

THE USE OF A NOVEL POLYMER FROM THE STEM BARK OF CISSUS
POPULNEA IN THE FORMULATION OF CONTROLLED RELEASE MATRIX
TARLETS

BY

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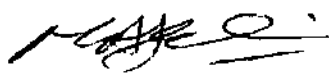
*A THESIS SUBMITTED TO THE POSTGRADUATE SCHOOL
AHMADU BELLO UNIVERSITY ZARIA
IN FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF
Ph.D PHARMACEUTICS*

JULY, 1997

DECLARATION

I hereby declare that the work reported in this thesis ~~was carried out~~ by me both in King's College University of London, England and in the Department of Pharmaceutics and Pharmaceutical Technology, University of Jos, Nigeria. The works of other investigators referred to are appropriately acknowledged.

I also do hereby declare that no part of this thesis has been accepted in substance, or concurrently submitted in candidature of any other degree.

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CERTIFICATION

This thesis titled "THE USE OF A NOVEL POLYMER FROM THE STEM BARK OF CISSUS POPULNEA IN THE FORMULATION OF CONTROLLED - RELEASE MATRIX TABLETS" by MUSA ANDREW IBRAHIM meets the regulations governing the award of the degree of DOCTOR OF PHILOSOPHY (Pharmaceutics) of AHMADU BELLO UNIVERSITY, ZARIA, NIGERIA, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

This work is dedicated to

My daughter Miss Ladi Ibrahim and

My mother Mrs. D.A. Ibrahim,

May the Lord grant them peace and prosperity.

The work is also dedicated to

My departed brother and father,

Late Mr. Henry R. Ibrahim and Late Mr. W.A.Ibrahim respectively.

May Almighty God grant them eternal rest, Amen.

ACKNOWLEDGEMENT

The author is especially most grateful to Professors A.B. Bangudu and P.F. Olurinola of the Faculty of Pharmaceutical sciences, A.B.U. Zaria, for their able supervision of this work from inception of the idea to the experimental work and the final write-up of the thesis. Their guidance and comments were extremely valuable in developing and completing this work. I wish to deeply thank Mr. V.H.Dawes for supervising a significant part of the experimental work during my stay in King's College, University of London. His brilliant contributions and kindness to me are most highly appreciated. Many thanks also go to the Laboratory staff at King's College, London.

I wish to express my sincere gratitude to all my sisters and brothers for their support throughout the period of preparing this thesis. My sincere gratitude goes to my colleagues in the University of Jos for their encouragement and interest in the work. Of special note amongst them are Professor E.N. Sokomba (former Dean of Pharmaceutical Sciences), Professor T.A. Iranloye (Dean of Pharmaceutical Sciences), Mr. S.S. Gyang, Mrs.G.O.Banwo, Mr.P.O. Olorunfemi, Dr.(Mrs) B. T. Kolarova, Dr. P.Ozo-Eson, Mr.E.G.Eseyin, Mr.D.I.Madubuko, Mr. J.G.Alhassan, Mr. Jilli-Dandam and Mr.E.Ameh.

A lot of my friends in and outside Jos were a source of inspiration and encouragement and I deeply thank them for everything. They include Mr & Mrs Yahaya Dikko, Mr. P.Adikwu, Mr.B.A.Ameh, Mr & Mrs Charles Sani, Mr.F.Williams, Mr. H. Edah, Dr. M.Umaru, Mr. Abba Dikko, Mr. J.B. Mamman, Mr.I.Kitchener, Dr. J.E. Ojile, Professor G.Ogbadu, Mr. J.M.Bello, Mr. Joe T. Yusuf, Alhaji Bala Hamman, Mr. Aliyu Bello and Dr. Nyang. Finally, I wish to thank most sincerely Mr. M.Akwu, Mr. S. Gyang, Mrs. A.U.Enweremadu and Mr. E.Chikwendu for their co-operation in typing and preparing the draft copy of this thesis including the graphics and Mr. S.J. Vem and Mr. Dan.M.Mahwel for reproducing the final copy of the thesis.

ABSTRACT

Investigations were undertaken on the physico-chemical, microbiological and controlled-release properties of cissus populnea polymer (CPP), a hydrocolloid polymer obtained from the stem bark of **Cissus populnea amplidaceac (vitaccae)**, which grows wild in many parts of Nigeria. The mucilage is widely used for preparing edible thick viscous soup ("draw soup"). Theophylline and Potassium chloride were used as drug models for poorly water soluble and very water soluble drugs respectively in evaluating the controlled-release properties of CPP. A spectrophotometric method and a flame photometric method were used in assaying the quantities of theophylline and potassium chloride respectively that were released from the formulated matrices. Thermal analysis using the Perkin - Elmer Differential Scanning Calorimeter was employed for investigating interactions between the CPP and these drugs as well as their thermal properties. Erosion and swelling of tablets with time were measured in different dissolution media to establish the conditions for "low" and "high" erosion and swelling used in the factorial design studies. CPP was seen to be insoluble in aqueous medium but swells into a viscous gel which provides a barrier to drug diffusion from the tablets, thus providing a means of **prolonging drug release** for hours. The controlled-release of theophylline and potassium chloride from CPP matrices were longer and more linear than from methocel/HPMC, CAP, lactose and dicalcium phosphate matrices. **Thermal studies using DSC** showed that CPP did not form any complex with either of these drugs, consequently no interference with the therapeutic effects of the drugs will occur. "Once-and twice-daily" theophylline tablets were formulated with the CPP. The "twice-daily" formulation showed chemical and release rate stabilities at room temperature, but these parameters were affected by higher temperatures and humidities.

Like xanthan gum investigated by other workers, CPP's prolongation of drug release was dependent on polymer concentration, but changes in pH, ionic strength and surfactant concentration did not significantly alter the release rate as shown by **ANOVA** and **t-test**. However other factors

such as compression pressure, dose content and agitation speed could affect the release rate. The correlation coefficients for various release models showed that CPP gave zero-order release kinetics for most test conditions. From **factorial design experiments** using "steady" and "non-steady" states it is evident that erosion is the main mechanism of theophylline release from CPP matrices while swelling (acting independent of erosion) imparts linearity to the release profile. Granulation increased the prolongation and linearity of drug release from CPP matrices, whereas magnesium stearate exhibited an optimum concentration for enhancing the prolongation of drug release from CPP matrices, below and above which drug release rate increased. These two factors also affected the thermal intrinsic properties of theophylline -CPP mixtures.

Computer pharmacokinetic simulations of the formulated products showed that the 22 hour release form of the "once-daily" tablets gave the best plateau in plasma drug level after 5 multiple doses, while the "twice - daily" tablets showed a reduced C_{max} and a much longer t_{max} than an equivalent immediate release formulation. Also the AUCs of the "twice-daily" and immediate release products were identical, showing that the "twice-daily" formulation would perform successfully in-vivo. The "once-daily" theophylline tablets formulated with CPP appear to be more satisfactory than the commercially approved products studied. The **microbiological studies** on CPP (as a substance from vegetable source) gave an acceptable limit of microbial counts and absence of pathogens. CPP's low water activity led to no microbial growth during the study period of 3 months. CPP could be a suitable substitute to presently used hydrocolloids and could greatly improve the in-vitro and in-vivo performances of many matrix controlled-release tablets in the market.

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CHAPTER ONE

CHAPTER ONE

GENERAL INTRODUCTION

The prime considerations in the design of a drug are safety and efficacy. The drug product must effectively deliver the active drug at an appropriate rate and amount to the target receptor site so that the intended therapeutic effect is achieved with minimal side effects. Recently great progress has been achieved in biopharmaceutical technology, and precise control of drug input to the body by different routes is now possible using a variety of sophisticated delivery systems (Prescott, 1989). By carefully choosing the route of drug administration and properly designing the drug product, the bioavailability of the active drug can be varied from rapid and complete absorption to a slow, sustained rate of absorption or even virtually no absorption, depending on the therapeutic objective. The review of control of drug input to the body from oral dosage forms will be the main focus of the introduction since the novel polymer under study, *cissus populnea* polymer (CPP) is intended to be used in formulating matrix tablets for oral use.

1.1 CONTROLLED-RELEASE ORAL DOSAGE FORMS

Oral administration of drugs using controlled-release formulations is today an extremely popular concept which has attracted the attention of pharmaceutical scientists for over twenty five years (Ganderton, 1984). Although the intrinsic pharmacological action of the active chemical drug species is responsible for the drug product's ultimate pharmacological effect, the dynamics of the drug's release from the dosage form and subsequent availability to its site(s) of action are equally important in determining the safety and effectiveness of the therapy (Smollen and Ball, 1985). These authors argue that once a drug has entered the body, there is no routine practical means of controlling its action. The course of its therapeutic and toxic effects becomes entirely determined

by the dynamics of its disposition and activity in the body. Controlling the manner by which a drug enters the body is the only feasible means of affecting the safety and efficacy of drug products.

1.1.1: **The rationale for controlled-release dosage forms:** The effects of a drug on the body result from its action on target "macromolecules" located either within or on the surface of particular cell types. Some drugs, certain hormones for example, are extremely specific since they interact with receptor mechanisms which are present in only one or a few cell types (Juliano, 1980). Many other drugs interact with enzymes or other macromolecules which are shared by a large number of cell types. Often the desired or therapeutic effect of a drug involves its action on one cell type, a tumor cell for example, while undesirable or toxic effects stem from action on other cell types. Thus one can promote the therapeutic effects by augmenting the amount and persistence of drug in the vicinity of the "target" cell, while reducing the drug exposure to "nontarget" cells (Juliano, 1980). This, according to Juliano is the basic rationale for the concept of controlled drug delivery i.e. the use of systems and techniques for altering and controlling the absorption, blood levels, metabolism, organ distribution, and cellular uptake of pharmacologically active agents.

1.1.2 **Advantages and disadvantages of controlled - release dosage forms:** Many of the early controlled drug delivery systems such as sustained-release systems, sought to avoid the sudden release of drug from a dosage form to avoid either local irritation in the gastrointestinal tract (g.i.t.) caused by for example ferrous salts, potassium chloride etc, or avoid undesirable side effects resulting from "spike" plasma levels; examples are theophylline, sympathomimetic amines etc (Jones, 1986). The additional benefit of prolongation of therapy conferred by these systems give the advantage over conventional dosage forms of reduction in dosage frequency which helps in improving patient compliance. The advantages of controlled - release products could be listed as follows:

- a) Some agents which were only marginally efficacious when formulated conventionally, have become highly effective in controlled-release formulations (Cowsar, 1981).
- b) Controlled - release allows for sustained therapeutic blood levels of the drug, which provides for a prolonged and consistent clinical response in the patient. Moreover, if the drug input rate is constant, the blood levels should not fluctuate between a maximum and minimum, as in a multiple - dose regimen with an immediate release drug product. Therefore unwanted side effects are avoided and therapeutic effects are promoted.
- c) Another advantage of controlled-release products is patient convenience, which leads to better patient compliance. For example, if the patient only needs to take the medication once daily, he or she will not have to remember to take additional doses at specified time during the day. Furthermore, because the dosage interval is longer, the patient need not interrupt sleep.
- d) The patient may derive an economic benefit in using a controlled-release drug product. A single dose of the controlled - release drug product might cost less than an equivalent drug dose given several times a day in rapid release tablets. For patients under nursing care like paediatric, geriatric and seriously ill, the cost of patients' nursing time required to administer medication is decreased if only one drug dosage is given to the patient each day.

There are also a number of disadvantages in using controlled-release medication as follows:

- i) If the patient suffers from an adverse drug reaction or becomes accidentally intoxicated, the removal of drug from the systemic circulation is more difficult than with a rapid-release drug product. If unexpected side effects occur with agents administered via controlled-release, many controlled-release formulations are not reversible, and the side effects persist until the dose regimen is complete. The more severe the effects, the greater the risk.

ii) With orally administered controlled-release drug products, erratic or variable drug absorption might occur due to various interactions of the drug with the contents of the g.i.t and changes in g.i. motility.

iii) The failure of controlled-release dosage form might lead to "dose dumping" i.e. the release of more than the usual fraction of drug or the release of drug at a greater rate than the customary amount of drug per dosage interval, such that potentially adverse plasma levels may be reached (Dighe & Adams, 1988 and Skelly & Barr, 1987).

iv) For delayed or enteric drug products, two possible problems might occur if the enteric coating is poorly formulated. First, the enteric coating might not prevent early release of the drug which might allow degradation of the drug in the stomach or cause irritation to the gastric mucosal lining. Secondly, the enteric coating may fail to dissolve at the proper site, and therefore, the tablet might be lost prior to drug release and absorption.

v) A constantly-activated biological response may be clinically disadvantageous because it leads to tolerance (Padfield, 1989). In such circumstances either a conventional dosage form or a controlled-release product with modified duration of release is required according to the author. When tolerance develops to a drug, the presence of constant plasma concentrations is of little relevance to the diminishing clinical response.

vi) In an oral controlled-release product, drug will be released in previously unexposed parts of the g.i.t. While the concentrations will never be as high with a conventional dosage form, an irritant drug could produce new side-effects at these sites.

1.1.3: Formulation requirements and difficulties:

a) Though extensive development of rate controlled oral dosage forms will eliminate many disadvantages of therapy via this route, such dosage forms cannot solve all the problems arising from medication by mouth. This is because the dosing interval must relate to the g.i.transit time, oral

therapy generally will still require at least daily dosing. Moreover, losses of drug prior to drug entry into the circulation are unavoidable due to variations in g.i.t absorption. Some of these variations arise from food intake and enzymatic activity. Subsequent metabolism by the liver removes an unpredictable proportion of the dose administered.

b) For some drugs such as chlorpheniramine which have long elimination half - lives, the inherent duration of pharmacologic activity is long. Moreover minimal fluctuations of blood concentrations of these drugs are observed after multiple doses are administered. Therefore, there is no rational for controlled-release formulations of these drugs (Lin and Chien, 1985). However, such drug products are marketed with the justification that controlled-release products minimize toxicity, decrease adverse reactions, and provide patients with more convenience and thus better compliance (Shargel and Yu, 1993). Because slow loss rate does not imply slow absorption rate, there is at least one rather convincing reason for preparing sustained - action forms of some drugs in this group. The blood level achieved from a properly designed sustained - action dosage form does not rise significantly above the desired blood level, even with accumulation considerations. Although administration of single doses capable of producing equivalently prolonged effects often yields significant blood level peaks immediately after each dosing interval, sustaining the action may well be indicated if toxicity or local gastric irritation is a hazard (Eriksen, 1970).

c) The formulation of controlled - release drug products for drugs usually given in large doses (>500mg) in conventional dosage forms may not be practicable. This is because the controlled - release drug product may contain two or more times that dose given in the conventional dosage form, therefore the size of the controlled - release drug product would become too large for the patient to swallow easily. It would appear that dry sustained - action dosage forms containing drugs

with single dose requirements of 1gm or more are inadvisable and they might be better formulated as liquid dosage forms where large dosing volumes are more acceptable.

d) The most critical issue is to consider whether the modified release dosage form truly offers an advantage over the same drug in an immediate release form. This advantage may be related to better efficacy, reduced toxicity or better patient compliance. Ideally, the extended release dosage form should provide a more prolonged pharmacodynamic effect compared to the same drug given in the immediate release form. However, a controlled-release dosage form of a drug may have a different pharmacodynamic activity profile. For example, transdermal patches of nitroglycerin which produce a prolonged delivery of the drug, may produce functional tolerance to the vasodilation activity that is not observed when nitroglycerin is given sublingually for acute angina attacks (Shargel and Yu, 1993). These authors have also reported that certain bactericidal antibiotics such as penicillin may be more effective when given in intermittent (Pulsed) doses compared to continuous dosing. They further reported that the continuous blood level of hormones such as a corticosteroid might suppress adrenocorticotrophic hormone (ACTH) release from the pituitary gland, resulting in atrophy of the adrenal gland. Furthermore, drugs that act indirectly or cause irreversible toxicity may be less efficacious when given in an extended-release rather than conventional dosage form.

e) Another unforeseen problem with a modified-release dosage form is an alteration in the metabolic fate of the drug, such as nonlinear biotransformation or site-specific disposition.

f) The selection of the drug and dosage form is important in formulating a sustained-release product. In general, a drug with low solubility should not be formulated into a non disintegrating tablet. The risk of incomplete dissolution is high. From a practical standpoint, drugs with very high or very low aqueous solubility are poor candidates. Because availability rate is closely related to solubility, compounds with very low solubilities are inherently long acting (indeed preparing slightly

soluble forms is one method in use for obtaining sustained - action), whereas compounds with very high solubilities have such high availabilities that it is difficult to slow them to within the limits desired. A drug with low solubility at neutral pH should be formulated so that most of the drug is released prior to reaching the colon. Erosion tablets are more reliable than non disintegrating tablets because the entire tablet eventually dissolves. With most single unit dosage forms, there is a risk of erratic performance due to variable stomach emptying and g.i.transit time. The selection of the pellet or bead dosage form may minimize the risk of erratic stomach emptying, because the pellets are usually scattered soon after ingestion. Disintegrating tablets have the same advantages because they are broken up soon after ingestion.

g) A drug that is highly soluble in the stomach but very insoluble at intestinal pH may be very difficult to formulate into a sustained - release product. Too much protection may result in low bioavailability while too little protection may result in "dose dumping" in the stomach. A moderate extension of duration with enteric - coated beads may be possible. However, the risk of erratic performance is higher than that of the conventional dosage form. The osmotic type of controlled system may be more suitable for this type of drug (Shargel and Yu, 1993).

h) Drugs with narrow requirements for absorption (positional within the gut, or pH) are poor candidates for oral sustained - action forms, and by their very nature sustained - action forms must use nearly all the pHs and absorption sites throughout the length of the gut.

i) Drugs with very slow intrinsic absorption rates (e.g.iron) present problem only in that the administration of any dosage form is essentially the administration of a sustained - action dosage form, the availability is controlled by intrinsic absorption itself. Considering that for control, the availability rate (R) must be slower than the intrinsic absorption rate, such low absorbers present

problems in preparing a suitable dosage form. Also the purpose of such a sustained - action dosage form from a drug that is inherently long acting is questionable.

1.1.4: **Kinetics of controlled-release dosage forms:** Drug treatment usually aims at the amelioration of a disease or its symptoms, promptly or continuously. To accomplish this, the drug is given at appropriate intervals in amounts capable of producing the desired biological action. The initial dose should be rapidly absorbed, subsequent doses should be designed to maintain an effective concentration of the drug for the duration of the treatment as shown below:

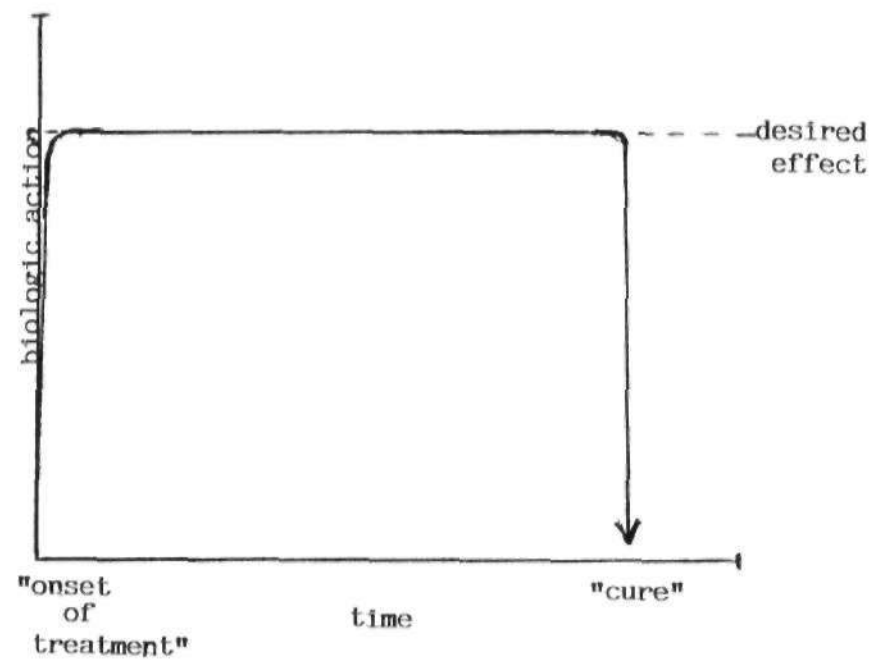


Figure 1.1: The theoretically optimum effect-time curve to be achieved by a "sustained - action dosage form" (Eriksen, 1970).

Such an effect has been defined as "sustained - action" (Ballard and Nelson, 1965) to distinguish it from "prolonged - action" and single dose activity profiles as shown in figure 1.2. The amount of drug required in a controlled - release dosage form to provide a sustained drug level in the body

is determined by the Pharmacokinetics of the drug, desired therapeutic level of the drug, and intended duration of action.

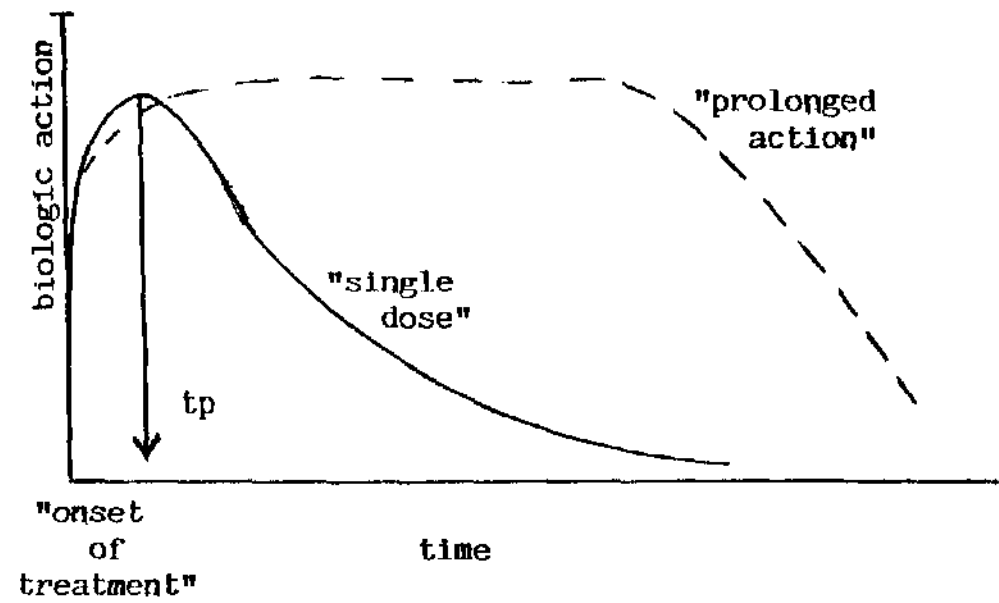


Figure 1.2: Biologic action - time curves for single dose and prolonged action dosage forms (Eriksen, 1970).

In general, the total dose required (D_{tot}) is the sum of the maintenance dose (D_M) and the initial dose (D_I) immediately released to provide a therapeutic blood level:

$$D_{tot} = D_I + D_M \text{ -----Equation 1.1}$$

In practice, D_M is released over a period of time and is equal to the product of the duration of action (t_d) and the zero-order release rate (K^0). Therefore,

$$D_{tot} = D_I + K^0 t_d \text{ -----Equation 1.2}$$

The mathematical design of a sustained - action dosage form incorporates all the concepts and assumptions of biopharmaceutics, that is, the biological absorption, distribution, metabolism

and excretion (ADME) of a drug. Much research effort has gone into the development of equations required to calculate the appropriate initial and maintenance doses for situations where a series of single doses are adjusted in size and frequency and for the more convenient situation of a single oral dosage unit capable of producing a biological activity - time profile approximating that in figure 1.1. The details of such equations and assumptions are given elsewhere by Eriksen (1970).

With most sustained - release products, the drug is administered for more than one dose, and there is no need for a built in loading dose. Having a loading dose in the subsequent dosing would introduce more drug into the body than necessary due to "topping" effect (Shargel and Yu, 1993). These authors point out that in situations where a loading dose is necessary, a rapid release product is used to titrate a loading dose that would bring the plasma drug level to therapeutic level. Thus for many sustained - release drug products, there is no build in loading dose (i.e $D_l = 0$). For a drug that follows a one - compartment open model, the rate of elimination (R) needed to maintain the drug at a therapeutic level (C_p) is as given by Shargel and Yu (1993):

$$R = C_p CL_T \text{ -----Equation 1.3}$$

Where CL_T is the clearance of the drug.

For a stable blood level of the drug, the release rate K^0 , must be equal to the rate of elimination (R) of the drug i.e the maintenance of a constant quantity of drug in the blood requires that the rate of drug entering the blood equals the rate at which it is lost. Substituting R for K^0 in equation 1.2, the total dose needed to maintain therapeutic concentration in the body for a period of T hours becomes:

$$D_{tot} = D_l + C_p CL_T T \text{ -----Equation 1.4}$$

since $D_l = 0$ as pointed out by Shargel and Yu (1993), The dose (D_M) needed to maintain therapeutic dose (C_p) for T hours is given by:

$$D_M = C_p CL_T T \text{ -----Equation 1.5}$$

This equation was used for calculating the maintenance doses needed for "once-and twice - daily" dosing of theophylline in the formulations studied in chapter 5.

1.1.5: **Types of controlled - release dosage forms:** The USP-XXI/NF-XVI adopted the term modified - release dosage forms to describe dosage forms that alter the timing and rate of release of the drug substance from the drug product. A modified - release dosage form is defined by the USP/NF "as one for which the drug - release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objective not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms". The USP/NF presently recognizes several types of modified release dosage forms:

- a) **Extended-release dosage forms** - These are dosage forms which allow at least a twofold reduction in dosage frequency as compared to an immediate - release (conventional) dosage form. Examples include controlled - release and sustained - release drug products (Shargel and Yu, 1993).
- b) **Delayed - release dosage forms** - These are dosage forms that release a discrete portion or portions of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration. Enteric - coated dosage forms are the most common delayed release products. Enteric coated tablets are designed to release drug in the small intestine e.g. aspirin enteric coated tablets formulated to prevent irritation of the gastric mucosa of the stomach. The tablet will later dissolve and release the drug in the higher pH of the duodenum where the drug is rapidly absorbed with less irritation of the mucosal cells.
- c) **Repeat - action dosage forms** - These are designed to release one dose of drug initially and a second dose of drug at a later time.
- d) **Targeted - release dosage forms** - These are dosage forms that release drug at or near the

intended physiologic site of action. Targeted - release dosage forms may have either immediate or extended - release characteristics.

Various other terms have been associated with controlled - release drug products including extended action, timed - release, long acting, and programmed drug delivery systems. In all cases, the drug product is designed so that the rate of systemic drug absorption is limited by the rate of drug release from the delivery system.

The four general physical procedures by which control over the delivery of drug to the absorption pool is achieved are shown in table 1.1. These Physical procedures (coating, matrix embedding, insoluble forms and ion-exchange) together with the osmotic mechanism of control and the alternative routes to oral route of administration form the basis of classification of types of controlled - release products given in table 1.1. Theophylline, one of the drugs used in the study is commercially available in sustained - release forms. The simulated in-vivo performances of some of the "once-daily" commercially available theophylline products are compared to the formulated "once-daily" product of this study (see section 5.3).

Table 1.1: Classification of types of controlled - release products

Physical procedure of availability control	Mechanism of availability control	Examples	Factors affecting drug release and (release kinetics)
Coating	dissolution and diffusion	Coated granules, and tablets, microcapsules and liposomes.	Thickness of coating, conc.gradient across coat, nature of coating material and coating method, solubility (first-order and diffusion kinetics)
Matrix embedding	dissolution, diffusion and erosion of matrix	Core tablets, gum-type matrix tablets, polymeric matrix tablets	Affected by nature and concentration of matrix former, solubility partitioning etc (zero-, first-orders, or cubic root kinetics)
Insoluble forms	dissolution, diffusion	less soluble salts or derivative (tableted), granulating with fatty or waxy lipophilic materials, prodrugs	Affected by solubility and diffusion (Diffusion or square root kinetics)
Ion-exchange forms	ion-exchange rate, diffusion	Preparations of drugs containing resins.	Dissociation of drug - resins complex, availability of ions in g.i.t (First - order Kinetics).
Osmotic controlled - release	Osmotic pressure	The ALZET mini-osmotic pump, the OSMET, the OROS system, the insulin Osmotic pump	Affected by membrane permeability, osmotic agent used (zero-order kinetics)
Controlled-release systems for other routes	Solubility of drug, diffusion	Transdermal therapeutic systems	Humidity, temperature, controlled by user.

1.1.6: **Bioavailability of drugs from controlled - release products:** The orally taken drug first enters the stomach and will remain there for varying lengths of times. Variations in the rate of gastric emptying and motility of the g.i.t. will result in different rates of drug movement along the alimentary canal and different degrees of drug exposure to the absorption site, thereby influencing the bioavailability of the drug. After disintegration of the dosage form, the drug particle comes in contact with contents of the g.i.t. e.g intestinal fluids, bile salts and food. The amount and types of food may affect the absorption of a drug. The drug must dissolve in the g.i. fluids before it can

become available for absorption through the mucosal layer of the g.i.t. This dissolution may be the rate-limiting step in the overall absorption process (Lin and Chien, 1985).

During the course of the g.i. transit, the drug may be exposed to various pH conditions, gut flora and enzymes. Decomposition and metabolism of the drug will reduce its systemic bioavailability. It is commonly known that the physicochemical characteristics of the drug molecule such as its lipophilicity, solubility, stability and pK_a will determine the extent and the rate of absorption. Before it enters the systemic circulation, the drug molecule is also subjected to biotransformation in the liver by the "first pass effect". The brand and dosage form of the drug product, as well as the physiological conditions and disease states of the patient, may also influence the systemic bioavailability of an orally administered drug. It is important to understand the variations and limitations of these factors and how to control them when developing delivery systems for a therapeutic agent, since these factors could limit the achievement of an optimum bioavailability of drugs.

Ideally, a controlled - release drug product should release the drug at a constant, or zero-order rate. After release from the drug product, the drug is rapidly absorbed, and the absorption rate should follow zero-order kinetics similar to an intravenous infusion of the drug. Thus, the drug product is designed so that the rate of systemic drug absorption is limited by the rate of drug release via the drug delivery system. Unfortunately, most controlled-release drug products that release drug by zero-order kinetics in-vitro, do not demonstrate zero-order drug absorption when given in-vivo. The lack of zero-order drug absorption from these controlled-release drug products after oral administration may be due to a number of unpredictable events happening in the g.i.t. during absorption, e.g. the effect of presence of food in the stomach, metabolism of drug by bacteria in the colon etc. Appendixes 13 and 14 show some of the physiologic factors and drug interactions respectively that can influence the bioavailability of theophylline, one of the drugs used in this study.

Other factors worthy of mention that can affect bioavailability include; (a) formulation factors e.g. additives, dosage form, manufacturing processes etc, (b) variation in products between manufacturers, (c) physicochemical nature of the drug e.g. solubility, stability, particle size, polymorphism etc.

1.2: DRUG RELEASE FROM CONTROLLED-RELEASE POLYMERIC DELIVERY SYSTEMS.

The **cissus populnea polymer (CPP)** under study is a hydrocolloid polymeric material and the drug release profile from the material will determine its suitability for **controlled-release formulations**. A review of the mechanisms and factors affecting drug release from polymeric delivery systems is therefore of great importance to this study as this will help in understanding how the drug release characteristics of the novel polymer CPP can be influenced.

The rate of drug release from polymeric devices will depend on the physical properties of the polymer matrix and of the drug itself. Polymeric delivery devices can be used to achieve sustained and relatively constant systemic levels of drug, or they can be used to maintain high levels within a local body compartment (e.g. intrauterine space, intraocular space, etc). The basic concept underlying the use of polymeric-type delivery devices is that a sustained drug level can be produced in a certain body compartment by balancing the biological processes of drug metabolism and elimination against the drug-release characteristics of the polymeric delivery system (Juliana, 1980).

Most of the controlled-release preparations work by a combination of processes involving dissolution, permeation and diffusion. The single most important factor is water permeation, without which none of the product release mechanisms would operate. Controlling the rate of water influx into the product generally dictates the rate at which the drug dissolves. Once the drug is dissolved, the rate of drug diffusion may be further controlled to a desirable rate. Basically, the controlled -

release of therapeutic agents from both capsule and matrix type polymeric drug delivery systems is governed by Fick's law of diffusion which defines the rate of diffusion (dQ/dt) across a plane surface of a unit area as given by equation 1.6:

$$dQ/dt = \frac{DA(C_1 - C_2)}{h} \quad \text{.....Equation 1.6}$$

Where D is diffusion coefficient, A is area across which diffusion is taking place, C_1 is conc. at the surface of the plane, C_2 is the conc. in the bulk medium and h is the thickness of the hydrodynamic layer.

Kinetically however, the release of therapeutic agents from the capsule and matrix types of polymeric drug delivery systems is theoretically controlled by two different mechanistic patterns which result from the time dependency of the diffusional flux defined by Fick's law (Chien,1980). In the case of the capsule-type drug delivery device, the concentration gradient dc/dh of drug across a thickness of polymeric membrane dh is essentially constant and invariant with time. On the other hand, the concentration gradient in the matrix-type drug delivery devices is time dependent, because of the fact that the thickness of the diffusional path dh grows progressively as time passes. Therefore, different theoretical models should be developed for mechanistic analyses of the controlled - release of therapeutic agents from these types of polymeric drug delivery systems (Chien,1980). According to this author, in order to do this, several assumptions have to be made:

1. The diffusivity (D) is constant, irrespective of time, distance and concentration.
2. Dissolution of drug crystals into the surrounding medium, either a solution or a polymer phase, to form a dissolved specie, is the very first step of the drug release process.
3. A pseudosteady state exists in the controlled-release process.

1.2.1: Capsule-type drug delivery systems.

This type of polymeric drug delivery system includes silicone capsules for subcutaneous drug administration, Progestasert IUDS for intrauterine contraception, ocusert devices for glaucoma treatment, and other drug delivery devices having therapeutic agents encapsulated within a closed compartment surrounded by a polymeric membrane with a well-defined thickness (Chien, 1980). According to this author, the release of drugs from capsule type delivery devices can be visualized as follows: the drug molecules in the first layer of crystals, which exist as a suspension in an undiffusible liquid medium or as a dry power in direct contact with the inner surface of the polymer wall, have to dissociate themselves from the crystal state, dissolve into either the liquid medium or the polymer structure, diffuse through it, and finally partition into the tissue fluid surrounding the drug delivery device. There is a stagnant solution layer called the hydrodynamic diffusion layer. Here drug molecules diffuse under a concentration gradient from the surface of the device to the bulk of tissue fluid. Chien investigated the in- vitro and in vivo release of progestins from the silicone capsule (Chien, 1976b; Chien *et al*, 1975). He used a theoretical model to device the following mathematical expression, which defines the cumulative amount of drug released (Q) from a unit surface area of a capsule-type drug delivery device:

$$Q = (C_p K D_s D_p / K D_s h_p + D_p h_d) t \dots \text{Equation 1.7}$$

where C_p = solubility of drug in the polymeric membrane

K = partition coefficient of drug between polymeric device and the surrounding tissue fluid.

D_s = diffusion coefficient of drug in the surrounding tissue fluid

D_p = diffusion coefficient of drug in the polymeric membrane

h_p = thickness of the polymeric membrane

h_d = thickness of the hydrodynamic diffusion layer

t = time

Chien's mathematical expression suggests that the drug release profile from the capsule-type drug delivery device is constant. He showed that under the two possible extremes, release of drug is controlled by membrane limiting process in one situation, and by the hydrodynamic diffusion layer limiting process in the other. According to him, under both situations, the controlled - release profile of drug from the capsule-type polymeric delivery device follows zero-order kinetics as given by the equations for the two conditions:

$$Q/t = C_p D_p / h_p \text{ for } K D_{shp} \gg D_{phd} \dots \text{Equation 1.8}$$

$$\text{and } Q/t = C_s D_s / h_d \text{ for } K D_{shp} \ll D_{phd} \dots \text{Equation 1.9}$$

where Q/t is the rate of drug release

1.2.2: Matrix-type drug delivery systems: A matrix is an inert solid vehicle in which a drug is uniformly suspended. A matrix may be formed simply by compressing or fusing the drug and the matrix material together. Generally, the drug is present in a smaller percent, so that the matrix gives extended protection against water and the drug diffuses out slowly over time. Most matrix materials are water insoluble, although some may swell slowly in water. Matrix type of drug release may be built into a tablet or small beads depending on the formulation composition (Shargel and Yu, 1993). The three common approaches by which the matrix mechanisms are employed are shown below:

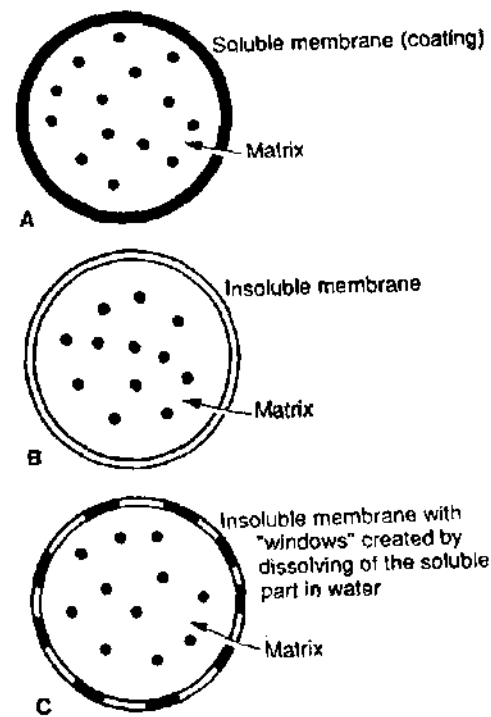


Figure 1.3: Example of three different types of modified matrix - release mechanisms. (Shargel & Yu, 1993)

In case A, the drug is coated with a soluble coating, so drug release solely relies on the regulation of the matrix material. If the matrix is porous, water penetration would be rapid and the drug would diffuse out rapidly. A less porous matrix may give a longer duration of release. The Higuchi equation describes the release rate of a matrix tablet of the type of case A:

$$Q = Ds(p/\lambda) (A-0.5SP)^{1/2} \sqrt{t} \quad \text{.....Equation 1.10}$$

where Q = amount of drug released per cm² of surface at time t

S = solubility of drug in g/cm³ in dissolution media

A = content of drug in insoluble matrix

P = porosity of matrix

D = diffusion coefficient of drug

λ = tortuosity factor.

Case B represents a matrix enclosed by an insoluble membrane, so that drug release rate is regulated by the permeability of the membrane as well as the matrix. Case C represents a matrix tablet enclosed with a combined film. The film becomes porous after dissolution of the soluble part of the film, e.g. the combined film formed by ethylcellulose and methylcellulose. Close to zero-order release has been obtained with this type of release mechanism.

The matrix type of polymeric drug delivery system includes the subdermal implant for synchronization of estrus (Syncro-Mate-B), the vaginal ring for cyclic intravaginal contraception, the scopolamine-releasing transdermal bandage for motion sickness, and other drug delivery devices with drug crystals or particles homogeneously dispersing in a matrix structure formed by the cross-linking of linear polymer chains (Chien, 1980). This author points out that the dispersing drug particles cannot delocalize, but must be eluted from the matrix structure, first by dissolution in and then by diffusion through the polymer network. One must visualize, microscopically, the solid drug particles on the surface layer of the polymeric device as being eluted first, when this layer becomes exhausted, the next layer then begins to deplete. A depletion zone, with a thickness of h_m , thus forms after a finite time following drug elution and becomes thicker as elution continues. The interface between the drug dispersion zone and the drug depletion zone moves further into the core of the polymeric device and a concentration gradient exists across the distance from the interface to the outermost layer of the device. Microscopically, a thin layer of stagnant tissue fluid, termed the hydrodynamic diffusion layer is also imagined to exist on the immediate surface of the polymeric device. Within this layer, drug molecules move under a concentration gradient, from the surface of the device to the bulk of tissue fluid. Mathematical analysis reveal that at steady state, the cumulative amount of drug delivered by the device is as given by Chien *et al* (1975) and Roseman and Higuchi (1970) and defined by equation 1.11

$$Q = ((2A - C_p) C_p D_p t)^{1/2} \dots \dots \dots \text{Equation 1.11}$$

where A = the initial amount of drug incorporated in a unit volume
of matrix-type polymeric device.

C_p = the solubility of drug in the polymeric phase

D_p = the diffusivity of drug in the polymer matrix structure.

The release profile of a drug from a matrix-type polymeric delivery device is thus defined by:

$$Q/t^{1/2} = ((2A - C_p)C_p D_p)^{1/2} \dots\dots\dots \text{Equation 1.12}$$

and the rate of drug release becomes time dependent and is defined as:

$$dQ/dt = \left(\frac{(2A - C_p)C_p D_p}{2t} \right)^{1/2} \dots\dots\dots \text{Equation 1.13}$$

A remarkable difference can be distinguished between the pattern of drug release from a capsule-type polymeric delivery device and that from a matrix type device. A constant drug release profile is achieved with a capsule-type drug delivery device and the rate of drug release is basically independent of both time and drug content. On the other hand, the drug release profile from a matrix-type device is not constant, but depends on both time and drug content (Chien, 1980). However, it is interesting to note that both types of drug release profiles are determined by the magnitude of C_p (polymer solubility of the drug) and D_p (diffusivity of the drug in polymer phase). One of the major drawbacks of many practical approaches for fabricating diffusion-controlled matrices for drug delivery is that the release rates decrease with time. From a pharmaceutical standpoint, it would be desirable for many such systems to display zero-order release kinetics. Furthermore, in some circumstances (e.g. insulin delivery in diabetics) it would be useful to be able to achieve increased dosages on demand (Hsieh and Langer, 1981). These authors in their studies demonstrated that matrix systems can be modified to produce either zero-order or modulated sustained-release devices when they used coated hemispheres having centre uncoated concavities

and magnetically modulated sustained-release systems respectively. The hemisphere geometry relies on the fact that diffusion of the drug through the polymer is the rate-limiting step for zero-order release (Langer, 1980). If surface erosion was rate limiting, then a geometry whose surface area did not change as a function of time (e.g. a long thin slab) would be required to obtain zero-order release kinetics (Hopfenberg, 1976).

1.2.3: Effect of system parameters on drug release profiles.

(i) Partition coefficient (K)

The release of drugs from both capsule-and matrix-type polymeric drug delivery devices is rate-limited by the interfacial partitioning of the drug molecules from polymer surface toward an elution medium. The coefficient for this interfacial partitioning (K) is defined as:

$$K = C_s/C_p \dots \dots \dots \text{Equation 1.14}$$

where C_s and C_p are the solubilities of the drug species in the elution solution and in the polymer structure respectively.

It was observed that the cumulative amount of drug released from a unit surface area of the capsule-type polymeric delivery devices increased as the magnitude of partition coefficient increased (Chien, 1976b). A linear relationship was established between the rates of drug release (Q/t) and the partition coefficient of the drug. The dependency of the drug release profile from matrix type polymeric drug delivery devices on the partition coefficient is twofold: both the mechanism and the rate of drug release depend on the variation of the partition coefficient (Chien and Lambert, 1974). It was reported that in the region of partition- controlled process, where the magnitude of partition coefficient was small, a plot of Q versus t yielded a zero-order release profile and the magnitude of the Q/t values increased linearly with the increase in partition coefficient of the drug species. With further increase in partition coefficient beyond a critical point ($K = 0.5$), the matrix-controlled mechanism became predominant and a Q versus $t^{1/2}$ release profile was then observed. The

magnitude of $Q/t^{1/2}$ values are found to be virtually independent of any variation in partition coefficient. This behaviour is obviously quite different from that observed in the controlled - release of drug from the capsule-type polymeric drug delivery systems.

b) **Polymer Solubility (C_p)**

Encapsulated drug particles in both capsule - and matrix-type polymeric delivery devices are released from the device only when the drug molecules on the outermost surface layer of the drug particles dissociate themselves from the crystal lattice, dissolve into the surrounding polymer structure, diffuse through it, and finally partition into the elution medium surrounding the delivery device (Chien, 1978). This mechanistic analysis reveals that the solubility of a drug specie in the polymer phase plays a rate-limiting role in its controlled - release from a polymeric drug delivery device. The rate of drug released (Q/t) from the capsule-type drug delivery device is directly proportional to the magnitude of C_p . On the other hand, the magnitude of the $Q/t^{1/2}$ value for the release of a drug species from the matrix-type polymeric delivery device is a function of the square root of C_p i.e. $C_p^{1/2}$.

If polymer is treated as a solid solution, microscopically, then the solution process of a drug crystal in a polymer can be visualized as consisting of two consecutive steps: (1) the dissociation of drug molecules from their crystal lattice, and (2) the solvation of these dissociated drug molecules in the polymer structure. Thermodynamically, the first step requires a dissociation energy and is dependent on the melting point temperature. The second step requires a solvation energy and is therefore a system-temperature-dependent process (Chien 1976a,b).

The polymer solubility of a drug specie is also very much dependent on its chemical structure i.e. variation in functional groups and their stereochemical configurations. A typical example is demonstrated by the addition of hydroxyl groups to the positions 11,17 and 21 on the

progesterone skeleton. A substantial reduction in polymer solubility resulted from changes of the number and the position of hydroxyl groupings (Chien *et al*, 1979).

c) **Solution Solubility (C_s)**

It was observed that the in-vitro release rates of norgestrel and megestrol acetate through silicone capsules were greater when the elution medium was plasma than when it was distilled water (Sundaram and Kincl, 1968). It was further discovered that the release rates of various steroids from silicone capsules in human plasma were 2 to 15 times greater than those in normal saline (Schuhman and Taubert, 1970). This difference in the rates of steroid release in different elution media is probably due to the enhancement of the solution solubility of steroids resulting from their binding to plasma proteins. These observations pointed to the role of solution solubility in determining the rate of drug release from a polymeric drug delivery device.

Solution solubility was reported to affect the mechanisms and rate profiles of drug release from matrix-type polymeric delivery systems. When the solution solubility of ethynodiol diacetate was maintained at a level below 200 $\mu\text{g/ml}$, its release was observed to be a partition-controlled process and a zero order release pattern resulted. The rate of drug release (Q/t) was directly proportional to the magnitude of solution solubility (C_s) as defined by the relationship:

$$Q/t = K D_s C_s / h d \dots\dots\dots \text{Equation 1.15.}$$

where K is a constant, which accounts for the relative magnitude of the concentration gradients in both diffusion layer and depletion zone. On the other hand, as the solution solubility was increased beyond 780 $\mu\text{g/ml}$, a matrix-controlled process became predominant and a Q versus $t^{1/2}$ release pattern was observed according to equation 1.11:

$$Q = ((2A - C_p) C_p D_p t)^{1/2}$$

The magnitude of $Q/t^{1/2}$ values was essentially constant and independent of the variation of solution solubility.

