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Master Thesis in Pharmacy

PLATFORM MODULES AND FLEXIBILITY IN ORAL DRUG DELIVERY; THE DOME SHAPED MATRIX

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To my husband Øyvind

1. CONTENTS

2. SCOPE

The scope of this thesis has been organized in three objectives:

The first objective was to find a method to measure the size of the surface area of hydrophilic matrices during their swelling. The surface areas of the different shapes were explored: that of a cylindrical matrix and that of the Dome Matrix. The Dome Matrix is a cylindrical tablet with two curved bases, one convex and the other concave. Since the axial section of the matrix appears as a dome it was called Dome Matrix.

The second objective was to study the drug release from hydrophilic matrices with different geometries but the same formulation and mass. The different geometries would lead to different surface area:volume ratios and therefore the drug release would proceed with different release rates and different mechanisms of release.

In the third objective a new method of matrix assembly was developed. The assembly was done by the use of ultrasound and the effects that ultrasound could have on drug release from a hydrophilic matrix was studied.

3. ABBREVIATIONS

BPP	Buflomedil Pyridoxalphosphate
CAPr	Cellulose Acetate Propionate
CR	Controlled Release
EC	Ethylcellulose
F.U.XI	Farmacopea Ufficiale (Italian) 11th edition
GIT	Gastrointestinal Tract
GR	Gastric Retention
HPMC	Hydroxypropyl methylcellulose
MMC	Migrating Myoeletric Cycles
T_g	Glass Transition Temperature
UV	Ultraviolet
US	Ultrasound

4. INTRODUCTION

4.1 THE SWELLABLE MATRIX SYSTEMS

4.1.1 Swelling-controlled release systems

Swelling-controlled systems, also known as hydrogel matrices, polymeric matrices, hydrocolloid matrices or hydrophilic matrix, (1,2,3,4) can be utilized to manipulate the release of a drug in order to give a controlled time or site of release. The different types of swelling-controlled systems include free-swellable matrices, where the matrix can swell unhindered, swelling-restricted matrices, where the matrix surface is modified to alter the swelling of the preparation; and finally, the swelling-controlled reservoir systems, where the formulation is coated with swellable polymers that control the diffusion of the drug from the inner reservoir (5). The advantages of such controlled release systems include among others reliable and pH-independent drug release as well as better patient compliance, drug targeting to specific anatomical areas and protection of drugs from degradation by enzymes or hydrolysis.

4.1.2 Swelling of hydrophilic polymers

It's the swellable polymer's viscoelastic properties, rising from the internal crosslinks that create a polymer network, which control the release of the drug from the preparation. When a swellable matrix is immersed in water, a steep water concentration gradient is formed at the interface between the water and the polymer matrix. The water first interacts with the hydrophilic groups of the polymer, and as these water molecules are quite firmly bound to the polymer they are not able to dissolve the drug incorporated in the matrix. As the water is further imbibed into the matrix, there are created water-filled spaces inside the polymer network that hydrate and dissolve the drug particles. The water acts as a plasticizer and lowers the glass transition temperature, T_g, until it reaches the actual temperature of the system. The polymer chains then relax and the polymer swells (6). If the T_g is above the temperature of the system, the polymer chains are in the glassy state and they are too rigid for the drug to be

released from the formulation; in the case of HPMC, as it's glass transition temperature is lowered from 184°C in the dry state to less than 37°C when immersed in water, the polymer transforms from the glassy state to the rubbery state and the polymer chains become more flexible. The swelling causes great changes in the matrix with regard to the concentrations of drug, polymer and water, the structural organization of the polymer and the mobility of the polymer chains (7). The factors that decide the nature of the drug release from a hydrophilic matrix are as follows:

- The polymer content
- The drug:polymer ratio
- The solubility of the drug
- The viscosity of the polymer
- The particle size of the drug
- The particle size of the polymer
- The particle size of any excipients
- The solubility of the excipients
- The structure and hydrophilicity of the polymer (8)

4.1.3 Relevant fronts

The interface between the outermost edge of the matrix and the water is called the ”erosion front”, since this is where the polymer eventually reaches a level of hydration that allows it to disentangle and dissolve, and hence, to erode (9). Depending on the characteristics of the polymer, the erosion front will move outwards from the core of the matrix if the swelling rate is faster than the rate of dissolution of the polymer; and the front will move inwards if the dissolution rate exceeds the swelling rate. The swelling- and dissolution properties of the polymer are important in determining the matrix' dimensions and the diffusion pathways that the drug may take to leave the system (7). As the water further penetrates the polymer matrix, the front where the polymer swells is known as ”swelling front”. This front always moves inwards towards the core. The swollen polymer is termed ”rubbery phase”, and the dry polymer or matrix is termed

”glassy phase” (10). If the matrix contains a drug of high solubility and high diffusion rate, it is most likely that there will only be these two fronts present. However, one may observe a third front if the drug has a low solubility or a slow dissolution rate. This front is termed ”diffusion front” and can be found between the swelling front and erosion front (11,12), see Figure 1. The diffusion front in the rubbery phase of the matrix represents the boundary where the drug becomes dissolved. In the same manner as the swelling front the diffusion front also moves inwards towards the centre of the matrix. The diffusion front is only present if the drug dissolves after the polymer has swelled. Otherwise, the front moves in a parallel with the swelling front. Since the polymer swells, the drug diffusivity increases as a consequence of the increased water content. When the water concentration exceeds the solubility of the drug, complete dissolution occurs. The drug can then diffuse out of the matrix (7). As the swelling of the matrix advances inwards towards the centre, the diffusional pathway of the drug increases, and so the release rate of the drug will gradually diminish.

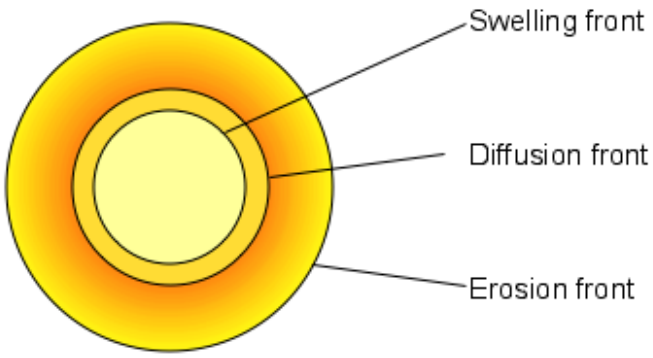


***Figure 1**: The different fronts shown as a cross-section of a spherical matrix.*

4.1.4 Mechanisms of drug release

After the polymer has swelled, the dissolved drug can be released from the matrix by diffusional mechanisms, termed Fickian, or other mechanisms, such as erosion or convective release. The release of the drug is controlled by the interaction between the solvent, the polymer and the drug, and the kinetics depend on the development of drug gradient in the gel. Therefore the thickness of the gel, the drug loading and solubility are the major factors that determine the drug release kinetics (10). For example, a large matrix will have a different drug release rate than a small matrix because the diffusional distance will be quite diverse. A high drug loading under perfect sink conditions will give a steeper concentration gradient in the rubbery phase, and the solubility of the drug will affect the dissolution time; in fact, a poorly soluble drug might not be released by diffusion at all, but by mechanisms such as polymer erosion and convective transport. For a polymer that is non-swellable drug release is almost solely dependent on diffusion. In this case there is almost no lag time for the equilibrium state after the matrix has been solvated. Time-independent, non-Fickian or case II transport of the drug can be observed in a two-dimensional film of hydrophilic polymer when polymer dissolution is equal to the polymer swelling. More commonly, in hydrophilic matrices one sees a transport mechanism intermediate between Fickian and non-Fickian, namely anomalous transport (5). Polymer relaxation and erosion of the swollen polymer contribute to non-Fickian drug release. Other ways of manipulating the drug release pattern from a hydrophilic matrix include restriction of the swelling of a hydrophilic matrix with an impermeable film, or to create a drug concentration gradient within the matrix. If the concentration of drug is gradually increased from the outermost border to the centre of the drug delivery device, this will compensate for the longer path of diffusion (13).

4.1.5 The significance of matrix shape for drug release mechanisms

The shape of the swellable matrix tablets and it's impact on the drug release mechanisms have already been examined by amongst others Ritger and Peppas (14), Siepmann, Kranz, Peppas and Bodmeier (15) and Sandaker (16). Ritger and Peppas described the change of the diffusional exponent *n* in relation to contribution of diffusional or non-Fickian release as the geometry of the releasing device changed. Sandaker treated the release and the mechanisms of release of the dome shaped matrices in the flow-through dissolution apparatus. It has earlier been found that if the drug releasing surface area remains constant, while the swelling front and the erosion front is moving in a parallel manner, the drug release will be constant, or in other words it will follow zero-order kinetics. By coating one base and the lateral side of a cylindrical matrix with an impermeable film (swelling restricted matrix), the area available for drug release and swelling would be constant. However, this cannot be achieved with HPMC except for very low polymer concentrations, because the solubility of HPMC is too low. Although the use of HPMC in this way did not produce zero-order drug release, it changed the kinetics of drug release (5). In the thesis of Sandaker (16) the restriction of swelling in dome matrices was studied. The dome shaped matrix showed different drug release compared to a cylindrical matrix having the same composition and mass. The thesis also showed by coating the base surface or the base and lateral surfaces with an impermeable polymer film that the drug release from surfaces with nearly the same area but with different geometry have different drug release patterns, and also quite varying drug release mechanisms. For example was the fractional drug release from the concave surface of a dome shaped matrix less than that from the convex surface. The concave surface had less contribution of diffusional drug release than the convex surface (16). Hence, the shape *and* the surface area of the swellable matrix generally decided the drug release rate and mechanisms.

Two or more dome shaped matrices can be assembled in various configurations. Dome matrices containing different concentrations of a drug or different drugs can be combined after desired patterns. Such an assembly can

give patients who need to take more than one drug advantages and enhance the compliance of the patient and the convenience of health workers. This creates new possibilities for tailoring the drug treatment. It might also solve certain production problems that may be connected with production, such as compression force, and polymer coating of drugs or tablets. In this thesis the assembly of swellable matrices and the influence of assembly on the drug release will be studied more closely.

4.2 THE POLYMERS

The polymers used in the experiments for this thesis were ethylcellulose and hydroxypropyl methylcellulose, two ether derivates of cellulose. Cellulose is a natural unbranched polysaccharide composed of glucopyranose units, connected by 1,4-β links, and is the major constituent of plant material (17).

4.2.1 Ethylcellulose, EC

Ethylcellulose (EC) is a semi-synthetic cellulose ether, partly O-ethylated. The percentage of ethylated groups must according to Ph.Eur.(18) be between 44.0 and 51.0 percent. The ethylcellulose is insoluble in water, but soluble in some organic solvents. It does not swell in water. Common uses are as filling agent and thickening agent.

