PHARMACEUTICAL AVAILABILITY ON NEWLY FORMULATED ORAL SUSTAINED RELEASE PELLETS CONTAINING THE ANTIHISTAMINE, CHLORPHENIRAMINE MALEATE.

by

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To Haroun and my parents

For more reasons than can

be listed here

SUMMARY

The main objective of the present study was to determine the feasibility of obtaining aqueous polymer-coated pellet formulations using Eudragit^{R} NE 30 D dispersion and chlorpheniramine maleate as the model drug. Many factors influence the rate of drug release from coated beads including, the substrate, the coating formulation and the coating process. A drug release profile that was comparable to that of the reference standard, Dykatuss^{R} Capsules was obtained with a formulation employing 8.3% Eudragit^{R} NE 30 D, 0.5% talc and 1% polyethylene glycol. *In vitro* dissolution tests on this formulation showed drug release to be predictable, reproducible and independent of the dissolution methods or media. Short term storage confirmed the stability at room temperature (20°C) and low temperature (5°c). Scanning electron micrographs of pellets stored at elevated temperatures i.e. 37°C with 80% relative humidity and 40°C illustrated the phenomenon of 'further gradual coalescence' which corresponded to the decrease in release of drug from the pellets.

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CHAPTER ONE

INTRODUCTION, AIMS AND OBJECTIVES OF STUDY

1.1 INTRODUCTION

With the current world-wide decline in the numbers of new drug entities reaching the market place, there has been a resurgence of interest in the development of novel drug delivery systems from the presently available pharmaceutical agents.

There are also good commercial reasons for the strong trend toward controlled release systems. In the next few years, drug patents on the majority of today's most well used drugs will expire. Formulating of drugs in controlled/sustained release systems is one method of extending the proprietary protection against generic products, particularly if the controlled/sustained release drug system is patented.

Slow release technology is thought to have begun with the 1938 patent of Israel Lipowski, in which he described the coating of pellets (Conrad and Robinson, 1982). This work is said to have been the forerunner of the coated particle dosage forms which have become popular since the early

1950's e.g. the Spansule^{R} dosage form that was introduced by the SKF Corporation. There have been 40 years of research and development experience in the sustained drug release area since the patent, and a number of strategies have been developed to prolong drug levels in the body. These range from the very simple slowly dissolving pellets or tablets to the technologically sophisticated controlled drug release systems which have recently started to appear on the market, and research on which has appeared in the pharmaceutical literature (Erikson, 1970; Theeuwes and Higuchi, 1974).

With many drugs the basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically active and safe for an extended period of time. The design of proper dosage formulations is an important element in accomplishing this goal. A basic objective in such dosage form design is to optimise the delivery of medication so as to achieve a measure of control of the therapeutic effect in the face of uncertain fluctuations in the *in vivo* environment in which drug release takes place. This is usually accomplished by maximising drug availability i.e. by attempting to attain a maximum rate and extent of drug absorption; however, control of drug action through formulation also implies controlling bioavailability to retard drug absorption rates (Lordi, 1986).

For drugs formulated into modified dosage forms, the release of drug from the delivery system ideally should be at a controlled and predictable rate.

Successful fabrication of sustained release products is usually difficult and involves consideration of the physico-chemical properties of the drug, pharmacokinetic behaviour of the drug, route of administration and the disease state to be treated.

Chlorpheniramine maleate is a potent alkylamine antihistamine used for the symptomatic relief of common cold and allergic conditions. The usual recommended daily oral dose for adults is 4mg every 4-6 hours or 8-12mg every 8-12 hours. It is rapidly and extensively metabolised, displaying extensive 'first-pass' effect after oral administration. Thus, chlorpheniramine maleate shows marked inter- and intra-subject variation of metabolism dependent on many factors such as liver disease and asthma.

To overcome variability in metabolism and unpleasant side effects, it was proposed to control the rate of input of the drug into the body over a desirable duration by the appropriate choice of a controlled delivery system (sustained release pellets).

1.2 AIMS AND OBJECTIVES

The study involved the development of a suitable and stable oral sustained release pellets formulation containing 8mg chlorpheniramine maleate that would provide desirable constant drug blood levels over 6-8 hours. It is known that the sub-division of an oral dosage form leads to the scattering of the dosage form throughout the gastrointestinal tract (GIT), thus releasing the drug at different rates for absorption (Chapter 2). Hence the chosen dosage form contains the drug incorporated into several pellets, each coated with a pH-independent diffusion rate-controlled membrane. Various combinations of polymers and other suitable excipients were evaluated for their influence on the rate of drug release and the facilitation of the manufacturing process.

While numerous sophisticated techniques are available to assess the release characteristics of newly formulated dosage forms (Hanson, 1987), compendial methods remain the most popular techniques. These methods continue to be popular due to their proven reliability and reproducibility and also because of the stringent regulatory requirements. In view of these considerations, compendial methods (USP XXII, 1990) were employed as a means to assess drug release from the newly formulated controlled release preparations.

To meet the objectives of the investigation on the sustained release pellets formulation, the development of specific and sensitive procedures based on high pressure liquid chromatography was necessary. Other analytical techniques e.g. ultraviolet spectrophotometry were also used for the analysis of the compound, chlorpheniramine maleate.

Stability studies will be investigated and confirmed for a formulation exhibiting the desirable release profiles under various conditions. The integrity and morphology of the coating will be examined by scanning electon microscopy.

CHAPTER 2

CONTROLLED RELEASE ORAL DOSAGE FORMS: CONCEPT, APPROACHES, TECHNIQUES AND MATERIALS USED.

2.1 THE CONTROLLED RELEASE CONCEPT

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, slow release, delayed release and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time after administration of a single dose. The term 'controlled release' has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. For the purpose of this presentation the terms controlled release and sustained release will be used interchangeably.

The goal of controlled release technology is to produce a convenient, self administered dosage form that yields a constant infusion of the drug for the desired duration of activity (Ansel, 1985).

2.2 TERMINOLOGY AND LITERATURE SURVEY

Over the years, there have been several attempts to classify long-acting oral dosage forms (Ritschel, 1973; Ballard and Nelson, 1975). One classification of such products (Ballard and Nelson, 1975) proposes that there are three basic types:

A) Sustained Action
B) Prolonged Action
C) Repeat Action

A *sustained release* product may be considered as one in which a drug is initially made available to the body in an amount sufficient to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption; and one which provides for maintenance of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual single dose of drug. Sustained release products are probably the first long acting dosage forms purposely designed to deliver the drug at different times of release (Abdou, 1989).

Prolonged-action products may be considered to be those in which a drug is initially made available to the body in an amount either sufficient to, or not dangerous or undesirable in excess of, the amount needed to cause the desired therapeutic response. Such dosage forms also provide for replenishing the supply of drug to the body at some rate which extends the length of the pharmacological response to the single dose of the drug. Note that with prolonged action systems, constant drug levels are not maintained.

A *repeat-action* product may be considered to provide a usual single dose of drug immediately upon administration and a second dose, which is released some later time after administration.

Figure 2.1 shows the relationship between activity and time for the usual single dose of a drug, a sustained release formulation, and a prolonged action formulation.

Figure 2.2 shows the relationship between drug concentration and time for a repeat action product.

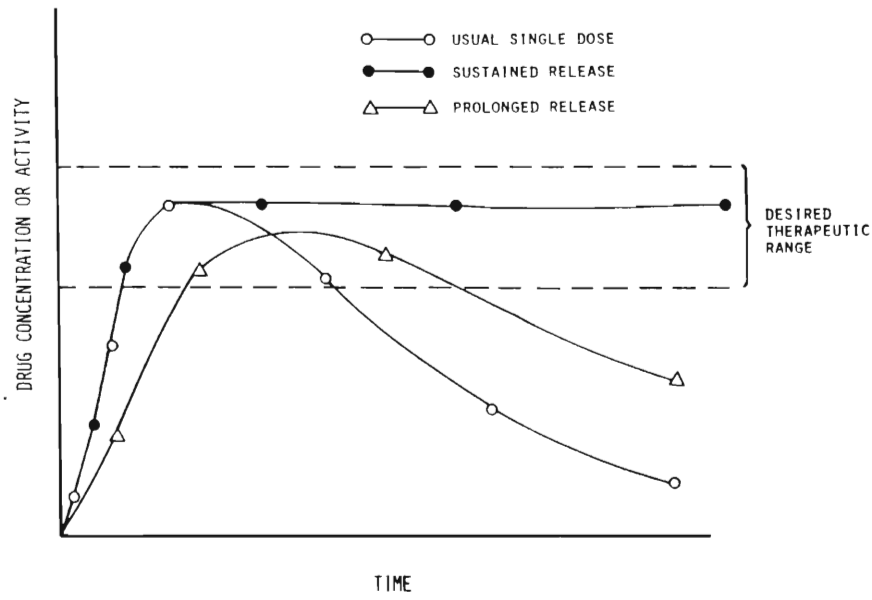


FIGURE 2.1 : RELATIONSHIP BETWEEN DRUG ACTIVITY AND TIME (BALLARD, 1982; page 4)

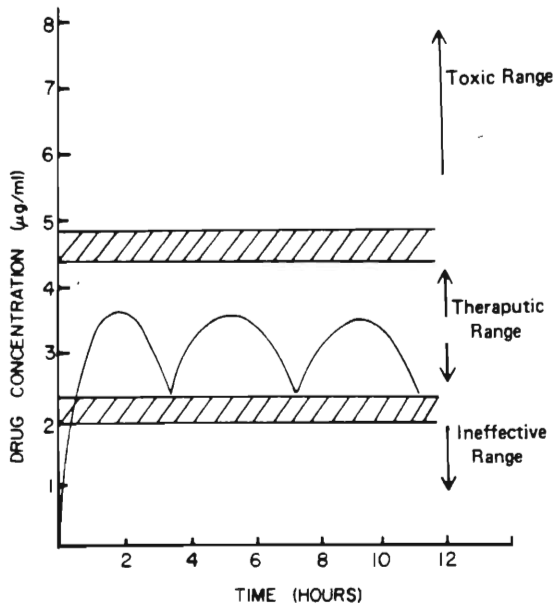


FIGURE 2.2 : RELATIONSHIP BETWEEN DRUG ACTIVITY AND TIME FOR A REPEAT ACTION PRODUCT (LEE AND ROBINSON, 1982; page 135)

In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period of time. This is generally accomplished by attempting to obtain 'zero order' release from the dosage form. Zero order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system (i.e. a constant release rate). Sustained release systems generally do not attain this type of release and usually try to mimic zero order release by providing the drug in a slow first order fashion (i.e. concentration dependent). Ideally, the controlled release drug product should release the drug at a constant rate independent of both the pH and the ionic content within the entire segment of the gastrointestinal tract (Grass and Robinson, 1990).

2.3 THERAPEUTIC ADVANTAGES OF ORAL CONTROLLED RELEASE PREPARATIONS

Despite the complexity of designing a controlled release drug product that behaves ideally, these dosage forms offer several important advantages over immediate release dosage forms of the same drug (Shargel and Yu, 1985).

Controlled release dosage forms that provide sustained drug release require less frequent drug administration than ordinary dosage forms. This is considered an advantage in assuring patient compliance in taking of medication (Cartwright, 1987). Patients required to take 1 or 2 tablets a day are less likely to forget a dose than if they were required to take their medication 3 or 4 times a day. Also, depending on the medication and the dosage forms, the daily cost to the patient may be less with the frequent dosage administration (Ansel, 1985).

Probably the most important reason for sustained drug delivery, and one which is often under-emphasised in the literature, is improved disease management. Proper drug delivery should lead to the more prompt cure or control of the condition on hand as well as better management of acute and chronic conditions. This effect has many therapeutic and non-therapeutic ramifications, including perhaps a financial saving to the patient in terms of lost work days, less hospitalisation and fewer visits to the physician (Lee and Robinson, 1982).

The severity or frequency of untoward side-effects which occur immediately after administration due temporarily to too high a concentration of the drug in the body may be reduced by the administration of medication in the controlled release dosage form (Krowczynski, 1987). In the case of oral dosage forms, it minimises local irritation of the gastrointestinal mucosa induced by high local concentration of drug. For example, a prolonged action tetracycline hydrochloride preparation was reported to be equally effective when compared to the standard tablet in the treatment of acne vulgaris. This formulation could be administered at half the daily dose compared to the conventional tablet, hence reducing the possible incidence of undesirable side effects (Lim *et al.*, 1974).

There have been reports that gastrointestinal blood loss can occur with different dosage forms of prolonged action aspirin. However, significantly less gastric bleeding occurred with prolonged action aspirin formulation compared to conventional aspirin preparations (Lee and Robinson, 1982).

Controlled drug delivery systems also facilitate the combination of drugs that have complementary therapeutic actions but differ with respect to their pharmacokinetics. Each drug can be released at an optimum rate, so identical periods of drug action will be obtained (Mutschler, 1980).

Special effects e.g. sustained release aspirin provides sufficient drug so that on awakening the arthritic patient has symptomatic relief (Conrad and Robinson, 1980).

The potential benefits to be gained from controlled drug delivery depends on the specific drug delivery system-disease state-route of administration. Each of these have been amply documented in the literature and a few examples are given below.

TABLE 2.1 : SOME REPORTED ADVANTAGES TO CONTROLLED DRUG DELIVERY SYSTEMS

DRUG	ADVANTAGE	REFERENCE
Levodopa	Eliminates drug induced dyskinesias.	Eckstein *et al.*,1973
Nitro-glycerin	Lowers drug requirement, reduces incidence and severity of angina attacks.	Winsor *et al.*, 1972 Hirshleifer, 1973
Aspirin	Alleviates morning stiffness in arthritis. Eliminates gastric irritation and erosion.	Koch-Weser, 1973

2.4 LIMITATIONS OF ORAL CONTROLLED RELEASE DOSAGE FORMS

Accidental poisoning with controlled release dosage forms, although infrequent, do pose special treatment problems not seen with conventional oral dosage forms. The slow release of drug into the gastrointestinal tract and its extended absorption often results in slow clearance of drug from the body. If a patient is brought into the hospital after overdosage symptoms develop, often several hours after drug ingestion, it may be impossible to retrieve the dose from the stomach (Bingle *et al.*, 1970; Simpson and McKinlay, 1975; Ballard, 1982).

On rare occasions, a prolonged action dosage form, like its non-prolonged action counterpart, becomes impeded in its transport through the gastrointestinal tract. This is particularly troublesome for drugs which have a high tendency to cause damage to the gastrointestinal mucosa. One cardiac patient developed deep ulcers in various mucosal regions of the oral cavity after sucking a prolonged action potassium chloride tablets (McAvory, 1974).

A drawback of the medication with controlled action preparations is the loss of flexibility in use. Dosage forms which are designed to last at least eight hours are less flexible in accommodating the individual needs of patients (De Haan and Lerk, 1984). If the patient experiences some undesirable effect, such as drowsiness from an antihistamine, he cannot adjust his regimen as readily as with a dosage regimen of every 3-4 hours, where he could skip a dose intentionally (Notari, 1980).

The size of the dosage form may present disadvantages. Formulation of controlled drug products for drugs usually given in large doses (>500mg) in conventional dosage forms may not be practical. Since the controlled release product may contain three or more times the dose given at more frequent intervals, the size of the controlled release drug product would have to be quite large, too large for the patient to swallow easily (Shargel and Yu, 1985).

The possibility of 'dose dumping' a term used to describe inadvertent rapid release of drug material due to faulty formulation, is theoretically important for potent drugs which have a narrow therapeutic index. Erroneous intake of controlled release preparations (grinding, mastication) may have severe consequences of dose dumping (De Haan and Lerk,

1984). Since controlled release dosage forms contain two to four times the usual dose of the drug, additional unexpected immediate release of significant, or all of the drug from the dosage form, is possible. However, good manufacturing practice, and also the highly sophisticated dosage forms currently appearing on the market, make the possibility of this unlikely.

2.5 PARAMETERS INFLUENCING THE DESIGN OF ORAL CONTROLLED RELEASE DOSAGE FORMS.

Apart from the above limitations, some drug types are inherently unsuited for controlled release formulations, and considerable time and effort may be wasted in their development. Some typical drug characteristics are described in Table 2.2.

TABLE 2.2 : GENERAL CHARACTERISTICS THAT MAY MAKE A DRUG UNSUITABLE FOR CONTROLLED RELEASE FORMULATION.

1. Short biological half-life
2. Long biological half-life
3. Potent drugs with a narrow therapeutic index
4. Large doses
5. Poorly absorbed
6. Low/high solubility
7. Active absorption
8. Extensive first pass effect

For drugs with a short biological half-life of less than 2 hours, or those which are administered in large doses, a controlled release dosage form may need to contain a prohibitively large amount. On the other hand, drugs with a long biological half-life of 8 hours or more are sufficiently sustained in the body from conventional doses, and prolonged release dosage forms are generally not necessary (Welling, 1983).

Absorption of poorly water soluble compounds is often limited by its dissolution rate. Incorporation of such compounds into a controlled release formulation is therefore unnecessary, and is likely to reduce absorption efficiency. On the otherhand drugs with high solubility may be difficult to convert to slowly dissolving forms (Abdou, 1989).

There are several exceptions to the characteristics mentioned above. Nitroglycerin is reported to have a short biological half-life of 0.5 hours. It is rapidly metabolised in the liver and is generally considered to be poorly absorbed orally. However, a large number of oral controlled release nitroglycerin products are available, in addition to an increasing number of topical and transdermal preparations (Welling, 1983). The low circulating levels of nitroglycerin

obtained from these products appear to provide adequate prophylaxis against anginal attacks, but would be inadequate to treat acute anginal attacks.

2.6 TYPES OF ORAL CONTROLLED RELEASE PRODUCTS

Oral controlled release formulations can be classified as:

2.6.1 Enteric coated preparations
2.6.2 Repeat action products
2.6.3 Matrices of waxes and fats
2.6.4 Matrices of polymers
2.6.5 Ion exchange resins
2.6.6 Drug release by osmosis
2.6.7 Pellets type preparations

2.6.1 Enteric Coated Preparations

Usually preparations with enteric coating are designed to resist or reduce dissolution of the active compound in the stomach in order to prevent destruction and inactivation of the drug by the gastric contents, or to protect the stomach from the drug. A local high concentration of the drug can irritate the gastrointestinal mucosa and may produce intolerances, chiefly in the form of nausea and vomiting, at the same time interfering with proper absorption. In addition, when release of the drug occurs only in the intestine, dilution in the stomach is avoided to enable the drug to reach the intestine in a concentrated form.

Many substances are used for enteric coating such as cellulose acetate phthalate (CAP) (Polli *et al.*, 1970; Osterwald and Bauer, 1981), shellac (Sheorey *et al.*, 1991), acrylic polymerised resins like Eudragit L and S (Spitael and Kinget, 1977; Bauer and Osterwald, 1979), and fatty acids (Toplis, 1915; Renwanz *et al.*, 1969).

The most extensively used polymer for enteric coating is cellulose acetate phthalate (CAP). However it only dissolves above a pH of 6 and may delay release longer than desired. It is permeable to moisture and simulated gastric juice in comparison with other enteric polymers and is susceptible to hydrophilic breakdown on storage.

Cracking of the film, either during application or on storage will result in a loss of enteric properties. Cracking problems can effectively be overcome by plasticisation. This concept will be discussed later.

2.6.2 Repeat Action Products

Repeat action products are constructed by applying a dose containing layer around a coated core by the usual coating technique (pan or compression coating). The dose in the outer layer is released immediately after ingestion. The release of the subsequent dose in the inner core is delayed by use of either a time barrier or an enteric coating, so drug delivery may occur after a certain time interval or in a certain environment in the GIT.

With a timed release coating, e.g. Polaramine Repetab^{R} one attempts to delay the release of the active ingredient from the core, usually for 4-6 hours after ingestion of the tablet. The drug should be released at definite intervals after ingestion, regardless of the location of the coated material in the alimentary canal. Once the coating is breached, complete release of the drug occurs. The onset of release is usually controlled by physical factors such as pH, and/or gut action (De Haan and Lerk, 1984).

Apart from the convenience to the patient, the repeat action tablet has no therapeutic advantage over individually administered single doses. This dosage form is not designed for steady-state therapy (Notari, 1980). The so-called peaks and valleys in drug concentration in the blood are quite similar to those after administration of conventional dosage forms.

2.6.3 Matrices of Waxes and Fats.

Drugs are often incorporated into a mixture of digestible and indigestible fatty substances . Examples of waxes and fats which are considered to be resistant to digestion are carnauba wax, beeswax, stearyl alcohol, cetostearyl alcohol, solid and liquid mineral oils. Digestible fats and fat-soluble agents commonly used are glyceryl monostearate, stearic acid, and others (Lordi, 1986; Chalabala and Starka, 1970).

The active ingredient is often dissolved or suspended in a fat-wax mixture. Drug release from matrices occurs by gradual surface erosion of the tablet or leaching. Fats which are affected by pH or enzymes are less suitable, because individual variations may provide differences in drug

release. In Slow-K^{R} tablets, potassium chloride is embedded into a mixture of indigestible fatty alcohols (Gumma *et al.*, 1971).

2.6.4 Matrices of Polymers.

This type of controlled release preparations is mostly made by mixing or granulating the drug in a polymer and excipients, such as channelling agents and lubricants, and subsequent compression into tablets (Dittgen *et al.*, 1977; Georgakopoulos, 1981).

Diffusion of the drug through the polymer in matrix systems is the rate limiting step, but the release rate decreases with time. The drug can elute out of the matrix, first by dissolution and then by diffusion through the polymer. The drug molecules at the surface of the matrix are the first to be eluted, and after the surface layer becomes exhausted, the inner layer then begins to be depleted. As more drug particles elute out of the matrix, the drug depletion zone becomes larger and the thickness of the polymer to be passed by the drug becomes greater. The insoluble plastic skeleton will generally be excreted in the faeces. The release rate is not zero order but proportionate to the square root of time.

The basic principle of the Durettor^{R} design has been extensively studied (Fryklof *et al.*, 1960; Sannerstedt, 1960). The tablets are processed by comprising a granulate of the active substance within an insoluble plastic matrix or mixture of plastics (polyvinyl acetate, polyvinyl chloride, ethylcellulose, etc.). Drug release from a tablet prepared according to the Gradumet^{R} principle, is somewhat similar to that of the Durettor^{R} tablet.

A totally different release mechanism is created when a hydrophilic matrix material like CMC is used, HPMC (Christensen and Dale, 1962; Huber *et al.*, 1966), carboxyvinyl polymers or acrylic acid copolymers (Johnson, 1967). The soluble polymer forms a gelatinous-layer around the tablet after exposure to gastrointestinal fluids. The release mechanism is limited by the rate of water penetration into, and diffusivity of drug through the pseudo-gel formed (Bamba *et al.*, 1979).

2.6.5 Ion Exchange Resins

These agents are water soluble resinous materials containing salt-forming groups in repeating positions on the resin. Either cationic or anionic groups can be used to produce the desired ion-exchange resin.

The drug-charged resin is prepared by mixing the resin with the drug solution either by repeated exposure of the resin to the drug in a chromatography column or by keeping the resin in contact with the drug solution for extended periods of time. The drug resin is then washed to remove contaminated ions and dried to form particles or beads (Lee and Robinson, 1982).

The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion exchange groups.

$$Resin^{+} - Drug^{-} + X^{-} \rightleftharpoons Resin^{+} - X^{-} + Drug^{-}$$

conversely

$$Resin^{-} - Drug^{+} + Y^{+} \rightleftharpoons Resin^{-} - Y^{+} + Drug^{+}$$

where X^{-} and Y^{+} are ions in the GI tract

This system is advantageous for drugs that are highly susceptible to degradation by enzymatic processes since it offers a protective mechanism, by temporarily altering the substrate (Grass and Robinson, 1990).

Coating of the resin beads with the appropriate polymers, which act as a diffusion barrier to both exchange ions and exchanged drugs and water, provides a controllable rate-limiting factor that minimises the effect of *in vivo* variables (Raghunathan, 1981).

Pennwalt's 'Pennkinetic' system is a recent innovation that incorporates a polymer barrier coating and bead technology in addition to the ion-exchange mechanism. The initial dose comes from the uncoated portion, and the remainder from the coated beads. The coating does not dissolve and the release is controlled over a 12 hour period by ion-exchange e.g. Delsym^{R} (Anon, 1983; Abdou, 1989).

This approach to sustained release, however, has the limitation that the release rate is proportional to the concentration of ions present in the area of absorption. Although the ionic concentration of the gastrointestinal tract remains rather constant within limits (Erikson, 1970) the release rate can be affected by variability in diet, water intake, and individual intestinal content.

2.6.6 Drug Release by Osmosis

The construction of the Oros^{R} system and the principles of drug delivery can be summarised as follows: an osmotically active drug containing core is surrounded by a rate controlling semi-permeable coating, provided with an orifice (Figure 2.3). When immersed in gastrointestinal fluids, water is osmotically imbibed through the semi-permeable barrier at a controlled rate, determined by barrier permeability to water and by the osmotic pressure of core formulations. The rate of release of the drug in this system can be altered by changing the specific permeability of the membrane or by altering its thickness. As long as excess solid is present inside the device, a constant volume per unit time saturation, equal to the volume of solvent uptake, will be dispensed through the orifice (Figure 2.3).

The osmotic pump represents a relatively new concept in controlled release preparations. The first commercial product containing indomethicin (Osmosin^{R}) was introduced in clinical practice in many countries, but due to ulcerogenic effects in a small number of patients, the product was withdrawn in 1983 from the market (Anon, 1985).

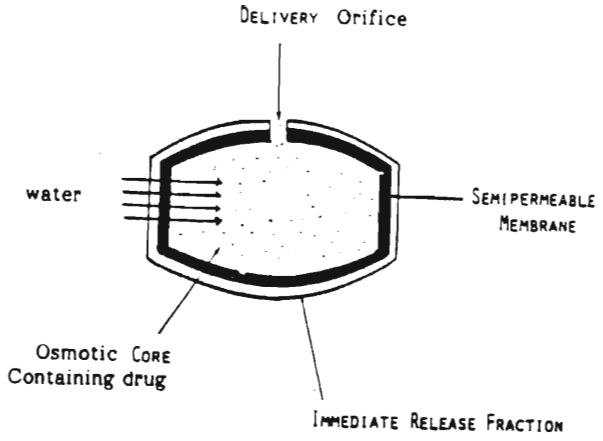


FIGURE 2.2 : CROSS SECTION OF AN OSMOTIC PRESSURE CONTROLLED RELEASE SYSTEM (ABDOU, 1989; page 231)

Acutrim^{R} (phenylpropanolamine hydrochloride) the appetite suppresant from Ciba Geigy, relies on the Oros^{R} osmotic delivery system. The drug resevoir is surrounded by a semi-permeable membrane in which a single opening has been drilled using a laser (Anon, 1985).

An osmotic system uses acetazolamide for the treatment of ocular hypertension in glaucoma (Shargel and Yu, 1985). The frequency of side effects experienced by the patients using the osmotic system was consistently less than that of the conventional tablet (Figure 2.4).

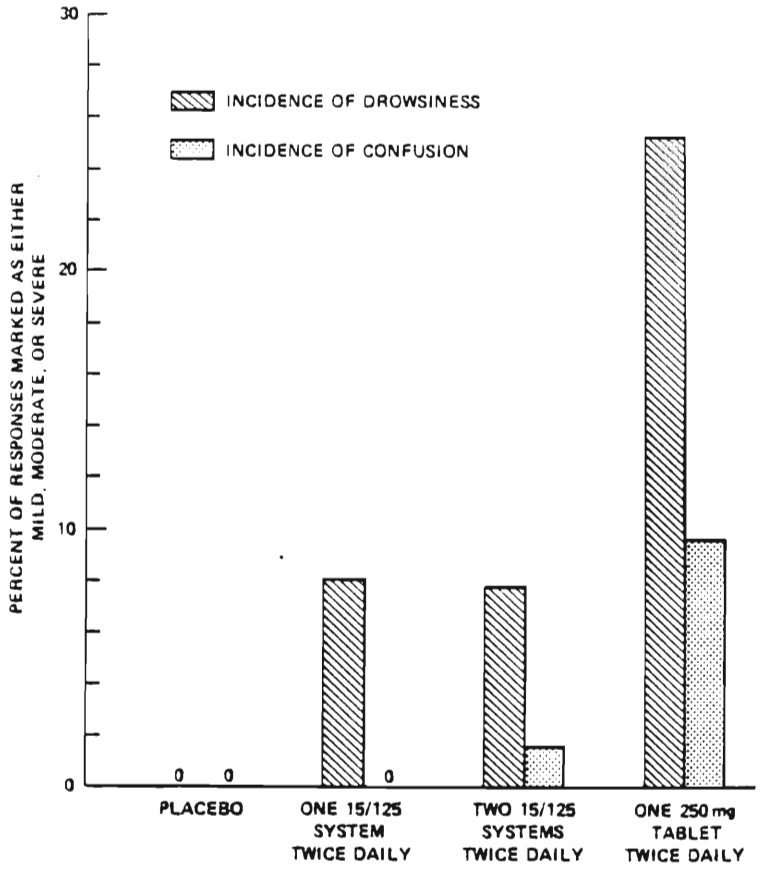


FIGURE 2.3 : INCIDENCE OF DROWSINESS AND CONFUSION ON ACETAZOLAMIDE GIVEN IN THREE REGIMES (SHARGEL AND YU, 1985; page 370)

When the therapeutic system was compared to the regular 250mg tablet given twice daily, ocular pressure was effectively controlled by the osmotic system. More frequent incidence of side effects were seen with the tablet as compared to the osmotic system.