The aqueous solubility of many therapeutic active agents, like that of most steroids, is very low. This presents a difficult task for researchers in their attempts to maintain a perfect sink condition for drug release studies. Several physical methods can be applied to improve the solution solubility of these agents, such as emulsification (Elworthy *et al*, 1968), complexation, and co-solvency (Chien and Lambert, 1975; Yalkowsky *et al* 1972a, 1972b). Thermodynamically, the dissolution and solvation of a drug molecule in an aqueous solution is also an energy requiring process and shown to depend on temperature.

d) **Polymer diffusivity (Dp)**

The diffusion of drug molecules in a polymer structure is an energy-dependent process in which the diffusing molecules move to successive positions of equilibrium when a sufficient amount of activation energy has been acquired by the diffusing molecule and its surrounding medium (Crank and Park, 1968). Based on his activated-state model calculation, Brandt (1959) concluded that the molecular diameter of the diffusant affected the apparent activation energy very strongly. Comparing the diffusivities of simple gas molecules like O₂, N₂ and CO₂ in silicone polymer with the self-diffusion coefficient of the silicone polymer chain, Robb (1968) suggested that the diffusion of these simple gas molecules required the motion of a silicone chain segment of the order of three monomer units in length. The molecular motion of such a length of silicone chain will create an opening sufficiently large for the gas molecules to jump from one hole to another. Applying the same approach, Chien *et al* (1974) determined that the diffusion of steroids like ethynodiol diacetate in silicone polymer matrix structure would require the motion of a silicone chain segment of the order of 10 monomer units of length. The diffusion of molecules in a polymer is also affected by factors like the polymer structure and density, crosslinking of the polymer, the content of adsorbent filler, the physicochemical nature of the diffusant species etc.

e) **Solution diffusivity (D_s)**

Molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration until the concentration of the system is uniform throughout. The diffusivity of a molecule in aqueous solutions usually decreases as its concentration increases. This reduction in solution diffusivity is frequently enhanced by the increase in solution viscosity which usually accompanies the increase in concentration (Chien, 1980). Solution diffusion is also an energy-activated process (Chien, 1978).

f) **Drug content (A)**

In the preparation of a drug delivery device, varying amounts of drug are incorporated into the device. The appropriate amount of drug added depends on the rate of drug release, the intended length of treatment and the type of polymeric delivery system. In the case of matrix-type drug delivery systems, a linear relationship exists between the magnitude of the drug release profile ($Q/t^{1/2}$) and the square root of drug content $(2A)^{1/2}$ as defined by Equation.

1.12:

$$Q/t^{1/2} = ((2A - C_p)C_p D_p)^{1/2}$$

This relationship suggests that any attempt to prolong the duration of medication by incorporating a greater amount of drug into the matrix-type polymeric delivery device would also inevitably yield a greater value of $Q/t^{1/2}$. In the case of the capsule-type drug delivery system, the rate of drug release (Q/t) is independent of the variation in the amount of drug incorporated according to the equation:

$$Q/t = C_p K D_s D_p / K D_{shp} + D_{phd} \quad \dots \dots \text{Equation 1.16.}$$

As long as the drug molecules maintain an intimate contact with the capsule wall, a constant and dose-independent drug release profile will be achieved.

g) **Membrane thickness (h_p)**

Release of drugs from both capsule - and matrix-type polymeric drug delivery systems is essentially governed by Fick's law of diffusion. The observed difference in release patterns between the two, apparently results from the difference in the time dependency of their rate-controlling membrane thickness (h_p). In the capsule-type devices, the thickness of the polymeric capsule wall is essentially constant and invariant with time. However, the rate of drug release can be varied by encapsulating the drug in polymeric capsules with different wall thickness. The rate of drug release has a reciprocal relationship with the thickness of the capsule wall; the thicker the polymeric membrane, the lower the rate of drug release. On the other hand, the thickness of the diffusional path across the drug depletion zone in the matrix-type device grows progressively with time. The increase of the thickness of the diffusional path (h_p) is a linear function of the square root of time ($t^{1/2}$). The higher the drug content in the drug delivery device, the slower the rate of growth of the diffusional path thickness (Chien, 1978).

h) **Thickness of hydrodynamic diffusion layer (h_d)**

By looking at the equations describing the release profiles, the rate-limiting role of the hydrodynamic diffusion layer in determining the rate of drug release (Q/t) from a capsule type drug delivery device becomes obvious. However, its role in the determination of the drug release profile ($Q/t^{1/2}$) from a matrix-type drug delivery device is not apparent. Chien *et al* (1975) however observed experimentally that the magnitude of $Q/t^{1/2}$ values was also dependent on the thickness of hydrodynamic layer (h_d). The hydrodynamic diffusion layer can be minimized and maintained at a constant thickness in vitro by the use of a constant rotation drug elution system (Chien *et al*, 1974).

Moving Boundaries.

The diffusional release of a dispersed or dissolved drug from a polymeric matrix generally involves the presence of a moving diffusional front separating the undissolved core and the partially extracted region. In the case of an erodible or swellable polymer matrix, the release kinetics is further complicated by the presence of a second moving boundary namely the eroding or swelling polymer front (Lee, 1981). Except for some special cases, the presence of a moving boundary introduces a non-linearity so that only a few exact solutions are known (Crank, 1975; Ockendon and Hodgkins, 1975; Wilson *et al*, 1978). Only very simple pseudosteady state approximations have been used to analyse the release of a dispersed drug from a polymeric matrix (Baker and Lonsdale, 1974; Higuchi, 1961). A familiar example is Higuchi's treatment for a rigid matrix under perfect sink condition. For the release of a dispersed drug from an erodible polymeric matrix, Hopfenberg (1976) treated the case of no diffusional contribution, whereas Baker and Lonsdale (1976) presented a brief pseudosteady state analysis of the more general system including diffusional contribution. For drug release from a swellable polymeric matrix, Peppas *et al* (1980) recently presented theoretical and experimental results taking into account the countercurrent diffusion of solvent. However, a steady state assumption was also made in the treatment. This is valid only when the drug loading is in great excess of the drug solubility ($A \gg C_s$). In reality, however, one often encounters situations where the polymer hydrophilicity, drug solubility, dosage level, and rate requirements do not permit loading in great excess of the solubility. The direct application of pseudosteady state results to such systems is certainly undesirable (Lee, 1981). This author in his studies using planar polymeric matrices developed more accurate and more convenient analytical solutions to rigid, surface erodible and swellable matrices as follows: For a planar polymeric matrix with uniform initial drug loading per unit volume (A) and equilibrium drug solubility (C_s), the general diffusion equation describing the kinetics of drug release under perfect sink condition is:

$$dc/dt = d/dx (Ddc/dx) \dots\dots\dots \text{Equation 1.17}$$

where $x = 0$ at the centre and $x = a$ at the surface.

i) **Rigid Matrix:** The only moving boundary involved here is the diffusion front $R(t)$ whereas the polymer surface $S(t)$ is stationary i.e. $S(t) = a$. The equation for the release of drug in this case is given by:

$$m = \frac{1+H}{\sqrt{31\pi}} \left(C_s \sqrt{Dt} \right) \dots\dots\dots \text{Equation 1.18}$$

$$\text{where } H = 5(A/c_s) - 4 + \sqrt{(A/C)^2 - 1} \dots\dots\dots \text{Equation 1.19}$$

m is the amount of solute released per unit area.

The above equation predicts the amount of solute released per unit area (m) to be linear in square root time similar to the Higuchi equation. However in contrast to the Higuchi equation, this equation is uniformly valid over all A/C_s values.

ii) **Surface erodible matrix:** Drug release from surface erodible matrices having constant geometry will be zero order. This is because the eroding front moves at a constant velocity in the same direction of the diffusion front. With some manipulations the resulting equations for $A > C_s$ can be simplified to:

$$M/M_\infty = (1 - 1/2(C_s/A))\delta + (Ba/D)\tau \dots\dots\dots \text{Equation 1.20}$$

and

$$\tau = 1/6h(3(A/C_s) - 2)(\delta - 1/2h \ln(1 + 2\delta h)) \dots\dots\dots \text{Equation 1.21}$$

$$\text{where } h = 1/2(1 - A/C_s)(Ba/D) \dots\dots\dots \text{Equation 1.22}$$

M_∞ is the total amount released per unit area

M/M_∞ is the fractional release

Ba is the surface erosion rate constant (velocity units)

δ is the relative separation between the diffusion and the eroding fronts defined as $(S(t) - R(t))/a$. Ba/D is the erosion rate to matrix permeability ratio which measures the relative contribution of erosion and diffusion processes.

The studies conducted here show that as the erosion process dominates the diffusion process, e.g. $Ba/D = 10$, almost total zero-order release results. The release generally starts with a typical first order kinetics, then shifts toward a zero-order one with a limiting slope approaching Ba/D . Similar to the results of Baker and Lonsdale (1976) the zero-order release is primarily contributed by the identical rate of movement of the diffusing and eroding fronts at large time. It is seen that the larger the value of Ba/D , the sooner the synchronization can be reached.

iii) Swellable matrix

The method of solution for the surface erodible matrix can easily be extended to the case of a swellable matrix. The swelling polymer surface now moves in an opposite direction to that of the diffusion front (Lee, 1981). This situation is generally encountered in the drug release from a hydrogel or hydrophilic polymer matrix.

With the assumption that Fickian diffusion is obeyed and the increase in linear dimension of the planar membrane is proportional to the solvent uptake i.e. proportional to the square root of time $S(t) - a = L\sqrt{t}$ with a proportionality constant L having the same dimension as the square root of diffusion coefficient, the following equations are obtained:

$$M/M_{\infty} = (B(1-1/2Cs/A) - (L/2\sqrt{D})\sqrt{\tau}) \sqrt{\tau} \dots\dots\dots \text{Equation 1.23}$$

Where:

$$B = \frac{\left[-(1-A/Cs) \left(\frac{L}{2\sqrt{D}} \right) + \sqrt{(1-A/Cs)^2 \left(\frac{L}{2\sqrt{D}} \right)^2 + 2(A/Cs) - 4/3} \right]}{(A/Cs - 2/3)} \dots\dots\dots \text{Equation 1.24}$$

The concentration dependence of the drug diffusion coefficient (D) and the external mass transfer resistance are neglected in the treatments above. The author however reports that they can

readily be incorporated through the use of a concentration dependent diffusion coefficient and an external mass transfer coefficient.

From the foregoing, it is evident that drug release from hydrophilic polymer matrices is a complex combination of many factors. This has resulted in different authors reporting different release kinetics from hydrophilic matrices. For example Chien *et al* (1975) and Roseman and Higuchi (1970) have reported square root kinetics as given by equations 1.11 and 1.12. Whereas Lee (1981) reported a square root release kinetics for rigid matrices, but a zero order release kinetics for surface erodible matrices similar to the results of Baker and Lonsdale (1976). In this study, the contributions of porosity, erosion and swelling to theophylline release profile from a formulated CPP matrix were assessed using a factorial design experimental setup. These factors determine if diffusion through the polymer or erosion becomes the rate limiting step in the release mechanism which could influence the achievement of zero-order release.

1.2.4: Factorial design experiment.

The usual approach to kinetic studies is to examine one at a time, the factors that are thought to affect the rate process. In many cases this approach is sufficient since either some fundamental relationship is to be examined or the effect of the various factors may be fairly well understood (Bolton, 1983). Bolton however pointed out that one disadvantage of this experimental method is that, when present, interactions of factors may not be observed. Usually, little or no extra effort is required to uncover all possible effects by use of the factorial design. According to this author, factorial experiments are particularly advantageous in situations in which (a) the effects of several factors and their interactions are to be determined simultaneously in the absence of prior information, (b) relatively small preliminary screening experiment is desired to obtain an estimate

of the magnitude of effects of various variables, (c) the effects of factors are determined in a complex experimental situation (e.g., many simultaneously varied factors), and (d) the experimental error (e.g. assay) is relatively large. Statistical techniques may then be applied to test the significance of the main effects and interactions. Bolton (1983) has stated that in typical kinetic studies, effects are usually additive, but it is important to consider carefully any analysis based on a model that also shows multiplicative relationships.

Factorial designs are extremely useful in a wide variety of experimental situations and applications of these designs to pharmaceutical problems have appeared in the literature (Plaizier - Vercammen and DeNeve, 1980; Fonner et al, 1970; and Dincer and Ozdurmus, 1977). A factorial experiment considers the effects of various factors at several levels e.g, 2 levels, one high and one low, where results of all combinations of the factor levels are observed. When all factors are at two levels, a 2^n factorial design is employed (where n is the number of factors, the effects of which are to be investigated) as stated by Bolton (1983). According to this author, the main effect is the difference in response (e.g rate constant) caused by the change in level of a factor averaged over all levels of the other factors. If the effect of one factor is dependent on the level of another factor, an interaction between those factors is said to exist.

1.3: EVALUATION OF MODIFIED-RELEASE PRODUCTS

1.3.1: Considerations in the evaluation of modified - release products.: There are two important requirements for preparing controlled - release products: demonstration of safety and efficacy and demonstration of controlled drug release.

For many drugs, data are available demonstrating the safety and efficacy for drugs given in a conventional dosage form. These include all drugs in the official books. Bioavailability data

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demonstrating comparable blood level to an approved controlled - release product are acceptable.

The bioavailability data requirements include the following:

- a). the product should demonstrate sustained - release as claimed without "dose dumping" (abrupt release of large amount of drug in an uncontrolled manner).
- b) the drug should show steady -state levels comparable to those reached using a conventional dosage form given in multiple doses, which was demonstrated to be effective.
- c). the drug product should show consistent pharmacokinetic performance between individual dosage units.
- d). the product should allow for maximum amount of drug to be absorbed while maintaining minimum patient - to - patient variation.
- e). the demonstration of steady - state drug levels after the recommended doses are given should be within the effective plasma drug levels for the drug.
- f). an in vitro method and data that demonstrate the reproducible controlled - release nature of the product should be developed. The in-vitro method usually consists of a suitable dissolution procedure that provides a meaningful in - vitro / in - vivo correlation.
- g). in - vivo pharmacokinetic data consist of single and multiple dosage regimens comparing the controlled - release product to a reference standard (usually an approved non-sustained - release or a solution product). The pharmacokinetic data usually consist of plasma drug data and/or urinary drug excreted.

1.3.2: Regulatory studies for the evaluation of modified - release products

a) Dissolution studies.

Design and selection of controlled - release products are often aided by dissolution tests carried out at different pHs for various time periods to simulate the conditions of the g.i.t. Skelly

and Barr (1987) have shown that controlled - release preparations of theophylline such as Theo-24[®] have a more rapid dissolution rate at a higher pH of 8.4 whereas Theodur[®] is less affected by pH. These dissolution tests in-vitro may help to predict the in-vivo bioavailability performance of the dosage form.

Dissolution requirements for each of the three types of modified - release dosage form are defined by the U.S.P. The clarification is useful for the submission of modified release products for approval for marketing. Some of the key requirements for the in-vitro dissolution/drug release studies include: (i) reproducibility of the method, (ii) proper choice of media, (iii) maintenance of sink conditions, (iv) control of solution hydrodynamics, (v) dissolution rate as a function of pH (ranging from pH1 to pH8 and including several intermediate values), and (vi) selection of the most discriminating variables (media, pH, rotation speed, etc) as the basis for the dissolution test and specification.

The dissolution studies should show lack of "dose dumping", controlled - release characteristics, complete drug release from dosage form (a minimum of 75 to 80% of the drug should be released at the last sampling interval), pH dependence/independence of the dosage form as indicated by percent dissolution in water, appropriate buffer, simulated gastric juice or simulated intestinal fluid. A number of compendial dissolution methods are described in the USP-XXII / NF-XVII and include the rotating basket method, paddle method, transdermal product testing methods, enteric coated products test methods etc. Other unofficial methods of dissolution testing are available and include, the rotating bottle method, the flow-through dissolution method, the intrinsic dissolution method and the peristalsis method.

There are a number of equipment and operating variables associated with dissolution testing. The centering and alignment of the paddle is critical in the paddle method. Turbulence can create increased agitation, resulting in a higher dissolution rate. Wobbling and tilting due to worn equipment should be avoided. The basket method is sensitive to clogging due to gummy materials or pieces of small particles. Such clogging can create local non sink condition. The paddle method is therefore preferred for gummy materials. Also dissolved gas in the medium may form air bubbles on the surface of the dosage form unit which can affect dissolution in both basket and paddle methods. A low-density preparation may be poorly wetted in the basket method. For many drugs, a satisfactory dissolution test may be obtained with more than one method by optimizing testing conditions. In this study, the paddle method was used since the CPP is a gummy material. Air bubbles were removed from the dissolution media by sonication.

The analysis of theophylline in the dissolution media was conducted using a **spectrophotometric** method, while potassium chloride was analysed by the use of a **flame photometer**.

Spectrophotometry: When molecules of a liquid or a solution are exposed to continuous light radiation in the visible regions (4,000 to 8,000 Å) and the ultraviolet regions (below 4,000Å) of the spectrum, they absorb light of various frequencies or wavelengths depending on the energy of the electronic transitions which accompany the absorption (Martin et al, 1969). Thus, the wavelength of maximum absorbance is characteristic of different chromophores. The quantitative measurement of light is made in a spectrophotometer, and the absorbance can be plotted against the wavelength of the light i.e. the spectra to obtain the wavelength of maximum absorbance (λ_{max}). In order to use the spectrophotometer in quantitative analysis, the absorbance of solutions of varying concentrations are determined at a convenient wavelength, usually the λ_{max} . The absorbance is then plotted against

the concentrations to obtain what is known as a Beer plot from which the concentration of a sample with known absorbance at $\lambda_{\max}$ can be determined as given by the Beer law:

$$A = \log \frac{I_0}{I} = abc \text{ Equation 1.25}$$

where I_0 is the intensity of the incident light or radiant energy, I is the intensity of transmitted light after passing through b centimeters of solution of concentration c (g/l). The term $\log (I_0/I)$ or A is known as the absorbance (optical density), and a is a proportionality constant known as the absorptivity (extinction or absorption coefficient).

Flame photometry: When metal ions in solution are aspirated into a low temperature flame (in an aerosol form) the electrons of the ion are excited to higher energy states. When these electrons return to the ground state, they lose the excitation energy and a discrete wavelength of visible light is emitted. This light wavelength can be isolated from other light wavelengths by an optical filter and the amount of light emitted can be detected with a suitable photodetector. The amount of light emitted is proportional (for low concentrations of metal ion only) to the number of ions in the flame and hence the number of ions in solution. In the 410 science model, the electrical signal from the photodetector is amplified and displayed on a digital readout. The 410 clinical model incorporates a linearizer to compensate for the non-linear response of the signal. (Reference: Operating manual).

b) **Pharmacokinetic simulation of controlled - release products:**

Complete simulation of the absorption pool is probably unrealistic, but simulation of the parameters of concern, perhaps exaggerated to speed response, is both possible and desirable, and good relationships between some *in-vitro* and *in-vivo* tests have been reported (Stelmach *et al*,1965; Levy *et al*,1965 and Wood and Syarto,1964).

The plasma drug concentration profiles of many controlled - release products fit an oral one-compartment model assuming first-order absorption and elimination. Compared to an immediate

release product, the controlled - release product would typically show a smaller absorption rate constant due to the slower absorption of the controlled- release product. The time for peak concentration (t_{max}) is usually longer and the peak drug concentration (C_{max}) is reduced. If the drug is properly formulated, the area under the plasma drug concentration curve should be the same. These parameters conveniently show how successful the controlled - release product performs in-vivo (Shargel and Yu, 1993). For example, a product with a t_{max} of 3 hours would not be very satisfactory if the product is intended to last 12 hours. Similarly, if the C_{max} is excessively high, it would be a sign of "dose dumping" due to inadequate formulation. The pharmacokinetic analysis of single-and multiple- dose plasma data has been used to evaluate many controlled - release products by regulatory agencies. The analysis is practical because many products can be fitted to this model even though the drug is not released in a first - order manner. Various models have been used to simulate plasma drug levels of controlled - release products by Welling (1983). The plasma drug levels from a zero-order controlled - release drug product may be simulated with the following equation:

$$C_p = \frac{D_s (1 - e^{-Kt})}{V_D K} \text{-----Equation 1.26}$$

Where D_s = maintenance dose or rate of drug release (mg/min)

C_p = plasma drug concentration

K = overall elimination constant

V_D = volume of distribution

In the absence of a loading dose, the drug level in the body rises slowly to a plateau with minimum fluctuations. The simulation assumes (1) rapid drug release without delay, (2) perfect zero-order release and absorption of the drug, and (3) that the drug is given at the exact dose interval. When

a controlled-release drug product with a loading dose (rapid release) and a zero-order maintenance dose is given, the resulting plasma drug concentrations are described by:

$$C_p = \frac{D_i K_a}{V_D (k_a - k)} (e^{-kt} - e^{-k_a t}) + \frac{D_s}{K V_D} (1 - e^{-kt}) \quad \text{-----Equation 1.27}$$

Where D_i = immediate-release dose (loading dose)

D_s = maintenance dose (zero-order)

A pharmacokinetic model that assumes first-order absorption of the loading and maintenance doses has also been proposed. This model predicts spiking peaks due to loading dose when the drug is administered repeatedly in multiple doses (Welling, 1983).

c) Stability of availability rate during storage

Sustained - action dosage forms are tested for (1) stability of the availability rate during storage, (2) in-vivo sustaining action, (3) in-vitro sustaining action, and (4) because of the relative instability of currently used sustaining materials, the customary chemical stability is studied (Eriksen, 1970). The substances used in the formulation of sustained - release dosage forms often present some special problems with regard to their physical stability on storage. For example, the waxes most often used for availability control alter their physical nature on prolonged standing, unless precautions are taken to stabilize them at the time of manufacture or to prevent the change from occurring. Fats and waxy materials may crystallize into unstable forms, which exhibit different physical properties like lower melting point, lower bulk densities and varying water vapour transmission which may lead to cracking or gross availability rate changes from drug products. Water vapour transmission and drug diffusion through film coats have been shown to be affected by some intrinsic thermal properties of polymers (Moelter and Schweizer, 1949; Okhamafe and York, 1983, 1985a,b and Rogers, 1976). This study therefore employed the Differential Scanning

Calorimetry (DSC) technique to conduct thermal studies on CPP, and its mixtures with theophylline, potassium chloride, magnesium stearate etc.

Thermal analysis (TA): Temperature is an important parameter in drug-excipient compatibility and the effects of some system parameters like polymer solubility, solution solubility and polymer diffusivity on drug release are thermodynamic processes depending on temperature as reported in section 1.2.3. The thermal effects are caused by melting, evaporation, solid-solid transformations, decompositions and other chemical reactions, and these thermal effects provide significant information (Riesen, Application Laboratory instruments No.801).

Thermal analysis embraces a group of analytical methods in which a physical property e.g. enthalpy, mass, volume or birefringence is measured as a function of temperature. The definition originally proposed in 1969 by the Nomenclature Committee of the International Confederation for Thermal Analysis (ICTA) and later reaffirmed in 1978, thermal analysis includes a group of analytical methods by which a physical property of a substance is measured as a function of temperature while the substance is subjected to a controlled temperature program. Thus thermal analysis involves a physical measurement and not, strictly speaking, a chemical analysis (Gedde,1990).

Perhaps the greatest number of applications of differential thermal analysis (DTA) and differential scanning calorimetry (DSC) in recent years has been in the area of polymeric materials. These two techniques are routinely used to measure glass transition temperatures (T_g), melting points (T_m), degree of crystallinity, heats of fusion and/or crystallization, decomposition temperatures and numerous other parameters. For routine drug excipient interaction studies, DSC and an isothermal stress test are normally employed. According to Van Dooren (1983), DSC curves are difficult to evaluate and positive conclusions are rarely obtained, thus the latter test is still

necessary. Van Dooren claims that numerous considerations must be made before a positive identification of drug-excipient interaction by DSC can be made.

The intrinsic thermal properties of materials being compressed could be important, because during compaction, friction causes a localized temperature rise at the contact points between granule/particle surfaces, at die walls and punch surfaces. The rise in temperature assists bonding before the heat generated is dispersed through the mass (Shotton and Hersey, 1970). Such bonding could be a result of softening, melting, plastic deformation etc of the material being compressed which are dependent on intrinsic thermal characteristics like glass transition temperature (T_g), softening point (T_s), melting point (T_m), crystallinity etc. Thus addition of excipients and formulation processes that influence intrinsic thermal properties of the material to be compressed may influence the bonding strengths in the tableted mixture and probably also therefore influence the release rate of drug from the tablets.

1.4: CISSUS POPULNEA POLYMER (CPP)

CPP is obtained from the stem bark of Cissus populnea amplidaceae. The stem bark mucilage is commonly used in many parts of Nigeria to prepare edible thick viscous soup ("draw soup"). The stem bark has a CPP yield of 13.84% w/w as reported by Ibrahim *et al* (1992). These authors have studied the pharmacognostic aspects of the stem bark of *C. populnea* and the mucilage. They have reported that the mucilage consist of D-glucuronic acid and sugars galactose and xylose. They have also demonstrated the binding properties of CPP at concentration levels of 1-5%w/w in paracetamol tablet formulations.

CPP a mucilage is a polysaccharide having colloidal properties. Generally mucilages swell in water like gums to form gels (Miller, 1957). They are sulphuric acid esters, the ester group being a complex polysaccharide (Balbaa,1976). Mucilages are normal "physiological products" being

secreted in the cell and laid down like hemi-cellulose often in large quantities as to completely fill the cells, as opposed to gums which are "pathological products" brought about by injury or by unfavourable conditions of growth by the process called gummosis and are usually formed by changes in existing cell-walls (Wallis, 1967; Balbaa, 1976). According to Wallis (1967) the mucilages are usually grouped together with the gums especially by the industrial users as there is no clear sharp demarcation between them, both of which are hydrocolloid polymers.

The linear polymers are less soluble than those with branched constituents, and yield solutions with greater viscosity. These features are due to the increased possibility for good alignment and considerable intermolecular hydrogen bonding among linear molecules. The hydrocolloids may be acidic, basic or neutral. Basic polymers have very limited commercial importance, acidic and neutral ones are widely used (Wallis, 1967; Tyler *et al*, 1981).

1.5: MICROBIAL CONTAMINATION OF NON-STERILE PHARMACEUTICALS.

There have been several reports over the years of infection arising from the administration of pharmaceutical products that are not normally required to be sterile e.g. ointments, lotions and tablets etc. This has led to the introduction of official microbiological standards in for example B.P. 1973, USP XIX and BPC 1973. It is also common practice for manufacturers these days to look closely at their raw materials, methods of manufacture and product formulation to minimise microbial contamination and eliminate certain indicator pathogens. The matrix former under study is of plant origin, and for it to be industrially acceptable for the formulation of pharmaceutical products, its microbial quality has to be considered. The microbial quality of CPP was assessed in comparison to that of hydroxypropylmethylcellulose (HPMC) to determine: (a) the total numbers

of viable organism per gm of powdered sample and (b) the absence/presence of specific pathogenic organisms.

Some of the organisms most likely to cause human infection are Salmonella spp., Pseudomonas spp., Clostridium spp., and Staphylococcus aureus. Also the presence of coliform bacteria particularly Escherichia coli can be an indication of faecal pollution and of the possibility that faecal pathogens are present, even if the presence of pathogens cannot be demonstrated directly (Rawlins, 1980). Numerous Salmonella spp. comprise the agents of typhoid and paratyphoid fevers (enteric fever), and many of the common causative agents of food poisoning. Staphylococcus aureus is carried by many individuals in the nose and throat and sometimes on the skin, as a harmless parasite. However, under appropriate conditions, it can cause wound infections which may be difficult to treat and it is a common cause of food poisoning if some foods infected with it are left so that the organism can grow and produce exotoxin (Rawlins, 1980). Although Pseudomonas aeruginosa is of relatively low virulence, it is a common wound pathogen since it establishes itself readily in damaged tissue or in debilitated patients (Rawlins, 1980). According to this author, it has been reported as the causal agent of deaths in burns unit, and of loss of sight, and may also cause systemic infections. Furthermore, the organism is resistant to many antibiotics apart from carbenicillin and colistin, and it readily acquires resistance by the transfer of resistance factors.

1.6: AIM AND SCOPE OF WORK.

There is the need to search for new materials for use in the formulation of controlled-release matrix tablets since many of the evaluated ones currently in use have some shortcomings. Many of them are particularly sensitive to variations in g.i.t. conditions, for example nearly all gums possessing a carboxyl acid function such as carbopol are influenced greatly by change in pH (Talukdar and Plaizier-Vercammen, 1993). Also there is the need for local sourcing of

pharmaceutical raw materials in this part of the world to conserve scarce foreign exchange. The abundance of the plant Cissus Populnea from which the material under study (CPP) is extracted and the very good binding properties of CPP at low concentrations of 1-5%w/w in tableting (Ibrahim *et al*, 1992), necessitated the study of the material as a novel polymer for matrix tablet formulations for controlled - release of drugs.

The study is intended to examine the physicochemical and microbial properties of CPP itself, evaluate it in comparison to known materials and use it for the formulation of controlled-release drug products, examine the physical, chemical and release properties of the formulated products, and then determine their sensitivity to variations in simulated g.i.t. conditions. Also factors like erosion, swelling and porosity that control drug release profiles are to be studied.

CHAPTER TWO

CHAPTER TWO

MATERIALS AND METHODS.

2.1: MATERIALS.

The materials used in this work including chemicals, culture media, extract and others are as underlisted.

List of Materials used.

- a) Cissus populnea polymer (CPP), as extracted.
- b) Theophylline anhydrous (1,3- Dimethylxanthine) anhydrous
Sigma chemical company, st. U. S. A.
- c) Potassium chloride (KCl)
BDH Chemicals Ltd, Poole England.
- d) Hydroxypropylmethylcellulose (HPMC), NF XII, Lot No.55-754.
Shin-etsu chemical company, Tokyo Japan.
- e) Methocel E4M Premium EP, Batch NO.MM91060611E.
Colorcon Ltd, Kent England.
- f) Cellulose acetate phthalate EP (CAP), Lot No.P1113.
CAP - Wako, Osaka Japan.
- g) Lactose EP D80 (Regular grade)
Whey products ltd. England.
- h) Dicalcium phosphate
Edward Mendell Co. Inc., U. S. A.

- i) Magnesium stearate(various batches)
Boots Company Ltd., England
- j) Industrial methylated spirit (I.M.S.)(various batches)
Hays Ltd., Greenwich England.
- k) Acetone (various batches)
BDH Laboratory supplies, Loughborough England.
- l) Hydrochloric acid (HCl) (various batches)
FSA Laboratory Ltd., Poole England.
- m) Potassium dihydrogen orthophosphate (KH_2PO_4) (various batches)
BDH chemicals Ltd., Poole England.
- n) di-sodium hydrogen orthophosphate dihydrate($\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$)
BDH chemicals Ltd., Poole England.
- o) Sodium chloride B.P. (NaCl)
BDH chemicals Ltd., Poole England.
- p) Tween 80
Serva Feinbiochemica GmbH & Co., Germany.
- q) Gelatin B.P.
Macarthys, Romford Essex, England.
- r) Stearic acid
M & B Chemicals, England
- s) Carnauba wax
Merck, Darmstadt
- t) Beeswax
Merck, Darmstadt

- u) Nutrient agar
Oxoid Ltd., Basingstoke England
- v) Nutrient broth
Oxoid Ltd., Basingstoke England
- w) MacConkey agar
Oxoid Ltd., Basingstoke England
- x) Deoxycholate citrate agar
Oxoid Ltd., Basingstoke England
- y) Triple sugar iron agar
Oxoid Ltd., Basingstoke England
- z) Mannitol salt agar
Oxoid Ltd., Basingstoke England
- aa) Salt meat agar
Oxoid Ltd., Basingstoke England
- ab) Selenite and tetrathionate broth
Oxoid Ltd., Basingstoke England
- ac) Cetrimide
BDH Chemicals Ltd., England.
- ad) Povidone (PVP - 40T), Lot 102F - 0297.
Sigma Chemical Company, St. Louis U.S.A.

2.2: **EQUIPMENT**

The items of equipment used are as underlisted. Details of their manufacturers are indicated where first mentioned under "methods".

1

List of Equipment used.

- a) Manual single punch tableting machine, 0-5 tons load on ram.
- b) Dissolution system 2000 consisting of:
 - i) U.S.P. paddle dissolution unit.
 - ii) Rotation speed control
 - iii) Temperature control.
- c) Automated dissolution apparatus (Appendix 1) consisting of:
 - i) U.S.P paddle dissolution apparatus
 - ii) U.V./VIS/NIR spectrophotometer
 - iii) Pump system
 - iv) Amstrad 512k personal computer
 - v) Opus 14" RGB data display
 - vi) Printer
- d) U.V. Scanner
- e) Corning flame photometer 410 (Appendix 2)
- f) Ultra sonic heater (Sonicator)
- g) Electron scanning microscope (Appendix 3)
- h) Differential scanning calorimeter (Appendix 4)
- i) Olympus CH microscope
- j) Hot stage
- k) Central processor
- l) Nikon labophot microscope 230361
- m) pH meters:

- i) WPA C10 PH & mV meter
- ii) Whatman PHA 230
- n) Sartorius analytical balance
- o) Gallenkamp magnetic stirrer thermostat hotplate
- p) Gallenkamp drying oven
- q) Monsanto tablet hardness tester
- r) U.S.P. tablet disintegration tester
- s) Tablet friability tester
- t) Sieve shaker with a set of sieves
- u) Fume cupboard
- v) Electronic micro balance
- w) Micrometer calipers
- x) Hand crimping machine
- y) Incubator
- z) Portable autoclave
- aa) Water bath

1

2.3: **GENERAL METHODS**

2.3.1: **Extraction of CPP:** Strips of dried peeled stem bark of Cissus populnea plant were immersed in distilled water for 48 hours. The mixture was filtered through a fine muslin cloth and the mucilage was mixed with four times its volume of a mixture of I.M.S: acetone (2:1 ratio). This was accompanied by stirring with a smooth glass rod to separate the precipitate which was washed several times with more I.M.S: acetone mixture. The extract was then dried at 50-55°C in an air oven

(Gallenkamp, England) for about 36 hours. The dry hard product was subsequently crushed using pestle and mortar and passed through sieve No.60 (250 μ m) to produce a fine light brown powder.

2.3.2: Determination of Solubility of CPP in distilled water at 25°C: A modified method of that described by Carter (1972) was adopted. A sufficient quantity to produce a supersaturated suspension (0.5gm) of the powdered extract was shaken in sufficient quantity of distilled water to produce 100mls. The mixture was vigorously agitated several times during a period of 24 hours. It was then left to stand undisturbed for another 24 hours, and the clear supernatant was decanted. 10mls of the supernatant was evaporated to dryness in a pre-weighed crucible over a water bath. The combined weight of the crucible and dry content was noted and the weight of the content determined by subtraction. The solubility of CPP was then expressed as a percentage weight in volume (% W/V) as shown in section 3.3.1a..

2.3.3: Determination of pHs of CPP solutions/dispersions: Various concentrations of CPP solutions/dispersions were freshly prepared in distilled water and their pHs were measured using a pH meter (WPA Saffron Walden, England). The results are shown in table 3.2

2.3.4: Absorbance Spectra of Theophylline solution: Theophylline solutions in pH 1.2 and pH 7.2 dissolution media were scanned on a UV/visible scanner (Perkin-Elmer spectrometer) to determine their wavelengths of maximum absorbance (λ_{max}). The results are shown in table 3.3.

2.3.5: Beer's Law plot for the determination of theophylline: Several concentrations of theophylline solutions ranging from 50mg/L to 750mg/L were prepared both in pH 1.2 and in pH 7.2 dissolution media. The absorbance of the solutions were then measured at 270nm using a UV/VIS/NIR spectrophotometer (Phillips PU 8620, Pye Unicam England). The Beer's plot was constructed by plotting absorbance against concentration (Appendix 6). This plot served as calibration curve, from which a reference concentration was used on the automated dissolution apparatus.

2.3.6: Beer's Law plot for the determination of KCl: Several concentrations of KCl solutions ranging from 1ppm to 10ppm were prepared using an appropriate concentration of coming diluent. The photometer readings of the solutions were measured using a calibrated coming flame photometer (Corning Ltd., England). The readings were then used in constructing the Beer's Law plot of absorbance against concentration (Appendix 7). This served as a calibration curve for determining the KCl concentrations of solutions from their respective photometer readings.

2.3.7: Preparation of tablets

(i) Direct compression method

The weighed quantities of powders were triturated together by the principle of geometric dilution, using pestle and mortar to produce a homogenous mixture. The powders were then individually weighed according to the unit dose on an analytical balance (Sartorius, GmbH Germany), and fed into the die cavity of a manual single punch tableting machine (RHIC, England) and compressed at the appropriate pressures.

(ii) Wet granulation method

Granules were prepared by triturating the weighed out CPP, theophylline and diluent powders together in a mortar using the principle of geometric dilution to ensure homogeneity. The gummy CPP was then activated by wetting the powder mixture with a little quantity of distilled water and massing. The resultant doughy mass was subsequently passed through sieve NO. 40 (420 μ m). The granules produced were spread evenly in the air oven and dried at $55^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 110 minutes followed by resieving.

The granules were mixed with the appropriate quantities of magnesium stearate for 10 minutes on a roller mixer (Pascal Engineering, England). The granules were weighed for individual

tablets and fed manually into the die cavity of the manual single punch tableting machine and compressed at the appropriate pressures.

2.3.8: **Determination of theophylline release from matrices:** A calibrated automated dissolution system consisting of the following was used:

- (i) U.S.P. Paddle dissolution apparatus (Copley instruments Ltd., England).
- (ii) UV/VIS/NIR spectrophotometer (Phillips PU 8620 Pye unicam Ltd., England). The wavelength of 270nm was used.
- (iii) Pump system (Watson Marlow Ltd., England)
- (iv) Amstrad 512K personal computer (PC 1512)
- (v) Opus 14" RGB data display (Taiwan)
- (vi) Epson LX-800 printer.

A sample of the computer result printout is shown in Appendix 5.

2.3.9: **Determination of KCl release from matrices.** The KCl tablets were placed in a U.S.P. Paddle dissolution system (Hanson research Corp., U.S.A.) and samples were withdrawn at intervals followed by filtration through a millipore filter. The withdrawn samples were replaced with equal volumes of the dissolution media. The filtered samples were diluted with appropriate concentration of Corning 460/405 diluent and then analysed using the calibrated Corning flame photometer 410, operated using natural gas.

2.3.10: **Scanning electron microscopy:** The tablets were mounted on stubs using either double sided adhesive tape or araldite after gold plating their surfaces using Polaron E 5100 sputter coater. They were then examined under a scanning electron microscope (Phillips EM 501B), and

photographed using Ilford FP4 plus 125 ASA 120 format film. The electron micrographs are shown in figures 5.4 and 5.13.

2.3.11: **Pharmacokinetic simulation of Plasma level:** A computer program was used to obtain simulated plasma theophylline levels of the formulated "once - and twice-daily" tablets and immediate release tablets from their dissolution data according to equation 1.26:

$$C_p = \frac{Ds(1-e^{-kt})}{V_dK}$$

Total plasma level curves for multiple doses were obtained by using the principle of superposition (Shargel and Yu, 1993). The Pharmacokinetic data of theophylline used are as follows:

Elimination half - life ($t_{1/2}$) = 8.1 hours

Volume of distribution (V_d) = 35 litres

Oral bioavailability (%) = 96

The simulated curves are shown in figures 5.8 - 5.11 and 5.19 - 5.24 of chapter 5.

2.3.12: **Erosion studies:** Six individually weighed tablets were placed into the six vessels of a U.S.P. Paddle dissolution apparatus (Copley instruments Ltd., England) and at one hour intervals, one tablet was removed, weighed and dried to constant weight. The difference between the dried eroded tablet and its initial weight represents the erosion. The study was conducted using 50 rpm ("Low" erosion) and 100 rpm ("high" erosion). The results are shown in figure 6.1

2.3.13: **Swelling Studies:** The thicknesses of tablets were measured using calipers. The tablets were then placed on a stage in either pH 7.2 dissolution media ("low" swelling rate) or distilled water

("high" swelling rate). The increase in the thickness of each tablet was followed with time and represents the swelling. The results are shown in figure 6.2.

2.3.14: Stability Studies.

a) Shelf-storage stability studies.

Several batches of "twice-daily" theophylline tablets were prepared and stored at room temperature (25°C) in well closed containers for varying periods of time ranging between 3 to 8 weeks. At the end of the storage periods, the following tests were conducted on the tablets:

i) Release profile stability.

The drug release profiles of the tablets were determined using the calibrated automated dissolution apparatus described in method 2.3.8 above. The release profiles of the different batches were then compared as shown in figure 3.9.

ii) Drug content stability

Two tablets from each of the batches were tested. The tablets were crushed into fine powder. A quantity of the powder equivalent to 362mg theophylline was accurately weighed on the analytical balance and placed in a vessel of the calibrated automated dissolution system described in method 2.3.8 above to determine the theophylline content. The theophylline content was then calculated as a percentage of 362mg theophylline to represent the percentage potency as shown in figure 3.10.

b) Accelerated stability studies

Two types of accelerated studies were conducted:

i) Elevated temperature storage.

Tablets were stored in an air oven (Gallenkamp, England) at 50,60,70 and 80°C for varying periods of time between 2 to 26 hours. The results are shown in figures 3.11 - 3.13

ii) **Elevated humidity storage**

The chamber of the air oven was saturated with water vapour (to give 100% RH), by placing a beaker of distilled water in the oven at 38-40°C. The bottles containing the tablets were loosely closed and stored for 1 week in the oven chamber.

After storage at these elevated conditions, the drug release profiles and active ingredient contents were determined as previously described in 2.3.14 (i) above and the results are shown in figure 3.15.

2.3.15 **Thermal studies**

a) **Thermal microscopy**

Approximately 50mg samples were placed on a mettler FP82 hot stage. The heating rate was set at 10°C/minute rise by a mettler FP80 central processor. The hot stage was mounted on an Olympus CH microscope to observe the thermal changes in the sample with change in temperature between 50°C-300°C. The observations were used as guide for the interpretation of the differential scanning calorimetry (DSC) results.

b) **Differential scanning calorimetry**

Approximately 9.0mg samples weighed on Sartorius electronic micro balance 4401 MP8 were placed in aluminium crucible containers and sealed with a crimping hand machine. The samples were then placed in a Perkin - Elmer DSC 7 differential scanning calorimeter to determine their glass transition temperatures (T_g), softening points (T_s) and relative crystallinities. Nitrogen gas was the purge gas (60cm³/minutes) and a heating rate of 10 °C/minute over a temperature range of 45 °C - 350 °C was used. The results are shown in figures 3.3, 3.5 & 3.6 of chapter 3.

2.3.16: **Friability test:** Ten tablets were weighed and introduced into a Roche friabilator (Erweka GmbH, Germany) which was set to rotate at 25rpm for 4 minutes. At the end of the 100 revolutions,

the tablets were reweighed and compared to the initial weight. The percent loss in weight was subsequently calculated and represents the friability:

$$\% \text{ Friability} = \frac{\text{loss in weight}}{\text{initial weight}} \times 100 \text{ -----Equation 2.1}$$

The results are shown in table 3.6.

2.3.17: Disintegration time test: Six tablets were placed in six tubes of the U.S.P. tablet disintegration apparatus (Erweka GmbH, Germany). The apparatus was operated in accordance with the U.S.P. - XX procedure to determine the disintegration time of the tablets as follows:

The assembly of tubes was suspended in a beaker containing the disintegration medium (pH1.2 and pH7.2 solutions) that was maintained at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ by an electrically heated water bath. The assembly of tubes was made to move up and down in the medium so that the tablets were constantly agitated. The time taken for all the particles of the disintegrated tablets to pass freely through the mesh at the lower end of the tubes is usually considered to be the disintegration time. However, the tablets in this study did not disintegrate as shown in table 3.6.

2.3.18: Hardness Test: One tablet was placed between the two plungers of the Stokes-Monsanto hardness tester (CT 40 Engineering Systems Ltd, England). Force was then applied to the tablet via a compressed spring by screwing down the upper plunger. The force (in kg) at which the tablet fractured was then read off as indicated by a pointer that rode along a gauge on the barrel of the tester. The results are shown in table 3.6.

2.3.19: Measurement of tablet dimensions: The thickness and diameter of the various tablets were measured by the use of micrometer calipers. The results are shown in table 3.6.

2.3.20: **Particle size analysis:** The sieving method of the U.S.P. for testing powder fineness was used. A nest of 4 sieves (ranging in size from 180 μ m to 840 μ m) was mounted on a mechanical shaker (Endecott EFL1 MK3) with the coarsest at the top. A carefully weighed amount of granules was then placed on the top sieve, and after the sieves were shaken for 5 minutes, the granules retained on each sieve were weighed. The cumulative percent weight oversize was plotted against the particle size on a logarithm probability graph from which the geometric mean weight diameter (dg) was obtained. The results are shown in tables 3.4 & 3.5 and figure 3.8.

2.3.21: **Microbial Quality Determination.**

a) **Viable Count.**

In the present study, the pour plate method (Rawlins, 1980) was used since the sample suspensions were not too turbid as to make colony counting difficult. This method is more accurate than other methods like the roll tube, membrane filtration or tube dilution methods for determining the total bacterial count and was conducted for CPP and HPMC as follows:

- i) A 1% W/V suspension of the polymer under test was prepared in nutrient broth.
- ii) 1ml of the suspension was inoculated into 15mls of molten nutrient agar at 45^o C- 48^o C.
- iii) The mixture was poured into a plate (petridish) and allowed to solidify after which the plate was incubated inverted at 37^o C for 72 hours.
- iv) The colonies formed on the solidified agar were counted and using the dilution factors, the counts per gm of the polymer samples (CPP and HPMC) were calculated. The results are shown in table 3.7.

(b) **Testing for the presence of specific pathogens.**

The general procedure for the examination of pharmaceutical products for the presence of specific contaminants as described by Cowan (1974) is as follows:

1st Stage: Dissolve or suspend sample to be tested in nutrient broth which is a general purpose medium. This medium functions as a non-toxic diluent which preserves the viability of organisms.

2nd Stage: A sample of the suspension is then transferred to suitable selective media. These are enrichment media designed to grow selectively the organisms of interest and permit their ready identification later.

3rd Stage: The culture is then subcultured onto various differential media to further identify organisms.