4.2.2 Hydroxypropyl Methylcellulose, HPMC

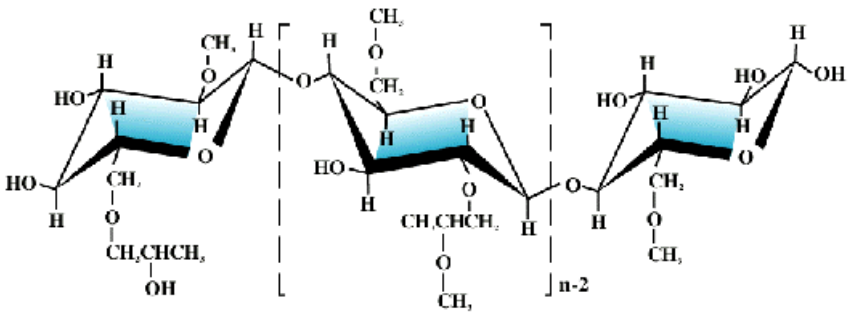


***Figure 2**: The chemical structure of HMPC.*

HPMC is also a semi-synthetic cellulose ether with varying degrees of methoxy- and 2-hydroxypropoxy-substitution. As one can see from Figure 2, there are no ionisable groups and hence the polymer is not sensitive to changes in solvent pH. The proportions of the substitutions determines the qualities of the polymer, for example the swelling properties, solubility, etc. In the UK the grade of the polymer is distinguished by giving the polymer a number that indicates the viscosity of a 2% w/w solution at 20°C, in the United States the different grades are described by assigning a number where the two first digits indicate the percentile of methoxy groups and the third and fourth digits describe the percentile of hydroxypropoxy groups. The USP defines four different grades of HPMC, based on the percentage of substitution, namely 1828, 2208, 2906 and 2910 (17). The HPMCs are soluble in cold water, but insoluble in hot water or dehydrated alcohol (18). When introduced in water or another hydrophilic solvent, the HPMCs swell, creating a network of entangled chains held together by secondary forces. This process is reversible, and on drying a solution of HPMC a film is formed. Except from the use as a slow release agent, drug carrier, coating agent, etc in drug formulations, HPMC is also used as an emulsifier, gelling agent, stabilizer, film former and suspending agent in foods (19,20). In the research for this thesis HPMC with the trade name Methocel® was used. The Methocel K100M HPMC corresponds with the USP quality 2208, with 19,0-24,0% methoxy substitution and 4,0-12,0% hydroxypropoxy substitution. The Methocel used was of the K100M type, which has longer chains and is of the least erodible quality (16).

4.3 ASSEMBLY WITH ULTRASOUND

4.3.1 Ultrasound background

Ultrasound is energy in the form of sound waves with a frequency of 1 to 5 megahertz. It is inaudible to the human ear, and so far no significant risks of health damage have been observed with the use of ultrasound for medical examinations. In addition to the diagnostic application ultrasound has previously been used for industrial purposes such as welding and molding plastic materials

for purposes such as car manufacturing and product packaging. Ultrasonics has also been used for cleaning objects such as surgical instruments (21). It has also been shown that ultrasound can enhance transdermal penetration of drugs, also drugs with a higher molecular weight, such as proteins (22,23). Rodriguez et al. (24) applied ultrasound to compact tablets consisting of Eudragit® and theophylline. Using ultrasound as a method of welding the modules together as mentioned previously in part 4.1.5 is very efficient (the modules remained assembled throughout the entire duration of the dissolution test) and it does not involve the use of organic solvents nor is it time consuming. The assembly of release modules with different composition given together can ease the problems of polypharmacy and create personalized dosage systems with dosaging and release kinetics adapted for the individual patient.

4.3.2 Mechanism of ultrasound soldering

The soldering of the single units in one piece depends on the thermoplasticity of the contents in the release units. The energy of the ultrasound waves is transferred to the release unit or module and there is a consequent rise in temperature. As the temperature exceeds the T_g of the contents, in this case the HPMC, the polymer chains become more flexible. While the temperature still is higher than the T_g of the polymer the chains of the different modules entangle and as the temperature drops, the polymer becomes rigid once more. The energy applied has created a new conformation and entanglement of the chains of the separate modules, and this has led to their attachment (see Figure 3). All this happens during a very short amount of time. In the work performed for this thesis, ultrasound was applied for 0.55 seconds.

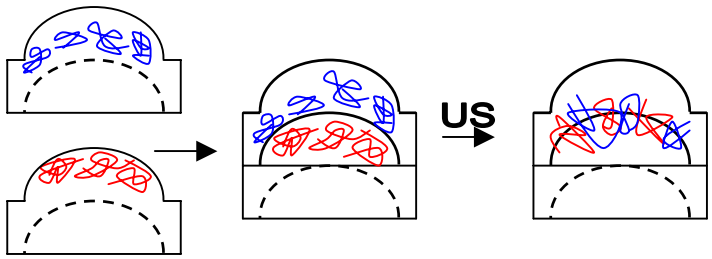


***Figure 3**: The behaviour of polymers during ultrasound soldering, the red lines representing the polymers of the lower module and the blue lines representing the polymers of the upper module.*

The energy of the ultrasound waves that were applied had to be changed accordingly to how many modules we wanted to assemble. For the assemblage of two or three modules the energy required was around 15J. For four to six matrices to be united, a higher energy was needed, about 25-30J.

4.4 MECHANISMS OF RELEASE AND THE MATHEMATICAL MODELS

4.4.1 Models for description of release mechanisms

Many different mathematical models have been proposed to describe the drug release mechanisms from hydrophilic matrices. Using an appropriate equation would make it possible to calculate and predict these processes. However, at the present the most common equations have limitations to their use, as it is necessary to make certain assumptions about the models. One example is the model proposed by Cohen and Erneux (25,26), which assumes that there is only swelling in one dimension. Consequently, this model cannot successfully be applied to a three-dimensional system such as the dome-shaped matrices studied in this paper.

4.4.2 Fick's Law

Fick's Law describes the purely diffusional release rate of a drug. In the case of swellable matrices the drug diffusion rate is proportional to surface area and the drug concentration gradient between the diffusion front and the erosion front. Assuming quasi steady-state conditions, Equation 1 could be applied to swellable matrices:

$$\frac{dm}{dt} = \left(\frac{Dk}{h}\right) \cdot A \cdot \Delta C \qquad \text{Equation 1}$$

Here, *dm*/*dt* represents the diffusion rate, *D* the drug's diffusion coefficient in the swollen polymer, *k* the partition coefficient of the drug, *h* the drug's distance of diffusion inside the swollen matrix, i.e. the distance between the diffusion front and the erosion front, *A* is the surface area of the matrix and ΔC is the concentration gradient of the drug, that is C_0-C_i where C_0 is the drug concentration at the diffusion front and C_i the concentration at the erosion front.

4.4.3 The Ritger-Peppas equation

In this paper we have applied the Ritger-Peppas equation (Equation 2), a semi-empirical model for the analysis of release data.

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{Equation 2}$$

In this equation M_t is the amount of drug released at time *t*, M_∞ is the amount of solute released after infinite time. M_t/ M_∞ is the fractional solute release. *t* is the release time and *k* is the release constant, which is dependent of the system, i.e. polymer, solvent, drug loading, excipients, etc. *n* is the diffusional exponent characteristic of the release mechanism of the system.

4.4.4 Advantages and disadvantages of the Ritger-Peppas equation

Equation 2 was used to study the mechanism of release, because this equation has favorable aspects as regards limitations and assumptions. One assumption that must be made is that there are perfect sink conditions during the swelling, and that diffusion is concentration independent. The Ritger-Peppas equation can only be applied to the first 60% of fractional drug release (14). It is also important to consider that there is a delay before the outermost edges of the matrix have been hydrated (27). In our experiments we have assumed that steady state for the HPMC-matrices occurs after 10 minutes, and this is considered in our calculations. Thus, we insert the lag time *l* in Equation 2:

$$\frac{M_t}{M_\infty} = k(t-l)^n \qquad \text{Equation 3}$$

4.4.5 The diffusional constant *n*

The release of drug from the matrices depends mainly on diffusion through the matrix, swelling of the polymer and erosion of the swollen polymer (9). Diffusional release shows first order kinetics or Fickian kinetics. In the case of Fickian release the release kinetics are therefore proportional to the square root of time, or $t^{1/2}$. With a pure diffusional drug release, *n* in Equation 2 is equal to 0.50 if the swellable device is a thin film. This is however not the case with matrices of other shapes. Previously, it was assumed that only the value of *k* would change with varying geometries of the matrix systems, but Ritger and Peppas showed that not only the *k* changes with different shapes of the formulation, but also the value of *n*. As can be seen from Table 1, in the case of pure diffusional release, *n* may have a value in the range between 0.43 in a spherical system and 0.50 in a thin film (14).

***Table 1**: Diffusional exponent and mechanism of diffusional release from various non-swellable controlled release systems* (14).

Diffusional exponent			Drug release mechanism
Thin Film	Cylindrical sample	Spherical sample	
0.50	0.45	0.43	Fickian diffusion
0.50<*n*<1.00	0.45<*n*<1.00	0.43<*n*<1.00	Anomalous (non-Fickian)
1.0	1.0	1.0	Zero-order release

When the only mechanism of release is non-Fickian, the release rate is independent of time. This means that the value of *n* is 1, and that the drug release is zero order. This fact does not change with any change in the geometry of the system. Normally, the value of *n* lies somewhere in between the limits, as the release mechanism rarely is purely diffusional or purely non-Fickian. However, Ritger and Peppas stated that the aspect ratio of the matrix influences the value of *n* (14), so that it is not always correct to assume that the value should be 0.5 (see Table 1). The aspect ratio is given by the equation $2a/l$, where *2a* represents the diameter of the matrix when the radius is *a*, and *l* is the thickness of the matrix.

Another equation regarding the contributions of Fickian and non-Fickian drug release has been proposed, by the Peppas-Sahlin's equation, which is valid for the first 60% of drug released.

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \qquad \text{Equation 4}$$

In this equation k_1 is the kinetic constant for Fickian contribution of drug release and k_2 is the kinetic constant for Case II contribution, and *m* is the diffusional exponent. *m* is equal to *n* in Equation 2 when the case II mechanism is negligible. As in the example of a thin polymer film, *m* would be 0.50 for a pure diffusional release mechanism and in this situation *2m* would equal 1. Because of the uncertainty concerning the contribution and importance of polymer

relaxation in the drug release from the Dome Matrix, this equation will not be used to estimate *m* in this thesis.

4.4.6 The swelling area number (the Parma number)

Another way of describing the mechanisms of drug release is to apply the swelling area number, S_a (Equation 5).

$$S_a = \frac{1}{D} \cdot \frac{dA}{dt} \qquad \text{Equation 5}$$

In the equation of the swelling area number, *D* represents the drug's diffusion coefficient. It must be stressed that *D* in this case is the diffusion coefficient in a *gel* and not that in water. *DA/dt* represents the change in area within a certain amount of time. The swelling area number is dimensionless and the different values describe the contribution of diverse drug releasing mechanisms:

$S_a >> 1$ indicates diffusional drug release
$S_a = 1$ indicates anomalous drug release
$S_a << 1$ indicates case II drug release

Another important feature of this equation is that it states that drug release is proportional to the releasing area, a part that Ritger and Peppas' equation fails to describe.

