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Evaluation of the release kinetics of a press-coated biconvex core with an impermeable coat

Par

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Ce mémoire est intitulé :

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Présenté par :

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À été évalué par un jury composé des personnes suivantes :

Professeur Fahima Nekka	***Président-rapporteur***
Professeur Jean Norbert Mc Mullen	***Directeur de recherche***
Docteur Grégoire Leclair	***Membre du jury***

To

my wife, for her support and understanding

To my parents

To my brothers and sisters

with admiration and appreciation

for their encouragement

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Sommaire

Une forme pharmaceutique à libération modifiée basée sur un principe géométrique a été développée et évaluée pour la libération orale contrôlée et soutenue d'agents bioactifs. Cette forme pharmaceutique est composée d'un noyau biconvexe obtenu par compression directe, enrobé d'une membrane imperméable à l'exception d'une surface de libération radiale. La libération de l'agent bioactif se fait à partir d'une fenêtre radiale de forme cylindrique à un taux relativement constant. Le tartrate de métoprolol et l'aminophylline ont été utilisés comme modèles d'agents bioactifs. Ces agents ont été choisis en raison de leurs propriétés physico-chimiques (solubilité). De nombreuses formulations ont été faites pour chaque principe actif avec différents excipients. Afin de développer un enrobage imperméable pour le noyau et améliorer l'adhésion entre le noyau biconvexe et cet enrobage, quelques études ont été effectuées pour évaluer l'efficacité de libération de la drogue, étudier l'effet des excipients dans la formule sur la cinétique de libération, étudier l'effet de la concentration ou du niveau de drogue basé sur le rapport de la partie fortement soluble à la partie moins soluble et étudier l'effet de la surface de libération (non enrobée). Une étude comparative a été faite pour évaluer l'efficacité de libération de drogue en employant un noyau plat et un noyau biconvexe (RRBD). L'effet de la vitesse d'agitation sur le taux de libération a été étudié. L'effet de la force de compression employée pour fabriquer les comprimés sur le taux de libération a été évalué et la valeur de porosité sous différentes forces de compression a été déterminée. Toutes les expériences ont été faites *in vitro* en utilisant un appareil de dissolution automatisé. Les résultats

obtenus à partir de ce projet de recherche ont démontré l'efficacité du dispositif de RRBD pour contrôler la libération de drogue.

Mots clés : cinétique de libération, noyau biconvexe, membrane imperméable.

Summary

A drug delivery device based on a geometric design was evaluated for the controlled and sustained oral delivery of bioactive agents. The device consists of a directly compressed biconvex core, coated with a totally impermeable coat with the exception of the radial releasing window. The drug release from these cores radially, starting from the cylindrical releasing area at the periphery and release the model drug at nearly constant rate. Metoprolol Tartarate and Aminophylline were used as model drugs. These model drugs were selected because of their physico-chemical properties (solubility). Numbers of formulations were made for each pharmaceutical active principle (Metoprolol Tartarate, Aminophylline) with different excipients. In order to develop the coating of Radially Releasing Biconvex Device (RRBD) (i.e. to have a totally impermeable coat) and to improve the interlocking between the biconvex core and the impermeable coat some studies were made. Several studies evaluated the efficiency of these devices; study the effect of the level of excipients in the formulation on drug release, based on the ratio of highly soluble ingredients to low soluble ingredients, study the effect of drug loading , study the effect of the releasing surface (uncoated), comparative study was made to evaluate the efficiency to control the drug delivery by using flat core and biconvex core coated tablet (RRBD), study the effect of agitation speed on the release rate, study the effect of compression force used to press the tablets on the release rate and evaluate the porosity value under different compression forces. All the experiments were made in-vitro by using dissolution apparatus. The results obtained from this research project demonstrated the efficiency of RRB device to control the drug delivery.

Key words: Release kinetic, biconvex core, and impermeable coat.

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I. Introduction

A. Overview of modified release drug delivery

During the last decades, research in modified drug delivery has led to increasingly sophisticated sustain drug delivery systems. It has also stimulated greater awareness among the pharmaceutical industry, the regulatory agencies, the health care profession, and the public at large for the therapeutic advantages of modified drug delivery systems. Presently, the majority of these systems are based on the use of synthetic polymers that differ in their degree of erodibility, swellability, and sensitivity to the biological environment in which they are placed. These polymers have been used to design systems such as microcapsules and nanoparticles for implantation, hydrogels for oral and parenteral drug delivery, the osmotic pump for oral drug delivery, and patches for transdermal drug delivery. (1)

Drug concentration, aqueous solubility, molecular size, crystal form, protein binding, and pK_a are among the physicochemical factors that must be understood in order to design a delivery system that exhibits controlled or sustained release characteristics. Controlled and sustained release preparations using alternative routes have been formulated but the oral route still remains the most widely studied and used. It is obvious that, very highly water soluble drugs (hydrophilic) are more difficult to deliver orally in sustained or controlled release manner than hydrophobic drugs. (2, 3)

1. Generalities

The pharmaceutical dosage form can be defined as a pharmaceutical system delivering a drug to an organism. There are two different parameters relating to drug delivery: the amount of drug released over a unit of time and the drug elimination process, including drug metabolism (biotransformation) and excretion. The rates of these two concurrent processes, physicochemical and physiological, determine the length of time that an effective drug level in the circulation to obtain a specific pharmacological action is maintained. This length of time is determined by the so-called biological half-life, on which basis duration of drug action can be established.

A drug characterized by short biological half-life must be administered at short intervals to maintain the pharmacological action, which makes patient compliance difficult to obtain. The ideal dosage form would be a once-daily dosage form, i.e., one which when administered once daily would remain the therapeutic drug level in the body for 24 h without the risk of toxic concentration. (4)

2. Considerations

Both of the absorption and elimination processes should be taken in consideration when considering the theoretical possibilities of prolonging the time of drug retention in an organism. Therefore the following possibilities should be considered:

- Prolongation of absorption
- Prolongation of metabolism
- Prolongation of excretion

3. Definitions

Over the years, there has been available a variety of pharmaceutical dosage forms which have attempted to control the time course and specificity of drugs in the body; these have been identified by various names, such as "controlled release," "sustained release," "prolonged release," and "timed release."

The term "**Controlled release dosage forms**" (CRDF) implies that the drug release kinetics, prolonged, sustained, or timed, is predictable and reproducible from batch to batch and from patient to patient. CRDF is not influenced by the external environment in which the drug is released, but by the device itself. The release of active agent is, therefore, largely independent of external factors.

Sustained release means that the release of the active agent is constant over time. (5, 6)

Long-acting or prolonged-action system: in which a dosage form containing a therapeutic substance modified chemically in order to prolong biological half-life. (4)

4. Advantages and disadvantages of controlled release

Controlled release delivery systems offer many advantages over conventional or traditional formulations that deliver the entire active ingredient over a short period of time. We can summarize them as the following:

One of the most important advantages that can be achieved by using sustained release devices is constant blood levels of active ingredient release requiring considerably less ingredient to produce a given duration of action in comparison to conventional system.

A second advantage of sustained release system is maintaining the concentration of a drug between the minimum effective and toxic levels, (above the minimal therapeutic level), eliminating the peaks and valleys of the conventional systems.

Controlled release systems usually offer a mean of circumventing the problems of overdosing and underdosing inherent to conventional formulations. Controlled release system can be designed in which the rate of drug release equals to the elimination rate, in order to achieve zero or near-zero order drug kinetic (steady state). (7)

Controlled release technique makes it possible to deliver the agent locally by its containment at the site of action. Local delivery and containment reduces the dosage required and the possibility of side effects. A good example for local drug delivery system is intrauterine contraceptive delivery system, when the steroids estriol and progesterone are given as

contraceptive. Theses steroids produce a contraceptive effect at release rates as low as 10 to 100µg/day, while the same steroids given systemically would require more than 1,000 times the local dose to be effective. Because of the low dose required, a controlled release device can contain sufficient drug to produce a contraceptive action for a year or more. (7)

To reduce the frequency of dosage during the day, this simplifies the dosage regimen and reduces the risk of missed doses administered either by patient or by the hospital staff (to improve patient-comfort), thereby insuring patient compliance (7)

5. Classification of controlled release dosage forms:

Controlled release dosage forms (CRDF) are designed to maintain drug plasma concentrations within a therapeutic range. However, pharmacokinetic response from each CRDF varies from product to product. The pharmacokinetics information on the drug is an essential element to determine the feasibility of a controlled-release dosage form for that drug. Obviously, drugs with relatively short half-lives (less than 6 hours) and specifically defined minimum therapeutic blood levels would be the most likely candidates for controlled delivery. Drugs with half-lives in the blood exceeding 6 h could be dosed in conventional dosage forms such that therapeutic blood levels would be established and then be self-sustaining, allowing for twice daily dosing or less. One limitation to this approach would be encountered with a drug with a narrow safety margin. Furthermore, well-

defined minimum therapeutic blood levels of a drug generally are difficult to establish. (9)

A useful classification of controlled release dosage forms according to the mechanism controlling the drug release as follows:

a) Chemically-controlled systems

(1) Bioerodible systems

(2) Drug-polymer conjugates

b) Diffusion-controlled systems

(1) Membrane-reservoir systems

(a) Solution-diffusion

(b) Osmotic pumping

(2) Matrix systems

(a) Porous matrix

(i) Geometric-controlled

(ii) Gradient distribution

(b) Polymer erosion

(c) Polymer swelling

B. Oral controlled-release drug delivery systems

1. The design of controlled release systems

Most of the oral controlled release systems rely on dissolution, diffusion, or a combination of both mechanisms, to create slow release of drug to the gastrointestinal milieu. In order to achieve a systematic approach to the design of an oral controlled release product, it is necessary to understand the following:

a) Physicochemical characteristics of the drug

b) Dosage form characteristics and formulation techniques.

c) Gastro-intestinal physiology and pharmacokinetics

A review of the literature has revealed the recent development of several novel drug delivery systems that can be utilized for the controlled delivery of drugs in the GI tract. (1, 10, 11).The following classification of such systems is chosen because it includes both the conceptual approach of the design and some elements of physiology of the GI system.

(1) Continuous-release systems

(a) Dissolution control

(b) Diffusion control

(c) Dissolution and diffusion control

(d) Osmotically controlled devices

(e) Slow-dissolving salts and complexes

(2) Delayed-transit and continuous-release systems

(a) Density-based systems

(b) Size-based systems

(c) Bioadhesive-based systems

(3) Delayed-release systems

(a) Intestinal release

(b) Colonic release

2. Dissolution control

When a tablet or other solid dosage form is introduced into a beaker of water or into the gastrointestinal tract, the drug begins to pass into solution from the intact solid form. Unless the tablet is a contiguous polymeric device, the solid matrix also disintegrates into fine particles and/or granules. Disintegration, deaggregation, and dissolution may occur simultaneously with the release and dissolution of drug from its delivery form.

Drug release over a prolonged period can be achieved by employing dissolution as the rate-limiting step in drug release. The delivery of some drugs is inherently sustained because of their intrinsic low aqueous solubility which. Examples of drugs in this category include Griseofulvin, Salicylamide, and Digoxin.

While for highly soluble drugs, the solubility rate can be controlled by one or both of the following:

a) Coating of a drug particles or granules with materials of varying thickness having low solubility

b) Dispersing the drug particles into an insoluble polymeric matrix

The main principle of dissolution control is as follows: (12) when the dissolution process is diffusion layer controlled, where diffusion from the solid surface through the aqueous diffusion layer (stagnant liquid film) to the bulk solution is rate limiting, the flux J is given by:

$$J = -D(dc/dx) \qquad \text{(Equation 1)}$$

Where,

D = the diffusion coefficient

dc/dx = concentration gradient from solid surface to the bulk solution

The flux can also be defined as the flow rate of material (dm/dt) through a unit area (A):

$$J = \frac{dm/dt}{A} \qquad \text{(Equation 2)}$$

If the diffusion layer thickness is h and the concentration gradient is linear,

$$(dc/dx) = (C_b - C_s)/h \qquad \text{(Equation 3)}$$

Where,

C_b = concentration in the bulk solution

C_s = concentration at the solid surface (saturation)

By combining the above equations, the flow rate of material is given by:

$$(dm/dt) = -(DA/h)(C_S - C_b) = kA(C_S - C_b) \quad \text{Eq. 4}$$

Where,

K = the intrinsic dissolution rate constant.

Equation 4 predicts constant dissolution rate if the thickness of diffusion layer, diffusion coefficient, concentration difference, and surface area maintained constant. However, as dissolution proceeds, the surface area decreases.

A practical expression that describes the dissolution of dosage forms of various geometries is available (13)

Thus,

$$M_t/M_\infty = 1 - [(1 - k_0 t)/c_0 a]^n \quad \text{(Equation 5)}$$

Where,

M_t = the amount of drug released in time t

M_∞ = the amount of drug released at infinite time

a = the thickness

n = to 3 for a sphere, 2 for a cylinder, 1 for a slab (1)

3. Diffusional systems

In diffusional systems drugs can diffuse through polymeric matrix while either leaving the latter intact or the polymers themselves may undergo subsequent biodegradations following exhaustion of the drug. Biodegradable systems do not need to be surgically removed after therapy. The simplest example of a diffusional system is one in which a drug is included in a reservoir (core) from which it can diffuse out through a membrane. The kinetic behavior of a drug can follow zero-order as long as the drug concentration in the core is maintained in highly saturated state.

4. Reservoir devices

Reservoir systems are commonly used in the field of controlled release, as diffusion-controlled systems. To achieve optimum therapeutic effects particularly for drugs with short biological half-lives, it is often desirable to have a zero-order drug release. The kinetics of drug release from such a membrane-reservoir system generally follows either a solution-diffusion or an osmotic pumping mechanism. In a membrane-reservoir system, a water-insoluble polymeric material encases a core of drug. Drug will diffuse through the membrane and exchange with the media surrounding the tablet or particle. Additional drug will enter the membrane, diffuse to the periphery, and exchange with the surrounding media. To keep the drug release constant, the reservoir must be

saturated. The movement of drug or solvent is governed by membrane. The membrane permeability to the solvent and the drug determines the diffusion rate of molecules through the membrane. The most important advantage of using reservoir systems is the possibility of achieving a constant rate of release over a substantial portion of their lifetime. A second advantage is that the level of drug loading can be higher compared to other systems.

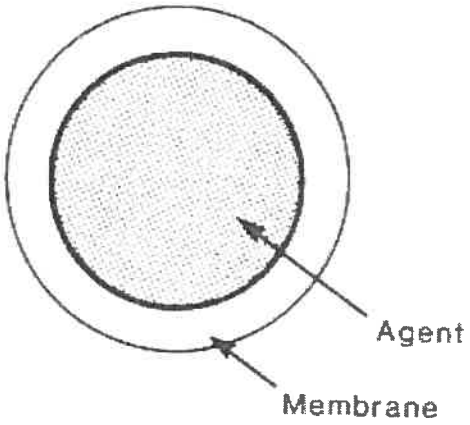


Figure 1: Reservoir device

The diffusion rate across the membrane is given by Fick's law:

$$J = -D\,dc/dx \qquad \text{(Equation 6)}$$

Where,

D = diffusion coefficient in area / time

dc/dx = the change of concentration C with distance x

At steady state, equation (6) is integrated to give by

$$J = -D\Delta C / \ell \qquad \text{(Equation 7)}$$

In terms of the amount of drug released, the release rate dM/dt is given by

$$dM / dt = ADK\Delta C / \ell \qquad \text{(Equation 8)}$$

Thus,

A = the area

D = the diffusion coefficient

K = partition coefficient of drug between the membrane and drug core

ℓ = the diffusional path length (thickness of coat in the ideal case)

ΔC = the concentration gradient across the membrane

A significant factor in Equation (8) the partition coefficient which is defined as the concentration of drug in the membrane over the

concentration of drug in the core. If the partition coefficient is high, the core will be depleted of drug in a short time so that zero order release will be observed only over a short segment of the time course of drug release.

In fact, to get a constant drug release rate from a reservoir device it is crucial to keep constant area, diffusional path length, concentration, and diffusion coefficient. (1, 6, 7, 15)

5. Effect of device geometry on drug release rate

As discussed previously the diffusional controlled matrix systems have some advantages over other systems particularly when compared to the fabrication of reservoir systems. A main disadvantage is that they do not inherently possess zero-order release kinetics. However, these systems can avoid the diminishing release rate as the drug diffuses from longer diffusion length or lower drug concentration distribution. This difficulty is particularly severe for spherical and cylindrical shaped devices. An achievable solution to get zero-order release behavior is to modify the matrix geometry. Examples of different geometries, e.g. pie, hemisphere, or cone are illustrated later.

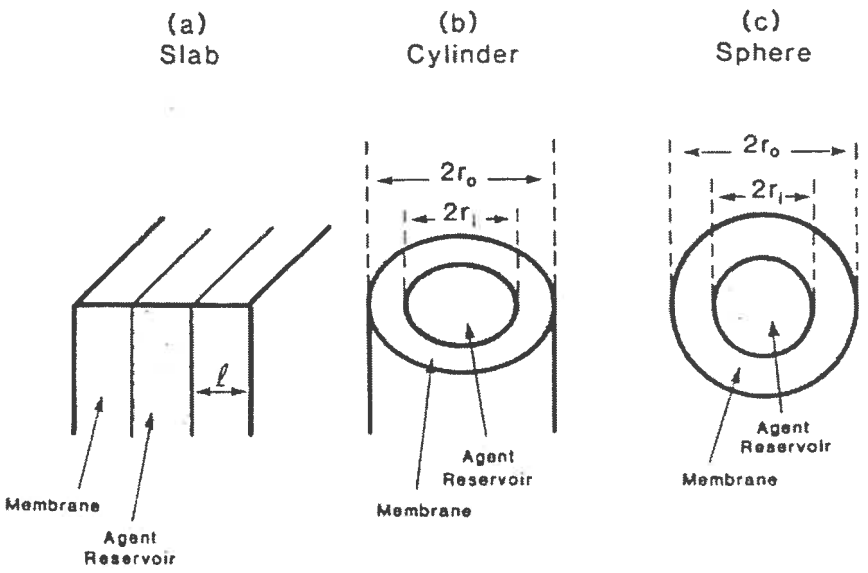


Figure 2: Comparison of different geometries (slab, cylinder and sphere geometries of reservoir systems

The rate of release of an active material from a reservoir device can be controlled through geometric factors. Equation 6 can be modified for the slab or sandwich geometry as show in Figure 2

$$dM_t / dt = AJ_{\lim} / l = ADKC_s / l \qquad \text{(Equation 9)}$$

Where,

M_t is the released drug mass at time t and since dM_t/dt is the steady state release rate at time t. A is the total surface area (edge effects being ignored), and J_{lim} is the membrane-limiting flux. (7)

For the cylinder, the steady-state release rate (ignoring end effects) is given by

$$dM_t / dt = 2\pi h J_{\lim} / \ln\left(r_0 / r_i\right) = 2\pi h DKC_s / \ln(r_0 / r_i) \qquad \textbf{(Equation 10)}$$

Where

r_o and r_i are the outside and inside radii of the cylinder, respectively, and h is the length of the cylinder.

For the sphere,

$$dM_t / dt = 4\pi J_{\lim} \frac{r_0 r_i}{r_0 - r_i} = \frac{4\pi DKC_s r_0 r_i}{r_0 - r_i} \qquad \textbf{(Equation 11)}$$

The sphere is a particularly interesting geometry since in the limit as $r_o/r_i \rightarrow \infty$, $dM_t / dt \rightarrow 4\pi DKC_s r_i$

That is, the release rate becomes independent of the outer radius of the device, r_o. A plot of flux against the ratio r_o/r_i, as illustrated in Figure 3, when r_o/r_i exceeds approximately 4, further increases in device size for a fixed radius core does not significantly affect on the release rate. Since almost all the concentration decrease is within a distance of a few radii of the inner core. Thus, a given size reservoir provides a constant release rate for any thickness of membrane beyond a certain limit, making membrane thickness a noncritical parameter in device fabrication.