2.6.7 Pellets Type Preparations

Lipowski's (1938) patents were the first to describe an oral dosage form consisting of a number of small drug-containing pellets, having different thicknesses of the coating to give slow and constant release of drug on ingestion (De Haan and Lerk, 1984).

The principle involved in dividing a dose of drug into many small bodies as described by Lipowski (1938) is quite sound. Gastrointestinal absorption of drugs is in general, quite erratic. In many cases erratic absorption is due to variations in release of drug from the dosage form. Division of the dose into many parts increases the probability that an effective dose of the drug will be made available for absorption and hence, properly designed long acting products can be expected to make gastrointestinal absorption more regular and predictable.

The construction of the Spansule^{R} type brand of encapsulated pellets intended to provide sustained release of drugs has been described by Blythe and co-workers (1958) who reported:

'We theorized that there would be less physiological impedance to the passage of the pellets through the pylorus. If a single tablet fails to disintegrate, one loses the complete benefit of the entire dose, however, if a few of the mydriad of small pellets fail to distintegrate at the desired site, this failure will not noticeably alter the effect of the particular dose they contain.'

The pellets type of sustained release preparation is often referred to as the 'bead'-type preparation. In general, the beads are prepared by coating drug powder onto preformed cores called non-pareil seeds (20-40um). These non-pareil seeds are made from a slurry of starch, sucrose and lactose. The drug coated beads generally provide a rapid release carrier for the drug depending on the coating solution used in coating the drug. Sucrose solution provides a convenient way of coating the drug onto the beads without impairing the rapid release of the drug. Once the drug beads are prepared, they may be further coated with a protective coating to allow a sustained or prolonged release of the drug (Shargel and Yu, 1985).

The drug powder can be coated onto the inert non-pareil seeds by dissolving it in a non-aqueous solvent such as a mixture of acetone and alcohol. In instances in which the dose of the drug is large, the starting granules of material may be composed of the drug itself.

Some of the beads or granules (one third) remain uncoated and are intended to provide the initial therapeutic dose when taken; coats of a lipid material like beeswax or ethyl-cellulose are applied to the remainder (two thirds to three quarter) of the granules. A careful blending of these pellets coated with different coating thicknesses may achieve any release profile desired. The coating material may be coloured with a dye material so that the beads of different coating thicknesses will be darker in colour and distinguishable from those having fewer coats and being lighter in colour (Ansel, 1985). Alternatively, a blend of pellets coated with materials of different solubility may also provide a means of controlling dissolution.

The pellets dosage form can be prepared as a capsule or tablet. When pellets are prepared as tablets, e.g. Peltab^{R}, the pellets must be compressed lightly so that they do not break. A disintegrant is included in the tablet causing the beads to be released rapidly after administration.

The first product was introduced in 1952 by Smith Kline and French, as multiples of specially coated tiny beads filled in hard gelatine capsules. The system known as 'Spansules' was used to sustain the release of Dexedrine^{R} (dexamphetamine) (Abdou, 1989)

2.6.7.1 *Advantages of Pellets*

A major advantage of the pellets dosage form is that the pellets are less sensitive to the effect of stomach emptying. Since there are numerous pellets within a capsule, some will gradually reach the small intestine and deliver the drug (Shargel and Yu, 1985).

In clinical tests using about 400 subjects exhibiting various types of allergic distress, Green (1954) found that the drug chlorpheniramine maleate, which contained pellets formulated into sustained release capsules, gave excellent symptomatic relief to 66% of the subjects who received a 12mg dose 12 hours. The incidence of side effects to the dosage form was unusually low, and patient compliance of the drug was excellent because of the convenience of dosage.

There is a substantial body of clinical data on pellets coated into tablets. Steigman *et al.*, (1959) described the clinical evaluation of Belladenal Spacetabs^{R}, a combination of belladonna alkaloids and phenobarbital, in patients with gastrointestinal disorders. They measured gastric secretion and bowel motility and found that the result with the Spacetab^{R} formulation was as good as, if not better than, that obtained with conventional forms, recognising the convenience of less dosing with the sustained form (Upton *et al.*, 1980).

The delivery mechanism from sustained release pellets was demonstrated *in vivo* using radiological studies (Galeone *et al.*, 1981). The results confirmed that the release and hence absorption of the active drug material from the pellets took place over a large area of the GIT, thereby avoiding high concentrations of potentially irritating material in any one area.

A diffusion rate-limiting membrane-controlling drug release from subdivided dosage units is therefore preferable to one from which the release of drug depends on membrane rupture or unit erosion. The release of drug from the latter type is less predictable and more variable, depending totally on the condition of the GIT (Bechgaard and Baggenson, 1980)

2.6.7.2 *Recent Studies Utilizing Pellets*

Most of the reported methods of producing controlled release pellets employ aqueous-based polymeric coating or matrix materials in the form of an emulsion or colloidal suspension of water-insoluble polymers such as ethylcellulose (Ghebre-Sellasie *et al.*, 1988; Gilligan and Po, 1991) or acrylic resin derivatives (Ghebre-Sellasie *et al.*, 1987; Chang and Hsaio, 1989; Li *et al.*, 1989).

The preparation of a drug-coated core formulation using a methylcellulose or hydroxypropylmethylcellulose polymeric system with diphenhydramine as a model drug was studied by Wan and Lai (1991). *In vivo* drug release from the coated granules were shown to be dependent on the drug-loading, hydrophilicity, adhesive properties, viscosity and total amount of polymer in the drug polymer coat. These results have important implications for the design of drug coated granules as in modified release dosage form employing a water soluble polymeric system.

Gilligan and Po (1991) formulated sustained release pellets of dextromethorphan hydrobromide using ethylcellulose (Aquacoat^{R}, FMC Corp.). It was shown that adequate post-coating curing is important to ensure consistency of release rates. Curing at 60°C for at least 1 hour is necessary in order to ensure that the formulation produced show no ageing effects in release rates. Similar studies using ethylcellulose (Surelease^{R}, Colorcon Inc.) were performed by Ghebre-Sellasie *et al.*, (1987). To ensure the stability of the coating during storage and handling over a wide range of temperatures, dosage forms coated with Surelease^{R} must be cured at elevated temperature.

The relationship between the film thickness on a bead (pellet) and the pellets size and mass in a polydispersed system was studied by Westdyk *et al.*, (1990). The larger beads exhibited much slower release rates compared to the smaller beads and the differences could not be explained by relative surface areas. Examination of the beads by scanning electron microscope indicated that the larger and heavier beads received a thicker film compared to the smaller or lighter beads. This trend was attributed to differences in the fluidisation patterns and velocities of the various size beads.

Controlled release beads containing chlorpheniramine maleate, coated with Eudragit^{R} RL/RS were prepared using the Wurster process. The effect of membrane thickness, polymer ratio of coating material, agitation speed, and pH of dissolution medium on drug release were investigated using the USP XXI dissolution basket method. The results indicated that the release of the drug can be controlled by formulation factors such as thickness of the membrane and concentration of the Eudragit^{R} polymer in the coating fluid.

The pH of the dissolution media can influence the release of drug if the drug exhibits pH-dependent solubility characteristics. The results obtained in this study demonstrate that the transport of the drug from coated beads is determined by a membrane controlled permeation process (Jambhekar *et al.*, 1987).

2.7 CRITERIA TO BE CONSIDERED IN THE SELECTION OF A CONTROLLED RELEASE DOSAGE FORM

When a drug meets the criteria which make the incorporation into a controlled release form appropriate, one has to decide which type of dosage form is suitable for the drug in question.

Ideally the dosage form chosen would not only release drug at a constant rate, but would also allow for constant drug absorption by the gastrointestinal tract.

Sustained release products may be divided into two basic categories: single unit and multiple unit systems. It is the objective of this section to demonstrate the advantages of administering multiple unit systems over single unit oral dosage forms.

2.7.1 Factors which Affect the Bioavailability of the Drug

There are a variety of factors that may alter drug absorption by affecting the rate or extent of absorption. Interactions in absorption are mediated by physico-chemical or physiological factors. Physico-chemical considerations include the characteristics of the dosage form such as pH and pk_a and altered solubility, dissolution, or chemical stability by fluids and other materials present within the GIT (Mayersohn, 1981).

2.7.1.1 *pH and pk_a*

Most drug molecules are either weak acids or bases which will be ionized to an extent determined by the compound's pk_a and the pH of the biological fluid in which it is dissolved.

Over the years there has been an unqualified acceptance of the pH-partition hypothesis and, as a result, many texts and considerable literature on drug absorption indicate that acidic drugs are best absorbed from the acidic gastric fluids of the stomach and basic drugs from the more alkaline fluids. If all other conditions are the same, the non ionised form of a drug in solution would be more rapidly absorbed than the ionised form. However, conditions along the GIT are not uniform and hence most drugs, whether ionised or non-ionised (i.e. regardless of pH) are best absorbed from the small intestine as a result of the large absorbing surface area of this region.

2.7.2 Physiological Factors Influencing Bioavailability

Gastric emptying is subject to both neural and hormonal regulation, apart from being influenced by factors like the degree of distension, composition, and viscosity of the stomach contents, as well as pH and temperature (Nimmo, 1976; Melander, 1978).

The gastric emptying rate is influenced by a large number of factors as listed in Table 2.3.

TABLE 2.3 : FACTORS WHICH AFFECT GASTRIC EMPTYING

1. Physical state of gastric contents
2. Volume (starting volume)
3. Type of meal
4. Chemicals (acid or alkali)
5. Drugs (antacids, anticholinergics)
6. Body position
7. Viscosity
8. Emotional states
9. Disease States
10. Exercise
11. Obesity
12. Gastric surgery

Source : Mayersohn, (1981).

Gamma scintigraphy has been used to follow the gastrointestinal transit of a variety of pharmaceutical formulations. The *in vivo* distribution of pellets (Davis *et al.*, 1984a), controlled release pellets (Bechgaard and Ladefoged, 1978; Davis *et al.*, 1987), tablets (Sangekar *et al.*, 1987), controlled release tablets (Daly *et al.*, 1982; Davis *et al.*, 1991), osmotic tablets (Davis *et al.*, 1984b) and capsules (Kaus *et al.*, 1984) have been reported. This technique not only provides data on release characteristics, but also on the position of the delivery system within the GIT.

The gastrointestinal transit of a pharmaceutical dosage form will depend not only upon the size, shape, and nature of the system, but also upon the physiological factors, the most important being the presence or absence of food in the stomach (Bechgaard, 1982; Davis *et al.*, 1984a). Solutions are emptied rapidly from the stomach, as are small particles of less than 1-2mm in diameter (Kelly, 1981). Particles greater than this (1-2mm) have to be reduced in size by the normal digestive phase and to be cleared by the stomach by the so called interdigestive housekeeper wave (Szurszewski, 1969).

Administration of the particles during or soon after a meal is likely to prolong the duration of action of the preparation, whilst minimising fluctuations in bioavailability. The bigger the meal, the slower the emptying, and pellets would spread along the length of the intestine. But the time a preparation spends in the small intestine was always 2-3 hours no matter what the dosage form tested or what the patient had eaten (O'Reilly *et al.*, 1987).

The gastrointestinal transit time of a single-unit tablet, determined as the physical appearance of a tablet that remains intact, varies between and within the subjects from a few hours to more than 30 hours. This incidence is also reflected in the well known considerable variation in the rate of availability observed after ingestion of single-unit enteric coated tablets, as drug availability from this type of formulation is mainly dependent on the location of the depot, being either in the stomach or in the small intestine (Hulme *et al.*, 1975; Bogentoft *et al.*, 1978).

Variations in transit time are surprisingly high when compared to the general conception that single-unit preparation tend to follow food, which is assumed to have a normal transit time through the small intestine between 3 and 18 hours (Prescott, 1974). Gastric emptying of a single-unit dosage

form may be characterised by an essentially random process with an inherently large intra- and intersubject variation. The application of the multiple-unit dosage principle mainly eliminates the dependency of the depot on gastric emptying, since the sub-units are sufficiently small (diameter less than 1mm) to pass through the pylorus even when the sphincter is closed (Feinblatt and Fergusen, 1957; Feinblatt and Fergusen, 1958; Bechgaard and Ladefoged, 1978; Galeone *et al.*, 1981). Accordingly, individual variations in the gastric emptying of the sub-units are small. When measured by external scanning, it has been shown that the sub-units are emptied gradually from the stomach with a mean time of 1.5 hours (Bogentoft *et al.*, 1981).

In some instances it is desirable to detain the drug depot in the upper gut to ensure optimal absorption or to prolong the absorption phase, as with drugs having short biological half-lives, in order to facilitate a lower dosage frequency (once daily). As the sub-units of multiple-units formulations are distributed more freely throughout the gastrointestinal tract, they offer the possibility of achieving a longer-lasting and more reliable source of the drug.

The sub-units from a multiple-unit formulation are scattered as they pass down the gastrointestinal tract, and depending on their density, the sub-units show longer and more reproducible average transit times compared to single-unit tablets. This is confirmed by the high reproducibility of the rate of availability achieved with enteric-coated sub-units (Green, 1966; Bogentoft *et al.*, 1978; Bechgaard *et al.*, 1982).

Since the influence of gastric emptying on intra- and inter-subject variations can be eliminated by the application of a multiple-unit dosage form, the only expected influence of a pH-dependent diffusion rate-limited process on the rate of availability would be one related to the pharmacokinetic characteristics of the drug, i.e. with an absorption rate dependent mechanism.

2.8 MECHANISM OF CONTROLLED RELEASE

Among the many types of commercial preparations available, there is probably hardly any one type that works on one pure mechanism. Most of the controlled release preparations work by a combination of processes involving dissolution and diffusion. Controlling the rate of water influx to 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.

A zero order release of drug is needed for the dosage form, which means the rate of drug release is independent of drug concentration. To attain a zero order release rate there are several mechanisms and dosage form modifications that can be employed, viz. resevoir devices and osmotically controlled systems. We will restrict our coverage of potential mechanisms to those that can be employed in the coating approach to sustained release i.e.

2.8.1 Diffusion
2.8.2 Dissolution

2.8.1 Diffusion

Diffusion is defined as a process of mass transfer of individual molecules of a substance, brought about by random molecular motion and associated with a concentration gradient.

Fick's first law of diffusion states that a drug diffuses in the direction of decreasing concentration across a membrane where J is the flux of the drug in amount/area-time.

$$J = -D \frac{dc}{dx} \qquad \text{Equation 1}$$

where D is the diffusion coefficient in area/time, c is the concentration, and x is the distance. Assuming steady state, equation 1 can be integrated to give:

$$J = \frac{-D \Delta C}{l} \qquad \text{Equation 2}$$

or expressed in more common form when a water insoluble membrane encloses a core of drug and the drug must diffuse through the membrane, the drug release rate dM/dt is given by:

$$\frac{dM}{dt} = \frac{ADK \Delta C}{l} \qquad \text{Equation 3}$$

where A is the surface area, D is diffusion coefficient, K is the partition coefficient of drug, l is the diffusional pathlength (thickness of coat in the ideal case), and C is the concentration gradient across the membrane.

In most cases the drug must partition into a polymeric membrane of some sort and then diffuse through the membrane to reach the biological milieu. When the tablet or microcapsule contains excess drug or suspension, a constant activity of drug will be maintained until the excess has been removed, giving rise to a constant drug release.

The more common diffusional approaches for sustained drug release are shown in Figure 2.5.

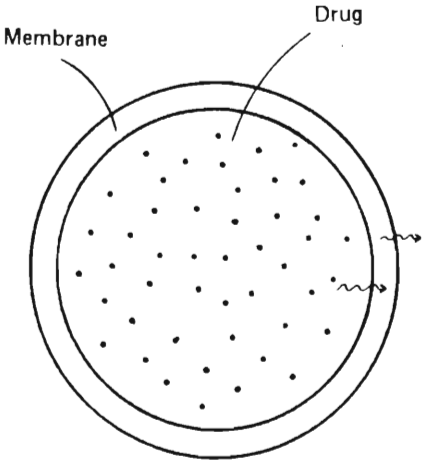


FIGURE 2.5 : DIFFUSION CONTROL OF DRUG RELEASE BY A WATER INSOLUBLE POLYMER. E.G. MICROENCAPSULATED DRUG (LEE AND ROBINSON, 1982; page 141)

In Figure 2.5 the polymer is water soluble and the important parameter is solubility of the drug in the membrane since this gives rise to the driving force of diffusion. The water-soluble polymer then dissolves out of the film giving rise to small channels through which the drug can diffuse. The small channels would presumably give a constant diffusional pathlength and hence maintain constant conditions as described earlier. Although diffusion through the channels should be much more rapid than diffusion through the membrane noted in Figure 2.5, it is possible to have a situation whereby membrane diffusion, being quite rapid in this case, is within an order of magnitude of pore diffu-

sion. In this event, both types of diffusion, membrane and pore, will provide contributions to the overall diffusion rate and the equations would have to be modified to account for these combined effects.

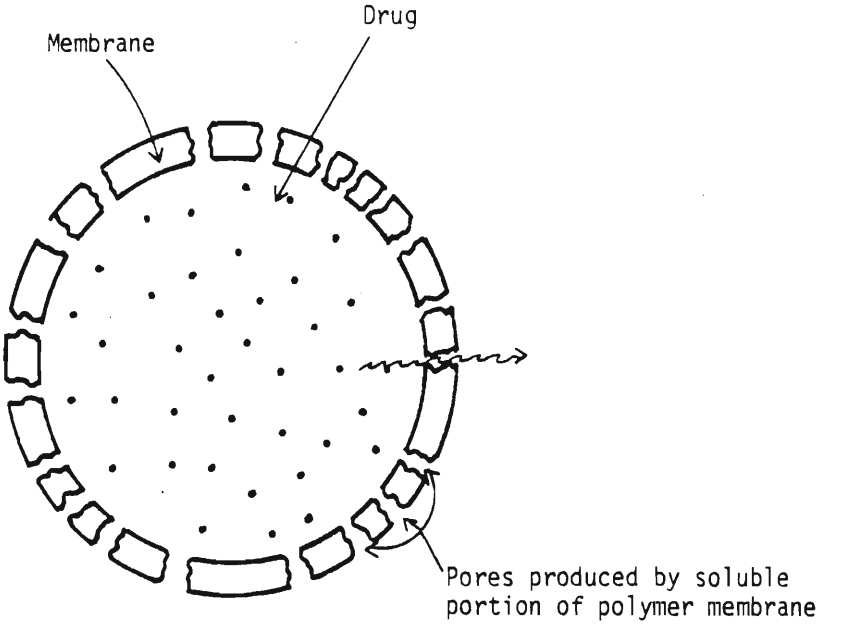


FIGURE 2.6 : DIFFUSION CONTROL OF DRUG RELEASE BY A PARTIALLY WATER-SOLUBLE POLYMER. E.G. POLYMER COATING CONSISTING OF ETHYLCELLULOSE AND METHYLCELLULOSE (LEE AND ROBINSON, 1982; page 143)

An alternate type of diffusion controlled system is shown in Figure 2.6. Here a solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

2.8.2 Dissolution

In this case the drug is embedded (coated) in a polymeric material and the dissolution rate of the polymer dictates the release rate of the drug. The drug release rate dm/dt, if governed by erosion or dissolution, can be expressed as

$$\frac{dM}{dt} = A\frac{dx}{dt} f(c)$$

where dx/dt is the erosion rate, f(c) is the concentration profile of the matrix and A is the area.

A constant erosion rate can produce zero order release kinetics, provided the drug is dispersed uniformly in the matrix and the area is maintained constant. Often, swelling of the system or a significant change in area produces non zero order release. The common forms of dissolution are shown in Figure 2.7.

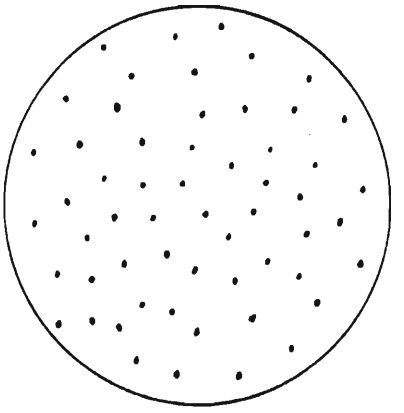


FIGURE 2.7 : DISSOLUTION CONTROL OF DRUG RELEASE VIA DRUG IMPREGNATED EROSION. E.G. MICROENCAPSULATED DRUG WHERE THE DRUG IS UNIFORMLY DISTRIBUTED IN THE MATRIX AND THE COATING IS ERODABLE (LEE AND ROBINSON, 1982; page 151)

In Figure 2.7 there is a barrier coat across a microcapsule or non-pareil seed containing drug and the release of drug is dictated by the dissolution rate and the thickness of the barrier coat. Varying the coating thickness, or layering the concentric spheres of coating material and the drug reservoir material, gives rise to different release times producing the repeat action dosage forms. Once the polymer has dissolved, all of the drug contained in the capsule or seed is available for dissolution and absorption.

2.9 FORMULATIONS OF ORAL CONTROLLED RELEASE PELLETS

2.9.1 Introduction

The coating of 'pills' has been practised for at least 10 centuries. It was not until the 19th century that pills were coated in rotating pans. One of the first to sugar coat pills was Warner, a Philadelphia pharmacist. Machinery was later developed for the compression of tablets and this form gradually replaced pills. Formulas and methods used for sugar coating tablets tend to be classical and have not changed in five or six decades.

Coating equipment, other than rotating pans, was described in the literature in the 19th century. It was not until 1953 that the first of these came into use. The first press-coated tablet was marketed in that year and shortly thereafter tablets were marketed which were coated by a fluid bed process.

The concept of film coating of tablets was first described in the literature in 1930; the first commercial product was introduced in 1954. Film coating is now replacing sugar coating for many new tablet products due to certain basic disadvantages of sugar coating, such as cost of coating time

and bulk. The advantages of the film coating process compared to sugar coating are its higher speed of agitation and superior mechanical properties of the coat (Horvath and Ormos, 1989). Film coating is the technique of choice in the coating of controlled release dosage forms where the most commonly used polymers include the modified acrylates and the water-insoluble celluloses.

There are many important reasons for coating dosage forms or their components (Robinson, 1980). Pharmaceuticals have been coated to:

- Mask unpleasant taste and improve appearance (Olsen and Mehta, 1985)
- Prevent contact with drug which is irritating or potentially allergenic (Robinson, 1980)
- Control the site of drug release (enteric coating) Chang *et al.*, 1987)
- Delay or prolong absorption of the drug component by retarding release of drug from the dosage form (sustained release) (Robinson, 1980).

2.9.2 Parameters Affecting Core Coating

The manufacturing of controlled release pellets is a highly complex process influenced by the following parameters.

2.9.2.1 The active substance

2.9.2.2 The core

2.9.2.3 The coating technique and equipment

2.9.2.4 The membrane material and formulation

2.9.2.1 *The Active Substance*

The physico-chemical properties of the active substance restrict the formulation of the core as well as the choice of membrane composition. The water solubility of the drug is of the utmost importance in the formulation. Both the magnitude and possible pH dependence of water solubility is critical to the formulation in respect of obtainable release characteristics. Besides solubility properties, the chemical nature of the drug with respect to stability must be taken into consideration during development. As the encapsulated particle is protected against the outer environment by the membrane, opportunities arise to create an inner condition beneficial to the stability of the drug.

2.9.2.2 *The Core Properties*

Besides giving the desired drug loading the core must have the following:

- sufficient mechanical strength and density
- suitable shape and size
- good flow properties and stability

To withstand the mechanical attrition during the fluidisation process, the core should have a certain degree of toughness without being brittle. The most advantageous geometric shape for a core in respect of tenacity, surface smoothness, minimum surface area and flow properties, is the sphere (Eskilson, 1985a).

2.9.2.3 *The Coating Technique*

The coating process is the effective application of a polymer dissolved in a solvent onto the core material. The coating of cores can be performed in a variety of equipment utilizing utilizing several methods and techniques available for the coating process. These methods will be be considered later in 2.9.4.

2.9.2.4 *The Membrane Composition*

The membrane is the rate controlling barrier to drug release and as such constitutes an essential part of the formulation. Factors affecting its properties are:

- type of polymer
- additives as plasticizers
- solvents
- manufacturing conditions
- membrane structure and thickness

Many polymers are suitable as membrane formers for pharmaceutical application. The polymer itself (bulk properties) control the nature of the membrane, i.e. diffusion membrane or dissolving membrane. The chemical nature of the polymer determines the solubility and hydrophilic/lipophilic characteristics of the membrane. The molecular weight of the polymer which is related to the tensile strength of the film and the glass transitional temperature influences the quality of the membrane (T_g) (Eskilson, 1985b).

Plasticizers act by reducing the glass transitional temperature of the polymer and thus its flexibility. The plasticizer can also be used to alter the hydrophilic/lipophilic character of the membrane. In practice, plasticizers are added to modify their physical properties so as to make them more suitable for the task of film coating (Hogan, 1988).

2.9.3 Film Coating Techniques

Film coating is a process which involves the deposition of a thin polymeric film (typically in the region of 10-100um thick) consisting of a polymer, plasticizer, colourant and possibly other minor additives onto the surface of a pharmaceutical dosage form, typically a tablet or granule. The film is applied by spraying the various components, dissolved or dispersed in a solvent system, onto a moving bed of tablets or granules using one of the many pieces of equipment designed for this purpose. By careful manipulation of all the constituents of the film formulation, it is possible to manufacture consistent controlled release oral dosage forms (Rowe, 1985)

2.9.4 Coating Equipment and Processing

The methods that are most suitable and applicable to the production of controlled release preparations are:

2.9.4.1 Phase separation (coacervation)

2.9.4.2 Spray drying and spray congealing

2.9.4.3 Pan coating

2.9.4.4 Air suspension

2.9.4.1. *Phase Separation (Coacervation)*

Coacervation is a phenomenon associated with colloidal solutions. The term 'coacervation' was introduced in 1929 by H.G. Bungenberg de Jong and H.R Kryt to describe the flocculation or separation of liquid from solution containing colloidal solute, under the influence of different factors such as temperature, pH, addition of electrolyte or solvents and initiation of chemical reactions.

Microencapsulation by coacervation-phase separation is generally attributed to the National Cash Register Corporation and the patents of B.K. Green. As a process, it is a means of applying relatively thin film forming polymeric coatings to small particles of solids, droplets of liquids or dispersions. Microcapsules provide a means to convert liquid to solids, separate reactive components, and control the release of materials.

The uniqueness of microcapsules lies in the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms. The salient features of microencapsulation are as follows. The coating material can be selected from a wide variety of natural and synthetic polymers, depending on the material to be coated and the characteristics desired. The amount of coating material used ranges from 3-30% of total weight which corresponds to a dry film thickness of from less than 1um to 200um, depending on the surface area to be coated.

Different film formers have been investigated for use in the formulation of coating materials as indicated in Table 2.4.

TABLE 2.4 : FILM FORMERS USED AS COATING MATERIALS

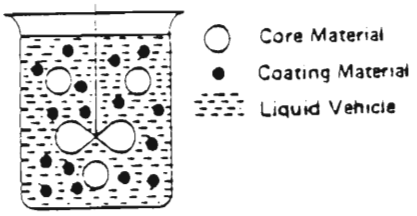
*Non enteric	*Enteric
Acacia	Anionic acrylic resins
Beeswax	Cellulose acetate phthalate
Ethylcellulose	Shellac
Polyethylene Glycol	
Polymethyl methacrylates	

* Sources : Deasy, (1984); Notari, (1980).