4th Stage: Where the presence of particular organisms are indicated by the characters of growth differential, selected biochemical tests are performed. The procedure conducted for testing the presence of each of these organisms in CPP and HPMC samples is as follows:

- (a) 1gm of polymer sample was transferred into 9ml of nutrient broth and mixed thoroughly.
- (b) 1ml of the resultant mixture/suspension was added to 10mls of each of the selective media given in table 2.1. All the tubes were incubated for 48 hours at 37° C and the results recorded.
- (c) From each of the above enrichment cultures, streaks were carefully made onto differential agar media indicated in table 2.1. to obtain discrete well isolated colonies whose characteristics can be observed clearly. Confluent growth is likely to lead to false results. The plates were incubated for 48 hours at 37° C and the results were recorded.
- (d) Confirmatory biochemical test were carried out where necessary to establish the identities of any colonies suspected to be Staph aureus, Salmonella spp., Pseudomonas aeruginosa or E Coli.

The results are shown in tables 3.8 & 3.9.

Table 2.1: Selective and differential media and biochemical tests

Organism	Selective media	Differential agars	Biochemical tests
<u>Staph aureus</u>	Salt meat Broth	VogelJohnson, Mannitol salt	Gram stain, Coagulase, Phosphatase
<u>Salmonella spp</u>	Selenite and tetrathionate broths	Xylose lysine deoxycholate (XLD), Bismuth sulphite, Triple sugar iron, Deoxycholate citrate.	Sugar fermentation: glucose, lactose, dulcitol, sucrose, mannitol.
<u>E.Coli</u>	Minerals Modified glutamate broth	MacConkey, Eosin methylene blue	Indole (44 ^o), MRVP, citrate lactose, ricino lead, broth (44 ^o)
<u>Ps. aeruginosa</u>	Lilly Lowbury broth (contains Nalidixic acid)	King's A and King's B containing 0.03% cetrinide	Oxidase, Diffusible pigment production Growth at 42 ^o C

CHAPTER THREE

CHAPTER THREE

PHYSICOCHEMICAL AND MICROBIAL STUDIES.

3.1: INTRODUCTION.

Drug deterioration, release and absorption may be influenced by chemical and physical factors. The physicochemical profile of a drug, excipients and their combinations are important considerations in drug product design. The chemical stability of the product is important in ensuring that the patient receives a uniform dose of drug throughout the shelf-life of the product and in preventing the economic repercussions of marketing unstable products (Rawlins, 1980). On the other hand, drug release from drug products may be controlled by physical processes like dissolution, diffusion, particle size, polymorphic form etc. Some excipients may influence the release and absorption of drugs, while other excipients may increase the retention time of drugs in the g.i.t. thereby increasing the amount of drug to be absorbed. Also the physical properties of tablets are important for their successful performance, for example, the tablets should be strong enough to withstand handling, transportation etc. Equally important is the microbial quality of pharmaceutical products as specified by official books. These considerations necessitated the physicochemical and microbial studies conducted in this chapter.

3.2: EXPERIMENTAL.

3.2.1: Physicochemical and microbial properties: The following physicochemical and microbial properties of CPP, theophylline, potassium chloride and formulated tablets were studied using the methods described in chapter 2:

- (a) solubility (b) pHs of solutions/dispersions (c) absorption spectra and Beer law plots (d) thermal analysis, (e) particle size analysis (f) physical properties of tablets - disintegration, friability,

hardness etc (g) chemical stability-shelf and accelerated tests (h) microbial quality - total viable count and test for specific pathogens.

The Beer law plots were used for the quantitative determination of theophylline and potassium chloride released from formulated products.

3.2.2: Preparation of tablets and determination of theophylline release: The tablets were prepared both by the direct compression and wet granulation methods described in chapter 2. The formulae of the tablets used in the study are given in table 3.1 and drug release from the formulations were determined by the methods described in chapter 2.

The “twice - daily” tablets used for the shelf and accelerated stability studies were prepared by the wet granulation method and the composition of the tablets is as follows:

Theophylline -----	362.00mg (55.26%)
CPP -----	127.03mg (19.39%)
Lactose -----	165.38mg (25.25%)
Mag stearate -----	0.66mg (0.10%)
Tablet weight =	<u>655.07mg</u>

The tablets were compressed at 2tons compression pressure

3.2.3: Thermal studies.: The intrinsic thermal properties of powders and granules were determined as follows:

(a) Determination of glass transition temperature (T_g)

The method of Brennan (Thermal analysis application study 7) was used and involves extrapolating the pretransition and post-transition baselines. The point on the thermal curve that is equidistant to the two extrapolated baselines represents the T_g.

TABLE 3.1: FORMULAE OF CONTROLLED-RELEASE PRODUCTS FOR CORRELATING DRUG RELEASE AND THERMAL PROPERTIES
Effect under study

Effect under study	Formulation number	Content of ingredients in mg and (%) per tablet:			Drug: Polymer ratio	Compression technique pressure (tons)
		Theophylline	CPP	Mag. Stearate		
Comparing Direct Compression and granulation	F1	200 (66.7)	100(33.3)		2:1	Direct Comp. (3.625)
	"	"	"		"	Wet gran (3.625)
	F2	200(75)	66.67(25)		3:1	Direct comp. (2)
Mag. Stearate Content of theophylline: CPP (2.5:1) mixture	"	"	"		"	Wet gran (4)
	F3	362(71.4)	144.8(28.6)		2.5:1	" (3)
	F4	362(71.4)	144.8(28.5)	0.51(0.1)	"	"
	F5	362(71.3)	144.8(28.5)	1.02(0.2)	"	"
	F6	362(71.3)	144.8(28.4)	1.53(0.3)	"	"
	F7	362(71.2)	144.8(28.4)	2.04(0.4)	"	"
	F8	362(75)	120.67(25)		3:1	"
Mag. Stearate content of theophylline: CPP (3:1) mixture	F9	362(75)	120.67(24.9)	0.48(0.1)	"	"
	F10	362(74.9)	120.67(24.9)	0.96(0.2)	"	"
	F11	362(74.9)	120.67(24.8)	1.44(0.3)	"	"
	F12	362(74.8)	120.67(24.8)	1.92(0.4)	"	"

(b) **Determination of softening point (Ts)**

The linear portion of the ascending curve of the melting endotherm was extrapolated to the baseline and the point of intersection represents Ts. (Bernnan; Thermal analysis application study 7)

(c) **Determination of relative crystallinity.**

The area under the crystal fusion endotherm provides a measure of the relative degree of crystallinity (Okhamafe and York, 1985). The area of the parent sample (theophylline: CPP mixture of 2.5:1 ratio) represented 100% crystallinity. The areas under the fusion endotherm of other samples were calculated relative to the parent sample.

3.3: **RESULTS AND DISCUSSIONS.**

3.3.1: **Solubility of CPP and the pHs of its dispersions.**

(a) **Solubility of CPP.**

The solubility of CPP in distilled water at 25°C was calculated as follows:

10mls contain 0.018g CPP.

$$\therefore 100\text{mls will contain } \frac{(0.018 \times 100)}{10} \text{ gm}$$

$$= 0.18\text{gm}$$

Thus the solubility of CPP in cold distilled water at 25°C is 0.18%w/v.

Lee (1980) and Peppas *et al* (1980) have reported that the mechanism of drug release from drug-loaded HPMC matrices is controlled by two factors: Matrix swelling and polymer dissolution. The low solubility of CPP (0.18%W/V) in water and its observed high swelling capacity would be expected to confer good control of drug release from CPP matrices into aqueous environments such

as the g.i.t. in accordance with the observation of DeHaan and Lerk (1984) who pointed out that another principle of delivering active material is to use a coating membrane that is supposed not to dissolve at all for slow release pellets. Most matrix materials are water insoluble, although some may swell slowly in water (Shargel and Yu 1993). This would afford drugs protection against water and slow down the diffusion.

(b) **pHs of CPP solutions/dispersions.**

Table 3.2. The pHs of CPP solutions/dispersions.

CPP Conc(% w/v)	pH
0.125	6.34
0.25	6.29
0.5	6.25

pH could sometimes play a very significant role in the dissolution, release and stability of drugs from matrices. The pH of a hydrated matrix polymer may therefore be an important factor in drug release, and also in the stability of the drug.

The pHs of the CPP solutions/dispersions are slightly acidic (pH 6.25-6.34) as shown in table 3.2. Within such a pH range and indeed at physiological pHs, theophylline would only slightly be ionised (Hendeles *et al*, 1984). Consequently dissolution in the aqueous dissolving medium will remain low and release would be slow. Furthermore theophylline is weakly acidic with pKa 8.8 at 23°C and 8.3 at 37°C, thus would not form a soluble salt in the slightly acidic CPP matrix and solubility in the dissolving medium remains low and release is thus prolonged.

3.3.2: The U.V/Visible absorption spectra of theophylline Solution.

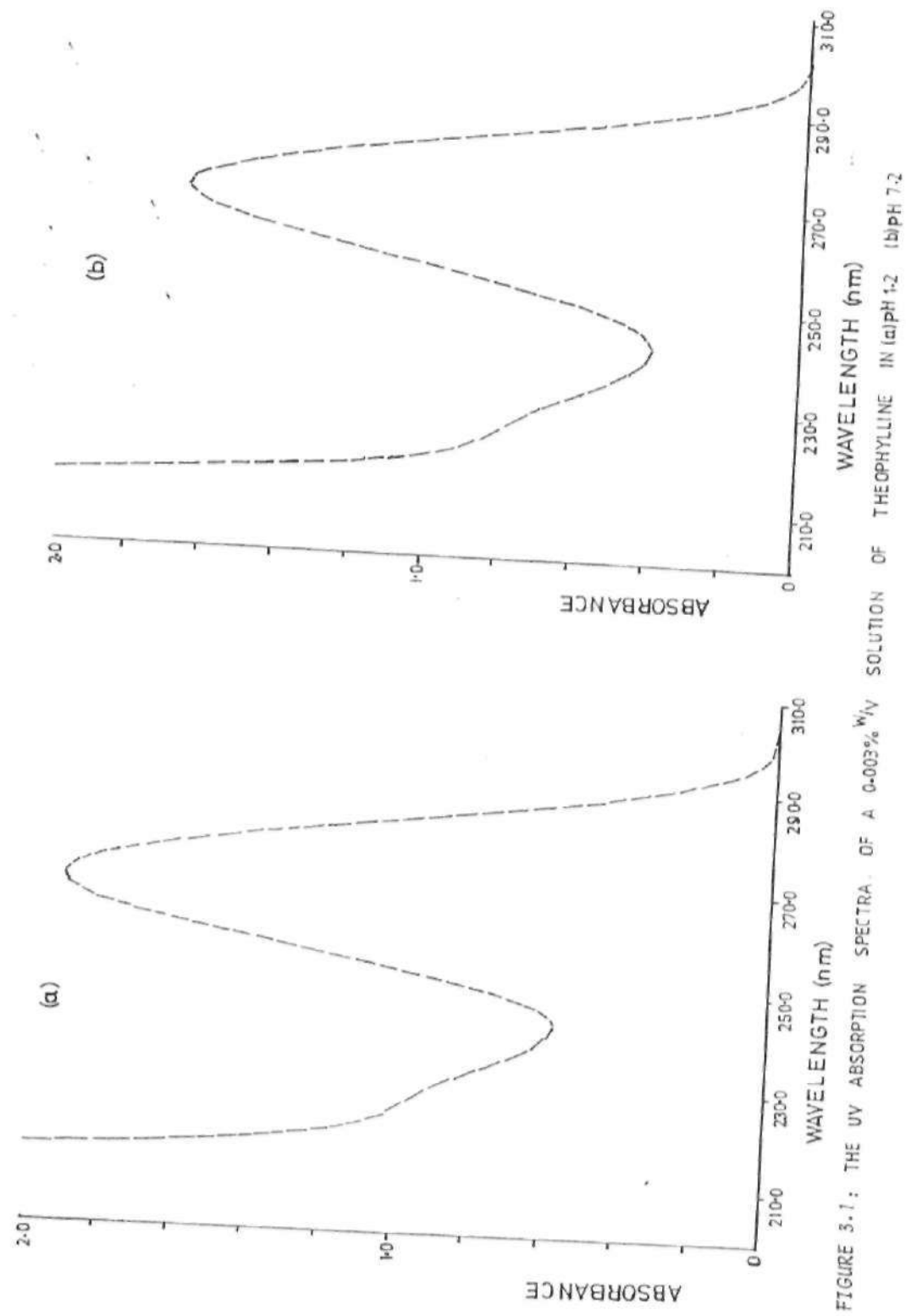
Table 3.3 **The U.V absorption values for theophylline**

Medium	λ_{max} (nm)	Absorbance at:		
		λ_{max}	270nm	272nm
pH 1.2	270.5	1.903	1.900	1.901
pH 7.2	271.7	1.665	1.625	1.660

The absorption spectra of theophylline in pHs 1.2 & 7.2 are shown in figure 3.1, from which the wavelength of maximum absorbance (λ_{max}) in each case was determined, as given in table 3.3.

3.3.3: The Beer plots for Theophylline and potassium chloride:

The Beer plots for theophylline and potassium chloride were constructed as shown in Appendixes 6 and 7. By the use of such a graph, the concentration of a sample may be determined, once the absorbance at the specified wavelength is obtained (Martin *et al*, 1969). Appendix 6 gave linear calibrations for both pH 1.2 & pH 7.2 indicating that theophylline obeys Beer's law. On the other hand potassium chloride exhibited a non-linear calibration curve as shown in Appendix 7. Wordsworth (1980) pointed out that calibration plots may be non-linear if the sample does not obey Beer's law due to "unusual sample properties" exhibited by samples that scatter incident energy, fluoresce, are photo-active or produce interference effects. Potassium chloride is photo-active and was quantitatively determined using a flame photometer. Wordsworth showed that in cases of non-linear absorbance responses, it is usually necessary to accept the fact that the sample does not obey Beer's law. According to the author, this need not invalidate the assay procedure if an accurate calibration curve of absorbance against concentration is constructed by taking many measurements on solutions of different concentrations, and such calibration curve can be used for routine assays of the compound. Indeed the non-linear absorbance response in using flame photometers is well recognized by the manufacturers of the equipment and the coming 410 clinical



model incorporates a linearizer to compensate for the non-linear response of the signal as reported in the operating manual.

3.3.4: **Thermal analysis:** The DSC thermograms of CPP, theophylline and potassium chloride are given in Appendixes 8-10, those of the mixtures of CPP and theophylline in Appendix 11, and those of CPP and KCl in Appendix 12. The melting endotherm of theophylline and the exothermic peak of CPP were still present in the CPP- theophylline thermogram (Appendix 10). This together with the absence of any new peak indicate that there is no molecular interaction between the two. KCl did not give any peak of its own (Appendix 8), and the mixture of CPP-KCl did not produce any new peak separate from those due to CPP, thus no molecular interaction is likely between CPP and KCl either. The therapeutic activities of theophylline and KCl would not therefore be affected by formulating them in CPP matrices.

The effects of formulations and manufacturing processes may affect thermal intrinsic properties like softening, melting, crystallinity, plastic deformation of materials been compressed. These properties are important in bonding which is assisted by heat of friction during compression. The effects of granulation and magnesium stearate content on release rates and thermal intrinsic properties were therefore studied:

3.3.5 **Effect of granulation:** With granulation there was a significant reduction in amounts of theophylline released and an enhancement of sustaining power and linearity of release profile (figure 3.2). This is particularly more noticeable with the theophylline: CPP ratio of 3:1, where directly compressed fine powder had very low sustained-release properties. But on granulation good sustained-release effect was observed in both gastric and intestinal pHs. This might be as a result of better coating and binding of drug particles by polymer that would be expected during massing in wet granulation.

From DSC studies, the presence of theophylline in CPP polymer lowered T_g & T_s of the polymer (figure 3.3). The lowering of T_g was more pronounced when the mixture was granulated. The lowering of these properties signify plasticization as reported by Moelter and Schweizer (1949) and by Okhamafe and York (1983,1985a,b). This according to Rogers (1976) would increase diffusivity of drugs through film coats in the case of controlled - release tablets. Since granulation produced a greater fall in T_g (figure 3.3) and eliminated crystallinity (figure 3.6), greater diffusivity from the matrix will be expected with the compressed granules. However, a reduction in drug release was observed with the tableted granules as compared to directly compressed tablets (figure 3.5). This might suggest that diffusion is not the dominant factor in theophylline release from CPP matrices, and other mechanisms like erosion may be more important as observed in another study reported in chapter 6. On the other hand, an increased initial permeability of the matrix to water due to plasticization may cause faster swelling of the matrix thereby reducing drug release rate and improving linearity of the release profile since from the other study, swelling was seen to be responsible for imparting linearity in the zero-order release profile.

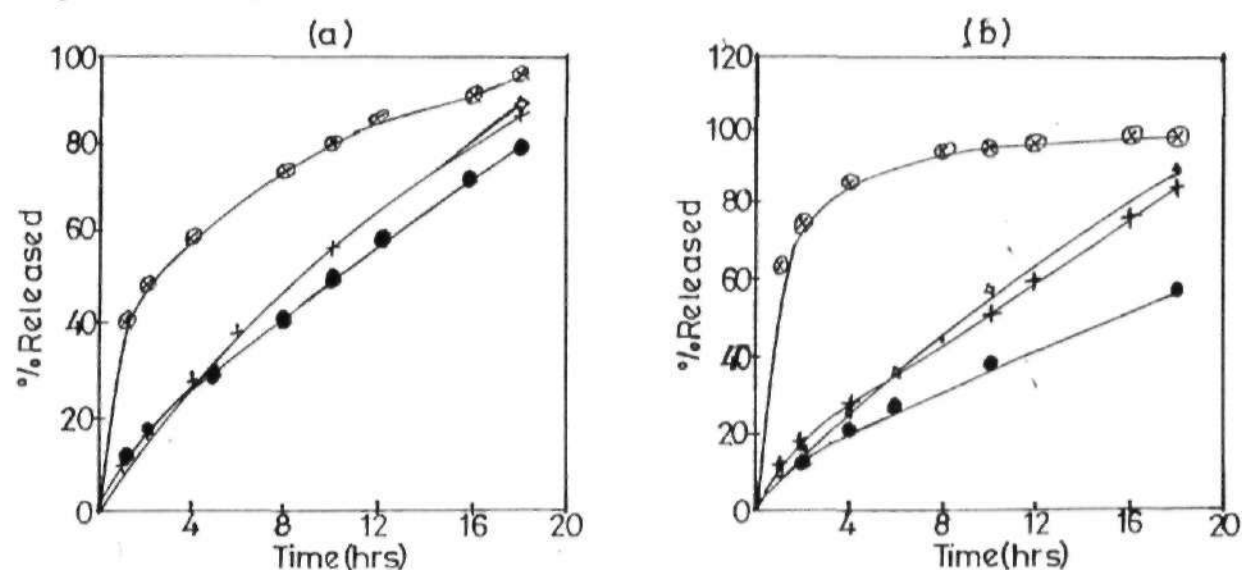


Figure 3.2 : Effect of granulation on theophylline release in (a) pH 1.2 (b) pH 7.2 using the paddle method at 100rpm and 37°C. Key: + = Directly compressed powder (2:1: Theoph: CPP ratio); ● = Compressed granules (2:1 Theoph: CPP ratio); ⊗ = Directly compressed powder (3:1 Theoph: CPP ratio); ◇ = Compressed granules (3:1 Theoph: CPP ratio).

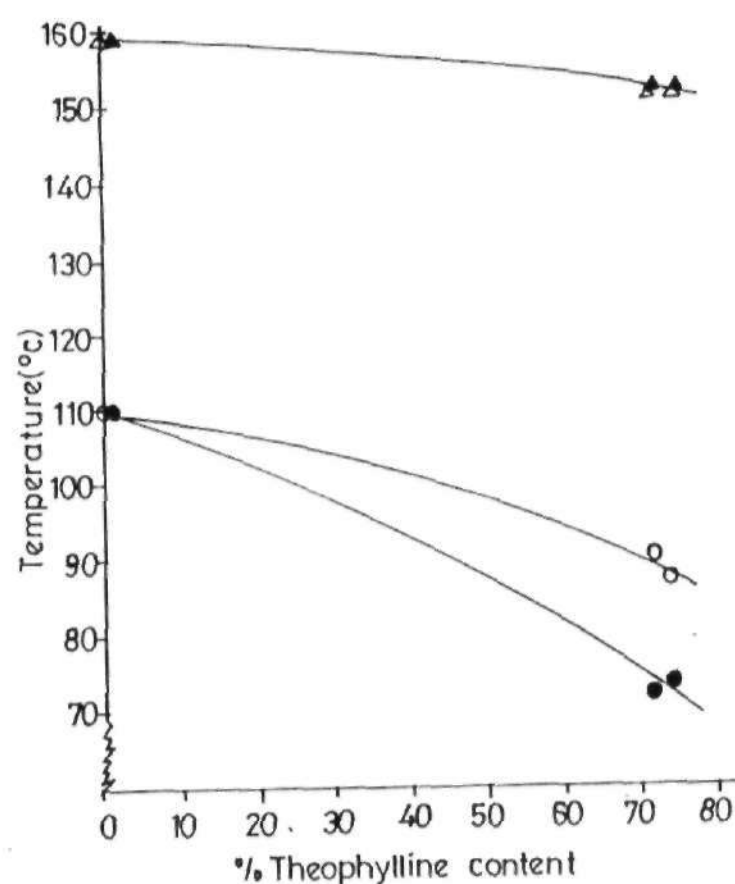


Figure 3.3: The effect of theophylline concentration in CPP on some intrinsic thermal properties of CPP. Key: ○, ● = Glass transition temperature curves; Δ, ▲ = Softening temperature curves. Open symbols for powders and closed symbols for granules.

3.3.6: **Effect of magnesium stearate:** As magnesium stearate concentration increased from 0-0.4%W/W, a minimum was observed in amounts of theophylline released at 0.1%W/W to 0.2%W/W magnesium stearate concentration depending on the theophylline: CPP ratio and dissolution medium (figure 3.4). Magnesium stearate is a hydrophobic lubricant and as its concentration in tablet formulations increase, the penetration of water into the tablet would be reduced and drug release would in turn be reduced. The increase in drug release at higher concentrations of 0.3%W/W and 0.4%W/W may therefore be attributed to the changes in intrinsic thermal properties. The reduced

plasticizing effect at these higher magnesium stearate concentrations could result in reduced diffusivity to moisture. This may suggest a reduction in the absorption of water by the matrix and consequently swelling is reduced. When swelling is reduced, the formation of a gelatinous barrier to drug release is slowed down and drug release is improved.

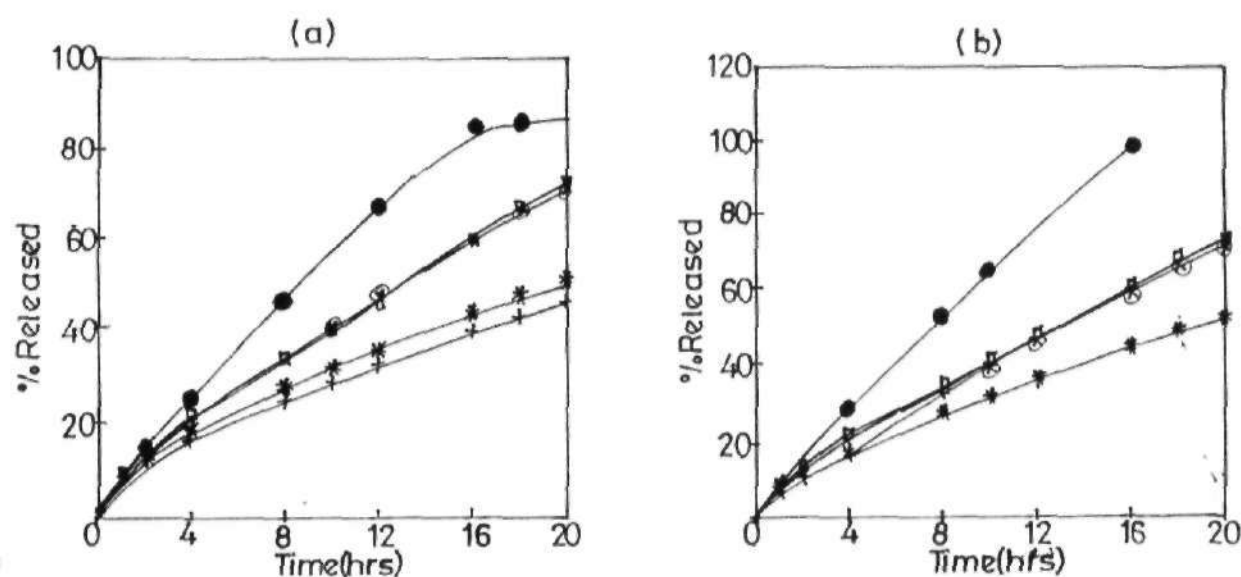


Figure 3.4: Effect of magnesium stearate concentration in theophylline: CPP (2.5:1) compressed granules on theophylline release in (a) pH 1.2 (b) pH 7.2, using the paddle method at 100rpm and 37°C. Key: ● = Without magnesium stearate; + = 0.1% w/w magnesium stearate; ★ = 0.2% w/w magnesium stearate; □ = 0.3% w/w magnesium stearate; ⊗ = 0.4% w/w magnesium stearate.

Figures 3.5 & 3.6 show the effect of magnesium stearate on T_g , T_s and relative crystallinity of a 2.5:1 theophylline: CPP powder mixture. A minimum is exhibited in each of the curves at 0.2%W/W above and below which plasticizing effect reduced with consequent increases in T_g and T_s . Diffusivity would therefore be greatest at a magnesium stearate concentration of 0.2%W/W. However, figure 3.7 shows that the lowest release rate occurs at 0.1%W/W and 0.2%W/W magnesium stearate content in pH 1.2 and pH 7.2 respectively. This again as with the granulation

studies may suggest that diffusion of dissolved drug from the matrix may not be the dominant factor in theophylline release from CPP matrices.

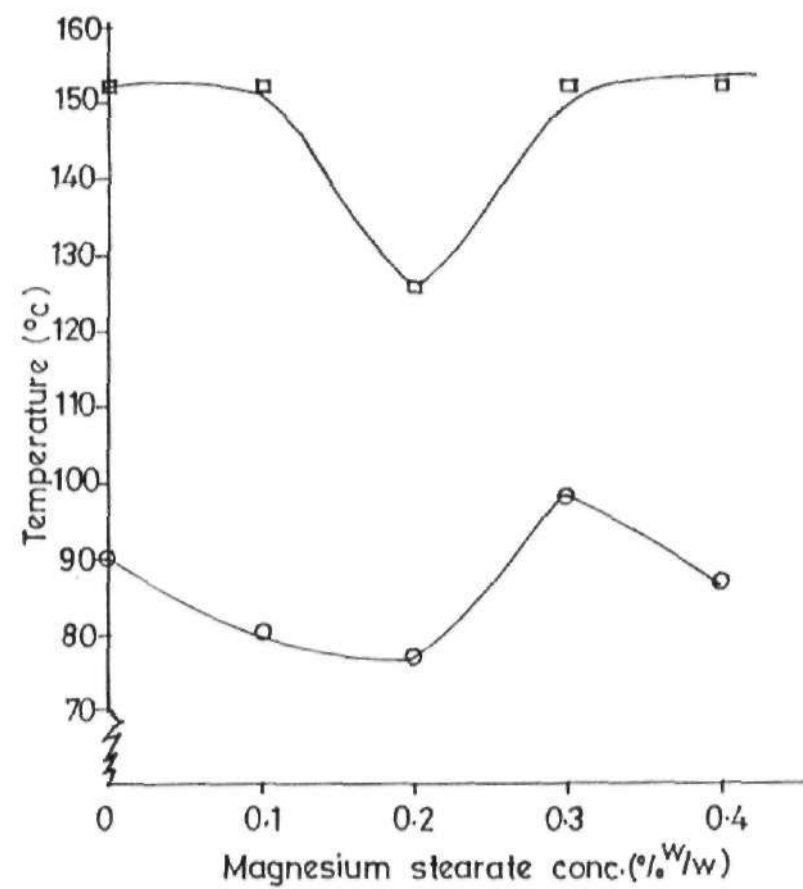


Figure 3.5: The effect of magnesium stearate content on some thermal intrinsic properties of a 2.5:1 mixture of theophylline : CPP powder. Key: o = Glass transition point curve, □ = Softening temperature curve

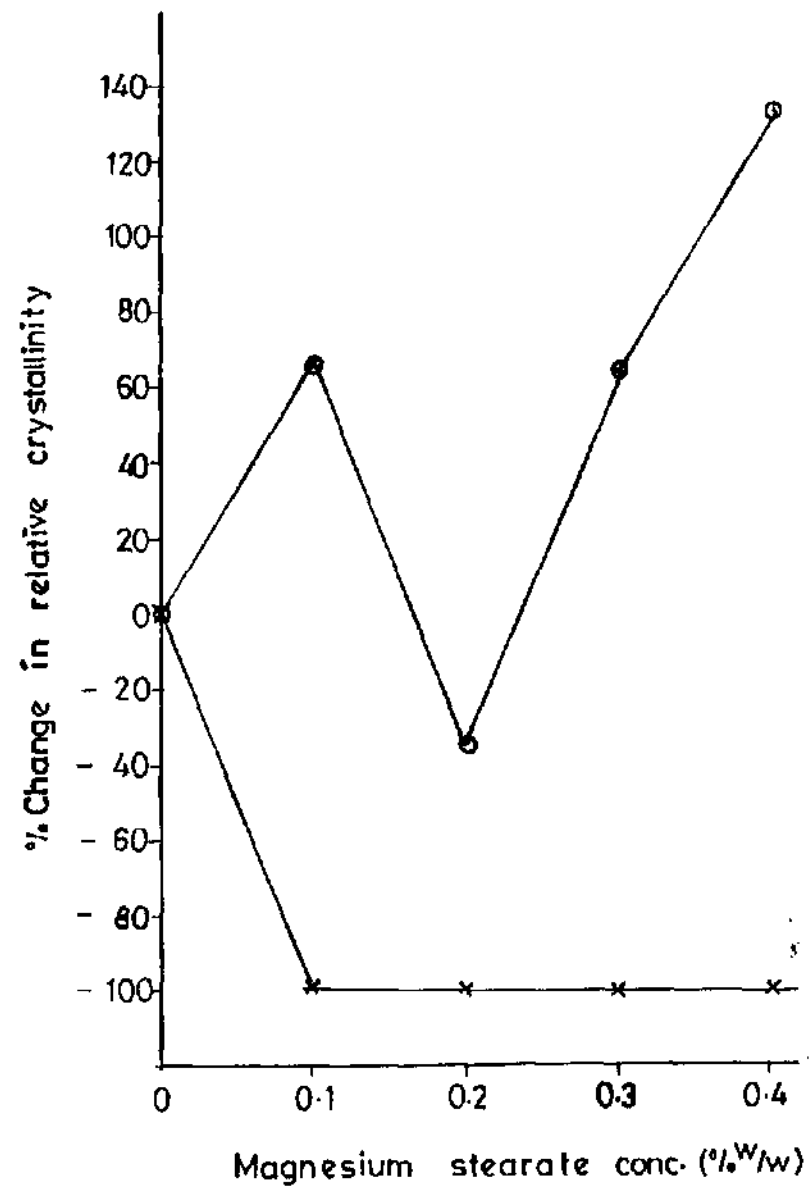


Figure 3.6: The effect of magnesium stearate concentration on the relative crystallinity of theophylline: CPP (2.5:1) samples. Key: O = Powder samples; x = granule samples.

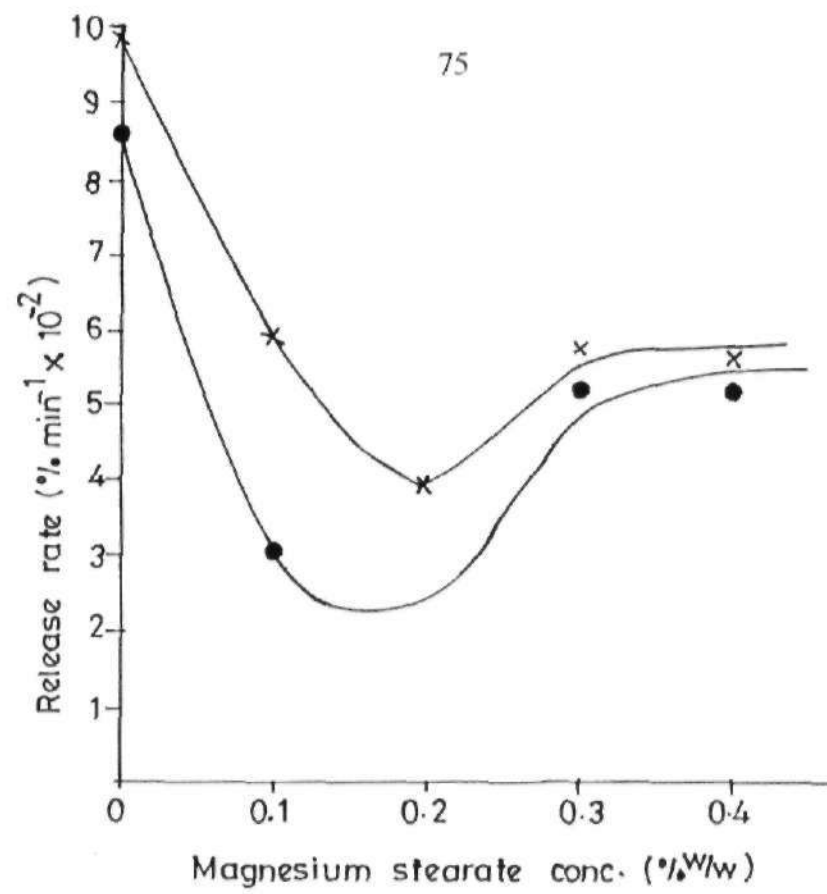


Figure 3.7: The effect of magnesium stearate concentration in compressed granule matrices on theophylline release rates in pH 1.2 and pH 7.2, using the paddle method at 100rpm and 37°C. Key: ● = pH 1.2; x = pH 7.2 dissolution media.

3.3.7: Particle Size analysis of granules for tablets

Table 3.4: Sieve Size analysis of granules for "Once-daily" tablets

Sieve Size (μm)	wt retained (gm)	% wt Oversize	Cumm. % wt Oversize
840	3.818	21.45	21.45
425	8.313	46.7	68.15
180	4.162	23.38	91.53
<180	1.509	8.47	100
	17.802gm	100.00	

Table 3.5: Sieve Size analysis of granules for "Twice - Daily" tablets

Sieve Size (μm)	wt retained (gm)	% wt Oversize	Cumm. % wt Oversize
840	3.572	16.4	16.4
425	9.429	43.3	59.7
180	7.332	33.67	93.37
<180	1.443	6.63	100
	21.776gm	100.00	

Knowledge and control of the size and size range of particles is of profound importance in pharmacy (Martin *et al*, 1969). According to these authors, the successful formation of suspensions, emulsions and tablets, both from the viewpoint of physical stability and pharmacological response, also depends on the particle size achieved in the product. In the area of tablet and capsule manufacture, control of the particle size is essential in achieving the necessary flow properties of granules and powders. Sieves are generally used for grading coarser particles e.g powders coarser than fines, tablet granulations and granular salts. The mean particle sizes of $490\mu\text{m}$ and $480\mu\text{m}$ for the "once - and twice-daily" formulations respectively would ensure good flow, since sizes bigger than about $180\mu\text{m}$ are generally non-cohesive.

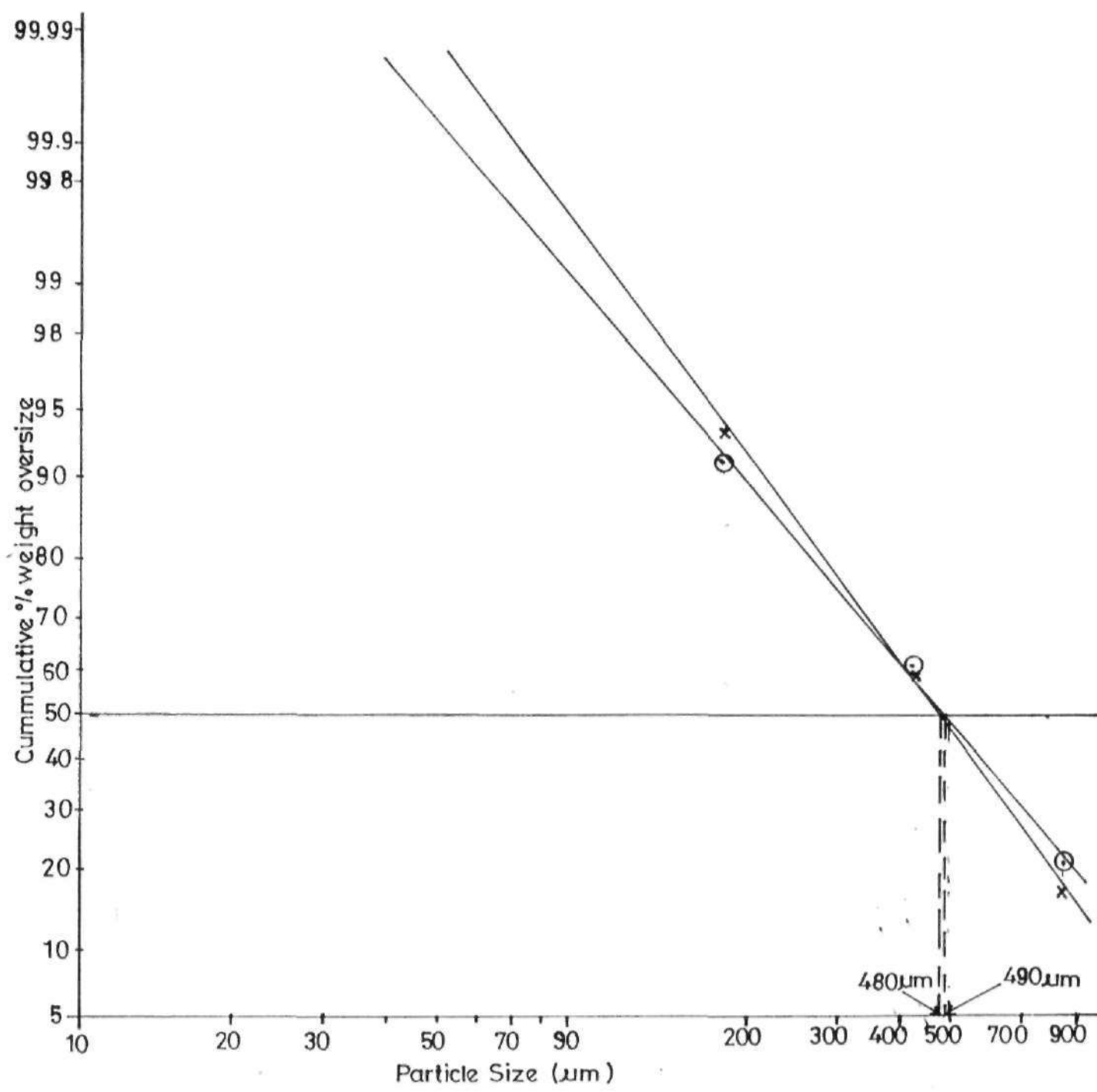


Figure 3.8: Particle Size Analysis of Granules for "Once - and Twice - Daily" tablets (log-Probability scale). Key: ○ = Granules for "Once - daily" tablets; x = Granules for "Twice - daily" tablets

3.3.8: Physical properties of tablets.

The physical properties of tablets are important for the successful performance of the tablets. The CPP formulated tablets had a smooth shiny appearance with a light brown colour. The light brown colour was due to the CPP content and not due to the addition of colourants. This might not therefore be a breach of the BPC (1973) prohibition of the use of colours except for specific tablets and those which are enteric or compression coated. It is noteworthy to state that the shades of the light brown colour appeared constant for all the proportions of CPP used in the formulations. This will ensure uniformity of colour in the products even when they are to be manufactured by different pharmaceutical companies, a problem source reported by Rawlins (1980). All the formulated tablets were compressed using the normal concave punches and they all therefore had the same shape. The physical properties of the tablets are given in table 3.6

Table 3.6: Physical properties of "once - and Twice-daily Tablets.

Property	"Once-daily" tablets	"Twice-daily"Tablets
Disintegration	tablets eroded gradually but did not disintegrate, even well beyond 24 hours.	
Friability (% loss)	0.18	0.10
Hardness (kg/in ²)	22.82	32.93
Diameter (mm)	10.7	10.7
Mean thickness(mm)	4.85	5.85

(a) Disintegration time.

This is an official test which is described in many pharmacopoeias. In the test, attempts are made to simulate in - vivo conditions. Nonetheless, a careful perusal of all the in - vitro procedures

show that no available disintegration test actually simulates physiologic conditions (Gunsel *et al*, 1970). Thus the in vitro test represents a more or less empirical approach with a principal function of ensuring product uniformity according to these authors. However, the test also ensures that the tablet will disintegrate within a reasonable time in the g.i.t. to increase the surface area of particles and consequently hasten the total process of absorption. On the contrary, in matrix formulations, disintegration is not desired rather an extended protection of the drug against water by the matrix is aimed at (Shargel and Yu, 1993). This would make the drug to diffuse out slowly over time to give a sustained pharmacological response. The non disintegration of the formulations as shown in table 3.6 will therefore promote controlled-release effect. Furthermore, if the erosion of the tablets maintains constant geometry, then drug release will be zero-order (Lee, 1981). Indeed, controlled - release or prolonged or repeat action products together with troches and tablets intended to be chewed are exempted from disintegration tests (Shargel and Yu, 1993). However the consistent non-disintegration of tablets in various batches indicate uniformity of the products. The non disintegration of the tablets could result in delayed stomach emptying. But this would not have any adverse effect since theophylline is stable in both gastric and intestinal pHs and is also well absorbed throughout the g.i.t. Infact delay in gastric emptying could be advantageous in the sense of prolonging the controlled - release of the drug, and the method of delayed stomach emptying by, for example, making the tablet to float on stomach content has been used as a means of achieving sustained - release effect (Muller-Lissner *et al*, 1981).

(b) Friability (% loss).

Friction and shock are the forces that most often cause tablets to chip, cap, or break. As a result, equipment such as the Roche friabilator was developed (Gunsel *et al*, 1970). The unit induces self-abrasion of the tablet as the cylinder section rotates. The tablets also undergo shock as they fall six inches on each turn. Acceptable limits of weight loss for each tablet size must be based upon

correlation with other physical factors, although friability values are usually considered satisfactory when the product exhibits a weight loss of less than 0.8 percent (Gunsell *et al*, 1970). The values of 0.10% to 0.25% shown in table 3.6 for the formulated products are therefore very satisfactory and shows that the tablets can withstand friction and shock.

(c) **Hardness.**

The ability of a tablet to withstand the shock of handling, packing and shipping has been the traditional measure of tablet strength requirements (Gunsell *et al*, 1970). Several types of mechanical hardness testers have been developed, amongst which are the Strong-Cobb, Stokes-Monsanto, Eureka, and Pfizer units. All these instruments actually measure resistance to crushing.

From the hardness readings of about 22 and 32kg/in² shown in table 3.6, the tablets can be concluded to be very strong and would therefore resist crushing effectively. They can therefore withstand the rigors of handling, packing and shipping much more than the conventional immediate release tablets that usually have hardness values of less than 10kg/in².

(d) **Tablet thickness and diameter.**

The dimensional specifications of a tablet are important for many reasons. The thickness of the tablet is often directly related to tablet hardness and can therefore be used as an initial control of hardness. During the routine manufacture of tablets, changes in thickness often can indicate a problem in flow through the feeder or faulty deposition of granulation in the die.

Manufacturers set limits on the thickness of the tablets of their various products in order to assure trouble free packaging. Tablets that are of inconsistent thickness block the channels of counting machinery. When tablets are thicker than normal, the container may prove to be inadequate to hold the required count, especially when the count is 500 or more. Therefore if the formulations above are to be produced commercially and packaged in 500s or 1,000s, then the dimensions given in table 3.6

measured by use of micrometer calipers must be maintained within a reasonable limit of tolerance for the packaging container to be designed specifically for the count desired per pack.

3.3.9: The stability of formulated "Twice-daily" controlled-release theophylline matrix tablets.

As with all pharmaceutical dosage forms, it is important to determine the stability of sustained - action dosage form during storage. Many pharmaceuticals may suffer chemical, physical and microbiological changes due to dosage form and storage conditions leading to therapeutic or toxicological changes. The influences of additives, packaging, production and storage conditions are therefore important for determining optimal conditions for therapeutic efficacy. Robinson (1966) has suggested that the same standards as are employed to determine active ingredient stability should be used. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure that the product will over its designated shelf-life, provide medication for absorption at the same rate as when originally formulated.

The deterioration of products due to the absorption of moisture is normally accelerated by placing them in an environment of high relative humidity and controlled temperature (Rawlins, 1980). This author points out that in order to obtain as much information as possible, it is preferable to employ a range of humidities. In this study however, only 100% humidity at 38-40°C was used due to limited time of stay at Kings' College London.

a) **Shelf-storage test:** Tablets stored for varying lengths of time between 3 to 8 weeks did not show an appreciable change in theophylline release in either gastric or intestinal pH as shown in figure 3.9. Also the theophylline content did not show any significant variation as shown by figure 3.10 and by the t-test when the variations in theophylline content between the batches were tested. The calculated t-values are $t = 0.01$ for pH 1.2 data and $t = 0.003$ for pH 7.2 data while the tabulated t value

(at $\alpha = 3$ and $p = 0.05$) is given as 3.18. This indicates good chances of product stability at room storage conditions with no significant difference in the batches stored for varying periods. However longer storage periods may be required to draw a final conclusion.