4.5 GASTRIC RETENTION

Because the modules can be assembled in such a way that they create a floating device, the subject of floating devices for enhanced gastric retention will also be treated in this thesis. There have been developed several different gastroretentive devices based on various techniques; among others the effervescent floating systems, where excipients such as sodium bicarbonate and citric or tartaric acid develop a gas upon contact with the acidic contents of

the lumen (28). Others are microballoons, hydrodynamically balanced systems, expanding systems, etc.

4.5.1 Advantages and possibilities of gastroretentive systems

The scope of creating a gastroretentive (GR) device is to improve the bioavailability and consequently the therapeutic efficacy of the drug. Firstly, this is achieved by prolonged gastric retention time (GRT), a favorable effect since the gastrointestinal passage time is very variable, from a few minutes to more than 12 hours into the stomach. This provides more time for the drug to be released, so that sustained release devices do not run the risk of going through the passage of the gastrointestinal tract (GIT) too quickly with insufficient amounts of drug being released (29). Secondly, gastroretention may also provide site-specific drug delivery, for example localized treatment of ulcers with prostaglandins. This localized treatment may also decrease systemic side effects and increase the dosage intervals (30). Also, prolonged GRT can provide site-specific drug delivery for drugs that have a greater absorption from the upper GIT than the lower parts of the intestine and colon, an example being the drug furosemide (29). However, it has not been shown that prolonged GRT gives any greater absorption of drugs that already have good absorption qualities along the full length of the GI (31). GR formulations may also be used as formulations for drugs that are acid-soluble or that are unstable and/or have poor solubility in the intestinal environment (32,33).

4.5.2 Limitations of GR systems

Nevertheless, there are also limitations to the floating gastroretentive formulations. The influence of the presence of food in the stomach is decisive for the amount of time that the formulation remains in the lumen. The passage though the stomach in the fasted state is variable, from almost immediate gastric emptying up to 3 hours retention due to the migrating myoelectric cycles (MMC). This cycle involves four phases with different contractional activity. The third phase is also called “the housekeeper wave”, and is the phase with the most intense contractions, completely emptying the gastric content and

sweeping it down the intestine. As a result of this, if a GR device is taken immediately before such a “housekeeper wave” there will be no gastric retention and the scope of the formulation will be lost. However, in the fasted state the MMC is interrupted and the gastric emptying is delayed. Consequently, in the fed state the gastric retention time is more predictable and prolonged, even though there may be great inter- and intrasubject variations (34). Another disadvantage of GR devices is that drugs with high first-pass metabolism might have their bioavailability reduced by increased gastric retention (31). In addition, the buoyancy of the device is dependent of than a sufficient volume of liquid is present in the lumen.

5. EXPERIMENTAL

5.1 EQUIPMENT AND MATERIALS

5.1.1 Equipment

1. Reciprocating tableting machine: Emil Korsch Maschinenfabrik Berlin 9341-72, Germany.
2. ”Mitutoyo”, an advanced caliper.
3. USP 26 Apparatus 2; ERWEKA DT 6 R, Germany.
4. Peristaltic pump: ESAPUMP, Advanced Products srl.
5. UV/VIS spectrophotometer: Jasco V-530
6. Ultrasound apparatus: Branson WPS21
7. Turbulator: WAB Turbula, Type T2A nr.720213

5.1.2 Materials

1. Hydroxypropyl methylcellulose (Premium Methocel® K100M), Colorcon, Orpington, UK (Particle size < 125μm).
2. Buflomedil pyridoxalphosphate (Pirxane®), Lisapharma S.p.A., Erba, CO, Italy (Particle size < 125μm, solubility in water at 37°C: 65g/100ml).
3. Magnesium stearate 24762 Eigenmann & Veronelli S.P.A.
4. Acetone, RPE Carlo Erba Reagenti, Milan, Italy
5. Ethylcellulose, provided by Lisapharma S.p.A., Erba, CO, Italy
6. Eudragit L30, a 30% w/w dispersion of Methacrylic Acid and Ethyl Acrylate Copolymer (1:1).
7. Castor oil (F.U.XI.)
8. Cellulose acetopropionate (CAPr) (Eastman Chemical Company, Kingsport, TN, USA)
9. Titanium dioxide: A.C.E.F. (F.U.XI).
10. Triethylcitrate (Fluka-Chemie GmbH).
11. Methylene blue: A.C.E.F. (F.U.XI).
12. 2-propanol, RPE

6. METHODS

6.1 THE MATRICES

6.1.1 Matrix preparation

The formulation of the matrices studied in this thesis was intended to be as simple as possible, avoiding the use of any excipients, to facilitate the study of drug release without having to consider the effects of other substances than the polymer and the drug. Therefore, it was chosen to use a binary powder mixture for direct compression. The mass of the matrices was kept constant, with only the geometry varying.

When preparing the powder mix for the matrices, the buflomedil pyridoxalphosphate (BPP) powder was previously kneaded in a mortar, and the powder was then sieved with a sieve with a mesh size of ≤125μm. This powder was then mixed with polymer, either hydroxypropyl methylcellulose (HPMC) or ethylcellulose (EC), in a Turbula mixer. The relative ratio of drug and polymer was 60 parts drug to 40 parts polymer. The powder mix was ready for compaction after approximately 15 minutes of mixing. The matrices were made by direct compression in a tableting machine operated by hand. Since there were no other excipients, it was necessary to lubricate the punches frequently using a suspension of magnesium stearate in acetone to prevent the matrices from sticking to the punches. The different polymers and the different shapes of the punches demanded different frequencies of lubrication and cleaning. There were made HPMC matrices of four different geometries: cylindrical dome shaped matrices, cylindrical flat based matrices, cylindrical matrices with one base flat and the other convex and cylindrical matrices with one base flat and the other concave. The diameter of the punches used was 7.4mm. Of the BPP:EC mixture there were only made two kinds of modules, the dome shaped module and the cylindrical flat based module. The compression force for each type of module, having different volume/surface ratios was between 25kN and 35kN. The tablets produced with the higher force appeared to have a brighter yellow color than those produced with a lower compression force. According to

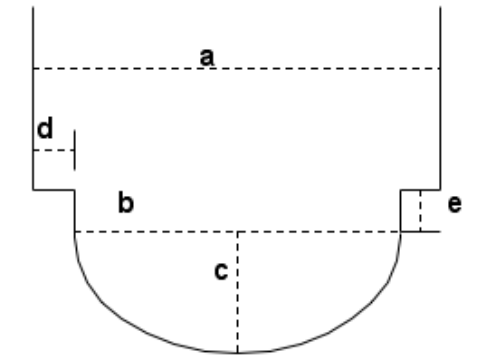
Bettini et. al. (35) the compression force has no influence on the kinetics of matrix swelling, and subsequently it isn't necessary to consider the differences between the pressures used when producing the matrices when performing the dissolution tests. After the compression of the matrices, each matrix was weighed to assure that the weight was within the desired interval, 120mg ± 5mg, and the thickness of the lateral border was measured to guarantee that all the tablets of the same geometry were not significantly different in size.

6.1.2 BPP content of the matrices

For each of the different powder mixes used for the production of the tablets, the content of BPP in the different matrices was determined. This was performed by randomly taking six matrices and kneading them in a mortar. From the powder thus produced, there were taken three samples of approximately 120mg, the average weight of the matrices. Each of these three samples were then dispatched in 500ml of distilled deionized water, which were let to dissolve with agitation at 37°C for at least 2 hours. After the all the powder had dissolved, 3 samples of 5ml each were taken from the solution and individually diluted until 50ml with distilled deionized water. These dilutions were then subjected to measurement of UV absorbance at a wavelength of 282nm with the path length of the cells being 1cm. The absorbance coefficient of Beer's law for BPP had previously been determined to be 11.93L*mol^{-1}*cm^{-1}, and thus using the measured absorbance with Beer's law gives the resultant amount of BPP in the matrices. The stability of BPP in water is high enough that degradation doesn't need to be taken in account when calculating the percentage of BPP in the formulation.

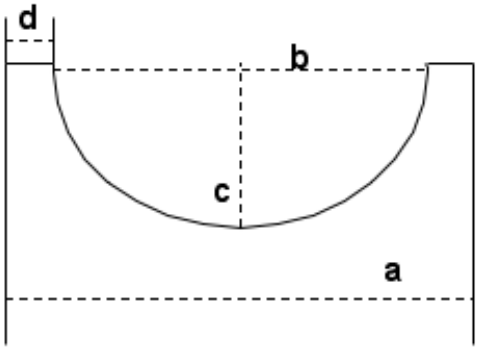
6.1.3 The geometry of the matrices

The modules used in the drug release experiments had as previously mentioned in total 4 different geometries. They were made either with the punches with curved surfaces at the tips, with punches with circular, flat surfaces or a combination of these two sets of punches. The punches have a circular shape in the lateral section and have the dimensions shown in Figure 4.



Upper punch
(Concave face of matrix)

a = 7.46 mm
b = 6.06 mm
c = 1.35 mm
d = 0.70 mm
e = 0.85 mm



Lower punch
(Convex face of matrix)

a = 7.47 mm
b = 6.16mm
c = 1.80 mm
d = 0.645 mm

***Figure 4**: Shape and approximate dimensions of the punches with curved tips.*

The flat punches have a diameter of 7.4 mm and have a flat shape. The four different geometries of the matrices are as follows:

1. The dome module, made with the upper and lower punch having curved tips. The matrix has an axial section that resembles a dome, hence the name Dome Matrix®. The shape is a cylindrical matrix with one base concave and the other base convex.
2. The cylindrical module. This is made with the cylindrical punches having flat tips.
3. The flat/concave module, made with the upper punch having a convex shape, and the lower punch having the flat shape. The shape is a cylindrical matrix with one side concave. The axial section resembles a cup shape, with one base concave and the other base flat.

4. The flat/convex module, made with the upper punch with the flat tip and the lower punch with a concave shape. The matrix has a shape with a convex base and a flat base.

The shapes are shown below in Figures 5 and 6.