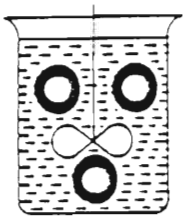
In addition such coatings may also contain plasticizers, surfactants, antitackiness agents, and dispersed solids such as pigments and opaque extenders together with suitable solvent systems (Deasy, 1984)

The general outline of the process consists of 3 steps carried out under continuous agitation (Figure 2.8).

- Formation of three immiscible phases
- Depositions of the coating
- Rigidization of the coating



2. DEPOSITION OF LIQUID-POLYMERIC COATING MATERIAL



3. SOLIDIFICATION OF COATING MATERIAL

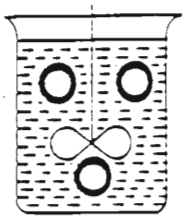


FIGURE 2.8 : PROCESS SCHEMATIC FOR MICROENCAPSULATION (BAKAN AND POWELL, 1985; page 182)

2.9.4.2 *Spray Drying/Spray Congealing Technique*

The spray drying technique consists of rapid evaporation of the solvent from the droplets. Spray drying results in the production of free flowing monodispersible particles which can be directly compressed into tablets, filled into capsules, or made into suspensions.

Spray congealing is a similar technique to spray drying. The difference is that the drug suspension in the melted substance which forms the coating (fats or waxes) is sprayed and then quickly cooled.

2.9.4.3 *Pan Coating*

A variety of shapes, sizes, and designs are available. The coating pans are motor driven, sometimes with variable-speed drives, and the pan is usually tilted at some angle from the horizontal in order to facilitate efficient mixing to obtain a uniformly coated product. Baffles or flights may be placed in a pan.

Coating solutions such as sugar syrup can be poured or 'ladled' onto the rotating mass in the coating pan. Most solutions however, are sprayed using atomizers that break up the liquid into rather fine droplets. Devices used for this purpose include pneumatic nozzles, wheel atomizers, and pressure nozzles. Traditionally, solvents have been evaporated from the coating by passing air over the surface of the tumbling particles or pellets in the pan. Presently, the use of side- and hub-vented pans which permit drying air to move through rather than over the coated pellets are preferred (Yoakum and Campbell, 1984).

Basically, the side-vented pans function in the same way as the traditional pan coaters, but the drying capacity has been considerably increased. The main advantage of the pan type coaters is that they can carry out both sugar coating and film coating even in large batch sizes. The disadvantages are poor control of the product flow pattern and low drying capacity. The flow pattern results in increased wear because the product is moved more than necessary. The low drying capacity limits the spray rate and all together the total coating time is fairly long.

2.9.4.4 *Air Suspension*

Microencapsulation by air suspension technique is generally ascribed to the inventions of Professor Dale E Wurster. The Wurster process consists of dispersing a solid particulate core material in a supporting air stream and the spray coating of the suspended particle. Figure 2.9 depicts a type of Wurster air suspension unit.

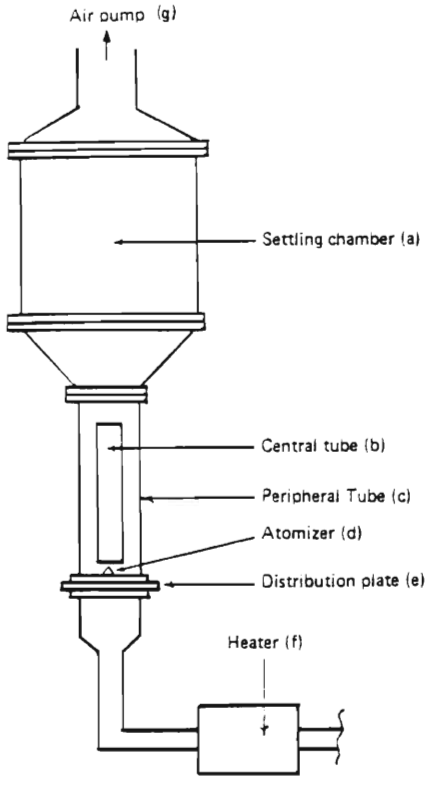


FIGURE 2.9 : SCHEMATIC DRAWING OF WURSTER AIR SUSPENSION COATING APPARATUS (WURSTER, 1982; page 121)

Within the coating chamber, particles are suspended on an upward moving air stream. The design of the chamber and its operating parameters effect a recirculating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution, is spray applied to the moving particles. During each pass through the coating zone, the core material receives an increment of coating material. The cyclic process is repeated, perhaps several hundred times during the processing, depending on the purpose of microencapsulation, the

coating thickness desired, or whether the core particles are thoroughly encapsulated. The supporting air stream also serves to dry the product while it is being encapsulated. Drying rates are directly related to the volume temperature of the supporting air stream.

Processing variables that receive consideration for efficient, effective encapsulation by air suspension technique include the following:

- Density, surface area, melting point, solubility, friability, volatility, crystallinity, and flowability of the core material.
- Coating material application rate.
- Coating material concentration.
- Volume of air required to support and fluidize the core material.
- Amount of coating material required.
- Inlet/outlet operating temperatures (Robinson, 1980).

The proper adjustment of the air flow, the temperature, and the fluid application rate are critical to the successful operation of the process. Obviously, the drying kinetics are influenced by the air flow rate and the temperature. These kinetics inturn dictate the fluid application rate.

There are three main types of coaters based on fluid beds:

2.9.4.4.1 Bottom spray

2.9.4.4.2 Tangential spray

2.9.4.4.3 Top spray

2.9.4.4.1 *Bottom spray*

This is based on the old Wurster process. Figure 2.10 shows a typical bottom spray coater.

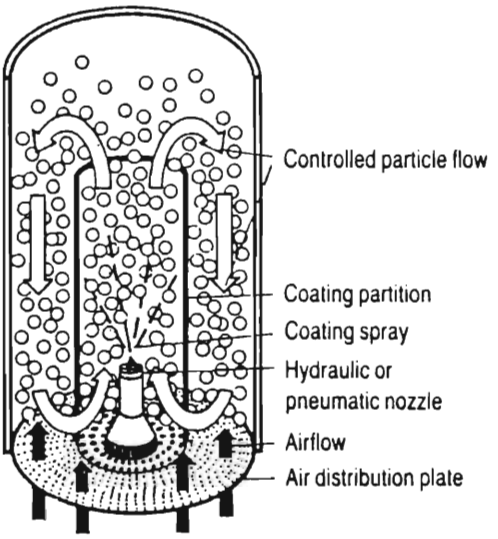


FIGURE 2.10 : BOTTOM SPRAY METHOD USED IN WURSTER AIR SUSPENSION COLUMNS (MEHTA, 1988)

The coating material is atomized from one of several nozzles just below the internal column and the actual coating takes place inside the column. The main advantages of the process is that it can provide a fast and tight coating especially with smaller particles like granules and pellets. Disad-

vantages are the rough handling of the product inside the column, the requirement of tall equipment and the general unpredictability of product distance from the nozzle.

2.9.4.4.2 Tangential Spray

In tangential spray film coaters (Figure 2.11), the air distributor plate is substituted by a rotating disc providing an annular motion to the product. The coating medium is introduced by nozzles around the periphery of the container just above the rotating base plate and sprayed directly into the moving particles.

Examples of two new tangential spray coater systems are the Ultra coater, which is used for the film coating of tablets and capsules and the Roto-Processor system, which is used for pelletizing and coating of the pellets, all in one unit. The primary advantage of the rotating units are a relatively well controlled product flow pattern, almost no loss of the coating agent and for some systems, very short processing times. Disadvantages include the complex construction with rotating devices inside the product area and the nozzles being very close to part of the product.

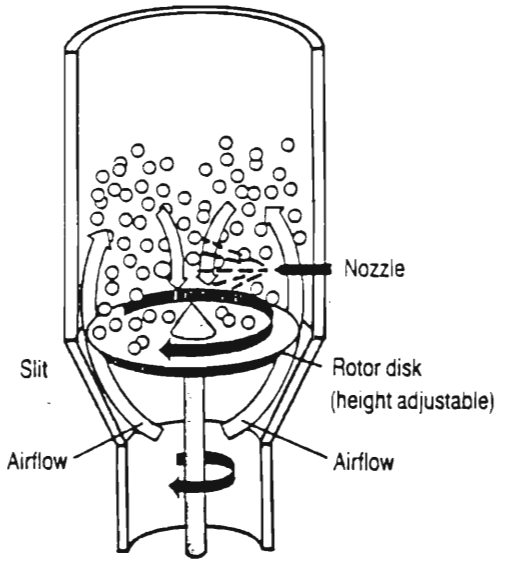


FIGURE 2.11 : TANGENTIAL SPRAY METHOD USED IN ROTARY FLUID BED COATERS (MEHTA, 1988)

2.9.4.4.3 Top Spray

Top spray systems (Figure 2.12) have been used for many years as granulate and to some extent as coaters for pellets and powders and pellets. In the case of tablet coating the use of top spray coaters has been limited, mainly due to lack of properly designed equipment. Top spray coating performs extremely efficiently in a well-controlled system, especially for the aqueous coating of tablets. The main advantages are a uniform application of the coating, short processing times, no mechanical parts in the tablet bed, and a very high drying capacity. The main disadvantage is the loss of coating material due to spray drying, especially with organic solvent based coating on small particles.

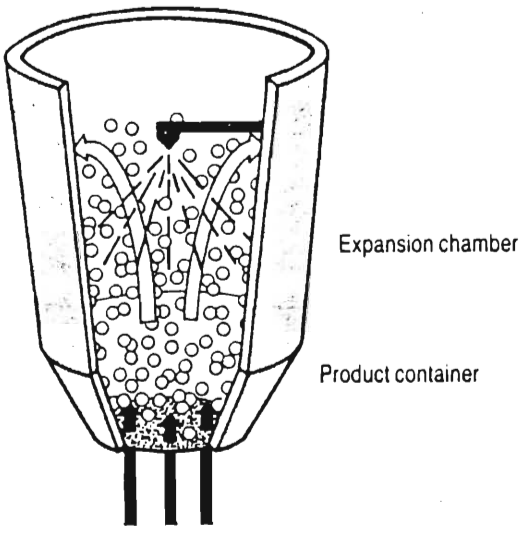


FIGURE 2.12 : TOP SPRAY METHOD USED IN CONVENTIONAL GRANULATION COATERS (MEHTA, 1988)

2.9.5 AIR SUSPENSION AS A TECHNIQUE FOR THE FUTURE

The air suspension technique is particularly suited for the coating of small particles. This applies not only to spherical micro-tablets and pellets but also to irregular shaped particles to produce controlled release dosage forms (Chang and Rudnic, 1991; Fukumori *et al.*, 1988; Li *et al.*, 1988).

The method is sufficiently flexible to make it extremely versatile, because it is possible to control the variables of the process. Solvents can be reclaimed from the exhaust so that contamination of the environment does not occur. The air suspension process operates as a closed system, people are protected from exposure to hazardous chemicals and solvents.

2.10 COATING MATERIALS

A decisive advance was made with the introduction of semi-synthetic derivatives such as methylcellulose and cellulose acetate phthalate and of the wholly synthetic polyethylacrylic esters - with specific solubility characteristics adapted by the pH conditions in the human digestive tract. These chemically modified polymethacrylates for pharmaceutical uses have become known by the tradename **EUDRAGITS**[R]

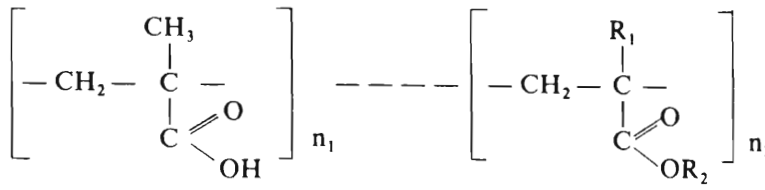
2.10.1 Eudragits®

They possess characteristic properties of solubility and permeability in the digestive juices of the gastrointestinal tract, depending upon the content of the acidic, basic and hydrophilic groups in the polymers. An extensive range of different forms are available, which make possible the controlled release of active ingredient in practically all usual, or conceivable dosage forms (Lehmann and Dreher, 1981).

2.10.1.1 *Methacrylic Acid Copolymer*

Polymethacrylate resins with the designation L and S are used as enteric coatings, because of their content of carboxylate groups, which make them insoluble in acids and pure water Table 2.5.

TABLE 2.5 : METHACRYLIC ACID COPOLYMERS



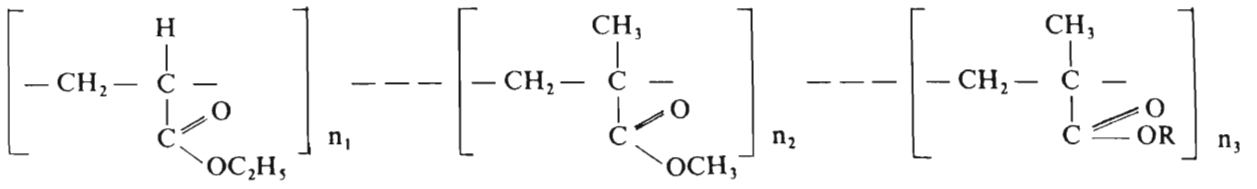
Scientific name*	n_1:n_2	MW	R_1	R_2	Behaviour in digestive juices	Eudragit® type
Poly(methacrylic acid, ethylacrylate)	1:1	250,000	H	C_2H_5	soluble pH > 5.5	L 30 D
Poly(methacrylic acid, methylmethacrylate)	1:1	135,000	CH_3	CH_3	soluble pH > 6.0	L 12.5 L 100
Poly(methacrylic acid, methylmethacrylate)	1:2	135,000	CH_3	CH_3	soluble pH > 7.0	S 12.5 S 100

Source : Lehmann and Dreher (1981)

2.10.1.2 *Methacrylate Ester Copolymers*

Eudragit^R RL/RS and Eudragit^R defined swelling capacity and permeability with respect to water and dissolved drugs, which are independent of pH.

TABLE 2.6 : METHACRYLATE ESTER COPOLYMERS



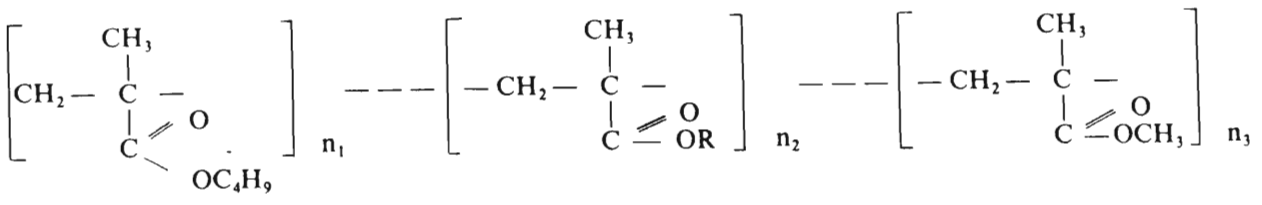
Scientific name*	$n_1:n_2:n_3$	MW	Behaviour in digestive juices	Eudragit® type
Poly(ethylacrylate, methylmethacrylate)	2:1	800,000	permeable	E 30 D
Poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride) R = $CH_2 - CH_2 - N^+(CH_3)_3Cl^-$	1:2:0.2	150,000	strongly permeable	RL 12.5 RL 100
Poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride) R = $CH_2 - CH_2 - N^+(CH_3)_3Cl^-$	1:2:0.1	150,000	weakly permeable	RS 12.5 RS 100

Source : Lehmann and Dreher (1981)

2.10.1.3 *Methacrylate Amino Ester Copolymer*

The introduction of amino-ester groups in polymethacrylates results in basic products which are insoluble in water but dissolve by salt formation in acids i.e. below pH 4 (Table 2.9).

TABLE 2.3 : METHACRYLATE AMINOESTER COPOLYMERS



Scientific name*	$n_1:n_2:n_3$	MW	Behaviour in digestive juices	Eudragit® type
Poly(butylmethacrylate, (2-dimethylaminoethyl) methacrylate, methylmethacrylate R = $-CH_2 - CH_2 - N(CH_3)_2$	1:2:1	150,000	soluble pH < 4	E 12.5
			permeable pH > 4	E 100

Source : Lehmann and Dreher (1981)

As a film former Eudragit^R NE 30 D offers the following special advantages and properties:

- As a lacquer film, it is insoluble in water and digestive fluids but is permeable and swellable.
- Possess a high binding capacity, offering special opportunities for application in granulation and in the pelleting of active substances.
- The films are permeable to water and active substances, thus providing a means of controlling active-substance release via diffusion process. The thickness of the lacquer film can be selected to match the release rate

to pharmacokinetic and therapeutic requirements.

- Possesses release characteristics are independent of the fluctuations in pH prevailing in the digestive tract.
- The short processing times, economical production and reproducible results characterise the use of this polymer as a modern method for the manufacture of sustain release preparations.

Eudragit^{R} NE 30 D is an aqueous dispersion of a neutral copolymer based on poly(meth)acrylates. The chemical structure of the polymer Eudragit^{R} NE 30 D is reflected in Figure 2.13.

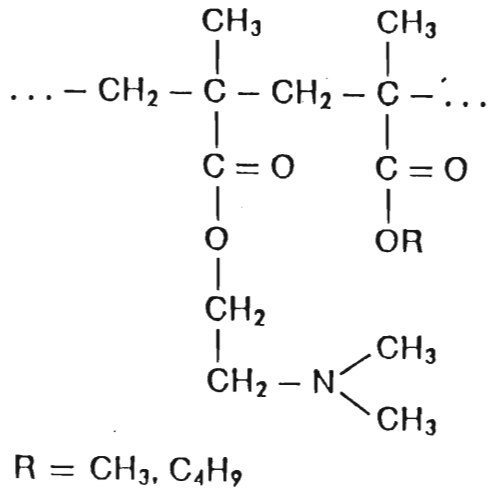


FIGURE 2.13 : STRUCTURE OF EUDRAGIT^{R} NE 30 D (EUDRAGIT DATA SHEETS, 1990)

Talc and magnesium stearate serve as separator and polishing agent. They reduce the tackiness of drying lacquer films and afford a smooth surface.

When using Eudragit^{R} NE 30 D in the manufacture of retard coatings it must be noted that the permeability of the lacquer film can be reduced by additions of hydrophobic substances and be increased by hydrophilic substances. This property can be used systematically, in addition to layer thickness, as a means of controlling diffusion. Very often polyethylene glycols, polyvinylpyrolidone, and polyoxyethylene sorbitan fatty acid esters are used as emulsifiers, wetting agents and stabilizers.

CHAPTER 3

ANTIHISTAMINES AND CHLORPHENIRAMINE MALEATE

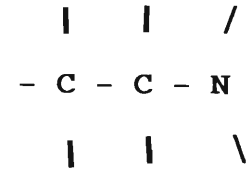
3.1 ANTIHISTAMINES

H_1-blocking drugs have an established and valued place in the symptomatic treatment of various immediate hypersensitivity reactions, in which their usefulness is attributable to their antagonism of endogenously released histamine, one of several autocoids that together elicit the allergic response.

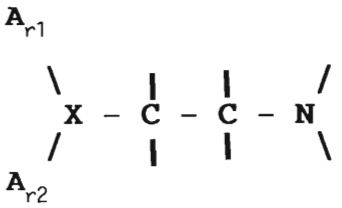
3.1.1 H_1-Blocking Agents

3.1.2 Structure Activity Relationship

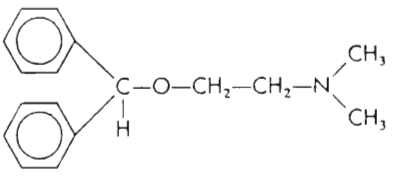
All of the available antagonists are reversible, competitive inhibitors of the interaction of histamine with H_1 receptors. Like histamine, most H_1 antagonists contain a substituted ethylamine moeity



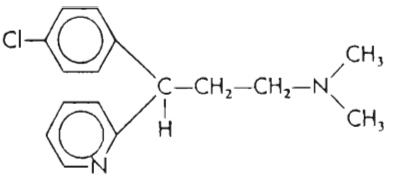
Unlike histamine which has a primary amino group and a single aromatic ring, most H_1 blockers have a tertiary amino group linked by a two- or three-atom chain to two aromatic substituents and conform to the general formula:



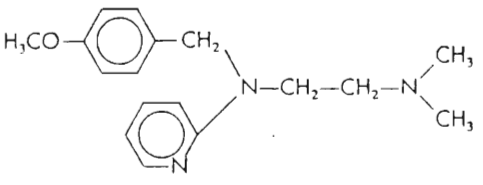
where Ar is aryl and X is a nitrogen or carbon atom or a -C-O- ether linkage to the B-aminoethyl side chain. Sometimes the two aromatic rings are bridges, as in the tricyclic derivatives, or the ethylamine may be part of a ring structure. Other variations are also possible; for example, the newer piperadine H_1 antagonists terfenadine and astemizole have aromatic ring structures on either side of the carbon chain (Ganellin, 1982) (Scheme 3.1).



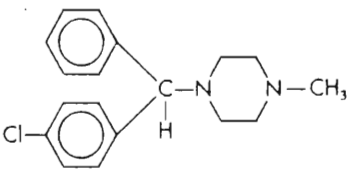
Diphenhydramine * (an ethanolamine)



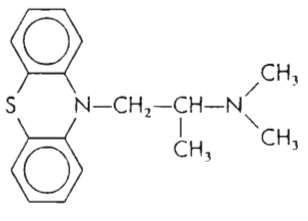
Chlorpheniramine † (an alkylamine)



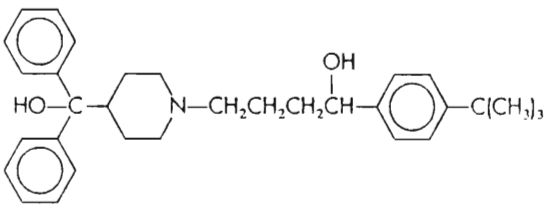
Pyrilamine ‡ (an ethylenediamine)



Chlorcyclizine § (a piperazine)



Promethazine (a phenothiazine)



Terfenadine (a piperidine)

* Dimenhydrinate is a combination of diphenhydramine and 8-chlorotheophylline in equal molecular proportions.
† Pheniramine is the same less Cl.
‡ Tripelennamine is the same less H_3CO.
§ Cyclizine is the same less Cl.

SCHEME 3.1 : REPRESENTATIVE H_1-RECEPTOR BLOCKING AGENTS (GARRISON, 1991; page 583)

A list of some antihistamines that are currently available in South Africa is outlined in Table 3.1. The brief discussion that follows is intended to provide only an indication of the different classes of H_1-blocking drugs and their properties.

TABLE 3.1 : SOME ANTIHISTAMINES THAT ARE CURRENTLY AVAILABLE IN SOUTH AFRICA (MIMS OCTOBER, 1991)

CLASS AND NONPROPRIETARY NAME	RECOMMENDED DAILY DOSE	TRADE NAME®	DOSAGE FORM	MANUFACTURER
Ethanolamines				
Diphenhydramine hydrochloride	25-50mg	Benadryl	C,E	Parke-Davis
Dimenhydrinate	50mg	Dramamine	T,S	Searle
Ethylenediamines				
Mepyramine maleate	50mg	Anthisan	T,E,I,CR	Maybaker
Alkylamines				
Chlorpheniramine maleate	4mg 8-12mg	Allergex Chlor-trimeton	T,E R,I,T,S	Propan Scherag
Brompheniramine maleate	8-12mg	Dimetapp	EX,E	Cont. Ethicals
Piperazines				
Hydroxyzine hydrochloride	25mg	Aterax	T,D,S,I	UCB
Cyclizine hydrochloride	50mg	Triazine	SUP,S	Lennon
Cyclizine lactate	50mg	Valoid	SUP,S, I,T	Wellcome
Phenothiazines				
Promethazine hydrochloride	25mg	Phenegan	T,I, E,	Maybaker
Piperidines				
Terfenadine	60mg	Triludan	T	Mer-National
Astemizole	10mg	Hismanal	T,SUS	Janssen

C = Capsule
E = Elixer
T = Tablets
CR = Cream
EX = Extentabs
I = Injection
R = Repetabs
S = Syrup
D = Drops
SUS = Suspensions
SUP = Suppositories

3.1.2.1 *Ethanolamines (Prototype: Diphenhydramine).*

The drugs in this group are potent and effective H_1 blockers that possess significant antimuscarinic activity and have a pronounced tendency to induce sedation. With conventional doses, about half of those who are treated with these drugs experience somnolence. The incidence of gastrointestinal side effects, however is low in the group. The biological half-life is 4-6 hours and the duration of action 4-6 hours.

3.1.2.2 *Ethylenediamines (Prototype: Mepyramine).*

These include some of the most specific H_1 antagonists. Although their central effects are relatively feeble, somnolence occurs in a fair proportion of patients. Gastrointestinal side effects are quite common. The duration of action is 4-6 hours.

3.1.2.3 *Alkylamines (Prototype: Chlorpheniramine).*

These are amongst the most potent H_1-blocking agents and are generally effective in low doses. The drugs are not so prone to produce drowsiness and are among the more suitable

agents for daytime use. CNS stimulation is more common in this than in any other group. The biological half-life is 12-15 hours and the duration of action 4-6 hours.

3.1.2.4 *Piperazines (Prototype: Chlorcyclizine).*

Chlorcyclizine is an H_1 blocker with prolonged action and a comparatively low incidence of drowsiness. Hydroxyzine is a long-acting compound that is widely used for skin allergies; its central-depressant activity may contribute to its prominent antipruritic action. Cyclizine and meclizine have been used primarily to counter motion sickness although promethazine and diphenhydramine are more effective. The biological half-life is 6 hours and the duration of action 12-24 hours.

3.1.2.5 *Phenothiazines (Prototype: Promethazine).*

Most drugs of this class are H_1 blockers and also possess considerable anticholinergic activity. Promethazine was introduced for the management of allergic conditions. The prominent sedative effects of this compound and its value in motion sickness were recognised. The biological half-life is 10-14 hours and the duration of action 12 hours or more.

3.1.2.6 *Piperidines (Prototype: Terfenadine).*

H_1 antagonists of this class include terfenadine and astemizole. These agents are highly selective for H_1 receptors and are devoid of significant anticholinergic actions. Together with these drug's poor penetration into the CNS, these properties appear to account for the low incidence of side effects. The biological half-life is 4-5 hours and the duration of action is 12 hours or more.

3.3 CHLORPHENIRAMINE MALEATE

Chlorpheniramine maleate, a potent alkylamine antihistamine, is widely used to alleviate symptoms of the common cold and allergic conditions (Martindale, 1989; B.P., 1988).

Chemical Names: (3-(4-chlorophenyl)-3-(2-pyridyl) propyl-N-N-dimethylammonium hydrogen maleate.
2-[p-chloro-a-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1).
Empirical formula : $C_{16}H_{19}ClN_2, C_4H_4O_4$
Molecular weight : 390.9
Description : A white or creamy white powder or waxy solid, odourless or almost odourless.

Solubility : Soluble, at 20°C, in 4 parts of water, 10 parts of alcohol and chloroform, and very slightly soluble in ether.

Acidity : A 1% solution has a pH of 4.5

Melting Point : 132 -135°C

Dissociation constant : pKa 9.1 (25°C)

Storage : Should be protected from light.

Identification : A. The infra-red absorption spectrum (Figure 3.1) is concordant with the reference spectrum of chlorpheniramine maleate.

B. The light absorption is in the range 230 to 350nm. A 0.002% (m/v) solution in 0.05M sulphuric acid exhibits a maximum at 265nm. The absorbtivity at 265nm is 0.85. The ultraviolet absorbance of an aqueous solution occurs at 262nm.

Note : The potential impurities present in chlorpheniramine maleate and the synthesis of the drug are given in Appendix 1. (Euderma, 1991)

References on the degradation products of chlorpheniramine maleate due to exposure to light were not available.

