

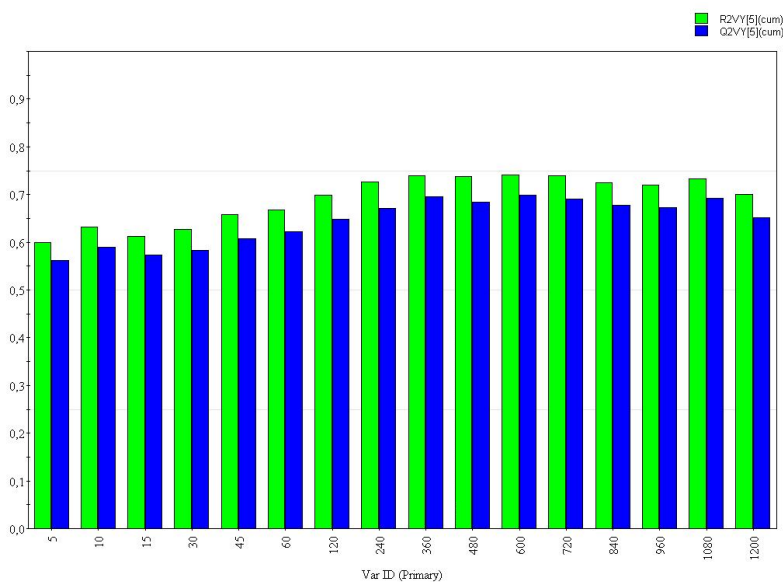


Figure 15. The ability of PLS analysis to model (R^2) (left bar at given time points) and to predict (Q^2) (right bar at given time points) the amount of the drug release at given time points.

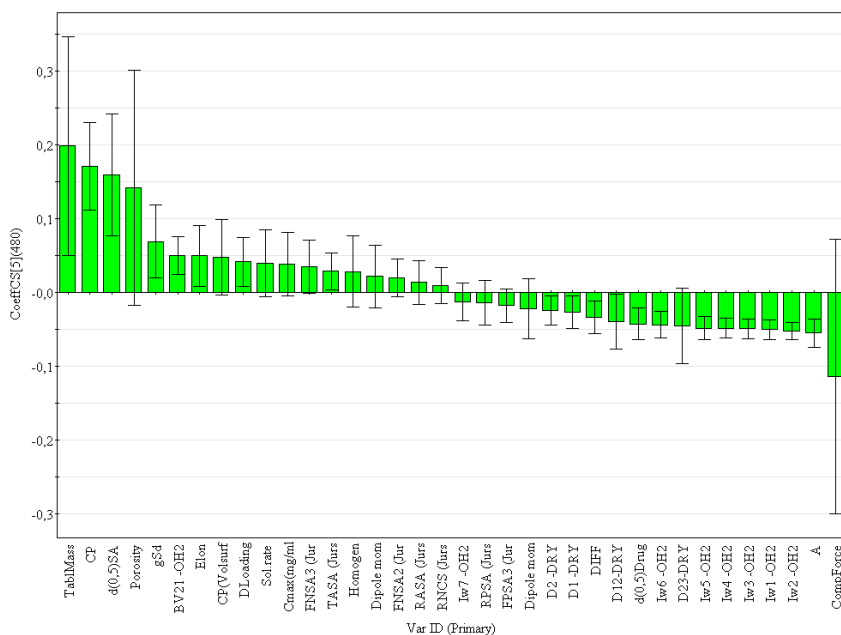


Figure 16. The coefficient plot showing the importance and effect of the variable at time point of 480 min. An increase of variable with a positive value will have a positive influence on drug release and vice versa. The height of the bar indicates the importance: the higher the bar the more important variable. Standard deviations are shown as error bars.

5.12 The factors affecting the drug release (III)

By investigating Figure 16, it can be concluded that the most important variables affecting drug release are connected to the structure of the tablet and, in consequence, the formulation. The strongest positively affecting variables are the mass of the tablet, the value of *CP*, the mean particle size of SA and the porosity of the tablet. In contrast, compaction force has a strong negative impact on drug release. These findings were not surprising since in chapter 5.3 it was pointed out that the structure of the tablet is responsible for the drug release mechanism and rate can be controlled by means of particle size of SA and compaction.