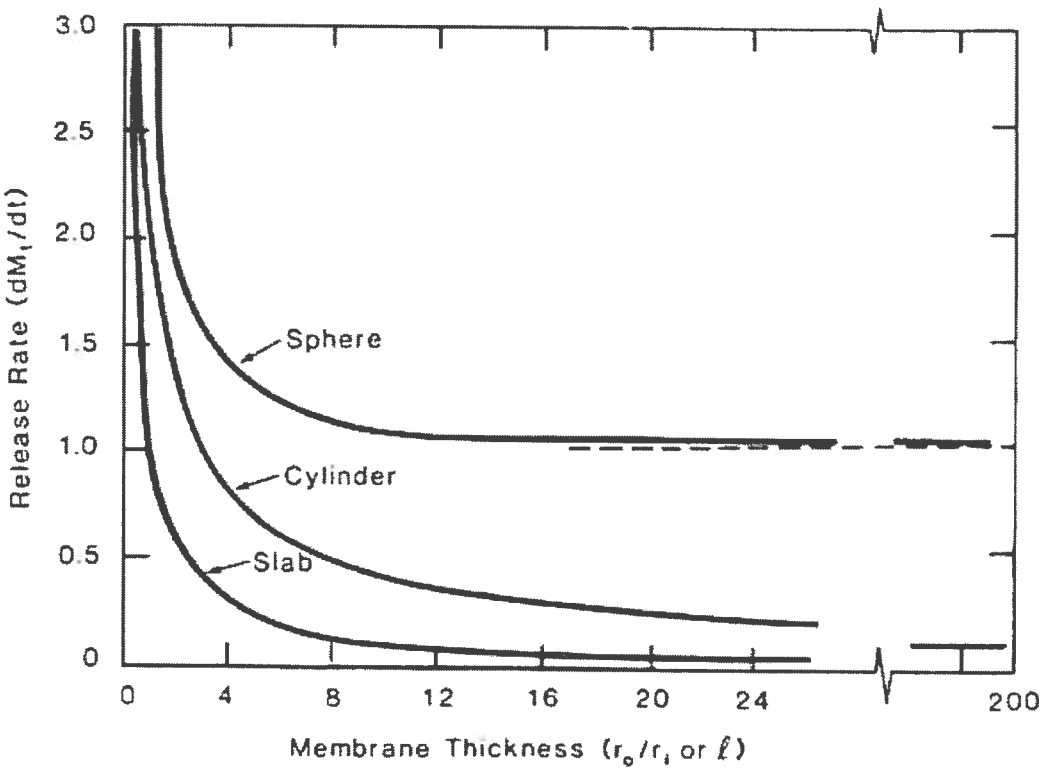


Figure 3: Release rate against membrane thickness for different geometries of reservoir devices

Increasing membrane thickness with the various other geometries affects release rate quite differently. As shown in Figure 3, in which the release rate is plotted as a function of membrane thickness for devices of various configurations. In figure 3 it is obvious that none of these geometries give zero-order release for the following reasons. For the slab geometric device, the area remains constant, yet the distance of the receding boundary from the releasing surface increases with time. Therefore, the increase in diffusional path length results in a release rate

that decreases with time. The release rate is inversely proportional to thickness, and release rates are thus easily scaled over a wide range. For the cylinder and the sphere, the decrease in the release rate is more pronounced, since the area decreases with time, whereas the distance of receding boundary increases with time.

a) **Matrix device systems**

Diffusional matrix systems are the earliest most utilized means of bioactive agents delivery. In this system the drug particles are dispersed uniformly in an insoluble polymer. The drug releasing rate is governed by the penetration rate of surrounded medium into the matrix from the surface. This, in turn, is controlled by the porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particle surface.

When a diffusional matrix system comes in contact with an external medium, as the drug dissolves, the diffusional path length increases because as the dissolution front recedes from the surface.

The main disadvantage of matrix devices is that drug release rate continuously decreases with time. This is an end result of increased diffusional distance and decreased surface area at the penetrating solvent front; therefore it is not possible to obtain zero-order kinetic by using this kind of device. The geometry can be modified to compensate for the increase in diffusional distance through a corresponding increase in

surface area for dissolution, thereby increasing the amount of solubilized particles per unit of time resulting in near zero order release from matrix device. (16, 17)

In this matrix system the releasing rate of a drug is based on the diffusion rate of a drug. Higuchi's equation can be used to express the amount of drug released from this device:

$$Q=\left[D\varepsilon/T\left(2A-\varepsilon C_s\right)C_S T\right]^{1/2} \quad \textbf{(Equation 12)}$$

Where

Q = drug released in g per unit surface area

D = diffusion coefficient of drug

ϵ = porosity of the matrix

n = turtousity of the matrix

C_s = solubility of drug in release medium g/ml

A = concentration of drug in the tablet

To derive this equation the following assumptions were made:

- The particles size of the drug is much smaller than particles in the matrix
- No interaction between the drug particles and the matrix
- Constant diffusion coefficient
- A pseudo- steady state is maintained during release
- C = 0 in the bulk solution at all times
- A >> Cs (saturated conditions)

This equation can be reduced to

$$Q = Kt^{1/2} \qquad \textbf{(Equation 13)}$$

A plot of drug released (mg) versus the square root of time should be linear if the rate drug release is diffusion controlled. The rate of drug release from a homogenous matrix can be controlled by changing one of the following parameters :(18)

- The solubility of drug
- Initial concentration of drug in the matrix
- Porosity of the matrix
- Tortuosity
- Leaching solvent composition
- Polymer system making up matrix

Membrane-coated tablets were developed to provide a dosage form which exhibits zero-order kinetics. The delivery system consisted of a soluble tablet core surrounded by a porous membrane which controls the diffusion rate. The water from the gastric juices diffuses through the pores to reach the core to dissolve the drug which then diffuse back through the water filled pores and eventual release into the gastric juices. Such a device using membrane coating as a diffusional barrier is represented in Figure 4 Membrane-Coated Tablets (19):

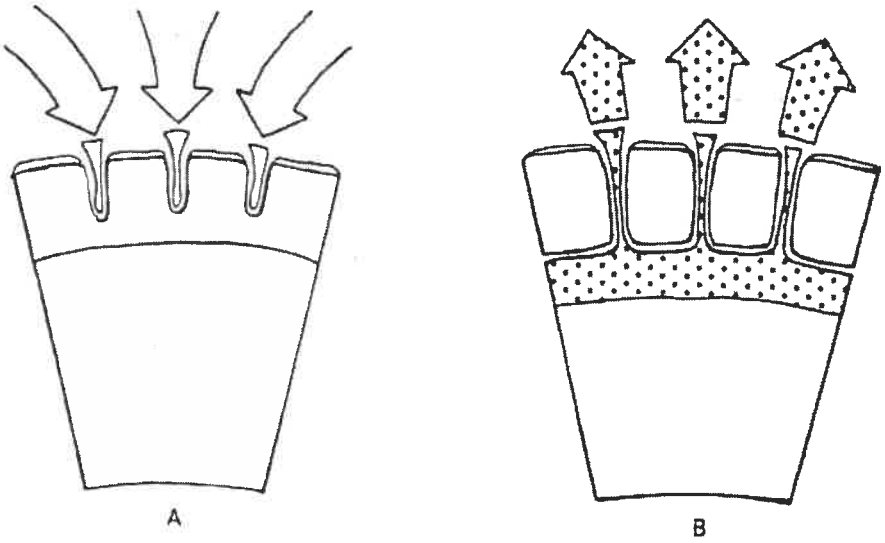


Figure 4: segment of membrane-coated tablet (A) liquid penetrating into the membrane, and (B) drug solution diffusing through the membrane.

The rate of release of drug from the tablet through the pores can be calculated by using Fick's first law of diffusion.

$$Q = D\left(C_s - C_u\right)A/h$$ **(Equation 14)**

Where

Q = rate of release

D = diffusion constant

A = surface area

h = thickness of the diffusion layer (i.e. film)

As long as there is a saturated solution together with solid drug substance inside the coating shell, the concentration inside the coating shell, C_s, is much higher than the concentration outside the coating shell, C_u. which means C_u is negligible compared to C_s and equation (14) can be reduced to:

$$Q = DC_s/hA$$ **(Equation 15)**

This implies that the diffusion should proceed at a constant rate (zero-order reaction). At the point where no solid substance is left within the membrane coating, the rate of diffusion declines with decreasing concentration (first-order reaction).

C. The influence of geometric design

1. Dissolution of solid dosage forms

Once a solid dosage form is placed in a liquid medium dissolution begins. The dissolution rate of a solid dosage form decreases with time because of the decrease in dissolution front surface area. Furthermore, the diffusional path length increases making it difficult to keep the release rate of drug in constant level and then no zero-order kinetic. From that point the geometric design promises to overcome the decrease in dissolution front surface area.

The familiar cube-root law for dissolution of solids was derived by Hixon and Crowell on the basis of diffusion away from the surface of a spherically-shaped solid. The convex surface of a sphere decreases in area as solid mass is lost from the surface so that the dissolution rate decreases in portion to the decrease in area until the solid is completely dissolved. By including shape factors, this model has been extended to describe the dissolution of various prismatic forms (20). As in the case of spherical particles, the dissolution rate decreases with time as the dissolution process progresses because of the decrease in area.

The surface area in the case of a concave device increases as solid mass is eroded from the surface. Therefore the rate of dissolution increases with time. Rippie and Johnson (21) studied the dissolution characteristics of solid pellets that were designed to minimize loss in surface area during dissolution. This was accomplished by employing pellets having a cross

section such that both convex and concave surfaces were present. Dissolution rates of pellet cylinders having a cross shape and clover leaf cross sections were measured and compared with that of a right circular cylinder. Although the dissolution rates of the uniquely-shaped pellets decreased over time, with partially coated pellets the rates decreased much less than that of the circular cylinder, e.g., after 60% mass loss the rates were approximately 55% greater than that of the circular cylinder.

When a hole is present in a nondisintegrating tablet, the convex surface of the hole will increase in area as the surface dissolves. A theoretical analysis by Cleave (22) on tablets in the form of parallelepipeds indicated that the presence of one or more holes in a tablet can alter significantly the dissolution rate of the tablet over time. It was concluded that a two-hole tablet is basically a better configuration than the others for maintaining a constant dissolution rate. (14)

2. Geometrically Modified Systems

The diffusion-controlled monolithic matrix systems have some advantages over other systems especially when compared to the fabrication of reservoir systems. A major disadvantage is that they do not inherently follow zero-order release kinetics. However, these systems can overcome the decreasing release rate as the drug diffuses from longer diffusion length or lower drug concentration distribution. This difficulty is particularly severe for spherical and cylindrical shaped devices. Geometric

factors have been utilized to compensate for the increasing diffusional distance and decreasing area at the dissolution front generally encountered in matrix systems. Many geometric designs have been proposed in the literature which modifies the planar geometry of a matrix device from which the fraction of drug released was linear with the square root of time (23, 24).

3. Planar geometry

The release kinetic of a drug from planar geometry composed of a homogenous matrix, where the amount of drug released from planar device into the surrounded media acting basically as a perfect sink can be described by the following relationship;

$$Q=\sqrt{Dt\left(2A-C_S\right)C_S} \qquad \textbf{(Equation 16)}$$

Where,

Q = drug released after time t

D = drug diffusitivity

A = the total amount of drug present in the matrix per unit volume

C_s= drug solubility in the matrix substance.

For the release from a planar system having a granular matrix composed of dispersed drug particles in an inert polymer. The above relation must be modified to account for the effective volume where diffusion can occur and the effective diffusional path. It can readily be seen for this system that

$$Q=\sqrt{D\varepsilon/T\left(2A-\varepsilon C_S\right)C_S t} \qquad \textbf{(Equation 17)}$$

Where,

Q = the amount of drug released after time t per unit exposed area

D = the diffusivity of the drug in the permeating fluid

τ = the tortuosity factor of the capillary system ≈ 3

A = the total amount of drug present in the matrix per unit volume

C_s= the solubility of the drug in the permeating fluid

ϵ = the porosity of the matrix

The origin of the above expression is basically the same as for Eq.16, except that the effective diffusional cross sectional area must be reduced by the porosity factor ϵ, and the solubility of the drug in the total system per unit volume must also be decreased by the same factor.

The tortuosity factor, τ, is introduced to correct, for the lengthened diffusional path caused by the necessary lateral excursions.

For both equations (25) it is assumed that there exists a pseudo steady state condition during the release process and that the drug particles are quite small and is uniformly distributed in the matrix. The equations would be fundamentally valid for systems in which A is greater than C_s or ϵC_s by a factor of three or four. Of course, if A < C_s or ϵC_s, the drug would not longer be present as a solid and a different equation would be apply.

Since the porosity factor in Equation17 refers to the porosity of the leached portion of the pellet, it differs from the initial porosity of the initially formed matrix. The difference would correspond directly to the volume of space previously occupied by the extracted component or components.

Thus

$$\varepsilon=\varepsilon_o+KA \qquad \textbf{(Equation 18)}$$

For systems where the drug is the only extractable component, K being introduced to convert A to its corresponding volume fraction. K is equal to the specific volume of drug = 1/ (density of the drug) if A is expressed in terms of grams of drug per milliliter. For those instances where the initial porosity, ϵ_o, is very small or where the fraction of the matrix volume occupied by the drug is relatively large $\epsilon \approx KA$ and equation 17 reduces to

$$Q = A\sqrt{DK/T}\left(2 - KC_s\right)C_s t \qquad \textbf{(Equation 19)}$$

Therefore in this system the amount of drug released at anytime is basically independent of A.

4. Multi-layers tablet and cylindrical geometry

To design controlled release dosage forms for oral use there are various ways: from tablets or capsules, film coated pellets, to more complicated drug delivery systems. Hydrophilic matrix systems are considered to be the easiest way to formulate a drug into a prolonged release dosage form. Generally the mechanism of drug release from hydrophilic, swellable matrices couples polymer macromolecular relaxation with drug diffusion with the resulting kinetics depending on the relative ratio of relaxation to diffusion. (26, 27)

Cone et al. (28) developed a multi-layer tablet system (Geomatrix®) as shown in figure 5

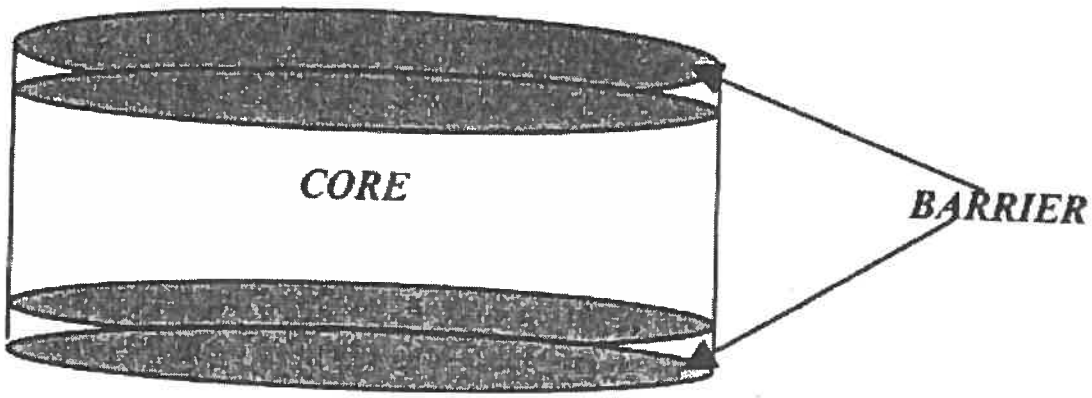


Figure 5: Schematic diagram of triple-layer tablets (Geomatrix®)

A core tablet is sandwiched between two barrier layers. By using hydrophilic swellable/erodible polymer zero-order kinetics can be achieved. However, zero-order release kinetics also depends on the solubility of drugs. If the two layers were hydrophilic swellable polymer, the drug release rate is controlled by several mechanisms. When the device is placed in water, hydration of the polymer will start and then the drug diffuses toward the surrounded media. When liquid penetrates through the barrier layer, the drug will dissolve and then diffuses out. Then the swollen barrier can be considered as a membrane. Initially, the drug kinetic release is governed by the diffusion of drug through the swollen barriers because the total lateral surface area is greater than the radial surface area. Core tablet hydration is delayed due to the drug-free barrier layers. In addition, the thickness of the swollen barrier layers diminishes with time, leading to a decrease in the diffusion resistance of the membrane. This counterbalances the effect of the reduced concentration of the drug in the core tablet on the drug release

kinetics, leading to the prolonged zero-order release. Since, the release of a drug from this system is essentially based on the solubility of a drug, when the solubility of a drug is low, then the release kinetic can be much close to zero-order.

Formulating tablets containing different dose levels with identical release kinetics is considered to be the greater source of trouble during the development of controlled release dosage forms based on tablet geometry

The tablet design necessitates altering the formulation and tablet size. Therefore, each tablet requires a unique formulation for each dose level. Cone et al. (29) developed small tablets with multi-layer system design which can be placed in a hard gelatin capsule. In this system, the release kinetics of different dose levels shows the same release profile.

This multi-layered tablet system has been reserved to press-coated tablet system. The press coated tablet system consists of an outer low drug (or drug-free) content layer and a high drug content core (30). This device was prepared as follows: A specific amount of blend of coat excipients is put into a die (bottom layer) then compressed with a flat-faced punch followed by placing the core tablet in the middle of the bottom layer. The rest of the mixture is then poured into the die forming the side and top layer. In press-coated system the drug release delay by the coating barrier varies according to the coat thickness and the type of materials. The barrier is able to slow down the hydration/swelling process of the core tablet for a long period of time. Further more, the outer barrier layer works as a controlling

membrane producing a linear release profile as long as the drug concentration in the core is at saturation level.

5. Spherical geometry

By applying the Fick's first law in this system

$$Qt=-4\pi r^2 D dC/dr \qquad \textbf{(Equation 20)}$$

Where,

Qt = the diffusion rate

D = the diffusion coefficient of drug molecules in the matrix

C = the concentration of the drug in the polymer

As in the cylindrical geometry approach and under the same boundary conditions and presuming that the diffusion rate of solute from the matrix is constant (pseudo-steady state), the next equation can be derived:

$$Qt = -4\pi D \frac{(C_M - C_b K)}{[1/R(t)] - [1/R_O]} \qquad \textbf{(Equation 21)}$$

Similar to the cylindrical geometry, as equation 21 shows, the concentration profiles for the pseudo-steady assumption are no longer linear with respect to the radius. The following equation is achieved, which illustrate the correlation between R (t) and t.

$$t = \frac{C_T}{D(C_M - C_b K)}\left[\frac{R^3 - R_0^3}{3R_0} - \frac{R^2(t) - R_0^2}{2}\right] \qquad \textbf{(Equation 22)}$$

It is obviously that all of the three different geometries do not follow zero-order kinetic release behavior for different reasons. In both cases of sphere and cylinder the decline in the release rate is more marked, resulting from the decreasing in the area with time, and the increasing diffusional distance because of the receding boundary. In the case of slab geometry the main cause is that while the surface area stays constant, the diffusional distance increases with time.