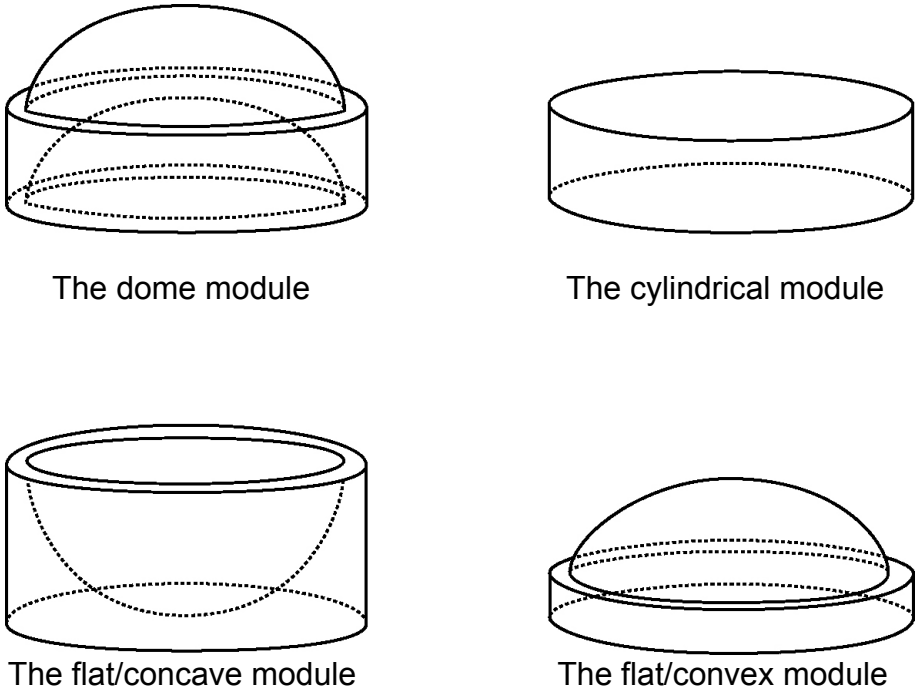


***Figure 5**: The shapes of the different matrices. The dotted lines represent the edges on the inside or on the backside of the matrices.*

***Figure 6a**: The dome module.*

***Figure 6b**: The cylindrical module.*

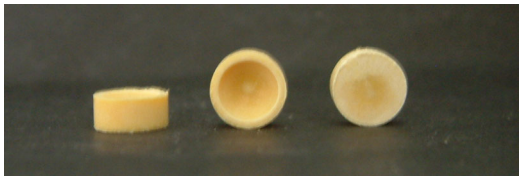


***Figure 6c**: The flat/concave module.*

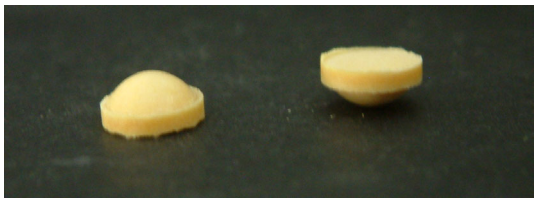


***Figure 6d**: The flat/convex module.*

As can be seen from Figures 5 and 6a, the dome module has the possibility of different ways of assembly. The dome module may be assembled with the convex face of one matrix inserted into the concave face of another matrix, such creating a monolithic structure, which in this thesis is called the stacked configuration. This last type of assembly was applied to 2, 3, 4, 5 or 6 matrices at a time, see Figure 7. In this way it was possible to create structures that would require an excessively large compression force if made with a standard tableting machine.

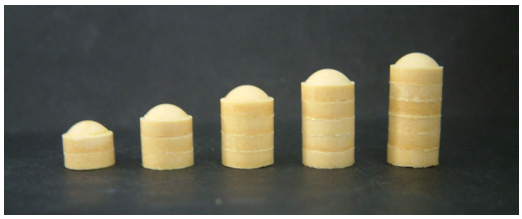


***Figure 7**: The different "stacked" configurations with 2,3,4,5 and 6 modules assembled.*

Also, modules with different drug and excipient compositions could be assembled into these structures giving rise to dosage forms with a heterogeneous distribution of drug(s) and/or polymer(s), which would be difficult using normal direct compression as method of production.

The second conformation created by dome module assembly that was tested was the configuration as seen in Figures 8 and 9, where there is a void inside the final structure by assembling two dome shaped matrices with their concave bases facing each other. This void will create a density of the dosage form that is lower than that of water, and hence floats. This can for example be utilized to create a gastroretentive dosage form of the polymer matrix, or as a press-on coating for other formulations.

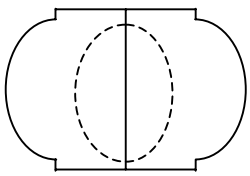


***Figure 8**: The void conformation.*

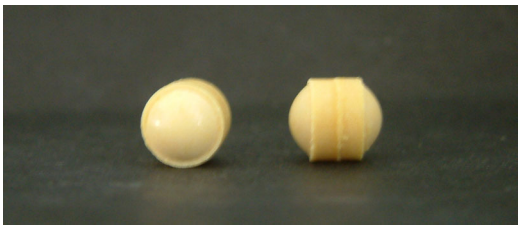


***Figure 9**: The "void" configuration, seen from two diverse angles.*

6.1.4 The dimensions of the matrices

The dimensions of the different surfaces of the matrices were measured using a precision caliper. The different modules used in the experiments were measured, and the average measurements of the different surfaces were then used to calculate the surface area of the matrices. The weights of the matrices were kept the same for all the different geometries of the matrices. For example the flat/concave and the flat/convex matrices have a quite significant difference in surface area. We decided that the matrix mass should be the same for all the matrices to facilitate the comparison between different release curves. The compression force was kept between 25kN and 35kN to obtain satisfactory crushing strengths for all the different modules.

The different dimensions have the characterizations shown in Figures 10, 11, 12 and 13, and these will be referred to in Table 2 and 3:

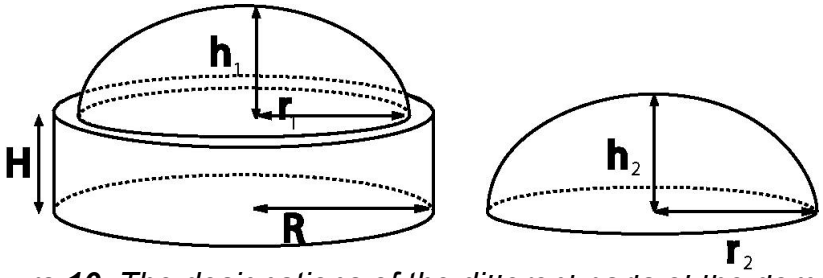


***Figure 10**: The designations of the different parts of the dome matrix. The figure with the dotted lines represents the inside of the dome module, for practical reasons.*

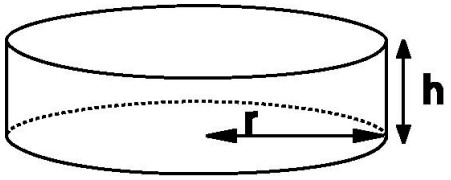


***Figure 11**: The designations of the different parts of the cylindrical modules.*

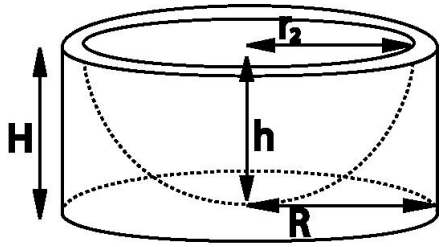


***Figure 12**: The designations of the different parts of the flat/concave modules.*

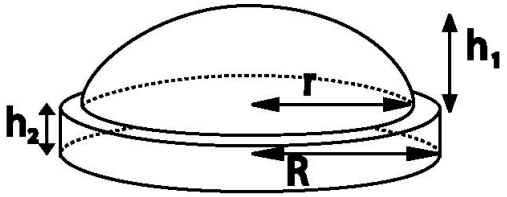


***Figure 13**: The designations of the different parts of the flat/convex modules.*

***Table 2**: The average dimensions and areas of the manufactured BPP-HPMC modules.*

SURFACE	FORMULA	DOME	CYLINDIC	FLAT/ CONCAVE	FLAT/ CONVEX
Convex	$A = \pi\left(r^2 + h^2\right)$	h_1=2.1 r_1=3.2 A=45.2	-	-	h_1=1.9 r=3.2 A=42.9
Shelf border	$A = \pi\left(R^2 - r^2\right)$	R=3.7 r_1=3.2 A=12.8	-	-	R=3.8 r=3.2 A=13.3
Lateral	$A = H * 2\pi R$	H=2.4 R=3.7 A=56.6	h=2.2 r=3.7 A=51.8	H=3.3 R=3.8 A=77.7	h_2=1.4 R=3.8 A=33.4
Concave	$A = \pi\left(R^2 + h^2\right)$	h_2=2.2 r_2=3.0 A=43.6	-	h=2.3 r_2=3.0 A=44.1	-
Base border	$A = \pi\left(R^2 - r^2\right)$	R=3.7 r_2=3.0 A=16.1	-	R=3.8 r_2=3.0 A=16.8	-
Flat face	$A = \pi R^2$	-	r=3.7 A=43.3	R=3.8 A=44.4	R=3.8 A=44.4
Sum mm^2	$\sum A$	174.3	138.5	182.9	134.0
Sum cm^2		1.74	1.39	1.83	1.34

Where not indicated, the numbers are given in the dimension of millimeters.

***Table 3**: The average dimensions and areas of the manufactured BPP-EC modules.*

SURFACE	FORMULA	DOME	CYLINDIC
Convex	$A = \pi\left(r^2 + h^2\right)$	h_1=1.9 r_1=3.2 A=43.1	-
Shelf border	$A = \pi\left(R^2 - r^2\right)$	R=3.8 r_1=3.2 A=12.7	-
Lateral	$A = H * 2\pi R$	H=2.4 R=3.8 A=57.5	h=2.3 r=3.7 A=54.0
Concave	$A = \pi\left(R^2 + h^2\right)$	h_2=2.2 r_2=3.0 A=43.0	-
Base border	$A = \pi\left(R^2 - r^2\right)$	R=3.8 r_2=3.0 A=16.4	-
Flat face	$A = \pi R^2$	-	r=3.7 A=43.8
Sum mm^2	$\sum A$	172.8	141.6
Sum cm^2		1.73	1.42

Where not indicated, the numbers are given in the dimension of millimeters.

6.1.5 The coating of the matrices

In the previous work done by Sandaker (16), the drug release from partially coated matrices was studied. To achieve this, a solution that would create an impermeable film upon drying was produced by mixing 7.5 g of CAPr, 1.05 g of castor oil (1.1 ml), 1.48 g of triethylcitrate (1.3 ml), 0.01 g of methylene blue, 4.5 g 2 -propanol (6.2 ml) and 15.7 g acetone (20 ml). A sufficient volume of this liquid was then applied to the base surfaces or the base and lateral surfaces and left to dry at room temperature. Methylene blue was added to ease the visual control of the position of and complete coverage by the film (Figure 14).

***Figure 14**: Example of partially coated matrices.*

In this thesis we wished to examine further the swelling and release rates of the matrices, and so the coating was repeated as described above.

6.2 THE ASSEMBLY OF THE DOME MODULES

6.2.1 Assembly with ultrasound

A new method for assembly of two or more matrices with the application of ultrasound (US) waves was developed using a Branson ultrasound machine. This method consisted of stacking the matrices in the desired conformation and then placing them in a cylindrical die made especially for every conformation under a custom-made ultrasonic probe made from titanium. The sonotrode emitted ultrasonic waves at desired frequency, time and energy. The matrices would then attach to each other. The parameters used for assembly of the matrices were an energy of 15-30J, duration of application of US 0.55 seconds.