In general, the impact of drug property based variables is not as high as compared as those of tablet structure and formulation variables. The physical drug particle properties affecting positively on drug release are surface energy and dissolution rate. The importance of surface energy is not surprising: particles having a high surface energy are indicated of a greater potential to interact with a large range of substances,

including water (Rupp et al. 2006). An increase in the mean particle size of the drug compound has a negative impact on the drug release rate, as predicted. All of these physical drug particle variables can be altered, e.g. by milling (York et al. 1998).

It can be summarised that the chemical properties affecting positively on drug release are connected directly or indirectly to water solubility and hydrophilicity. These drug release enhancing molecular properties represent an interaction potential with water by measuring not only truly hydrophilic areas, but also the amount of solvent accessible surfaces, both apolar and negatively charged. Furthermore, there are descriptors that are connected to diffusivity which depict the flexibility of the molecule: the more flexible molecule, the more easily it diffuses.

Like drug release promoting descriptors, chemical properties that have a negative impact on drug release are mostly linked directly or indirectly to hydrophobicity. These descriptors represent the amount of the water repulsive hydrophobic areas, e.g. hydrocarbons having no highly electronegative atoms close to them, and even provide detailed parameters by describing the consistency of these areas and comparing their volume to hydrophilic volumes. In contrast to the drug release promoting negative charge, if there is an increase in the areas which are charged positively this seems to restrict drug release, since they might interact with the highly electronegative areas, i.e. the slightly negative oxygen atoms of SA (Fig. 1).

5.13 Unexpected drug release rates of acyclovir and salicylamide (III)

As discussed in the previous chapter, the structural properties of the tablet have the greatest impact on drug release. Thus, the unexpected rapid drug release of acyclovir compared to its maximum water solubility may be explained by variations in the structure of the tablets which are due to the physical properties of the drug particles. The drug release controlling matrix was formed with acyclovir only when SA size fractions of $< 53 \mu\text{m}$ and $53\text{-}149 \mu\text{m}$ are used (Table 9). When other SA fractions were used, this resulted in tablets where the percolating network consisted of both drug and matrix compound or of only drug compound. It appears that percolating networks made out of a hydrophilic drug compound almost act as a disintegrant enabling rapid drug release. This behaviour can also be seen with other drug compounds when the CP value is more than 1 and the porosity of the tablet exceeds 20 %, with the exception of salicylamide (Table 9 and Fig. 14e).

Tablets containing salicylamide exhibited almost identical drug release behaviour regardless of the structural changes of the preparation. This behaviour could be due to salicylamide's slightly larger particle size, though this is unlikely. The numerical values of descriptors, which are most important in order to interpret the interaction between salicylamide and SA, are presented in Table 10. It can be seen that salicylamide has the lowest values of drug release promoting descriptors TASA(jurs), which represents the sum of solvent-accessible surface areas of all apolar atoms, and BV21 -OH2, which stands for the best volume of hydrophilicity generated by a water molecule when it interacts with a target.

A further examination of Table 10 reveals that salicylamide displays high values in descriptors which have a negative impact on the drug release. Descriptor A is defined as a vector pointing from the centre of the hydrophobic domain to the centre of the hydrophilic domain, i.e. it defines the distance between the hydrophobic and hydrophilic areas. The descriptor integrity moment (Iw1-7 -OH2) represents the unbalance between the center of mass of a molecule and the position of the hydrophilic regions around it. If the integrity moment is high, the hydrated regions are clearly concentrated in only one part of the molecule. D12 -DRY represents the distances between the best two local minima of interaction energy when the hydrophobic probe interacts with a target molecule. Finally, descriptors D1 and 2 -DRY represent the interaction between a hydrophobic probe and the target molecule, i.e. the magnitude of hydrophobicity.

Table 10. Selected drug molecule descriptors of model compounds acyclovir (AC), allopurinol (AP), metrodindazole (MD), paracetamol (PC), salicylamide (SC) and theophylline (TF).