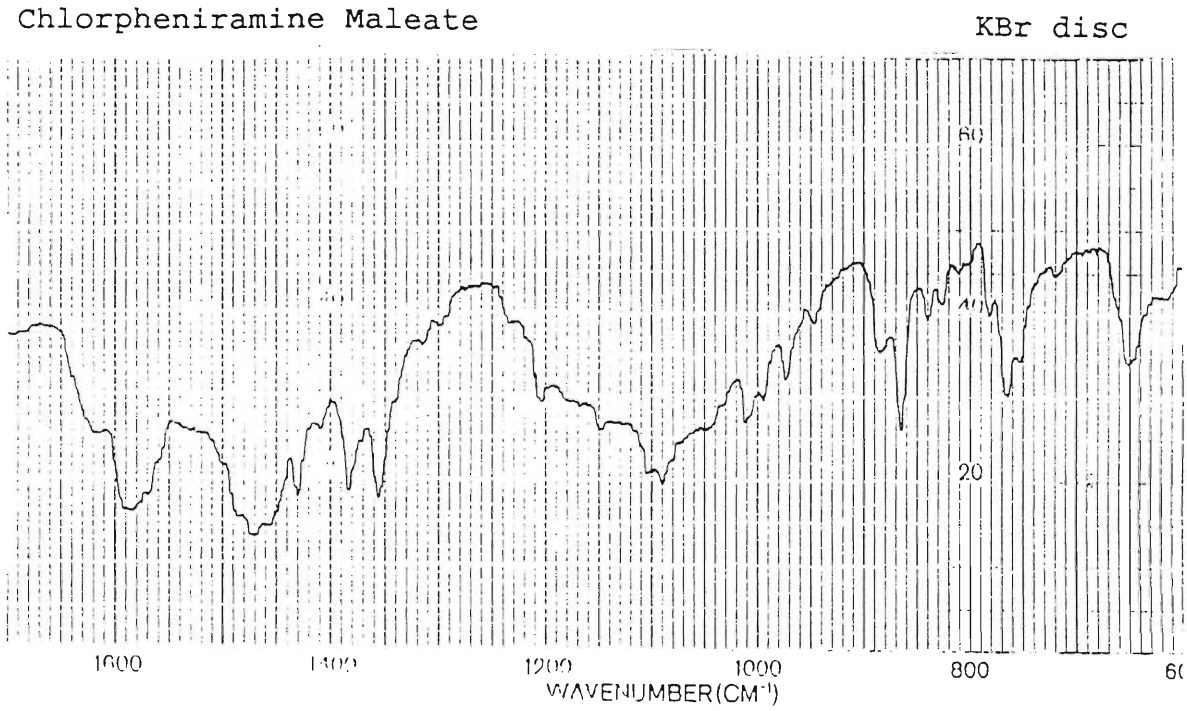


FIGURE 3.1 : INFRA-RED ABSORPTION SPECTRUM OF CHLORPHENIRAMINE MALEATE

3.4. ABSORPTION

Chlorpheniramine absorption is sensitive to local gastrointestinal conditions such as water volume (Kabasakalian *et al.*, 1968); presence of food (Huang *et al.*, 1981); the effect of multiple dosing (Kabasakalian *et al.*, 1968) and the formulation employed (Vallner *et al.*, 1982; Kotzan *et al.*, 1982; Barrett *et al.*, 1981; Hsu and Ayers, 1989).

The site of absorption is thought to be the small intestine because of its large surface area and the basicity of chlorpheniramine (Huang *et al.*, 1981).

The absolute oral bioavailability (F) following oral administration of chlorpheniramine maleate is incomplete, ranging from 25-50 percent in most studies (Huang *et al.*, 1980; Huang *et al.*, 1982).

Several bioavailability studies have compared immediate-release and sustained-release products, (Vallner *et al.*, 1982; Yacobi *et al.*, 1980; Kotzan *et al.*, 1982; Barrett *et al.*, 1981). Hanna and Tang (1974) observed bioavailabilities of (65-70 percent absorbed) from various chlorpheniramine oral syrup formulations.

Yacobi *et al.*, (1980) compared the bioavailability of a chlorpheniramine sustained-action capsule administered 12 hourly with conventional-release chlorpheniramine tablets administered every six hours. Since the rate and extent of absorption were virtually identical, the author concluded that the two formulations were bioequivalent.

3.5 DISTRIBUTION

The results of pharmacokinetic studies indicate a rapid and extensive distribution, which can be described by a two-compartment open model (Vallner *et al.*, 1982; Kotzan *et al.*, 1982). Tissue distribution studies or isolated overdose cases showed extensive uptake by lungs, kidney, liver and brain (Huang and Chiou, 1981; Reed, 1981).

Chlorpheniramine is ± 70 percent bound to plasma proteins (Huang *et al.*, 1980; Huang and Chiou, 1981). Huang and Chiou (1981) observed that *in vitro* binding of chlorpheniramine to serum protein in human plasma was linear over a wide concentration range : 73 percent at 40-90 ng/ml, 72 percent at 280 ng/ml and 69 percent at 1240ng/ml.

3.6 METABOLISM

Chlorpheniramine appears to be metabolised rapidly and extensively via demethylation in the liver, forming mono and didesmethyl derivatives (Peets *et al.*, 1972; Huang and Chiou, 1981). Chlorpheniramine is also metabolised by an oxidative deamination mechanism to form its polar metabolites, an alcohol and an acid (Figure 3.2) (Osterloh *et al.*, 1980; Peets *et al.*, 1972; Athanikar and Chiou, 1979).

An extensive gut and hepatic first pass effect has been observed (Huang *et al.*, 1980; Huang *et al.*, 1981; Huang and Chiou, 1981; Athanikar and Chiou, 1979). The discrepancy between the observed half-life and the accepted short duration of action may be due to enterohepatic cycling or due more to the metabolites than unchanged drug (Peets *et al.*, 1972). However, it has not been determined if these metabolites are active.

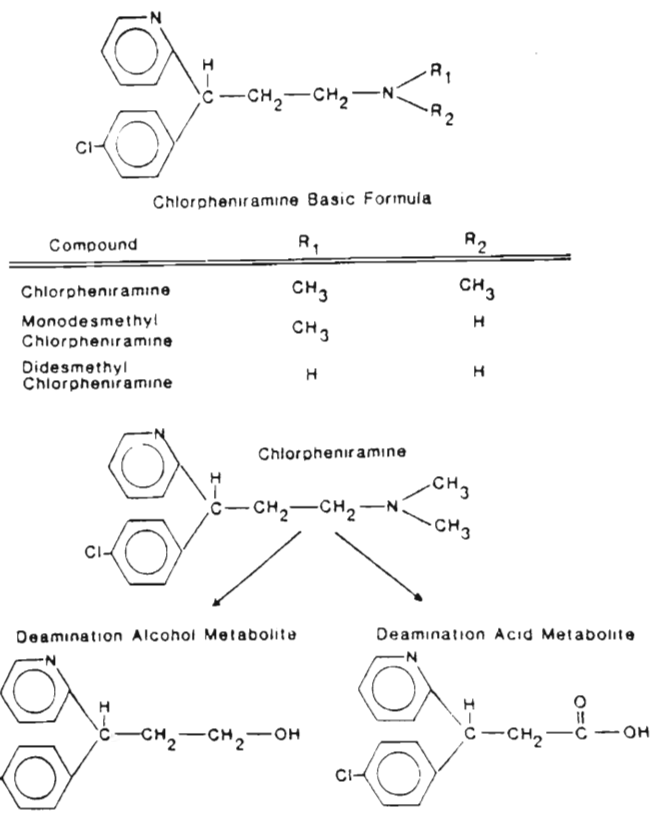


FIGURE 3.2 : METABOLISM OF CHLORPHENIRAMINE MALEATE IN MAN (RUMORE, 1984; page 703)

The antihistaminic activity of racemic chlorpheniramine exists predominantly in the (S)-(+) enantiomer (Roth and Govier, 1958; Thompson and Shioshita, 1981). The half-life of (S)-(+)-chlorpheniramine is 60 percent longer than that of (R)-(-) chlorpheniramine, which suggests the possibility that stereoselective metabolism occurs with this drug (Miyazaki and Abuki, 1976).

An age-related reduction in metabolic enzyme pathways, such as oxidation and glucuronidation, with a consequent decrease in chlorpheniramine metabolism, has been postulated as accounting for the faster clearance rate for chlorpheniramine in children (Simons *et al.*, 1982); however, demethylation, the major metabolic pathway, usually is well developed at birth.

3.7 EXCRETION

Urinary excretion of chlorpheniramine and its two demethylated metabolites has been found to depend on urine pH and flow rate (Yacobi *et al.*, 1980; Lai *et al.*, 1979, Simons *et al.*, 1984). Beckett and Wilkinson (1965) found that 20 - 26.5 percent of unchanged chlorpheniramine was excreted in acidic urine (pH = 5.5 $\pm$ 0.5) in 24 hours, but only 0.3 -

0.4 percent was excreted in alkaline urine (pH= 8.0 $\pm$ 0.5). When the pH was kept constant, a high urine flow rate resulted in a high excretion rate.

Several studies showed a large individual variation in chlorpheniramine urinary excretion (Sande *et al.*, 1989; Hsu and Ayers, 1989). Fluctuations in urine pH due to variations in diet, diurnal excretion pattern, or antacids, and fluctuations in urine flow due to daily fluid intake or salt consumption may have been responsible. Theoretically, chlorpheniramine is ionized less at high urinary pH's. Thus, it will be reabsorbed in the distal portion of the kidney tubules to a greater extent, resulting in increased retention in the body. Factors influencing urinary pH should, therefore, be considered in studies of the therapeutic effectiveness and duration of action of chlorpheniramine.

3.8 DRUG CONCENTRATION TIME PROFILE

Half-life values of 2-43 hours have been documented in adults. The longer half-lives appearing in the literature have been attributed to long blood sampling periods and assay differences.

The time taken to achieve peak levels of chlorpheniramine in the blood depend on the type of dosage form. Mean peak times vary between 2-3 hours (Peets *et al.*, 1972; Lange *et al.*, 1968) after administration of commercial tablets, 5.7-8.1 hours (Barrett *et al.*, 1981; Vallner *et al.*, 1982) after sustained-release products, 7.6-8.4 hours (Kotzan *et al.*, 1982; Vallner *et al.*, 1982) after repeat-action tablets and 2-4 hours (Huang *et al.*, 1982) for syrup or solution formulations. Therefore, as anticipated, the time to peak for tablets and liquid formulations are similar to each other but are different from sustained-release or repeat-action tablets. The controlled-release products extend the time necessary to attain peak drug levels and do not release a large quantity of drug immediately (Vallner *et al.*, 1982; Yacobi *et al.*, 1980, Kotzan *et al.*, 1982).

3.9 CLINICAL APPLICATION OF PHARMACOKINETIC PARAMETERS

It has been stated that the onset of action of chlorpheniramine is 15-30 minutes, effects are maximal within one or two hours, and the duration of action is four to six hours (Douglas, 1980; Batenhorst, 1986). However, on the basis of the plasma level data reported in the pharmacokinetic studies the duration of action should be longer in most subjects (Chiou *et al.*, 1979). However many other

clinical studies failed to confirm such a long duration of action for chlorpheniramine. In one study, only 26,5 percent of hay fever patients were controlled adequately on a single daily dose of controlled-release chlorpheniramine (Maddison *et al.*, 1970). This may have been attributable to a formulation problem.

Backhouse *et al.*, (1982) noted that the total symptom scores in allergic rhinitis patients were reduced by 64,5 percent after chlorpheniramine 8mg twice daily was given. Similarly, in other studies, significant inhibition of wheal and flare sizes occurred at 12, but not 24 hours (Burns and Shelanski, 1977), and only up to 11 hours (Chapman and Rawlins, 1981).

Arbesman (1950) studied the onset and duration of action of oral chlorpheniramine in 990 patients with allergic conditions. In 75 percent of patients, the onset of action was 15-30 minutes and the greatest percentage of patients (64 percent) had relief from 3-6 hours. Therefore, it is apparent that large intersubject variation in duration of action occurs; this may be consistent with the large intersubject variation noted for pharmacokinetic parameters

(Thompson *et al.*, 1981; Huang *et al.*, 1982) and might explain in part the large dose range of this drug required for some patients (Bryant and Cormier, 1982).

3.10 SIDE EFFECTS AND SPECIAL PRECAUTIONS

Slight to moderate drowsiness is the most frequent side effect of chlorpheniramine maleate. This may include inability to concentrate, lassitude, dizziness, hypotension, muscular weakness and inco-ordination. Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating machinery.

Other possible side effects of chlorpheniramine maleate include gastrointestinal disturbances such as nausea, vomiting, diarrhoea, constipation and epigastric pain. Antihistamines may also produce headache, blurred vision, tinnitus, elation or depression, irritability, anorexia, difficulty in micturition, dryness of the mouth, tightness of the chest and tingling, heaviness and weakness of the hands. Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, and blood dyscrasies, have also been reported with the use of antihistamines.

3.11 RATIONALE FOR FORMULATING A LONG ACTING ORAL DOSAGE FROM OF CHLORPHENIRAMINE MALEATE

Although the observed plasma half-life of chlorpheniramine maleate is longer than would be expected in relation to the pharmacological half-life, the therapeutic effect of chlorpheniramine is generally accepted as no longer than 4 hours (Wilhelm, 1961; Roth, 1965; Douglas, 1980) and the drug has to be given at 4 hour intervals if the desired antihistaminic action is to be achieved. In this light, it can be concluded that the plasma levels of the drug do not reflect its pharmacological activity and that the half life of the drug at tissue sites at which it exerts its activity may be a great deal shorter than that in plasma. Alternatively, the concentrations of the drug in plasma measured at times greater than 4 hours might represent sub-threshold levels of the drug i.e. concentration at which the pharmacological activity of the drug is not attainable. Indeed, both of these conditions might explain the discrepancy between the drugs half-life and that of its pharmacological activity (Peets *et al.*, 1972).

CHAPTER 4

DISSOLUTION STUDIES

4.1 INTRODUCTION

It is well recognised that knowledge of the dissolution behaviour and factors affecting such behaviour are essential to the design, evaluation, control, and therapeutic efficacy of most solid dosage forms (Dakkuri and Shah, 1982).

Dissolution is the act of dissolving, while *in vitro* dissolution is the rate of dissolving in water or aqueous solution of a chemical or drug from the solid state.

Dissolution testing in the pharmaceutical industry is a means of measuring *in vitro* release rates of active ingredients from formulations in simulated biological fluids. The test is valuable because it reduces measurement of a multitude of variables that are responsible for the release of active ingredients.

Dissolution testing has the following applications in pharmacy:

1) For research purposes to elucidate the mechanisms involved in the processes and to determine the relative importance of various variables related to drug dissolution and absorption (Sande and Waaler, 1990).

2) For development purposes to guide the pharmaceutical formulator in the preparation of optimal dosage forms of drug for clinical trials (Baweja, 1987)

3) For control purposes to ensure that a given pharmaceutical product is essentially uniform from lot to lot (Hanson, 1982).

4) For predictive purposes so that one may estimate rate(s) of absorption *in vivo* and/or availability of drug for absorption in man from measurement of disintegration time and/or rates of dissolution *in vitro*. Such predicting requires careful correlation of *in vitro/in vivo* results (Williams *et al.*, 1991)

4.2 PERFORMANCE CRITERIA FOR DISSOLUTION TESTS.

A meaningful and reliable dissolution test must meet at least six basic performance criteria (Dakkuri and Shah, 1982):

4.2.1 Reproducibility is essential. The dimensions and geometry of the apparatus should be rigidly specified, together with tolerances, so that inter- and intra-laboratory variations are kept to a minimum (Withey and Mainville, 1969).

4.2.2 Sensitivity to detect the effect of small differences of the active ingredient from the dosage form must be optimal.

4.2.3 Correlation of observed differences of *in vitro* release to *in vivo* bioavailability must be accomplished; that is, the method must simulate the *in vivo* environment to such a degree that the attainment of the *in vitro*/*in vivo* correlation is possible.

4.2.4 Flexibility of the test that will make it applicable to a wide range of drug products is essential.

4.2.5 Simplicity is a key factor. The system must be relatively easy to operate on a routine basis and must not require extensive investment of time in setting up the apparatus.

4.2.6 Automation is a final consideration. The method should lend itself to automation, if so desired.

4.3 FACTORS AFFECTING DISSOLUTION RATE

Many factors, both intrinsic and extrinsic to the product, have been shown to influence the dissolution testing. Factors intrinsic to the product - such as the physico-chemical properties of the drug and the composition and method of manufacture of the drug product itself - are expected to influence the dissolution behaviour, but, to an almost equivalent degree, so do extrinsic factors associated with the dissolution method thereof.

The extrinsic factors include, amongst others, type and volume of dissolution medium, type and intensity of agitation, geometry of container, state of homogeneity existing in the system, and adsorption or adherence of the drug to solid surface of the apparatus.

In recent years, automated dissolution systems that maintain sink conditions by continually replacing withdrawn samples with equivalent volumes of fresh solution have been described. In such systems, direct concentration measurements of dissolution fluid circulating continuously between a single dissolution vessel and the flow through cell of a spectrophotometer have been used (Embil *et al.*, 1983).

Factors affecting the dissolution profiles of controlled-release dosage forms obtained with automated systems include flow rate, lag time, changes in flow rate attributable to filter saturation, interference resulting from air bubbles, and errors associated with highly absorbing chromophores. (Embil *et al.*, 1983)

4.4 CLASSIFICATION OF DISSOLUTION MODELS

A large number of different test methods are adequately described in the literature (Krowczenski, 1987; Abdou, 1989). The dissolution test methods described below have been classified according to a variety of factors. Dakkuri and Shah (1982) used hydrodynamics (that is natural and forced convection) as a basis of classification.

In natural convection methods there is no forced agitation while in forced convection methods, a stirring, rotating, or and oscillating mechanism is used. The great majority of the models in this category belong to the stirred vessel type (Figure 4.1).

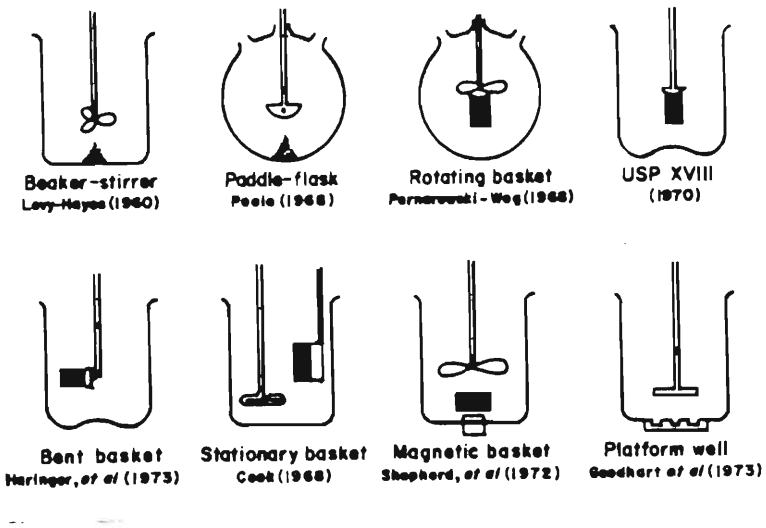


FIGURE 4.1 : DISSOLUTION APPARATUS OF THE STIRRED-VESSEL TYPE (ABDOU, 1990; page 116)

The rotating bottle method was first devised (Souder and Ellenbogen, 1958) to follow the release of dexamphetamine sulphate from sustained release pellets. An inherent disadvantage of this method was the need to stop the apparatus and remove the samples.

The rotating basket method was originally described by Searl and Pernarowski in 1967, and it was based on the original beaker method (Levy and Hayes, 1960). A basket was chosen to overcome the problems inherent in simply dropping a tablet randomly into a dissolution vessel. The basket had the further advantage of keeping floating dosage units, such as capsules, completely submerged in the dissolution medium until disintegration has occurred (Pernarowski *et al.*, 1968). Later systems, including the stationery basket (Cook, 1968), magnetic basket (Shepherd *et al.*, 1972), bent basket (Haringer *et al.*, 1973) and platform-well apparatus (Goodhart *et al.*, 1973), were all developed with the intent of holding the sample (tablet or capsule) at a predetermined position in order to allow for its complete immersion in the fluid medium.

The flask and stirrer methods was used as a partial solution to the problem of sample location by Poole (1969). He used a three-neck, round bottom flask as the dissolution vessel and a standard Teflon paddle as the stirring device. Due to the curvature of the flask, the dosage unit usually positions itself at the bottom of the flask directly under the paddle, thus maintaining a constant geometry.

In the USP dissolution methods, it is important that the dosage form be agitated only by the motion of the paddle or basket and that the release of the drug into the medium be a function of the solid/liquid interface. In other words, the disintegration, deaggregation, and dissolution of the drug should depend only on the rate at which fresh medium contacts the surface of the dosage form.

The USP XXII (1990) recognises two official methods:

a) The rotating basket method or Apparatus 1

b) The rotating paddle method or Apparatus 2

These two methods are described in greater detail in Chapter 5. Another method that is popularly used is the rotating bottle method (National Formulary XIII) which is also discussed in Chapter 5)

4.5 COMPARISON OF DISSOLUTION METHODS

Sande *et al.*, (1990) compared the *in vitro* dissolution rates of two plain tablets and two controlled release tablets containing d-chlorpheniramine using the USP XXI paddle and basket method, a rotating flask and a flow-through device. Small differences in the dissolution rate were found with the ordinary tablets, however large variations in the dissolution rate of the controlled release preparation were

seen depending on the method used. In a similar study using long acting quinacrine hydrochloride pellets, Onay-Bassaran (1986) found no significant difference between the dissolution methods.

Embil *et al.*, (1983) tested two experimental controlled release formulations manually as well as using an automated system. Excellent correlation between manual and automatic dissolution determinations were found, but the multipoint dissolution profile obtained by the automated procedure more accurately defined the time course of drug release from these products.

The science of dissolution testing is evolving rapidly. The development of powerful new drugs and the proliferation of novel controlled delivery systems necessitates the use of more specific and sensitive analytical techniques.

CHAPTER 5

MATERIALS, EQUIPMENT AND METHODS

5.1 MATERIALS

The materials that were used in the study are listed with their sources in Table 5.1

TABLE 5.1 : MATERIALS AND SOURCES

MATERIAL	SOURCE
Non-pareils No. 833	Adcock-Ingram
Dykatuss® capsules 8mg	Vesta
Chlortrimeton Repetabs®	Scherag
Chlorpheniramine maleate 500g (Used in pellet preparation)	Adcock-Ingram
Chlorpheniramine maleate RS (500mg)	Scherag
Chlorpheniramine maleate RS (500mg)	United States Pharmacopeial Convention
Eudragit® NE 30 D	Rohm Pharma
Talc (purified)	Merck
Polyethylene Glycol 6000	BDH Chemicals
Potassium Dihydrogen Orthophosphate	SAAR Chem
Potassium chloride	SAAR Chem
Potassium bromide	SAAR Chem
Sodium hydroxide	BDH Chemicals
Ephedrine hydrochloride	BDH Chemicals
Triethylamine	Merck
Methanol	Waters
Sodium Perchlorate	Merck
Glacial acetic acid	SAAR Chem
Perchloric acid	SAAR Chem
Hexane	Kleber Chemicals
Polyvinylpyrrolidone (PVP) (MW 44000)	BDH Chemicals
Ethyl Alcohol (96%)	Protea
Ammonium Sulfate	May and Baker
Empty gelatin capsules size 000	Eli Lilly

5.2 EQUIPMENT

The equipment used during the study is listed in Table 5.2.

TABLE 5.2 : DESCRIPTION/PURPOSE OF EQUIPMENT

DESCRIPTION/TEST	EQUIPMENT
HPLC analysis	Waters 590 programmable pump Lambda MAX Model 481 Spectrophotometer C_{18} radial pak column
Infrared analysis	Gallenkamp Infrared Lamp Perkin Elmer Infrared Spectrophotometer
Assays	Gallenkamp Flask Shaker Branson Ultrasonic Bath
Coating process	Aeromatic AG Fluidised Bed Equipment GMN 50/90 Friac Air Compressor
Dissolution studies	Caleva Model 7 ST - rotating paddle Hanson SR2 - rotating basket Hanson Research Model 6460 - rotating bottle
Relative Humidity	Casella Hygrometer
Scanning Electron Microscopy	Polaron Sputter Coating Unit E5000 Phillips SEM 500 Ilford Pan-F Film

5.3 METHODOLOGY

5.3.1 Quality Control

5.3.1.1 *Chlorpheniramine Maleate Powder*

5.3.1.1.1 *Identification*

5.3.1.1.1.1 *Infrared Spectroscopy*

This method of analysis is presented in Appendix 2 and was used for the identification of the drug.

5.3.1.1.1.2 *Ultraviolet Spectroscopy*

The scan obtained by ultraviolet spectroscopy was compared to that of chlorpheniramine maleate RS (USP).

5.3.1.1.2 *Assay*

According to the USP XXII (1990), the purity of chlorpheniramine maleate should not be less than 98 percent and not more than 100.5 percent of the labelled content. The volumetric method of analysis (USP XXII, 1990) presented in Appendix 2, was selected for the assay of the drug.

The chlorpheniramine maleate obtained from Adcock-Ingram was assayed using chlorpheniramine maleate RS (QC 120780)(100% stated purity) obtained from Scherag as a reference standard.

5.3.1.2 *Chlorpheniramine Maleate Drug Products*

5.3.1.2.1 *Chlortrimeton Repetabs*®

5.3.1.2.1.1 *Identification*

The identification of the tablets was carried out as outlined in Appendix 3.

5.3.1.2.1.2 *Assay*

According to the USP XXII (1990), the purity of chlorpheniramine maleate tablets should contain not less than 93 percent and not more than 107 percent of the labelled amount. The method of analysis (USP XXII, 1990) is presented in Appendix 3 and the drug content determined using the Beckman DU-64 Spectrophotometer set at a lambda max of 264nm.

The quantity (mg) of chlorpheniramine maleate, in the portion of the tablets taken is given by:

$$C\ (A_u/A_s) \ldots\ldots\ldots\ldots \text{(USP XXII, 1990)}$$

in which C is the weight in mg, of USP chlorpheniramine maleate RS in the portion of the standard preparation, A_u and A_s are the absorbances of Chlortrimeton Repetabs^R and USP chlorpheniramine maleate RS respectively.

5.3.1.2.2 *Dykatuss^R capsules*

5.3.1.2.2.1 *Identification*

The HPLC method of analysis (USP XXII/NF XVII SUPPLEMENT 2), presented in Appendix 4 was used for the identification test on Dykatuss^R capsules (T00884)(Vesta).

In this system, the following parameters were used:

Flow rate	1ml/min
Attenuation	16
Sample volume	20 microlitres
Chart speed	0.5cm/min
Detector	261nm
Pressure	2124 kpa

The retention time of chlorpheniramine maleate in the sample preparation was compared to that of the reference standard.

5.3.1.2.2.2 *Assay*

The HPLC method as presented in Appendix 4 was also used for the assay of the drug.

The quantity of chlorpheniramine maleate in the sample was calculated using the formula:

$(1000\ C)(r_u/r_s)$ .....USP XXII/NFXVII Supplement 2

in which C is the concentration, in mg per ml of USP chlorpheniramine maleate RS in the standard preparation, and r_u and r_s are the peak responses obtained from the assay preparation and the standard preparation respectively. The actual percentage purity of chlorpheniramine maleate was taken as the average of three such determinations. A typical example of an HPLC chromatogram for chlorpheniramine maleate and an example of the chromatogram with an internal standard (ephedrine hydrochloride) are presented in Figure 5.1 and Figure 5.2 respectively.

This HPLC method of analysis was also used to assay all the prepared pellets and also for stability studies on selected batches of pellets (refer to 5.3.4.2).