***Figure 15**: The Branson ultrasound machine.*

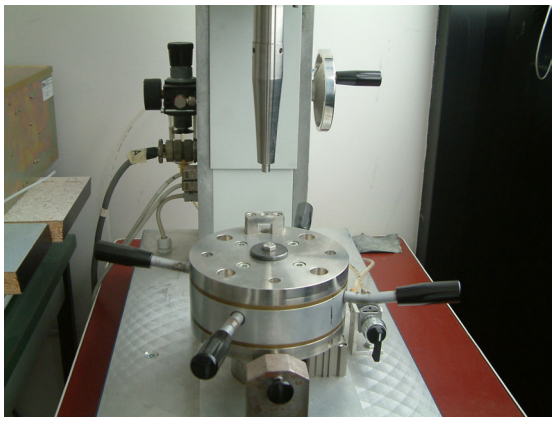


***Figure 16**: Detail of the ultrasound machine, the sonotrode and the die for the matrices.*

Assembly was only performed with the BPP-HPMC dome modules. The surface area of the configurations produced by the ultrasound assembly is shown beneath in Table 4, and their surface area:volume ratios in Table 5.

***Table 4**: The surface area of the assembled HPMC modules.*

CONFIGURATION/ SURFACE	2 modules stacked	3 modules stacked	4 modules stacked	5 modules stacked	6 modules stacked	Void
Concave base	59.7	59.7	59.7	59.7	59.7	-
Convex base	58.0	58.0	58.0	58.0	58.0	58.0 x2
Lateral	56.2	56.2	56.2	56.2	56.2	56.2
Sum area (mm^2)	230.2	286.5	342.7	398.9	455.2	228.5
Sum area (cm^2)	2.30	2.87	3.43	3.99	4.55	2.29

Where not indicated, the numbers are given in the dimension of millimeters, the areas are derived from table 2.

***Table 5**: The volumes and the surface area:volume ratios of the single dome and the assembled configurations.*

CONFIG-URATION	1 single dome	2 modules stacked	3 modules stacked	4 modules stacked	5 modules stacked	6 modules stacked	Void
Volume (cm^3)	0.10	0.21	0.31	0.41	0.52	0.62	0.21*
Surface area: volume ratio	17.40	10.95	9.25	8.37	7.67	7.33	10.90

* This does not include the volume of the void inside the assembled configuration.
The areas are taken from table 4,

6.3 THE DRUG RELEASE EXPERIMENTS

The drug release experiments were performed using an USP apparatus II (see Figure 17), paddle speed being 75 rotations per minute and the temperature 37°C. The release medium was distilled, degassed water. The volume of water used was either 500ml or 1000ml. Since the solubility of BPP was very good the perfect sink conditions were maintained though the whole drug release experiments, and thus the experiments were not influenced by the volumes of water that were used. During the dissolutions the perfect sink conditions were maintained. The wavelength used to measure the absorbance and the amount of drug released was 282nm. The cell path length was 1mm. Measurements were performed at fixed time intervals, controlled by computer programs. The time length of the intervals between every measurement was adjusted after which polymer that was used. For the EC modules, the measurements were first made every 3 minutes for 51 minutes and then every 15 minutes. For the HPMC modules, the measurements were made every 15 minutes for 2 hours, and thereafter every hour. All the dissolutions were continued until the increase in UV absorbance had stagnated, a sign of completed drug release.

***Figure 17**: The computer, spectrophotometer, pump and paddle apparatus used during the dissolution.*

6.4 MATHEMATICAL TREATMENT OF THE RELEASE DATA

6.4.1 Finding the drug fraction released

After obtaining the values of absorption from the dissolutions, the absorbance of the blank, that is the absorbance of the dissolution medium, was subtracted from the absorbance measured at different times. The resulting value was then applied in Beer's law (Equation 6) as the absorbance, *A*.

$$A = a \cdot b \cdot c \qquad \text{Equation 6}$$

In this equation *a* represents the absorbance coefficient of BPP, previously determined experimentally (value 11.93). *b* is the path length of the cells (0.1cm). *c* is the concentration of drug in the solution under examination. By knowing the volume of the dissolution medium in which the matrix has been introduced it was possible to find the mass of drug that has been released. This was then divided by the total amount of drug originally contained by the matrix in order to calculate the fraction released.

$$\text{Fraction released} = \frac{m}{m_\infty} = \frac{V}{m_\infty} \cdot \frac{A}{a \cdot b} \qquad \text{Equation 7}$$

6.4.2 Finding *n*

To find the diffusional constant *n*, the first 60% of the drug released is plotted versus time using a mathematical computer program, Kaleidagraph (Synergy Software, Reading, USA). Then, a power equation of the type $y = a \cdot x^n$ was fitted to the data. The program calculated the values of the two coefficients of the Ritger-Peppas equation (Equation 2). Finally, the computer adjusts the coefficients to match the data at an error of not more than 0.05%, and the value of *n* was found.

6.4.3 Finding the release rate

The experimental release rate was easily found by taking the derivative of the curve fitted to fraction released vs. time and then multiplying the resultant values with the total amount of drug originally contained by the matrix.

6.5 AREA OF THE MATRICES DURING THE SWELLING PROCESS

As the matrices were introduced into the drug release medium, it was imbibed into the matrix. This caused the polymer to swell and the volume of the system to increase. HPMC swells faster than it dissolves, and as a consequence of this the surface area of the matrices also increased. The swelling and enlargement of the matrix developed over time. As the matrices reached a gel-like consistency, direct measurements of the magnitudes of the different sides were difficult without changing the three-dimensional shape of the matrices.

The partially coated matrices (see section 6.1.5) were attached to a glass plate (with the coated base down facing the plate) and introduced into the vessel holding the drug release medium. The glass plate enabled the removal of the matrix from the vessel during the drug release experiment without deforming the geometric shape. The matrix removed from the vessel was then placed next to a ruler and a photo was taken with a digital camera. This was repeated with regular intervals of time for all the different matrices, that is, until ~80% of the drug was released from the matrices. The matrices were returned in the dissolution medium as quickly as possible to interfere as little as possible with the normal swelling of the modules. The drug release was recorded during the whole dissolution period as a means to ensure that the swelling of the matrices was no different than the normal release during dissolution under the same circumstances. These release data were however not used for further calculations due to the disturbance in the experiment. Then a computer program (Image J, USA) was applied, which enabled us to find the real size of the objects in the photos. Then the outlines of half of the swollen matrices were

traced using the computer program, creating a two-dimensional outline of the matrices (see Figure 18).

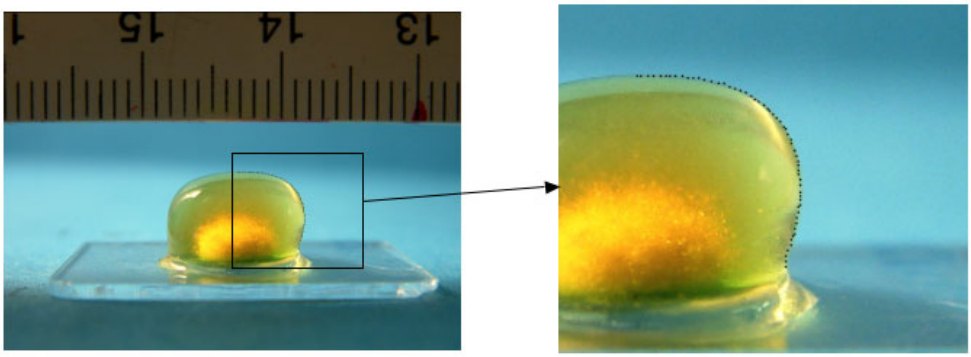


***Figure 18**: Example of photo taken of a cylindrical matrix after 300 minutes, with tracing of the outline on the right hand side.*

The points that were created during the tracing process are coordinates later used to calculate the surface area of the swollen matrices by then applying an integral formula, as shown in Equation 8:

$$A_x = \int_a^b |f(x)| \sqrt{1 + [f'(x)]^2}\, dx \qquad \text{Equation 8}$$

In this manner an approximate number for the magnitude of the three-dimensional surface of the swollen matrices could be found. The method was validated by taking a photo of a sphere of known size and applying the method to calculate the surface of the sphere. The area was calculated with an error of 9.6%.

7. RESULTS

7.1 THE DISSOLUTION EXPERIMENTS

7.1.1 Visual observations

In addition to the UV measurements, there were also made visual observations of the matrix behaviour. In general, the BPP-HPMC modules, both single and assembled first remained at the bottom of the drug release medium, and after 120-240 minutes they started to float. This does of course not include the floating devices, which remained buoyant during all of the dissolution tests. During the dissolution experiments of the flat/concave a hole was seen in the base of the tablet.

7.1.2 The single BPP-HPMC matrices

The dissolutions performed with single BPP-HPMC matrices gave the results displayed in Figure 19 and showed that there was a slight but varying difference between the release patterns of the four different shapes. That is, the dome, the flat/concave, the flat/convex and the cylindrical matrices. The slowest release pattern is the one of the flat/convex matrices. Due to these matrices' different areas of release (see Table 2 in section 6.1.4) this result makes sense, as a larger initial area of release gives a faster release of the drug. However, the fraction released does not give any information on the relative contribution of the different mechanisms of drug release from the swollen matrix. The Ritger-Peppas equation was applied to study the effects of matrix geometry on the drug release mechanisms.

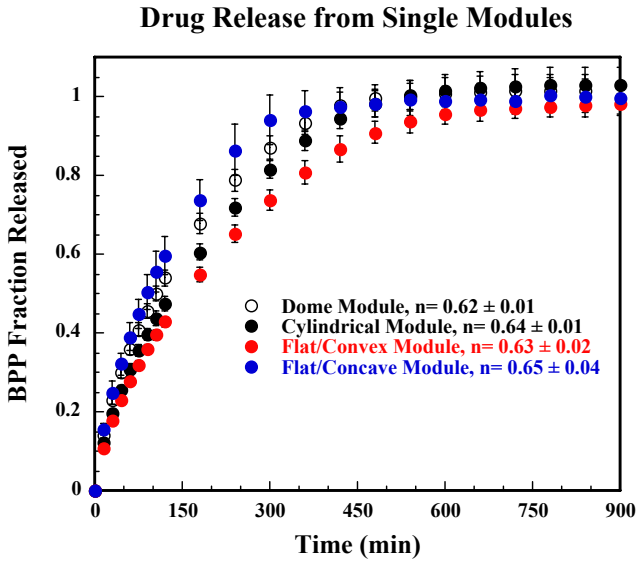


***Figure 19**: Drug release from the single swellable units and the respective diffusional values of n for the first 60% released.*

The different shapes produce different paths of drug diffusion. In fact, the distances for the drug to diffuse in order for the drug to be released were of different length depending on the matrix geometry. For example the diffusion path in the flat/concave modules was quite small, since the walls of the matrix were quite thin, and drug was in this was released faster. This fact contributes to differences in release rates, as seen below in Figure 20. The flat/convex matrix has, even though the size of the initial releasing area is close to the one of the cylindrical matrix, the lowest release rate of the modules. The difference between the release rates was not very great.