Descriptor	AC	AP	MD	PC	SC	TF
BV21-OH2	114.25	109.75	108.75	99.38	69.62	127.25
TASA (jurs)	196.62	159.48	262.35	230.80	158.90	204.56
A	1.66	0.71	2.73	2.40	4.27	1.17
D1 -DRY	69.38	68.38	78.12	104.25	118.38	92.38
D2 -DRY	51.25	49.12	44.25	61.62	71.25	58.75
D12 -DRY	1.58	6.22	1.66	0.71	6.20	6.12
Iw1 -OH2	0.07	0.05	0.06	0.11	0.23	0.04
Iw2 -OH2	0.08	0.07	0.08	0.16	0.38	0.06
Iw3 -OH2	0.13	0.11	0.11	0.28	0.63	0.08
Iw4 -OH2	0.25	0.17	0.25	0.51	1.04	0.17
Iw5 -OH2	0.40	0.22	0.48	0.76	1.41	0.41
Iw6 -OH2	0.64	0.41	0.68	1.10	1.75	0.41
Iw7 -OH	1.62	0.70	0.28	1.72	2.13	0.64

If one tries to interpret these descriptors, it seems that salicylamide has a strong and large one-sided hydrophobic area. Indeed, by investigating all of drug compounds' molecular structures (Table 8), it can be seen that they contain one or more of the following strongly hydrophilic groups: hydroxyl (acyclovir, allopurinol, metronidazole and salicylamide), amide (acyclovir, paracetamol, theophylline and salicylamide), nitrite (metronidazole) and primary and secondary amine (acyclovir, allopurinol and theophylline). Furthermore, these groups consist of highly electronegative atoms, mainly oxygen and nitrogen, i.e. they can affect the carbon atoms located next to them by attracting the electron cloud and this can make the carbon atoms more accessible to the water by generating slightly positive charge around the carbons. In most cases, these groups are located all around the molecule. However, in the case of salicylamide, hydroxyl and amide groups are located on the same side of the aromatic ring, leaving a hydrophobic area on the other side (Table 8). This unusual structural property explains the outcome of the descriptors: the hydrophobic aromatic ring contains poorly water accessible apolar atoms and this area is located at a great distance from the hydrophilic area. In conclusion, the descriptors correlate well with salicylamide's molecular structure and it can be assumed that the molecule's one sided hydrophobic area interacts with the surrounding hydrophobic starch acetate. This interaction seems to be a hydrophobic interaction, since it takes place only when there is an adjacent hydrophobic substance and it does not influence the water solubility of the salicylamide. Due to this proposed strong interaction, all tablets containing salicylamide exhibit almost identical drug release properties.

5.14 The characterisation of model compounds (IV)

The suitability of the USP II paddle *in vitro* dissolution test was examined using two physicochemically different drug compounds. The physical characterization of SA, caffeine and riboflavin is presented in Table 11. It seems that the drug compounds have identical mean particle sizes. However, the particle size distribution of caffeine is notably wider, i.e. there are sufficiently large particles present which can be indicated by the values of D10% and D90%. Thus, as the powder for the tablet is mixed, riboflavin settles more uniformly onto the surfaces of the SA particles, resulting in the formation of a homogenous matrix when it is compressed into a tablet.

The particles of caffeine are more likely to be clustered throughout the matrix in SA tablets due to their wider particle size distribution.

In order to interpret the complex spectral data and consequently to generate accurate images from the maps obtained from the tablets' cross-sections, it was important to find the characteristic peaks of all compounds that would remain constant, regardless of the sample preparation procedure. Freeze drying of caffeine did not change its crystal form, this being confirmed by DSC and FTIR (results not shown). The greatest and least overlapping single absorbance peaks for caffeine and SA were at wavenumber of 745 cm^{-1} and 1023 cm^{-1} , respectively (Fig. 17). Unlike caffeine, the riboflavin polymorph changed during freeze-drying. This was unambiguously demonstrated by the changes in the DSC thermograms (results not shown) and FTIR spectra (Fig. 17). However, despite the polymorphic change of the compound, riboflavin's characteristic peak, which is not dominated by the spectrum of SA, remained constant at a wavenumber of 1531 cm^{-1} . For the FTIR mapping of starch acetate, the peak at the wavenumber of 1023 cm^{-1} was used. It can be seen from Figure 17 that there is some overlapping with the spectrum of riboflavin and SA at wavenumber of 1023 cm^{-1} . Furthermore, there is another peak in the spectrum of SA at wavenumber of 1212 cm^{-1} which could be potentially used in the analysis. However, the results were similar with both wavenumbers (results not shown), but the peak at wavenumber of 1023 cm^{-1} was used due to its greater absorbance.