D. Controlling release rate with geometric matrix systems

a) **Pie shaped system**

Brook and Washkuhn (31) have presented the pie shaped device to deliver a drug in order to reach zero-order kinetic. The release of a drug from a polymer matrix could be governed by dissolution or diffusion. The principle of this design is based on compensating for the increase in diffusional path length by increasing the dissolution front area thereby increasing the amount dissolved within the device. The device composed of a nonpermeable section of a cylinder with a cavity having a circular sector cross section as shown in figure 6. The cavity communicates (releasing window) with the medium (fluid) in which the device is placed

only through a narrow opening of width a. The release from this device was tested by following the release of stearic acid into ethanol. The device has demonstrated a good linearity following an initially higher rate, "burst" The ideal behavior of this device depends in theory, however, on both the drug molecules and the releasing window through which they must pass having infinitely small dimensions.

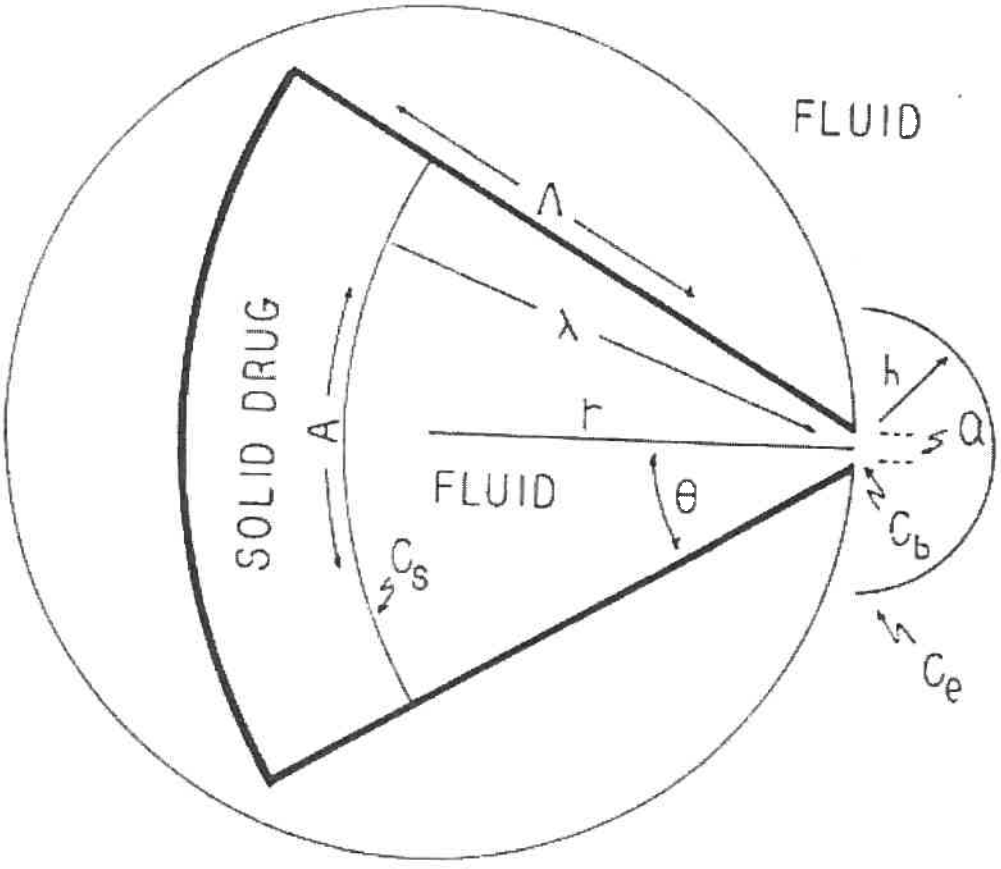


Figure 6: Cross section of zero-order drug delivery system containing solid drug

Lipper and Higuchi (32) took the size of the opening into their considerations to present a theoretical expression for drug release from pie-shaped devices. The flux J, for diffusion path length s, is given by:

$$J = 2\theta\pi LD(s+n)\frac{dC}{ds} \qquad \textbf{(Equation 23)}$$

Thus,

J = the flux at r

Θ = the half-angle of the pie

D = the diffusion coefficient of the drug in the dissolution medium

S = the diffusion path length

n = the opening radius

C = the drug concentration

At pseudo-steady state (constant flux), integration of equation (23) with respect to both distance and concentration yields:

$$J = \frac{2\theta LD(C_s - C_b)}{\ln\frac{\lambda}{n}} \qquad \textbf{(Equation 24)}$$

Where

C_s = the drug concentration at the drug dissolution moving front

C_b = the drug concentration at the opening

λ = the distance between the centre of pie device and the moving front

However, diffusion from the opening of the device into the surrounded medium is expressed for sink conditions by:

$$J = 2\theta LDnC_b / h \qquad \textbf{(Equation 25)}$$

Where

h = the stagnant film thickness

By solving equations (24) and (25) for C_b, and taking into account the mass dissolved at time t, $M = (\lambda^2 - n^2)\, L\theta\rho$, the following relationship between the mass dissolved and time can be obtained:

$$T = [h/n - 1/2]M + \left[M + L\theta\rho n^2/2\right] \ln \frac{\left[M + 1/L\theta\rho n^2\right]}{2\theta LDC_s} \qquad \textbf{(Equation 26)}$$

However, if one considers the mass dissolved in the diffusion layer between λ and 0, the following equation may be derived for relating λ and M_r:

$$M_r = \left(\lambda^2 - n^2\right)\left[L\theta\rho - L\theta C_s + \frac{L\theta C_s}{2\left(\frac{h}{n} + \ln\frac{\lambda}{n}\right)}\right] - \frac{L\theta C_s}{\frac{h}{n} + \ln\frac{\lambda}{n}} \ln\frac{\lambda}{n} \qquad \textbf{(Equation 27)}$$

Hanssen et al (33) and Conte et al. (34) developed the perforated, coated tablet (PTC) and Boettner et al. (35) presented the multi-perforated trilaminate. A single perforated tablet, (as show in figure 7), is made by direct compression of drug and other excipients (magnesium stearate and lactose). Then the device was coated by spraying a polymer solution and after that a central hole has drilled.

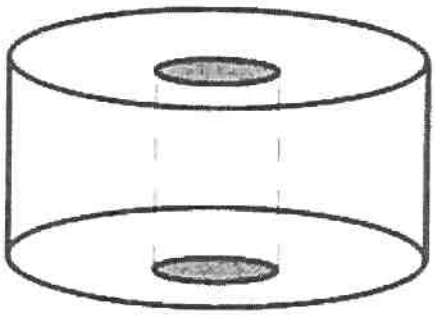


Figure 7: Cross-sectional view of a coated / perforated device

In this device the relationship between the drug release kinetics and the size of the hole is directly proportional; because of the increasing in inner releasing surface area as the dissolution front moves the kinetic

release of the drug from this device is linear. However, Hanssen et al. (36) when a water insoluble polymer is integrated into the matrix a considerable decrease in the rate of dissolution followed with obvious deviation from zero-order manner was observed.

Conte et al (34) made-up perforated coated tablet with a central hole by spraying a coating solution. This device is consisting of hydrophobic polymer; the central hole represents the window through which the drug is released to the surrounded medium, as long as the diffusional length increases the surface area at the dissolution front increases, giving a good linearity. During the coating operation, however, the inner surface of the central hole may be coated to form a film

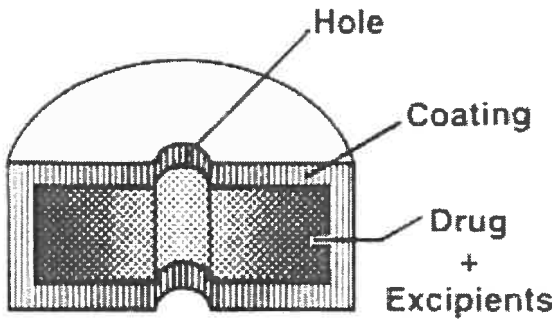


Figure 8: Cross section of a perforated coated tablet

Equation (27) can be modified to calculate the amount of drug released from perforated-coated tablets by replacing θ with π as:

$$M_r=\left(\lambda^2-n^2\right)\left[\frac{L\pi\rho-L\pi C_S+L\pi C_S}{2\left(h/n+\ln\lambda/n\right)}\right]-\left[\frac{L\pi C_S n^2/h/n}{h/n+\ln\lambda/n}\right] \qquad \textbf{(Equation 28)}$$

b) **The multi-perforated device**

It is composed of two layers coating the top and bottom side of core matrix. In this device the coating layers are totally impermeable to the drug. Circular perforations are punched from the top to the bottom. On the other hand, the drug can only release through the perforated holes and uncoated sides. The amount of drug released from this device basically depends on the number of perforations and size of the device as well. (37). Model equations have been developed to predict the release of drug from the multi-perforations as follows for a coated edge:

$$M_r = N(\lambda^2 - n^2)L\pi\varepsilon\left[\rho - C_s + \frac{C_s}{2\{\frac{h\varepsilon}{n\tau}+\ln\frac{\lambda}{n}\}}\right] - \frac{NL\pi\varepsilon C_s n^2}{\frac{h\varepsilon}{n\tau}+\ln\frac{\lambda}{n}} \qquad \textbf{Equation 29}$$

$$t = \frac{\left(\frac{h\varepsilon}{n\tau}-\frac{1}{2}\right)(\lambda^2 - n^2)\rho\tau + \lambda^2\tau\rho\ln\frac{\lambda}{n}}{2DC_s} \qquad \textbf{Equation 30}$$

And for an un-coated edge,

$$M_r = N(\lambda^2 - n^2)L\pi\varepsilon\left[\rho - C_s + \frac{C_s}{2\left(\frac{h\varepsilon}{n\tau} + \ln\frac{\lambda}{n}\right)}\right] - \left[\frac{NL\pi\varepsilon C_s}{\frac{h\varepsilon}{n\tau} + \frac{\lambda}{n}}\right] + S\left[\frac{D\varepsilon(2A - \varepsilon C_s)C_s t}{\tau}\right]^{1/2}$$

Equation 31

Where

ε and τ are the porosity and tortuosity of the matrix, respectively, N is the number of holes, and S is the surface perimeter of the edges.

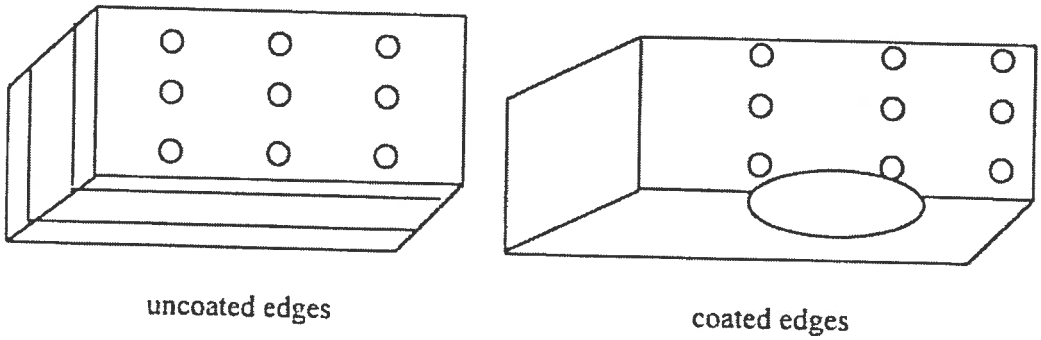


Figure 9: Schematic diagram of morantel sustained release trilaminate

Kim (38) proposed a simple un-coated-compressed (swellable /erodible) tablet with a central hole (donut-shaped). In this device the kinetic release is zero-order (i.e., 80 – 90% of theophylline was released) before rapidly decreasing. The release of drug in this system depends on the size of hole when the hole size is increased from 5/32" to 7/16", the

release rate increases and it is obviously that the time needed for release is shortened.

The combined process of boundary erosion and diffusion front progression during drug release from the donut-shaped tablets, Figure 10), compensate for the decrease of releasing surface area from the outer surface by the increase of releasing surface area from the central hole. At the end of drug release, the swollen gel thickness of the donut-shaped tablet is thin enough to be broken by fast stirring. (39)

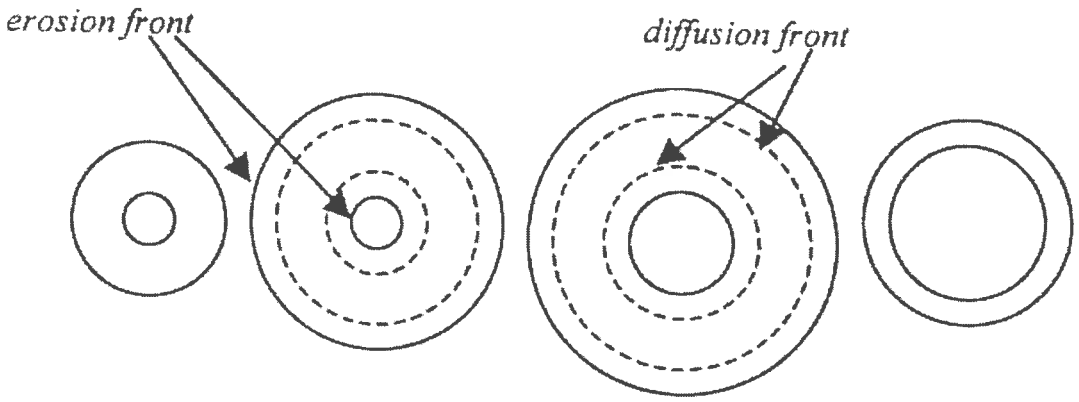


Figure 10: Schematic diagram of releasing surface area boundaries

However, if the hole size is smaller than 5/32", the hole collapses during drug release due to the inner swelling of the polymer from the central hole. As a result, the drug release from a small hole donut-shaped tablet tends to follow the drug release from the tablet without a hole.

Kim (40) has developed coated donut-shaped tablets, an improvement of perforated-coated and donut-shaped tablet. Water-soluble polymers and swellable/erodible polymers have been used in perforated-coated tablets. In this system, drug diffusion and/or polymer erosion govern drug release kinetics, providing parabolic or linear release profiles.

c) **Cone-shaped and Hemisphere Systems**

Nelson et al introduced the cone-shaped device, Figure 11, this system is essentially based on the theory that the surface area at the diffusional front increases as the diffusional path increases. The device consists of a non-permeable coat at the two sides (top and bottom), and then the drug can be in between or dispersed in the matrix. The drug can be released through the small hole at the bottom of the cone. Once the liquid starts to penetrate through the hole, a drug-depleted layer forms between the opening of the hole (a) and the solid suspension interface (r).

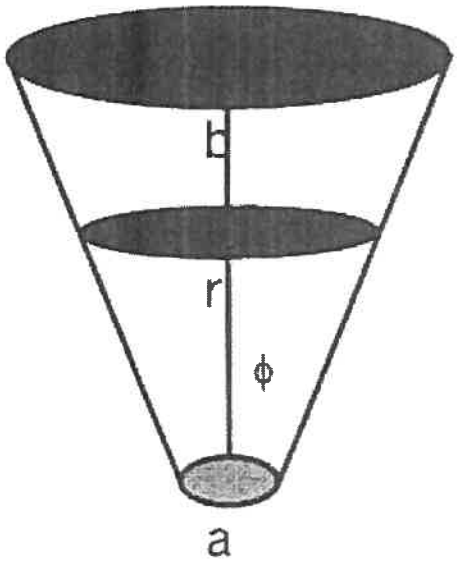


Figure 11: Cross-sectional view of a cone-shaped device

Nelson et al. (41) treated the release of drug from the device as a pseudo-steady state diffusion in a hallow sphere with a declination angle θ.

Hsieh et al. (42) studied the release kinetics from a hemispheric matrix as presented in Figure 12 in which the device is coated on all surfaces with an impermeable coating except for an orifice in the centre face. Hemispheric systems for low molecular weights drugs were prepared by heating and compressing poly-ethylene and drug (sodium salicylate) in a brass mold. Hemispheric systems for high molecular drugs were prepared by casting ethylene-vinyl acetate copolymer and protein in a hemispheric mold at – 80° C, followed by a two-step drying procedure (-20 and 20°).

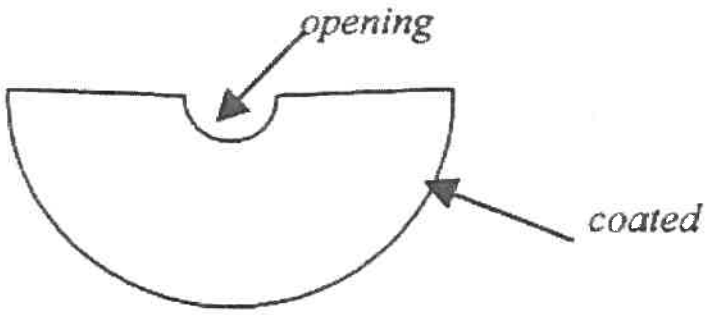


Figure 12: Hemisphere design

Experimental analysis of the device demonstrated that a hemispherical, receding layer is produced, with the radius of that layer increasing as a function of time. Theoretical analysis was also accomplished to develop release equations for the hemispheric device. In the theoretical analysis, it was supposed that the amount of drug present per unit volume, C_o, is substantially greater than the solubility of drug per unit volume of the vehicle, Cs. It is also assumed (43), which the solid drug dissolves from the surface layer of the device first. When the layer is depleted of drug, the next layer begins to be depleted. The interface between the region containing dissolved drug and dispersed drug moves into the interior as a front. According to these assumptions, and several others, the release rate equation was derived as follows:

$$\frac{dQ}{dt} = 2\pi C_s D A_i \left[\frac{R_{(t)}}{R_{(t)} - A_i} \right] \qquad \text{(32Equation 32)}$$

Where

C_s = solute solubility in the polymer

D = diffusion coefficient

$R_{(t)}$ = radius of the receding boundary

A_i = radius of the spherical cavity

When $R_{(t)} >> a_i$, equation (32) is reduced to

$$dQ/dt = 2\pi C_s D A_i \qquad \text{(33Equation 33)}$$

Equation 33 shows that the release rate is independent of time, t, and therefore a zero-order release kinetics is attained.

d) **Biconcave disc**

Benkorah and McMullen (57) have presented a biconcave disc. It is composed of a slow-dissolving biconcave core of a drug /excipient mixture coated with a totally impermeable membrane. After coating an opening is made through the center of the disk to expose a cylindrical releasing surface which represents the only way by which the device can contact

the surrounded medium. In this device the release kinetics depends on the increase in surface area at the dissolution front to counterbalance the lengthening of the diffusion path.

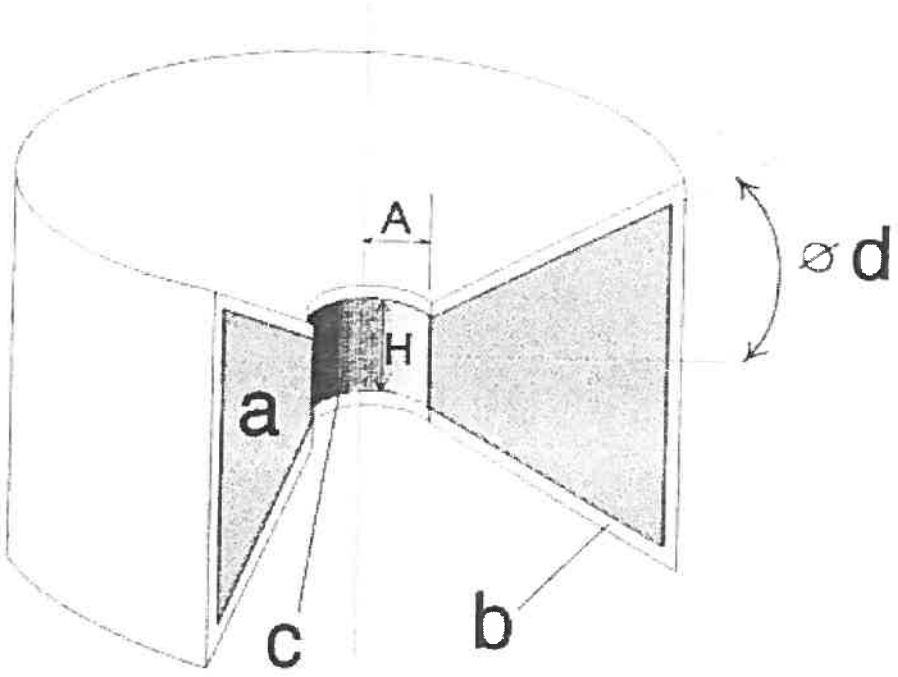


Figure 13: three dimensional cross-sectional view of the biconcave device (a) Dissolving core, (b) impermeable coating, (c) releasing hole, (d) tablet angle, (A) hole radius, (H) hole height.