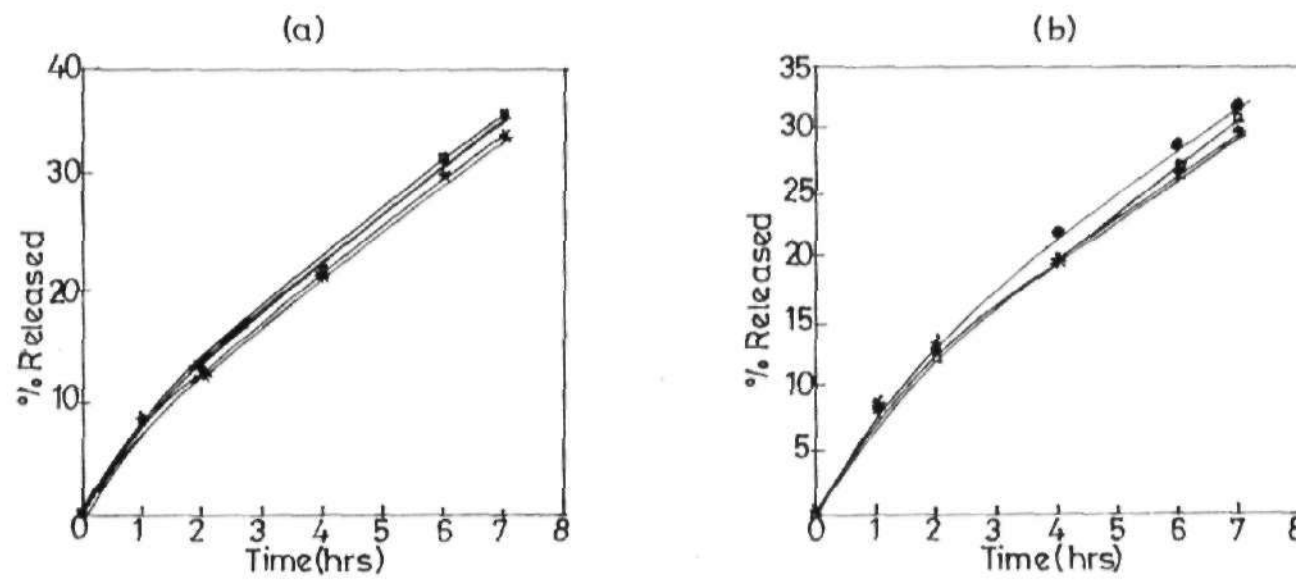


Figure 3.9: Effect of age of tablets on the dissolution of theophylline from "twice - daily" tablets in (a) pH 1.2 (b) pH 7.2, using the paddle method at 100rpm and 37°C. Key: □ = 3 week old tablets; + = 4 week old tablets; * = 6 week old tablets; ● = 8 week old tablets.

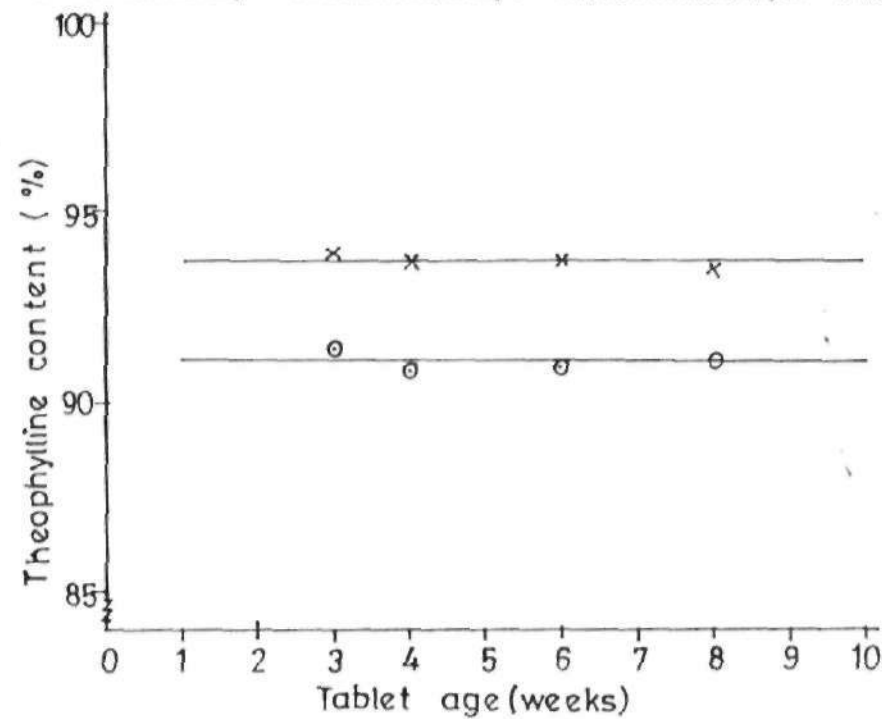


Figure 3.10: Effect of tablet age on theophylline content of tablets stored under shelf storage conditions. Key: O = pH 1.2; x = pH 7.2 dissolution media.

b) Accelerated stability studies

(i) Elevated storage temperature tests: The results are shown in figures 3.11 - 3.13 from which it can be seen that storage at elevated temperatures increased the release rate. There appears to be a tendency for "dose dumping" by tablets stored at high temperatures i.e. a failure of the dosage form resulting in a sudden release of the drug. This is indicated by the increasing rate of change in the slopes of the release curves per unit time. This observation appears to be more prominent when the stored tablets are tested in pH 1.2 medium. It might be possible that heat affects the polymeric structure of CPP resulting in changes in some of its intrinsic properties like the glass transition temperature (T_g), softening temperature (T_s), crystallinity etc. Some workers (Ferdous *et al*, 1993) have observed the effect of the thermal history of polyethylene glycol and glycerol on theophylline release from suppositories, and have reported increase in the melting endotherms of their suppository bases after cold storage.

In the theophylline content determination, there appeared to be an increase in the intensity of absorbance at the wavelength used (270nm) by tablets stored at elevated temperatures. The increase in absorbance intensity was again more noticeable in pH 1.2 in which the intensity was so high that it could not be measured. This high absorbance cannot be accounted for by even the total theophylline content of the sample. It will therefore appear that some chemical changes either in the molecules of the compounds used or due to some form of chemical reaction between formulation components may be responsible. There could be the possibility that a chemical reaction which ordinarily would not take place at room temperature is been catalysed at the elevated temperatures used in the study. This could yield a product that has an intense absorbance at the wavelength of 270nm. The formation of a new compound having a high intensity of absorbance could arise from any of the following possibilities:

- (1) degradation of any of the materials in the formulation e.g. lactose may decompose at high temperatures, since its discoloration is increased at elevated temperatures (Gunsel and Lachman, 1963).
- (2) electronic rearrangement in the molecules e.g. extended chromophore formation by Keto-enol equilibration, or
- (3) interaction between compounds of the formulation e.g. shift base/enamine reaction between the theophylline and sugar in lactose.

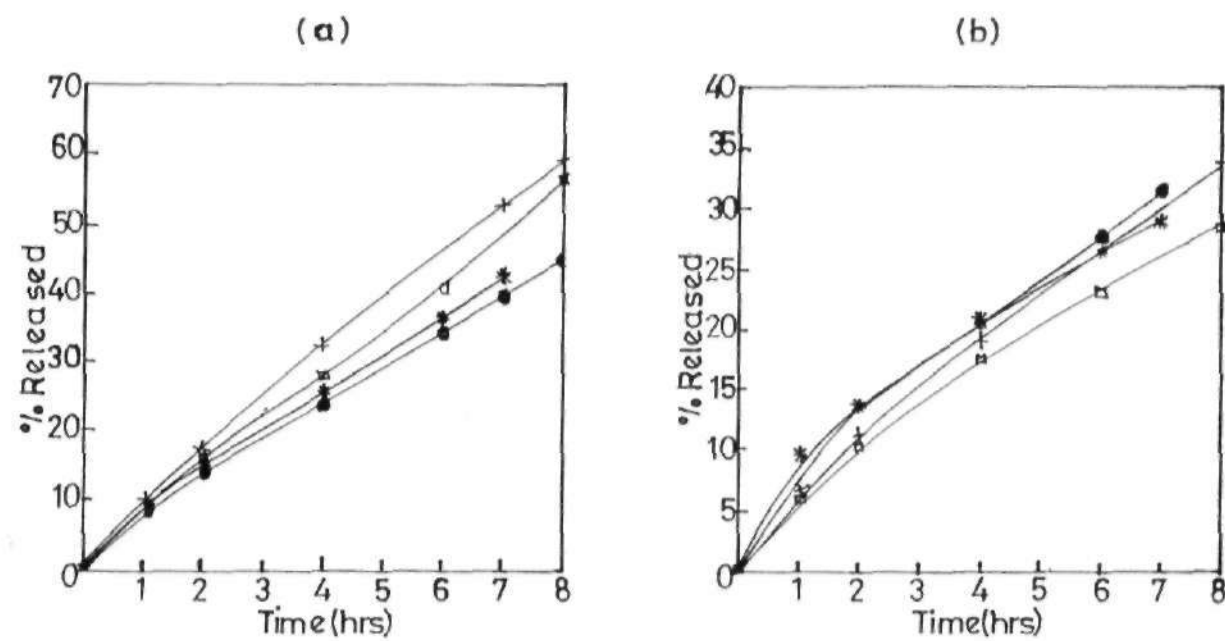


Figure 3.11: Theophylline release from "twice - daily" tablets stored for 2Hours at elevated temperatures in (a) pH 1.2 (b) pH 7.2, Using the paddle method at 100rpm and 37°C. Key: □ = Stored at 50°C; + = Stored at 60°C; * = Stored at 70°C; ● = Stored at 80°C.

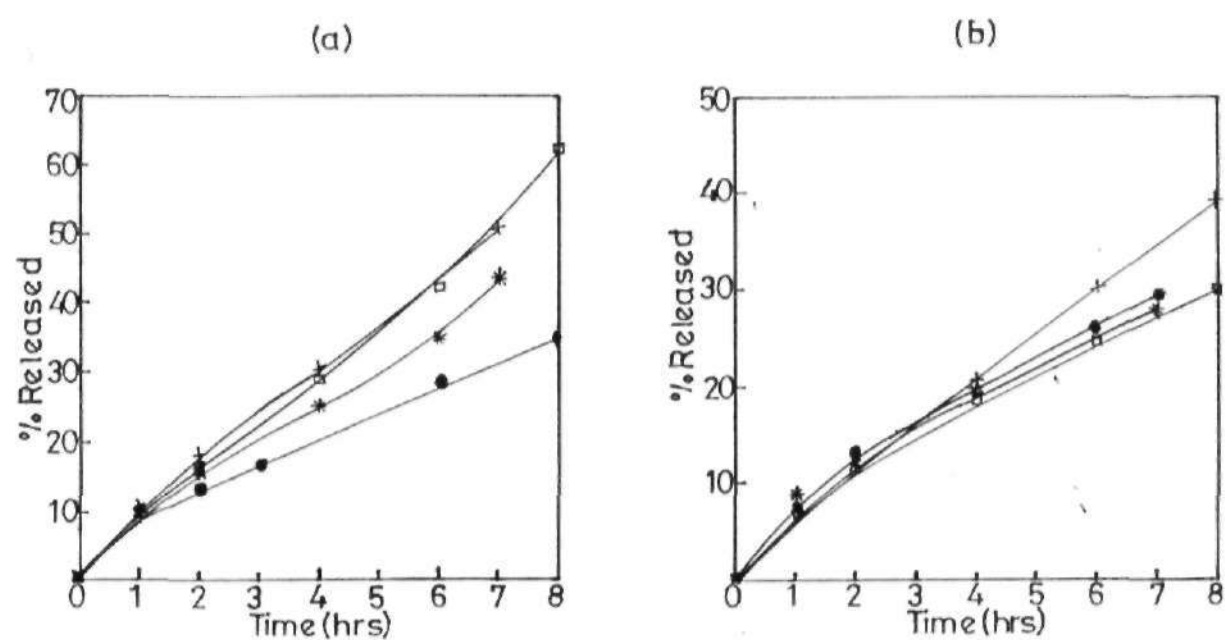


Figure 3.12: Theophylline release from "twice - daily" tablets stored for 6Hours at elevated temperatures in (a) pH 1.2 (b) pH 7.2, Using the paddle method at 100rpm and 37°C. Key: □ = Stored at 50°C; + = Stored at 60°C; * = Stored at 70°C; ● = Stored at 80°C.

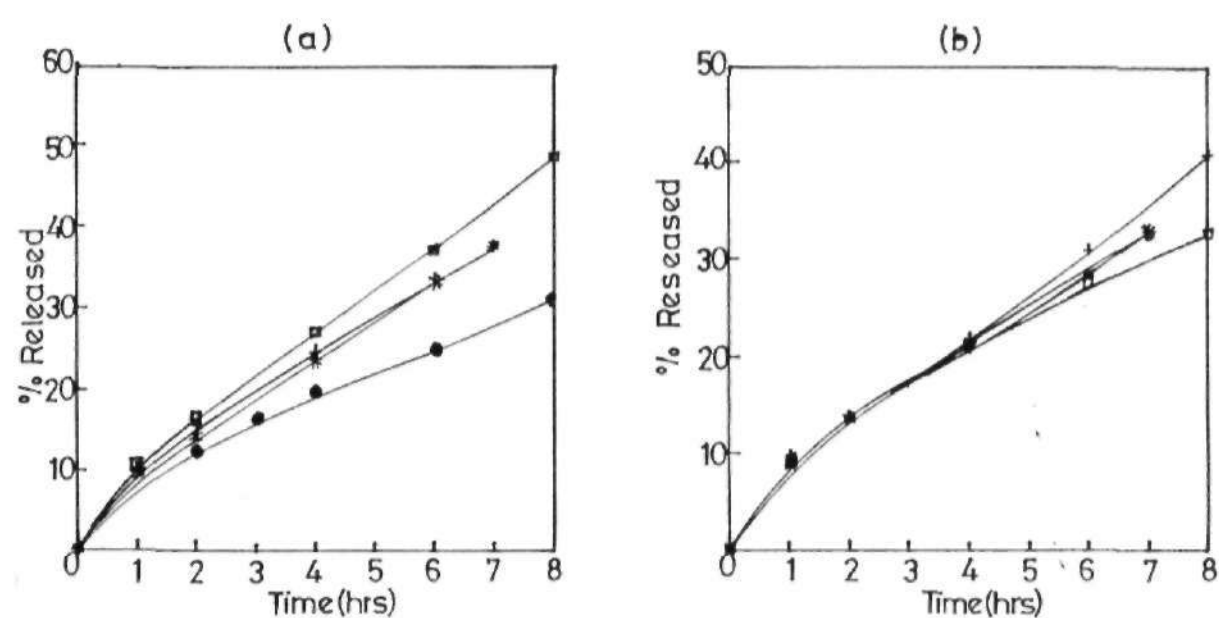


Figure 3.13: Theophylline release from "twice - daily" tablets stored for 26Hours at elevated temperatures in (a) pH 1.2 (b) pH 7.2, Using the paddle method at 100rpm and 37°C. Key: □ = Stored at 50°C; + = Stored at 60°C; * = Stored at 70°C; ● = Stored at 80°C.

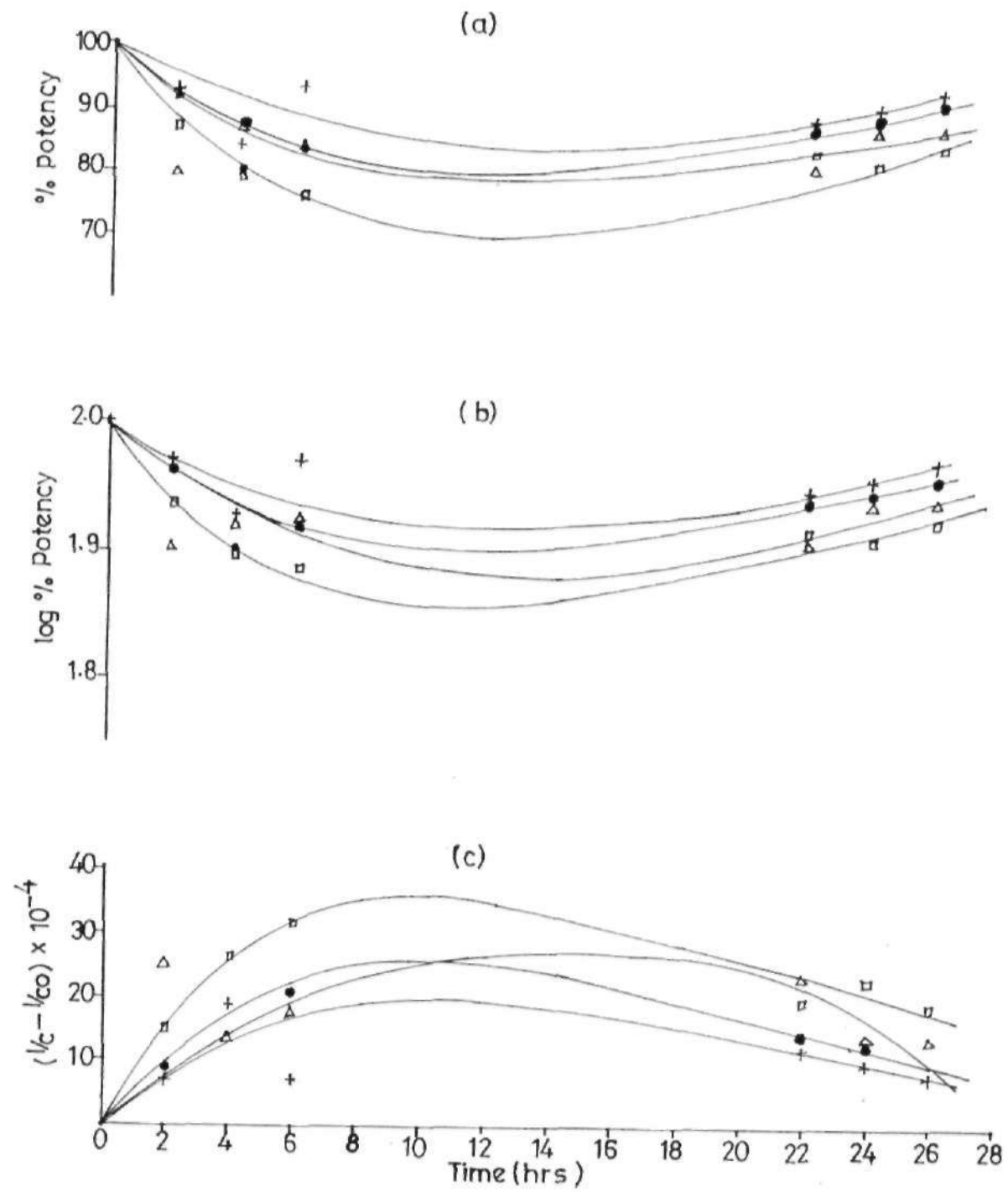


Figure 3.14: Deterioration kinetics of "twice-daily" theophylline tablets (a) zero-order plots (b) first-order plots (c) second-order plots. Key: ● = 50°C; + = 60°C; □ = 70°C; Δ = 80°C.

From the zero-first-and second-order plots (figure 3.14), the order of reaction could not be determined due to the increased absorption intensity with longer storage periods at the elevated

temperatures used. It was also not possible to calculate the reaction rate constants for the various storage temperatures, consequently the Arrhenius plot could not be constructed. In the absence of the Arrhenius plot, the room temperature degradation rate constant could not be obtained, thus the shelf-life of the product at room storage temperature cannot be calculated.

(ii) **Elevated relative humidity.**

The drug release rate was greatly reduced in both gastric and intestinal pHs when the tablets were stored at high relative humidity (figure 3.15). This could mean that the polymer gets partially hydrated during storage at high relative humidity (100% RH) and further hydration when placed in the dissolution media becomes much easier. Consequently swelling will be much faster and drug release becomes slower due to the faster development of viscous barrier gel to diffusion. Degradation of theophylline at the high relative humidity could also be a possibility and could result in reduced amounts ultimately being released. It is however clear that the product must not be stored at elevated relative humidity conditions.

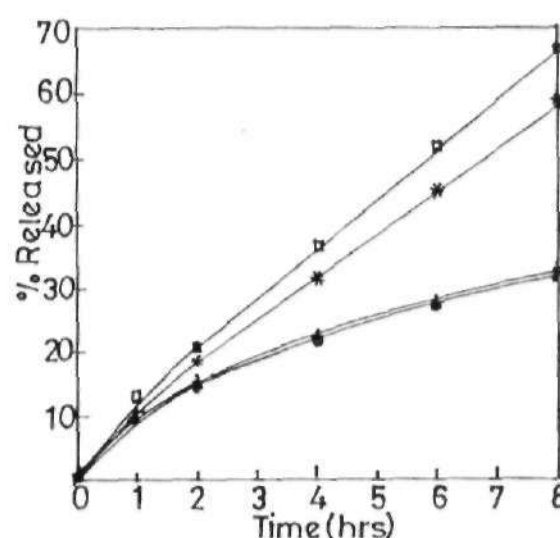


Figure 3.15: Effect of relative humidity on theophylline release from "twice - daily" tablets using the paddle method at 100rpm and 37°C. Key: Dissolution after 1 week storage in, □ = pH1.2 at 100% RH; * = pH1.2 at room RH; + = pH7.2 at 100% RH; ● = pH7.2 at room RH.

3.3.10: **Microbial Content of CPP and HPMC**Table 3.7: **The viable counts for CPP and HPMC samples**

	Variable counts in:	
Age of sample	CPP	HPMC
2 days	1,960 cfu/gm	10 cfu/gm
1 month	1,940 "	10 "
2 months	1,960 "	20 "
3 months	1,950 "	10 "

Table 3.8: **Selective and Differential Media and Biochemical tests for CPP and HPMC**

Organism	Selective media	Differential agars	Biochemical tests
Staph aureus	Salt meat broth CPP: No growth HPMC: No growth	Mannitol salt agar CPP: No growth HPMC: No growth	Gram stain test for organisms grown on nutrient agar gave gram +ve rods for both CPP and HPMC which were concluded to be Bacilli rods.
Salmonella SPP.	Selenite and tetrathionate broth CPP: No growth HPMC: No growth	Deoxycholate citrate agar. CPP: No growth HPMC: No growth Triple sugar iron agar CPP: No growth HPMC: No growth	
E. Coli		MacConkey agar CPP: No growth HPMC: No growth	
Ps. Aeruginosa		Cetrimide containing agar CPP: No growth HPMC: No growth	

Table 3.9: **Specific Pathogenic bacterial contents of CPP and HPMC Samples**

Organisms	Bacterial counts in:	
	CPP	HPMC
Ps.aeruginosa	absent	absent
E. Coli	"	"
Salmonella	"	"
Staph.aureus	"	"

The microbial quality of CPP was studied in comparison to HPMC which served as standard. HPMC has been used over the years in formulating pharmaceutical products.

From tables 3.7 to 3.9, it can be seen that both CPP and HPMC are free of the pathogenic organisms tested for. Also table 3.7 shows that there was no increase in viable counts in both samples which may be attributed to the dryness of the powders resulting in low water activity. The viable counts for both CPP and HPMC were found to be much lower than the standard limits of 10^6 to 10^9 /g set by an FIP working party (Report, 1972) for starting raw materials of animal and vegetable origin. However, the counts for the CPP sample was seen to be very much higher than that of HPMC. The organisms were mainly the spore forming *Bacillus* which are abundant in the air. This could be as a result of the soaking process of the bark in water. It might therefore be advantageous to incorporate a preservative in the distilled water used for the extraction of the mucilage from the bark. The effect of the preservative on the release profile should however be assessed. Alternatively, Hugo and Russel (1980) have reported that the use of natural products with a high non-pathogenic microbial count is possible if a sterilization stage is included either before or during the manufacturing process. Such sterilization procedures according to them may include heat treatment, filtration, irradiation or recrystallisation from a bactericidal solvent such as an alcohol. Also dry products if compatible may be treated with ethylene oxide gas. If the raw material is only a minor constituent and the final product

is adequately preserved either by lack of water activity (A_w) e.g. A_w of less than 0.60, or chemically or by virtue of its pH, sugar or alcohol content, an "in-process" sterilization stage may not be necessary if the product is not intended for parenteral or ophthalmic use. The CPP studied is intended for use in the formulation of oral tablets, and tablets would generally have a very low A_w resulting in adequate preservation of the formulated products. In the absence of E.Coli, Salmonella sp., Pseudomonas aeruginosa and staphylococcus aureus, sterilization of the CPP before or during manufacturing would not be necessary. However, if the sterilization of CPP is to be considered, the effect of sterilization method on its controlled - release efficacy must be assessed, since heat treatment for example may alter the intrinsic thermal properties of the polymer which in turn could alter the drug release profile from the matrix in accordance with the reports of Rogers (1976). In view of the fact that the contamination level of CPP is higher than the limit permitted for finished non - sterile pharmaceutical products, efforts must be made to ensure that the contamination is eliminated or considerably reduced below permitted limits in the final controlled - release products.

CHAPTER FOUR

CHAPTER FOUR

EVALUATION OF CPP FOR THE FORMULATION OF CONTROLLED- RELEASE MATRICES.

4.1: INTRODUCTION

Numerous hydrocolloids have been employed in the formulation of controlled-release matrix tablets, notably amongst them are gelatin, the celluloses, tragacanth, veegum, alginic acid, and very recently, xanthan gum has been studied by Talukdar and Plaizier-Vercammen (1993) and by Dhopeswarkar and Zatz (1993). The evaluation of CPP in the formulation of such products is aimed at contributing to the search for novel materials that might hopefully be less affected by g.i.t. variations than most of the presently available hydrocolloids as indicated in section 1.6.

According to Benedikt *et al* (1988) if in-vivo release of the active principle from a dosage form is to remain uninfluenced by the prevailing conditions in the g.i.t., the in-vitro release has to remain unaffected by pH value, surface tension and buffer concentration of the dissolution medium, type of dissolution model and rotational speed. Only then is there a chance that in-vivo release will remain essentially unchanged even under the extremely different intra individual conditions that may prevail during the course of one day. The evaluation of the novel CPP will therefore look at the effects of the above variables on drug release profiles. Theophylline and potassium chloride were used as drug models for poorly soluble and very soluble drugs. These drugs are usually used for long term therapy, thus their formulation into controlled-release forms would be useful as frequency of administration gets reduced resulting in great convenience to the patient.

4.2 **EXPERIMENTAL**

4.2.1: **Determination of drug release:** The determination of drug release from the formulated matrices is as given in methods 2.3.8 and 2.3.9. The formulations studied are given in table 4.1.

4.2.2: **Treatment of results:** Some authors have reported that discrimination between models is often difficult when data are plotted according to the different equations/models. According to Mank *et al* (1986), Agabeyoglu and Fak (1986), and Gaizer *et al* (1987), many authors decide the release rate process by simply comparing the correlation coefficients. The model with the highest correlation coefficient is then selected. Talukdar and plaizier-Vercammen (1993) used the linear portions for the determination of the release rate processes.

In this study, a computer programme was used to plot the linear portions according to the following different equations:

i) Zero order : % Released = $kt + \text{intercept}$ Equation. 4.1

ii) First order: $\ln \% \text{ Released} = kt + \ln \text{intercept}$ Equation.4.2

iii) Cube root (Hixson-Crowel model):

$$(\% \text{ Released})^{1/3} = kt + \text{intercept} \dots\dots\dots \text{Equation.4.3}$$

iv) Diffusion or square root (Higuchi model):

$$\% \text{ Released} = k \sqrt{t} + \text{intercept} \dots\dots\dots \text{Equation.4.4}$$

where k is apparent release rate constant and t is time.

The correlation coefficients and selected release rate processes are shown in table 4.2.

One way ANOVA was conducted on the entire zero order release data to evaluate the influences of the different variable parameters on the release of theophylline from the matrix tablets and the results are presented in table 4.3.

TABLE 4.1 CONTINUED:

Effect under study	Formulation No.	Content of ingredients in mg and (%) per tablet:							Drug: Polymer ratio	Compression technique and pressure (tons)
		Theophylline	CPP	KCl	Stearic Acid	Carnauba Wax	Beeswax	Mag. Stearate		
Rotation speed	F1	200 (66.7)	100 (33.3)						2:1	D.C. (3)
Ionic strength	"	"	"						"	"
Surfactant concentration	"	"	"						"	"
Comparison of different KCl Formulation	F15		300 (32.6)	600 (65.4)				18 (2)	2:1	W.G. (3)
	F16		1,200 (65.4)	600 (32.6)				36 (2)	1:2	"
	F17		200 (22)	600 (66)	100 (11)			9 (1)	3:1	Melt & gran. (3)
	F18		300 (31.5)	600 (63)		50 (5.2)		3.80 (0.3)	2:1	Gran. with chloroform "
	F19		300 (28.7)	600 (59.4)			100 (9.9)	10.0 (2)	2:1	Melt & gran.

D.C. = direct compression, W.G. = Wet granulation.

* Methocel E4M EP was used for theophylline products while HPMC NEXII 15cps was used for KCl products.

4.3: RESULTS AND DISCUSSIONS.**TABLE 4.2: KINETICS OF THEOPHYLLINE RELEASE FROM EVALUATION PRODUCTS.**

Study	Correlation coefficients in pH1.2 & (pH7.2) for :				Zero order rate (%min ⁻¹)	Release rate process
	Zero order	First order	Cube root	Diffusion		
<u>1.Comparison of different polymers/additive</u>						
Th: Lactose (1:1)	0.5088 (0.6324)	0.6856 (0.9090)	0.6136 (0.8064)	0.6888 (0.8070)	0.0341 (0.0652)	1st order “ “
Th: CPP (2:1)	0.9993 (0.9987)	0.9798 (0.0053)	0.9893 (0.9987)	0.9464 (0.9639)	0.0584 (0.0532)	Zero order Zero/cube rt.
Th: HPMC (2:1)	0.9964 (0.6024)	0.9990 (0.8614)	0.9998 (0.7609)	0.9740 (0.7778)	0.0466 (0.0476)	Cube root 1st order
Th: HPMC (1:1)	0.9957 (0.7556)	0.9995 (0.9810)	0.9995 (0.9272)	0.9728 (0.9019)	0.0440 (0.0943)	Cube rt./1st ord. 1st order
Th: CAP (1:1)	0.8916 (0.7529)	0.9444 (0.9254)	0.9290 (0.8779)	0.9757 (0.8984)	0.0767 (0.1009)	Diffusion 1st order
Th: Dical (1:1)	0.7222 (0.6590)	0.8209 (0.7921)	0.7891 (0.7478)	0.8778 (0.8180)	0.0517 (0.0596)	Diffusion “

<u>2. Effect of compression pressure(tons):</u>						
1.	0.9997 (0.9989)	0.9791 (0.9924)	0.9898 (0.9962)	0.9554 (0.9489)	0.0660 (0.0541)	Zero order " "
2	0.9993 (0.9988)	0.9804 (0.9948)	0.9928 (0.9982)	0.9651 (0.9603)	0.0806 (0.0567)	" " " "
3	0.9996 (0.9993)	0.9845 (0.9908)	0.9922 (0.9965)	0.9543 (0.9587)	0.0606 (0.0621)	" " " "
3.625	0.9987 (0.9992)	0.9901 (0.9910)	0.9944 (0.9962)	0.9446 (0.9543)	0.0532 (0.0601)	" " " "
<u>3. Effect of CPP Concentration:</u>						
50%	0.9988 (0.9995)	0.9983 (0.9982)	0.9664 (0.9995)	0.9664 (0.9637)	0.0422 (0.0400)	Cube root Zero/cube root
33.33%	0.9998 (0.9996)	0.9881 (0.9804)	0.9953 (0.9915)	0.9628 (0.9597)	0.0515 (0.0682)	Zero order " "
25%	0.9794 (0.7384)	0.9937 (0.9616)	0.9900 (0.8964)	0.9835 (0.8840)	0.0515 (0.0617)	1st order " "
20%	0.8131 (0.7593)	0.9887 (0.9129)	0.9544 (0.9543)	0.9360 (0.9078)	0.0701 (0.1079)	" " " "
<u>4. Effect of dose loading theoph: CPP ratio (2:1):</u>						
200mg	0.9947 (0.9999)	0.9578 (0.9890)	0.9738 (0.9503)	0.9208 (0.9503)	0.0731 (0.0600)	Zero order " "
400mg	0.9995 (0.9998)	0.9949 (0.9952)	0.9983 (0.9980)	0.9560 (0.9520)	0.0522 (0.0463)	Zero order " "
750mg	0.9993 (0.9998)	0.9985 (0.9981)	0.9995 (0.9993)	0.9566 (0.9597)	0.0372 (0.0371)	Cube root Zero order

<u>5. Effect of pH:</u>						
pH 1.2	0.9996	0.9845	0.9922	0.9543	0.0606	Zero order
pH 4.5	0.9998	0.9903	0.9956	0.9576	0.0573	" "
pH 6.4	1.00	0.9932	0.9971	0.9602	0.0538	" "
pH 7.2	(0.9993)	(0.9908)	(0.9965)	(0.9587)	(0.0621)	" "
<u>6. Effect of rotation speed (pH 7.2 data):</u>						
50rpm	(0.9962)	(0.9994)	(0.9988)	(0.9692)	(0.0316)	1st order
80rpm	(0.9993)	(0.9941)	(0.9973)	(0.9504)	(0.0464)	Zero order
100rpm	(0.9981)	(0.9895)	(0.9958)	(0.9583)	(0.0624)	" "
<u>7. Effect of ionic strength in distilled water:</u>						
0.1M NaCl	0.9999	0.9841	0.9931	0.9521	0.0615	Zero order
0.2M "	0.9989	0.9942	0.9980	0.9573	0.0528	" "
0.3M "	0.9989	0.9957	0.9987	0.9572	0.0517	" "
<u>8. Effect of surfactant conc. In pH 7.2 dissolution media:</u>						
0%w/v Tween 80	(0.9993)	(0.9908)	(0.9965)	(0.9587)	(0.0621)	Zero order
0.1%w/v Tween 80	(0.9999)	(0.9717)	(0.9880)	(0.9555)	(0.0767)	" "
0.1%w/v Tween 80	(0.9999)	(0.9772)	(0.9900)	(0.9561)	(0.0735)	" "

TABLE 4.3: ANOVA RESULTS FOR THE EFFECTS OF VARIOUS PARAMETERS ON THE RELEASE OF THEOPHYLLINE FROM CPP MATRICES

Parameters	Calculated Variance ratios and tabulated F values at P = 0.05:		
	pH 1.2	pH 7.2	Distilled water
1. Effect of compression pressure	13.31 > 3.24 (F^3_{16}) Not significant	0.356 < 8.68 (F^3_{16}) Not significant	
2. Effect of dose loading	16.5 > 3.89 (F^2_2) significant	37.44 > 3.89 (F^2_2) significant	
3. Effect of pH	3.6 < 4.46 (F^2_3) for all pHs (1.2, 4.5, 6.4 & 7.2) Not significant		
4. Effect of rotation speed		9.54 > 3.89 (F^2_{12}) significant	
5. Effect of ionic strength			1.88 < 3.89 (F^2_{12}) Not significant
6. Effect of surfactant conc.		1.72 < 3.89 (F^2_{12}) Not significant	

4.3.1: Comparative theophylline and potassium chloride (KCl) release profiles from CPP and other known Polymers/excipients.

The comparison of drug release from matrices of different polymers/excipients is shown in figures 4.1 and 4.2 for theophylline and KCl respectively. In gastric pH 1.2, both CPP and methocel gave approximately zero-order sustained-release theophylline tablets with CPP giving a higher release rate. Cellulose acetate phthalate (CAP) showed a non-linear sustained-release profile while lactose and dicalcium phosphate did not show any sustained-release properties. In intestinal pH 7.2, CPP was the only excipient that maintained sustained-release properties of approximately zero-order. Both methocel and CAP lost their sustaining power. CAP is an enteric coating material which will dissolve in intestinal pH to release its drug content.

In the KCl formulations, CPP showed a slower release rate than either hydroxypropylmethylcellulose (HPMC) or lactose (figure 4.2). All three excipients however showed

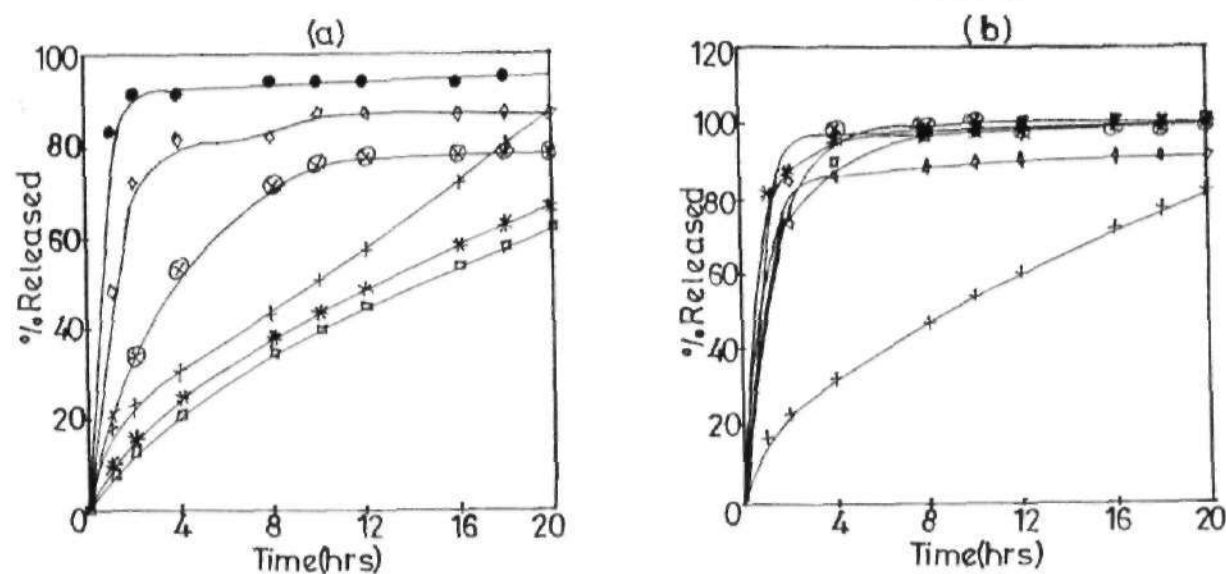
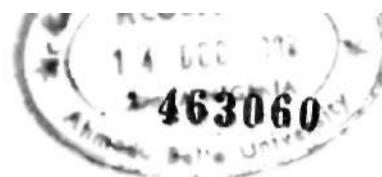


Figure 4.1: Comparison of Theophylline release from different polymer/excipient matrices, compressed at 3.625 tons, in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100 rpm and 37°C. Key: ● = Theophylline : Lactose (1:1); + = Theophylline : CPP (2:1); * = Theophylline : methocel (1:1); □ = Theophylline : methocel (2:1); ⊗ = Theophylline : C. A. P (1:1); ◇ = Theophylline : Dicalcium phosphate.

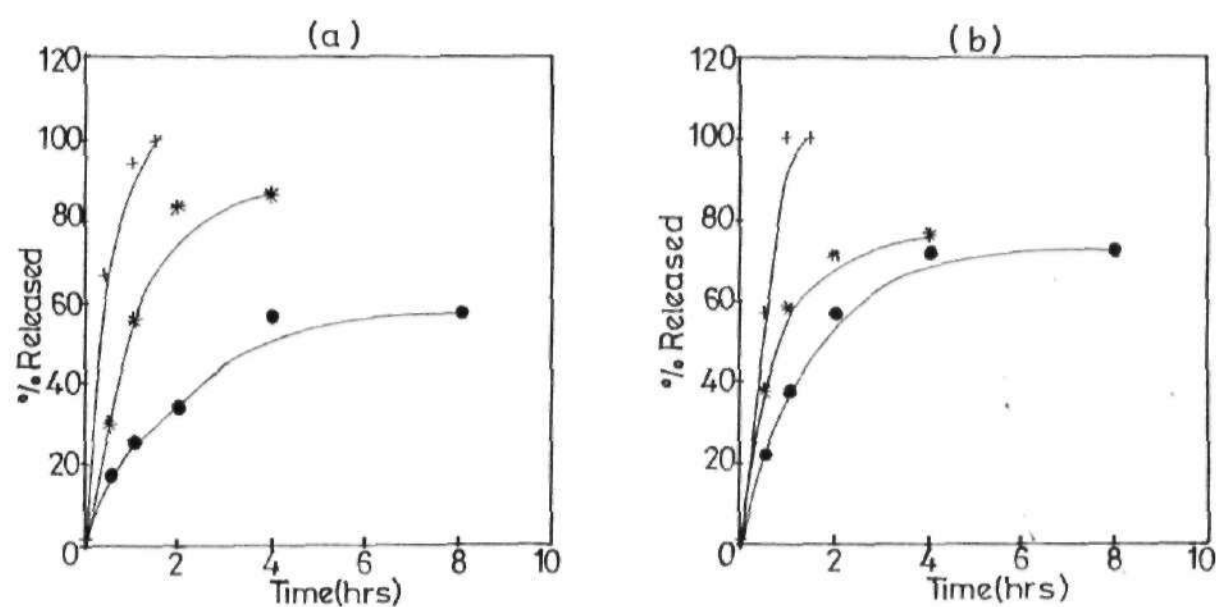


Figure 4.2: Comparison of Potassium Chloride release from different polymer/excipient matrices, compressed at 4 tons, in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100 rpm and 37°C. Key: + = KCl : lactose (2:1); * = KCl : HPMC (2:1); ● = KCl : CPP (2:1).

non-linear release patterns in both gastric and intestinal pHs. The CPP matrix showed a much more incomplete release especially in pH 7.2. The HPMC also showed an incomplete release despite the fact that the tablets disintegrated completely within 1.5 to 2 hours. This might mean that the disintegration is followed by swelling as observed by Talukdar and Plaizier-Vercammen (1993) in their study using HPMC. This swelling according to them may subsequently reduce drug release and result in incomplete drug release. The CPP matrices in both theophylline and KCl products did not disintegrate, rather slow erosion of the swollen matrices occurred well beyond 24 hours.

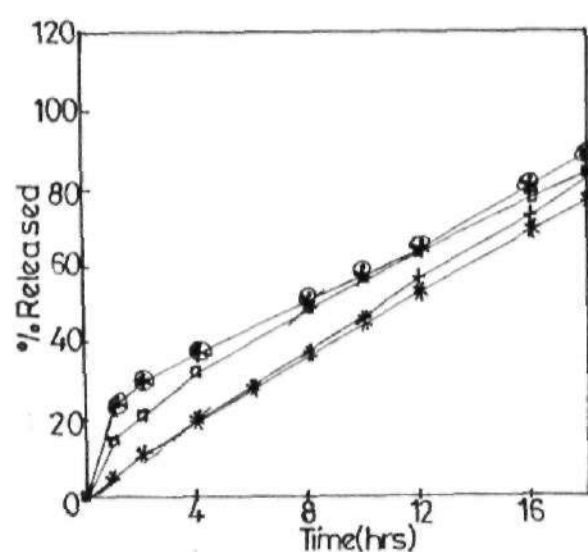


Figure 4.3: Theophylline release as a function of pH of dissolution media from F1, by the paddle method at 100rpm and 37°C. Key: ○ = pH 1.2; + = pH 4.5; * = pH 6.4; □ = pH 7.2.

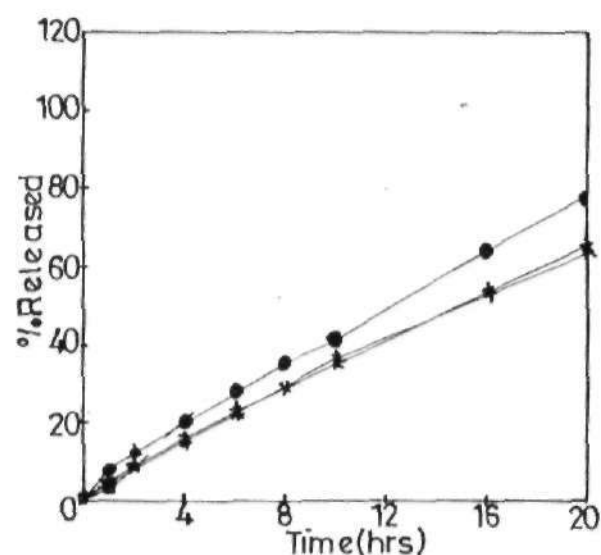


Figure 4.4: Theophylline release as a function of ionic strength of dissolution media from F1, by the paddle method at 100rpm and 37°C. Key: ● = 0.1M NaCl; + = 0.2M NaCl; * = 0.3M NaCl.

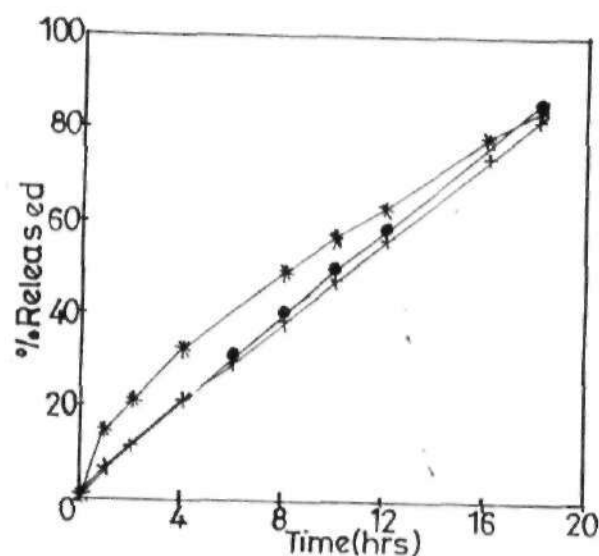


Figure 4.5: Theophylline release as a function of surfactant concentration in pH 7.2 dissolution medium from F1, by the paddle method at 100rpm and 37°C. Key: * = without surfactant; ● = 0.1%w/v Tween 80; + = 1%w/v Tween 80.

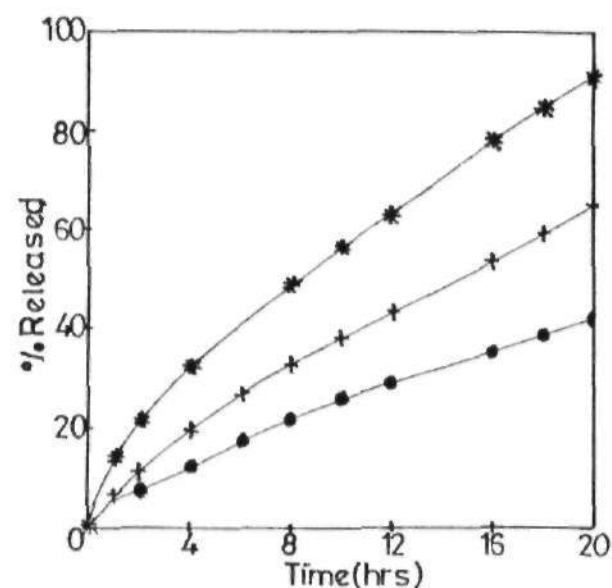


Figure 4.6: Theophylline release as a function of rotation speed from F1, in pH 7.2 at 37°C. Key: ● = 50rpm; + = 80rpm; * = 100rpm.

4.3.2: Influence of g.i.t. and processing variables on release profile of theophylline from CPP matrices.

a) Effect of pH.

Although a reduction in amounts of theophylline released at pHs 4.5 and 6.4 was observed as compared to pHs 1.2 and 7.2 (figure 4.3), the release rates were almost the same as indicated by the slopes shown in table 4.2. Also the ANOVA table shows that the difference was not significant.