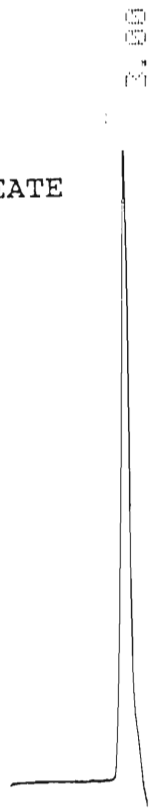
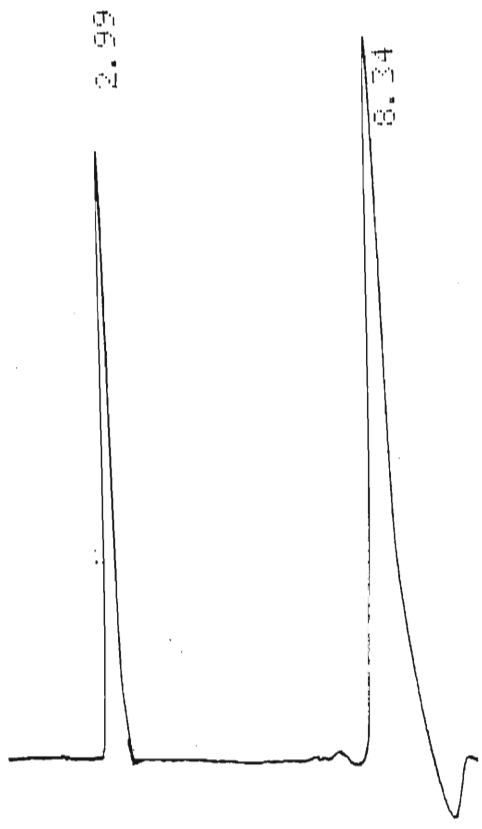


FIGURE 5.1 : HPLC CHROMATOGRAM OF CHLORPHENIRAMINE MALEATE

FIGURE 5.2 : HPLC CHROMATOGRAM OF CHLORPHENIRAMINE MALEATE (2.99 MINUTES) AND EPHEDRINE HYDROCHLORIDE (8.34 MINUTES)



5.3.2 Fabrication of Controlled Release Pellets containing Chlorpheniramine Maleate

All coating procedures for this study were performed in an Aeromatic AG Muttenz Model Strea-1 laboratory scale fluidized bed coating apparatus. The many advantages of using bottom coating in a fluidized bed apparatus have been outlined (2.9.4.4.1). The system was modified slightly by placing a 40 mesh (420 um) sieve onto the perforated bottom of the fluid bed drier in order to prevent the small non-pareils/pellets from falling through. The fluid bed apparatus was bottom-fitted with a 0.8mm binary nozzle and was coupled to a GMN 50/90 Friac air compressor which produced the compressed air necessary for atomization of the spray solution.

5.3.2.1 *Coating Technique*

There are many approaches to overlaying drug coated pellets with a drug release-controlling membrane of some kind. Recently there has been a shift towards the use of aqueous based methods of manufacture due to the increasing resistance to the usage of organic solvents (Yang and Ghebre-Sellasie, 1990; Mehta *et al.*,1986).

Small spherical sucrose/starch pellets were coated with powdered drug using a binder, and subsequently coated with a suitable film former, which has sustained release properties (Deasy, 1985). In this instance the drug coat and the polymer membrane exist as discrete layers.

All batches of pellets were prepared using the technique of discrete layers because of its convenience, simplicity and suitability for the preparation and analysis of chlorpheniramine maleate. The formulation and coating process was kept constant and standardised for every batch that was coated.

5.3.2.2 *Non-Pareil Composition*

The non-pareils (No. 833, Lot ERM Adcock Ingram), with 90 percent of the units in the range 0,850mm to 1.00mm (Average diameter 0.925mm) had the following composition.

Sucrose	75%
Maize starch	18%
Syrup	5%
Water	2%

5.3.2.3 *Formulation of Drug Coated Beads*

Initially a 4.5% aqueous solution of chlorpheniramine maleate was spray-coated onto a batch of non-pareils. No other excipients were used. The coating procedure was very time consuming and the non-pareils tended to agglomerate easily. In an attempt to improve the efficiency, various batches using different hydro-alcoholic concentrations of solvents were prepared, as outlined in Table 5.3.

TABLE 5.3 : OPTIMISATION OF A SOLVENT COMPOSITION FOR COATING OF CHLORPHENIRAMINE MALEATE ONTO NON-PAREILS

Water (parts)	Alcohol (parts)	Observation
100	--	agglomeration
50	50	agglomeration
25	75	intermittent coating
--	100	continuous coating

An alcoholic (96%v/v) solution was found to give the most efficient coating of the drug onto the non-pareils. However, only 19.85% of the drug adhered to the non-pareils (mass analysis). A binder was considered (Deasy, 1984) in an attempt to increase the adherence of the drug to the non-pareils. A 0.25% (m/m) concentration of polyvinyl-pyrolidone was used (Hogan, 1988) and was found to increase

the adherence of drug to non-pareil to 76%. Povidone was thus used as a binder to coat the drug throughout all studies.

The minimum load of the fluid bed drier was 200g. Hence to fill approximately 500 capsules a suitable formulation, as outlined in Table 5.4 was considered to prepare the drug coated beads.

The uniform mixture of chlorpheniramine maleate and povidone was dissolved in the alcohol (96%) and this clear solution was magnetically stirred and maintained at 50°C on an isomantle.

TABLE 5.4 : FORMULATION FOR DRUG COATED BEADS

CONSTITUENT	PURPOSE	1 CAPSULE	500 CAPSULES
Non-pareils	Substrate	392.0mg	196.0g
Chlorpheniramine maleate	Drug	8mg	6.75g
Povidone	Binder	1.0mg	0.5g
*Ethyl alcohol (96%v/v)	Solvent	0.5ml	100ml

*Not present in final product, ± 0.86g per capsule.

The non-pareils were charged into the pre-warmed chamber of the fluid-bed drier and fluidized at 50°C for 15 minutes. The atomised coating solution was then introduced and applied onto the pellets by spraying at 2.5ml/min over a period of about 45 minutes. After coating, the pellets were dried at 50°C for 30 minutes.

The general operating conditions of the fluid bed apparatus are given in Table 5.5

TABLE 5.5 : OPERATING CONDITIONS FOR DRUG COATING

OPERATING APPARATUS	SETTING
Atomising air pressure	30 kpa
Fluidised air velocity	75m^3/h
Inlet temperature	50°C
Outlet temperature	40°C
Solution temperature	50°C
Flow rate of coating solution	2.5ml/min
Drying time	30 min

5.3.2.4 *Application of Polymer Coat - Methacrylate Copolymers (Eudragit^{R})*

Eudragit^{R} NE 30 D is suitable for the manufacture of oral dosage forms that release drug independent of pH at any given site in the gastrointestinal tract. Drug coated non-pareils were coated with varying concentrations of this polymer using the operating parameters outlined in Table 5.6.

TABLE 5.6 : PROCESSING CONDITIONS FOR EUDRAGIT^{R} NE 30 D COATED DRUG PELLETS

OPERATING PARAMETERS	SETTING
Atomising air pressure	60 kpa
Fluidised air velocity	100-120m^3/hour
Inlet temperature	30-35°C
Outlet temperature	25-30°C
Dispersion temperature	30°C
Flow rate of coating solution	variable
Drying time	60 minutes

The different formulations were prepared by first mixing dispersion of talc and water or talc and polyethylene glycol 6000 (PEG 6000) separately in a specified quantity of deionised water (50ml) and then blending with the required quantities of Eudragit^{R} NE 30 D dispersion. The coating fluids were magnetically stirred at 30°C throughout the coating process.

Known weights of drug loaded pellets (200g) were then transferred into the fluidised bed apparatus, prewarmed for 15 minutes, and then coated with the formulation until the coating process was completed. The coating of the polymer onto the drug coated non-pareils was an intermittent process (taking up to 2 days in some cases), thus giving variable flow rates of the dispersion. As the intermittent coating was due to the inherent tackiness of Eudragit^{R} NE 30 D, talc and PEG 6000 were used to overcome this problem to a certain extent.

5.3.2.4.1 *Calculation*

For the production of chlorpheniramine maleate sustained release preparations, applications of 6-10mg of dry lacquer substance per cm^2 of surface were required (Lehmann *et al.*, 1986). As a specified thickness of coating was required on applying the lacquer, the amounts needed were derived from the surface area of the cores.

The surface area of pellets can be calculated by the following formula (Lehmann *et al.*, 1986; Eudragit Data Sheets, 1990):

$$\text{Surface area} = \pi(d^2)$$

where d is the diameter of the pellets.

The amount of polymer to be applied (percent dry lacquer substance)

$$\text{Amount to be applied} = \frac{\text{SA } (mm^2) \times 1 \ (mg/cm^2)}{w \ (mg)}$$

where SA = surface area, 1 = mg of dry lacquer substance per cm^2 and w is the weight of the individual pellet. To obtain a coating of $6mg/cm^2$, Eudragit^R NE 30 D as 6.6% (m/m) was applied to 200g of the drug loaded non-pareils in Batch L.

5.3.2.4.2 *Variation of Polymer Content (PEG 6000 Excluded)*

Eudragit^R NE 30 D films were also applied at 2 and $5mg/cm^2$ corresponding to 2% and 5% concentrations for Batch J and Batch K respectively and their effects on dissolution rate investigated.

Difficulty in coating Batch L was experienced, due to the tackiness of the non-pareils which was much worse than that experienced when coating with the other two batches (i.e. Batch J and K). Polyethylene glycol 6000 (PEG 6000) was used in an attempt to overcome this with some success. The reasons for using PEG 6000 are outlined in Chapter 6.

TABLE 5.7 : FORMULATIONS OF EUDRAGIT® NE 30 D COATED PELLETS

CONSTITUENT	PURPOSE	BATCH J	BATCH K	BATCH L
Eudragit® NE30D	Coating polymer	2% 4g	5% 10g	6.6% 13.33g
Talc	Glidant	0.5% 1g	0.5% 1g	0.5% 1g
Deionised* water	Dispersion medium	90.0ml	80.0ml	110.0ml

*Not present in the final product

5.3.2.4.3 *Effect of Curing*

The coalescence of polymer is often incomplete after the coating process, and a curing step has been recommended with Eudragit® NE 30 D to accelerate further coalescence and formation of a homogeneous film. A curing period of 24 hours is generally sufficient for complete coalescence. In this study, the coated pellets of Batch M (6.6% Eudragit® NE 30 D, 0.5% talc and 0.5% PEG 6000) were oven cured at 37°C for either 24 or 48 hours.

Prepared pellets were cured for 24 hours at 37°C before dissolution studies by the paddle method (4.4) were performed. Six representstive samples were tested from each batch.

5.3.2.4.4 *Variation of Talc Content*

To investigate the effect of talc content on the release rates of drug from the polymer, talc was added in various concentrations to 6.6% Eudragit^{R} NE 30 D dispersions (Batch G, Batch H and Batch L) Table 5.8. To determine if these results were consistent at all concentrations of Eudragit^{R} NE 30 D, various amounts of talc were added to 8.3% Eudragit^{R} NE 30 D dispersions which also contained 2% PEG 6000(Batch R, Batch T and Batch U; Table 5.9).

TABLE 5.8 : FORMULATION OF PELLETS COATED WITH 6.6% EUDRAGIT^{R} NE 30 D AND DIFFERENT CONCENTRATIONS OF TALC

BATCH	EUDRAGIT (Coating polymer)	TALC (Antitackiness agent)
G	13.33g (6.66%)	2g (1%)
H	13.66g (6.66%)	4g (2%)
L	13.66g (6.6%)	1g (0.5%)

TABLE 5.9 : FORMULATIONS OF 8.3% EUDRAGIT^{R} NE 30 D, PEG 6000 AND DIFFERENT AMOUNTS OF TALC.

BATCH	EUDRAGIT^{R} NE 30 (Coating polymer)	PEG 6000 (emulsifier plasticiser	TALC (Antitackiness agent)
R	16.66g (8.3%)	4g (2%)	1g (0.5%)
T	16.66g (8.3%)	4g (2%)	2g (1%)
U	16.66g (8.3%)	4g (2%)	3g (1.5%)

5.3.2.4.5 *Variation of Polyethylene Glycol 6000 Content*

The effect of PEG 6000 content on the drug release from a 8.3% Eudragit^{R} NE 30 D formulation and 0.5% talc was also investigated (Batch I, Batch P, Batch PQ, Batch Q and Batch T) Table 5.10.

TABLE 5.10 : FORMULATION OF 8.3% EUDRAGIT® NE 30 D, 0.5% TALC AND DIFFERENT AMOUNTS OF PEG 6000

BATCH	EUDRAGIT® NE 30 D (Coating polymer)	PEG 6000 (plasticizer emulsifier)	TALC (Antitackiness agent)
I	16.66g (8.3%)	0.5g (0.25%)	1.0g (0.5%)
P	16.66g (8.3%)	0.75g 0.88%)	1.0g (0.5%)
PQ	16.66g (8.3%)	1.5g (0.75%)	1.0g (0.5%)
Q	16.33g (8.3%)	2g (1.0%)	1.0g (0.5%)
T	16.33g (8.3%)	4g (2.0%)	1.0g 0.5%)

5.3.2.4.6 *Variation of Polymer Content (PEG 6000 Included)*

Batches T, TU, V, W, X and Y were prepared by coating drug laden pellets with Eudragit® NE 30 D (in concentrations varying from 8.3% to 20%) and 1% talc and 2% PEG 6000 (Table 5.11).

TABLE 5.11 : FORMULATION OF PELLETS COATED WITH DIFFERENT AMOUNTS OF EUDRAGIT^{R} NE 30 D, 1% TALC AND 2% PEG 6000

BATCH	EUDRAGIT^{R} NE 30 D (Coating polymer)	PEG 6000 (Plasticizer emulsifier)	TALC (Antitackiness agent)
T	16.66g (8.3%)	4g (2%)	2g (1%)
TU	20.00g (10%)	4g (2%)	2g (1%)
V	24.00g (12%)	4g (2%)	2g (1%)
W	30.00g (15%)	4g (2%)	2g (1%)
X	36.00g (18%)	4g (2%)	2g (1%)
Y	40.00g (20%)	4g (2%)	2g (1%)

5.3.3 Dissolution Studies

The release profiles of the drug from the various newly formulated preparations were determined using the rotating paddle method (USP XXII, Apparatus 2). Although this is the Official procedure for chlorpheniramine maleate tablets, other *in vitro* dissolution models were considered in order to establish the possible dependency of drug release on dissolution methodologies.

5.3.3.1.1 *Rotating Paddle Apparatus (USP XXII, Apparatus 2)*

The specifications for the rotating paddle apparatus are presented in Appendix 5. In all experiments a six bath Caleva Model 7ST dissolution apparatus, which complied with USP Apparatus requirements, was employed. The operating parameters are listed in Table 5.12. The dissolution apparatus consisted of six one-litre round-bottomed flasks and a one-litre flat-bottomed replacement fluid flask. All flasks were immersed in a thermostatically controlled water-bath. The paddles were connected to an electrically controlled drive.

TABLE 5.12 : OPERATING PARAMETERS FOR THE ROTATING PADDLE APPARATUS

OPERATING PARAMETER	SETTING
Temperature	37 ± 0.5°C
Volume of medium	900 ml
Rotating speed	50rpm
Media	a) Deionised water b) Phosphate buffer* c) Neutralised phosphate buffer* d) Hydrochloric acid*
Sampling times (hours)	1; 2; 3; 4; 5; 6; 7; 8
Sample volume withdrawn	4-10ml

* The preparation of the media is presented in Appendix 5A.

It should be noted that although deionised water was used as the dissolution medium in most studies, phosphate buffer, neutralised phthalate buffer and hydrochloric acid were used to determine the pH dependency of one batch (Batch Q) of pellets. Unless otherwise indicated, the dissolution medium is deionised water.

The dissolution medium (900ml), was degassed and pre-warmed to 37°C and then poured into each flask. Either 3.2g or 1.56g of pellets (equivalent to 80mg and 40mg of drug respectively), accurately weighed, was then transferred into each flask. In order to facilitate ultraviolet spectroscopy analysis (the absorbance of the solution in the region of 8mg is very low), either 10 times the amount of drug i.e. 80mg (during formulation studies) or 5 times the drug i.e. 40mg (during stability studies) was tested per dissolution vessel. Using different amounts of drug did not affect sink conditions or reproducibility of data (Chapter 6).

Accurately measured aliquots of about 4 to 10 ml of medium were withdrawn from each flask (at the indicated time intervals) using a syringe fitted with a 0.8um AA Millipore filters (25mm in diameter). Prior to these samples being withdrawn, the sampling tubes were flushed several times by withdrawing and reintroducing the same medium, thus removing any medium that may have been lodged in the sampling tubes.

These aliquots were analysed by ultraviolet spectrophotometry (UV) (5.3.3.2) for drug content. All six aliquots were withdrawn within a period of 60 seconds. Each withdrawn sample was replaced with an equivalent volume of fresh medium (37°C) through the same 0.8um filter.

Where dissolution studies were carried out on encapsulated pellets, the pellets were emptied from each hard gelatin capsules into the dissolution flask prior to the study. This was done to overcome possible interference of dissolution or disintegration of the capsule shell on drug analysis.

5.3.3.1.2 *Rotating Basket Apparatus (USP XXII, Apparatus I)*

The USP XXII (1990) requirements for a rotating basket dissolution apparatus are presented in Appendix 5. The Hanson SR 2 Research six bath dissolution apparatus that was used consisted of six one-litre round-bottomed flasks that were immersed in a heated bath with a thermostat control.

The operating parameters used in these studies were the same as those used for the rotating paddle experiments (Table 5.11) except that deionised water was the only medium used in the rotating basket method.

The dissolution methodology was also similar to that for the rotating paddle method (5.3.3.1.1). In these studies, however, pellets were placed in the dissolution basket (without capsule shells) rather than in the vessel.

5.3.3.1.3 *Rotating Bottle Apparatus*

A Hanson Research Model 6460 Rotating bottle dissolution apparatus was used for such studies. The instrument consisted of a dissolution tank, thermostatically controlled (circulating warm water) at 37 $\pm$ 1°C with one horizontal rotating shaft that was fitted with clamps capable of holding 20 amber 100ml capacity bottles. The horizontal shaft had a variable rotation speed (15-50rpm) that was set at 30rpm for the studies undertaken. Amber glass bottles (length 10.5cm, diameter 4.5cm, 100ml capacity) fitted with bakelite screw caps with an inner paper lining were used in the present study. The operating parameters for this system are given in Table 5.13.

TABLE 5.13 : OPERATING CONDITIONS FOR THE ROTATING BOTTLE APPARATUS

OPERATING PARAMETERS	SETTING
Temperature	37 ± 1°C
Volume of medium	100ml
Rotation speed	30 rpm
Medium	Deionised water
Sampling times (Hours)	0.5; 1; 2; 3; 4; 5; 6; 7; 8
Sample volume	3.0ml

The thermostated dissolution tank was allowed to equilibrate to 37°C prior to use. Six samples of the sustained release pellets were accurately weighed (173mg equivalent to 4.44mg of drug) and each transferred into a clean 100ml amber bottle containing 100ml of water, previously warmed to 37 ± 1°C. The bottles were tightly capped to prevent leakage and then placed onto the rotating shaft of the dissolution tank.

At each sampling time the apparatus was stopped, the bottles removed from the cabinet and an aliquot of 3ml of medium was syringed from each bottle for analysis. All aliquots were filtered through a 0.8um Millipore AA filter (25mm in diameter). 3ml of replacement fluid was then transferred into each bottle. The sampling did not take more than two minutes for six bottles. The amount of drug released from the pellets was analysed by ultraviolet (UV)

spectrophotometry as described under 5.3.3.2. Sink conditions were maintained with this particular method despite the small volume of the medium.

5.3.3.2 *Analysis of Dissolution Samples*

5.3.3.2.1 *Quantitation of Chlorpheniramine Maleate in Dissolution Media*

This method was used to determine the content of chlorpheniramine maleate released from the controlled release pellets during the dissolution tests and also for establishing the potency of the prepared controlled release pellets (5.3.3.2.3).

A stock solution was prepared containing 50mg of chlorpheniramine maleate in 50ml of deionised water. This stock solution was then diluted with deionised water to produce a standard solution of 0.1mg/ml) which was then suitably diluted to produce standard solutions containing 10.0, 20.0, 30.0, 40.0, 60.0ug/ml of chlorpheniramine maleate in 25ml volumes.

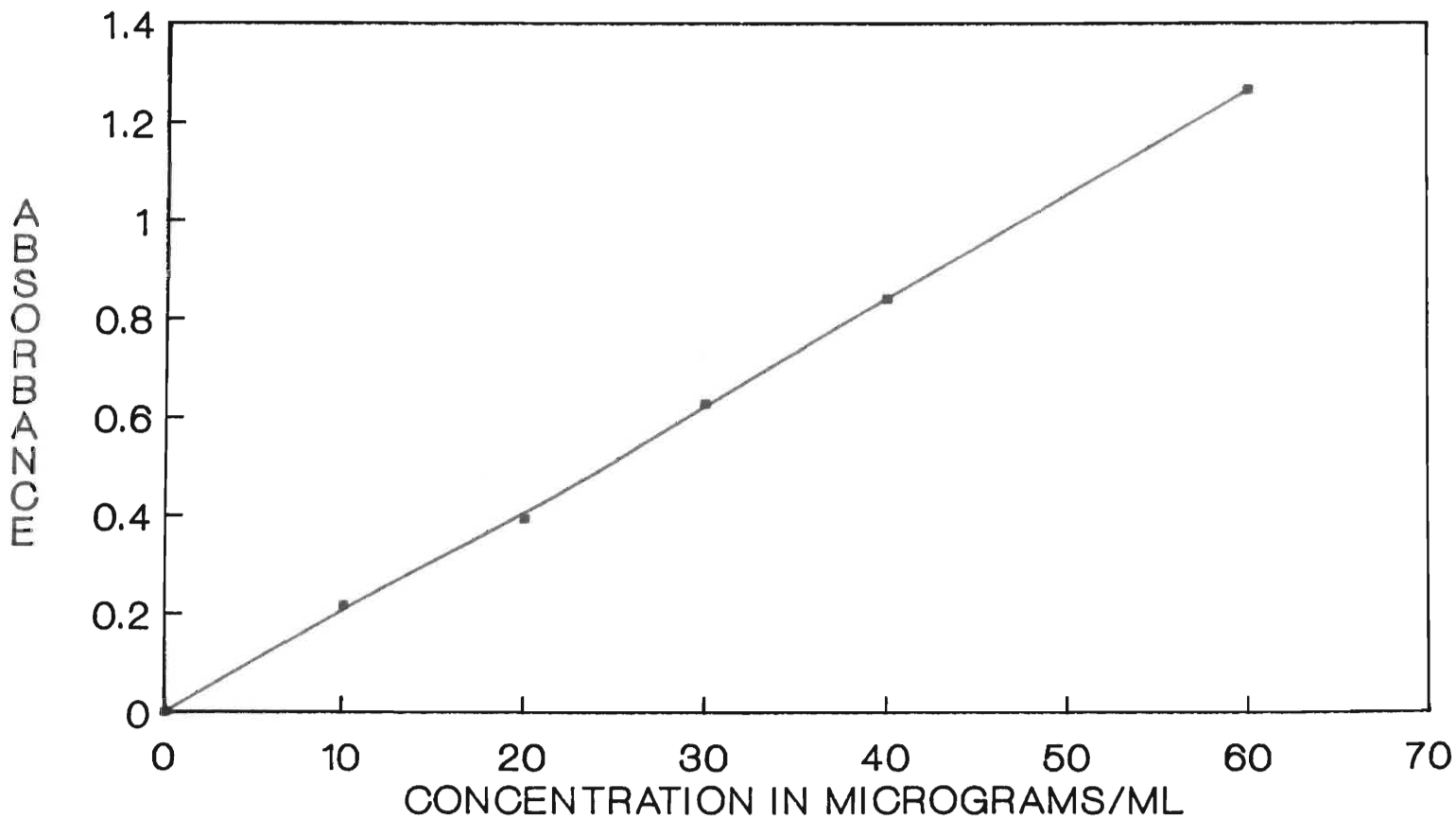
All determinations of ultraviolet absorption were performed in a Beckman DU64 Spectrophotometer using 1cm quartz cells. The absorption spectra for the standard solution of chlorpheniramine maleate were determined using deionised water as a reference solution. The absorbance, measured at 262nm for each solution, was plotted against the concentration of the solution to produce a calibration curve from which the concentration of unknown solutions could be determined.

The absorbance values for the various concentrations of chlorpheniramine maleate dissolved in deionised water, hydrochloric acid, neutralised phosphate buffer and phosphate buffer are presented in Table 5.14.

TABLE 5.14 : ULTRAVIOLET ABSORBANCE OF CHLORPHENIRAMINE MALEATE IN DEIONISED WATER, HYDROCHLORIC ACID, NEUTRALISED PHOSPHATE BUFFER AND PHOSPHATE BUFFER.