Table 11. Physical characteristics of starch acetate, caffeine, riboflavin sodium phosphate and their mixtures.

Material	Particle size distributions (μm)			Solubility in water (mg/ml)
	D10% ^a	D50% ^a	D90% ^a	
Starch acetate	6	152	520	-
Caffeine	2	20	215	15 ^b
Riboflavin	6	21	85	67 ^b

^a D10%, D50%, D90% = The percentage of particles having a diameter under an indicated size.

^b Ph. Eur. 5th edition.

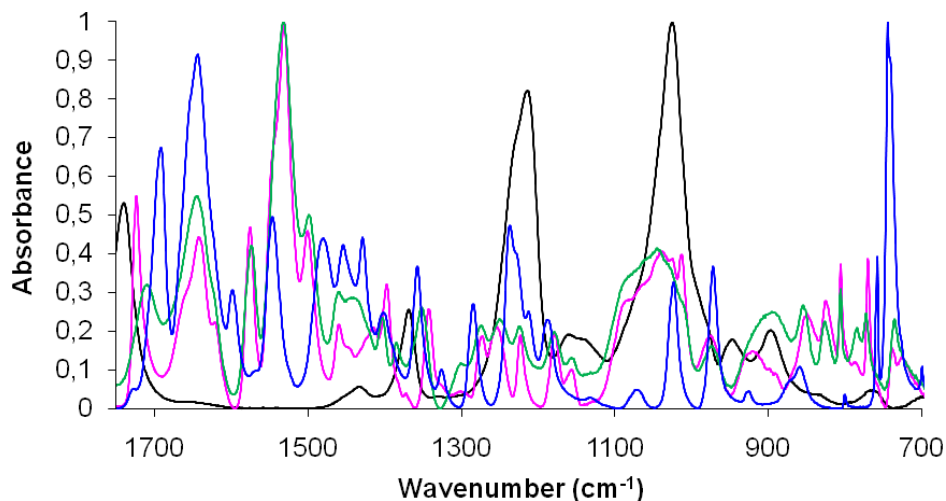


Figure 17. The spectra of caffeine (blue), freeze-dried (green) and untreated (purple) riboflavin, and SA (black).

5.15 The visualisation of drug release during USP II paddle method (IV)

Light micrographs of tablet cross-section surfaces and FTIR maps of ATR-scanned areas for both drug compounds and starch acetate at different time points are shown in Figures 18 and 19 respectively. Each of the three pictures at the same time point correspond to each other. This can be demonstrated from Figure 18 at a time point of 60 min. The visible micrograph is interpreted at this time point as follows: riboflavin's colour is yellow to red and the compound clearly stands out from the white matrix. The map for riboflavin and the light microscope picture of the cross-section both contain an island of drug compound at the same position, i.e. in the middle of the scanned area. In addition, there is a lack of matrix in the same place in the map for starch acetate at that same time point in support of this observation.