Usually, a change in pH of the dissolution medium can exert an influence on the solubility of the drug in the matrix or on the hydration of the polymer which has been noted with several polymers used in matrices (Talukdar and Plaizier-Vercammen, 1993).

Furthermore, the extent of ionization of drugs that act as weak electrolytes, will depend on both the pK_a of the drug and the pH of the medium in which the drug is dissolved (Shargel and Yu, 1993). According to Benedikt *et al* (1989), it is more difficult for ions to permeate most of the polymers used for controlled release than for undissociated molecules. They observed this phenomenon in their theophylline release studies.

b) Effect of ionic strength

An insignificant decrease in drug release was observed with increase in ionic strength from 0.1M to 0.3M NaCl as shown in figure 4.4. The ionic strength in the stomach is fairly constant. According to Talukdar and Plaizier-Vercammen (1993), it is important that controlled-release tablets are resistant in media of 0.1M ionic strength and somewhat higher. These authors reported an obvious influence of ionic strength on xanthan gum matrices and attributed the initial increase of dissolution in salt solutions to a decrease of swelling rate under the influence of the salts.

c) Effect of Surfactant.

The importance and influence of surfactants on release rate of drugs is well known. There are many surface active compounds present in the g.i.t. leading to the lowering of surface tension and possibly influencing the release rate of drugs. To simulate this behaviour in dissolution experiments, some authors recommend the addition of surfactants (Rowe, 1975), other authors however have an opposite opinion (Koch, 1984). Surfactants can also improve wettability of tablets and increase the penetration of solvent into tablets.

Figure 4.5 shows the effect of adding Tween 80 to simulated intestinal fluid at the concentration levels of 0.1%W/V and 1%W/V i.e. below and above the critical micelle concentration (CMC) respectively. The initial "burst effect" observed in theophylline release in simulated intestinal

fluid was noticeably reduced by the presence of surfactants. The release rates as indicated by the slopes of the curves, were only slightly higher when surfactant is present in the medium. This could be due to the improved penetrability of the matrices. An insignificant decrease in amount released was observed as surfactant concentration increased from 0.1%W/V to 1%W/V. This might suggest that if drug release is visualized as penetration and hydration of matrix by medium, dissolution of drug and subsequent diffusing out of dissolved drug, the better penetrating power of surfactants below their CMC is more important than the solubilizing effect of surfactants above their CMC for the release of theophylline from CPP matrices.

d) Effect of agitation speed.

Varying the paddle rotation speed is aimed at simulating varying g.i.t. motility and figure 4.6 shows the effect of rotation speed. The release rate of theophylline was significantly affected by rotation speed (table 4.2.). The higher the rotation speed, the higher the release rate. Talukdar and Plaizier-Vercammen (1993) noted a great positive influence of rotation speed in their studies with HPMC. They reported that as stirring speed increased, the thickness of the hydrated gelatinous layer surrounding the intact tablet core was noticeably decreased under the elevated stirring conditions, resulting in a more rapid release of the drug from the matrix.

e) Effect of CPP concentration

Figure 4.7 shows an inverse relationship in which release rate increased as CPP concentration decreased from 50%W/W to 20%W/W, and indeed sustaining power was lost at CPP concentration of 25%W/W and less. This effect was observed in both gastric and intestinal pHs. The observation is in agreement with previous reports (Talukdar and Plaizier-Vercammen, 1993; and Dhopeswarkar and Zatz, 1993). These authors reported that the release rate of drug is greatly influenced by the matrix polymer concentration. This is because at high concentrations of gum, a very thick layer of gel is

formed, consequently erosion of the tablet is inhibited and the release rate is delayed. Also the highly viscous gel barrier with high polymer concentration will reduce diffusion rate.

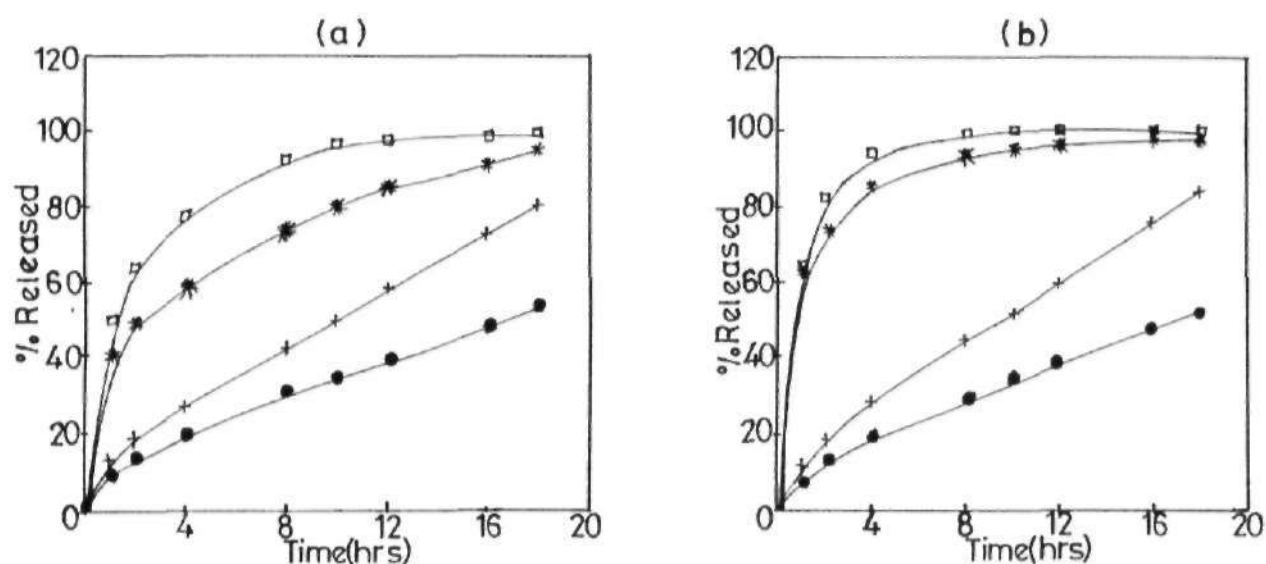


Figure 4.7: Theophylline release as a function of CPP polymer concentration in matrix tablets, compressed at 3.625 tons, in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100rpm and 37°C. Key: ● = 50% CPP content; + = 33.3% CPP content; * = 25% CPP content; □ = 20% CPP content.

f) Effect of compression pressure.

It has been published many times that compression force does not have much influence on the release rate of drugs (Ventouras and Buri, 1976). However, from the industrial point of view, it is important to know the influence of this parameter (Talukdar and Plaizier-Vercammen, 1993). In this study, the effect of compression pressure on theophylline release from CPP matrix (figure 4.8) was found to be insignificant in intestinal pH as indicated in table 4.2. However in gastric pH, compression pressure showed a significant effect on theophylline release with the exhibition of a maximum in the release rate as compression force increased.

g) Effect of dose content.

Theophylline dose content is shown to have a great influence on the release rate as given in table 4.2. and figure 4.9.

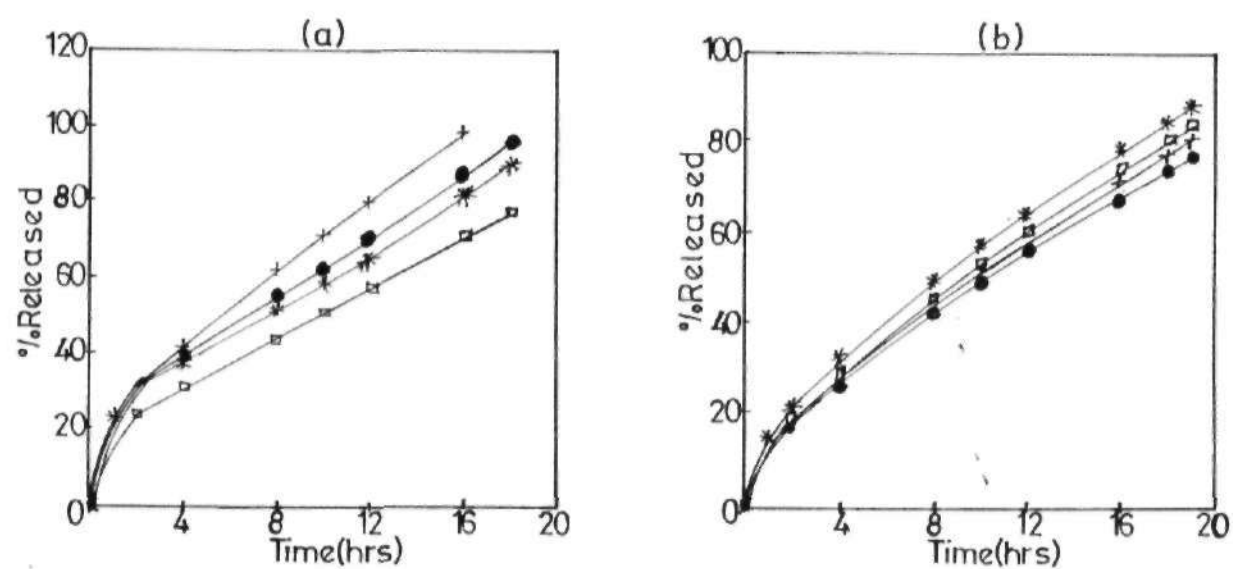


Figure 4.8: Theophylline release as a function of compression pressure from CPP matrix tablets, F1, in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100rpm and 37°C. Key: ● = 1 ton; + = 2 tons; * = 3 tons; □ = 3.625 tons.

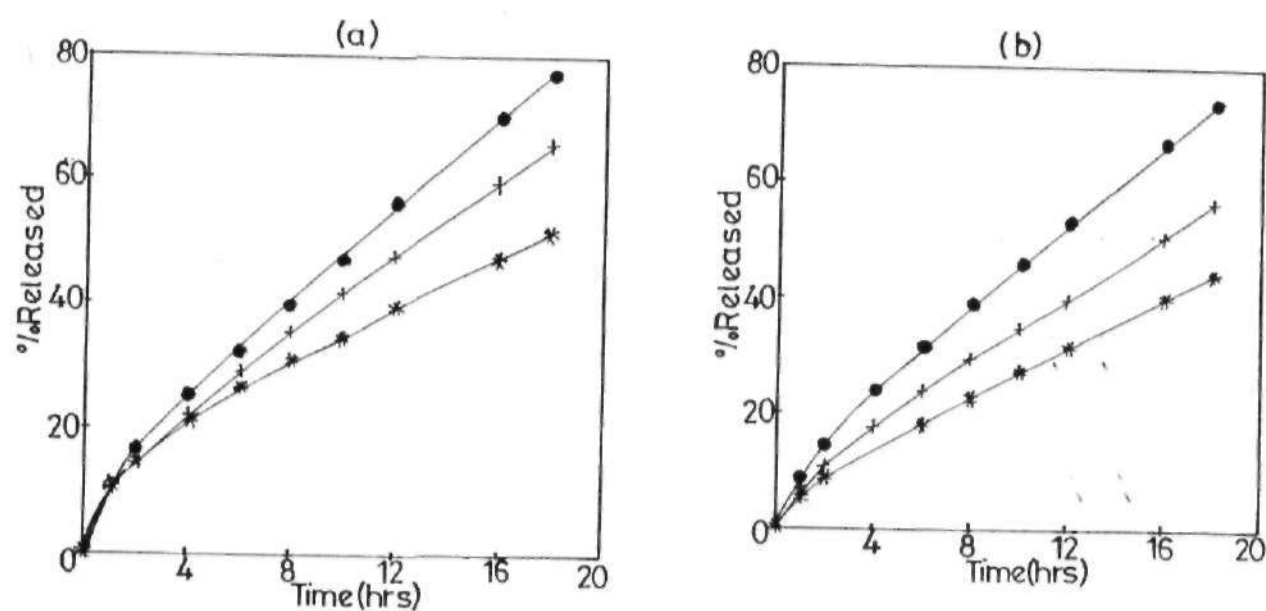


Figure 4.9: Theophylline release as a function of dose loading from CPP matrix tablets, in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100rpm and 37°C. Key: ● = 200mg dose; + = 400mg dose; * = 750mg dose.

The result shows that release rate decreases as the dose content increases as indicated by the slopes of the curves (table 4.2.). This contradicts the prediction of Chien (1978) who showed that in matrix-type drug delivery systems, a linear relationship exists between the magnitude of the drug release profile ($Q/t^{1/2}$) and the square root of drug content $(2A)^{1/2}$ as defined by equation 1.12:

$$Q/t^{1/2} = ((2A - C_p) C_p D_p)^{1/2}$$

This relationship according to Chien suggests that any attempt to prolong the duration of medication by incorporating a greater amount of drug into the matrix-type polymeric delivery device would also inevitably yield a greater value of $Q/t^{1/2}$. One possible explanation for the contradiction observed in this study could be the variation in tablet sizes (7.5, 9.5 and 12.5mm tablet diameters) used in this study. This variation in size was necessitated by the big differences in doses used (200mg, 400mg and 750mg). For the larger tablets, as the drug at the surface gets depleted, the diffusional path from the core to the surface increases at a faster rate than in the smaller tablets thereby resulting in slower diffusion according to Ficks' law of diffusion and consequently a reduction in dissolution rate.

h) Comparison of different KCl formulations:

Figure 4.10 shows the release of KCl from different matrix formulations (F15-F19) given in table 4.1. None of the formulations gave satisfactory prolongation of drug release. It appears that for soluble drugs, more efficient coating of the drug with a hydrophobic material is needed before dispersing in the CPP matrix. A spray dryer or fluid bed dryer might thus be needed for this purpose. The big sizes of some of the KCl formulations would warrant administering them in units of 2 tablets per dose for easier swallowing.

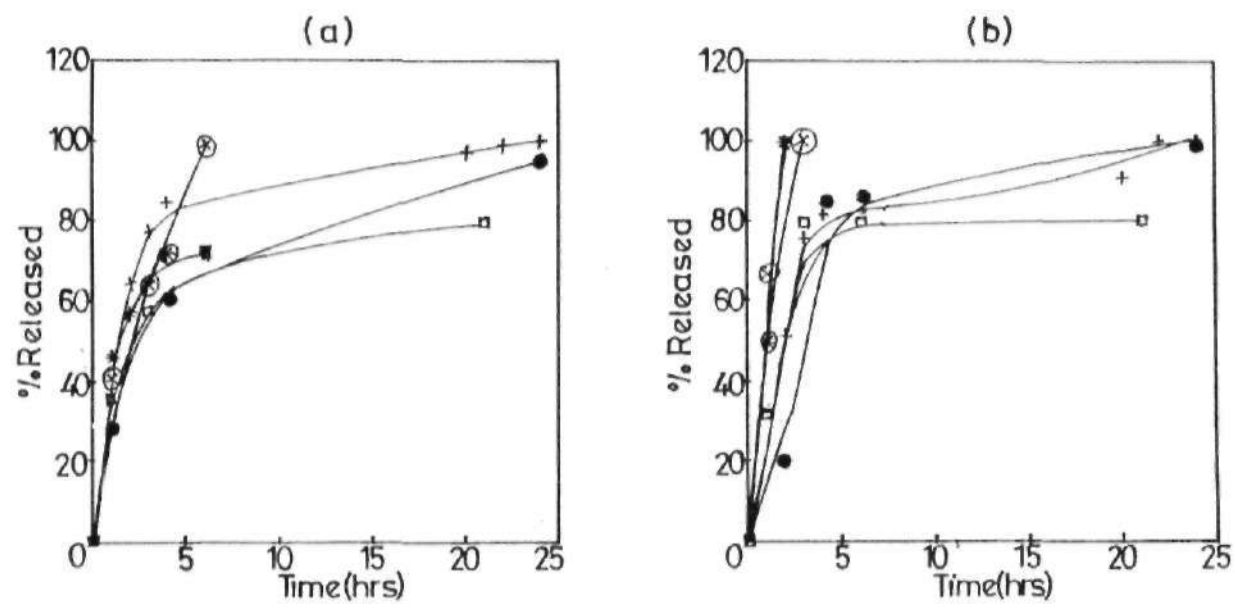


Figure 4.10: Comparison of Potassium Chloride release from different formulations, compressed at 3tons, in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100rpm and 37°C. Key: ● = F15; ■ = F16, + = F17; □ = F18; ⊗ = F19.

CHAPTER FIVE

CHAPTER FIVE

THE USE OF CPP IN THE FORMULATION OF CONTROLLED-RELEASE
THEOPHYLLINE MATRIX TABLETS5.1: INTRODUCTION

Most existing slow - and controlled - release formulations were introduced to extend drug action to allow more convenient "once- or twice - daily" dosing (Prescott, 1989). The mean transit time for a controlled - release oral pharmaceutical dosage form is about 25 hours (Davis, 1989). As reported by Fara (1989), for most of this time, the dosage form resides in the ileum, caecum and colon. Fara reported that many drugs are well absorbed from the entire g.i.t. and approximately three quarters of the compounds evaluated to date are well absorbed from the colon. This has important implications for dosage form design as "once-a-day" dosing is made possible for these drugs (Fara, 1989).

In 1976, Euphyllin® retard was introduced as the first sustained - release formulation in an effort to optimise theophylline therapy. This was followed by various improvements and in 1988, Benedict *et al* reported the development of Euphyllong® pellets, a micro - osmotic system for "once - daily" dosing of anhydrous theophylline, adding to the already approved "once - daily" theophylline products in the U.S.A. and the Federal republic of Germany. Theophylline is well absorbed from the colon although the rate of absorption is reduced, and poor absorption of slow-release formulations in the past was probably attributable to deficiencies in formulation rather than poor colonic absorption (Kaik, 1982). Staib *et al* (1989) have suggested that theophylline and nitrendipine are probably appropriate candidates for all forms of slow-release products.

This study undertook the formulation of "once- and twice - daily" controlled - release theophylline matrices using a novel hydrocolloid polymer CPP, and assessed their in-vivo performance

under varying g.i.t. conditions and from simulated plasma levels. The "once - daily" formulations were further compared to commercially approved "once - daily" theophylline products.

5.2: EXPERIMENTAL

5.2.1: Calculation of maintenance doses for "once-and twice - daily" products

The pharmacokinetic data of theophylline were used with the equation for a one compartment model given by equation 1.5:

$$D_m = C_p \gamma CLT$$

Doses of 723mg and 362mg for maintenance periods of 24 hours and 12 hours respectively were calculated and used for the "once-and twice-daily" formulations as follows:

"Once-daily" product

Theophylline-----	723.00mg (71.4%)
CPP-----	289.20mg (28.5%)
Magnesium stearate-----	<u>1.02mg (0.1%)</u>
	<u>1,013.22mg</u>

Each dose was compressed into two tablets, each weighing 506.61mg at 2 tons compression pressure.

This would ensure easier swallowing by patients.

"Twice-daily" product

Theophylline----- 362.00mg (55.26%)

CPP----- 127.03mg (19.39%)

Lactose----- 165.38mg (25.25%)

Magnesium stearate----- 0.66mg (0.1%)

Tablet weight = 655.07mg

The tablets were compressed at 2 tons compression pressure.

5.2.2: Determination of theophylline release.

A reference concentration and corresponding absorbance taken from the Beer law plot were used on the computer programme and theophylline release was determined as described in chapter 2.

5.2.3: Effect of variables on theophylline release.

The effects of some g.i.t. variables and some processing variables on theophylline release from both "once-and twice-daily" products were studied.

5.2.4: Treatment of results.

The procedure described in section 4.2 of chapter 4 was used to obtain the release rates, the best release model and the significance of the effects of the studied variables on theophylline release from both "once-and twice-daily" products. The results are shown in tables 5.1 & 5.2 and 5.4 & 5.5.

5.2.5: Pharmacokinetic simulation.

Assuming that early doses of theophylline do not affect the pharmacokinetics of subsequent doses, the principle of superposition may be used to obtain plasma drug concentrations after multiple doses given at timed intervals (Shargel and Yu, 1993). The principle involves adding the residual drug

concentration obtained after each previous dose to give the total plasma drug concentration. The plasma drug concentration for each dose was obtained from computer simulation by the use of a computer programme BASIC 2 locomotive software employing equation 1.26:

$$C_p = \frac{D_s (1 - e^{-kt})}{V_d K}$$

Shargel and Yu (1993) have given the following pharmacokinetic data for theophylline:

Volume of distribution (Vd)	=	35lt
Elimination half-life ($t_{1/2}$)	=	8.1hrs
Oral bioavailability (%)	=	96
Therapeutic plasma level	=	10-20 µg/ml

In view of the fact that theophylline release was not affected by pH change and also that theophylline is well absorbed from the entire g.i.t., the dissolution data of pH 7.2 was used for the simulation of plasma levels since most absorption occurs in the small intestine.

5.3: **RESULTS AND DISCUSSIONS**5.3.1: **"Once-daily" controlled-release theophylline matrices.****Table 5.1: KINETICS OF THEOPHYLLINE RELEASE FROM "ONCE-DAILY" TABLETS.**

Effect under study	Correlation coefficients in pH 1.2 and (pH 7.2) for:				Zero order slope/rate (% min ⁻¹)	Release rate process
	Zero order	First order	Cube root	Diffusion		
1. <u>Effect of pH</u>						
pH 1.2	1.00	0.9733	0.9882	0.9449	0.0550	Zero order
pH 4.8	0.9994	0.9732	0.9864	0.9342	0.0527	" "
pH 7.2	(1.00)	(0.9760)	(0.9891)	(0.9439)	(0.0532)	" "
2. <u>Effect of ionic strength in distilled water</u>						
0.1M NaCl	1.00	0.9511	0.9787	0.9497	0.0912	Zero order
0.2M "	0.9999	0.9465	0.9778	0.9507	0.0948	" "
0.3M "	0.9999	0.9437	0.9759	0.9484	0.0947	" "
3. <u>Effect of surfactant in pH 7.2 medium</u>						
0%w/v Tween 80	(1.00)	(0.9760)	(0.9891)	(0.9439)	(0.0532)	Zero order
0.1%w/v Tween 80	(0.9998)	(0.9794)	(0.9901)	(0.9429)	(0.0564)	" "
1%w/v Tween 80	(0.9998)	(0.9802)	(0.9904)	(0.9425)	(0.0558)	" "
4. <u>Effect of rotation speed(rpm):</u>						
50	1.00	0.9884	0.9948	0.9486	0.0486	Zero order
	(0.9999)	(0.9922)	(0.9970)	(0.9545)	(0.0471)	" "
80	0.9997	0.9758	0.9886	0.9436	0.0592	" "
	(0.9999)	(0.9696)	(0.9856)	(0.9433)	(0.0618)	" "
100	0.9998	0.9758	0.9889	0.9476	0.0591	" "
	(0.9998)	(0.9778)	(0.9892)	(0.9431)	(0.0569)	" "

5. Effect of particle size(μm):						
180	1.00 (0.9999)	0.9726 (0.9620)	0.9880 (0.9830)	0.9529 (0.9486)	0.0676 (0.0729)	Z e r o order
425	1.00 (1.00)	0.9736 (0.9609)	0.9884 (0.9829)	0.9519 (0.9546)	0.0670 (0.0790)	" "
710	0.9999 (0.9973)	0.9714 (0.9680)	0.9875 (0.9816)	0.9518 (0.9280)	0.0686 (0.0685)	" "

Table 5.2: **ANOVA RESULTS FOR THE EFFECTS OF DIFFERENT PARAMETERS ON THEOPHYLLINE RELEASE FROM "ONCE-DAILY" TABLETS**

Parameters	Calculated variance ratios and tabulated F values (at $P = 0.05$) in :		
	pH 1.2 medium	pH 7.2 medium	Distilled water medium
1. Effect of pH	0.125 < 19.41 (F^{12}_2) for all pHs used Not significant		
2. Effect of ionic strength	0.012 < 19.43 (F^{12}_2) Not significant		
3. Effect of surfactant		0.04 < 19.41 (F^{12}_2) Not significant	
4. Effect of rotation speed	0.521 < 19.41 (F^{12}_2) Not significant	0.79 < 19.41 (F^{12}_2) Not significant	
5. Effect of particle size	0.22 < 19.41 (F^{12}_2) Not significant	0.016 < 16.41 (F^{12}_2) Not significant	

a) **Effect of pH,**

Figure 5.1 shows that theophylline release was not significantly affected by pH change as confirmed by table 5.2. The release rates were similar for all the pHs studied as indicated by the slopes of the curves given in table 5.1. A slight decrease in amount released was observed in pH 4.5 medium. Benedict *et al* (1988) reported that one of the two approved "once-daily" products they examined was highly contingent upon pH, but that their formulated "micro-osmotic system" was hardly affected by pH changes.

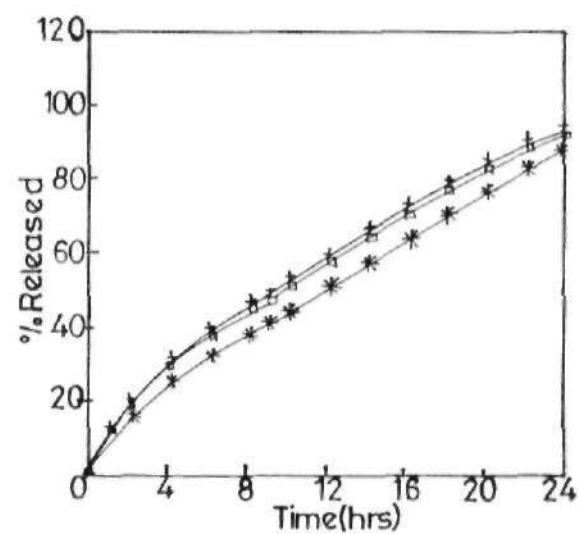


Figure 5.1: Effect of pH of dissolution media on theophylline release from "once - daily" tablets, by the paddle method at 100rpm and 37°C. Key: + = pH 1.2; ★ = pH 4.5; □ = pH 7.2.

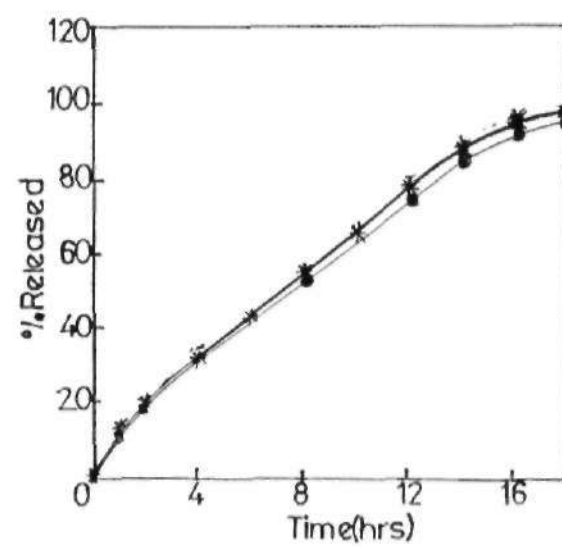


Figure 5.2: Effect of ionic strength of dissolution media on theophylline release from "once - daily" tablets by the paddle method at 100rpm and 37°C. Key: ● = 0.1M NaCl; + = 0.2 M NaCl; ★ = 0.3 M NaCl.

b) **Effect of ionic strength.**

There was virtually no change in drug release with change in ionic strength between 0.1M to 0.3M NaCl as shown in figure 5.2 and ANOVA (table 5.2).

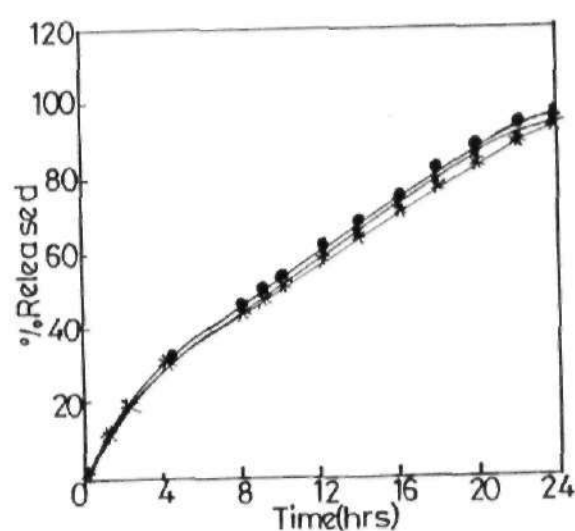


Figure 5.3: Effect of surfactant concentration in pH 7.2 dissolution media on theophylline release from "once - daily" tablets by the paddle method at 100rpm and 37°C. Key: ★ = Without surfactant; ● = 0.1%w/v Tween 80; + = 1%w/v Tween 80.

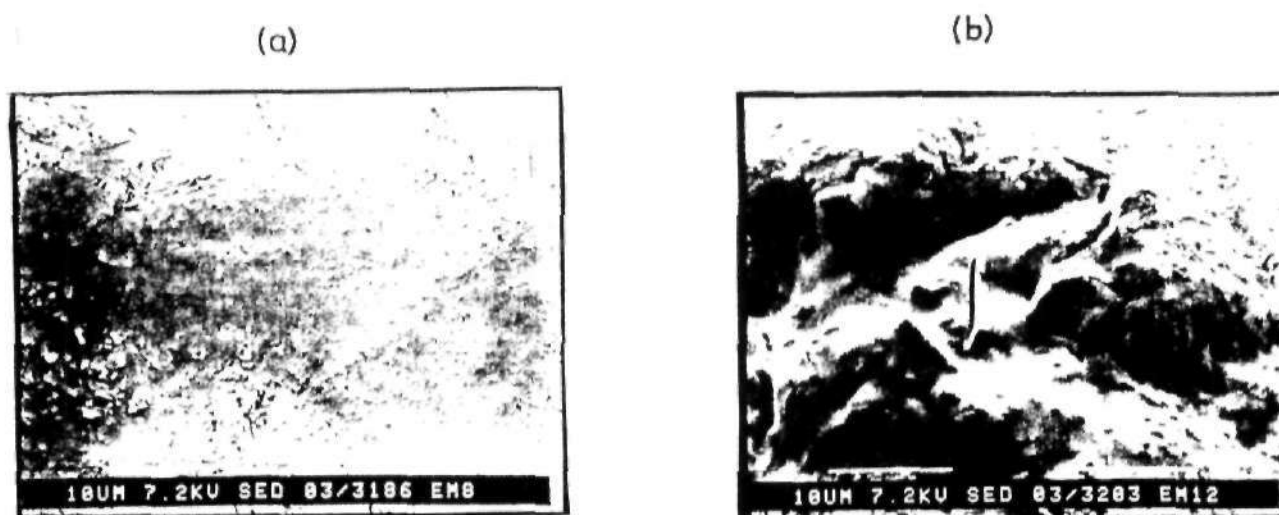


Figure 5.4: Scanning electron micrograph of the surface of "once - daily" tablets (a) before dissolution test (b) after 1 hour dissolution (2,500 x 0.65 enlargement).

c) **Effect of Surfactant.**

0.1%W/V Tween 80 showed a slightly greater drug release as compared to 1%w/v Tween 80, both of which however gave higher drug release than when surfactant was absent in the pH 7.2 dissolution medium (Figure 5.3). Shargel and Yu (1993) have reported that surfactants may affect drug dissolution in an unpredictable fashion. According to them, low concentrations of surfactants lower the surface tension and increase the rate of drug dissolution, whereas higher concentrations tend to form micelles with the drug and thus decrease the dissolution rate. The complete absence of surfactant would reduce the dissolution medium's penetration into the matrix due to absence of pores as shown in the electron micrograph (figure 5.4), and consequently reduced release rate as shown in figure 5.3. The effect of surfactant on theophylline release is however not significant as given by the ANOVA results in table 5.2.

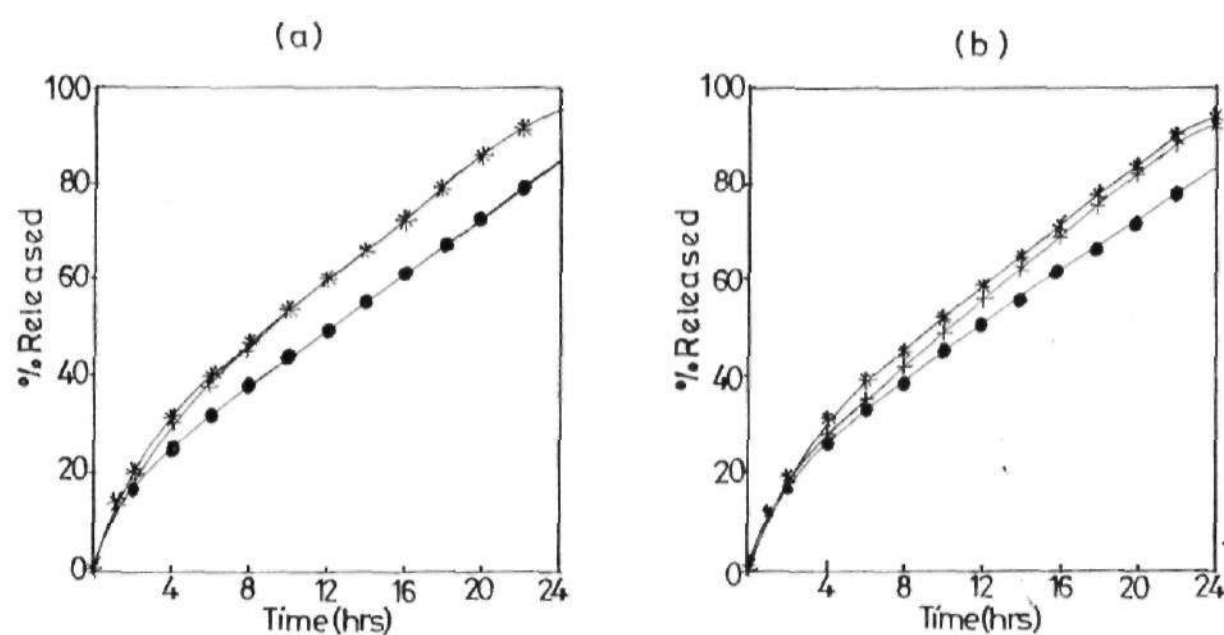


Figure 5.5: Effect of rotation speed on theophylline release from "once - daily" formulation in (a) pH 1.2, (b) pH 7.2, by the paddle method at 100rpm and 37°C. Key: ● = 50 rpm; + = 80 rpm; ★ = 100rpm.

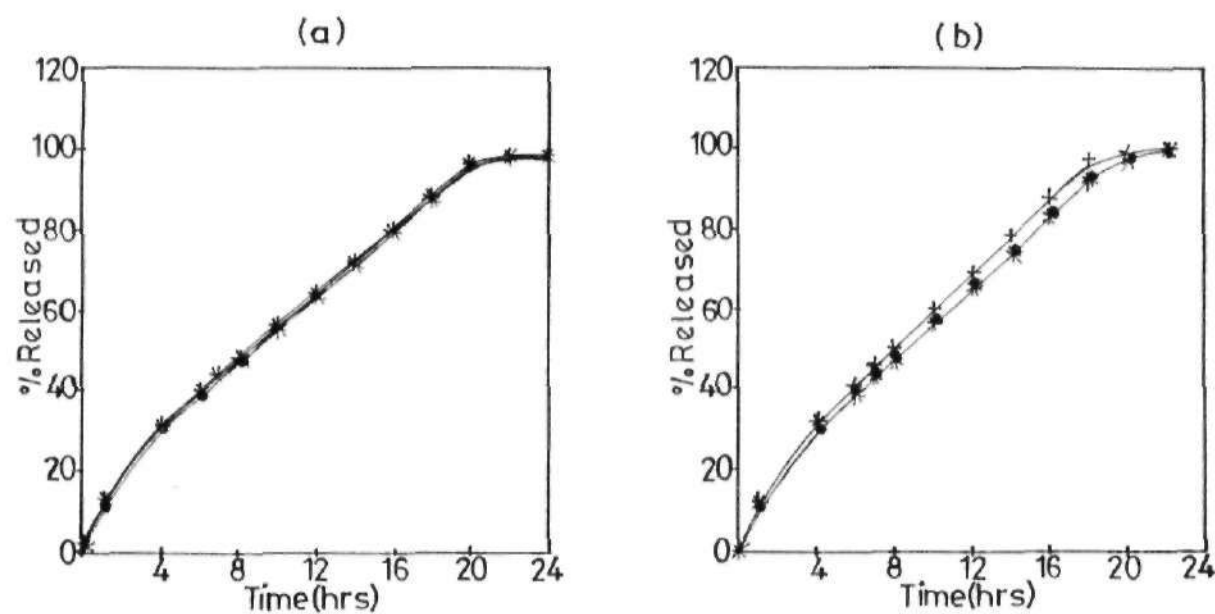


Figure 5.6: Effect of granule size used for compressing "once - daily" tablets on theophylline release in (a) pH 1.2 (b) pH 7.2, by the paddle method 100rpm and 37°C. Key: ● = 180µm granules; + = 425µm granules; ★ = 710µm granules.

d) **Effect of agitation speed.**

There was virtually no difference in drug release between the 80rpm and 100rpm speeds in both gastric and intestinal pHs as seen in figure 5.5. Although the 50rpm speed gave a reduced release of drug, the release rate as given by the slope is quite similar to those of 80 and 100rpms. Consequently the ANOVA showed a "no significant" difference. Usually an increase in agitation speed of the dissolution medium will reduce the thickness of the stagnant layer in the Noyes Whitney equation of dissolution thus allowing for more rapid drug dissolution. Also erosion of the matrix will increase with increased agitation speed which will increase dissolution rate. This effect of increase

in release rate with increased rotation speed was observed by Benedict *et al* (1988) with the two approved "once-daily" reference products they tested.

e) **Effect of particle size.**

Finholt and Solvang (1968) studied the effect of particle size of granules used for preparing phenacetin tablets on the dissolution rate. They observed an increased rate in diluted gastric juice as the particle size was decreased, however the opposite effect occurred when 0.1N HCl was used as the dissolution medium. In another study, no difference was detected in the dissolution of phenobarbital and phenacetin tablets containing starch and gelatin if the tablets were prepared from different sizes of granulation (Finholt *et al*, 1966). In the present study, granule sizes of 180, 425 and 710 μ m used for preparing theophylline "once-daily" matrix tablets did not produce any significant difference in theophylline release in both gastric and intestinal pHs (figure 5.6) as confirmed by ANOVA shown in table 5.2.

f) **Pharmacokinetic simulation of the "once-daily" tablets**

Figures 5.8 - 5.11 show the simulated theophylline plasma levels for 5 multiple doses of the 24 hour, 22 hour, 20 hour and 16 hour release forms of the "once-daily" tablets administered at 24 hour intervals. The 24 hour release form exhibited "topping effect" (figure 5.8) as described by Welling (1983). When a second dose is given after a time interval shorter than the time required to eliminate the previous dose, drug accumulates in the body. However, if the second dose is given after a time interval longer than the time required to eliminate the previous dose, the drug will not accumulate (Shargel and Yu, 1993). A suitable balance between accumulation and complete elimination will yield the desired plateau in the plasma drug level.

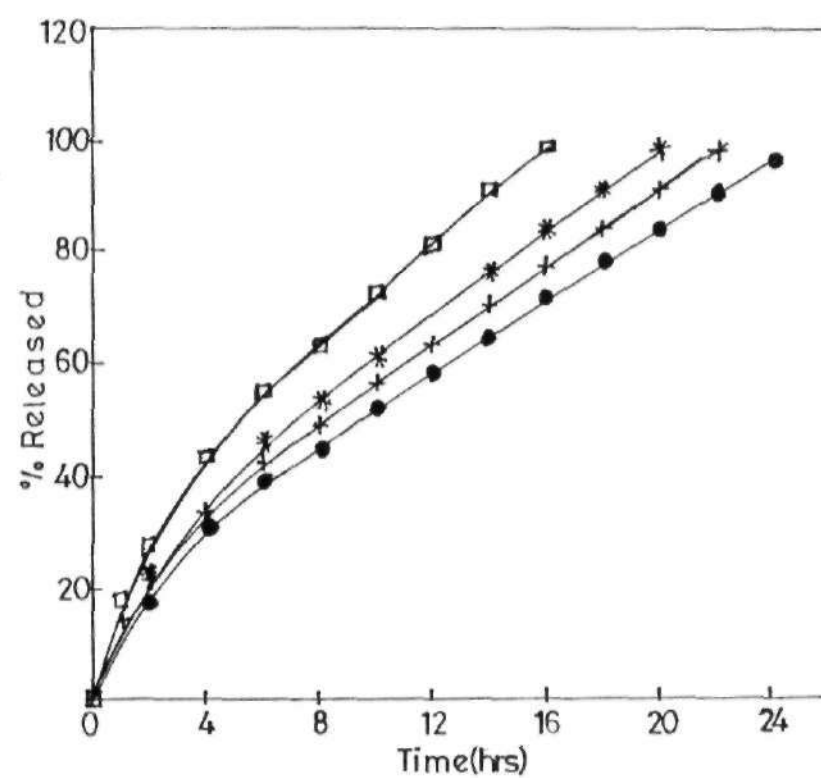


Figure 5.7: Theophylline release profiles from various release forms of the "once-daily" formulation in pH 7.2, at 100rpm and 37°C by the paddle method. Key: $\square$ = 16hr release form; $\star$ = 20 hr release form; $+$ = 22hr release form; $\bullet$ = 24 hr release form.