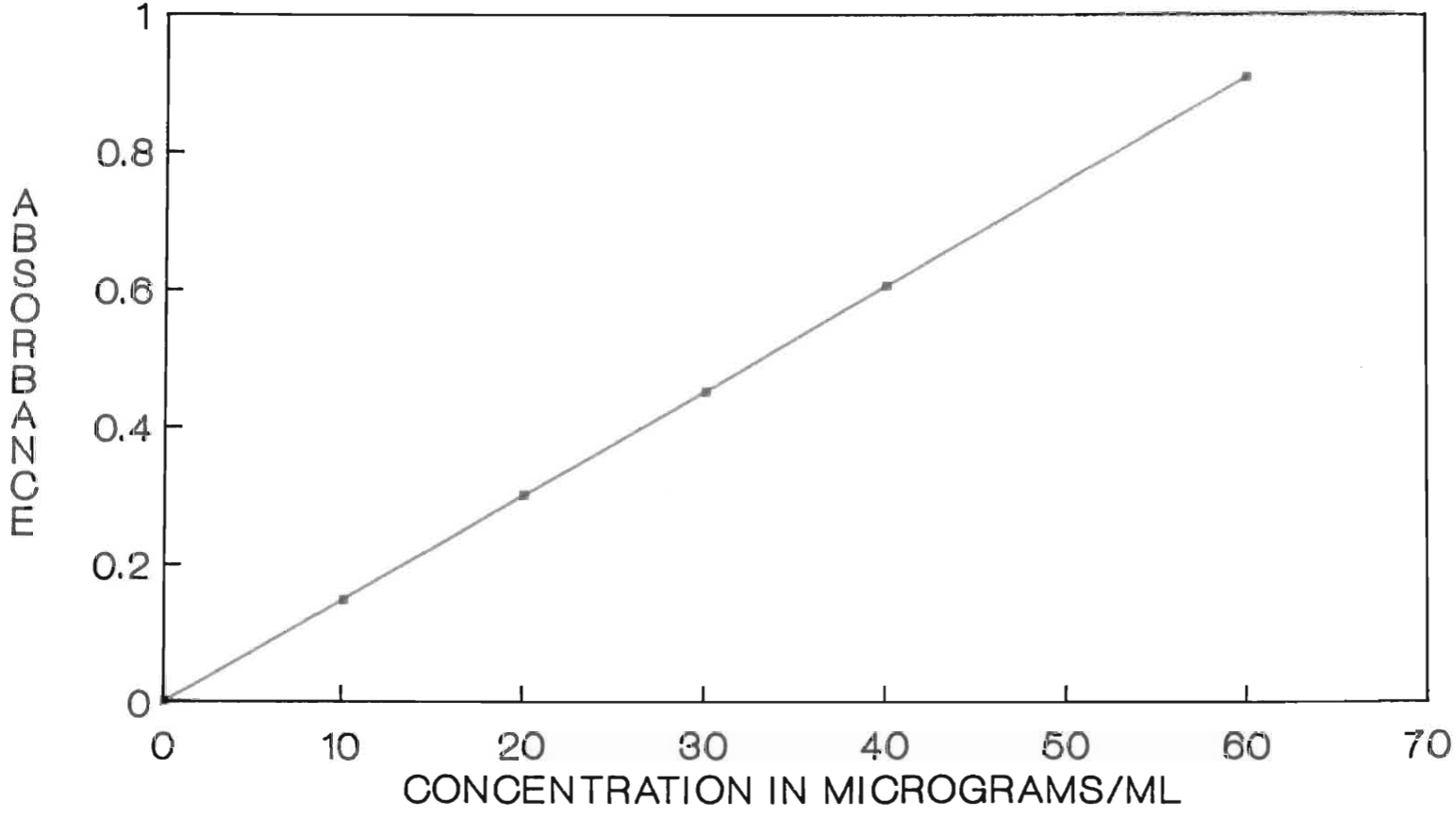
CONCENTRATION(UG/ML)	ABSORBANCE AT LAMBDA MAX			
	DEIONISED WATER pH 6.6 (262nm)	HYDROCHLORIC ACID pH 1.5 (262nm)	NEUTRALISED PHOSPHATE BUFFER pH 4.5 (259nm)	PHOSPHATE BUFFER pH 6.8 (259nm)
0.000	0.000	0.000	0.000	0.000
10.00	0.104	0.219	0.148	0.145
20.00	0.214	0.395	0.301	0.283
30.00	0.324	0.630	0.450	0.437
40.00	0.434	0.840	0.605	0.584
60.00	0.654	1.266	0.909	0.841
80.00	0.873			
100.00	1.091			

FIGURE 5.3 : CALIBRATION CURVE OF CHLORPHENIRAMINE MALEATE IN HYDROCHLORIC ACID (pH = 1.5)



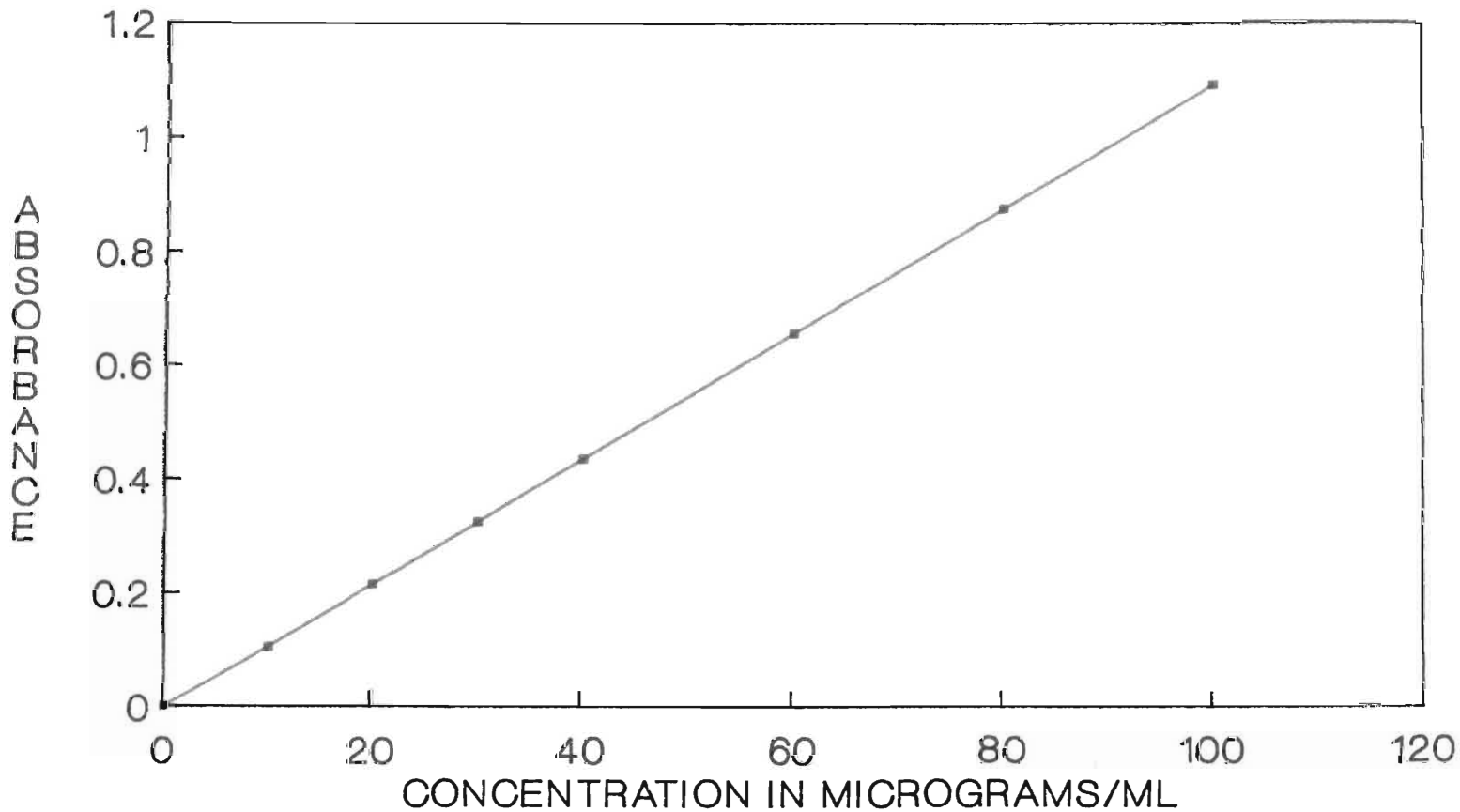
R SQUARE = 1.000
y = -0.004 + 0.0213x

FIGURE 5.4 : CALIBRATION CURVE OF CHLORPHENIRAMINE MALEATE IN NEUTRALISED PHOSPHATE BUFFER (pH = 4.5)



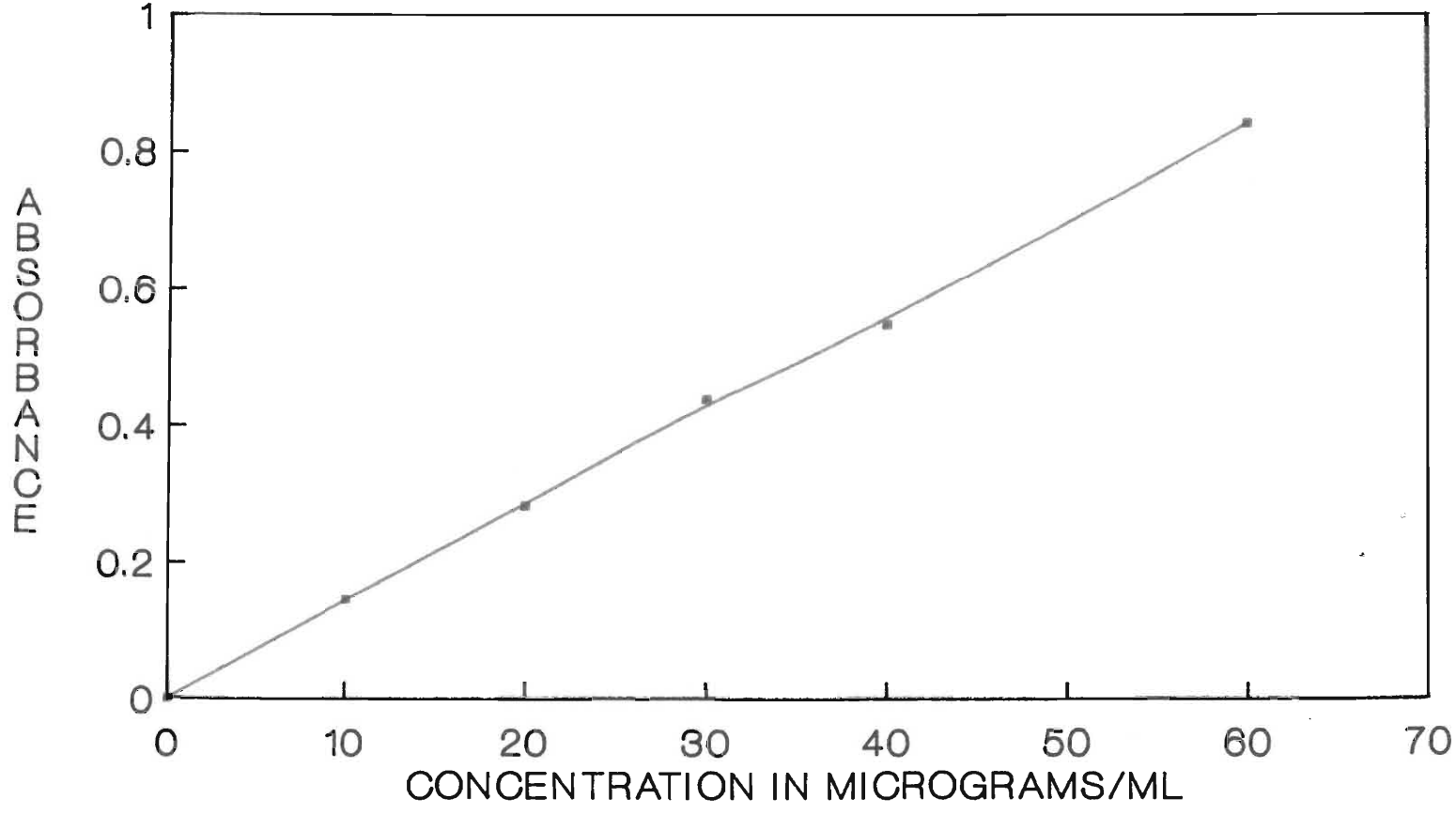
R SQUARE = 1.000
y = -0.002 + 0.0152x

FIGURE 5.5 : CALIBRATION CURVE OF CHLORPHENIRAMINE MALEATE IN DEIONISED WATER (pH = 6.6)



R SQUARE = 1.000
y = -0.003 + 0.011x

FIGURE 5.6 : CALIBRATION CURVE OF CHLORPHENIRAMINE MALEATE IN PHOSPHATE BUFFER (pH = 6.8)



R SQUARE = 1.000
y = 0.002 + 0.013x

Satisfactory calibration curves were obtained for all media. Systat statistical analysis program was used to determine the linear regression correlation coefficient. The r^2 values were obtained for all curves (Figure 5.3 - Figure 5.6).

5.3.3.2.2 *Determination of the Percentage of Drug Dissolved from Controlled Release Pellets*

The concentration of drug in the various samples studied was determined from the appropriate calibration curve. The amount in mg of drug in the dissolution flask/bottle was then calculated using the total volume of the dissolution medium employed.

For example, if 900ml of dissolution medium showed a concentration of 0.01mg/ml, then the amount of drug dissolved in 900ml is 9mg. The amount of drug dissolved was then corrected for any aliquots that had been previously removed from the dissolution flask and was replaced by an equal volume of fresh dissolution medium.

The following example serves to illustrate the method of correction. Four aliquots of dissolution medium were removed as follows:

a) At 1 hour, 4ml of a solution containing 25.34ug/ml of drug were removed,

b) At 2 hours, 4ml of a solution containing 50.03ug/ml of drug were removed,

c) At 3 hours, 4ml of a solution containing 60.02ug/ml of drug were removed, and

d) At 4 hours, 4ml of a solution containing 66.29ug/ml of drug were removed.

The amount of drug present in solution in 4 hours is 59.66mg (66.29ug/ml x 900ml). However, at 1 hour 0.101mg (4ml x 25.34ug/ml) were removed, at 2 hours 0.200mg (4ml x 50.03ug/ml) and at 3 hours 0.240mg (4ml x 60.02ug/ml) were removed as aliquots. Therefore the corrected amount of drug in solution at 4 hours is 60.20mg (59.66mg + 0.101mg + 0.200mg + 0.240mg).

The corrected amount was then expressed as the percentage yield at each sampling time using the expected yield (potency of controlled release pellets) as determined in 5.3.3.2.3.

5.3.3.2.3 *Determination of the Potencies of Controlled Release Pellets.*

About 1.56g (equivalent to 40mg chlorpheniramine maleate) of the controlled release pellets under investigation, accurately weighed, was crushed and ground in a mortar to obtain a fine powder. The powder was quantitatively transferred to a 100ml volumetric flask using about 50ml deionised water. The mixture in the volumetric flask was sonicated for 30 minutes, diluted to volume with sufficient deionised water, well shaken and then filtered (0.8um Millipore filter).

The first 25ml of filtrate was discarded, then 2.00ml was taken and diluted to 100ml with deionised water and its absorbance was measured at 262.0nm by ultraviolet spectrophotometry. This determination was performed in triplicate for all the batches of pellets that were investigated.

In addition, the potencies of the free drug and of the controlled release pellets, stored under different conditions of temperature and humidity, were measured, initially and periodically using the high performance liquid chromatography described under 5.3.1.3.1.

5.3.4 Stability Testing

The main purpose of stability testing is to establish the product's shelf-life and to evaluate stability of the formulation under various conditions. The stability related to potency and drug release characteristics of only one batch of prepared pellets (Batch Q) was studied following storage under different conditions. About 0.78g (equivalent to 20mg of drug) of the pellets were placed in Size 000 clear hard gelatin capsules. The capsules together with 2.0g of activated silica gel (as desiccant) were placed in each of four 100ml round, amber, glass bottles which were closed with bakelite screw-top lids. The four bottles were each placed under the following storage conditions:

5.3.4.1 Room temperature (20 $\pm$ 2°C)

5.3.4.2 40°C $\pm$ 1°C

5.3.4.3 37°C with 80% relative humidity

5.3.4.4 Refrigeration (5 $\pm$ 1°C)

In all instances the temperatures were monitored twice weekly, on a regular basis. Samples were removed at 2 weeks, 1 month and 2 months (and also at 3 months for room temperature studies) respectively following initial storage under different conditions in order to provide preliminary data on the newly formulated controlled release pellets (Batch Q).

Capsules were removed at the indicated intervals for assay and dissolution analysis (40mg of drug, i.e. equivalent to 2 capsules per dissolution vessel).

For initial potency and release rate data, the pellets were analysed prior to storage (40mg and 80mg of drug corresponding to 1.56g and 3.12g of pellets respectively). This was done in order to establish if there is reproducibility of release rates with change in the initial amount of drug used (1.56g vs 3.12g of pellets). In order to investigate the rates of drug release, all samples were analysed by the ultraviolet spectrophotometric method described earlier (5.3.2). All *in vitro* dissolution tests involved the use of the rotating paddle method using 900ml of deionised water at 37°C as the dissolution medium (5.3.3.1.1).

The potency of each batch of pellets stored under the various conditions, was determined using the high performance liquid chromatography method outlined in 5.3.4.2.

5.3.4.1.1 *Storage at Room Temperature*

The well closed 100ml amber bottle containing 60 capsule-filled pellets and desiccant were placed in a dark cupboard at room temperature (20 $\pm$ 2°C).

5.3.4.1.2 *Storage at Low Temperature (Fridge)*

The well closed 100ml amber bottle containing 40 capsule filled pellets and desiccant were placed in a refrigerator and the temperature was constantly maintained at 5 ± 1°C.

5.3.4.1.3 *Storage at 37°C - 80% Relative Humidity*

A saturated solution of ammonium chloride with a large sediment was prepared in order to obtain a constant humidity of 80% in a closed vessel. This solution was poured into a dessicator, allowed to equilibrate with its surroundings at 37°C and the humidity was confirmed using a hygrometer. A well closed bottle containing 40 capsule-filled pellets and desiccant was then placed in a air heated oven maintained at 37°C.

5.3.4.1.4 *Storage at 40 ± 2°C*

The well closed 100ml amber bottle containing 40 capsule-filled pellets was placed in an air heated oven maintained at 40 ± 2°C.

5.3.4.2 *Assay of Controlled Release Pellets*

High performance liquid chromatography (HPLC) was chosen as the method of analysis for the controlled release pellets that were stored under the various conditions. This technique of stability-indicating method was used where decomposition products of chlorpheniramine maleate may be detected. The method used in the assay was based on the USP XXII/NF XVII Supplement 2 method (Appendix 4) and was similar in most respects to the procedure outlined under 5.2.1. The only difference was that 2 x 1.52g lots of pellets were crushed instead of the contents of 15 capsules. All determinations were performed in triplicate.

5.3.5 Scanning Electron Microscopy Studies

5.3.5.1 *Principle of Electron Microscopy*

Electron microscopy is a collection of techniques which involves the bombardment of a sample by electrons. In this study, the samples used were newly formulated pellets. When the sample surfaces interact with the electron beam, it results in a deflection of electrons. The combination of scattered electrons forms an image which can be visualised either on a fluorescent screen, photographic film or can be digitised in some way.

5.3.5.2 *Experimental*

There are basically two types of electron microscopes, transmission electron microscope and scanning electron microscopes. Since only surface morphology of the pellets needed to be visualised, scanning electron microscopy (SEM) was used in this study. It was aimed to examine the surfaces, the drug coat and the polymer membrane of the pellets. This study was undertaken in an attempt to explain some of the dissolution and stability data observed on the newly formulated pellets of Batch Q.

Whole, intact, coated pellets were placed on a metal mount with double-backed adhesive tape. Additional pellets were cross-sectioned by splitting with a sharp sterile scalpel blade and placed face up on the adhesive tape.

Before examination with an SEM (Phillips SEM 500) the coated pellets were treated with a layer of sputtered gold for morphological evaluation. The images that were obtained were then captured on an Ilford Pan-F black and white 35mm film.

CHAPTER 6

RESULTS AND DISCUSSION

6.1 IDENTIFICATION AND ASSAY

6.1.1 Chlorpheniramine Maleate Powder

Chlorpheniramine maleate powder was identified by infra-red spectrophotometry (Figure 3.1). The identification by ultra-violet spectroscopy showed a maximum absorbance at 262nm (See scan - Appendix 6).

Chlorpheniramine maleate powder was assayed according to the USP XXII (1990) procedure as outlined in 5.3.1.1 and Appendix 2. The assay completed in triplicate, gave a percentage purity of 100.2 $\pm$ 0.081%.

6.1.2 Chlorpheniramine Maleate Products

6.1.2.1 *Chlortrimeton Repetabs*^{R}

Three assays of 8mg Chlortrimeton Repetabs^{R} (5.3.1.2 and Appendix 3) showed an average purity of 95.58 $\pm$ 1.11%, equivalent to 7.64mg of chlorpheniramine maleate per tablet.

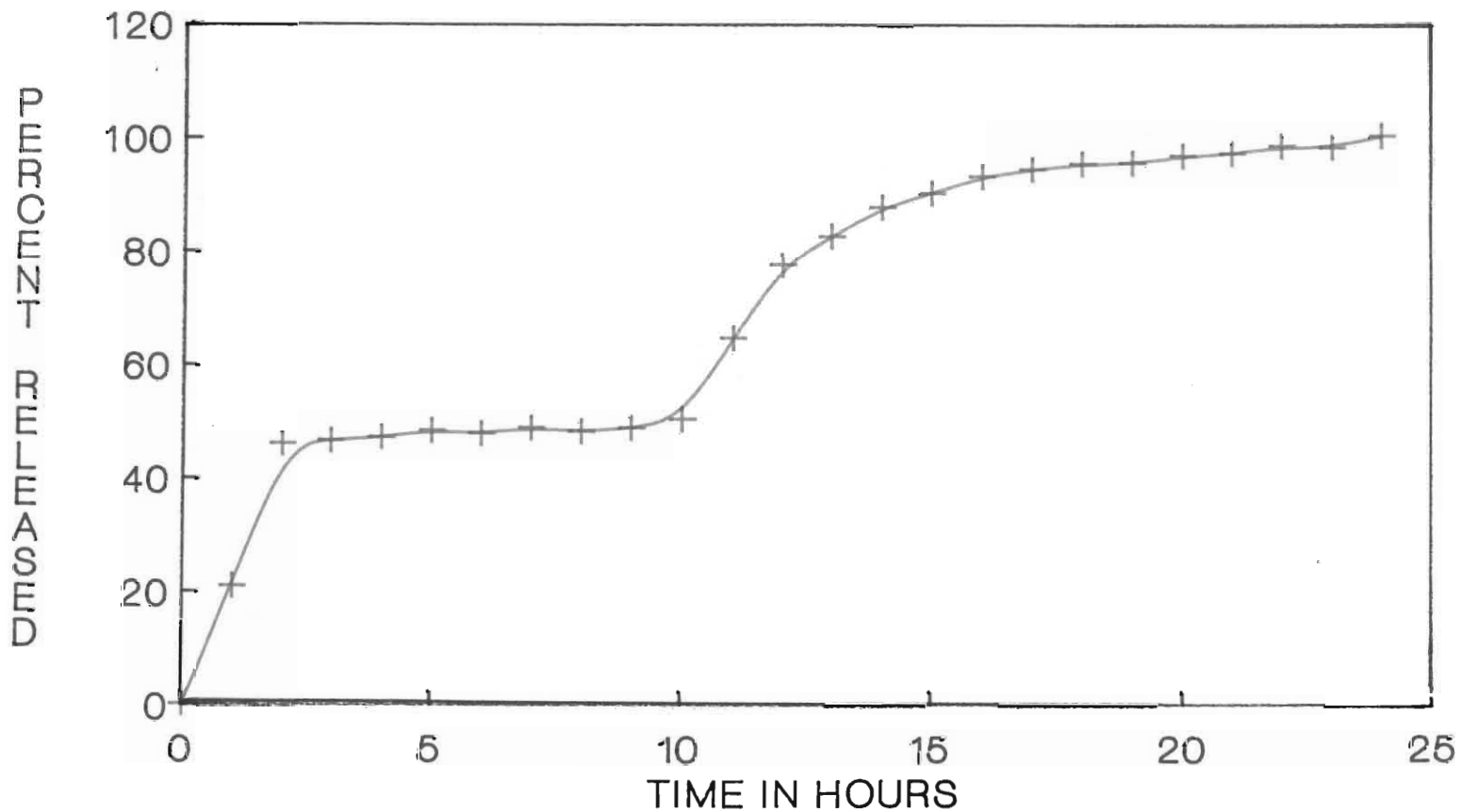
The cumulative release pattern in deionised water from Chlortrimeton Repetabs^{R} (Scherag) using the rotating paddle (50rpm) method is presented in Table 6.1 and Figure 6.1.

TABLE 6.1 : CUMULATIVE PERCENTAGES OF CHLORPHENIRAMINE MALEATE RELEASED FROM CHLORTRIMETON REPETABS^{R} 8mg REPEAT ACTION TABLETS.

SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE RELEASED S1*	S2*	S3*	S4*	MEAN SD
1	16.96	32.63	15.56	18.37	20.88 ± 6.86
2	48.17	43.47	44.96	46.01	46.67 ± 1.71
3	46.95	45.96	46.95	46.45	46.58 ± 0.41
4	49.45	45.46	46.95	46.82	47.17 ± 1.44
5	48.96	47.46	48.95	48.45	48.46 ± 0.61
6	46.45	47.95	48.45	48.45	47.83 ± 0.82
7	49.46	48.45	48.96	48.45	48.83 ± 0.42
8	47.45	48.45	48.45	48.45	48.20 ± 0.43
9	47.95	49.46	48.96	48.96	48.83 ± 0.55
10	49.46	49.46	49.96	52.46	50.34 ± 1.24
11	58.07	63.84	73.62	62.69	64.56 ± 5.66
12	84.52	71.00	80.50	74.15	77.54 ± 5.29
13	86.57	81.57	80.50	82.10	82.69 ± 2.32
14	87.47	89.63	85.86	88.01	87.74 ± 1.35
15	89.09	90.18	89.09	92.35	90.18 ± 1.33
16	89.09	92.89	95.62	94.53	93.03 ± 2.47
17	89.09	94.53	97.81	95.62	94.26 ± 3.21
18	89.63	96.17	98.91	96.17	95.22 ± 3.42
19	89.63	97.61	98.91	96.17	95.58 ± 3.57
20	90.18	98.36	100.0	97.81	96.59 ± 3.79
21	90.27	98.91	100.5	98.36	97.01 ± 3.97
22	96.71	98.36	100.5	97.81	98.35 ± 1.38
23	96.71	97.81	99.46	98.36	98.09 ± 0.99
24	97.81	100.5	102.7	103.3	101.1 ± 2.16

* 4 Repetab^{R} analysed

FIGURE 6.1 : CUMULATIVE PERCENTAGE DRUG* RELEASE FROM CHLORTRIMETON REPETAB[R] 8mg (AVERAGE)



*CHLORPHENIRAMINE MALEATE

PADDLE METHOD, WATER, 50RPM

Figure 6.1 reflects an initial rapid drug release (46.61%) in the first two hours followed by a gradual release between 10 and 16 hours and thereafter minimal drug release. This profile is typical of a repeat action product.

6.1.2.2 *Dykatuss[R] Capsules*

Dykatuss[R] capsules (Vesta) were assayed by the HPLC method outlined in Appendix 4. The retention times for chlorpheniramine maleate and ephedrine hydrochloride were 2.99 minutes and 8.34 minutes respectively. The mean percentage purity of three assays of Dykatuss[R] 8mg controlled release capsules showed an average percentage purity of 99.99% $\pm$ 0.41, equivalent to 7.99mg of chlorpheniramine maleate in each capsule.

The cumulative release pattern of chlorpheniramine maleate in deionised water from Dykatuss[R] Capsules using the rotating paddle method (5.3.1) is shown in Figure 6.2 and Table 6.2.

TABLE 6.2 : CUMULATIVE PERCENTAGES OF CHLORPHENIRAMINE MALEATE RELEASED FROM SIX DYKATUSS® 8mg CONTROLLED RELEASE CAPSULES.

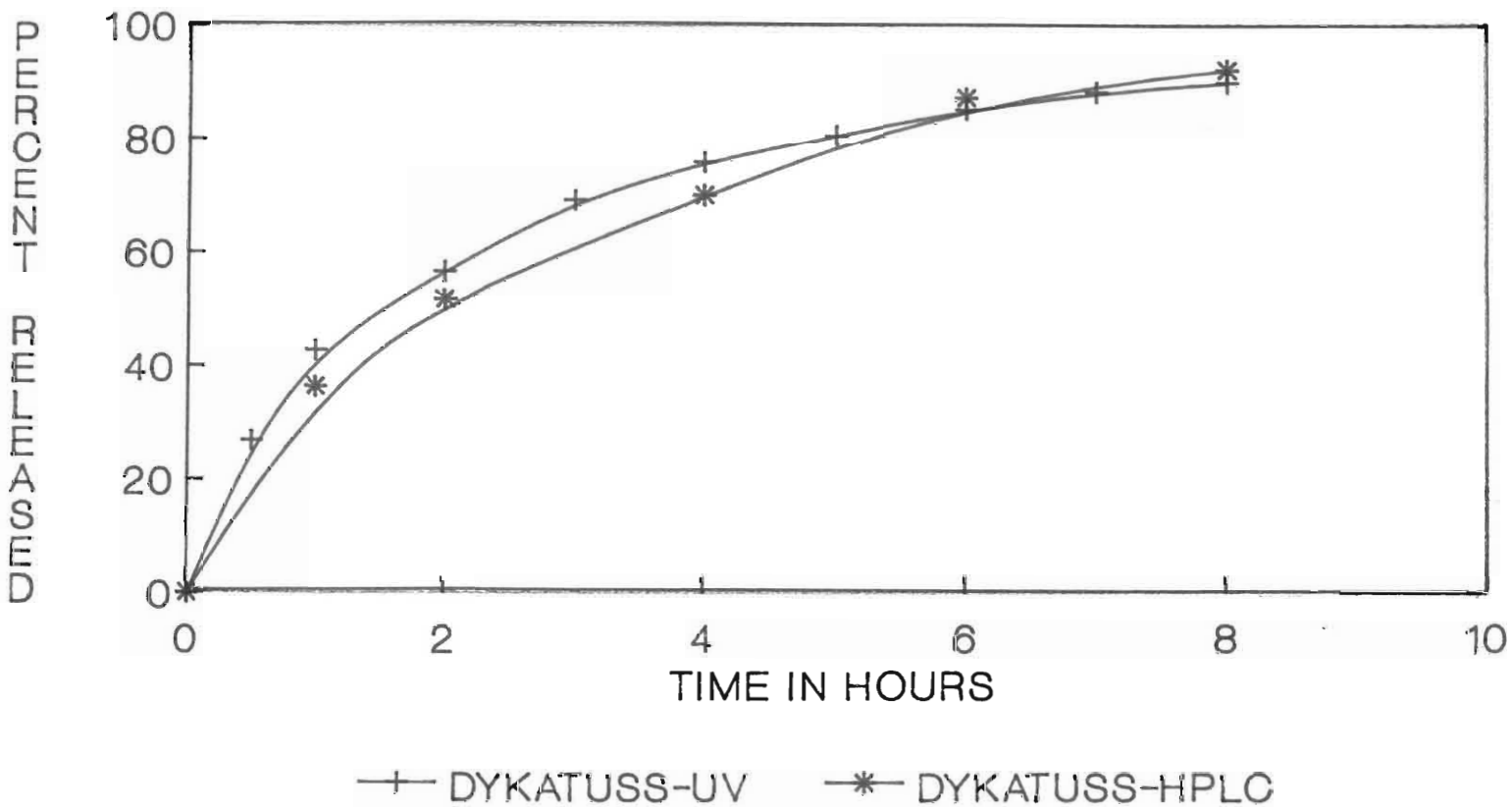
SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE RELEASED* S1	S2	S3	S4	S5	S6	MEAN SD
0.5	26.16	30.41	25.99	25.92	26.14	26.62	26.87 ± 1.59
1	45.13	47.92	40.97	40.85	41.19	41.12	42 86 ± 2.71
2	57.77	61.50	54.53	54.43	55.24	56.83	56.72 ± 2.46
3	67.50	71.66	68.42	65.86	70.85	71.75	69.34 ± 2.23
4	74.28	78.49	74.84	74.92	76.02	77.43	76.00 ± 1.51
5	78.06	82.51	80.29	80.34	80.67	82.16	80.67 ± 1.45
6	81.89	86.87	85.75	84.36	85.22	86.91	85.17 ± 1.72
7	83.35	88.30	88.57	88.88	89.22	90.61	88.16 ± 2.27
8	85.36	90.30	90.58	90.40	91.10	91.13	89.81 ± 2.02

The cumulative release pattern of chlorpheniramine maleate as quantitated by HPLC (5.2) is presented in Table 6.3 and Figure 6.2. Samples were injected manually in duplicate at the specified time intervals.