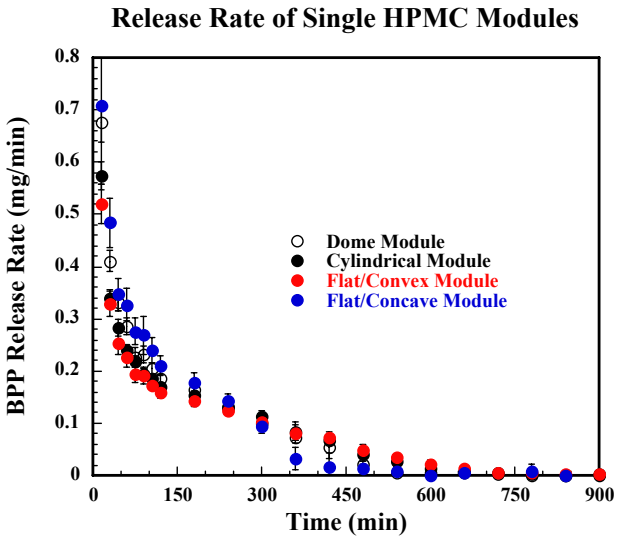


***Figure 20**: Release rates from the single matrices.*

7.1.3 The single BPP-EC matrices

As EC is an inert polymer, there was no swelling present during the release of drug from the matrices. Drug release should therefore depend solely on diffusion. After about 175 minutes the total amount of drug in the matrices was released, as shown in Figure 21. It can also be seen that drug was released faster from the dome module. It appears also as if that the release rate from the cylindrical module was quite constant between about 40 and140 minutes, as the shape of the curve is almost linear.

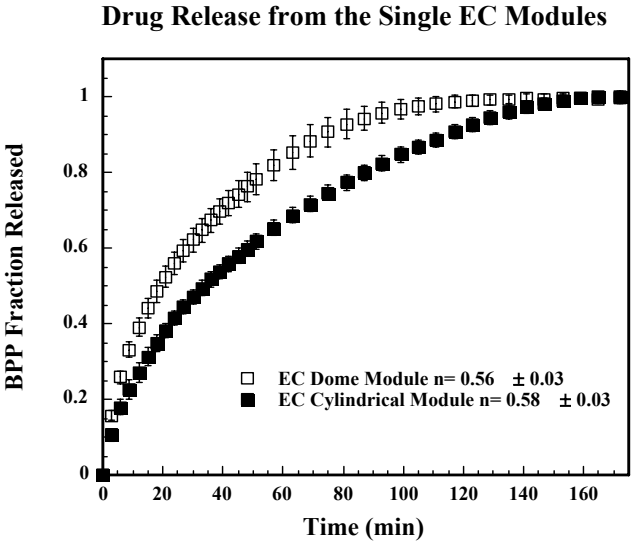


***Figure 21**: Fraction released from BPP-EC matrices.*

The release rate from the BPP-EC matrices is shown in Figure 22. The dome module had an initially higher release rate than the cylindrical module. After about 60 minutes this changed, and it was the cylindrical module that had a higher release rate. The release rate between 40 and 140 minutes was less constant, as first appearances of Figure 21 might imply, but had a slow decrease during all this period of time.

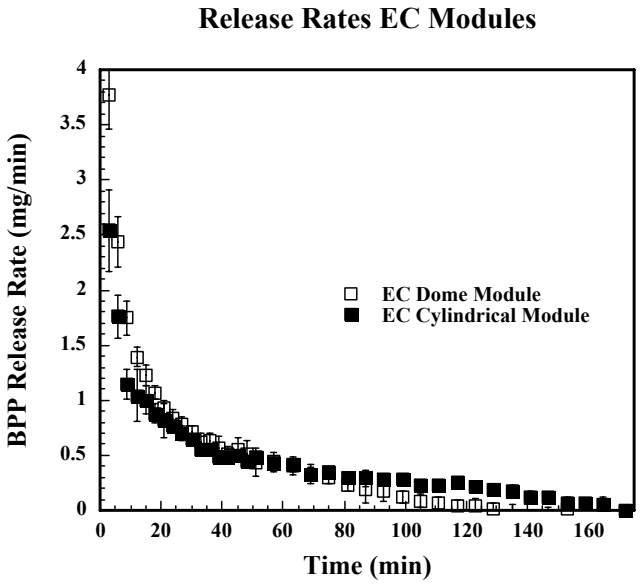


***Figure 22**: The release rates of the BPP-EC matrices .*

7.1.4 The stacked configurations

The matrices that were assembled in the stacked configuration showed a release pattern as shown in Figure 23.

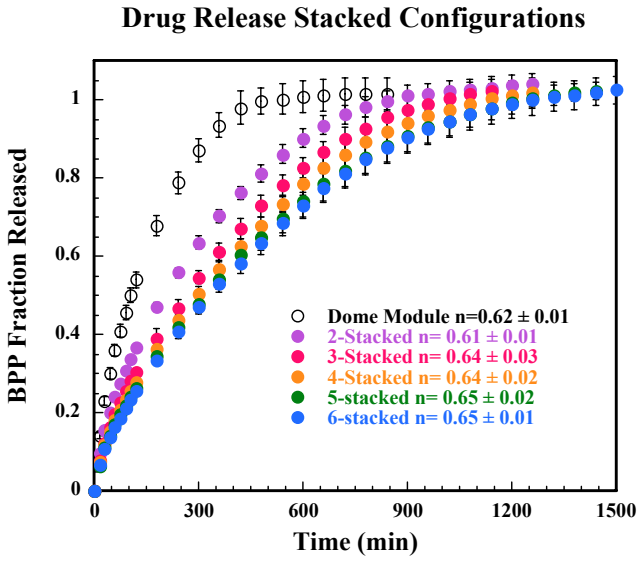


***Figure 23**: Fraction released vs. time for the single dome and the stacked configurations with the n values for the first 60% of drug released.*

As can be seen, the fractions released from the stacked modules fanned out with 2 stacked modules having the higher fractional drug release all times of the dissolution, then followed in order of decreasing fractional drug release 3, 4, 5 and 6 stacked modules. All the stacked modules had a more prolonged release than a single dome module. The diffusional values *n* were not very different

from the diffusional constants of the single dome modules. The release rates of the stacked configurations are presented in Figure 24.

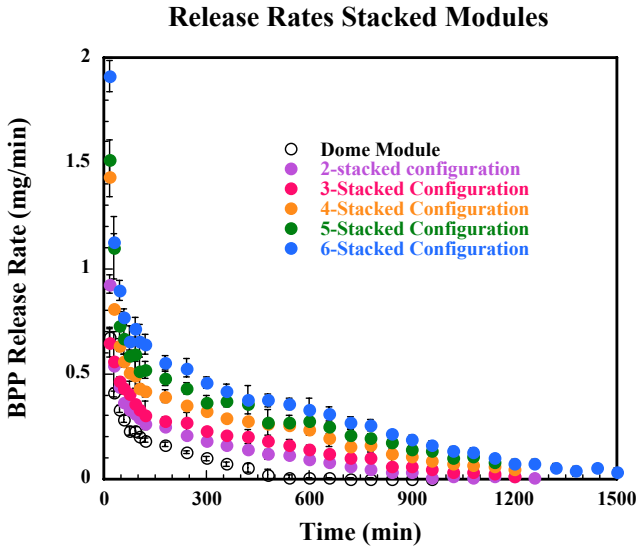


***Figure 24**: Release rates of the stacked configurations.*

It is clear that the release rate of the configuration with 6-stacked modules was the highest, followed in decreasing order by 5-, 4-, 3- and 2- stacked modules. The kinetics of release are however similar, as the paths of the curves show.

7.1.5 The void configuration

The result from the dissolution of the modules assembled in the void configuration is here shown together with the release patterns of a single module and the 2-stacked configuration. Only the results of the void matrices that stayed completely attached during the whole dissolution test were considered, even though the ones that disassembled kept their buoyancy during the whole experiment. Figure 25 shows that the drug release was very similar to that of the 2-stacked configuration.

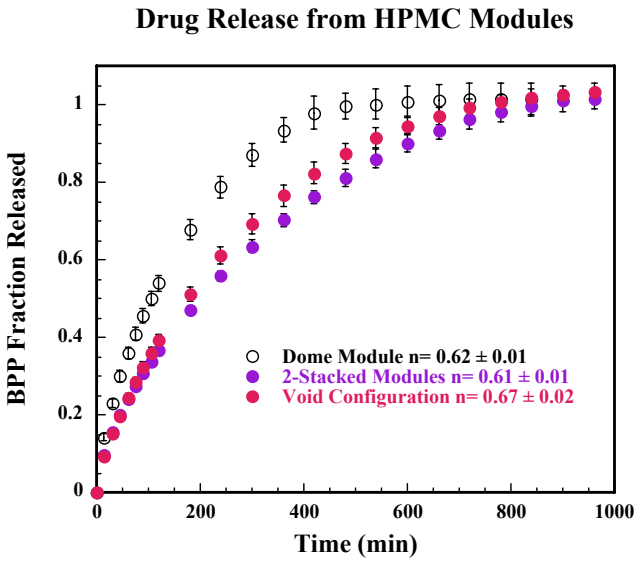


***Figure 25**: Release from dome, 2-stacked and void Modules and their respective n-values for the first 60% of drug released.*

Figure 26 shows the release rates from the void configuration compared with the release rate from the single dome module and the 2-stacked. It is clear that the void configuration had a release rate very close to the 2-stacked matrices.