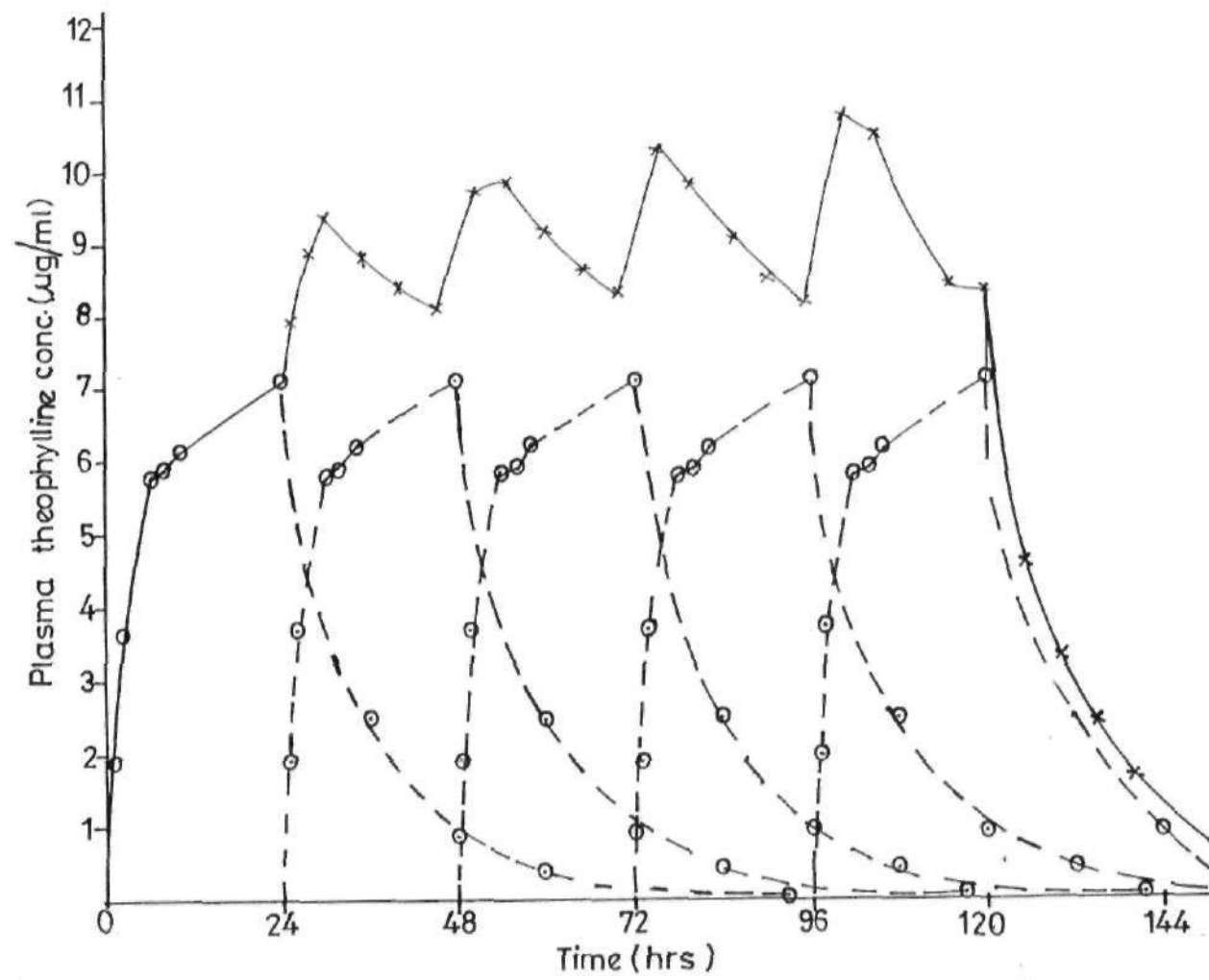


Figure 5.8: Computer simulation of plasma level curves of the 24 hour release form of "once-daily" theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

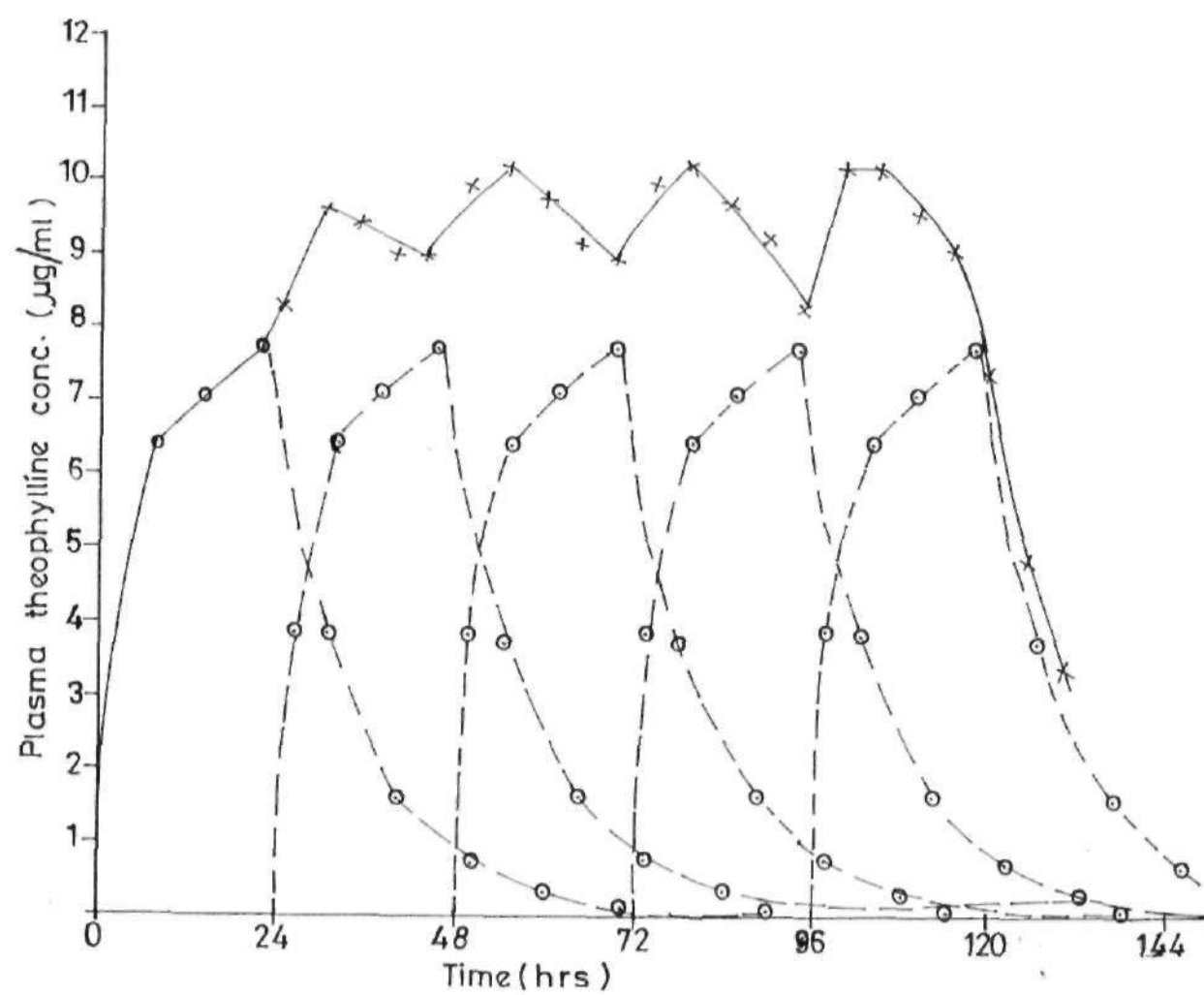


Figure 5.9: Computer simulation of plasma level curves of the 22 hour release form of "once-daily" theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

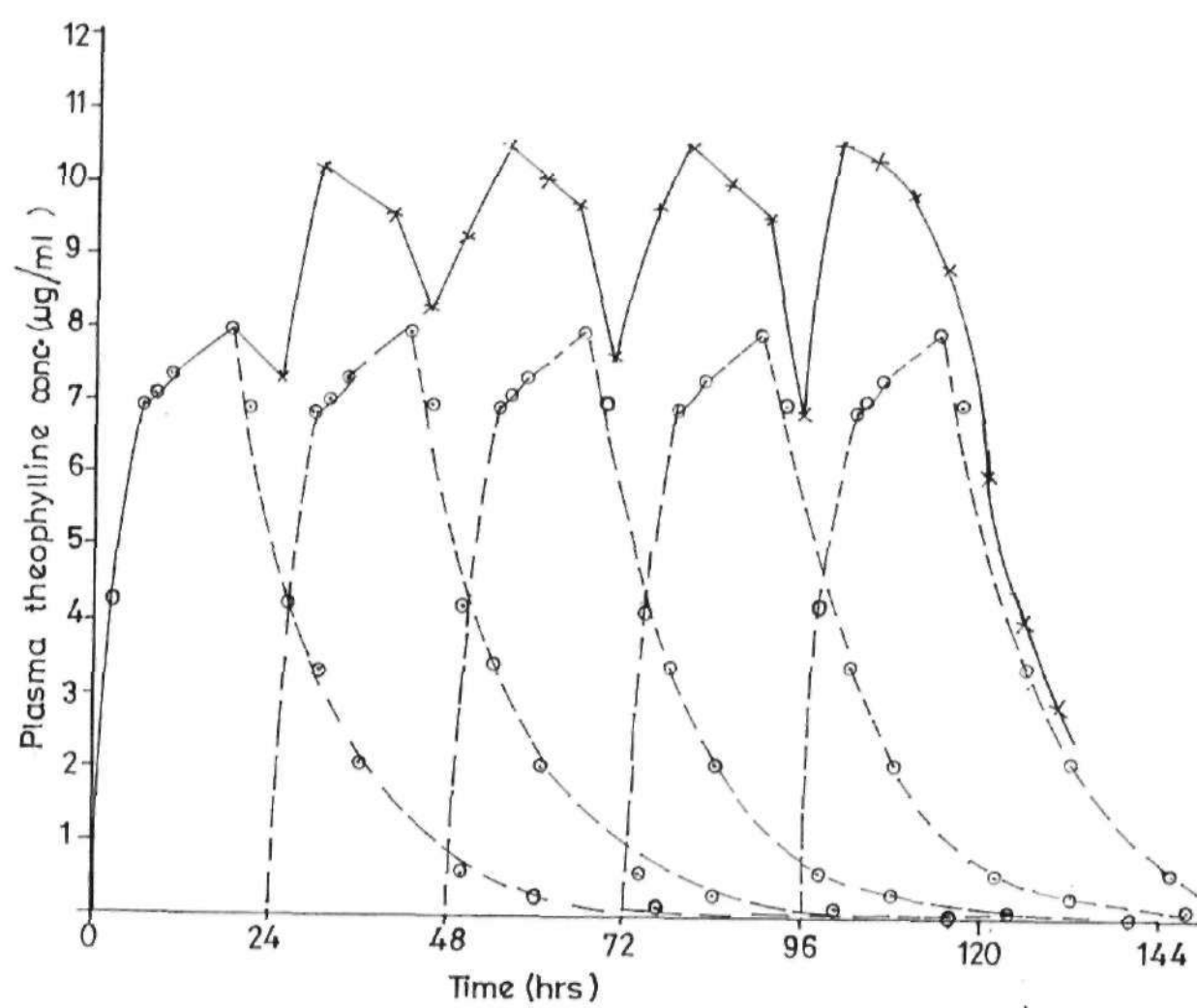


Figure 5.10: Computer simulation of plasma level curves of the 20hour release form of "once-daily" theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

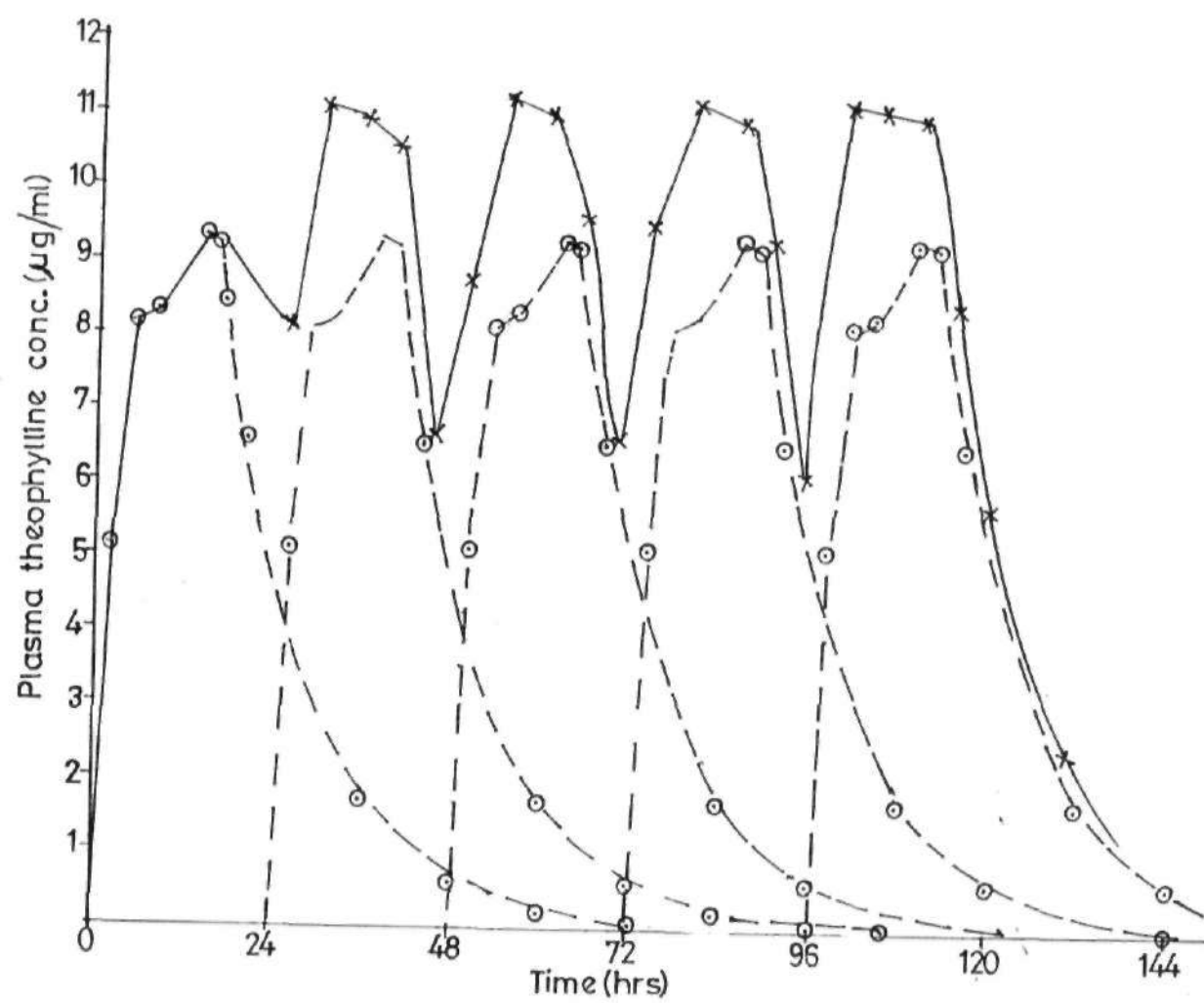


Figure 5.11: Computer simulation of plasma level curves of the 16hour release form of "once-daily" theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100rpm and 37°C. Key: ○ = Single dose components; x = Total plasma level curve.

To avoid "topping effect" by the formulated "once-daily" tablets, the formulation must release its drug content within a period of less than 24 hours. Dissolution data were therefore generated from the 24 hour release form by the use of multiplication factors to produce 22 hour, 20 hour and 16 hour release forms as shown in figure 5.7. These generated dissolution data were then used to obtain simulated plasma levels for the modified forms (figures 5.9-5.11). The 22 hour release form is evidently the most satisfactory as it gave the least "topping effect" and least peak - trough variation. The product thus needs to be reformulated to release its theophylline content within 22 hours. This can be achieved by for example decreasing the CPP concentration in the matrix. The simulated pharmacokinetic output for the various release forms are as summarised in table 5.3.

Table 5.3: Simulated Pharmacokinetic output parameters of "once-daily" theophylline matrix tablets from pH 7.2 dissolution data.

Release form	C _{max} (µg/ml)	t _{max} (hrs)	AUC 24(µgh/ml)
24 hour release form	7.1	24	223
22 hour release form	7.7	22	228
20 hour release form	8.1	20	227
16 hour release form	9.3	14	227

An initial titrated immediate - release dose (D_1) would be required to achieve the therapeutic theophylline plasma level of 10 - 20mg/ml followed by a sustained - release maintenance dose.

5.3.2: "Twice - daily" controlled - release theophylline matrices

Table 5.4: Kinetics of theophylline release from "Twice - Daily" tablets

Effect under study	Correlation coefficients for pH 1.2 and (pH 7.2) for:				Zero order rate (% h ⁻¹)	Release rate process
	Zero order	First order	Cube root	Diffusion		
1. Effect of pH:						
pH 1.2	0.9999	0.9663	0.9850	0.9551	0.1142	Zero order
pH 4.5	0.9998	0.9939	0.9975	0.9596	0.0796	" "
pH 7.2	(0.9993)	(0.9662)	(0.9872)	(0.9601)	(0.1248)	" "
2. Effect of ionic strength in distilled water:						
0.1M NaCl	0.9996	0.9937	0.9978	0.9601	0.0607	Zero order
0.2M "	0.9999	0.9942	0.9977	0.9535	0.0560	" "
0.3M "	0.9977	0.9944	0.9984	0.9701	0.0647	Cube root
D/water	0.9997	0.9846	0.9923	0.9487	0.0916	Zero order
3. Effect of surfactant in pH 7.2 medium:						
0%w/v Tween 80	(0.9993)	(0.9662)	(0.9872)	(0.9601)	(0.1248)	Zero order
0.1%w/v Tween 80	(0.9993)	(0.9829)	(0.9917)	(0.9568)	(0.0890)	" "
1%w/v "	(0.9990)	(0.9812)	(0.9898)	(0.9496)	(0.0848)	" "
4. Effect of rotation speed(rpm):						
50	0.9982	0.9972	0.9987	0.9586	0.0572	Cube root
	(0.9994)	(0.9991)	(0.9995)	(0.9618)	(0.0413)	" "
80	0.9985	0.9976	0.9994	0.9654	0.0651	" "
	(0.9992)	(0.9959)	(0.9976)	(0.9556)	(0.0524)	Zero order
100	0.9996	0.9391	0.9751	0.9566	0.1122	" "
	(0.9990)	(0.9596)	(0.9847)	(0.9660)	(0.1255)	" "
5. Effect of particle size(μ m):						
180	0.9992	0.9767	0.9879	0.9428	0.0692	Zero order
	(0.9996)	(0.9779)	(0.9907)	(0.9526)	(0.0778)	" "
425	0.9999	0.9798	0.9917	0.9541	0.0772	" "
	(0.9994)	(0.9932)	(0.9968)	(0.9483)	(0.9483)	" "
710	0.9998	0.9788	0.9900	0.9489	0.0719	" "
	(0.9997)	(0.9816)	(0.9911)	(0.9460)	(0.0698)	" "

6. Effect of compressure pressure(tons);							
2	0.9998 (0.9993)	0.9674 (0.9662)	0.9848 (0.9872)	0.9500 (0.9601)	0.1127 (0.1248)	“	“
3	0.9991 (0.9999)	0.9773 (0.9762)	0.9915 (0.9902)	0.9589 (0.9543)	0.1190 (0.0808)	“	“
4	0.9973 (0.9997)	0.9623 (0.9510)	0.9884 (0.9787)	0.9633 (0.9572)	0.0973 (0.1479)	“	“

Table 5.5: **ANOVA results for the effects of different parameters on theophylline release from “Twice - Daily” tablets**

Parameters	Calculated variance ratios and tabulated F values (at P = 0.05) in:		
	pH 1.2 Medium	pH 7.2 Medium	Distilled water medium
1. Effect of pH	5.21 > 3.89 (F^2_{12}) for all pHs used, $\therefore$ Significant. But Between pH 1.2 & pH 7.2 calculated t = 1.186 < 2.31 ($\phi = 8$, p = 0.05) $\therefore$ Not significant		
2. Effect of ionic strength (excluding pure d/water data)			1.07 < 3.87 (F^2_{12}) Not significant
3. Effect of surfactant		1.49 < 3.89 (F^2_{12}) Not significant	
4. Effect of rotation speed	12.21 > 3.89 (F^2_{12}) Significant	69.94 > 3.89 (F^2_{12}) Highly significant	
5. Effect of particle size	1.22 < 3.89 (F^2_{12}) Not significant	9.8 > 3.89 (F^2_{12}) Significant	
6. Effect of compressure pressure	2.03 < 3.89 (F^2_{12}) Not significant	7.24 > 3.89 (F^2_{12}) Significant	

a) **Effect of pH.**

From figure 5.12 and table 5.4, the release rate of theophylline is seen to be higher in pHs 1.2 and 7.2 than in pH 4.5 and distilled water. In a separate study the "twice-daily" tablets were seen to swell at a faster rate in distilled water than in pHs 1.2 and 7.2. This could lead to faster development of viscous gel in distilled water and so slower diffusion of drug. Swelling study was however not conducted in pH 4.5 medium. The "twice-daily" tablets in contrast to the "once-daily" tablets contain lactose, therefore water penetration into the "twice-daily" tablets would not be delayed due to the pores created as a result of the leaching out of lactose as shown by the electron micrograph (figure 5.13). Consequently, the retardant effect of swelling on theophylline release will be rapid.

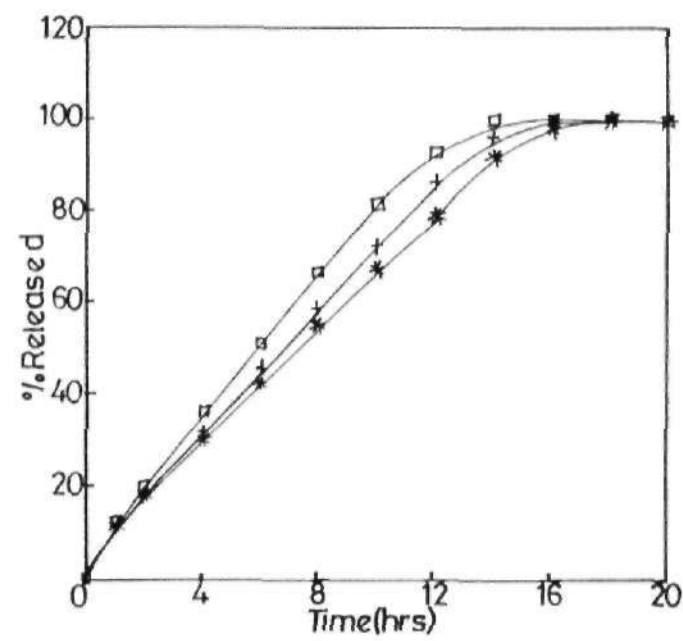


Figure 5.12: Effect of pH of dissolution media on theophylline release from "twice-daily" tablets by the paddle method at 100rpm and 37°C. Key: + = pH 1.2; ★ = pH 4.5; □ = pH 7.2.

(a)



(b)



Figure 5.13: Scanning electron micrograph of the surface of "twice-daily" tablets (a) before dissolution test (b) after 1 hour dissolution (2,500x0.65 enlargement).

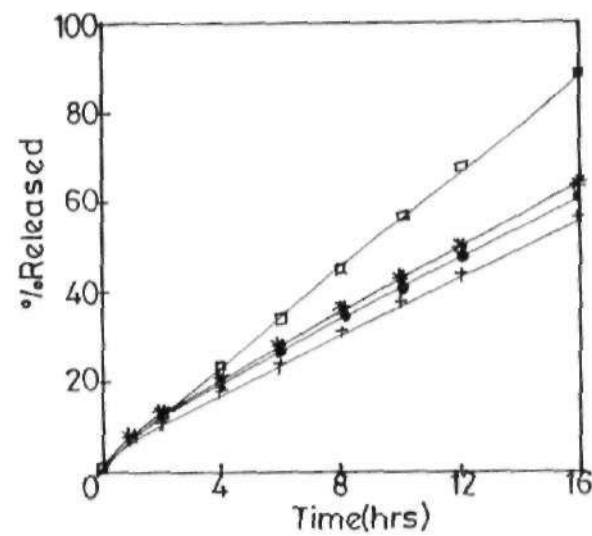


Figure 5.14: Effect of ionic strength of dissolution media on theophylline release from "twice-daily" tablets by the paddle method at 100rpm and 37°C. Key: ● = 0.1M NaCl; + = 0.2M NaCl; * = 0.3M NaCl; □ = D/water.

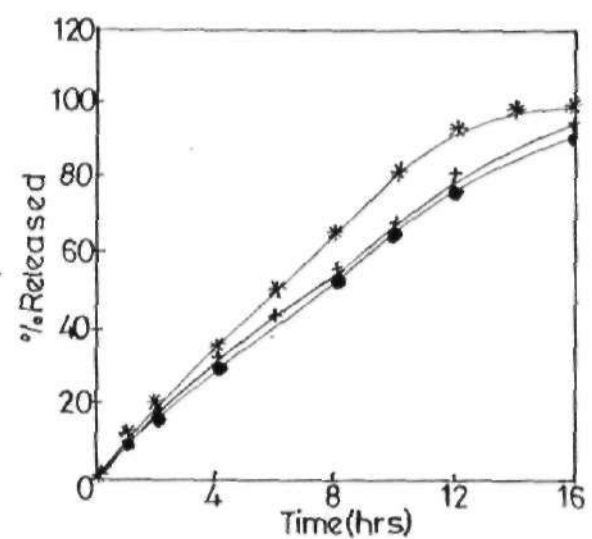


Figure 5.15: Effect of surfactant concentration in pH 7.2 dissolution media on theophylline release from "twice-daily" tablets by the paddle method at 100rpm and 37°C. Key: * = Without surfactant; ● = 0.1% w/v Tween 80; + = 1% w/v Tween 80.

The ANOVA results show a significant difference in release profiles when the three pHs studied are considered. However when considering the gastric and intestinal pHs alone, the calculated *t* - value

of 1.186 which is less than the tabulated t - value of 2.31 (at $\phi = 8$, $p = 0.05$) indicates no significant difference.

b) **Effect of ionic strength.**

Figure 5.14 shows the effect of ionic strength on theophylline release from the product, and the ANOVA table shows a no significant difference when 0.1M to 0.3M NaCl solutions are used as the dissolution media.

c) **Effect of surfactant.**

Table 5.5 shows that the difference in theophylline release is insignificant whether or not surfactant is present in the pH 7.2 medium used, and the release profiles are shown in figure 5.15.

The presence of water soluble lactose in the formulation would render the problem of matrix penetration by medium insignificant, whereas swelling could still be enhanced by the presence of surfactants as a result of improved wettability. The enhanced swelling in the presence of surfactants will slow down drug release due to faster formation of viscous barrier which resulted in slight decreases been observed when 0.1%w/v and 1%w/v Tween 80 solutions were used as compared to when no surfactant is added to the dissolution medium.

d) **Effect of rotation speed**

The 100rpm speed showed a big difference in theophylline release rate to those of 50rpm and 80rpm, the two of which were relatively similar in both gastric and intestinal pHs (figure 5.16).

The differences in release rates were seen to be very significant in both gastric and intestinal pHs as shown in table 5.5. An increase in agitation of the solvent medium will usually reduce the thickness of stagnant layer in the Fick's law equation of dissolution thus enhancing dissolution (Equation 6.1.). Also erosion of the matrix will be accelerated by higher agitation of the solvent medium.

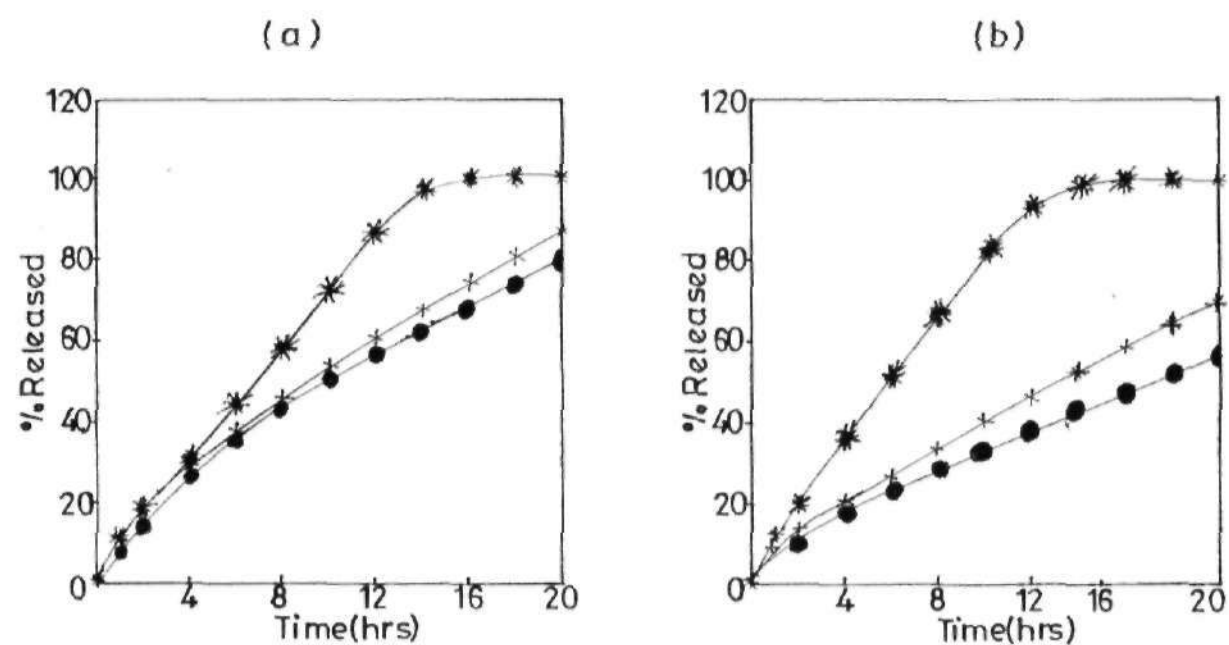


Figure 5.16: Effect of rotation speed on theophylline release from "twice-daily" formulation in (a) pH 1.2 (b) pH 7.2 by the paddle method at 100rpm and 37°C. Key: ● = 50rpm; + = 80rpm; * = 100rpm.

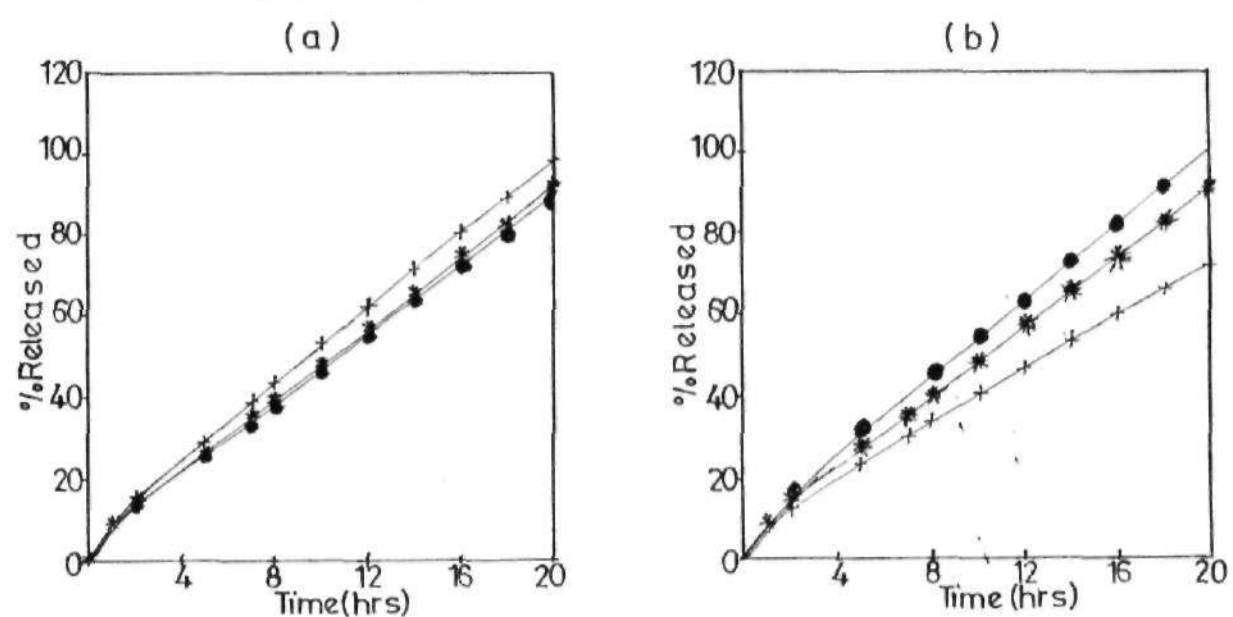


Figure 5.17: Effect of granule size used for compressing "twice-daily" tablets on theophylline release in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100rpm and 37°C. Key: ● = 180μm granules; + = 425μm granules; * = 710μm granules.

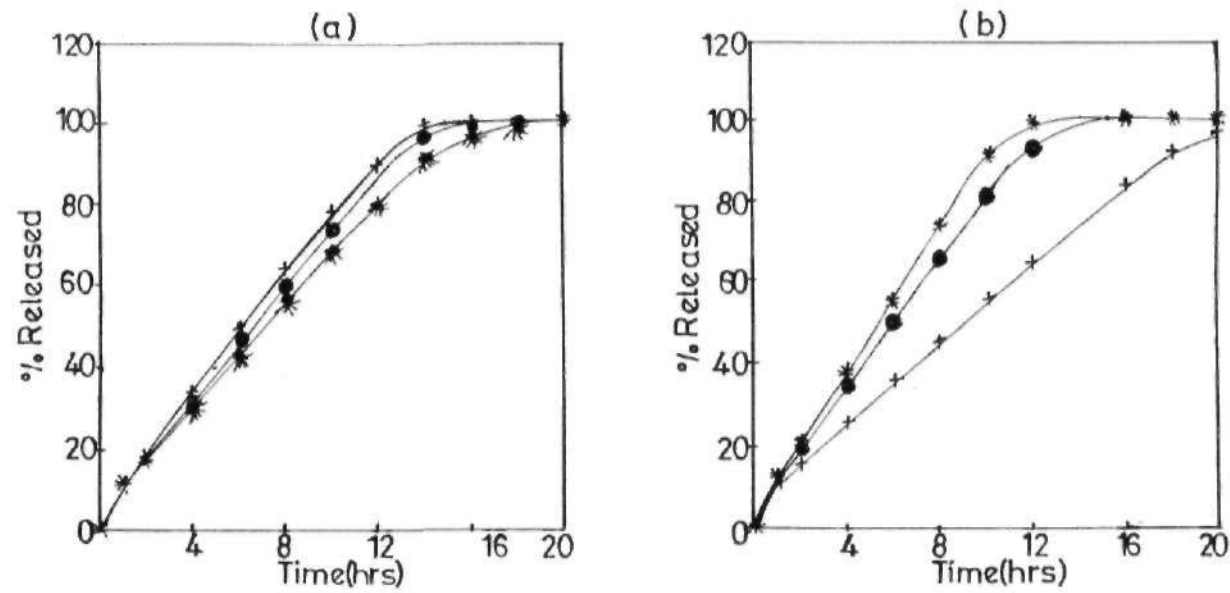


Figure 5.18: Effect of compression pressure on theophylline release from "twice-daily" formulation in (a) pH 1.2 (b) pH 7.2, by the paddle method at 100rpm and 37°C. Key: ● = 2 tons; + = 3 tons; * = 4 tons.

e) **Effect of particle size.**

Theophylline release from tablets prepared using granules of different sizes 180 μ m, 425 μ m, and 710 μ m, was studied (figure 5.17). The study showed a "no significant" difference for drug release in pH 1.2, but gave a significant difference in pH 7.2 (table 5.5). Finholt and Solvang (1968) reported opposing effects of particle size when different dissolving media were used for their phenacetin tablets. It thus appears that particle size has an unpredictable effect on drug release.

f) **Effect of compression pressure.**

A number of investigators have reported that the compression force used in manufacturing tablets affects the rate of dissolution (Higuchi *et al* 1953, Knoechel *et al* 1967, Kanke and Sekiguchi 1973). However, Iranloye and Parrott (1978) found that variation in compression force between 450 to 9,100kg produced no effect on the dissolution rates of aspirin and salicylic acid tablets. The effect of compression pressure on the "twice-daily" formulation of this study is shown in figure 5.18. Tablets

compressed at 3 tons showed a significant reduction in release rate in pH7.2, but apart from that exception, changes in compression force between 2 tons to 4 tons did not produce significant differences in release profiles (table 5.4). From the results, it can be seen that increase in compression pressure would yield a maximum in the release rate. This may mean that as compression force increases, the rate of polymer swelling is decreased resulting in faster release rate. After an optimum compression force, welding of the polymer surfaces may occur which will now reduce erosion and consequently reduce release rate.

g) **Simulated plasma theophylline levels of immediate release and "twice-daily" tablets.**

Figures 5.19 and 5.20 show the plasma theophylline levels of the immediate release and "twice-daily" tablets respectively. The pharmacokinetic output parameters (C_{max} , t_{max} and AUC) are summarised in table 5.6 for comparison of the two forms having the same theophylline contents.

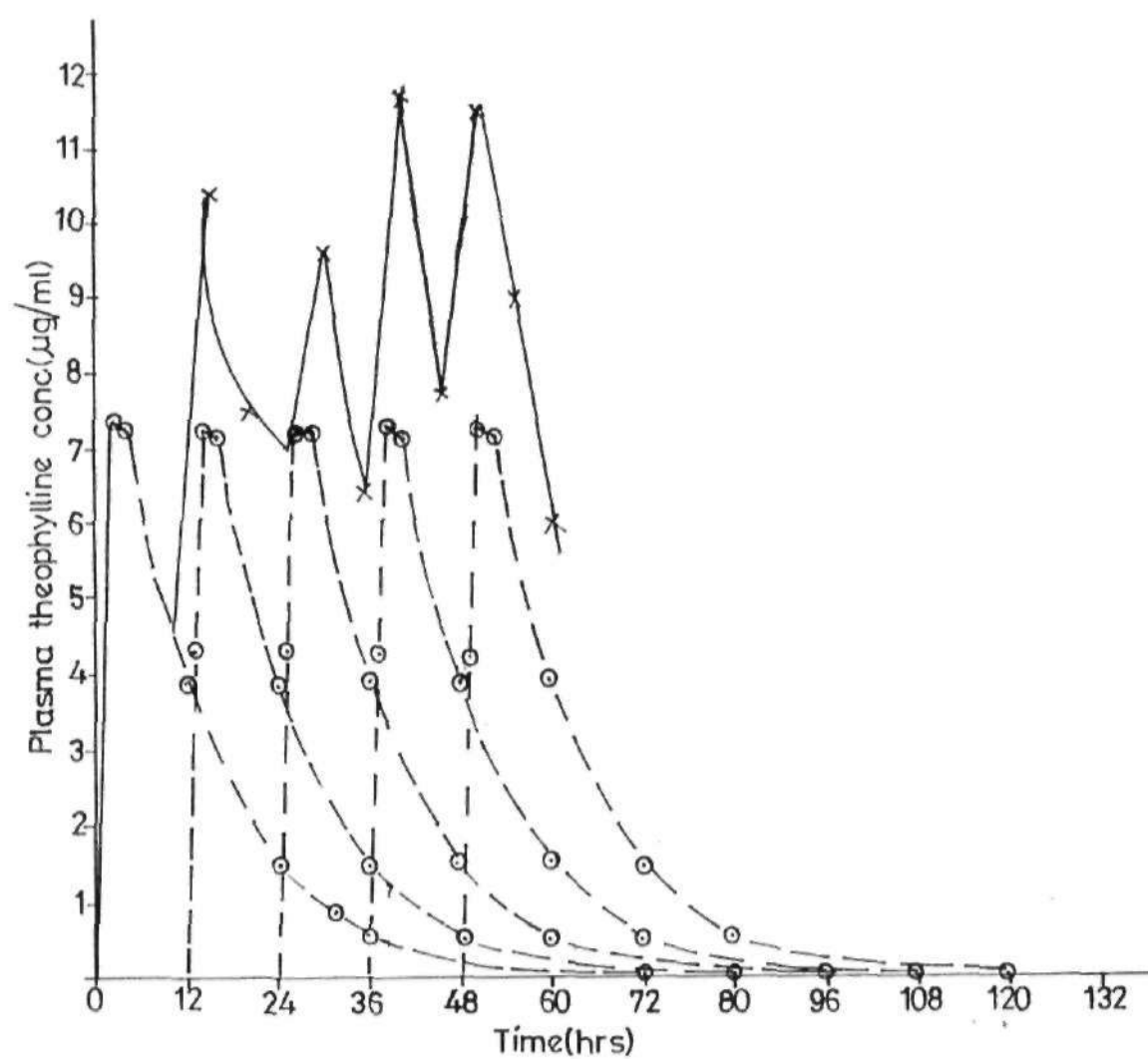


Figure 5.19: Computer simulation of plasma level curves of immediate release theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100rpm and 37°C. Key: ○ = Single dose components; x = Total plasma level curve.

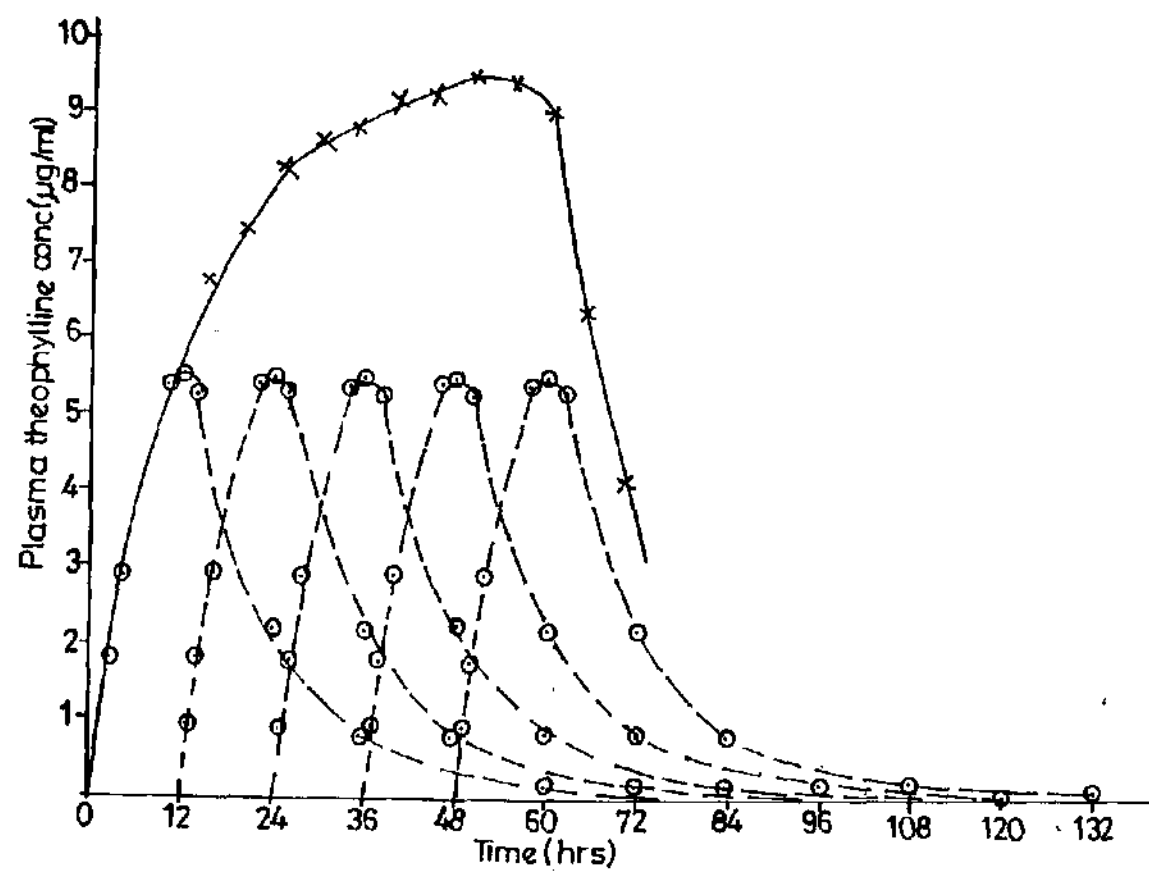


Figure 5.20: Computer simulation of plasma level curves of "twice-daily" theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100 rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

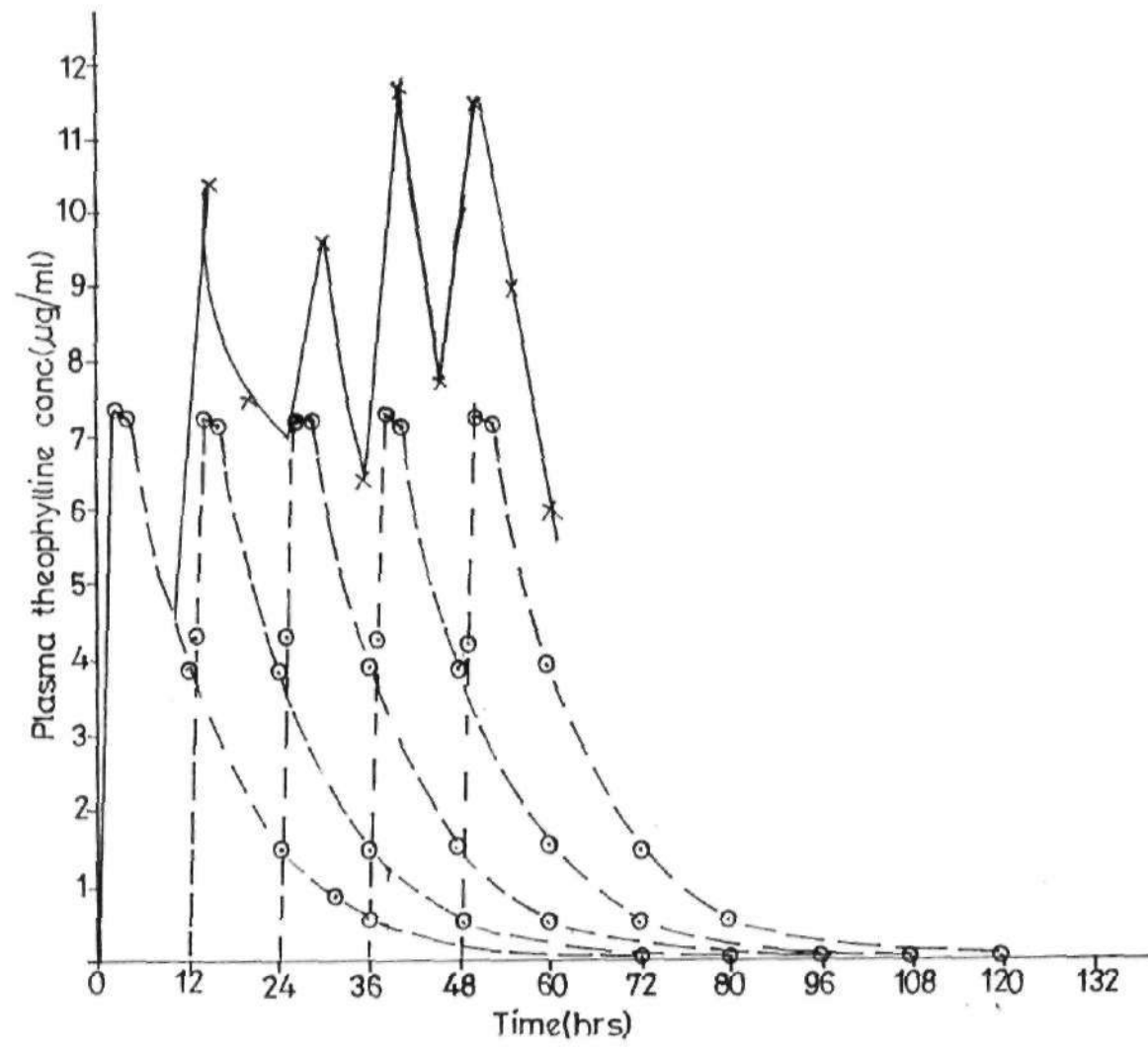


Figure 5.19: Computer simulation of plasma level curves of immediate release theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100rpm and 37°C. Key: $\circ$ = Single dose components; x = Total plasma level curve.

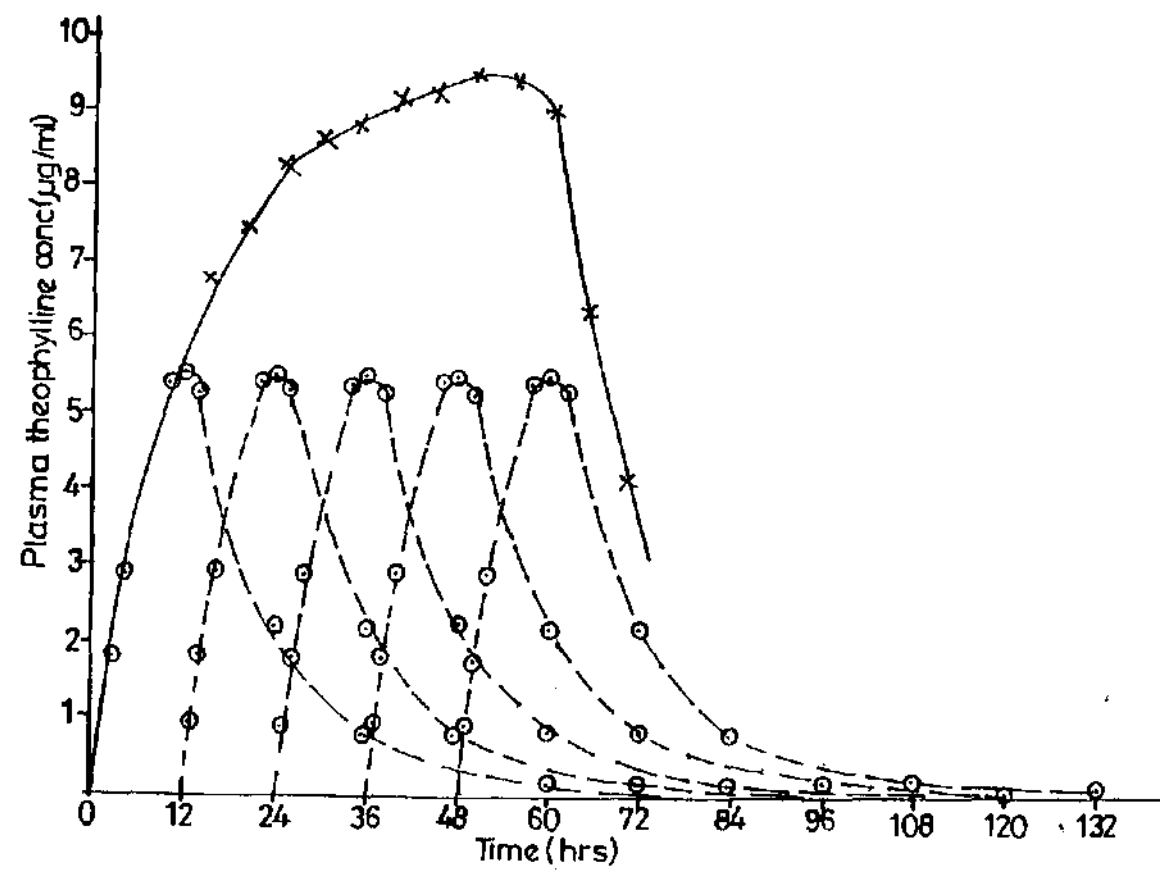


Figure 5.20: Computer simulation of plasma level curves of "twice-daily" theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100 rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

Table 5.6: **Simulated pharmacokinetic output parameters of immediate release and "twice-daily" theophylline matrix tablets.**

(a) **In pH1.2 dissolution medium.**

Formulation	Simulated output parameters:		
	C _{max} (µg/ml)	t _{max} (hrs)	AUC 12 (µgh/ml)
Immediate release tablet	7.4	2	109
"Twice-daily"Tablets	5.4	14	116

(b) **In pH 7.2 dissolution medium**

Formulation	Simulated output parameters:		
	C _{max} (µg/ml)	t _{max} (hrs)	AUC 12 (µgh/ml)
Immediate release tablets	7.3	2	113
"Twice - daily" tablets	5.5	12	116

It is clear from the output parameters that the "twice-daily" sustained - release product has demonstrated reduced C_{max} and a much longer t_{max} than the immediate release product of same theophylline content. Also the AUCs of both are quite similar especially in the intestinal pH studies. It may be concluded that the sustained - release product has performed satisfactorily devoid of "dose dumping" . Also the sustained-release product gave a near perfect plateau when the total plasma level curve for 5 multiple doses was simulated (figure 5.20) consequently side effects will be minimised as spike levels are absent. However an initial titrated immediate release dose (D_i) would be needed to achieve therapeutic theophylline plasma levels of 10-20µg/ml (Shargel and Yu, 1993), followed by the sustained - release product for maintenance of plasma level.