Studies of the effect of the geometry of the proposed device suggested that release rates, can be predetermined by controlling the diameter of the hole provided that suitable formulations are selected. The study also proposed that constant release rates are better achieved with smaller holes. A high altering from zero-order is obvious as a result of

large hole size large, mostly when formulations of highly soluble drugs, with high intrinsic dissolution rates, were used.

Another approach, developed by Bechard and McMullen (45) illustrates kinetics profile of a drug from a polymer matrix device. This device is composing of polymer matrix with a central hole, inwardly tapered disk which was planned to be implanted in order to release bioactive materials at a constant rate over an extended period of time.

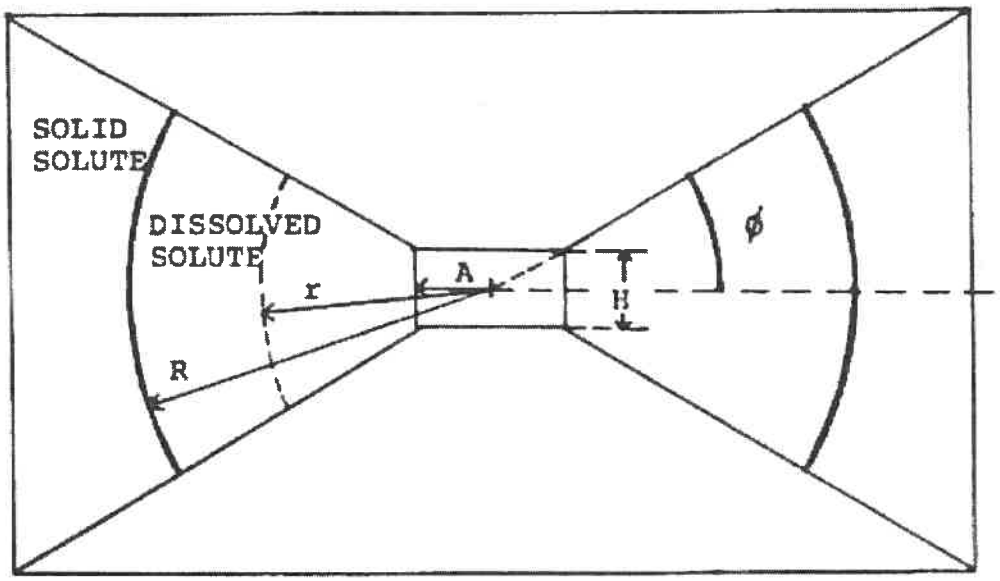


Figure 14: Cross sectional view of the proposed device (S. Bechard and McMullen; solute release from a porous polymeric matrix)

The principle of this approach based on the increases in drug diffusion path followed by the increase in area of the dissolution boundary.

In this approach a biconcave polyethylene disc matrices with a releasing hole on the center. (44, 45)In this research there were two types of matrix fabricated by compressing a sodium salicylate-melt polyethylene blend with sets of conical punches having two different angles (20° and 30°), with an axis perpendicular to the cone. The matrices were covered with wax and a hole in the centre was made to generate area through which the solute releases could occur. An approximate mathematical solution was developed for these devices and tested against experimental results. The solute release from this device is given by:

$$M_r = 4\pi \sin\theta\varepsilon \left[\frac{\rho\left(R^3 - A^3\right)}{3} - \frac{C_S R}{6\left(2R^2 - RA - A^2\right)} \right] \qquad \textbf{(Equation 34)}$$

And

$$t = \frac{\rho\left(2R^3 + A^3 - 3AR^2\right) - C_S\left\{2R^3 + A^3 + A^3 \ln\left(\frac{R}{A}\right) - 4AR^2 + RA^2\right\}}{6AD'C_S} \qquad \textbf{(Equation 35)}$$

Thus

Mr = the mass of solute released

t = the time

θ = the angle between the surface of the device and a horizontal plane

Passing though the mid-height of the disk

D' = the diffusion coefficient of solute in the dissolution fluid divided by

The tortuosity (τ)

ϵ = the porosity of the matrix

C_s = the solute solubility in the dissolution fluid

R = the distance from the dissolution front to the centre of the hole

A = the radius of the releasing hole

The experimental results and theoretical model using this matrix device demonstrated that this matrix geometry design could be valuable as a pharmaceutical dosage form to control the release of solute according to zero-order kinetics.

E. Powder characterization

1. Density

Density is the weight to volume ratio of a substance, expressed in g/cm^3 or lb/ft^3. Powders that the pharmacist deals with can be characterized by different types of densities which can give useful information about a powder and its constituent particles. And since powders normally flow under the influence of gravity, dense particles are generally less cohesive than less dense particles of the same size and shape. If a powder is poured (cascaded) into a container, it forms a bed, part of which is solid, part of which is void space (air). (46, 47)

In work with solids there is the following conventional density terminology:

- True or absolute density (ρ) is the weight to volume ratio of only the solid portion of the powder particles, i.e., the mass of 1 cm^3 of nonporous crystal.

- Bulk density or the ratio of the weight of a powder to the volume it occupies expressed in the same terms as the true density. This density term accounts not only for the volume of the solid portion of the particles (true density), and the voids within each particle (internal porosity), but also for the voids between the particles.

- Tap density: This is the density of a powder when the volume receptacle is tapped or vibrated under specified conditions while being loaded. Each particle of a solid material has the same true density after grinding, milling or processing, but more geometric space is occupied by the material.

2. Moisture content

The problem of hygroscopicity is of importance in pharmaceutics. If a drug product is to be made, and if it is known that it is moisture-sensitive, then obviously it cannot be allowed to pick up large amount of water during processing. The use of air conditioners is widespread, but capacities of such systems vary. (48, 49)The important aspect is to know how much moisture a solid substance will pick up at given conditions and to then assess how to change the surroundings so as to keep the quality of the drug product intact or optimum.

The moisture content of a wet solid is expressed as kg of moisture associated with one kg of the moisture-free or "bone-dry" solid. A moisture content of 0.4 kg of removable water is present per kg of the dry solid which will remains after complete drying. It sometimes expressed as % moisture content.

3. Powder flow properties

Powders are generally considered to be composed of solid particles of the same or different chemical compositions having equivalent diameters less than 1000μm. However, the term 'powder' will also be used here to describe groups of particles formed into granules which may have overall dimensions greater than 1000μm.

There are two main factors that affect powder flow: particle size and particle shape. The closer a particle is to spherical the better it flows (50). Small particles are very cohesive, making the flow poor (51) and (as a whole) increasing the particle size will improve flow.

If a powder flows poorly, then some improvement can at times attained by means of a so-called glidant. Talc is an example of a glidant. Often, however, this is not sufficient in itself to improve the flow sufficiently, and other means of flow improvement are necessary. (52)

Carr has been able to demonstrate that the percentage compressibility, C, of a powder bed gives an indication of the flow characteristics of the powder:

$$C = (\rho_f - \rho_o / \rho_f) \times 100$$

Where ρ_o is the initial bulk density and $\rho_{f\,is}$ the constant density.

4. Particle size analysis

Particle size analysis is the mean by which changes in size distribution of powder particles is determined as a result of milling, and for purpose of tablet making, can be divided into two ranges:

1. Subsieve size range-100μm or smaller

2. Sieve size range-44μm or larger

Although there is an area of overlap, each particle size range requires different methods of analysis, but both ranges use essentially the same mathematical treatment for the characterizing of the size distribution.

There are many methods of analyzing particle size distribution and mean particle size.

1. Sieve analysis.

2. Stream scanning.

3. Sedimentation in Gas or Liquid.

4. Optical Microscope.

5. Laser diffraction.

6. Laser diffraction.

- ***Sieve Analysis***

This is the most widely used method of determining the size distribution of a powdered and granular material. Sieves are generally used for grading coarser particles; if extreme care is used, however, they may be employed for screening material as fine as 44 micrometers (No. 325 sieve). Sieve analysis is a good method to cover a particle size from 44μm and greater. (53) The data collected from the difference in the tare weight of each screen and the total weight of the tare and the powder is entered in table form, and the cumulative percentages calculated. The mean of the class interval is obtained by taking the average of each pair of adjacent screens in the nest, e.g., 12 mesh= 1680μm and 20 mesh= 840μm: the mean of the class interval would be calculated to be:

(1680+840)/2 =1260μm

F. The objective of this study

The most important objective of this study is to evaluate the effect of a geometric design of a coated core for an orally controlled drug delivery device, and to optimize the formulation of the core by manipulating the drug/excipients ratio, drug loading and hydrophilic additive level (magnesium stearate), in order to get as close as possible to zero-order kinetics release behavior. The proposed device involves a particular geometry that is expected to counterbalance the increase in diffusional path by increasing the area of the dissolution front with time.

II. Materials and methods

A. Materials

1. Chemicals

- Metoprolol Tartrate, USP, (Sun, lot no. 109585) used as a model drug
- Aminophylline (Anhydrous), USP, lot no. D65854110 used as a model drug
- Lactose (spray dried), USP (Anachemia Ltd, Montreal, lot No. 481005) was used as diluent
- Ethyl cellulose, N.F. (The DOW chemical, lot. No. 840801-6) was used as impermeable compressed coat.
- Magnesium stearate, MS, Fisher scientific, jersey city, NJ., lot 765987)
- Chitosan, Practical grade (Sigma, St. Louis) lot No. 92H77031
- Methyl cellulose, USP, 4000 Centipoise (Medisca), lot no. MK12012N01
- Sodium chloride, potassium chloride, potassium phosphate monobasic, sodium phosphate dibasic, sodium hydroxide and hydrochloric acid were of reagent grade and used as received for buffer preparation
- Eudragit RS PO, powder(Rohm Gmbh), lot No. 0450938222

2. Instruments

- Turbula mixer (Wab Switzerland)
- Carver Laboratory press (model C,F. Carver Inc.,NJ)

- Hewlett Packard spectrophotometer (Model HP 8452 diode array)
- Dissolution apparatus (Distek, Model 2100,NJ) with the USP XXII paddle method
- Diffusion cell
- Tempered steel die with1 cm diameter, flat punches, and biconcave punches having 20° angle with a central hole
- Pharma test PTG-1 used as a flow meter
- Auto tap
- Sartorius MA30 used as moisture analyzer
- Octagon 2000 used as particle size distribution analyzer (sieve shaker).
- Gas adsorption porosimeter (Coulter A3100)

B. Methods

1. Methods of Tablet Manufacture

In this research project two different devices were prepared:

i. Flat tablet shaped cores were prepared by pouring 400 mg of the drug/excipient blend, Metoprolol Tartarate into a steel die (1 cm diameter) and compressed with flat punches at 69.0 MegaPascal, MPa, (10000 lb) for 30 sec. by using a Carver Laboratory press (model C, F. Carver Inc., NJ) then 200 mg of ethyl cellulose was poured on both sides of the core (top and bottom) leaving the edge of the core uncoated which represent the window by which the core can contact the surrounded medium.

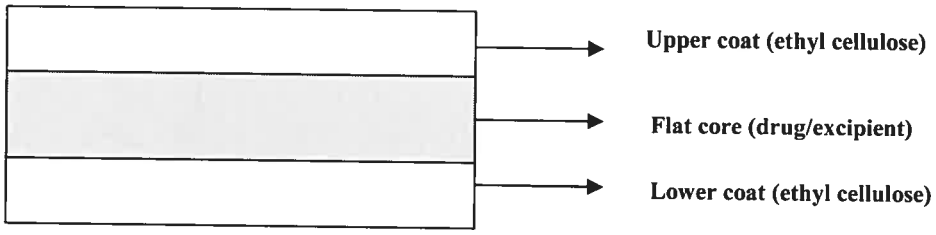


Figure 15: flat tablet shaped core

ii. Biconvex cores with central hole were prepared by pouring 400 mg of the drug/excipients blend into a steel die (1cm diameter), and compressed with biconvex punches having an angle 20° with a central rod (1.2mm diameter) for the formation of the hole in the middle. This central hole is required for the creation of a bridge between the lower and upper coat, to avoid the separation problems during the dissolution process. The cores were then coated as described previously by first pouring 200 mg of ethyl cellulose in the die followed by the insertion of the core then 200 mg of ethyl cellulose then the upper punch and finally compressed to 69.0 MPa (10000 lb).

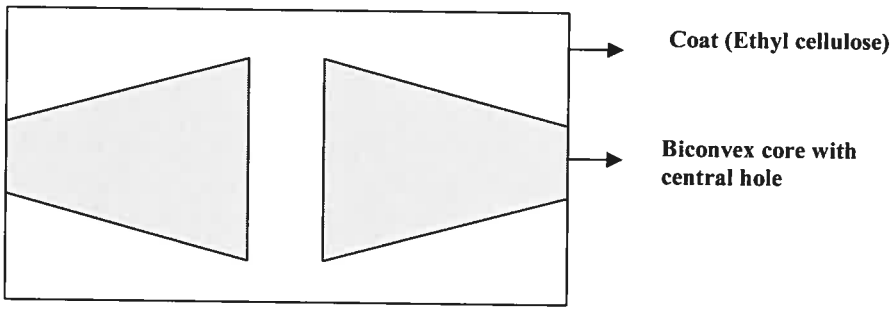


Figure 16: Radially releasing biconvex device (RRBD)

To achieve a controlled release delivery system, we need to have:

a. Coating membrane totally impermeable to water, therefore drugs can only be released through the uncoated edge of the core.
b. The core and coat should have good interlocking and be well adherent, to avoid either infiltration of medium in between the coat and the core or separation problems during the dissolution process, in order to maintain uniform and controlled release of the drug through the dissolution process.
c. The coating should be in intact until the end of the dissolution process.
d. An appropriate formula containing drug and appropriate excipients

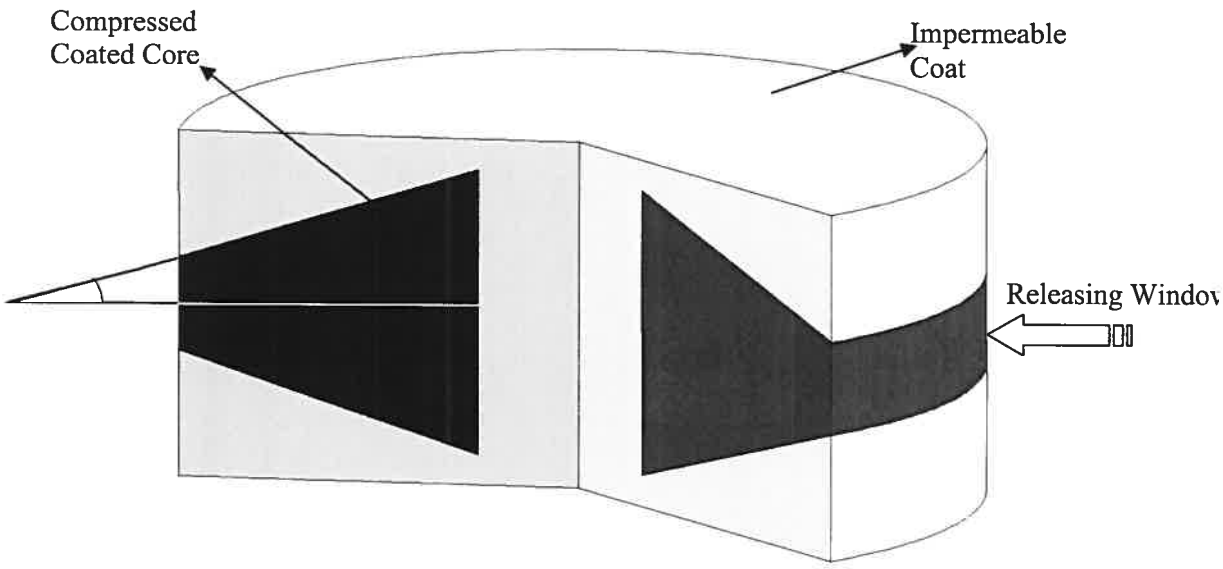


Figure 17: Cross sectional view of the proposed device

2. Analytical methods

a) Permeability test

For this proposed device it is critical to evaluate the permeability of the membrane to ensure that the drug release occurs through the uncoated periphery. Therefore, in order to investigate the permeability of the membrane, the following materials were tested: chitosan, methyl cellulose, ethyl cellulose and eudragit.

The permeability of ethyl cellulose was tested by using a diffusion cell. Compartment A was filled with a saturated solution of Aminophylline, Compartment B contained a buffer solution and a disc of compressed ethyl cellulose was put between them. The diffusion cell is then placed in a water bath, compartment A is continuously agitated by using magnetic stirrer to insure a minimal diffusion layer and homogenous drug solution. The release kinetics was evaluated by using a U.V. Spectrophotometer. No significant levels of Aminophylline over a period of 24 hours were detected indicating that the ethyl cellulose compressed disk is totally impermeable. (17, 54)

Table 1, summarizes the results obtained from the diffusion studies using the coating materials used for the biconvex core device:

Material	Dissolution Period	Results
1. Chitosan	Less than 10 min	Broke
2. Methyl cellulose	Less than 10 min	Broke
3. Ethyl cellulose	Over 18 hours	Intact
4. Eudragit RS PO	Over 18 hours	Intact

Table 1: Evaluation of the permeability of compressed insoluble polymers

b) **Powder characterization**

(1) **Density**

The density was evaluated using the Autotap Quantachrome. A sample weighing 120g was poured into graduated cylinder, then the ratio of the powder weight to the volume of the powder (bulk density) was noted, then tapped 10 times to determine V_{10} and tapping continued to determine V_{500} (tapped 500 time), the volume at which there is no any change in the density value (true density), as shown in Table 2.

(2) **Moisture content**

A sample weighing 1.5g (Lactose, Ethyl cellulose, magnesium stearate, Aminophylline and Metoprolol Tartarate) was spread into the dish of the moisture analyzer (Sartorius MA30) under fixed conditions

(temperature 105°C for 7 min.) then every sample was weighed again to calculate the difference in the weight which represents the moisture content. The results are shown in the Table 2

		Metoprolol	Aminophyl-line	Lactose (spray dried)	Ethocel
Bulk density m/V_0	g/mL	____	____	0.61	0.53
Tapped density m/V_{final}	g/mL	____	____	0.73	0.65
Tapping aptitude V_{10}-V_{500} for 100g	mL	____	____	13	13
Compressibility Index $(V_0-V_{final})/V_0*100$	%	____	____	16.9	18.7
Moisture Content	%	0.93	19.07	6.75	8.11

Table 2: Study the density, compressibility index and moisture content

(3) **Powder flow properties**

A sample weighing 110 g (spray dried lactose and ethyl cellulose) was poured into a funnel with 10 mm and 15 mm outlet orifice diameter. The time required for 100 g weight of the sample to pass through the orifice of the funnel represents the flowability of the sample as shown in Table 3.