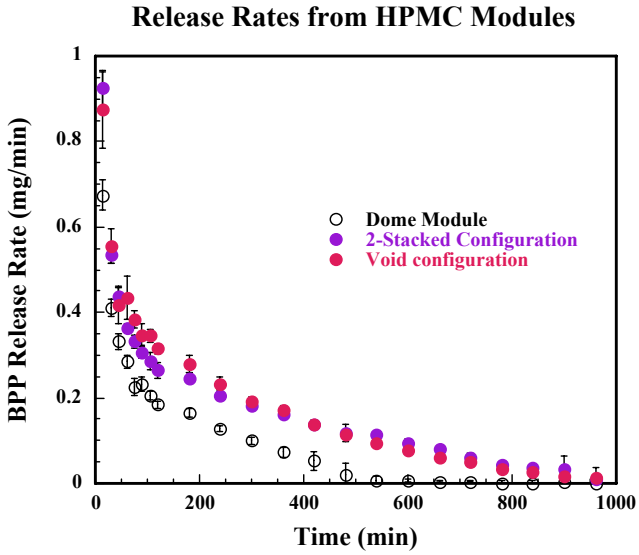


***Figure 26**: Release rates of dome, 2-stacked and void configurations.*

7.2 THE MEASUREMENT OF THE SWOLLEN SURFACES

The photos taken of the swollen matrices gave the sizes of the surface areas after the respective times shown in Tables 6 and 7:

***Table 6**: The area of swelling base surfaces vs. time.*

Surface / Time	Convex	Concave	Flat
60 minutes	103.9±2.3 mm^2	75.1±2.5 mm^2	82.0±1.7 mm^2
120 minutes	135.0±1.2 mm^2	99.1±3.2 mm^2	99.1±2.5 mm^2
180 minutes	170.4±8.3 mm^2	103.0±2.0 mm^2	121.3±3.7 mm^2
240 minutes	179.8±5.0 mm^2	105.7±2.7 mm^2	131.1±6.6 mm^2
300 minutes	174.0±3.5 mm^2	109.0±0.8 mm^2	146.5±2.1 mm^2
360 minutes	196.7±3.3 mm^2	115.6±5.6 mm^2	175.8±4.6 mm^2
420 minutes	206.6±1.3 mm^2	106.5±2.7 mm^2	164.5±5.0 mm^2

***Table 7**: The area of swelling base- and lateral surfaces vs. time.*

Surface / Time	Convex and lateral	Concave and lateral	Flat and lateral
60 minutes	163.8±6.5 mm^2	180.2±6.5 mm^2	167.7±18.2 mm^2
120 minutes	194.5±8.5 mm^2	209.5±8.5 mm^2	182.0±3.6 mm^2
180 minutes	232.0±3.5 mm^2	207.0±6.2 mm^2	197.7±10.0 mm^2
300 minutes	231.7±6.2 mm^2	255.6±4.0 mm^2	210.5±1.3 mm^2
360 minutes	252.3±7.5 mm^2	255.4±6.4 mm^2	216.8±7.6 mm^2

A better way to illustrate the increase in area vs. time is by using graphics (see Figure 27 and 28):

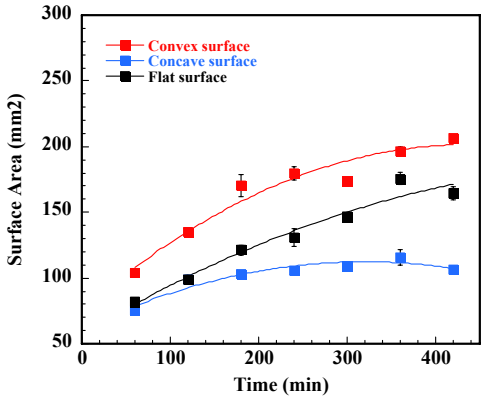


***Figure 27**: The increase of the area of the swelling of partially coated matrices with only one base free for swelling plotted against time.*

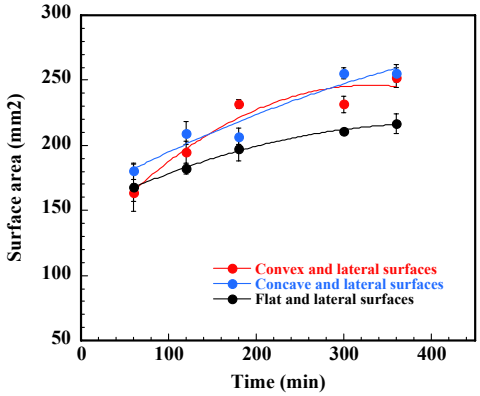


***Figure 28**: The increase of the area of the swelling of partially coated matrices with one base and the lateral surface free for swelling plotted against time.*

As can be seen, the surface area of all the matrices increased as the dissolution test progressed. For the matrices where one base and the lateral surface that were coated with an impermeable film (single base surfaces concave, convex and flat free for swelling), the largest surface area was exhibited by the convex module. The concave module had the smallest surface area. For the measurements performed on matrices having only one surface coated (one base and the lateral surface free to swell), the surface area was not so differentiated, but the matrices with one flat base and lateral surface showed the smallest surface area. However, the pattern of surface increase was not easy to describe with a simple equation, as the results show no clear sequential order except that of gradual increase; they can at best be described with polynomial equations of the second degree.

8. SOURCES OF ERROR

8.1 THE MAKING OF THE TABLETS

The measurements of drug release were performed by the use of an UV-apparatus. Since it was the amount of drug released that was measured in this manner, it was important that the stability of BPP was sufficient during the tablet production. BPP is a colored substance, and as other colored substances it is prone to be sensitive to degradation by light. To avoid this type of degradation, the compresses used were never older than six months and were kept protected from light except from during the experiments. By treating the matrices in this way it is unlikely that this is a source of great error.

The aspect of weighing, sieving and mixing the drug and the polymer in the tablets is dependent of the operator, and the risk of human mistakes was definitely present. In addition BPP exhibited electrostatic properties, and might have complicated the weighing and the mixing of the powders.

8.2 THE DISSOLUTION EXPERIMENTS

The stability of BPP could also cause erroneous measurements during the dissolution, as the drug would be exposed to light up to 27 hours. However, there was no clear tendency of the measurements made over such a period of time to imply that the experiments were affected by this.

The calculation of the surface area of the dry matrices was done with the caliper by hand. This means that the measurements were dependent not only on the precision of the instrument (precision= 0.01mm), but also on the operator. To avoid this the measurements were carried out by two persons. The results should therefore not be a major source of error.

Different pressures were probably used during the production of the tablets, as there were slight differences in the color of the matrices. This could depend on

the operator of the tableting machine, but also on the weight of the tablet in production. However, as mentioned earlier, since the tableting force and hence the porosity of the matrices are not of importance for drug release rate (35).

The volume of the dissolution medium might have varied some, as the temperature made the water evaporate and during the experiments there were observed droplets of water hanging under the lids of the vessels. In addition there were gaps in the lids where the vapor could diffuse out. Nevertheless, it is not probable that the loss of volume would be large enough to contribute to significant error.

The spectrophotometer sometimes showed instable measurements, and to avoid this to contribute to the errors, a blank sample was always run in parallel to the matrix samples. This way it was easier to find if the variances were caused by the spectrophotometer or actual fluctuations in the drug release, and variances caused by the UV-spectrophotometer could be adjusted. Nonetheless, this could be a rather large contribution to errors.

8.3 THE MODULE ASSEMBLY

As the modules were assembled with ultrasound one could observe a small particulate cloud that originated from the matrices. However, the assembled matrices were weighed after assembly and so the data used in the calculations are accurate.

There was not done any measurements or examinations to learn if the US treatment caused any changes in the matrices, for example drug breakdown or alteration of polymer structure. This may also be a cause of error, but as the dissolution results were considered “normal”, it is unlikely that this has great contribution to the sum of errors. However, this should have been examined, but lack of time limited these investigations.

The data from each assembly that was made were not recorded. They could have given more information of the process of assembly, but this is not a direct error source.

8.4 THE SWOLLEN AREA MEASUREMENTS

The method of measuring the surface of the matrices as they were swelling is still at an experimental level, and has many sources of error. There is for the moment the need to coat the matrix surfaces, so that the swelling does not occur in the manner that it would in a matrix with non-restricted swelling.
In addition, the matrix had to be attached to a glass plate in order to remove it from the dissolution medium. This glass plate plus the adhesive used might have changed the diffusion- and swelling pattern.

The matrices had to be removed from their vessels to be photographed, which means that the matrices were out of the dissolution medium for some time, and this clearly would affect swelling.

As the photos were taken, there was difficulty in placing the matrices in the exact same position every time. This would mean that they could be placed in various positions relative to the ruler used to set the scale of the photo, and the measurements of each photo would thus vary.

For the flat/concave matrices, it was not possible to calculate the surface area, because the concave part of the matrix would not appear on the photos as they taken from the lateral side showed a section of the matrix. There was no other angle that made possible the description of the flat/concave three-dimensional shape. This contributes to a large uncertainty of the area measurements made of the flat/concave modules.

9. DISCUSSION

9.1 THE DISSOLUTION EXPERIMENTS

9.1.1 Discussion of the single BPP-HPMC matrices

The different shapes of the matrices produce different paths of diffusion that give rise to differences in release rates. It is not unexpected that the drug release patterns of all the different types of matrices are slightly different, bearing in mind their diversity in geometry. Considering the initial releasing area of the matrices and assuming that the relative differences between the module's areas is sustained during the whole dissolution experiment, Figure 19 clearly shows that the modules with the larger releasing area, the flat/concave module, has the fastest fractional drug release compared to the others. Also, the hole that formed in the base of this module during dissolution contributed to the surface area of the module becoming even larger. Then in descending order of releasing area and release rate follows the dome module, the cylindrical module and at last with the slowest drug release the flat/convex module. The difference in initial surface area of the cylindrical and the flat/convex modules is rather small in comparison to the other modules, but still the release of drug from the flat/convex is significantly different from the cylindrical module. The divergence of release pattern may be explained by the longer diffusional distance for the drug molecules inside the flat/convex module compared to the cylindrical one. Also, the module with the fastest drug release is the one where the drug has a short diffusion path inside the matrix.

Hence, the modules with the larger initial area of release have the highest initial fractional drug release. The release rate found experimentally seems to indicate a shift in the release rates in the direction of higher release rate values in the modules that had the smaller initial area of release between 350-400 minutes. This is probably because the matrices with the preliminary slower release rates at this moment have a higher concentration of drug in the matrix, and so the

diffusion gradient ensures that the release rate doesn't slow down as quickly as for the other modules.

The diffusional exponents *n* of the diverse modules have slightly varying values, but they are not significantly different. This shows that the mechanisms of drug release are approximately the same for all the different geometries. In other words the equilibrium between the diffusional release and non-Fickian release is approximately equal between the different types of modules. The value *n* can't be directly applied since the aspect ratios of the different modules vary throughout their structures. Nonetheless, it can be said that there is considerable contribution of non-Fickian drug release mechanisms as the values were between 0.62 and 0.65.

As for the industrial aspect of producing the modules, the formulation of the matrices needs adjustments if there should be an upscaling of the module fabrication. So far the matrices have been made one by one using a hand-driven tableting machine, with the need for lubricating the punches for every two or three tablets produced. The powder mixture will at least need the addition of glidants and lubricants. A change in formulation will also require new tests of the matrices' properties.

9.1.2 Discussion of the single EC matrices

The drug release from the EC modules shows the same tendency as the release from the single HPMC modules, where the module with the larger releasing area, the dome module, has a faster release of drug. In this case the matrices do not swell and we can assume that the surface area of the matrices remains the same throughout the whole dissolution.

Even though the only mechanism of release from the EC modules should be diffusion, the value of *n* has the value 0.56 ± 0.03 for the dome shaped modules and 0.58 ± 0.03 for the cylindrical modules. The aspect ratio of the cylindrical matrices, found by dividing the diameter with the thickness, is 3.34 and should therefore have a value of about 0.45 according to Ritger and Peppas (14). A

probable reason for the elevated value of *n* might be that there was observed a disintegration of the tablets during the dissolution tests, in this manner erosion of the polymer matrix might contribute to these elevated values. Even though only the data of the tablets that didn't disintegrate in any degree possible to observe with the naked eye were used, it is very likely that there was a slight disintegration or dissolution of the polymer. This in turn will have affected the dissolution of the drug.