5.3.3: Comparison Of CPP Formulated And Some Commercially Approved "Once-Daily" Theophylline Tablets.

Benedikt *et al* (1988) performed in-vitro release studies of some theophylline "once-daily" products in the market along side their micro-osmotic Euphylong® pellets. Their pH 7.2 dissolution data obtained under similar conditions as those for the CPP "once-daily" product (i.e. obtained with the U.S.P paddle dissolution apparatus at 100rpm and 37° C) was used in simulating the plasma level of these commercially approved products hereby referred to as reference products A, B1, B2 and C. The simulated plasma levels of the reference products were then used for comparison to the simulated plasma theophylline profile of the CPP product.

The present study could not carry out dissolution tests on the commercial products due again to the authors' limited period of stay at Kings' College London. The use of Benedikt *et al's* data could however give an insight into the comparative performance of the formulated CPP product.

The simulated plasma profiles of 5 doses for the different products are shown in figures 5.8 and 5.21 - 5.24 while the pharmacokinetic output parameters are given in table 5.7 below:

Table 5.7: Pharmacokinetic parameters for the reference and CPP formulated products.

Product	Theophylline content (mg)	t _{max} (hrs)	C _{max} (µg/ml)	AUC (µgh/ml)
CPP product (22 hr., Release form)	2x361.5	22	7.7	228
Reference A	400	15	2.4	56
" B1	200	5	4.4	67
" B2	300	5	6.5	100
" C	800	10	14.3	256

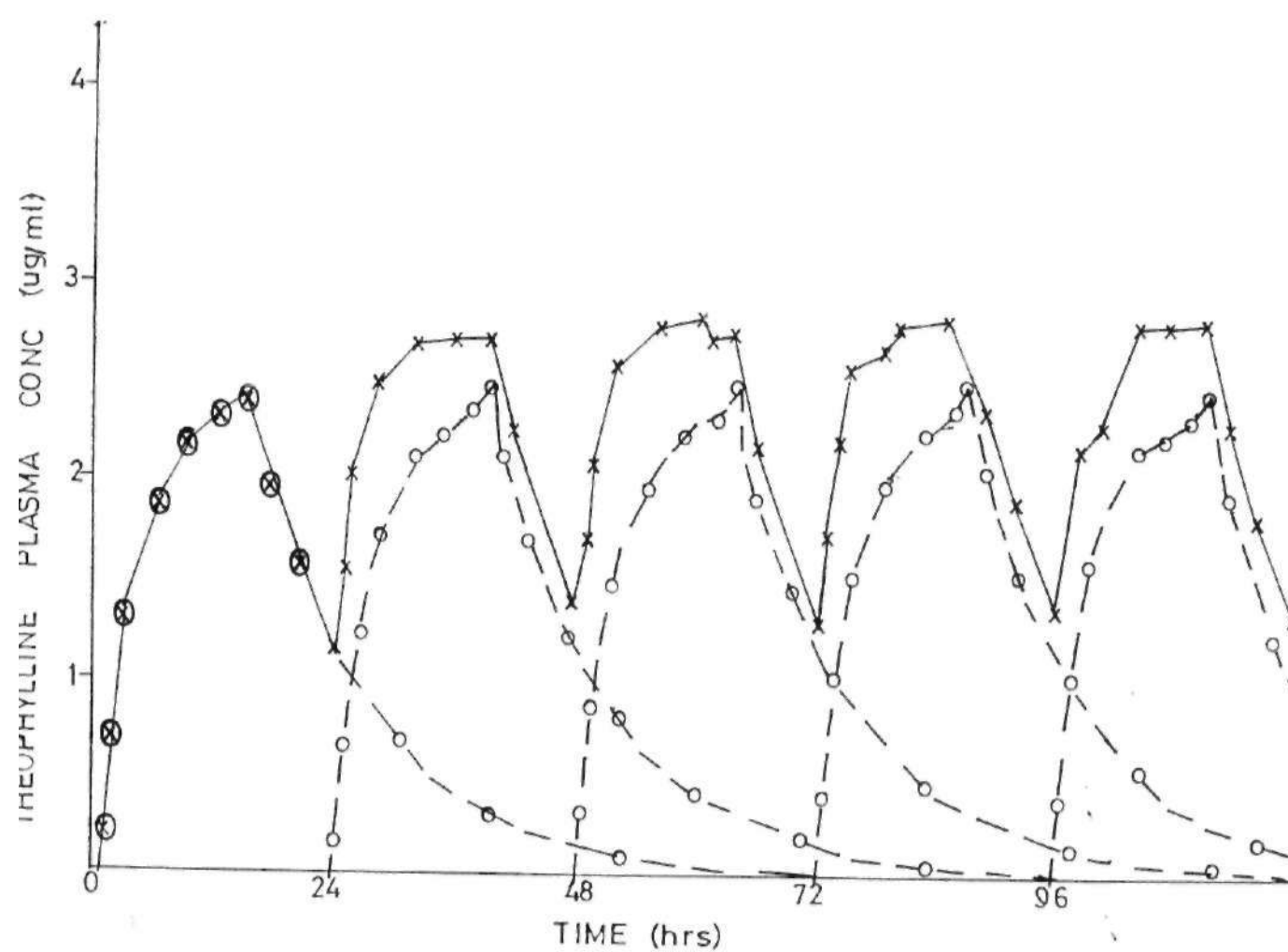


Figure 5.21: Computer simulation of plasma level curves of reference product A theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100 rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

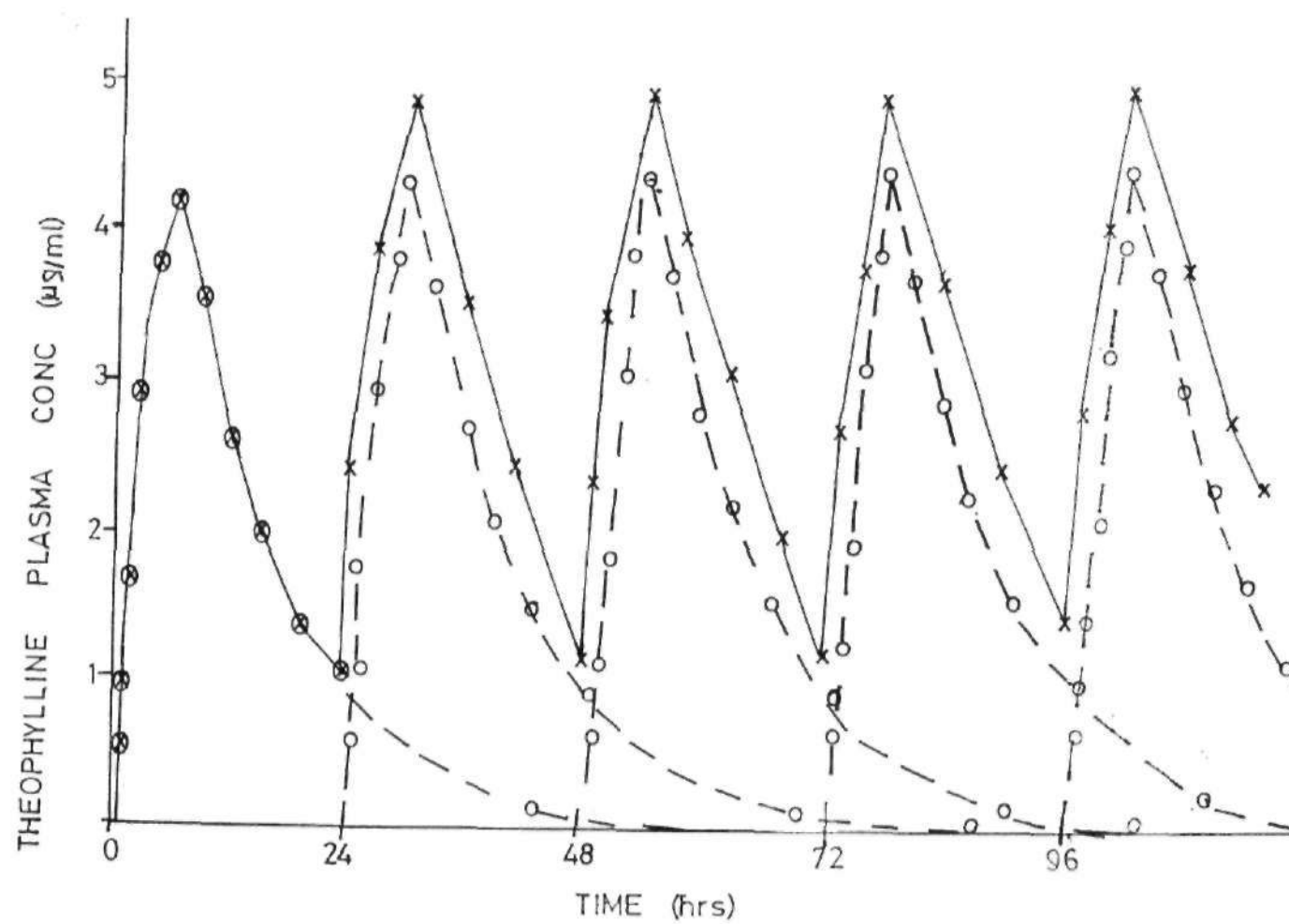


Figure 5.22: Computer simulation of plasma level curves of reference product B1 theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100 rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

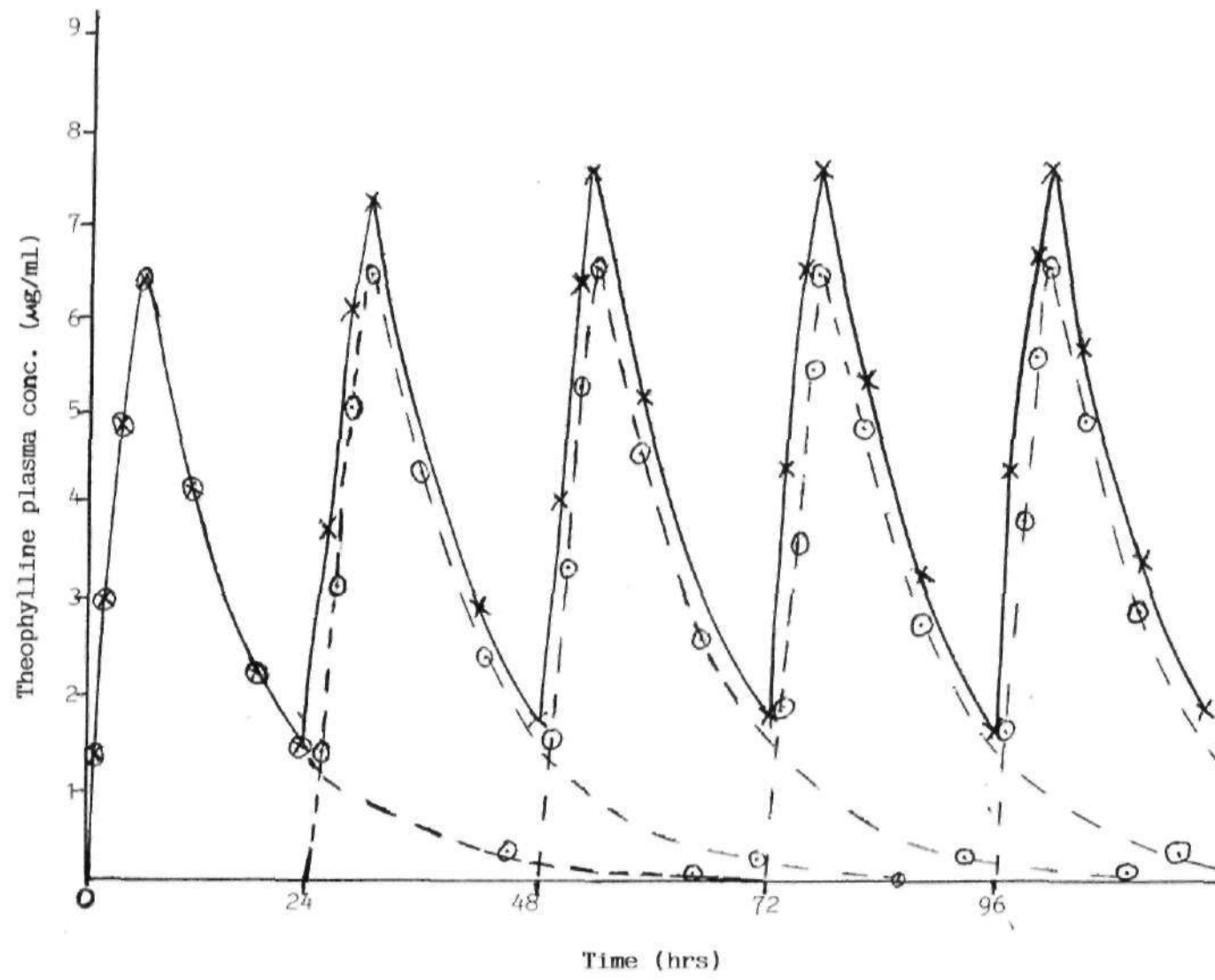


Figure 5.23: Computer simulation of plasma level curves of reference product B2 theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100 rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

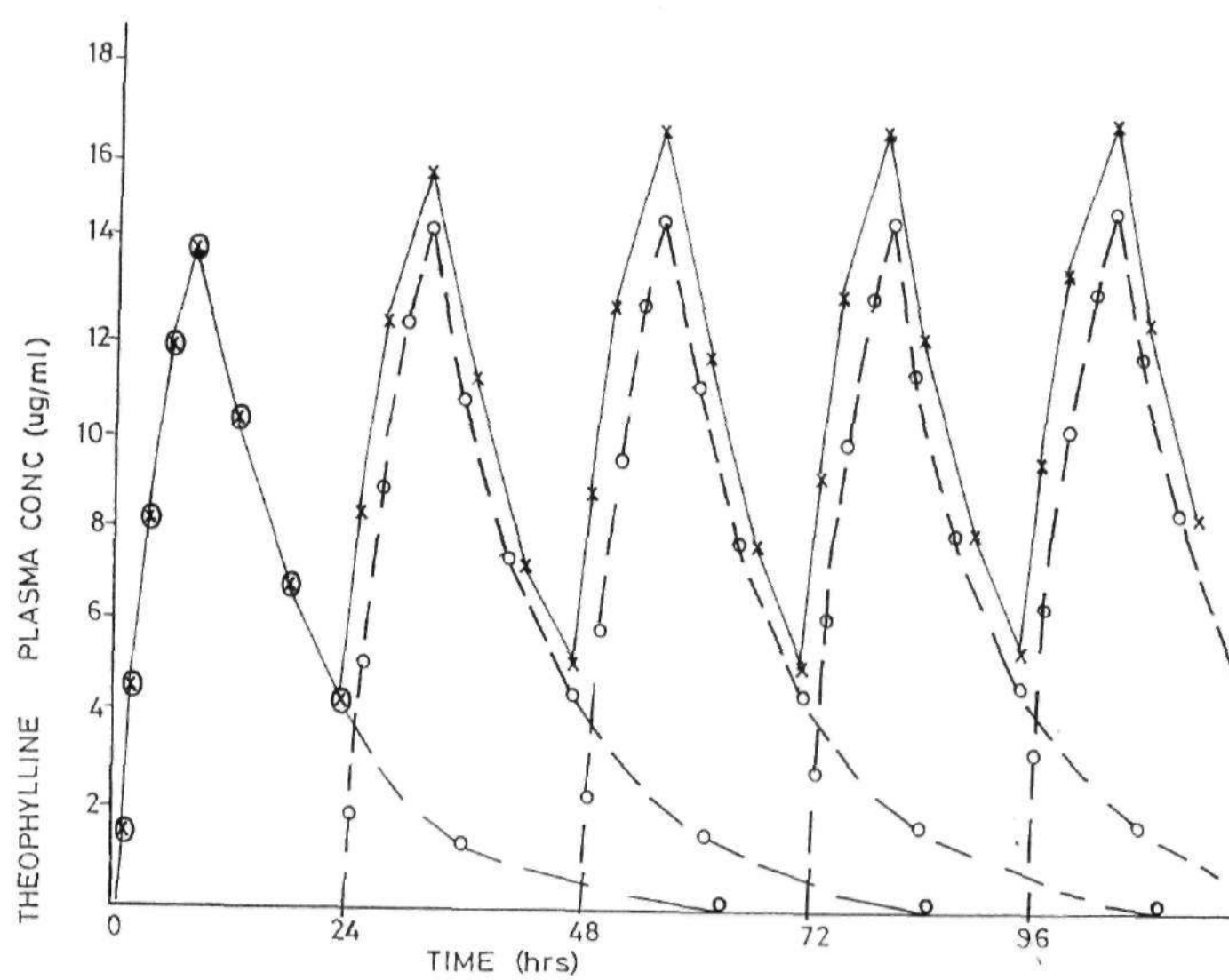


Figure 5.24: Computer simulation of plasma level curves of reference product C theophylline tablets using pH 7.2 dissolution data obtained by the paddle method at 100 rpm and 37°C. Key: O = Single dose components; x = Total plasma level curve.

According to Shargel and Yu (1993), the t_{max} , C_{max} and AUC conveniently show how successful a sustained-release product performs in-vivo. For example a product with a t_{max} of 3 hours would not be very satisfactory if the product is intended to last 12 hours. Similarly, if the C_{max} is excessively high, it would be a sign of "dose dumping" due to inadequate formulation according to the authors.

a) **Comparison of t_{max} .**

Table 5.7 shows that reference products B1, B2 and C have t_{max} of 5-10 hours each. These products might not be very satisfactory for a 24 hour dosage regimen. Reference product A and the CPP product having t_{max} values of 15 and 22 hours respectively might be more satisfactory.

b) **Comparison of C_{max} .**

With the exception of reference product C, none of the products been compared attained the therapeutic plasma level of 10-20 μ g/ml as shown by the C_{max} in table 5.7. Reference products A,B1,B2 and the CPP product would therefore each require an initial titrated dose of an immediate release product to raise the plasma theophylline levels to therapeutic levels. However, care must be taken to avoid intoxication.

c) **Peak-trough variation.**

Figures 5.9 and 5.21-5.24 show the peak-trough variations for the products. Reference products B1,B2 and C show "spike" plasma patterns with high peak-trough variations of 4-11 μ g/ml over about 20 hours. Reference product A shows less peak-trough variation of 1.5 μ g/ml over about 15 hours and attained the desired plateau in the plasma theophylline level lasting about 10 hours. The CPP product showed the least peak-trough variations averaging 0.8-1.0 μ g/ml for periods of about 10 hours, and showed more uniform optimum plasma level. The CPP product would therefore give less side effects as compared to the reference products due to less variation in peak-trough concentrations. Also

because of the minimal peak-trough variation, it would be possible to raise the trough plasma level to therapeutic levels with an immediate-release dose without raising the peak concentration to very high concentrations. Thus with the CPP product it would be possible to eliminate patient unprotection periods by making the peak and trough concentrations to fall within the 10-20 µg/ml therapeutic level. With reference product C having peak - trough variation of 11 µg/ml, raising the trough concentration to 10 µg/ml, will push the peak concentration to about 21 µg/ml which exceeds the therapeutic range.

From the comparison of t_{max} , C_{max} , peak-trough variations and figures 5.9 and 5.21 - 5.24 the CPP product would appear to be more suitable for "once-daily" dosing and would give less side effects with elimination of periods of unprotection of asthmatic patients more efficiently than the commercially approved reference products used in this study.

CHAPTER SIX

CHAPTER SIX

**THE CONTRIBUTIONS OF EROSION, SWELLING AND POROSITY TO
THEOPHYLLINE RELEASE FROM CPP MATRICES**

6.1: INTRODUCTION

The diffusional release of a dispersed or dissolved drug from a polymeric matrix generally involves the presence of a moving diffusional front separating the undissolved core and the partially extracted region. In the case of an erodible or swellable polymer matrix, the release kinetics is further complicated by the presence of a second moving boundary namely the eroding or swelling polymer front (Lee, 1981). For the release of a dispersed drug from an erodible polymer matrix, Hopfenberg (1976) treated the case of no diffusional contribution, whereas Baker and Lonsdale (1976) presented a brief pseudosteady state analysis of the more general system including diffusional contribution. For drug release from a swellable polymeric matrix, Peppas *et al* (1980) recently presented theoretical and experimental results taking into account the counter current diffusion of solvent. However, a steady state assumption was also made in the treatment. According to the authors, this is valid only when the drug loading is in great excess of the drug solubility.

Ganderton (1984) has reported that matrix devices may behave in one of three ways. In the simplest and most predictable, the matrix is inert and the release rate is defined by a pore structure created by leaching the soluble drug with if necessary soluble carriers. The release rate is theoretically proportional to the square root of time. Other matrix devices simply erode in the g.i.t. with the release rate declining as the surface area is reduced. Also the polymer may swell after ingestion with an increase in permeability of the matrix which offsets the effect of depletion and the larger diffusional distances which the drug must cross as the product becomes exhausted. The present study was conducted to evaluate the contributions of erosion, swelling and porosity to theophylline release from

CPP matrices. Each of these contributing factors was chosen at "low" and "high" levels. The release patterns of theophylline from the matrices were then studied under the different factor combinations as given by a simple 2ⁿ factorial experimental design.

6.2: EXPERIMENTAL.

6.2.1: Matrix formulations used in study and factor Combinations.

a) "High" porosity tablets (F 6.1):

Theophylline----- 362.00mg (55.26%)

CPP----- 127.03mg (19.39%)

Lactose----- 165.38mg (25.25%)

Magnesium Stearate----- 0.66mg (0.10%)

Tablet weight = 655.07mg

Compression pressure = 2tons

b) "Low" Porosity tablets (F 6.2):

Theophylline----- 362.00mg (80.51%)

CPP----- 87.18mg (19.39%)

Magnesium Stearate----- 0.45mg (0.10%)

Tablet weight = 449.63mg

Compression Pressure = 2 tons

c) Factor levels and combinations

Figures 6.1 and 6.2 show the conditions for "low" and "high" levels of erosion and swelling, while "low" and "high" porosity are given by the formulations. The factor levels are thus given as follows:

Low erosion (a)----- 50rpm

High erosion (A)----- 100rpm

Low swelling (b)----- pH 7.2 dissolution medium

High swelling (B)----- Distilled water medium

Low Porosity (c)----- 0% lactose content (F6.2)

High Porosity (C)----- 25% lactose content.(F6.1)

The following eight factor combinations were used for the study: abc, Abc, aBc, abC, ABc,AbC,aBC and ABC.

6.2.2: **Determination of theophylline release, matrix erosion and swelling:** The methods described in chapter 2 were used.

6.3: **RESULTS AND DISCUSSIONS.**

6.3.1:**Responses from Different Factor Combinations:**

The responses of release rate and linearity as given by the slopes and correlation coefficients respectively of the zero-order plots are given as follows:

Table 6.1: **Responses from different factor combinations at Non Steady State (Entire release profile)**

S/NO	Combination	Release rate (% min ⁻¹)	Corr.coeff.
1	abc	0.0515	0.9874
2	Abc	0.0586	0.9882
3	aBc	0.0403	0.9962
4	abC	0.0578	0.9821
5	ABc	0.0849	0.9997
6	AbC	0.1339	0.9973
7	aBC	0.0539	0.9989
8	ABC	0.0769	0.9995

Table 6.2: **Responses from different factor combinations from Steady State Phase (Linear Portion)**

S/NO	Combination	Release rate (% min ⁻¹)	Corr.Coeff.
1	abc	0.0411	0.9994
2	Abc	0.0468	0.9999
3	aBc	0.0362	1.0000
4	abC	0.0450	1.0000
5	ABc	0.0830	0.9999
6	AbC	0.1260	0.9999
7	aBC	0.0511	0.9999
8	ABC	0.0752	0.9997

6.3.2: **Determination of the Effect of each Factor:** The effect of each factor is determined by averaging together the responses of all the combinations in which that factor occurs at "high" level and subtracting the average of responses resulting from all combinations in which the factor occurs at "low" level. The significance of such effects is then determined by a t-test:

$$t = \frac{\text{difference to be tested (d)}}{\text{standard error of difference (sd)}} \quad \text{-----Equation 6.1}$$

$$\text{Where } S_d = \sqrt{\left(\frac{S_1^2}{n_1}\right) + \left(\frac{S_2^2}{n_2}\right)} \quad \text{.....Equation 6.2}$$

$$d = (\bar{X}_1 - \bar{X}_2) \quad \text{..... Equation 6.3}$$

All symbols have their usual meanings. The calculated t-value is then compared with the tabulated t-value at $\phi = (n_1 + n_2 - 2) = 6$ and $P = 5\%$, given as 2.45 in statistical tables.

a) **Effect of erosion (a,A)**

$$1/4 ((Abc + AbC + ABc + ABC) - (abc + aBc + abC + aBC))$$

b) **Effect of swelling (b,B)**

$$1/4 ((aBc + ABC + aBC + ABc - (abc + Abc + abC + AbC))$$

c) **Effect of Porosity (c,C)**

$$1/4 ((abC + AbC + aBC + ABC) - (abc + Abc + aBc + Abc)).$$

The effects are summarised below as follows:

Table 6.3: **Effect of Factors using Non steady state condition**

Factor	Effect on:		Calculated t - value for:	
	Release rate (% min ⁻¹)	Corr. Coeff.	Release rate (% min ⁻¹)	Corr. Coeff.
Erosion (a,A)	0.0378	0.005	2.6	1.2253
Swelling (b,B)	-0.0115	0.0098	0.599	3.493
Porosity (c,C)	0.0218	0.0016	1.198	0.3534

Critical t-value (at $\phi = 6$ and $P = 5\%$) = 2.45.

Table 6.4: **Effect of factors using steady state phase.**

Factor	Effect on:		Calculated t - value for:	
	Release rate (% min ⁻¹)	Corr. Coeff.	Release rate (% min ⁻¹)	Corr. Coeff.
Erosion (a,A)	0.0394	0.00003	2.7266	0.1517
Swelling (b,B)	-0.0034	0.00008	0.1675	0.6202
Porosity (c,C)	0.0226	0.00008	1.2226	0.6137

Critical t - value (at $\phi = 6$ and $p = 5\%$) = 2.45

6.3.3: **Determination of Interactions Between Factors:** When determining whether there are any first order interactions between any two factors, the four combinations are chosen in which the two factors both occur at either "high" or "low" levels together and averaged. The remaining four

combinations are averaged and subtracted from the previous average. If there is no interaction, the difference between the means is zero, if however the difference is significantly different from zero, then interaction is indicated. Negative interaction values indicate opposing effects of the factors.

a) **Interaction between erosion and swelling (A & B)**

$$1/4 ((abc + abC + ABc + ABC) - (Abc + aBc + AbC + aBC))$$

b) **Interaction between swelling and Porosity (B & C)**

$$1/4 ((abc + Abc + aBC + ABC) - (aBc + abC + AbC + ABc))$$

c) **Interaction between erosion and Porosity (A & C)**

$$1/4 ((abc + aBc + AbC + ABC) - (Abc + abC + ABc + aBC))$$

These differences between means were statistically tested using equations 6.1 - 6.3 and the results are summarised as follows:-

Table 6.5: **Effect of interactions between factors using non steady state condition**

Interaction	Difference being tested:		Calculated t - value for:	
	Release Rate (% min ⁻¹)	Corr.Coeff.	Release rate (% min ⁻¹)	Corr. Coeff.
Erosion and swelling	-0.0039	-0.003	-0.202	0.6897
Swelling and porosity	-0.019	-0.0003	-1.056	0.0671
Erosion and Porosity	0.0119	0.0029	0.62	0.6654

Critical t - value (at $\phi = 6$ and $p = 5\%$) = 2.45

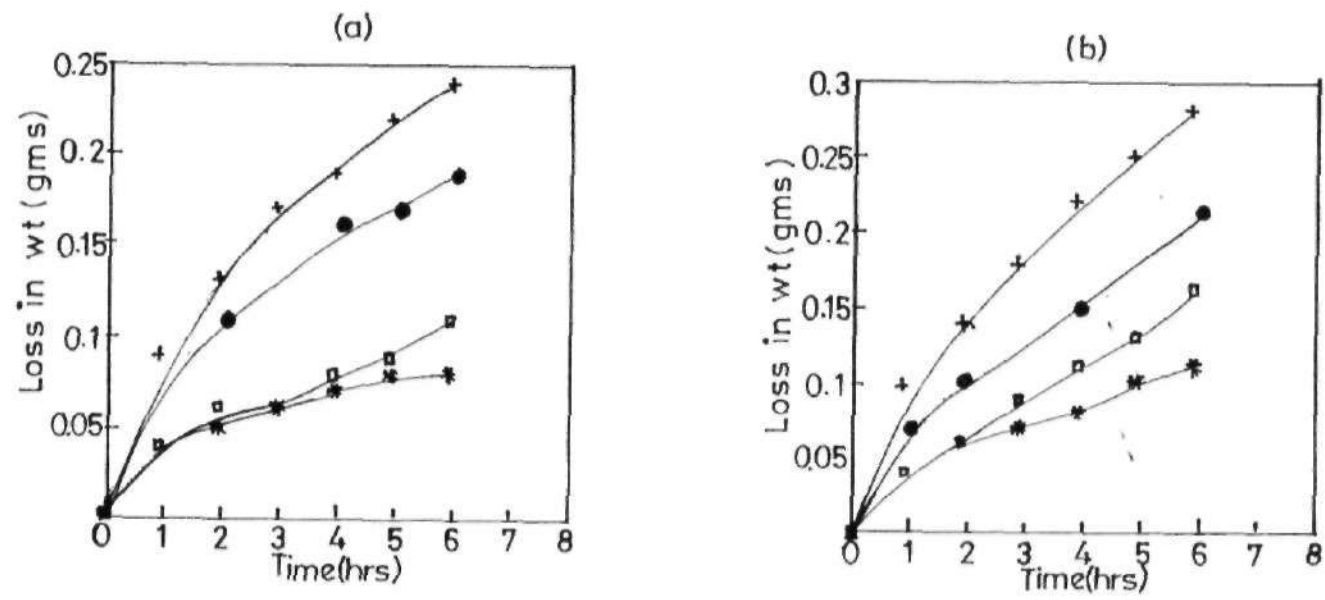


Figure 6.1: Loss in weight in tablets as a result of erosion with time at (a) 50rpm (b) 100rpm showing the conditions for "low" and "high" erosion using the paddle method at 37°C. Key: + = F6.1 in D/water; ● = F6.1 in pH 7.2 medium; □ = F6.2 in D/water; ★ = F6.2 in pH 7.2 medium.

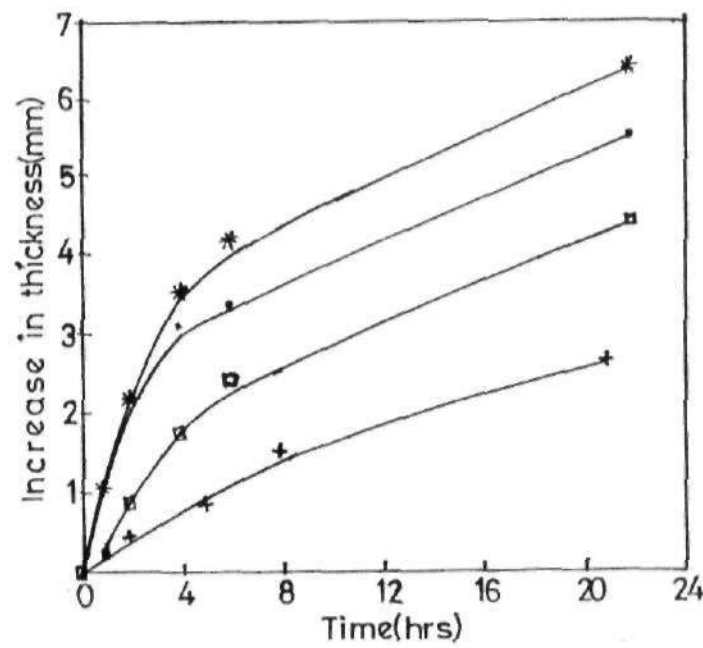


Figure 6.2: Increase in tablet thickness with time as a function of immersion medium showing the conditions for "high" and "low" swelling intensities. Key: ● = F6.1 in D/water; + = F6.1 in pH 7.2 medium; ★ = F6.2 in D/water; □ = F6.2 in pH 7.2 medium.

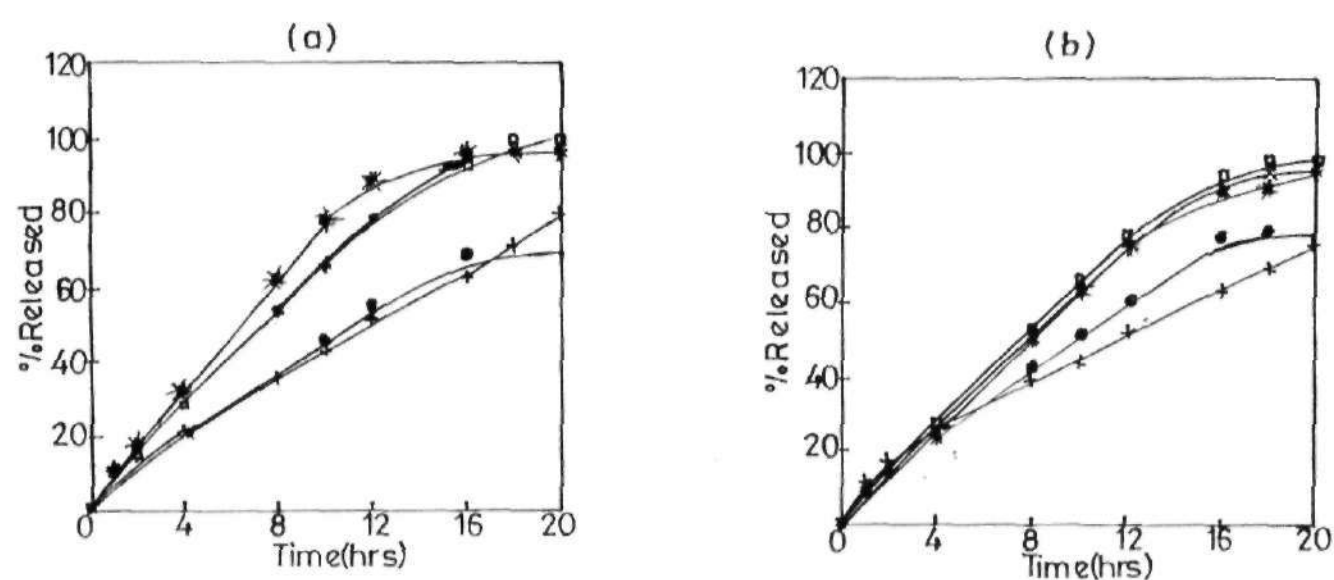


Figure 6.3: Effect of porosity due to presence of soluble additives on theophylline release in (a) pH 1.2 (b) pH 7.2 using the paddle method at 100rpm and 37°C. Key: ● = Without soluble additive; + = With 9% lactose; ★ = With 33% lactose; □ = With 10% Povidone; x = With 15% Povidone.

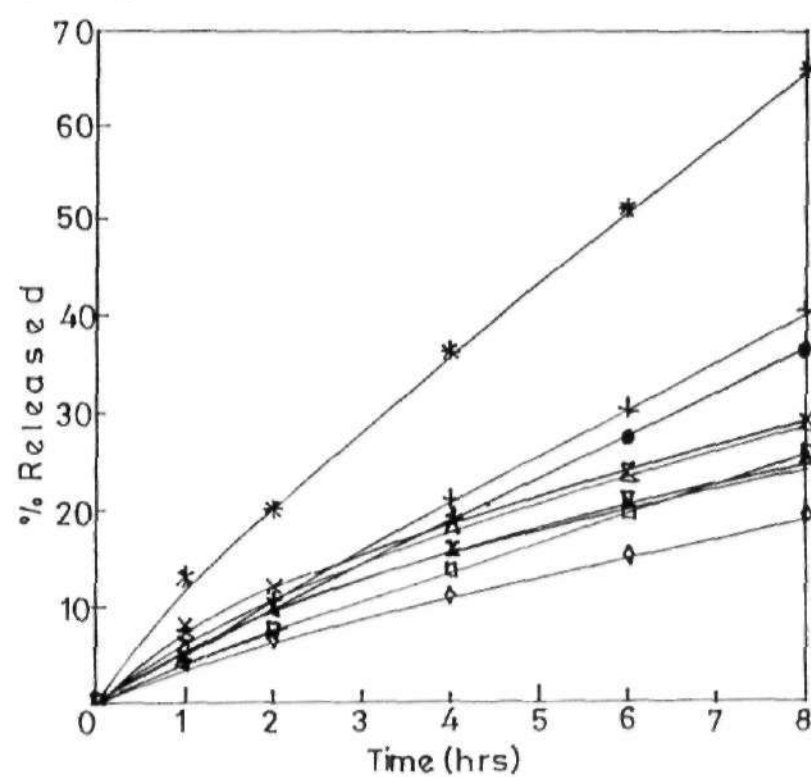


Figure 6.4: Theophylline release under the different factor combinations of a 2³ factorial design experiment using the paddle method at 37°C. Key: ● = ABC; + = ABc; ★ = AbC; □ = aBC; x = abC; ◇ = aBc; △ = Abc; ▽ = abc.

Table 6.6: **Effect of interactions between factors using steady state phase.**

Interaction	Difference being tested:		Calculated t - value for:	
	Release rate (% min ⁻¹)	Corr. Coeff.	Release rate (% min ⁻¹)	Corr. Coeff.
Erosion and Swelling	-0.0040	-0.00018	0.1958	1.5437
Swelling and Porosity	-0.019	-0.00023	1.0048	2.095
Erosion and Porosity	0.0132	-0.00018	0.6737	1.5437

Critical t-value (at $\infty = 6$ and $P = 5\%$) = 2.45.

Figures 6.1-6.3 show the conditions for "low" and "high" erosion, swelling and porosity respectively, while figure 6.4 shows the release profiles from the 8 different factor combinations. The statistical treatments of both the non steady state and the steady state phase of the release profiles show that increase in both erosion and porosity increase theophylline release while increasing swelling rate from "low" to "high" levels decreases theophylline release (tables 6.3 and 6.4). From table 6.3, it can be seen that using the entire curve i.e. non steady state, erosion and swelling showed significant effects on release rate and linearity respectively. While using the steady state phase, showed that only erosion had a significant effect on release rate. It thus appears that the non steady state treatment is more sensitive and might give a better picture of the contributions of the factors to theophylline release from the matrices.

Drug release from surface erodible matrices having constant geometry will be zero-order (Lee, 1981). According to this author, this is because the eroding front moves at a constant velocity in the same direction of the diffusion front. Lee showed in his studies that as the erosion process dominates the diffusion process, almost total zero-order release results. The eroding front may have been moving at a different rate to the diffusion front in CPP matrices and consequently erosion did not contribute to linearity directly. Wan *et al* (1990) used hydroxypropylmethylcellulose (HPMC) to show the

influence of matrix swelling and polymer dissolution on drug release. In contact with an aqueous environment, the HPMC matrix hydrates, a viscous gel layer forms and this controls drug release via two mechanisms: diffusion through the gel and erosion of the gel barrier. It thus appears that in our CPP matrix, swelling is the major contributor to linearity probably by exerting some control on diffusion and allowing erosion to dominate resulting in zero-order release as reported by Lee (1981).

In the interaction studies, both the non steady state and steady state conditions gave t-values less than the tabulated critical t-value of 2.45 in all the interaction analysis, indicating that non of the interactions was significant and the factors would thus be acting independently. Increasing the porosity of matrix by increasing lactose content may merely improve the initial penetrability of dissolving media, but may not necessarily increase the subsequent rate of diffusion of dissolved drug from the core, since pores will get blocked as swelling progresses. In such a case, a possible interaction between swelling and diffusion will not result in interaction between swelling and porosity. That is to say porosity is not synonymous with diffusion in this case. Similarly the dominance of erosion as a result of reduced diffusion caused by swelling could be an additive effect and not an interaction.

Higuchi (1963) reported that a number of factors may come into play which may modify the total drug release behaviour. According to the author, drug release from sustained-release systems may be complicated by (a) simultaneous break-up of the matrix (b) partial dissolution of the matrix substances (c) one fraction of the dose being in a matrix form and the remainder of the dose being in a different non-matrix and readily available form, and (d) drug on the surface being released more rapidly than drug in the matrix. These complications add to the processes of diffusion through and from an enveloping homogenous matrix and leaching of the medicament by the bathing fluid which is able to enter the drug matrix phase through pores. In drawing up a drug release model from CPP

matrices all these factors must be taken into account for deriving equations that will enable the prediction of drug release rates and amounts from the CPP matrices.

CONCLUSIONS

CONCLUSIONS.

1. This study, most likely the first detailed report of such on this novel polymer has shown that Cissus populnea polymer (CPP) is a very suitable controlled - release matrix former. The study showed that CPP gave a better prolongation and better linearity of drug release than other polymers/excipients used in the study. The prolongation and improvement of linearity in drug release is however not very efficient for every soluble drugs like potassium chloride.
2. Controlled-release theophylline tablets formulated with CPP have a good chance of withstanding the variations of the g.i.t that may prevail in patients, since the release profile is hardly affected by changes in pH, ionic strength, rotation speed, surfactant etc as shown by ANOVA. The "once-and twice-daily" theophylline tablets should perform satisfactorily in-vivo with minimal peak-trough variation in plasma drug levels as shown by the computer simulated pharmacokinetic parameters of C_{max}, t_{max} and AUC. They would therefore minimise toxic effects and also improve patient compliance as efficient "once-and twice-daily" dosing are feasible.
3. The mechanism of theophylline release from CPP matrices is mainly by erosion of the matrices, while swelling is responsible for imparting linearity to the release curve resulting in zero-order kinetics for most of the study conditions as given by the correlation coefficients for the various release models. Other factors that are important in theophylline release from the formulations include granulation and magnesium stearate concentration which were seen to also influence the thermal properties of theophylline-CPP mixtures.

4. Controlled-release theophylline tablets formulated with CPP are stable under room storage conditions but are affected by elevated conditions of temperature and humidity. They must therefore be stored in cool dry places.
5. CPP satisfies the microbial standards given by B.P. 1973 in terms of the absence of specific pathogenic organisms. Although the total viable count is within the permitted level for pharmaceutical raw materials of plant origin, efforts must be made to bring down the count that would guarantee finished products of high microbial quality.
6. CPP can therefore be a very useful novel polymer in the formulation of controlled-release matrices, and may prove to be a suitable substitute for many of the presently used hydrocolloid polymers that are more adversely affected by one or more variables of the g.i.t. The "once-daily" theophylline tablets formulated with CPP appear to be more satisfactory than the commercially approved products studied.

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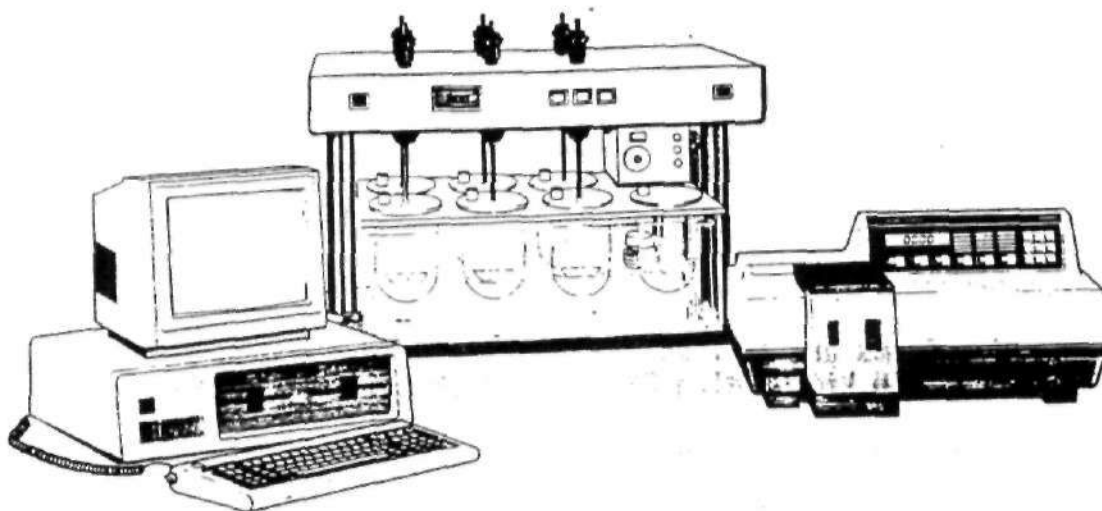
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APPENDIXES

INTRODUCTION

The PU8605/60 Tablet Dissolution Monitoring System comprises a Philips or IBM computer, a PU8620 series UV/VIS/NIR Spectrophotometer, a PU8605/50 Eight Cell Programmer and the PU8605/60 Tablet Dissolution System software program contained on flexible (floppy) disks. Fig 3.1 illustrates a typical system.

The picture shows a Dissolution Bath, this is for illustration purposes only. The dissolution bath and pump are not supplied by Philips Analytical. The choice of bath and pump is left entirely with the customer. The installation instructions in this manual refer to a typical dissolution bath. Refer to the handbook accompanying any Dissolution Bath and Pump for detailed instructions on their installation and operation.