Material	Outlet orifice diameter (15mm)		Outlet orifice diameter (10mm)	
	Mean(S/100)	St. Deviation (S/100)	Mean (S/100)	St. Deviation (S/100)
Metoprolol tartarate	*	*	*	*
Aminophylline	*	*	*	*
Lactose (spray dried).	5.3	0.3	18.6	0.1
Ethyl cellulose	8.0	0.2	45.4	11.2

* No flow

Table 3: Study the flow property of the used ingredients

Metoprolol, Aminophylline and Magnesium Stearate have poor flow characteristics because they have small particles size, in which the cohesive forces become stronger than the gravitational force, thereby affecting the flow through the orifice. This, of course, is a function of the size of the orifice, and flow might be possible in a larger orifice (which may not be relevant).

From Table 3, it is obviously that lactose (spray dried) and ethyl cellulose have very good flow properties. But in the case of Metoprolol Tartarate, Aminophylline and Magnesium Stearate they have very poor flow properties. Since the compressibility index can be a good guide to the

powder flowability, from Table 2 we see that the compressibility value of lactose (spray dried) and ethyl cellulose was low meaning that both of them have a good flow property.

(4) **Particle Size Analysis**

(a) **Metoprolol tartarate**

As shown in Figure 18 the geometric distribution of particles size of Metoprolol Tartarate reveals a positive skewed distribution, about 45% of particles are less than 75μm. in general, fine particles with very high surface to mass ratios are more cohesive than coarser particles which are influenced more by gravitational forces. Particles greater than 250μm are usually relatively free flowing, but as the size falls below 100μm, powders become cohesive and flow problems are likely to occur. Powders having a particle size less than 10μm are usually extremely cohesive and resist flow under gravity except possibly as large agglomerates. Since the flow property is function of particle size, shape and density, the combination of a high level of fines with rod shaped particles of Metoprolol results in poor flow properties (see Figure 19).

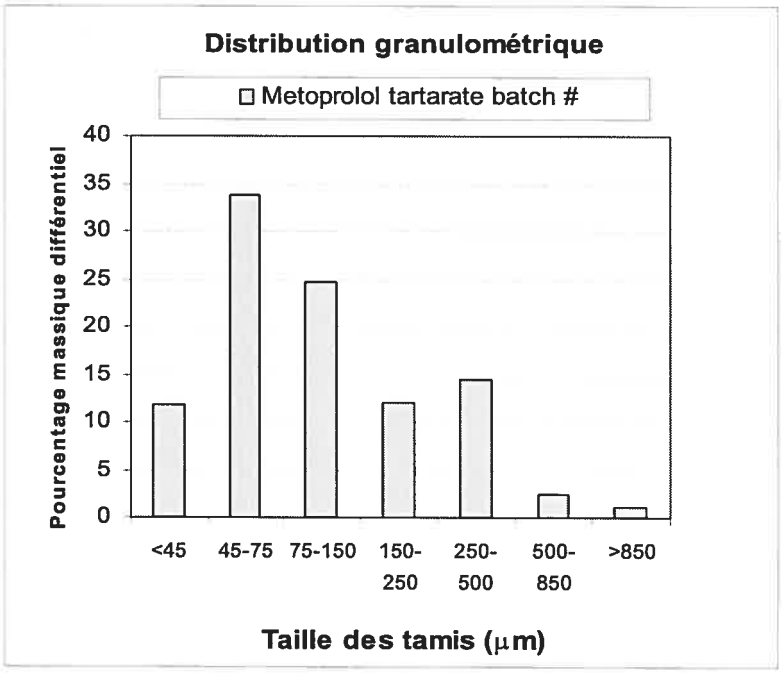


Figure 18: Particle size distribution of Metoprolol Tartarate

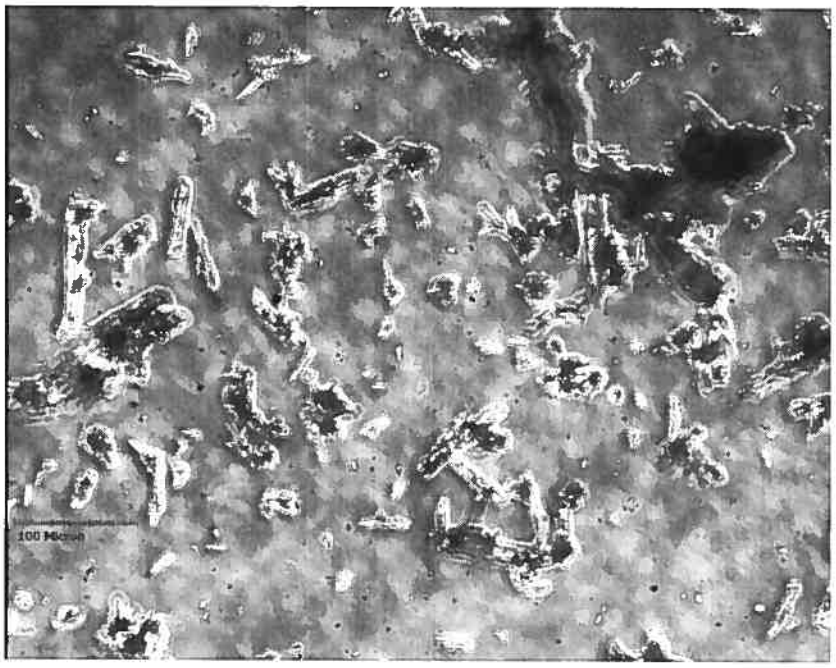


Figure 19: Microscopic picture of Metoprolol Tartarate particles

(b) **Aminophylline**

As seen in Figure 20, the geometric distribution of Aminophylline indicates that there are 70% of the particles in the powder having a size less than 75 µm which means that the particle size distribution is skewed toward fine particles which affect the flow property. Figure 21 as well illustrated that the particles size is fine and as a result of that Aminophylline has very poor flow properties

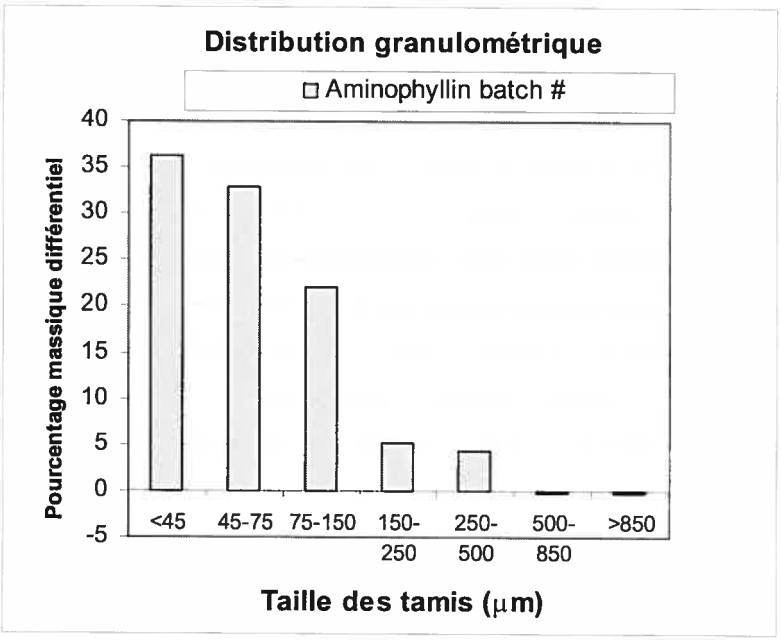


Figure 20: Particle size distribution of Aminophylline

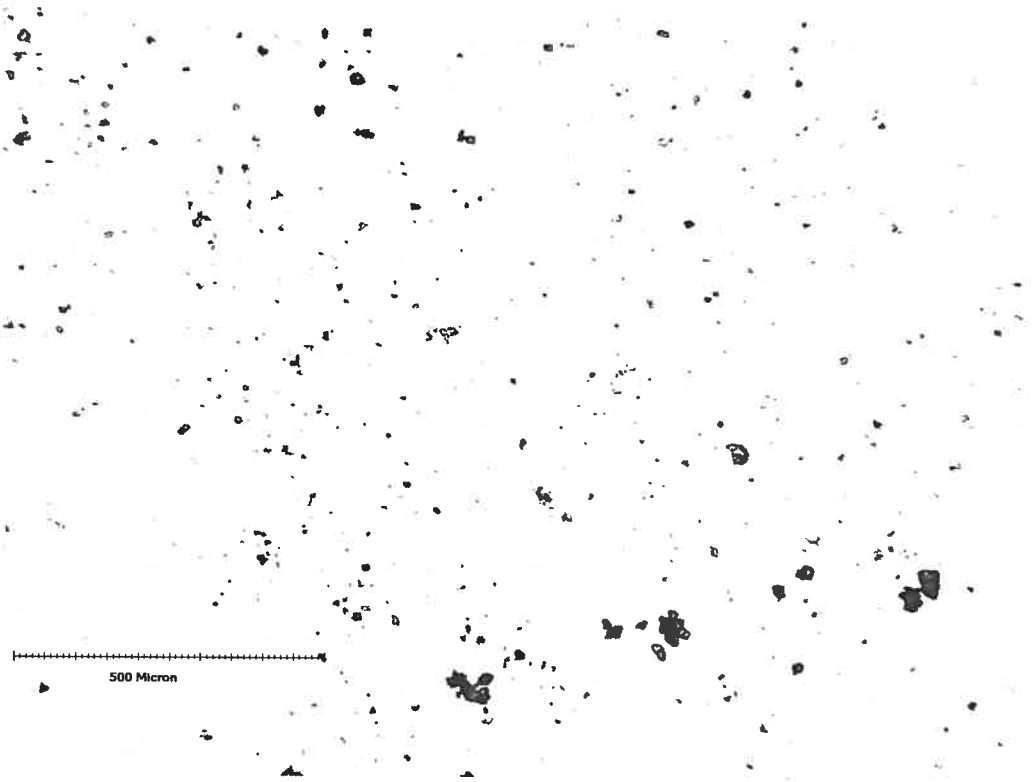


Figure 21: Microscopic picture of Aminophylline particles

(c) **Lactose (spray dried)**

As shown in Figure 22, the particles size distribution of Lactose reveals that there are less than 20% of the particles having size less than 75μm, and about 80% of the particles size is between 75 to 250μm. As result of that spray dried lactose has excellent flow properties. In addition to the compressibility index value of lactose is low which consider as a good proof for the powder flow ability.

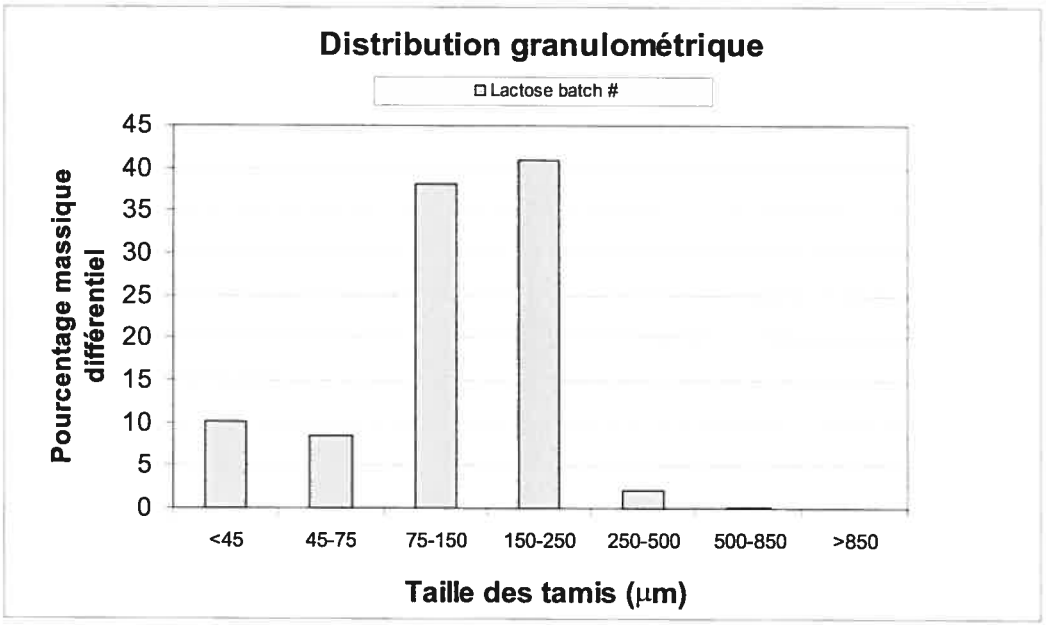


Figure 22: Particle size distribution of Spray Dried Lactose

(d) **Ethyl cellulose (Ethocel)**

As seen in Figure 23, the geometric distribution of ethocel reveals that about 18% of the total particles size are less than 45µm, and 10% from 45-75µm, and about 65% of total particles having size from 75 to 500 µm.

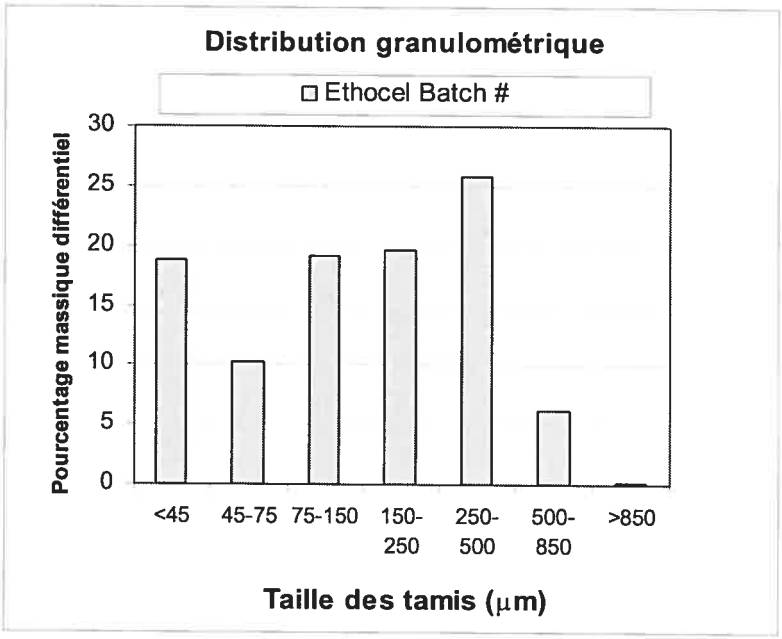


Figure 23: Particle size distribution of Ethyl cellulose

c) **Tablet Porosity**

The powder column is a mixed system consisting of a solid particulate material and air. Air can be present between particles (interparticulate void) and inside particles (intraparticulate voids). The physical nature of a powder column is different from that of a solid body, because powder can flow and have rheological properties typical of liquids. On the other hand, permanent deformation (plasticity), and brittle fracturing of particles, typical phenomena for solid bodies occur in powders. Therefore, the behavior of powder in pharmaceutical processes, e.g., during compression, is often very complicated. In die compaction of powders, materials are subjected to mechanical forces which lead to reduce the volume of powder column. A volume is reduced by decreases in the inter-

and intra particulate pore space. The process of volume reduction is generally divided into different stages: die filling, rearrangement of particles, deformation by elastic changes, permanent deformation by plastic flow, or particle failure by brittle fracturing. The measuring of porosity changes as a function of the compression pressure is a method widely used in describing the compaction processes of powders. (55, 56)

Porosity is a function of the voids in a powder column, and in general all pore space is considered, including both inter- and intraparticulate voids. For porosity measurements, the dimensions and weight of a powder column (i.e., apparent density) and the particle density (referred to often as true density) of the solid material should be known. The porosity, ϵ, can be expressed by the equation:

$$\varepsilon = 1 - \rho A / \rho T \qquad \text{(Equation 36)}$$

d) **Dissolution and drug releases studies**

The dissolution and drug release studies were achieved using a Hewlett Packard spectrophotometer (Model HP 8452a diode array) and Distek dissolution apparatus (Model 2100, NJ) in accordance with the USP XXII paddle method. Tablets were introduced in dissolution vessels containing 900 ml of an isotonic phosphate buffer PH 7.4 and subjected to 50 rpm of stirring speed. Amount of drug released was determined

spectrophotometrically at 244nm for aminophylline and 296nm for metoprolol.

III. Results and discussion:

A. Core Coat Development

At the beginning of the core coat design process, the core of the proposed device was made by using a biconcave punch set with 20° angle by pouring a specific amount of the blend into a die and compressing at 69.0 MPs (10.000 lb). After that the punches were pulled out and then a specific amount of coating powder impermeable membrane was added at the top and the bottom of the compressed biconcave core, and then flat punches were used to compress the whole tablet (i.e., biconvex core in the middle and the two layer of the an impermeable membrane) under 69.0 MPs (10.000lb) for 30 second. Within the same procedure and under the same conditions, another tablet was prepared but in this case the core has a central hole. Both of the different devices were put into a beakers filled with 900 ml of buffer solution.

During the first hours of analysis of the release of Aminophylline from those different devices the core swelled and the aqueous solution starts to penetrate between the biconvex core and the coating layer. Furthermore the drug release was much higher than the device (with central hole in the

core) and after that the two impermeable coats started to be separated from the core as shown the Figure 24 While in case of the core with a central hole the release was constant and the structure of the tablet stayed intact till the end of the dissolution (i.e., until all the amount of the drug in the core was released)

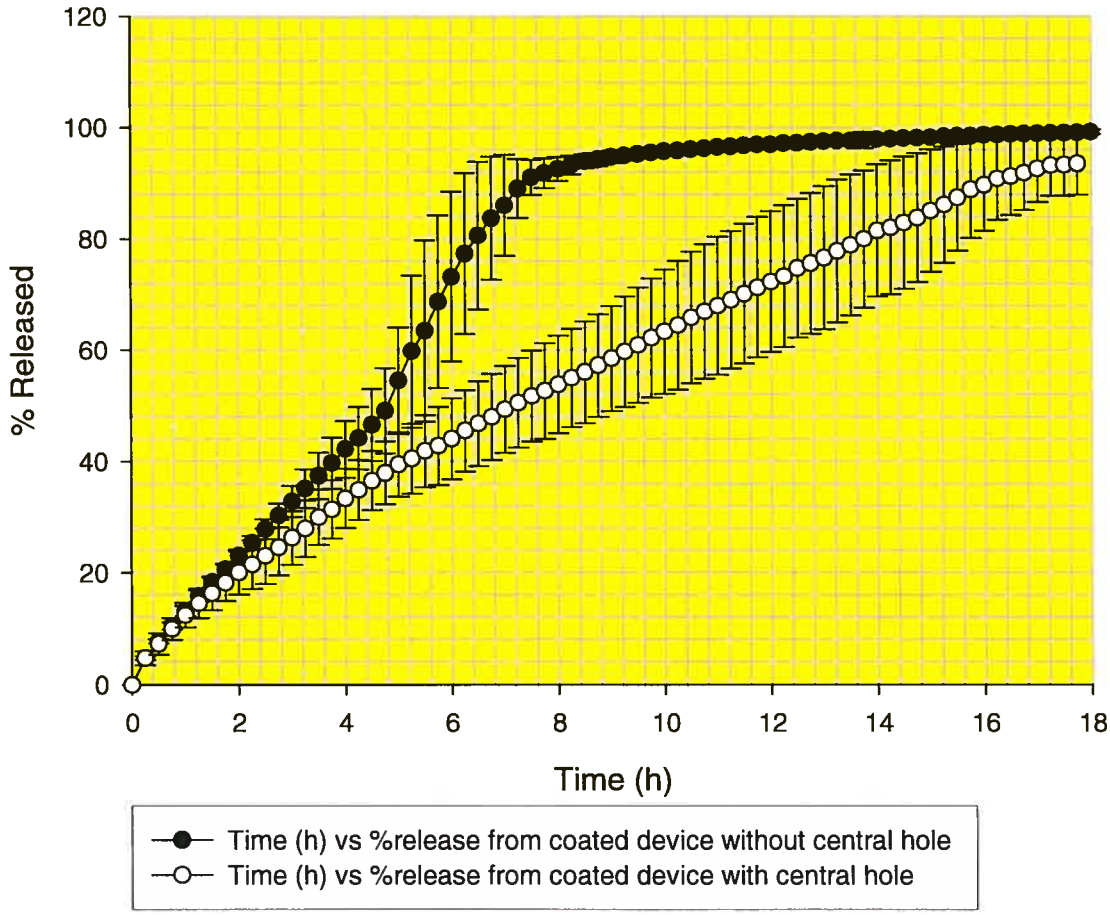


Figure 24: Study the release of Aminophylline from device with hole in the coat vs. press-coated device without central hole.