9.1.3 Comparison of release from BPP-EC matrices and BPP-HPMC matrices

The dissolutions with the BPP-EC matrices were carried out in order to compare the drug release from swellable matrices to matrices that contained a non-swellable polymer. Even though there is another release mechanism for the EC modules other than just diffusion, the values were used to show the significant difference in *n* values between a non-swellable and a swellable polymer matrix. It is also quite obvious from Figure 29 that the swelling of the HPMC has a great influence on the drug release. The time required for release the total amount of drug in the HPMC matrix is more than twice as long as for the EC matrix.

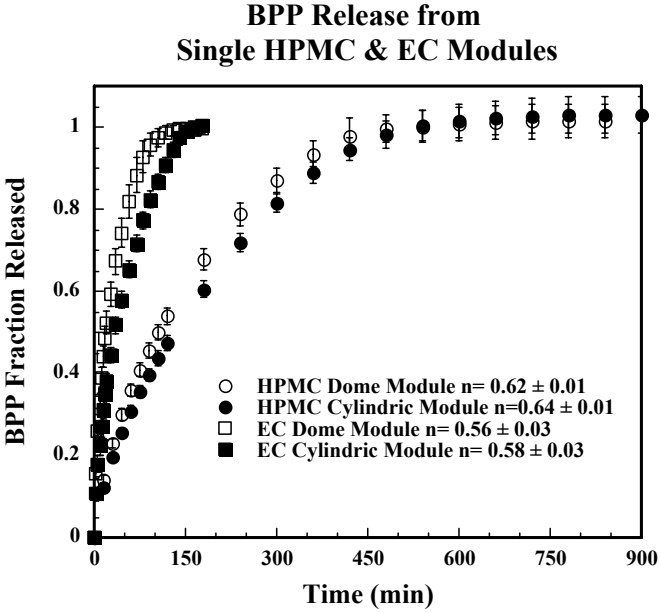


***Figure 29**: BPP release from matrices made from EC and HPMC and the respective n-values for the first 60% of drug released.*

Although in this case it is probable that other mechanisms such as erosion of EC might contribute to increase the value of the diffusional constant *n*, the value of *n* is significantly different ($P < 0.05$) for the two different polymer matrices, this confirms what Ritger and Peppas described (14), that the value of *n* increases with increasing contribution of non-Fickian drug release, a phenomenon typical of swellable matrices.

If another non-swellable polymer had been used instead of the EC, where the problems of erosion might have been avoided, one might have seen an even greater difference between the HPMC and the non-swelling polymer.

9.1.4 Discussion of the stacked modules

It is obvious that when the dome modules are assembled, the ratio of releasing area to drug mass of the releasing device will be different than the area:drug mass ratio of the single matrices. As a consequence the release of drug is also changed. It would obviously not give the same effect to use a certain number of single modules instead of one of the corresponding stacked configurations, since the release from single modules will not be dependent of the number of matrices as long as perfect sink conditions can be sustained. The diffusional exponents *n* of the stacked matrices were not very different from the diffusional constants of the single matrices. The shape, or surface area has little influence on the mechanism of release from the BPP-HPMC formulation that we have used. However, the *n* of the single modules or modules in the 2-stacked configuration was significantly different from the *n* of the 6-stacked configuration.

The differences in the kinetics when the release rate is normalized to the mass of drug, that is the derivate of the fraction released vs. time, are of such a small dimensions that they are negligible. The release rate is mostly dependent of the drug mass as the number of modules in the device increases, because the change in ratio between releasing area and drug mass does not decrease too much. Only for the 2- and 3- stacked ratios, the difference in release area is notable, and this explains the diminishing difference between the matrices of

different conformation. As more modules are added the change in releasing area vs. drug mass simply declines and would finally give a convergence of the fraction released vs. time.

The derivative of the curves of release rate is plotted against time for all the different stacked configurations in Figure 30, and since the curves in Figure 30 completely superposition each other it is clear that the difference in release rates from the differently stacked modules is mostly dependent on the drug mass in the matrix.

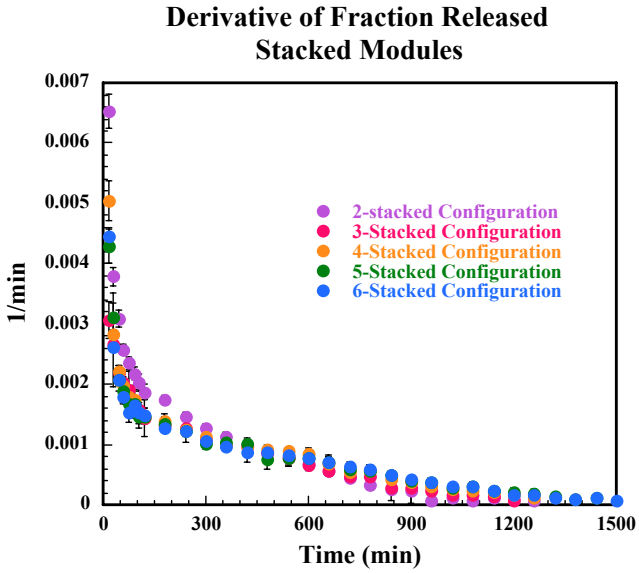


***Figure 30**: Derivative of fraction released stacked configuration.*

The thought of changing the drug release from matrices without changing the formulation, but only by assembling them is interesting and there is yet to be seen how the release from devices constructed by modules of varying contents will be. Different polymers in the different modules might bring about an enhancement or delay in drug release, and different concentrations of drug the same. Also the presence of another drug might give unforeseen effects on the drug release from the matrices.

9.1.5 Discussion of the void configuration

The drug release from the void modules is nearly equal to that of the 2-stacked configuration. This is not very surprising, as they have approximately the same releasing area. The significance of this is that there will be little or no difference in the drug release from a floating configuration and a drug delivery device made without creating buoyancy when dissolution otherwise is carried out under the same conditions. Hence, no particular considerations need to be taken to the drug or excipients when manufacturing tablets of the void configuration compared to when making oral formulations, as long as the final assembled module has a density that is less than that of the dissolution medium.

Another possible way to use the void configuration other than as a floating device is to fill the void inside the assembled polymer matrices with a tablet or powder that contains the same or a different drug. In this way, it is possible to release the drug in the outer part first followed by the release of the drug in the inner part. This could in addition be an alternative to spray-coating with HPMC, which does not only require the use of organic solvents, but also is time-consuming. One example of a possible use of the void is as a colonic release device, for example as a modification of the Chronotropic™ system, a device created by Sangalli et al., consisting of a drug core, surrounded by a layer of hydrophilic polymer applied by spray-coating and then coated with a gastro-resistant layer (36). By using the void configuration, the application of the drug polymer to the drug core would be a lot faster, without the need for solvents and it would also be much more facile to control the thickness of the polymer layer.

9.2 THE ULTRASOUND ASSEMBLY

The assembly of the modules by use of ultrasound was simple regarding the need of technical insight; this is a great advantage of this method, implying that it can easily be used by personnel in for example hospitals or nursing homes. However, often during the assembly the modules did not attach very well to each other, the height of the probe would have to be adjusted or the energy used would also have to be modified. It seemed that tablets that had been

made with a slightly higher force of compression adhered better to each other than the ones made with a slightly lower pressure. Also sometimes the modules would break or attach to the probe. The success rate became quite higher after there were made dies that could be assembled onto the ultrasound machine and hold the modules in place during the soldering process. The contact surface of the probe could also be modified to give a larger contact surface and less sharp edges.

As the formulation of the powder mixture used for the making of the tablets was made as simple as possible to ease the research of drug release and polymer swelling, it seemed that the mixture was not optimal for module assembly. If the mixture could be modified to enhance the soldering, one might achieve a greater ease of assembly. Also the dome-shaped modules did not have a perfect fit into one another and the shape should be adjusted so that the surfaces of the modules have the maximum contact surface area possible, as this will help adherence.

There has not been performed any studies of the effect of the energy the ultrasound waves has on the stability of the drug and polymer or if there are created any unwanted interactions between polymer and drug for this thesis. This obviously has to be investigated before going any further with research and *in vivo* experiments.

As for upscaling of matrix assembly, there should be no problems of mass-assembly as long as the one can construct an ultrasound machine made for this purpose. The biggest obstacle would probably be the cost of designing and constructing this kind of machinery.

9.3 THE SWOLLEN SURFACE AREAS

The problem of measuring the swelling area is evident; if one tries to measure the surface area of a matrix without attaching it to a surface, the shape of the matrix will be distorted due to the gel consistency that develops during swelling. Hence, some part of the matrix is not free for swelling and the process of

swelling is altered. This means that any direct measurement would be almost impossible to perform. In addition, whenever there was a concave curvature of the matrix, the angle necessary for making the photographs did not show the actual surface area, since the curvature was hidden inside the matrix. Also, the impermeable film probably intervenes with the natural swelling process and thus the surface areas measured in this thesis are not in accordance with the areas of a normal free-swelling module.

The measurement the surface area of the swelling matrices could be useful for applying the swelling area number, in order to understand the contribution of the different release mechanisms during drug dissolution. However, this requires the knowledge of the diffusional coefficients of the drug in gels. Yet, if these parameters are known, then one can also compare the swelling area number to the *n* to see if there is any connection between these two coefficients.

One alternative to measure the swelling area would be to develop an optical scan, preferably one that if capable to perform measurements while the matrix is still in the dissolution medium. Another alternative is to develop a topographical model that could describe the development of shape and surface area during the swelling.

10. CONCLUSIONS

10.1 RELEASE FROM THE DIFFERENT MODULES

From what has been seen from the experiments with the single modules of different geometry, it can be seen that the mechanisms of drug release changes when the shapes of the matrices are varied. The most important influence that the matrix geometry exerts is the enhanced release rate from the matrices with a larger initial surface area but with the same mass and formulation.

10.2 ULTRASOUND ASSEMBLY

The use of ultrasound seems to be a promising method of module assembly, being safe and easily applicable. The equipment and formulation of the tablets should be adjusted in such a manner that the assembly will be easier and have a higher success rate for each assembly. The ultrasound waves do not change the release from matrices, but the assembly leads to changes in the surface area: volume fraction that influences the drug release patterns.

10.3 SWOLLEN AREA CALCULATIONS

There are too many sources of error in the method of measurement that we have applied, thus the true swelling area of uncoated matrices was not calculated in this thesis, as there was no such applicable method. However, the measurements made give an idea of how the matrices swell, even though they don’t give an exact number. A better approach should be found to assure that the area calculated is correct. If the true swelling area is obtained, the swelling area number can be applied and used to study the drug release mechanisms.

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