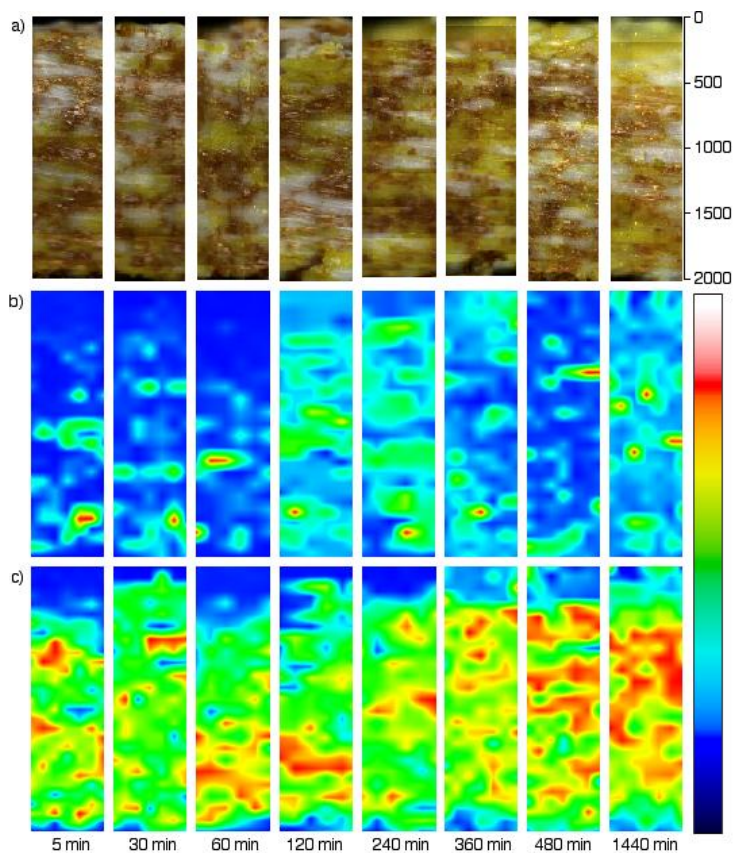


Figure 18. Light micrographs (a) and FTIR maps of riboflavin sodium phosphate (b) and starch acetate (c) of tablet cross-sections after immersion in dissolution medium. The extent of absorbance is indicated with the bar, where white denotes the highest and black the lowest absorbance.

In contrast to riboflavin, caffeine does not stand out from the matrix due to the similar appearance with starch acetate, as can be seen from Figure 19. It can be concluded that in the case of caffeine it would be almost impossible to distinguish the drug compound from the matrix without FTIR mapping.

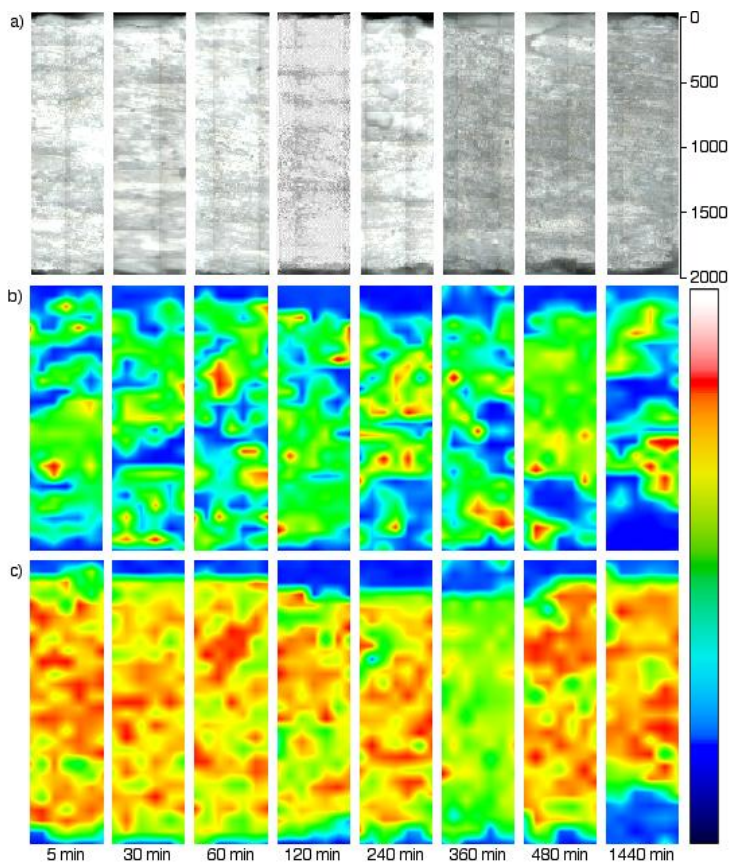


Figure 19. Light micrographs (a) and FTIR maps of caffeine (b) and starch acetate (c) of tablet cross-sections after immersion in dissolution medium. The extent of absorbance is indicated with the bar, where white denotes the highest and black the lowest absorbance.

When comparing the differences between the maps of the two compounds (Fig. 18 and 19), there appears to be more drug compound in tablets containing caffeine than riboflavin. The difference between the maps of caffeine and riboflavin might be due to the different particle size distributions of the drugs. It can be seen from Table 11 that riboflavin contains of more uniform and smaller particles than caffeine, and so is able to produce a more homogenous distribution throughout the SA matrix. Caffeine's particle size distribution is wider, and therefore, the obtained powder mixture and tablets are not as uniform, and they contain some large clusters of drug compound,

which affect the generation of maps. Another reason for the difference in maps is that at the chosen wavenumber, caffeine absorbs the infrared beam approximately 1.6 times more efficiently than riboflavin. This affects the maps with caffeine standing out much more clearly, despite the scaling and practically identical degree of drug loading.