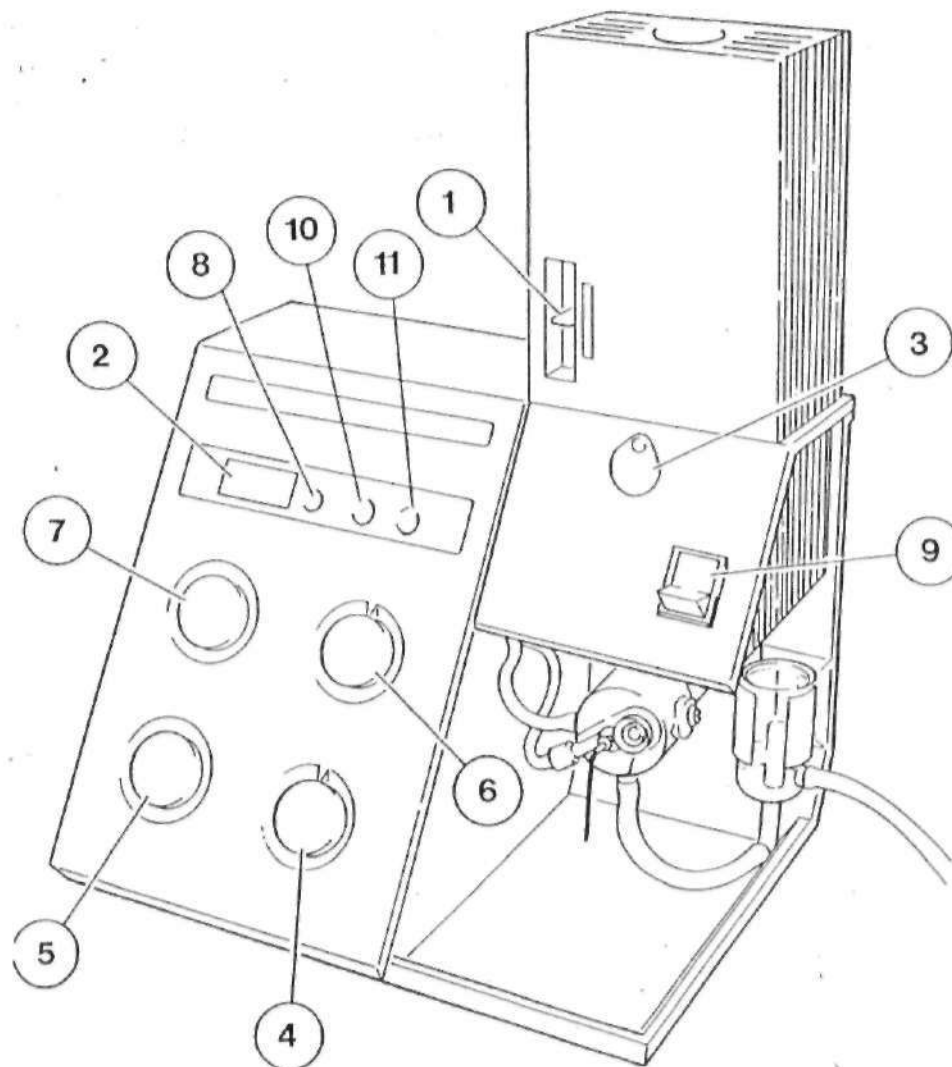


Typical PU8605/60 Tablet Dissolution System

INITIAL INSPECTION

Check the contents of the shipment as listed in the Data Station Supplement to Section 3 if a Data Station was ordered, and ensure that all separately ordered items are present.

If the contents are incomplete, or damaged, a claim should be filed with the carrier immediately. The nearest Philips Sales Organisation (or agents) should be notified of any damage and of items that have not been supplied, in order to facilitate repair or replacement.



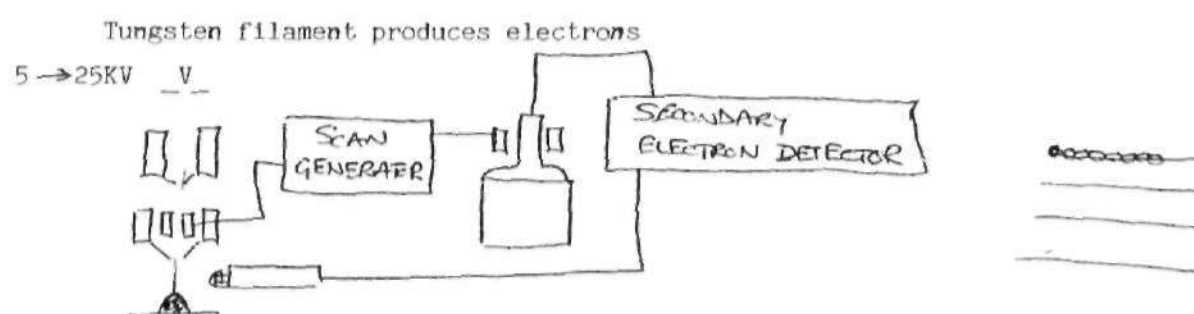
----- Front Panel

1. Filter selector. 2. Digital display. 3. Inspection flap. 4. fuel adjustment control. 5. blank control. 6. coarse sensitivity control. 7. fine sensitivity control. 8. decimal pushbutton. 9. power switch. 10. power on LED. 11. flame on LED.

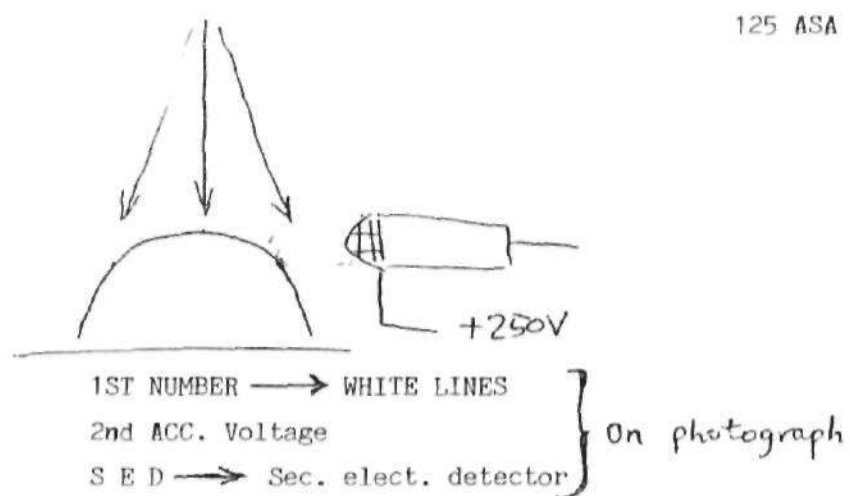
Mounted on Stubs using either double sided adhesive tape or araldite
Samples gold coated using POLARON E5100 Sputter coater

1
PHILIPS EM 501B SCANNING ELECTRON MICROSCOPE

- Works under vacuum
- Should be conductive (gold plating)
- Uses electron beam



FILM:-
ILFORD FP4 PLUS
125 ASA 120 FORMAT



Negative magnification is approx 0.65x magnification written on data sheet.

APPENDIX 4: SCHEMATIC DIAGRAM OF THE PERKIN - ELMER

DSC INSTRUMENT

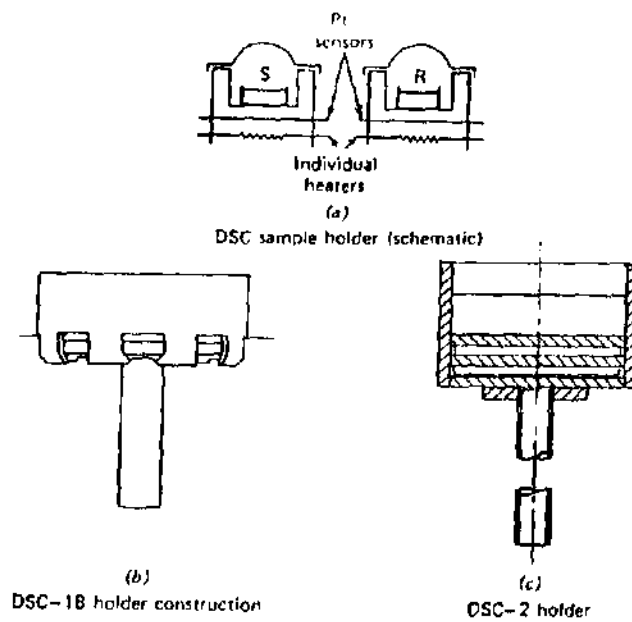
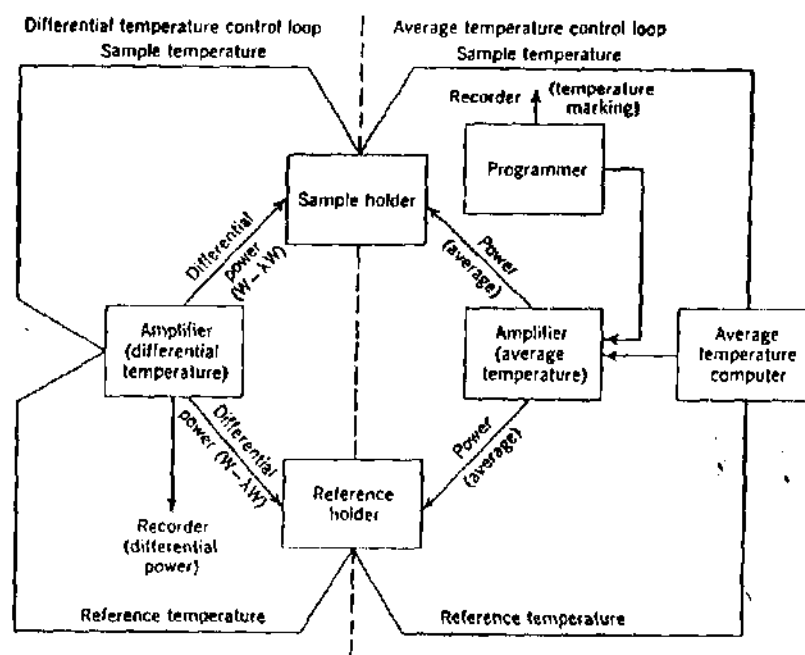


Figure 6.37. Sample-holder construction used in the Perkin-Elmer DSC instruments (24).



PHILIPS PU8620 Tablet Dissolution System V1.2 Date: 01:01:80 Time: 20:28:43

Data Name : RUN-B3 Date : 01:01:80 Time : 00:35:50

RUN-B3 Environment Description

Organisation : A Pharmaceutical Company
Installation : Any Street, Anywhere
Instrument : Serial no: 333333
Cell Changer ID : Serial no: 343434

```
*****
*                                     *
*   Contact: A.N.Other              *
*                               (New Site) *
*                                     *
*   Tel: 01-999-9999               *
*   Telex: 99999                   *
*                                     *
*                                     *
*****
```

RUN-B3 Method Description

Test Name : RUN-B3
Operator : M.A.IBRAHIM.
Lot : 1
Product Name : THEOPHYLLINE
Type of Drug : ANTI-ASTHMATIC
Type of Medium : 0.1N HCl
Wavelength : 270 nm

Dissolution System : USP Paddle
Rotation Rate : 100 r.p.m.
Temperature : 37 C
Filtration : 20 micron
Cell Path Length : 1 mm
Flow Rate : 18 ml/min

Test Mode : QUALITY CONTROL

Active Component : 200.0 mg
Volume of Medium : 1.000 l
Standard Conc. : 100.0 mg/l
Standard Abs. : 0.552 A

Sampling Mode : STEP

Number of Reads : 121
Sampling Interval : 00:10 hrs:mins
Total Testing Time : 20:00 hrs:mins

Print Method : FULL
Print Raw Data : ABS
Print % Dissolved : ON
Print Multiplot : ON
Print Weibull Regression : OFF
Print Weibull Linearisation : OFF
Print Mean : OFF

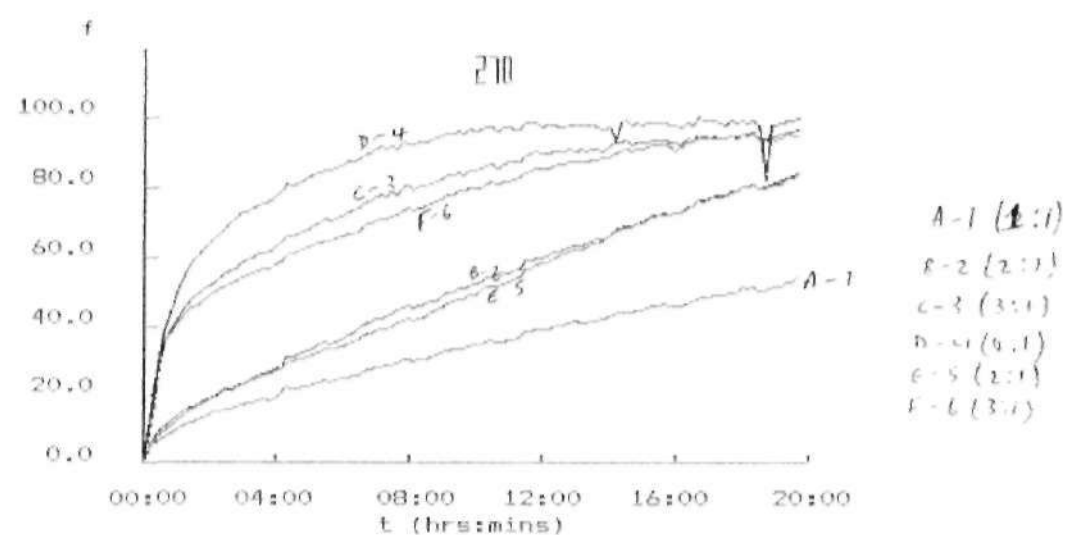
Rate Compliance Mode : OFF

179
Insertion Mode : SEQUENTIAL
Insertion Delay : 00:00 mins:secs

Vessels Included : 1 2 3 4 5 6 Calib. Control
(Cell) : (1) (2) (3) (4) (5) (6) (7) (8)

* THEOPHYLLINE TABLETS 200mg *
* A-1,B-2,C-3,D-4,E-5,F-6. *
* * *

Multiplot



Vessels Included : 1 2 3 4 5 6 Calib. Control
(Cell) : (1) (2) (3) (4) (5) (6) (7) (8)

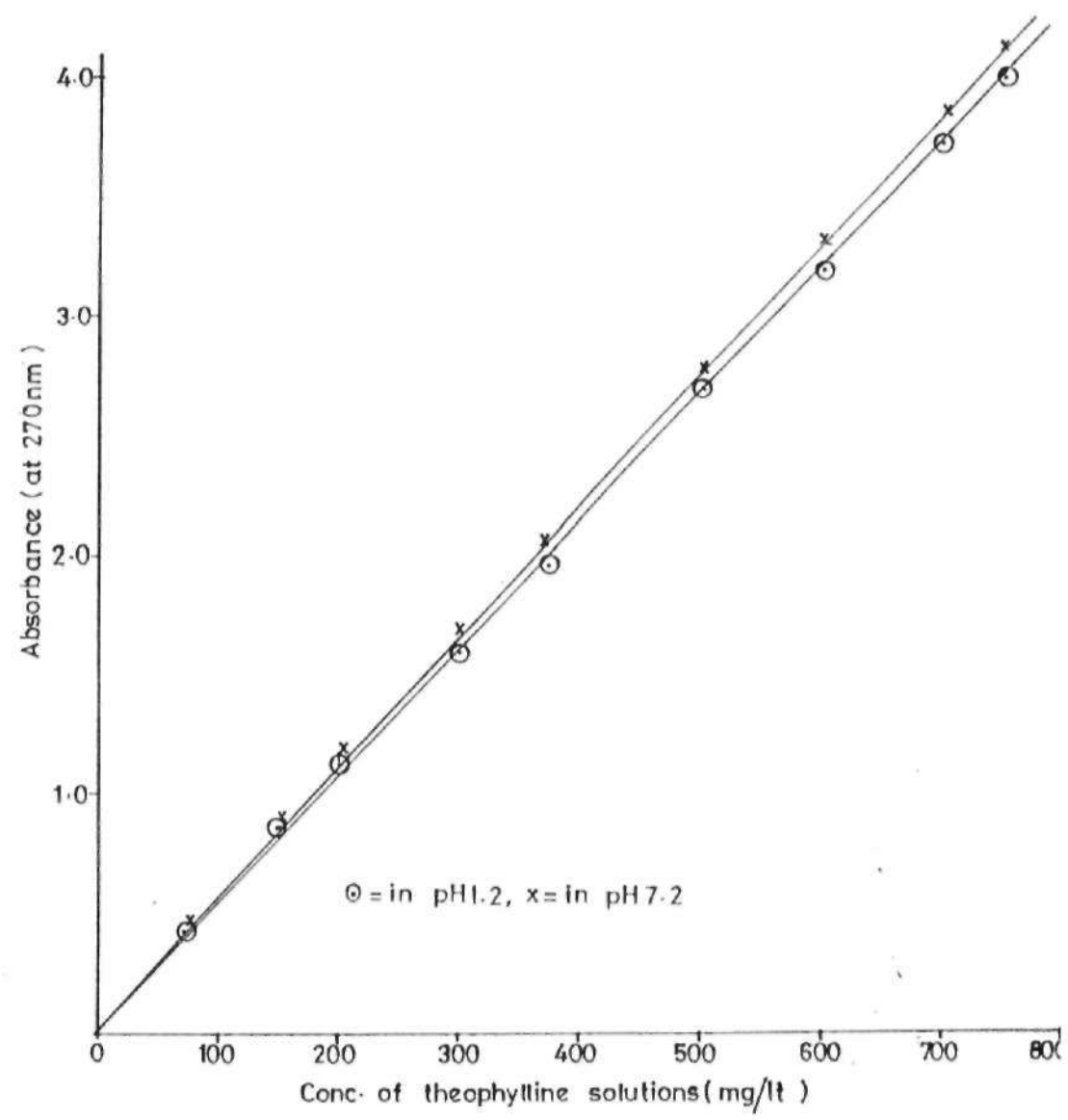
Absorbance Data 270 nm

Vessel	Abs	1	2	3	4	5	6	Abs	Abs	CV%	Control
(Cell)	(1)	(2)	(3)	(4)	(5)	(6)	Mean	S.Dev		(8) Abs	
rad	Mean										
lo.	Time										
1	00:00	0.002	-0.006	-0.001	-0.001	0.002	0.001	0.000	0.003	2.000	-0.002
2	00:10	0.034	0.041	0.110	0.091	0.051	0.073	0.067	0.027	40.99	-0.003
3	00:20	0.057	0.067	0.247	0.228	0.080	0.187	0.145	0.078	54.14	0.001
4	00:30	0.071	0.088	0.334	0.347	0.102	0.310	0.209	0.122	58.69	0.002
5	00:40	0.083	0.104	0.389	0.435	0.116	0.384	0.252	0.152	60.36	0.003
6	00:50	0.094	0.116	0.431	0.497	0.130	0.422	0.282	0.170	60.46	0.002
7	01:00	0.103	0.130	0.461	0.548	0.142	0.447	0.305	0.183	60.06	0.002
8	01:10	0.111	0.143	0.487	0.587	0.154	0.468	0.325	0.193	59.39	0.002
9	01:20	0.123	0.158	0.509	0.621	0.168	0.489	0.345	0.200	57.95	0.002
10	01:30	0.130	0.169	0.529	0.651	0.179	0.502	0.360	0.206	57.33	0.002
11	01:40	0.134	0.177	0.542	0.668	0.186	0.512	0.370	0.210	56.86	0.002
12	01:50	0.142	0.187	0.559	0.691	0.195	0.524	0.383	0.215	56.03	0.002
13	02:00	0.147	0.195	0.572	0.705	0.205	0.536	0.393	0.218	55.40	0.001

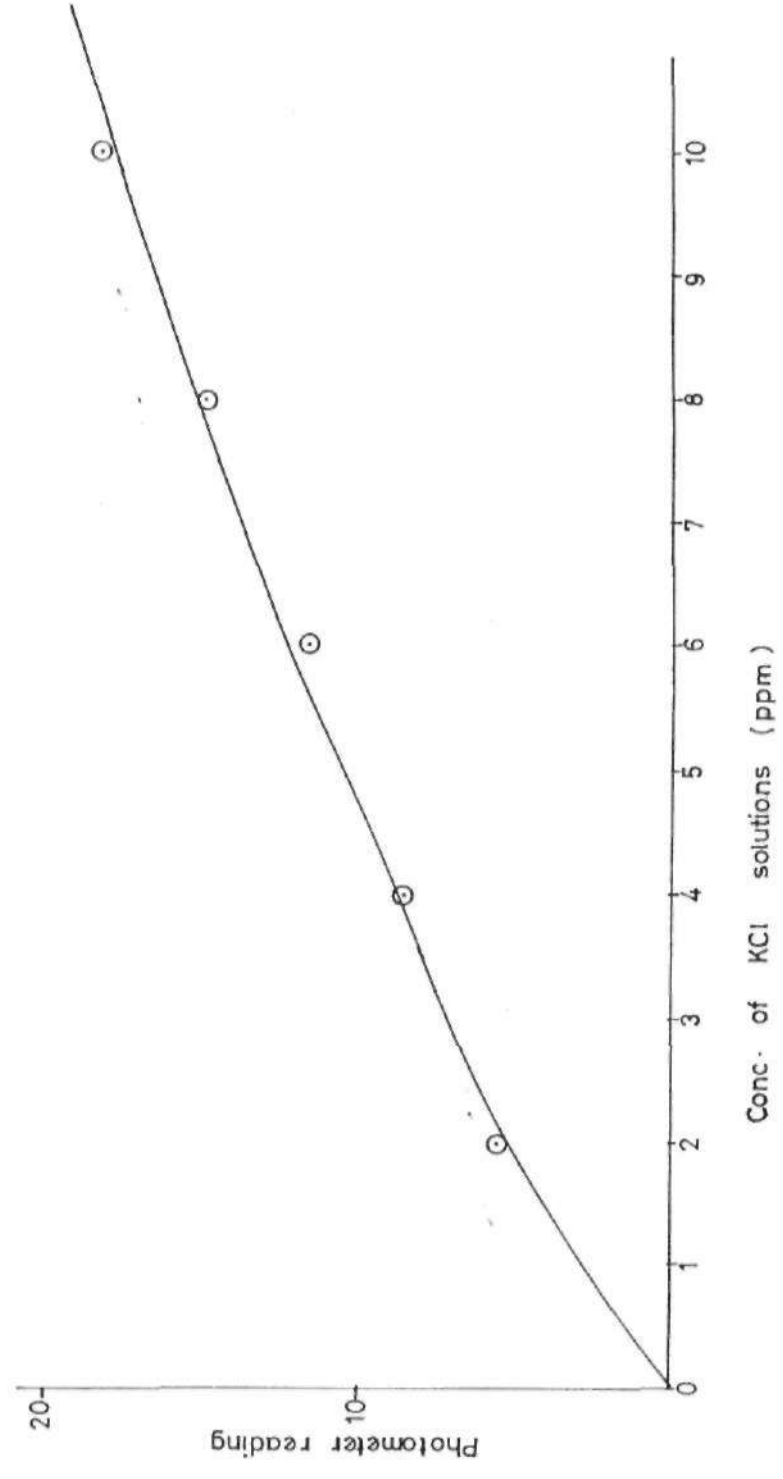
PHILIPS PU8620 Tablet Dissolution System V1.2 Date: 01:01:80 Time: 20:29:35

Absorbance Data 270 nm (continued)

APPENDIX 6: BEER'S LAW PLOT FOR THE DETERMINATION OF
THEOPHYLLINE CONCENTRATION



APPENDIX 7: BEER'S LAW PLOT FOR THE DETERMINATION OF
KCL CONCENTRATION IN CORNING 460/405 DILUENT

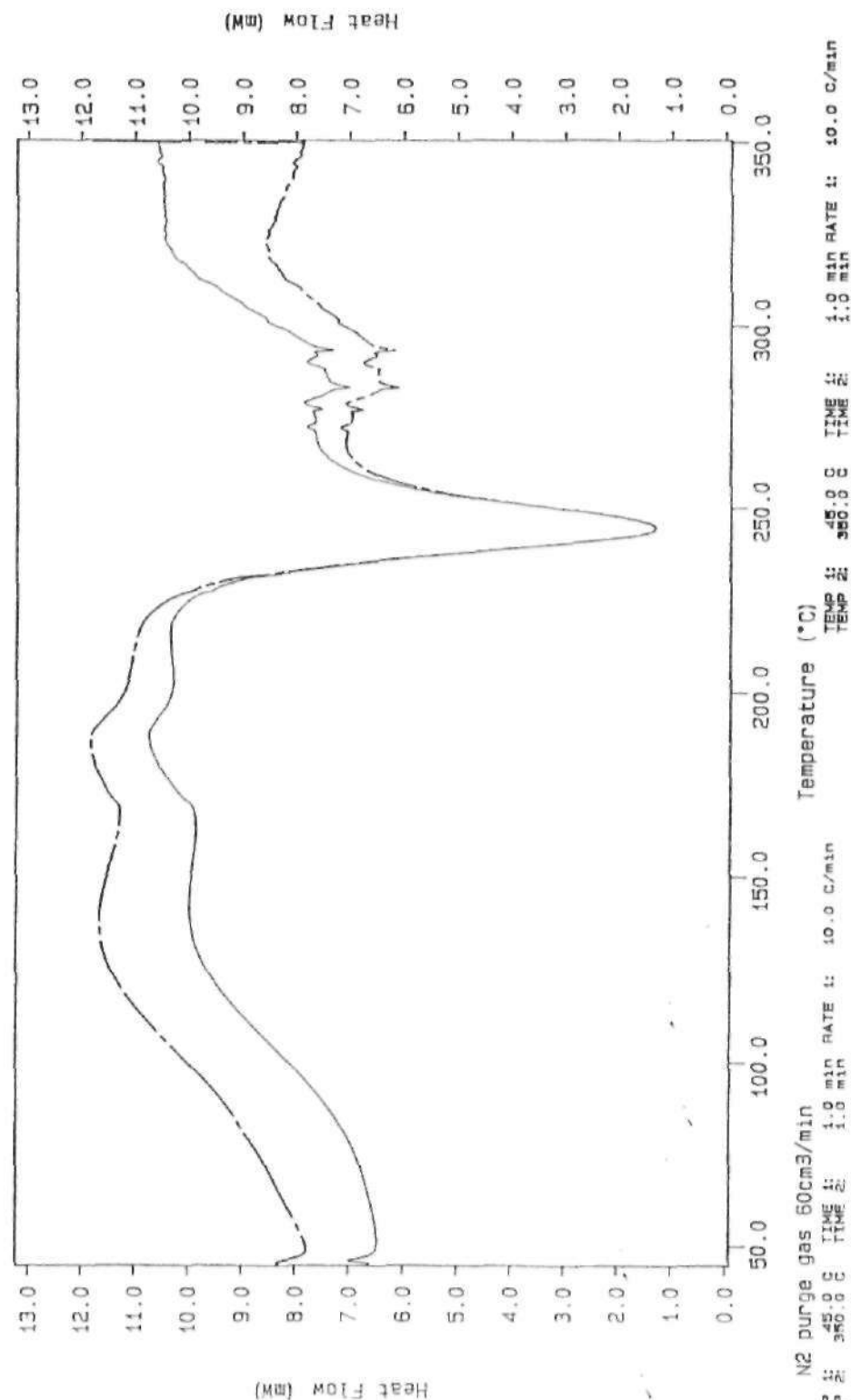


APPENDIX 8 : THE THERMOGRAM OF PURE CME

DSC Data File: cisal
Sample Weight: 8.665 mg
Tue Aug 24 20:01:28 1993
Pure cissus mucilage extract (CME)

PERKIN-ELMER
7 Series Thermal Analysis System
Pure cissus mucilage extract (CME)

DSC Subtraction
Sample Weight: 8.665 mg
Tue Aug 24 20:01:28 1993
Pure cissus mucilage extract (CME)
(Subtracted)

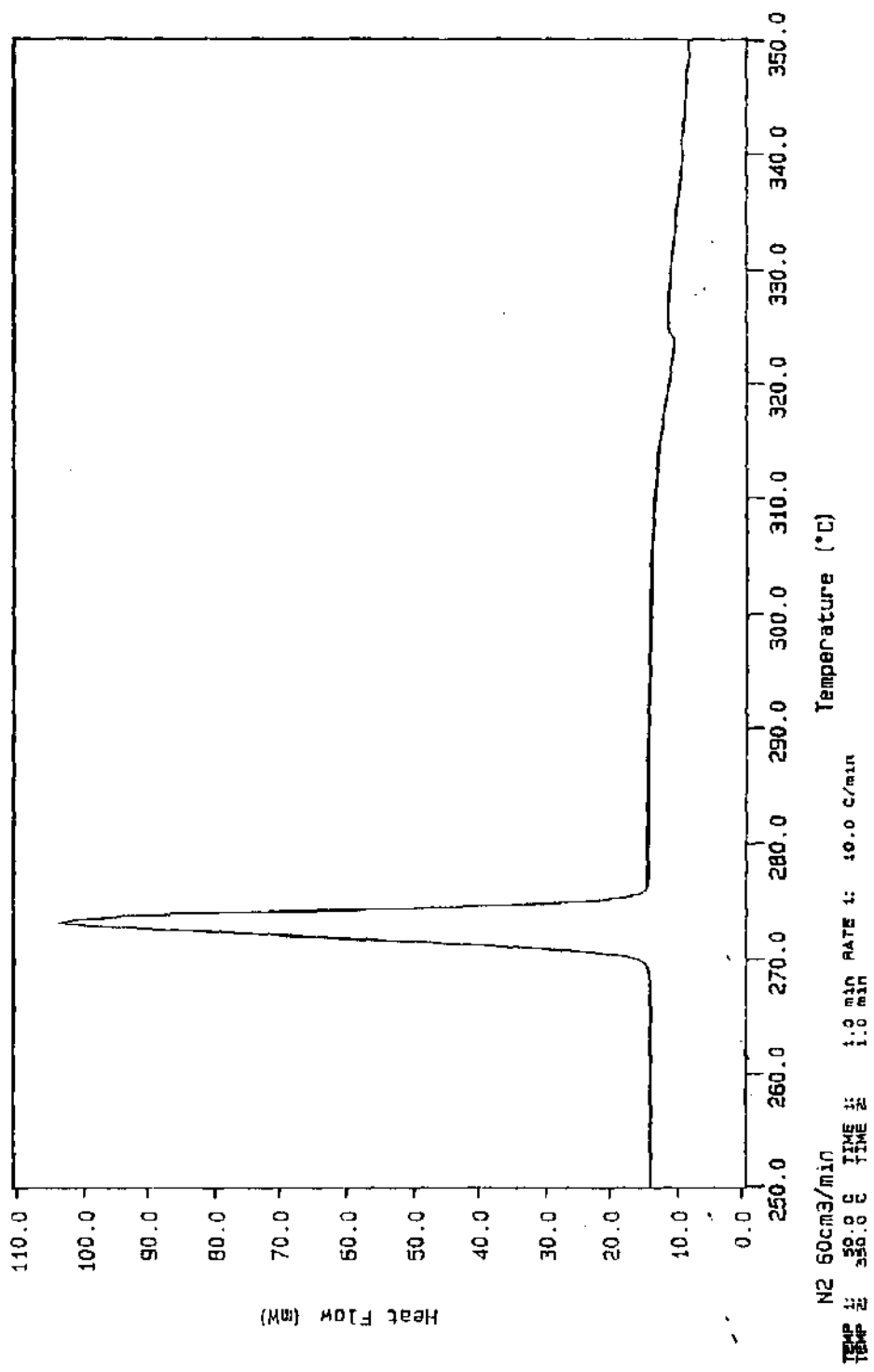


with 2
molecules

183
APPENDIX 9: THE THERMOGRAM OF PURE THEOPHYLLINE

DSC Data File: teap1
Sample Weight: 8.830 mg
Tue Oct 05 17:13:57 1993
Pure Theophylline A2

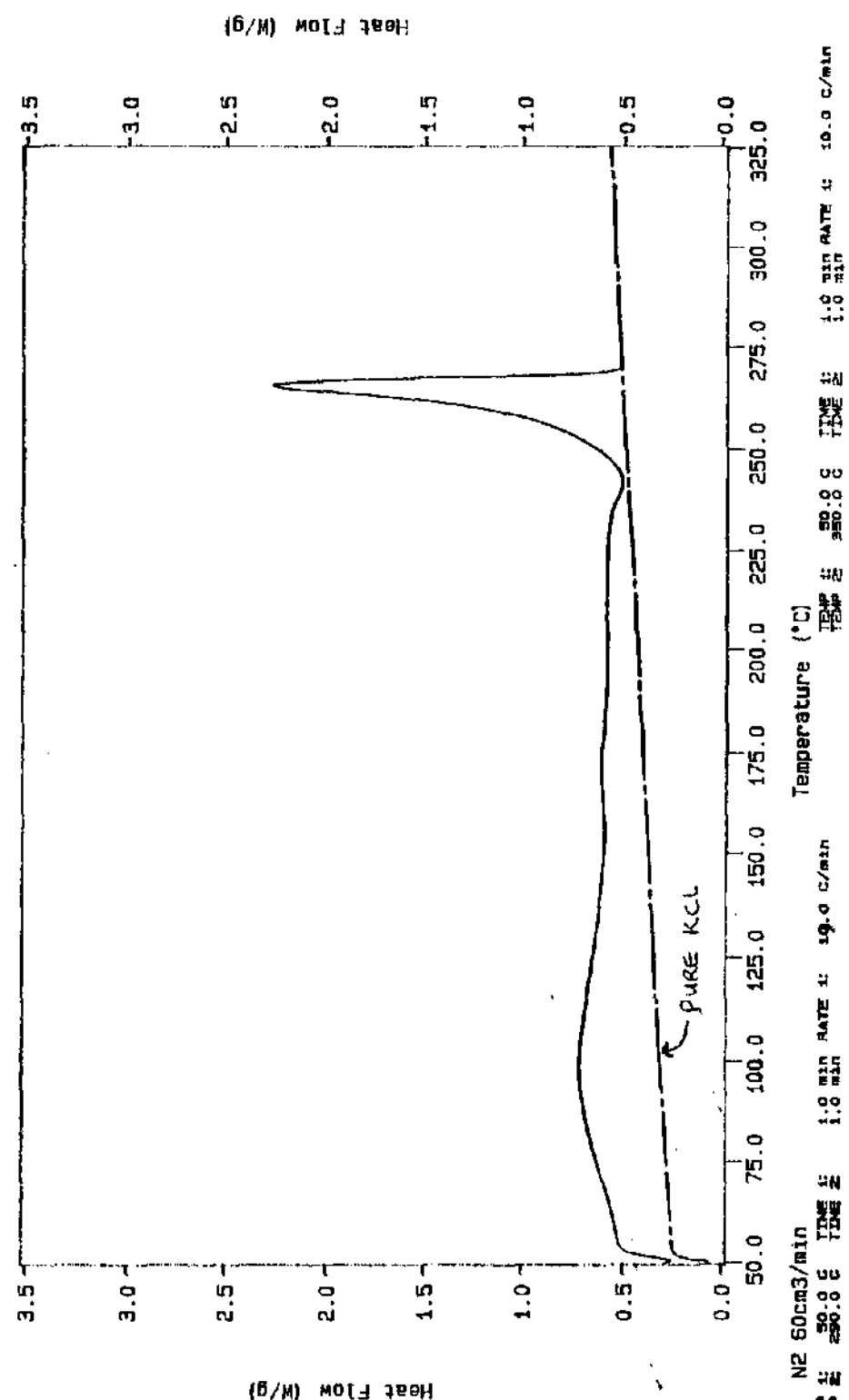
PERKIN-ELMER
7 Series Thermal Analysis System



DSC Normalization: 11
Sample Weight: 9.050 mg
Tue Oct 12 16:10:51 1993
Theop.CME (2.5:1) MgSt (0.1%) P/A11
(Normalized)

PERKIN-ELMER
7 Series Thermal Analysis System

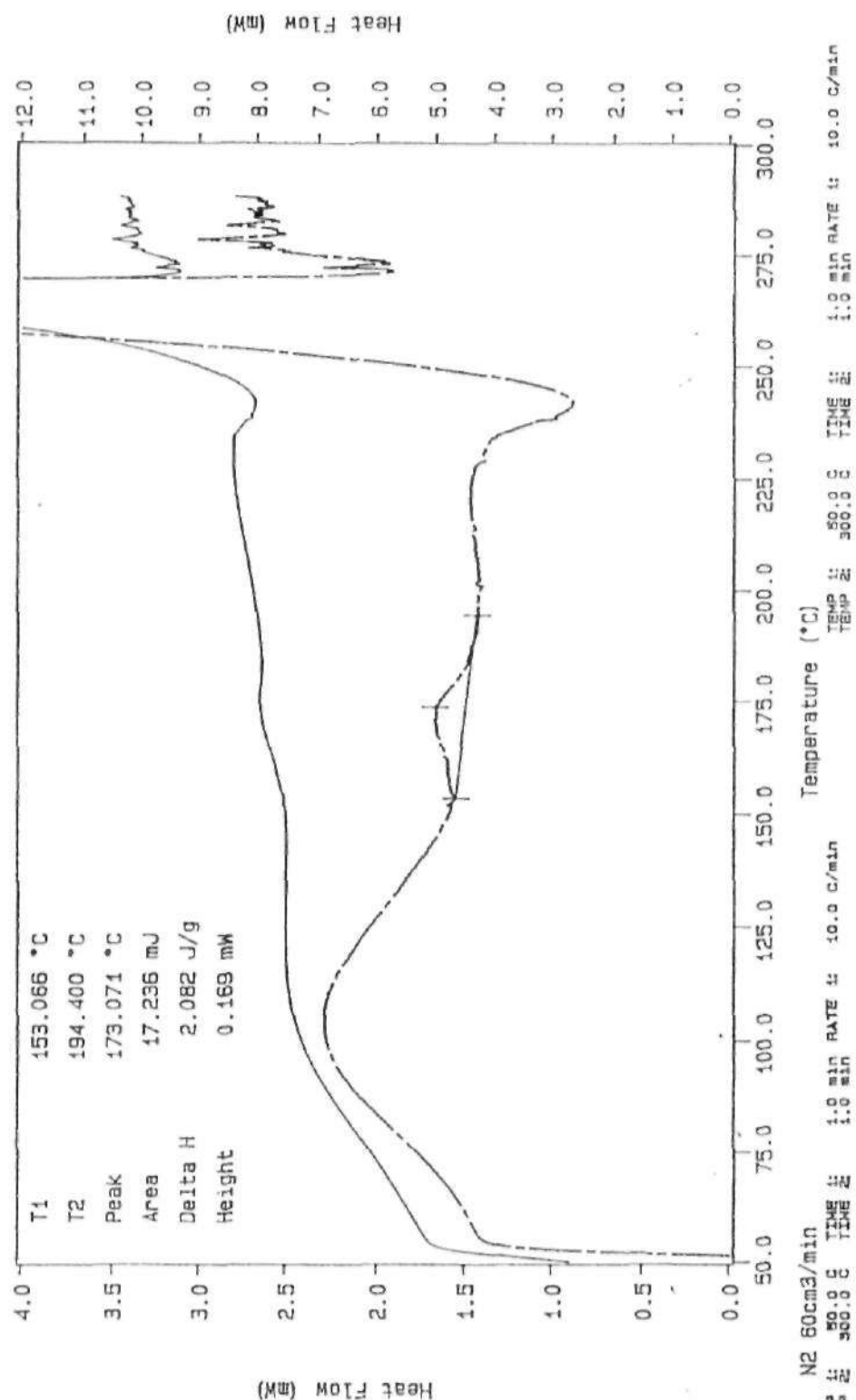
DSC Normalization: KCl01
Sample Weight: 9.039 mg
Wed Oct 06 11:28:14 1993
Pure KCl
(Normalized)



PERKIN-ELMER

DSC Subtraction
Sample Weight: 8.278 mg
Wed Oct 06 14:21:46 1993
Theophylline: CME (2.5:1)

DSC Data File: thcm5
Sample Weight: 8.278 mg
Wed Oct 06 14:21:46 1993
Theophylline: CME (2.5:1)P/A5



APPENDIX 12: THE THERMOGRAM OF CHE - KCL MIXTURE.

DSC Subtraction

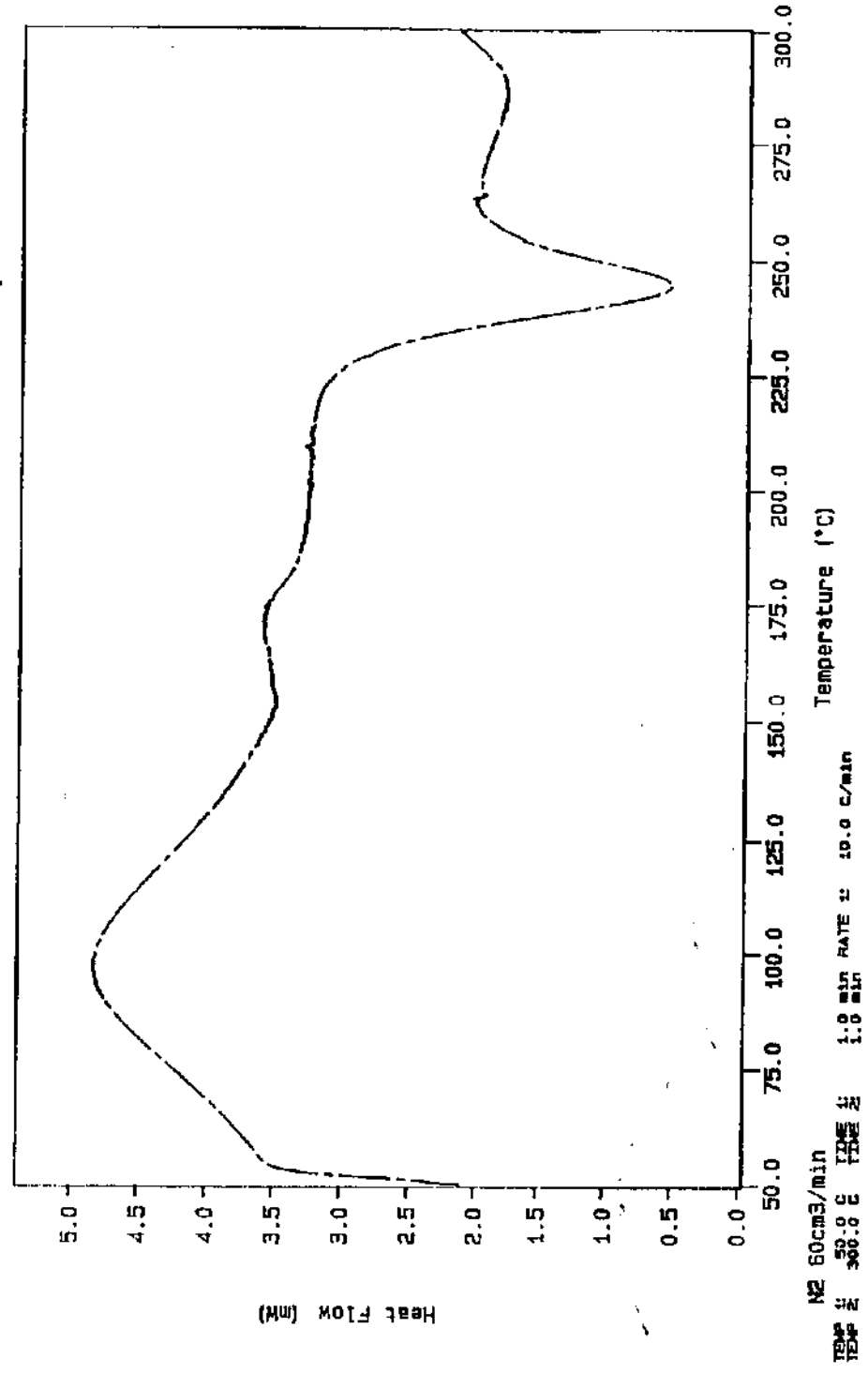
Sample Weight: 9.215 mg

Wed Oct 06 18:24:10 1993

KCl: CHE (2:1 P/A9
(Subtracted)

PERKIN-ELMER

7 Series Thermal Analysis System



Appendix 13: Summary of Factors Effecting Clinical Use
of Slow Release Theophylline Products

Factors Effecting	Effect	Comment
Diet	Conflicting data:- No effect - delay in absorption - dose-dumping	Patients should be instructed to take their theophylline in a constant fashion in relation to food.
Charcoal-broiled Beef	Significant decrease in plasma half-life (22%)	Warning to patients of the possible effects of Barbecued food to their treatment.
Smoking	Significant increase in elimination, decrease in half-life.	Dosages in cigarette smokers may need to be twice that of non-smokers. Patients should be warned that if they stop smoking they should consult their doctor.
Drugs	See Appendix 14	
Patient factors (age)	Rate of clearance differs with age: neonates less than adults with other children showing higher levels.	Care should be taken when calculating theophylline doses to adjust the dosage to the appropriate age range.
(disease state)	In general certain disease states cause a decrease in theophylline clearance.	Dosages need to be reduced in such patients.
Product factors	Rates of absorption are different between proprietary brands.	Patients should be titrated to one brand and not changed to another without further plasma monitoring

Appendix 14 Significant Drug Interactions with Theophylline

	Interactant	Mean clearance decrease	Appropriate action
Drugs That Decrease Theophylline Clearance*	Allopurinol	25%	Monitor serum levels and adjust theophylline dose accordingly.
	Cimetidine	40%	Monitor serum levels and adjust theophylline dose accordingly or ranitidine.
	Erythromycin	25%	Monitor serum levels and adjust theophylline dose accordingly or use another antibiotic.
	Propranolol	30%	Avoid nonspecific beta blockers in asthma. Use a β_1 -specific blocker (i.e., metoprolol).
	Troleandomycin	50%	Avoid completely. Utilize alternative antibiotic.

	Interactant	Mean clearance increase	Appropriate action
Drugs That Increase Theophylline Clearance**	Phenobarbital	25%	Monitor for breakthrough symptoms; monitor serum levels and adjust theophylline dose accordingly.
	Phenytoin	75%	Use cromolyn if possible; otherwise monitor serum levels every five days and adjust theophylline dose accordingly.

	Interactant	Effect	Appropriate action
Miscellaneous Interactions	Alcohol	Increased GI intolerance.	Avoid concurrent consumption
	Lithium	Reduced serum lithium levels.	Use cromolyn if possible; otherwise monitor serum levels and adjust lithium dose accordingly.
	Phenytoin	Decreased serum phenytoin levels.	Use cromolyn if possible; otherwise monitor serum levels and adjust phenytoin dose accordingly.

*Mean clearance decrease results in drug accumulation causing serum levels to increase, potentially to the point of toxicity.

**Mean clearance increase results in a more rapid excretion of drug causing serum levels to decrease, potentially precipitating an asthmatic attack.