B. Drug release studies

1. Metoprolol studies

The solubility of the model drug is a very important parameter in the evaluation of the efficiency of the proposed device. The control of the release of highly soluble drugs in water is much more difficult than those of low solublities. The proposed device was investigated using MT as model drug. MT belongs to $beta_1$-selective adrenoceptor antagonist with wide therapeutic usage, especially for hypertension and ischemic heart disease. It has a relatively short elimination half-life of about 3-4 hours and is consequently a candidate for an oral controlled-release preparation. Since MT is highly soluble in water then it is a good model drug to start with. This study is supported by a previous work conducted in our laboratory (58). Seven different formulations of MT were evaluated as shown in Table 4.

Formula	I	II	III	IV	V	VI	VII
Metoprolol	37.5	37.5	37.5	37.5	37.5	25	50
Mg.Strearate	0.5	1	2	2.5	5	2.5	2.5
Lactose	62	61.5	60.5	60	57.5	72.5	47.5

Table 4: Core composition, Metoprolol,(%w/w)

a) **The effect of magnesium stearate level on Metoprolol release kinetics.**

As shown in Figure 25, the study of the effect of different concentrations of MS on the percentage released of Metoprolol Tartrate (MT) from a Radially Releasing Biconvex Device (RRBD) having a releasing height of 1.2mm, where the model drug is released to the surrounding media, Each device having the same concentration of MT and different levels of MS and filled up with spray dried lactose as diluent, (Formula I, III, and V as shown in Table 4). The results show that MS has a significant effect on the percentage MT released and particularly on the releasing rate of the drug. By increasing the level of MS, the rate of release decreased.

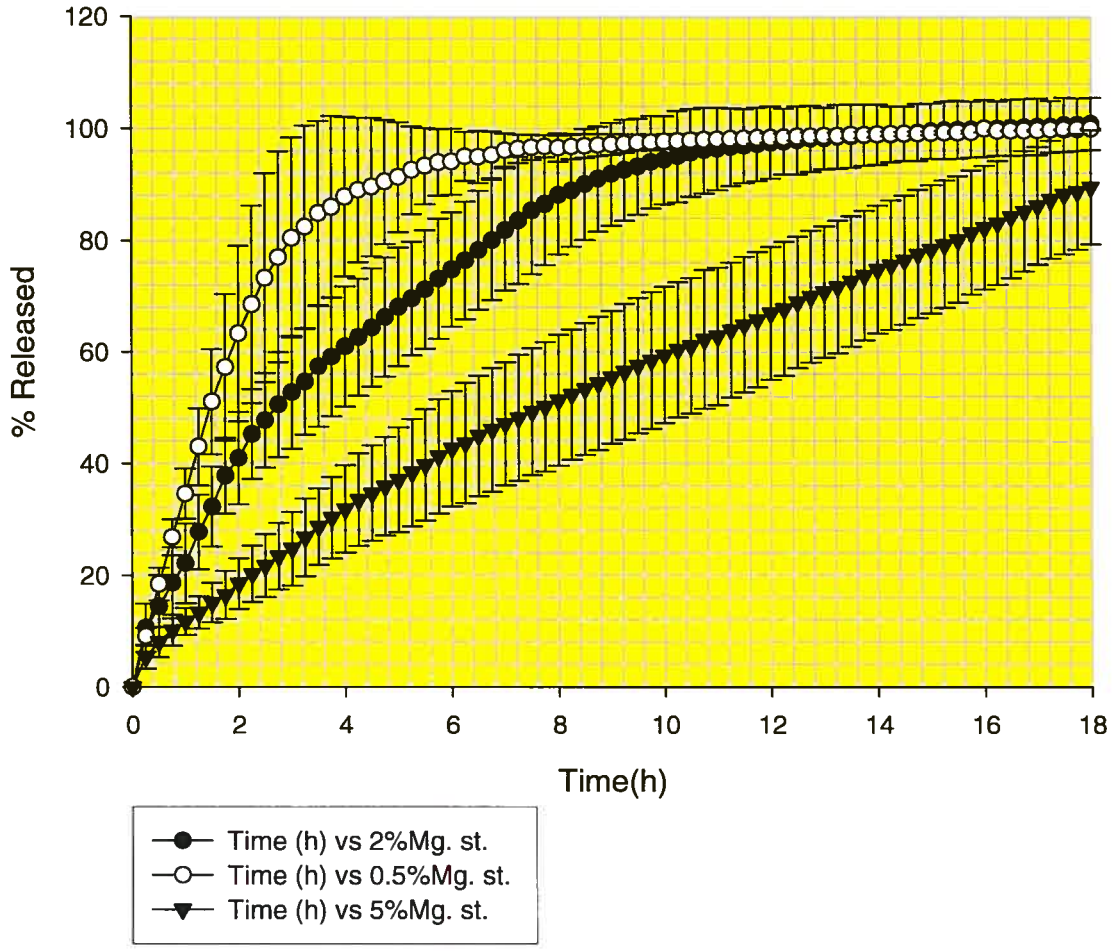


Figure 25: The effect of magnesium stearate loading on Metoprolol tartarate release (Formula I, III, and V)

As the concentration of the MS increases the release rate decreases and the release kinetic approaches zero order, (i.e. release curve is more linear). As seen in Figure 25, in case of 0.5% level of MS in the formula the percentage released of MT was very high over a short time, therefore, the release profile showed a very high burst followed by first order release kinetics. Significant reduction in drug release occurs by increasing the MS

level from 2 to 5% as a result of the increased hydrophobicity induced by MS. So when the level of MS increases the intrinsic dissolution of the blend (core) decreased. This study demonstrated that the ratio of the constituents of the formula (active to inactive ingredients ratio) has a very significant effect on the release kinetic in the formulation of this device.

b) **The effect of drug loading on release kinetics**

The results of the dissolution studies from the proposed device having different drug loading levels with the same level of magnesium stearate in each device, prepared under the same conditions are shown in Figure 26.

The release kinetic profiles for formula VI and IV (25% and 37.5% drug loading) are significantly different. Formula IV first order while VI near to zero order. In the case of formula VII (50% drug loading), where the drug loading was doubled, the drug release rate was higher and deviated significantly from zero-order. Since the solubility of Metoprolol is three to four times higher than lactose, moreover the ratio of the highly soluble portion to low soluble portion is high in formula VI resulting to that slower dissolving core. But in case of formula VII(50% loading) it is obvious that the ratio of highly soluble ingredient to low soluble is much higher than formula VI and IV, leading to the higher release rate for formula VII than for the release rate for formula VI and IV.

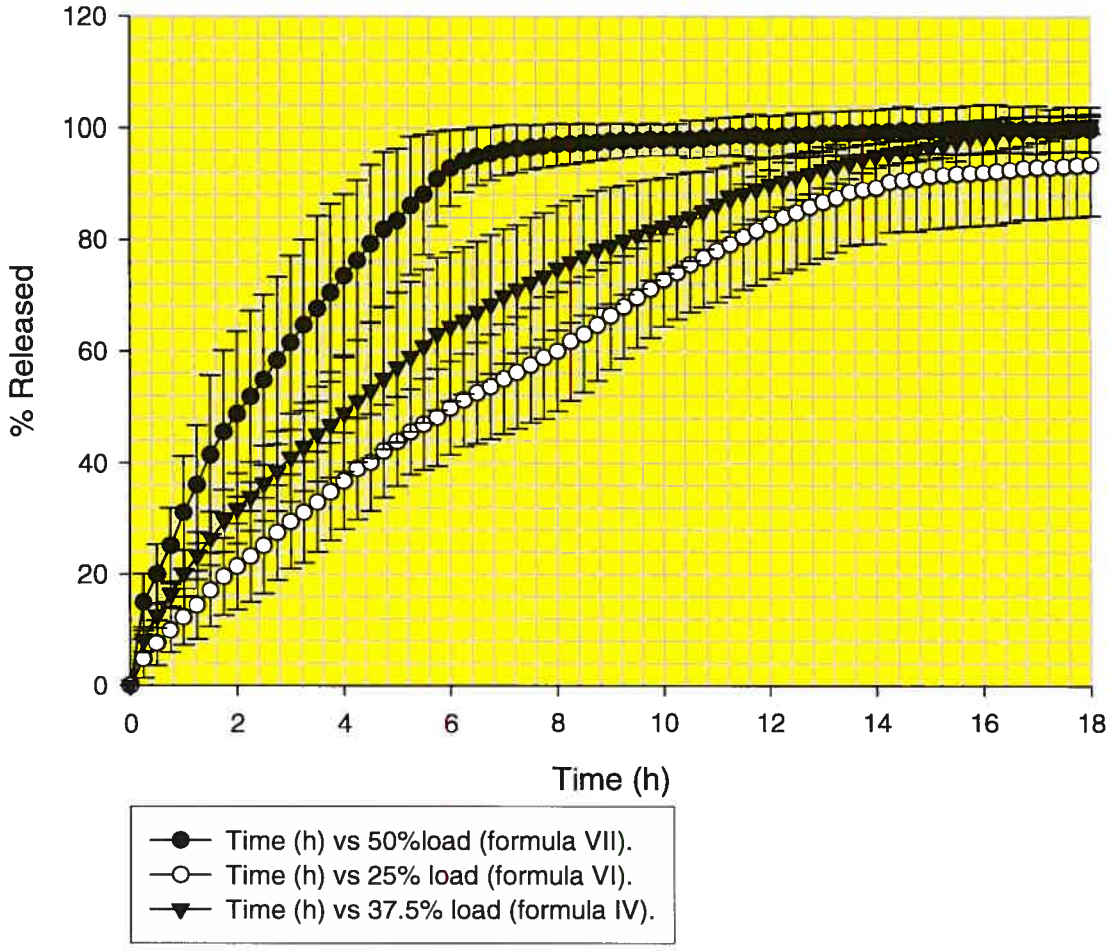


Figure 26: The effect of drug loading of Metoprolol on the kinetic release (formula IV, VI, and VII).

c) **The effect of height at the edge (Releasing window) on the drug release**

In this study the objective was to evaluate the effect of the surface area at the releasing surface on the percentage of drug released as a function of time. The devices were made up under the same conditions

and from the same blend as formula IV but with different heights at the edge of the tablet core, 0.5, 1.0, 1.5, 2.0, and 3.0 mm.

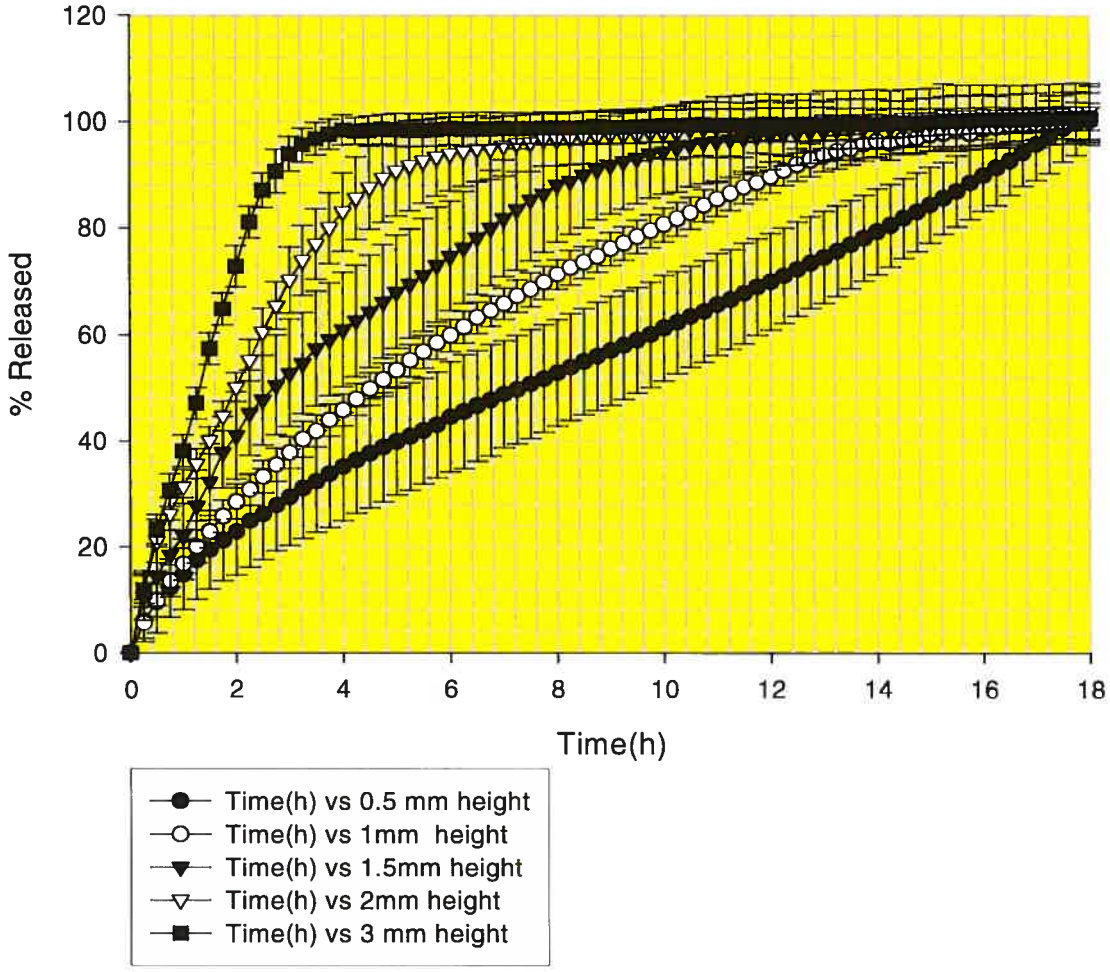


Figure 27: The effect of height at the edge (releasing window) on the drug release (formula IV)

As shown in Figure 27, in all cases, the release rates increased as the height at the edge increased from 0.5 to 3mm. it is obviously that there is a significant effect of the core peripheral height on the release kinetics. The increase in area exposed to surrounded media accelerated the

dissolution process, therefore decreasing the time for 100% release. From Figure 27, in the case of 3 mm height, more than 85% of the drug is released within 4 hours while in the case of 1 mm height it took more than 10 hrs to reach 85% pf drug released.

d) **The release of MT of formula IV from devices: Flat and Biconvex cores.**

Figure 28, demonstrates the percentage released of MT from biconvex vs. flat core devices. Both cores are made from the same blend (formula IV), pressed under the same compression force 69.0 MPs, (10.000lb), the same dwell time and had the same releasing surface area.

As seen in Figure 28, it is obvious that the release of the drug model, MT, from the proposed device is more constant and closer to zero order than in the case of the flat core device. Therefore, the drug release profile can be controlled over a more extended period of time with the proposed device as opposed to the continuously diminishing rate achieved from flat device. Figure 29, illustrates the release rate of MT from the two different devices, and it is clear that the release rate from the proposed device is more constant over a more prolonged period of time than in case of flat core device which is characterized by a very high burst followed by a rapidly decreasing rate until exhaustion.

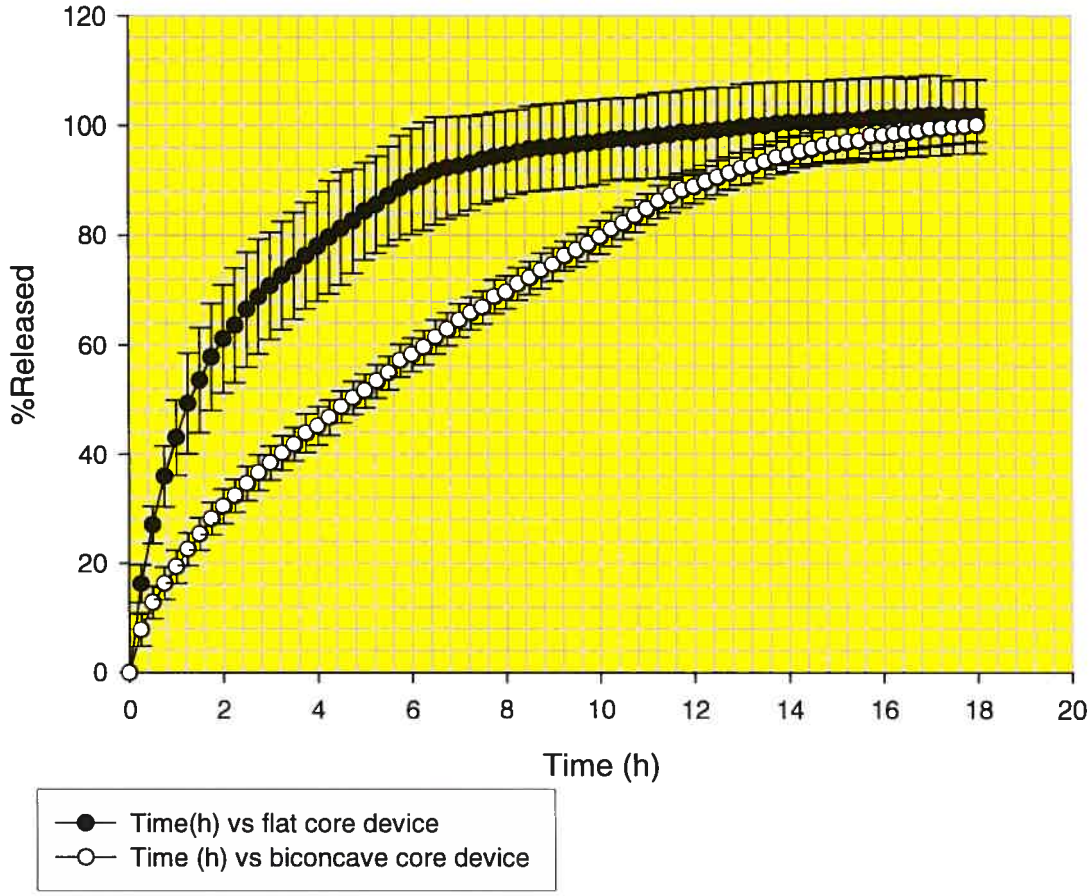


Figure 28: Study the effect of biconvex vs. flat core device on the release of Metoprolol tartarate (formula IV)