TABLE 6.3 : CUMULATIVE PERCENTAGE OF CHLORPHENIRAMINE MALEATE RELEASED FROM SIX DYKATUSS® 8mg CONTROLLED RELEASE CAPSULES USING HPLC

SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE RELEASED S1	S2	S3	S4	MEAN SD
1	36.12	35.68	36.55	37.42	36.44 ± 0.64
2	52.17	51.30	50.43	52.60	51.63 ± 0.83
4	71.11	72.00	70.22	67.55	70.22 ± 1.67
6	86.81	86.81	88.59	86.47	87.17 ± 0.83
8	94.90	94.94	89.01	89.01	91.97 ± 2.95

FIGURE 6.2 : CUMULATIVE PERCENTAGE DRUG* RELEASE FROM DYKATUSS^{R}CAPSULES 8mg (AVERAGE)



*CHLORPHENIRAMINE MALEATE

PADDLE METHOD, WATER, 50RPM

Figure 6.2 shows a rapid release of the drug (43%) in the first hour with a constant decrease in release of the drug from the capsules over the next seven hours. As Dykatuss^{R} is the innovators product, the release pattern of chlorpheniramine maleate obtained was used as a standard. Several batches of pellets were formulated in order to mimic this standard. The release pattern analysed on HPLC presented in Figure 6.2 showed a similar release profile. The different materials and techniques used in attaining this objective comprise the remainder of this chapter.

6.2.1 Methacrylates as Coating Polymers

6.2.1.1 *Effect of Polymer*

The preparation (Table 5.5) and formulation (Table 5.6) of pellets coated with Eudragit^{R} NE 30 D in various concentrations were described earlier (5.2.3.4). Four or six samples of pellets each weighing 3.2g (equivalent to 80mg of drug) of every batch was subjected to dissolution testing (5.3).

Talc had to be incorporated into the coating solution to facilitate the coating process as Eudragit^{R} NE 30 D is very tacky (Eudragit Data Sheets, 1990). Attempts to coat Eudragit^{R} NE 30 D (without talc) even at low coating levels (2%) were unsuccessful due to the inherent tackiness of the polymer and the tendency of the pellets to agglomerate. Also the processing times were excessively long (1 -2 days) thus making coating of these formulation laborious and undesirable.

The cumulative percent of drug released for the three batches (J, K and L) coated with Eudragit^{R} NE 30 D and talc (0.5%) are presented in Table 6.4 and the release profiles in Figure 6.3 respectively.

Pellets coated with 2% Eudragit^{R} NE 30 D (Batch J) released more than 95% of chlorpheniramine maleate after 1 hour (Figure 6.4) indicating that the coating did not appreciably retard drug release. Batch K (5% coating level) exhibited some sustained release with $\pm$66% of drug released in the first hour. Batch L (6.6% coating level) released drug relatively slowly (28% in the first hour). When Batch L is compared to the reference standard (Dykatuss Capsules^{R}), it is apparent that the release profiles are quite similar (Figure 6.4). Unfortunately, the difficulty experienced

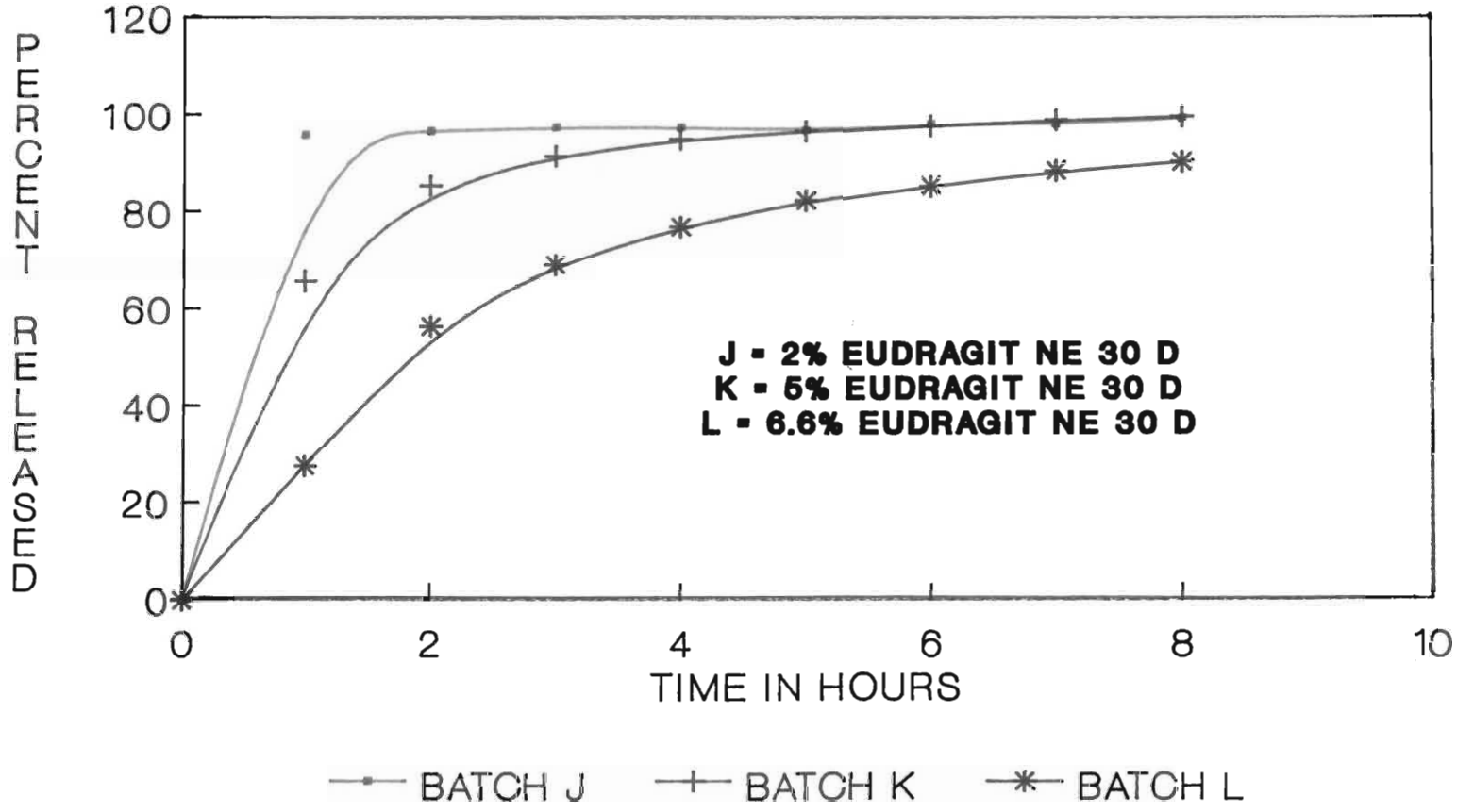
during coating i.e. the tendency of the pellets to agglomerate and clump together made this formulation (Batch L) unsuitable, thus the incorporation of more talc as well as PEG 6000 was investigated as a possible alternative to overcome this problem (6.2.1.3 and 6.2.1.4)

TABLE 6.4 : CUMULATIVE PERCENTAGES OF CHLORPHENIRAMINE MALEATE RELEASED FROM PELLETS COATED WITH VARIOUS AMOUNTS OF EUDRAGIT® NE 30 D AND 0.5% TALC.

BATCH	SAMPLING TIMES(HR.)	CUMULATIVE PERCENTAGE RELEASED S1	S2	S3	S4	MEAN SD
J	1	96.20	95.37	96.59	95.71	95.97 ± 0.46
(2%)*	2	97.48	96.53	96.37	96.80	96.80 ± 0.42
	3	98.47	97.07	97.14	97.56	97.56 ± 0.56
	4	98.05	97.38	97.20	97.57	97.55 ± 0.32
	5	97.91	96.47	96.39	96.92	96.92 ± 0.60
	6	98.53	98.89	97.75	98.39	98.39 ± 0.41
	7	98.77	98.37	97.79	98.32	98.31 ± 0.35
	8	100.0	99.16	99.35	99.74	99.57 ± 0.33
K	1	66.45	65.60	64.88	65.60	65.63 ± 0.56
(5%)*	2	83.84	86.80	86.80	83.71	85.29 ± 1.51
	3	91.76	92.05	90.75	91.15	91.43 ± 0.51
	4	93.99	95.88	94.88	94.92	94.92 ± 0.67
	5	95.31	97.30	97.02	96.88	96.63 ± 0.78
	6	96.26	99.29	97.71	98.13	97.85 ± 1.08
	7	98.15	100.16	98.78	99.04	99.03 ± 0.73
	8	98.75	100.77	99.57	99.69	99.69 ± 0.72
L	1	28.46	26.82	27.63	27.63	27.64 ± 0.58
(6.6%)*	2	56.84	56.21	56.74	56.59	56.60 ± 0.24
	3	68.93	68.51	69.72	69.28	69.11 ± 0.44
	4	76.76	77.57	76.75	77.02	76.93 ± 0.33
	5	82.21	81.78	83.22	82.40	82.40 ± 0.52
	6	86.24	85.41	85.04	85.88	85.64 ± 0.46
	7	89.07	87.93	89.29	88.79	88.77 ± 0.52
	8	90.68	89.95	91.41	90.65	90.67 ± 0.52

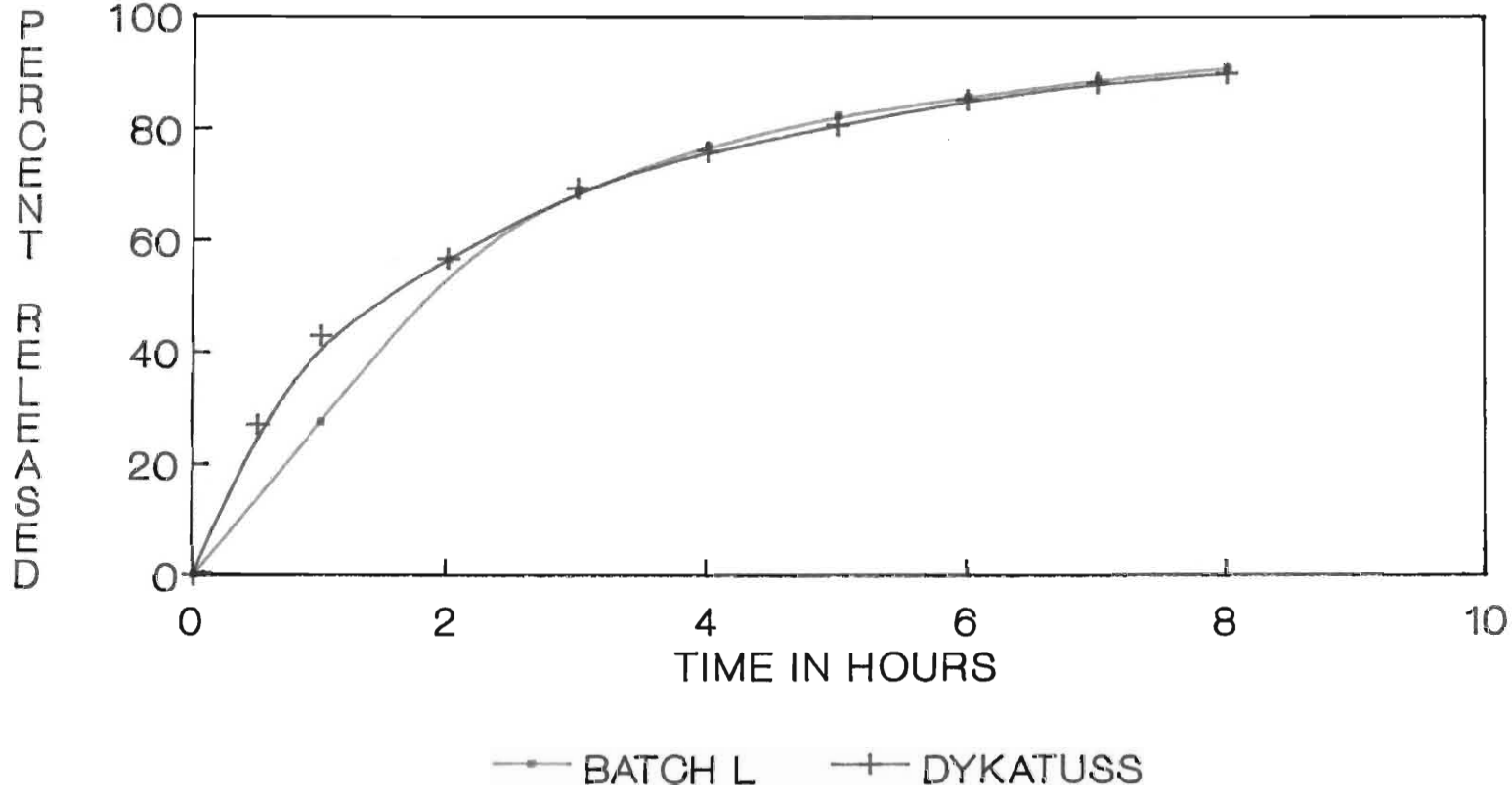
* Percent (m/m) Eudragit® NE 30 D applied.

FIGURE 6.3 : DISSOLUTION STUDIES ON PELLETS COATED WITH 2%, 5% AND 6.6% EUDRAGIT^{R}NE 30 D AND 0.5% TALC



PADDLE METHOD, WATER, 50RPM

FIGURE 6.4 : COMPARISON OF DRUG* RELEASE PROFILES OF BATCH L AND DYKATUSS^{R} CAPSULES



*CHLORPHENIRAMINE MALEATE

PADDLE METHOD, WATER, 50RPM

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6.2.1.2 : *Effect of Curing on Release Rates of Chlorpheniramine Maleate*

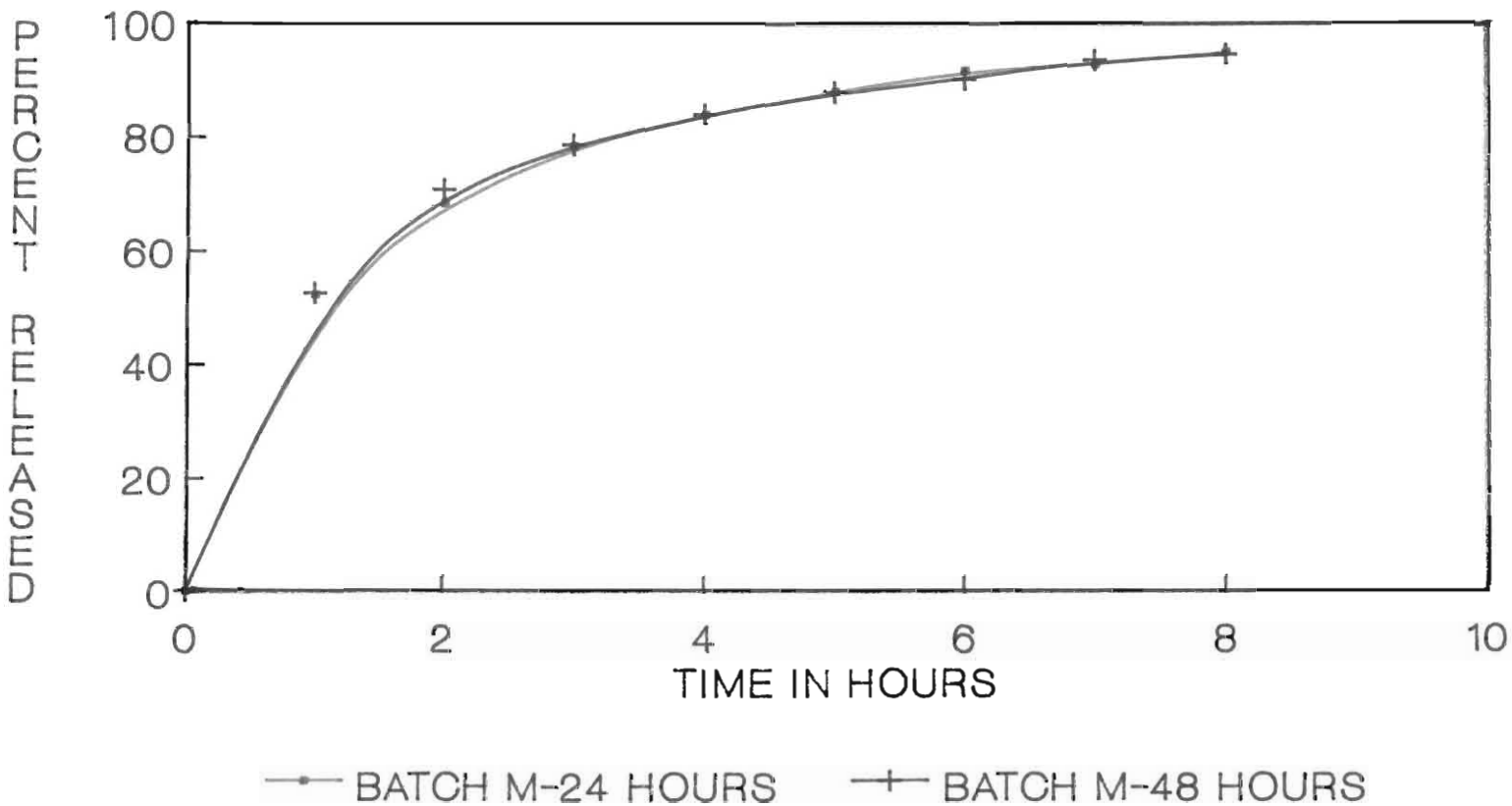
Pellets were prepared and cured for 24 and 48 hours to investigate the effect of curing on the release rates of drug from the co-polymer. Table 6.5 gives the mean drug release rates while individual release rates are presented in Appendix 7. Figure 6.5 show the drug release profiles obtained at these levels of coating.

TABLE 6.5 : CUMULATIVE PERCENTAGE* DRUG RELEASED FROM PELLETS COATED WITH 6.6% EUDRAGIT® NE 30 D, 0.5% TALC AND 0.5% PEG 6000 AND CURED FOR 24 AND 48 HOURS

SAMPLING TIME(HR.)	CURED FOR 24 HOURS	CURED FOR 48 HOURS
1	52.32 ± 2.35	52.63 ± 0.70
2	68.41 ± 0.81	70.86 ± 1.44
3	78.61 ± 2.23	78.85 ± 0.71
4	84.12 ± 1.58	84.18 ± 0.52
5	88.20 ± 1.32	88.08 ± 0.56
6	91.76 ± 1.17	90.72 ± 0.76
7	93.03 ± 1.74	93.76 ± 0.61
8	95.05 ± 0.49	94.75 ± 0.61

* each data point represents the mean and standard deviation of four samples.

FIGURE 6.5 : EFFECT OF CURING ON DRUG* RELEASE FROM PELLETS COATED WITH 6.6% EUDRAGIT^{R}NE 30 D, 0.5%TALC, 0.5%PEG6000



*CHLORPHENIRAMINE MALEATE

PADDLE METHOD, WATER, 50RPM

As can be seen from Figure 6.5, the drug release was independent of the duration for curing. There was no noteworthy difference between the drug release profiles of pellets stored for different periods of time viz. 24 and 48 hours respectively. All subsequent batches were cured at 37°C for 24 hours before analysis by dissolution. Curing at higher temperatures for long periods of time was not practicable because of sticking and agglomeration of the pellets.

6.2.1.3 *Effect of Talc*

Insoluble pharmaceutical additives, such as talc, have been incorporated to reduce the tendency of Eudragit^{R} NE 30 D polymer to become tacky during the coating process (Thoennes and McCurdy, 1989; Li *et al.*, 1989)). The effect of different amounts of talc on the release rate of drug from polymer was investigated (Table 6.6 and Figure 6.6).

The hydrophobic powder (talc) increased drug release from the coated pellets (Figure 6.6) with 27.63% of drug released during the first hour for Batch L (0.5% talc) compared to 44.54% released for Batch H (2% talc). This finding is consistent with the results of Hussain and Ayres (1990) and Ghebre-Sellasie *et al.*, (1986) who reported that water in-

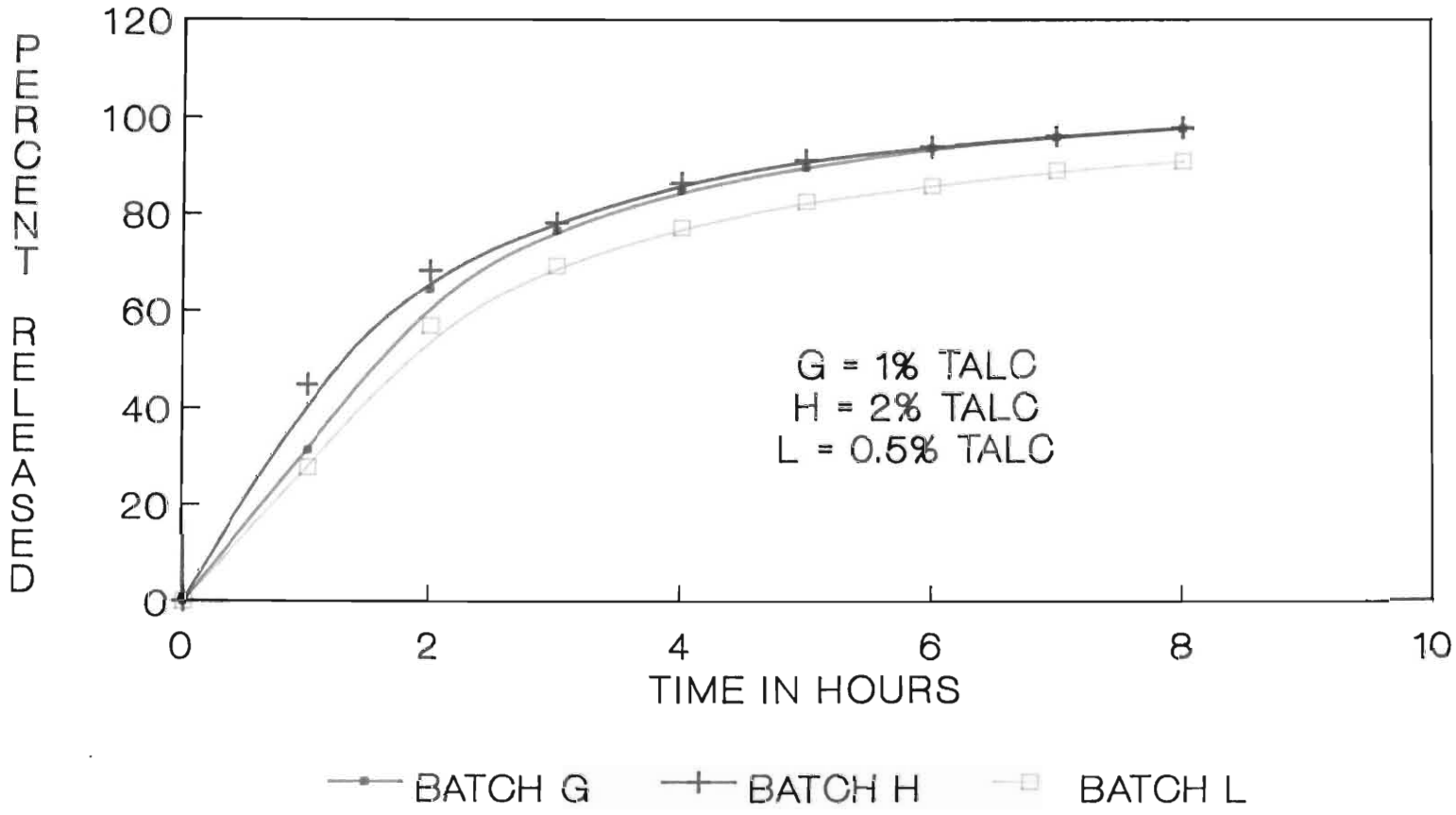
soluble additives like talc, when incorporated into Eudragit[R] NE 30 D formulations, increase drug release form coated pellets.

TABLE 6.6 : CUMULATIVE PERCENTAGE OF CHLORPHENIRAMINE MALEATE RELEASED FROM 6.6% EUDRAGIT[R] NE 30 D COATED PELLETS CONTAINING DIFFERENT AMOUNTS OF TALC

BATCH	SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE RELEASED S1	S2	S3	S4	MEAN SD
G	1	28.72	29.14	35.74	31.11	31.18 ± 2.78
(1%)*	2	62.36	62.26	68.40	64.35	64.34 ± 2.49
	3	74.77	75.28	79.09	76.35	76.37 ± 1.67
	4	83.29	84.23	86.91	84.78	84.80 ± 1.33
	5	88.43	88.75	91.24	89.46	89.47 ± 1.09
	6	92.14	93.18	95.16	93.50	93.50 ± 1.08
	7	94.82	95.57	96.51	95.65	95.64 ± 0.60
	8	96.59	97.29	98.28	97.41	97.39 ± 0.54
H	1	44.34	44.21	44.21	45.37	44.53 ± 0.49
(2%)*	2	67.63	66.91	68.91	68.86	68.08 ± 0.85
	3	78.08	76.44	78.65	78.32	77.87 ± 0.85
	4	87.07	84.73	85.79	87.19	86.19 ± 1.01
	5	92.10	89.86	90.56	91.06	90.90 ± 0.82
	6	94.97	92.47	93.78	93.68	93.73 ± 0.88
	7	96.31	95.57	96.30	95.13	95.83 ± 0.50
	8	98.94	96.59	97.15	97.14	97.46 ± 0.89
L	1	28.48	26.82	27.63	27.62	27.64 ± 0.59
(0.5%)*	2	56.84	56.82	56.74	56.60	56.75 ± 0.09
	3	68.93	68.51	69.72	69.28	69.11 ± 0.44
	4	76.76	77.57	76.75	77.02	77.03 ± 0.33
	5	82.21	81.78	83.22	82.40	82.40 ± 0.52
	6	86.24	85.41	85.04	85.88	85.64 ± 0.46
	7	89.07	87.93	89.29	88.79	88.75 ± 0.52
	8	90.68	89.95	91.41	90.65	90.67 ± 0.52

* Percent (m/m) talc applied.