Drug compound diffuses out from the matrix as the liquid penetrates into the tablet and dissolves the drug. As the drug release from the matrix proceeds, FTIR mapping reveals that the number of clusters of drug compound starts to diminish and the clusters smear and stretch as a result of dissolution and diffusion. This can be seen in Figure 18 especially at the time points of 240 and 360 min, and from Figure 19 at the time point 480 min. Changes in the FTIR maps, which are attributed to dissolution and drug release, start to appear earlier with riboflavin than with caffeine, which is likely due to its higher water solubility (Table 11). Riboflavin diffuses out from the matrix more uniformly than caffeine, i.e. there are only a few clusters of drug at the end of the dissolution test, and in addition, it does not gather at the edges of the matrix at any time. However, there are clusters of riboflavin particles observed at 1440 min, though the amount is not substantial. This can be concluded from the map of the starch acetate at the same time point: there is no deviation in the structure of the matrix although there is some riboflavin present. These rather small particles of drug compound were trapped inside the SA matrix and therefore they could not diffuse out. Unlike riboflavin, caffeine seems to gather at the edges of the matrix, which can be seen in Figure 19 at time points of 360, 480 and 1440 min.

5.16 Evaluation of functionality of USP II paddle method (IV)

It can be concluded by investigating equations (1) and (3) that several factors affect drug release by diffusion from the hydrophobic matrix *in vitro*, including the solubility and particle size of the drug compound, homogeneity of the content and pore structure of the matrix, and parameters of the *in vitro* test e.g. stirring speed and temperature of the dissolution bath.

Many authors have studied the hydrodynamics in the dissolution vessel during the USP paddle method test (Healy et al. 2002, Kukura et al. 2004, McGarthy et al. 2004, Baxter et al. 2005). These studies confirm that there is a low velocity domain of hydrodynamic flow at the bottom of the dissolution vessel. The drug release from the

lower part of the tablet which lies closest to the bottom surface of the dissolution vessel, is substantially inferior to other parts. Thus, drug potentially will not be released from the lower region of a matrix preparation immersed in the dissolution bath due to poor hydrodynamic conditions. It can be concluded that the factors promoting the drug release according to equations (1) and (3) are inadequate: there is no agitation of dissolution fluid between the tablet and dissolution vessel surface, which affects the concentration gradient, i.e. the driving force of solubility and drug release. The effect of this phenomenon can be seen from Figure 19, where caffeine is concentrated at the edge of the bottom part of the matrix, despite its optimal water solubility. This can be clearly seen at the time points of 360, 480 and 1440 min. The observation is not likely due to partition: the water soluble drug, caffeine, could not dissolve nor be absorbed in hydrophobic SA with as high d_s as 2.7. In addition, only approximately 50 % of caffeine had been released at 1440 min (Fig. 20). In contrast, riboflavin is practically unaffected by the poor hydrodynamic conditions: there is no observation of a congregating effect in Figure 18. This is most probably due to its higher solubility and smaller particle size distribution (Table 11). Riboflavin dissolves well and consequently is released from the preparation even when the conditions for dissolution are not favorable. Figure 20 supports this result: over 80 % of riboflavin had been released after 1440 min.

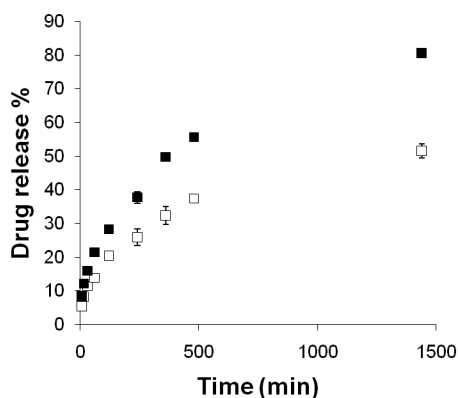


Figure 20. Percentage of riboflavin (■) and caffeine (□) released as a function of time. Standard deviations are given as error bars ($n=3$).