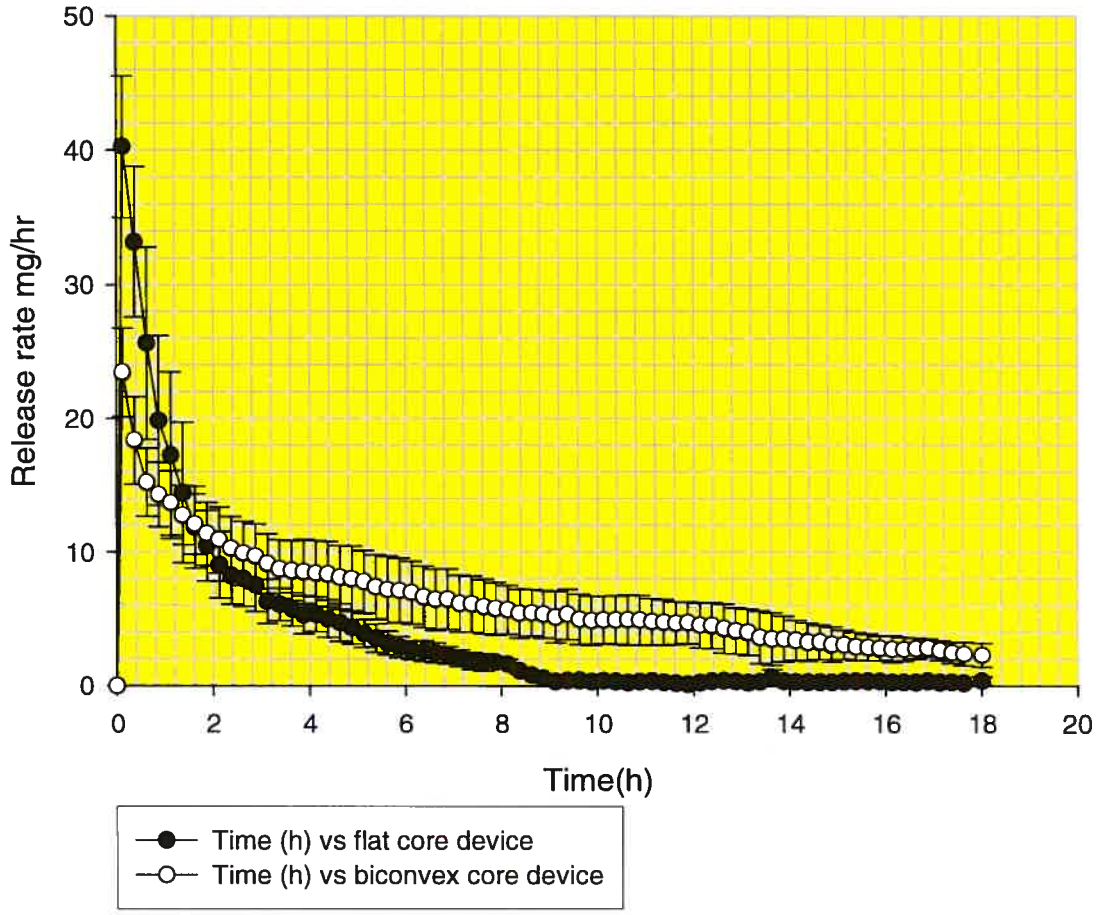


Figure 29: The release rate of Metoprolol from flat core device vs. biconvex core device

e) **Study the influence of agitation rate on the kinetics profile**

The proposed device containing formulation IV was tested under three different speed of agitation namely 50,100 and 150 rpm and the results are presented in Figure 30.It is clearly that the effect of increasing the speed of agitation on the release rate, from the proposed device, is very obvious. The high increase in release rate, with increasing agitation

speed, from 50 to 100 then to 150 observed for formulation IV can be attributed to decreasing diffusion layer at the dissolution front leading to decrease the path length of diffusion as expected for dissolution system.

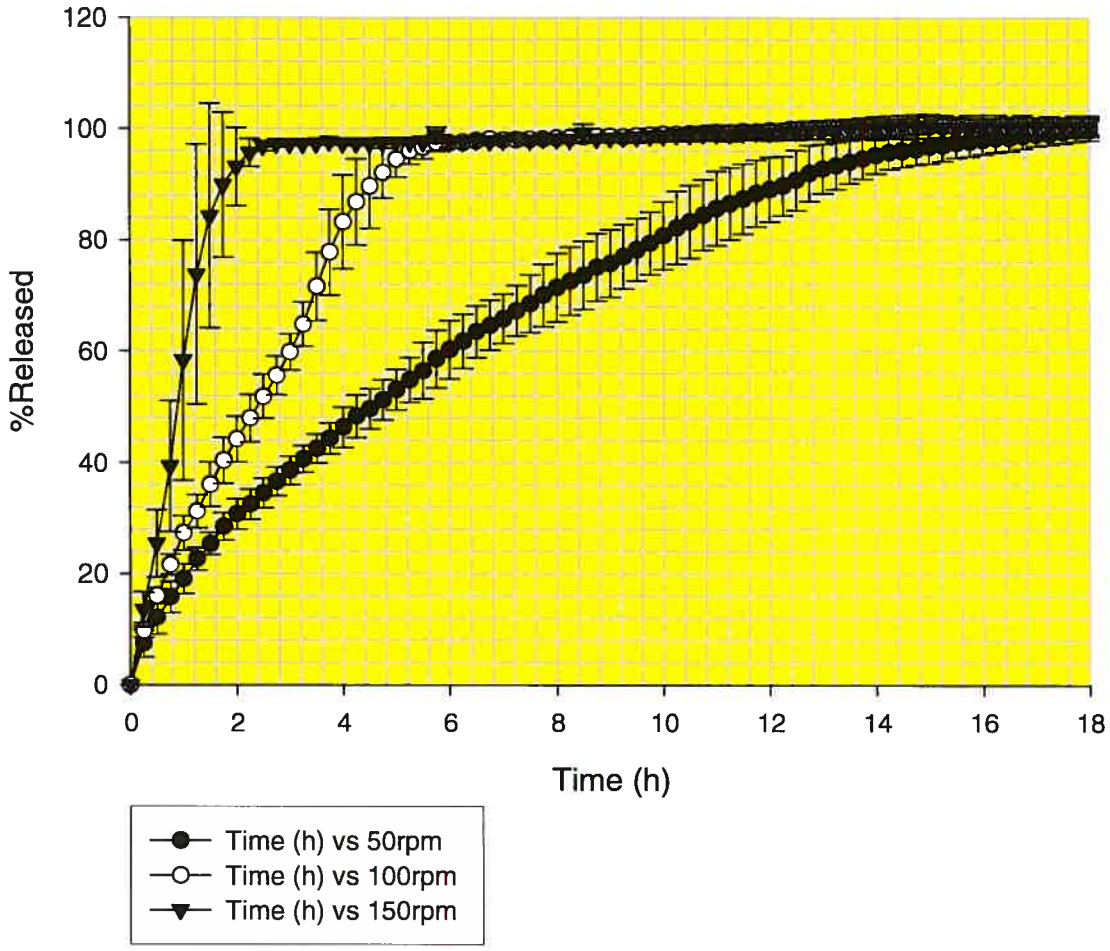


Figure 30: Study the effect of agitation speed on the kinetic profile of Metoprolol tartarate (formula IV).

2. Aminophylline studies

Aminophylline is a very soluble drug in water. In this research Aminophylline was selected as the second model drug in order to show the suitability of the proposed device and its reproducibility to control the release of a drug.

Formula	VIII	IX	X	XI
Aminophylline	33	33	33	33
Ethyl cellulose	40	30	20	15
Lactose(USP)	27	37	47	52

Table 5: Core composition, Aminophylline, (%w/w)

a) The effect of compression force on Aminophylline kinetic profile

The objective of this study was to investigate and validate the influence of the applied mechanical force on the kinetic profile of Aminophylline used as a model drug In order to determine the minimal compression force above which the porosity value does not further decrease (i.e., at which the increase in mechanical force is meaningless). Three devices were made from the same blend (formula VIII) and pressed

under three different compression forces 34.5, 69.0, 103.4 MPa (5.000 lb, 10.000 lb, and 15.000lb) for the same dwell time (30 sec.). The tablets were put in beaker filled with 900 ml of phosphate buffer (7.4pH); the kinetic profile was investigated by spectrophotometry at 244nm.

As seen in Figure 31, it is clear that the release of AM from the three devices was similar which demonstrates that there is no significant difference in porosity values between the three devices.

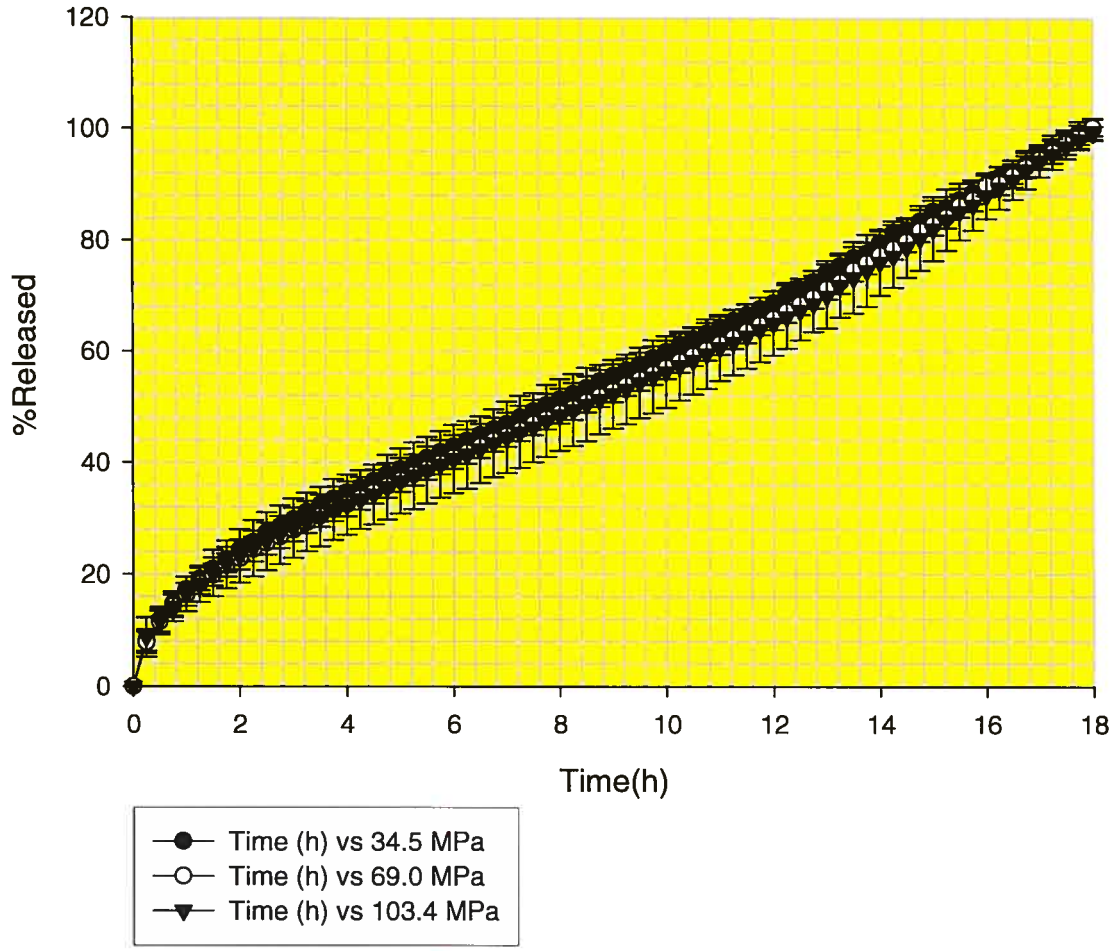


Figure 31: Study the effect of compression force on Aminophylline kinetic profile (Formula VIII)

To demonstrate the low porosity a Coulter SA 3100 was used to measure the porosity and pore size distribution of each tablet pressed under different compression force 34.5, 69.0, 103.4 MPa (5.000lb, 10.000lb, and 15.000lb). As seen in Table 6, and by comparing the compression force used with the total pore volume for every sample (tablet). The results revealed that there is no significant effect of compression force on the total pore volume above 34.5 MPa (5000 lbs) (i.e. total pore volume of tablet compressed at 34.5 MPa (5000 lbs) was 0.0024 mL/g, at 69.0MPa, 10000 lbs was 0.0050 and at 103.4 MPa (15000 lbs) was 0.0051 mg/Ml), therefore the compression force does not affect on the porosity value. But in case of pore size distribution and as shown in figure 32 the compression force has an obvious influence on the pore size distribution of each tablet. The results demonstrated that by increasing the compression force the pore size decreased. As seen in the Figure 32 in the case of compression force of 34.5 MPa (5000lb) the pore size distribution is wide. And by increasing the compression force to 69.0 MPa (10.000 lb) the pore diameter range decreased to less than 6 nm.

Pore diameter(nm)	% of 34.4 MPa	% of 69.0 MPa	% of 103.4 MPa
under 6	10.9	99.99	99.99
6 to 8	10.46	0	0
8 to 10	9.01	0	0
10 to 12	8.44	0	0
12 to 16	9.96	0	0
16 to 20	6.61	0	0
20 to 80	36.92	0	0
over 80	7.7	0	0

Table 6: Pore size distribution of different disks compressed under different forces

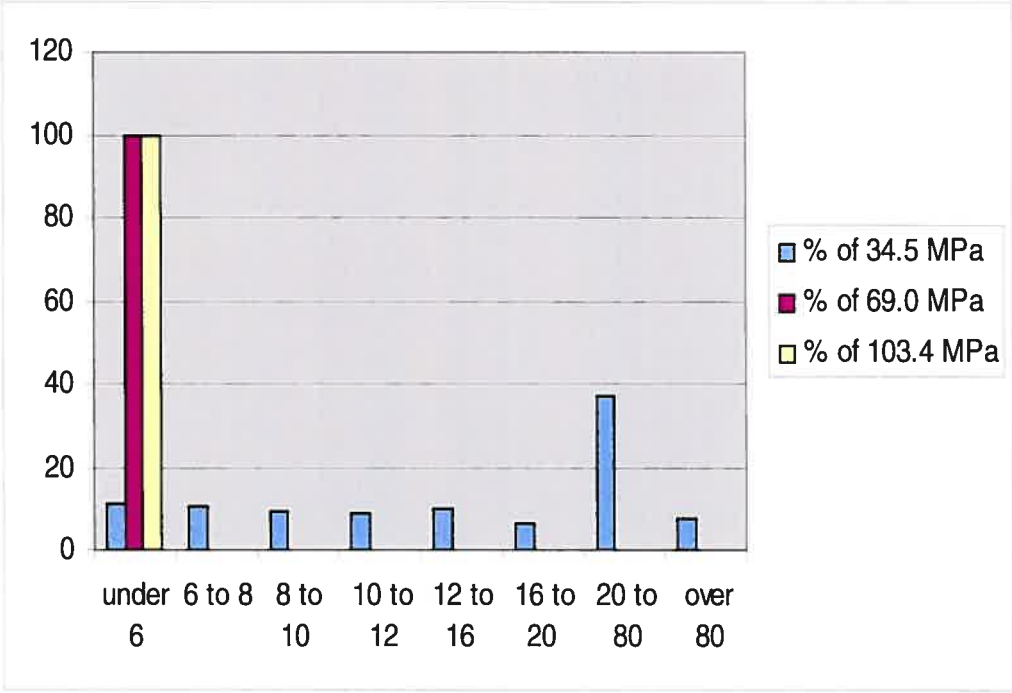


Figure 32: The effect of compression force on the pore size distribution

b) **The effect of ethyl cellulose on Aminophylline release profile**

This study evaluated the influence of ethyl cellulose as an excipient on the release of AM from the proposed device. Four devices were made according to the formulations (VIII, IX, X and XI), which contain 40%, 30%, 20% and 15% respectively, as shown in Table 5. The four devices were made under the same condition, and the release profile was monitored by using a spectrophotometer for 18 hours.

Figure 33 demonstrates the effect of increasing the ethyl cellulose level in each formula. By increasing the level of ethyl cellulose from 15 to 20% there is very significant effect on the release kinetic. By further increasing the level of ethyl cellulose from 20% to 30% does not have as significant an effect on the release kinetic, because at the 15% ethyl cellulose level in formula XI the core dissolves gradually allowing drug to diffuse through the media. In formula X (20% ethocel) the ethyl cellulose forms a gel that remains within the tablet which decreases significantly drug diffusion from the core. By increasing the level of ethyl cellulose to levels higher than 20% does not have as significant an effect because there is probably not a very significant change in the physical state of the gel. Therefore, there is a significant effect on the release kinetic by increasing the amount of ethyl cellulose to a critical level above which there is only a small effect on the release kinetic, Furthermore with increasing ethyl cellulose levels the release rate of Aminophylline is reduced, and the kinetic profile of the drug approaches zero-order.

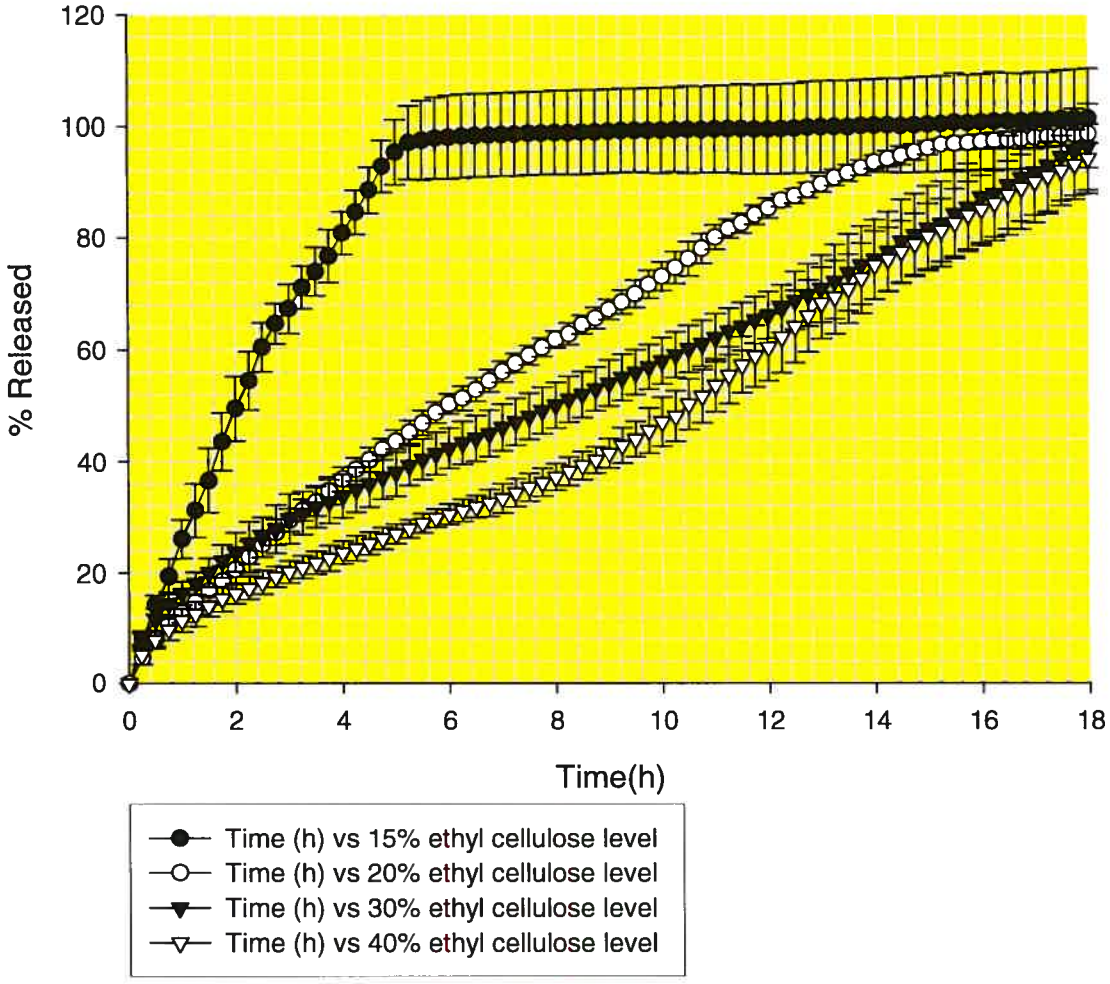


Figure 33: The effect of ethyl cellulose level on Aminophylline release (formula VIII, IX, X, and XI)

c) **The study of Aminophylline from biconvex and flat core devices**

In this experiment the cores of both devices were made from the same blend of formula X as shown in Table 5, in equal amounts as well, using the flat punches for one set and using biconcave punches with 20° angle and hole in the middle for the other set. Both sets of devices were compressed under the same compression force 69.0 MPa (10.000lb) for 30 sec. Figure34 obviously shows the advantage of using a biconvex over a flat device in providing a well controlled drug release rate over an extended period of time. In this Figure it is clearly that the proposed devices achieved a very close to zero-order kinetic behavior comparing to the flat devices. Figure 35, shows the rate of release of the two different devices and it is obvious that the release rate from the proposed device is much closer to zero order that in the flat core device. From the results it is noticeably that the advantage of using biconvex devices to an extend period of time is very clear over the flat devices.