5.17 Summary

The present study suggests that the powder blend organisation and consequent structure of the matrix tablet has an important role on drug release mechanism and rate. The structure of the matrix tablet can be controlled by altering the particle size fraction of the matrix forming hydrophobic excipient or making the tablet more porous by lowering the compaction pressure. It is possible to obtain an estimate of tablet structure if one combines carrier payload data with information about the fracture/yield strength. This is especially true if the estimation is related to the existence of an excipient matrix. When a hydrophobic excipient with an adequately small particle size fraction is used, it can form a percolating network within a matrix tablet. The consistency of the network matrix in the tablet is of major importance in determining the drug release mechanism and rate. A networking matrix of hydrophilic drug alone leads to immediate tablet disintegration and rapid drug release. Co-existing percolating networks of drug and excipient mean that there is surface erosion of the tablet and highly variable drug release. When the hydrophobic excipient is percolating, tablets maintain their shape and only crack during dissolution tests. Furthermore, tablet porosity affects also the drug release mechanism. In the mixtures examined here with increasing tablet porosities from 10% to 20 %, the difference in drug release was primarily the result of changes in relaxational component, and with higher porosities, due to the diffusional component.

Liquid penetration into the tablet is a prerequisite for the dissolution of the drug compound and its consequent release. However, in the case of tablets where the networking matrix is composed of a hydrophobic excipient, the penetrating liquid weakens internal bonds and initially this causes tablet expansion. After a certain period of time, the tablet expansion is transformed from tablet swelling into tablet cracking. The cracking increases the drug release rate by shortening the length of the diffusion path, increasing the effective surface area and lowering the degree of tortuosity.

Although the structure of the tablet has the greatest significance on drug release rate and mechanism, the properties of the drug compound cannot be overlooked. On basis of the results, it can be concluded that in most cases, the drug release rate of structurally identical tablets follows maximum water solubility and solubility rates, of which the latter can be promoted traditionally by means of formulation, e.g. milling. However, the formation of matrix and the combined mechanism of drug release may be

extremely complicated and, therefore, a knowledge of maximum water solubility and dissolution rate cannot describe the entire process adequately. Although a drug particle appears to have sufficient water solubility and dissolution rate for the desired drug release profile, other properties, such as the magnitude and location of hydrophilic and hydrophobic areas, can cause major interactions with controlled release excipients which might not be beneficial to the drug release. These chemical molecular properties cannot be eliminated by means of traditional pharmaceutical processes and, thus, properties and nature of the drug particle in question need to be comprehensively characterized in order to achieve a successful outcome in the formulation task.

The drug release mechanism and rate is most often studied using standardized *in vitro* tests described by the Pharmacopoeias. The USP paddle method produces relevant data describing the drug release of prolonged hydrophobic tablets if the preparation consists of an extremely water soluble compound, such as riboflavin sodium phosphate, with a homogenous distribution within the matrix tablet. However, in the case of caffeine, which was a less water soluble compound and whose particle size distribution is wide and as a consequence the drug distribution is less homogenous, the *in vitro* test may not produce results with adequate relevance. The results obtained by utilization of Fourier transform infrared mapping in ATR mode, which is a method for distinguishing the drug substance from the matrix compound, revealed that caffeine was clearly concentrated at the bottom edge of the tablet in contact with the dissolution vessel, although the poor hydrodynamic properties of the USP paddle method were considered to play a large part in this observation. The results would suggest that the *in vitro* dissolution test should be chosen extremely carefully for prolonged release preparations or the existing test should be modified, especially, when the drug compound is not highly water soluble and the matrix is a hydrophobic polymer based tablet.

6 CONCLUSIONS

The present study has examined the methods which can be used to modify the structure of the starch acetate (ds 2.7) matrix tablet. Furthermore the impact of the structure on the drug release mechanism was determined and possible interactions affecting this mechanism were investigated. Finally, the suitability of USP II paddle apparatus was evaluated. Based on the results presented, the following specific conclusion can be made:

1. The drug release mechanism and rate can be controlled by means of particle size distribution and compaction pressure when the SA with a degree of substitution 2.7 is used. When SA particles having a small particle size are used, the excipient can produce percolating network having drug release mechanism of diffusion. In addition, tablets consisting of both hydrophilic and hydrophobic matrices release their content by erosion and tablets having only hydrophilic matrix show rapid disintegration. For studied mixtures with increasing tablet porosities from 10% to 20 %, the difference in drug release is primarily the result of changes in the relaxational component, and with higher porosities, due to the diffusional component.
2. Tablets are complex systems consisting of inter- and intra-particulate bonds, where the energy generated during compression is stored. The liquid penetrates into positions among the polymer molecules and reduces bonding forces and the stored energy releases resulting in crack formation. Crack formation shortens the length of the diffusion path and decreases the tortuosity, which promotes the liquid penetration and increases the drug release rate.
3. The most important features affecting the drug release rate are formulation parameters responsible for the structure of the matrix. The drug compound properties, such as water solubility and dissolution rate, and factors which promotes these features become more important when the structure of the tablet is kept standardized. However, the interaction between a drug and

excipient arising from the molecular structures of both compounds may cause unexpected results in the drug release rate, which cannot be eliminated or overcome by traditional pharmaceutical processes, such as milling.

4. The USP paddle method can be used in order to estimate the drug release properties of prolonged preparations *in vitro* and it produces reliable results especially with preparations containing extremely hydrophilic drug compound with homogenous distribution. However, its suitability may be questionable with preparations consisting of less hydrophilic compounds with uneven distributions. Since the preparations have non-optimal hydrodynamic conditions, the drug compound may congregate at the bottom of the preparation and this can lead to incorrect results.

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APPENDICES

Appendix 1 (Table)

The list of formulation and drug property based parameters that were included in the final analysis. The most positively affecting parameters are placed at the top of the list and vice versa.

Appendix table 1. The list of formulation and drug property based parameters that were included in final analysis. The most positively affecting parameters are placed at the top of the list and vice versa.

Parameter	Designation
Mass of the tablet	TablMass
Carrier payload	CP
Mean particle size of the SA	d(0,5)SA
Porosity of the tablet	Porosity
Surface energy of the compound (γ_s^D)	gSd
Second best of three hydrophilic volumes of the molecule	BV21 -OH2
The maximum extension of molecule, when properly stretched (Elongation)	Elon
Critical packing	CP(VolSurf)
Drug loading of the tablet	DLoading
Dissolution rate of the drug compound	Sol.rate
Maximum solubility of the drug compound	Cmax
Fractional atomic charge-weighted negative surface area	FNSA3
Total apolar solvent -accessible surface area	TASA
Homogeneity of the powder	Homogen
Dipolemoment y	Dipole mom
Fractional charge-weighted negative surface area	FNSA2
Relative apolar solvent-accessible surface area	RASA
Relative negative charge solvent-accessible surface area	RNCS
Relative polar surface area	RPSA
Fractional atomic charge-weighted positive surface area	FPSA3
Dipolemoment x	Dipole mom
Hydrophobic regions	D1-D2-DRY ^a
Diffusitivity	DIFF
Local interaction energy minimal distances	D12 -DRY ^b
Mean particle size of the drug	d(0,5)Drug
Local interaction energy minimal distances	D23 -DRY ^b
Integy moment	Iw1-Iw7 ^c
Amphiphilic moment	A
Compaction force of the tablet	CompForce

^aHydrophobic regions have been calculated using two different energy levels (-0.2 and -0.4 kcal/mol)

^bLocal interaction energy minima distances are calculated from three different minimal, although two of them were important enough to end up into model

^cIntegy moment has been calculated using seven different energy levels (-0.2, -0.5, -1.0, -2.0, -3.0, -4.0 and -5.0 kcal/mol)

ORIGINAL PUBLICATIONS

- I** van Veen B, Pajander J, Zuurman K, Lappalainen R, Poso A, Frijlink HW, Ketolainen J: The Effect of Powder Blend and Tablet Structure on Drug Release Mechanisms of Hydrophobic Starch Acetate Matrix Tablets. *European Journal of Pharmaceutics and Biopharmaceutics* 61: 149-157, 2005

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- III** Pajander J, Korhonen O, Laamanen M, Ryyänen EL, Grimsey I, van Veen B, Ketolainen J: Effect of Formulation Parameters and Drug-Polymer Interactions on Drug Release from Starch Acetate Matrix Tablets. *Journal of Pharmaceutical Sciences* 98: 3676-3690, 2009

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