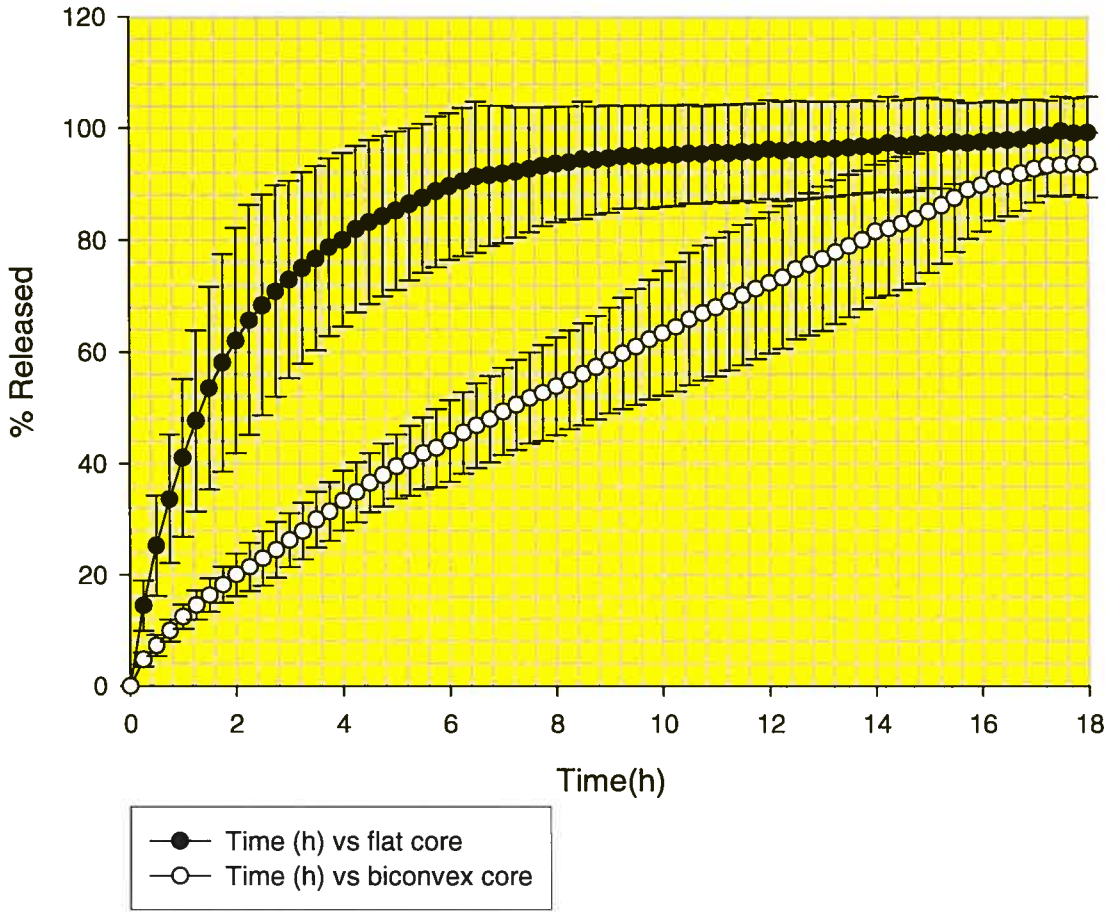


Figure 34: Study of Aminophylline release from biconvex vs. flat core device (Formula X)

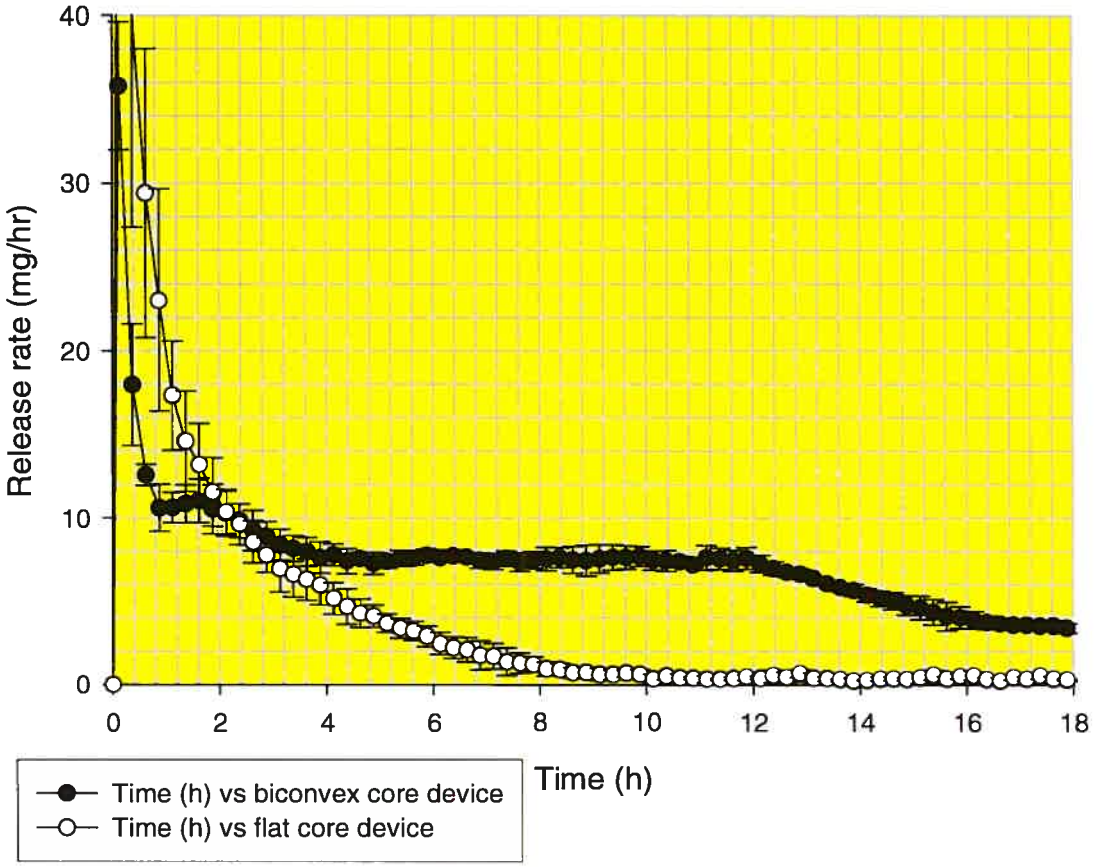


Figure 35: The rate of Aminophylline released from flat core vs. biconvex core devices

IV. **Conclusion**

The results presented in this research work demonstrated the flexibility of the developed system, in adjusting drug dissolution rate through the judicious selection of excipients. The influence of adjusting the drug loading level, and the level of lactose (filler) at constant and increasing levels of Magnesium Stearate revealed that the ratio of these ingredients is very significant in controlling the release of drugs. When lactose was used with highly soluble drugs like Metoprolol Tartarate, the formula needed high level of Magnesium Stearate (hydrophobic) to significantly lower the intrinsic dissolution of the blend and consequently the dissolution rate. In the case of the second model drug (Aminophylline), the effect of changing the level of Lactose and Ethyl cellulose at constant model drug level, revealed that the ratio of the ingredient in the formulation (revealed by its intrinsic dissolution) is very significant in the control of the release kinetics. The study of the effect of the releasing surface area of the RRB device was studied by varying the height at the releasing surface area. The results show that as the height of the releasing surface decreases the kinetics tends to approach zero order. Studies of the effect of the geometry of the proposed device compared to a flat core device suggested that the release kinetic profile is near to zero-order in the case of the proposed device while for the flat core device the release kinetics is typical first order because Radially Releasing Biconvex Device (RRBD) compensates for the increase in diffusional distance by increasing the surface of the dissolutional front resulting in more drug solubilized per unit time.

This research studied another important aspect, associated with the manufacturing process of the proposed device which is the compressional force. The core should be adequately hard to reduce the porosity, therefore avoiding the infiltration of dissolution medium. Moreover the core should have a central hole to prevent the separation problems and keep the whole device intact until the end of the dissolution process.

V. **Appendix**

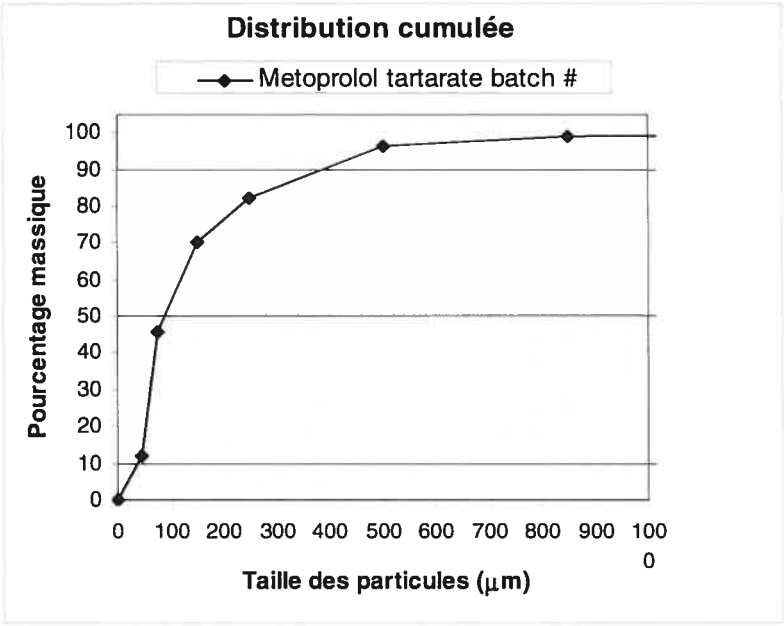
Appendix 1: Pharma test PTG-1 used as a flow meter

Appendix 2: Auto tap

Appendix 3: Particle size analysis machine (OCTAGON2000)

	Poids des tamis			% différentiels		% passant cumulés	
TAMIS	**Vide**	**Plein**	**Poudre**	(µm)	%	(µm)	%
Mesh	(g)	(g)	(g)	<45	11.70	0	0.00
20	348.91	349.39	0.48	45-75	33.75	45	11.70
35	322.91	324.13	1.16	75-150	24.60	75	45.45
60	297.18	303.80	6.62	150-250	12.05	150	70.05
100	286.56	292.12	5.56	250-500	14.35	250	82.10
200	315.50	326.85	11.35	500-850	2.51	500	96.45
325	320.75	336.32	15.57	>850	1.04	850	98.96
réceptacle	255.92	261.32	5.40	Total	100.00	1680	100.00
		Total :	46.14				
Échant. (g):	46.14	**% Récup: 100.00**		Moyenne µm 154			

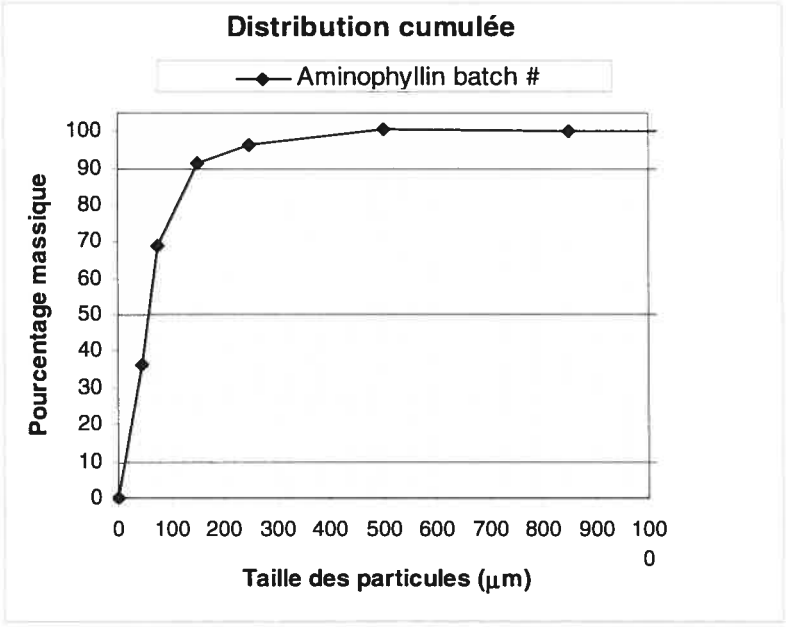
Appendix 4: Data of particle size analysis of Metoprolol Tartarate



Appendix 5: Cumulated distribution of the particles of Metoprolol Tartarate

	Poids des tamis			% différentiels		% passant cumulés	
Tamis	Vide	plein	Poudre	(µm)	%	(µm)	%
Mesh	(g)	(g)	(g)	<45	36.34	0	0.00
20	349.04	348.97	-0.07	45-75	32.76	45	36.34
35	322.90	322.84	-0.06	75-150	22.05	75	69.10
60	297.23	298.21	0.98	150-250	5.18	150	91.15
100	286.84	288.04	1.20	250-500	4.23	250	96.33
200	315.56	320.67	5.11	500-850	-0.26	500	100.56
325	320.69	328.28	7.59	>850	-0.30	850	100.30
réceptacle	255.90	264.32	8.42	Total	100.00	1680	100.00
		Total :	23.17				
Échant. (g):	24.36	**% Récup:**	95.11	Moyenne µm 75			

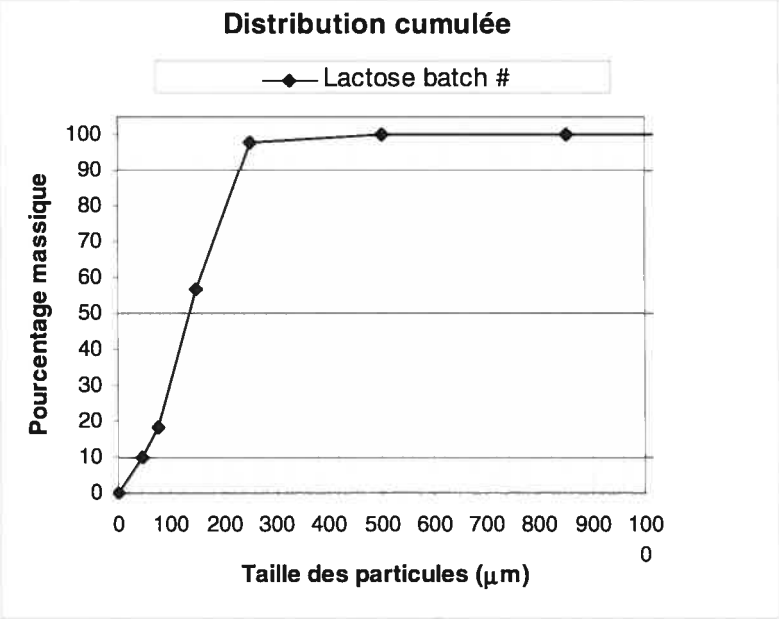
Appendix 6: Data of particle size analysis of Aminophylline



Appendix 7: Cumulated distribution of the particles of Aminophylline

	Poids des tamis			% différentiels		% passant cumulés	
Tamis	Vide	plein	poudre	(µm)	%	(µm)	%
Mesh	(g)	(g)	(g)	<45	10.04	0	0.00
20	349.27	349.28	0.01	45-75	8.48	45	10.04
35	322.96	323.13	0.17	75-150	38.16	75	18.53
60	296.97	298.94	1.97	150-250	41.00	150	56.69
100	286.54	324.67	38.13	250-500	2.12	250	97.69
200	315.55	351.04	35.49	500-850	0.18	500	99.81
325	320.51	328.40	7.89	>850	0.01	850	99.99
Réceptacle	255.81	265.15	9.34	Total	100.00	1680	100.00
		Total :	93.00				
Echant.(g)	92.79	**% Récup**:	100.23	Moyenne µm 142			

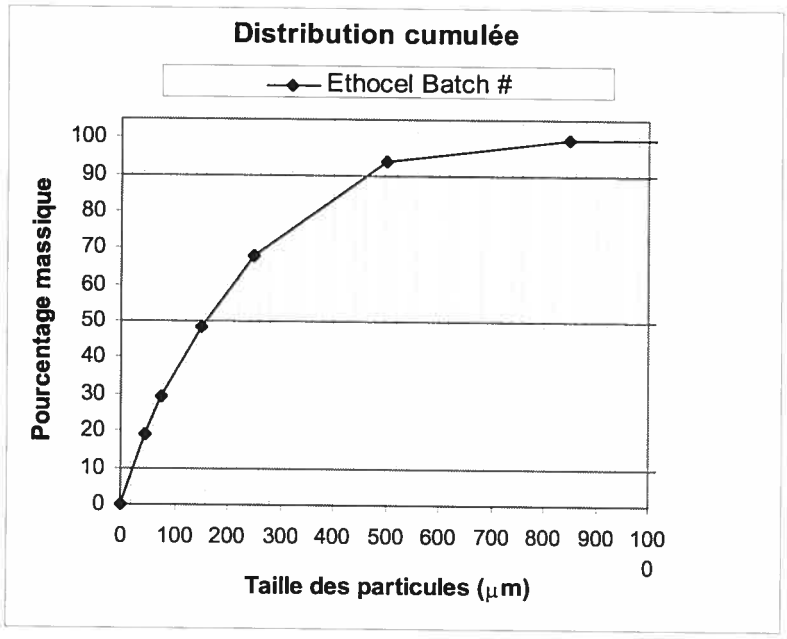
Appendix 8: Data of particle size distribution of Lactose



Appendix 9: Cumulated distribution of the particles of Lactose

	Poids des tamis			% différentiels		% passant cumulés	
Tamis	Vide	Plein	Poudre	(µm)	%	(µm)	%
Mesh	(g)	(g)	(g)	<45	18.85	0	0.00
20	349.18	349.37	0.19	45-75	10.28	45	18.85
35	322.97	327.82	4.85	75-150	19.08	75	29.13
60	297.32	317.41	20.09	150-250	19.57	150	48.21
100	286.66	301.92	15.26	250-500	25.76	250	67.78
200	315.70	330.58	14.88	500-850	6.22	500	93.54
325	320.82	328.84	8.02	>850	0.24	850	99.76
réceptacle	255.96	270.66	14.70	Total	100.00	1680	100.00
		Total :	77.99				
Echant.(g)	78.79	**% Récup:**	98.98	Moyenne µm 212			

Appendix 10: Data of particle size analysis of Ethyl cellulose (ethocel)



Appendix 11: Cumulated distribution of the particles of Ethyl cellulose

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