FIGURE 6.6 : EFFECT OF VARIOUS AMOUNTS OF TALC ON DRUG RELEASE FROM PELLETS WITH 6.6% EUDRAGIT^{R}NE 30 D



PADDLE METHOD, WATER, 50RPM

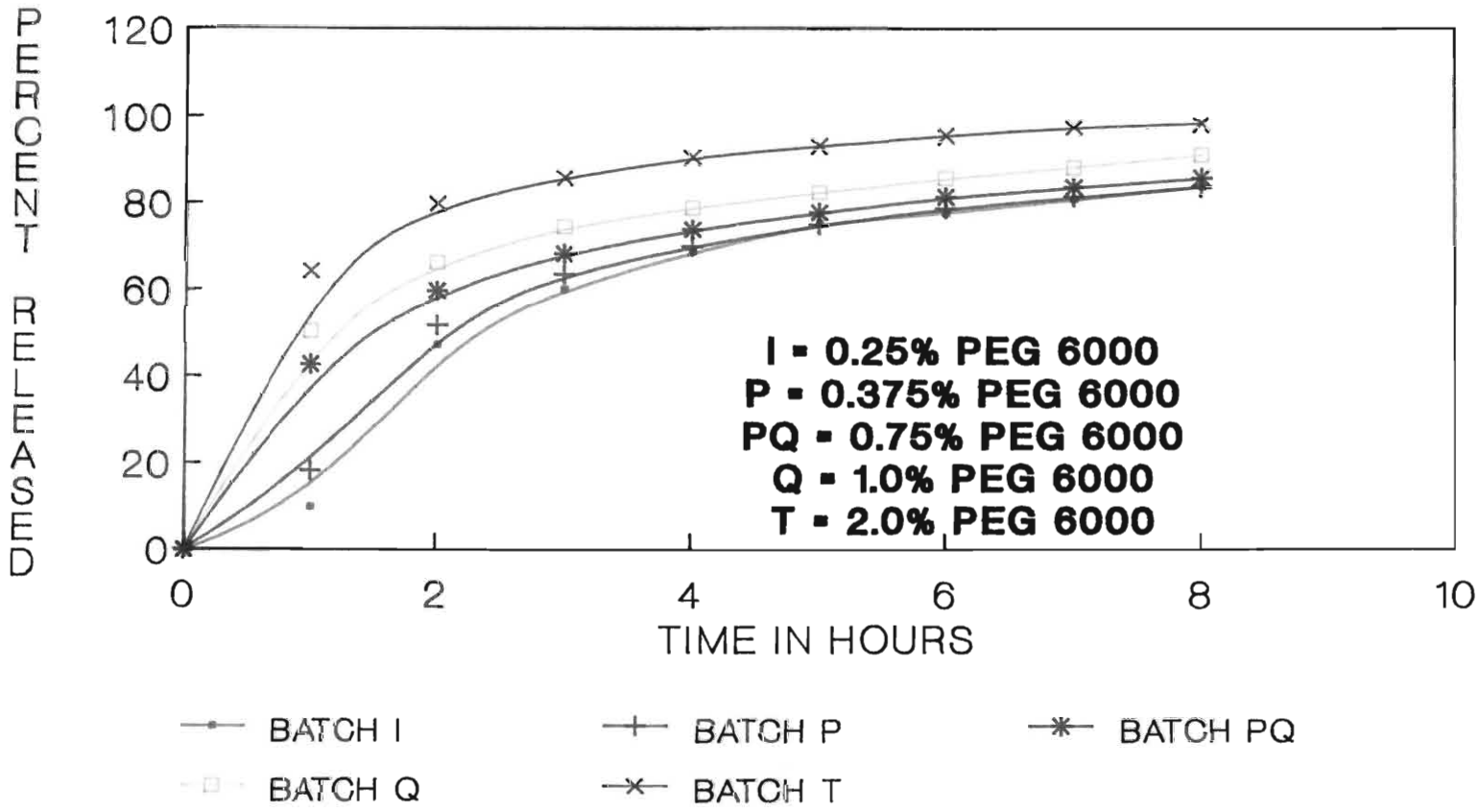
Due to the amount of talc incorporated into the coating formulation being relatively small (0.5 -2%), the release profiles obtained with all three batches were similar.

6.2.1.4 *Effect of Different Concentrations of PEG 6000*

Polyethylene glycol and other water soluble hydrophilic polymers, when employed in sufficient quantities, not only reduce the inherent tackiness associated with Eudragit^{R} NE 30 D, but also modify the permeability characteristics of the polymeric network and provide sustained release formulations (Lehmann and Dreher, 1981). Polyethylene glycols are used as emulsifiers, wetting agents and stabilisers (Eudragit Data Sheets).

The formulation and coating procedure (Table 5.5 and Table 5.10) were used to prepare the various batches (I, P, PQ, Q and T). The cumulative drug percentages released for the above mentioned batches are presented in Table 6.7 and Figure 6.7.

FIGURE 6.7 : EFFECT OF VARIOUS AMOUNTS OF PEG 6000 ON PELLETS COATED WITH 8.3% EUDRAGIT^{R}NE 30 D AND 0.5% TALC



PADDLE METHOD, WATER, 50RPM

TABLE 6.7 : CUMULATIVE PERCENTAGE OF CHLORPHENIRAMINE MALEATE RELEASED FROM PELLETS COATED WITH 8.3% EUDRAGIT® NE 30 D, 0.5% TALC AND VARIOUS AMOUNTS OF PEG 6000

BATCH	SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE RELEASED* S1	S2	S3	S4	MEAN SD
I	1	9.25	12.41	10.19	8.90	10.19 ± 1.37
(0.25%	2	45.95	49.59	47.82	46.18	47.39 ± 1.46
PEG6000)*	3	60.32	63.16	60.34	57.27	60.27 ± 2.08
	4	68.60	71.87	68.22	66.91	68.90 ± 1.83
	5	75.04	77.91	74.56	74.85	75.59 ± 1.35
	6	77.29	80.39	77.06	76.22	77.74 ± 1.58
	7	80.67	82.49	80.42	80.42	81.00 ± 0.87
	8	83.65	85.29	83.39	83.04	83.84 ± 0.86
P	1	17.27	17.56	17.47	20.37	18.17 ± 1.28
(0.375%	2	51.24	51.62	50.56	52.98	51.60 ± 0.88
PEG6000)*	3	63.39	63.50	63.39	63.89	63.54 ± 0.21
	4	70.80	69.11	69.88	70.03	69.96 ± 0.60
	5	76.12	74.64	74.47	74.76	75.00 ± 0.66
	6	78.59	78.58	78.67	78.87	78.68 ± 0.12
	7	81.82	81.37	80.76	81.35	81.33 ± 0.37
	8	84.04	83.56	82.86	84.24	83.68 ± 0.53
PQ	1	41.06	42.22	43.57	44.29	42.79 ± 1.24
(0.75%	2	58.98	60.42	60.15	59.86	59.85 ± 0.54
PEG6000)*	3	67.24	67.64	68.99	69.77	68.41 ± 1.02
	4	73.13	73.63	74.22	75.09	74.01 ± 0.73
	5	76.93	77.62	78.22	79.12	77.97 ± 0.81
	6	80.62	81.05	81.92	82.61	81.55 ± 0.77
	7	82.92	83.42	84.20	84.40	83.74 ± 0.60
	8	85.21	85.90	86.02	86.43	85.89 ± 0.40
Q	1	42.20	42.10	42.92	43.09	42.58 ± 0.43
(1%	2	62.62	62.98	63.53	63.89	63.26 ± 0.49
PEG6000)*	3	72.83	72.83	73.56	73.12	73.09 ± 0.30
	4	79.76	79.13	80.31	79.85	79.76 ± 0.42
	5	84.25	83.99	85.08	84.82	84.54 ± 0.43
	6	87.71	86.99	88.55	87.90	87.79 ± 0.50
	7	90.89	90.25	90.76	90.72	90.66 ± 0.24
	8	92.80	92.30	92.79	93.00	92.72 ± 0.26

BATCH	SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE RELEASED* S1	S2	S3	S4	MEAN SD
T	1	63.45	64.73	63.64	64.82	64.16 ± 0.62
2%	2	79.26	79.91	79.35	80.54	79.77 ± 0.51
PEG6000)*	3	85.78	85.32	85.02	86.87	85.75 ± 0.70
	4	90.28	90.75	90.37	90.94	90.59 ± 0.27
	5	92.34	93.11	93.13	94.23	93.20 ± 0.67
	6	94.79	95.28	95.09	96.30	95.37 ± 0.56
	7	97.51	97.15	96.96	97.91	97.38 ± 0.36
	8	97.84	97.75	97.66	99.43	98.17 ± 0.73

* Percent (m/m) PEG 6000 applied.

It is well known that the inclusion of an additive to a polymer film will alter the permeability characteristics of that film (Ghebre-Sellasie *et al.*, 1985; Ghebre-Sellasie *et al.*, 1987). Figure 6.6 show the effect of increasing the the proportion of PEG 6000 in the polymer coating from 0.25 to 2% m/m of the total polymer solids. As the amount of PEG 6000 in the coating formulation is increased from 0.25% to 2%, a corresponding increase (±10% to ±64% respectively) in release of drug (at 1 hour) from the pellets was evident (Figure 6.7). These results are comparable to studies undertaken by other investigators using polyethylene glycols (Ghebre-Sellasie *et al.*, 1986) where the film was more permeable .

It was observed (Figure 6.7) that Batch Q displayed drug release characteristics comparable to the reference standard preparation (Figure 6.8) and was therefore chosen for all future stability and reproducibility studies. The average of the differences at each sampling time was 2.43%.

A further Batch (Q1) of pellets was therefore prepared using formulation procedures that were identical to those for Batch Q in order to establish the effect of the following variables on dissolution characteristics:

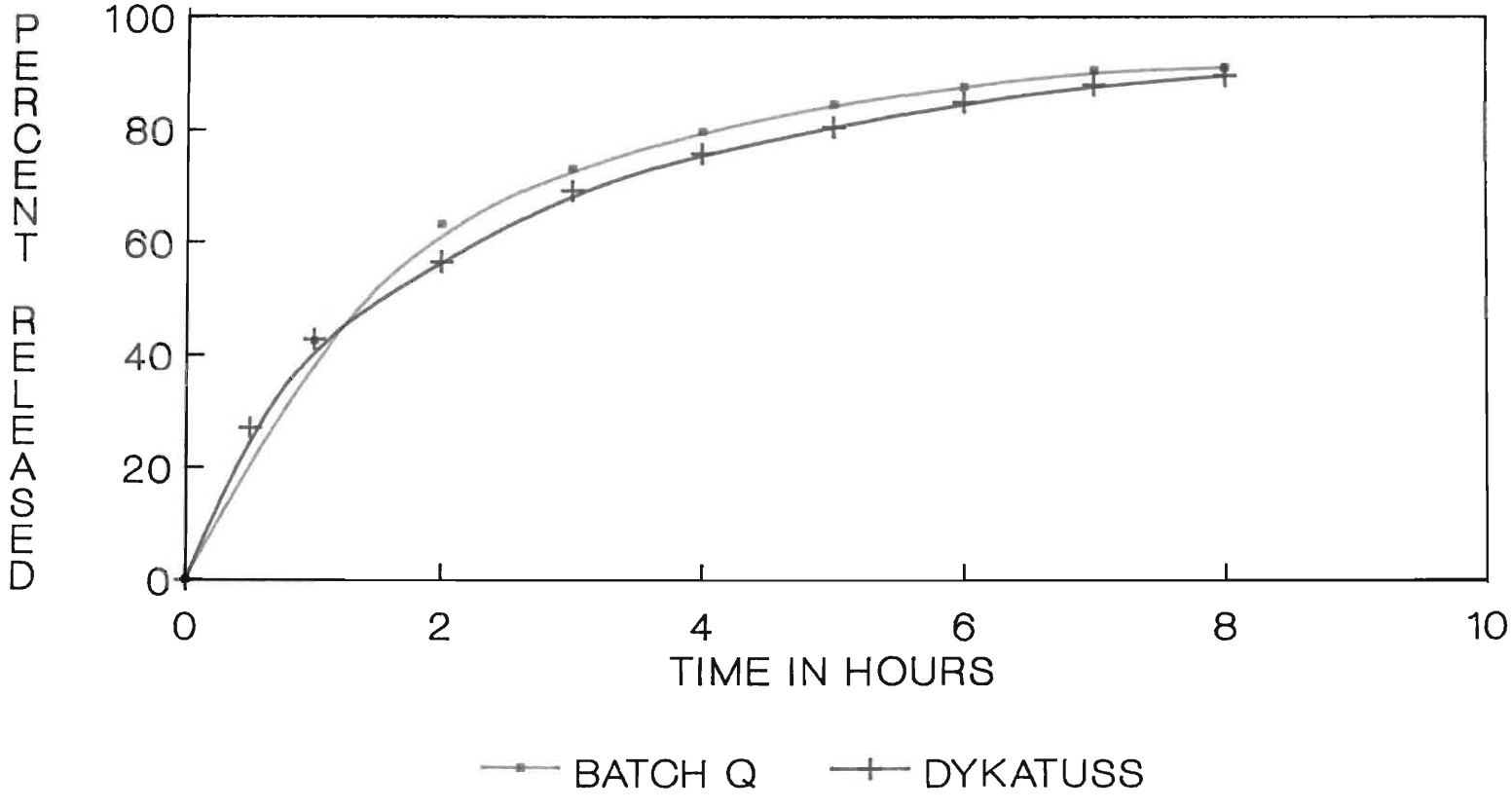
a) reproducibility of manufacture (6.3)

b) dissolution techniques (6.4)

c) dissolution media (6.5)

d) short term stability (6.6)

FIGURE 6.8 : COMPARISON OF DRUG* RELEASE PROFILES OF BATCH Q AND DYKATUSS^{R} CAPSULES



*CHLORPHENIRAMINE MALEATE

PADDLE METHOD, WATER, 50RPM

6.2.1.5 *Effect of Polymer (PEG 6000 Included)*

The dissolution profiles of pellets coated with various amounts of Eudragit^{R} NE 30 D were tabulated (Table 6.8) and presented graphically (Figure 6.9)

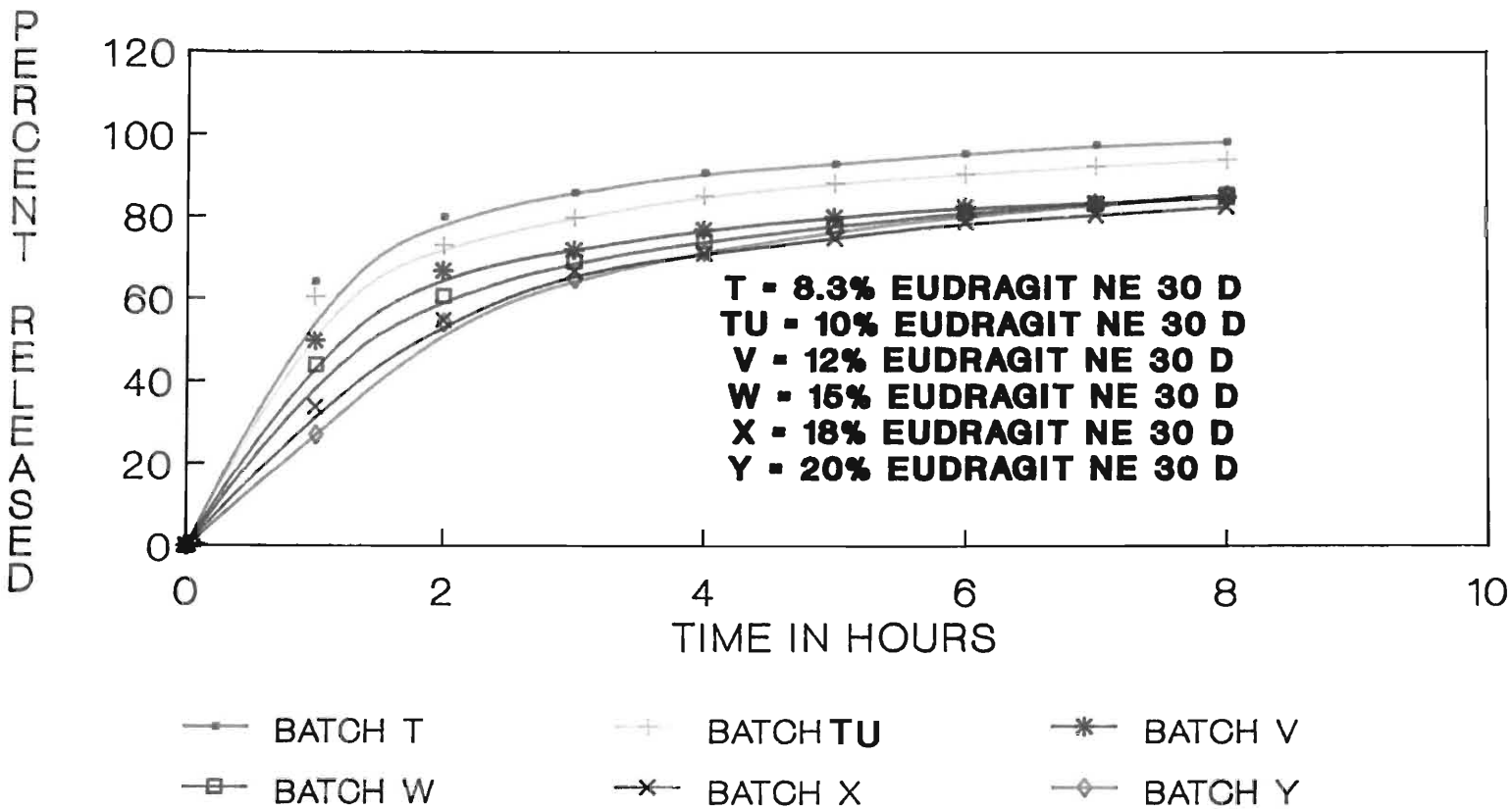
TABLE 6.8 : CUMULATIVE PERCENTAGE OF CHLORPHENIRAMINE MALEATE RELEASED FROM FORMULATIONS CONTAINING 1% TALC, 2% PEG AND VARIOUS AMOUNTS OF EUDRAGIT^{R} NE 30 D

BATCH	SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE RELEASED S1	S2	S3	S4	MEAN SD
T	1	63.45	64.73	63.64	64.82	64.16 ± 0.62
(8.3%	2	79.26	79.91	79.35	80.54	79.76 ± 0.51
NE30D*)	3	85.78	85.32	85.02	86.87	85.75 ± 0.70
	4	90.28	90.75	90.37	90.94	90.59 ± 0.27
	5	92.34	92.81	92.43	93.00	92.65 ± 0.27
	6	94.79	95.28	95.09	96.30	95.37 ± 0.57
	7	97.51	97.15	96.96	97.91	97.38 ± 0.36
	8	97.84	97.75	97.66	99.43	98.17 ± 0.73
TU	1	60.14	60.81	60.59	60.73	60.57 ± 0.26
(10%	2	74.31	72.49	72.49	73.03	73.08 ± 0.74
NE30D*)	3	80.02	79.71	79.83	79.95	79.88 ± 0.12
	4	85.15	85.39	85.15	84.95	85.16 ± 0.16
	5	88.15	88.39	88.05	88.01	88.15 ± 0.15
	6	90.85	90.62	90.51	90.07	90.51 ± 0.28
	7	92.63	92.26	92.26	92.60	92.44 ± 0.18
	8	95.14	93.56	93.80	93.60	94.03 ± 0.65
V	1	50.53	49.26	49.78	49.56	49.78 ± 0.47
(12%	2	67.86	67.86	66.84	64.84	66.85 ± 1.23
NE30D*)	3	72.08	72.08	71.94	71.67	71.94 ± 0.17
	4	77.52	77.48	76.90	75.71	76.90 ± 0.73
	5	80.11	80.31	79.91	79.31	79.91 ± 0.37
	6	82.42	83.40	82.51	81.72	82.51 ± 0.60
	7	84.64	83.19	83.42	82.42	83.42 ± 0.80
	8	85.99	84.43	84.93	84.38	84.93 ± 0.65

BATCH	SAMPLING TIMES(HR.)	CUMULATIVE PERCENTAGE RELEASED S1	S2	S3	S4	MEAN SD
W (15% NE30D*)	1	44.65	44.20	43.10	44.20	44.04 ± 0.57
	2	60.84	61.01	60.57	61.17	60.90 ± 0.22
	3	68.89	69.51	68.70	69.88	69.25 ± 0.47
	4	74.24	73.80	74.33	74.31	74.17 ± 0.22
	5	78.25	77.75	77.46	77.94	77.85 ± 0.29
	6	82.21	80.71	81.52	80.80	81.31 ± 0.61
	7	83.05	83.31	83.77	83.96	83.52 ± 0.36
	8	85.68	85.59	85.76	85.88	85.73 ± 0.11
X (18% NE30D*)	1	33.87	33.60	33.87	33.78	33.78 ± 0.11
	2	56.25	55.28	55.85	52.27	54.91 ± 1.56
	3	67.21	66.06	66.83	66.57	66.67 ± 0.42
	4	71.59	70.73	71.32	70.45	71.02 ± 0.45
	5	75.52	74.56	74.39	75.29	74.94 ± 0.47
	6	79.39	78.49	78.98	78.58	78.86 ± 0.48
	7	81.20	79.97	81.03	80.26	80.62 ± 0.51
	8	83.28	81.66	82.45	83.28	82.67 ± 0.67
Y (20% NE30D*)	1	25.75	28.09	26.39	27.72	26.99 ± 0.95
	2	53.93	54.80	54.87	54.05	54.41 ± 0.42
	3	65.09	65.66	64.25	64.72	64.93 ± 0.52
	4	71.66	72.26	70.92	71.12	71.49 ± 0.52
	5	76.58	77.26	75.56	76.31	76.43 ± 0.61
	6	80.67	81.18	79.84	80.40	80.52 ± 0.48
	7	83.38	83.89	81.78	82.92	82.99 ± 0.78
	8	85.61	86.59	84.63	85.06	85.47 ± 0.73

* Percent (m/m) Eudragit^{R} NE 30 D (m/m) applied.

FIGURE 6.9 : EFFECT OF VARIOUS AMOUNTS OF POLYMER ON DRUG* RELEASE FROM PELLETS COATED WITH 1% TALC AND 2% PEG 6000



*CHLORPHENIRAMINE MALEATE

PADDLE METHOD, WATER, 50RPM

The release profile of drug-loaded pellets depend, to a great extent, on the coating level of the final product. An increase in coating thickness is always accompanied by a decrease in the release rates of the pellets (Ghebre-Sellasie *et al.*, 1987). For example, at a coating level of 20% (Batch Y) the pellets release only 85.47% of drug in 8 hours, whereas those pellets coated with 8.3% (Batch T) and 10% (Batch TU) released 98.16% and 93.74% of the drug respectively. The relationship, however, is not linear and the variability with the properties of the active ingredient is large. Highly water-soluble drugs such as chlorpheniramine maleate generally require higher coating levels than poorly soluble compounds. This behaviour may be partially attributed to the different rates of migration of the drug species during the coating process. During film deposition, highly water soluble drugs dissolve in the sprayed droplets and remain embedded in the film after evaporation of water. As more and more layers of film are deposited to constitute the wall material, the migration of drug diminishes until a coating film devoid of drug is produced. Since the presence of drug in the inner parts of the coating leads to a porous structure during dissolution, a thicker coat is required to generate a specific release profile than would be the case with poorly water-soluble drugs.

The integrity of the coating was well preserved throughout the dissolution experiments; even when the drug was completely depleted from the pellet, the shell remained intact, which was true for pellets at the lowest level of coating (6.7.3) (Figure 6.26 - Figure 6.29).

6.3 REPRODUCIBILITY STUDY

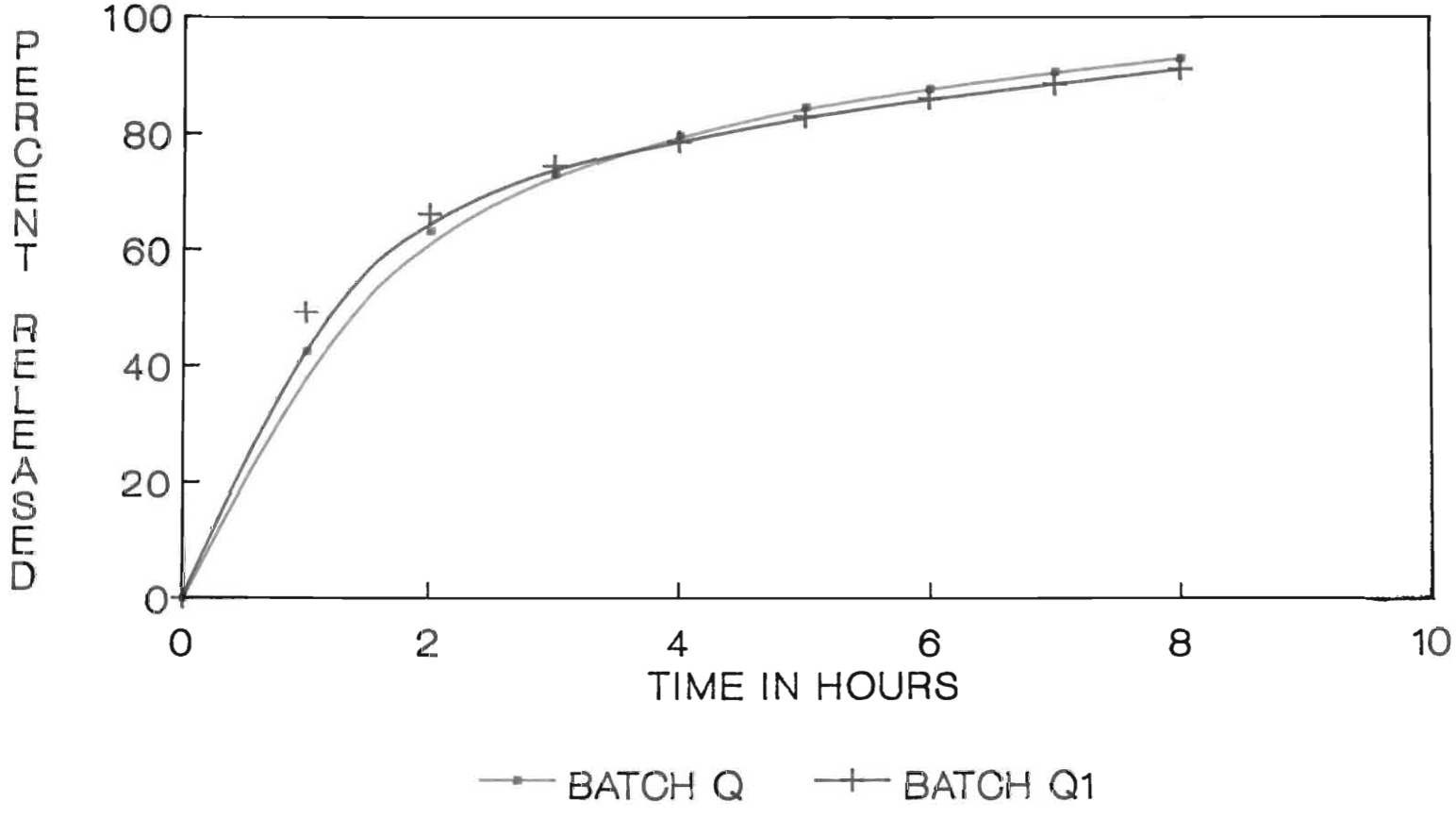
The reproducibility of the manufacturing process was demonstrated by preparing Batch Q1 using conditions outlined that were identical to those for Batch Q (Tables 5.5 and 5.6). The mean dissolution data on Batch Q1 in relation to Batch Q are presented in Table 6.9 and Figure 6.10.

TABLE 6.9 : COMPARISON OF THE RELEASE CHARACTERISTICS OF BATCH Q1 AND Q

	BATCH Q1							BATCH Q
SAMPLING TIMES	CUMULATIVE PERCENTAGE RELEASED* S1	S2	S3	S4	S5	S6	MEAN SD	MEAN
1	49.08	51.55	50.35	50.08	49.59	45.12	49.30±2.02	42.58
2	63.60	66.53	68.52	66.52	67.00	64.60	66.13±1.61	63.26
3	71.44	74.93	77.57	74.46	74.67	73.32	74.40±1.84	73.09
4	77.05	80.08	79.56	79.18	79.50	77.15	78.75±1.20	79.76
5	80.53	84.14	84.91	83.70	81.52	83.25	83.01±1.52	84.54
6	82.12	85.82	87.85	87.17	86.18	87.81	86.16±1.96	87.79
7	84.83	87.38	91.32	89.29	90.00	88.59	88.57±2.06	90.66
8	88.20	92.63	93.22	90.43	92.04	90.26	91.13±1.70	92.72

* 6 samples analysed

FIGURE 6.10 : REPRODUCIBILITY STUDY: COMPARISON OF DRUG RELEASE FROM PELLETS OF BATCH Q AND BATCH Q1



PADDLE METHOD, WATER, 50RPM

The results in Table 6.9 reflect that intra- and inter-batch variations were within an acceptable range. Figure 6.10 demonstrates the reproducibility and predictability of the coating procedure as the release profiles of Batches Q and Q1 are comparable and almost superimposable.

6.4 DIFFERENT DISSOLUTION TECHNIQUES

The dissolution profiles of controlled release chlorpheniramine maleate pellets for Batch Q1 (See 6.2.2.4) (Table 6.9) were investigated using the basket, paddle and rotating bottle methods as shown in Table 6.11 and Figure 6.11. There was no appreciable difference observed between these dissolution profiles. The individual results obtained are presented in Appendix 8.

TABLE 6.10 : *IN VITRO* DISSOLUTION PROFILES OF CHLORPHENIRAMINE MALEATE PELLETS (BATCH Q1) USING DIFFERENT METHODS.

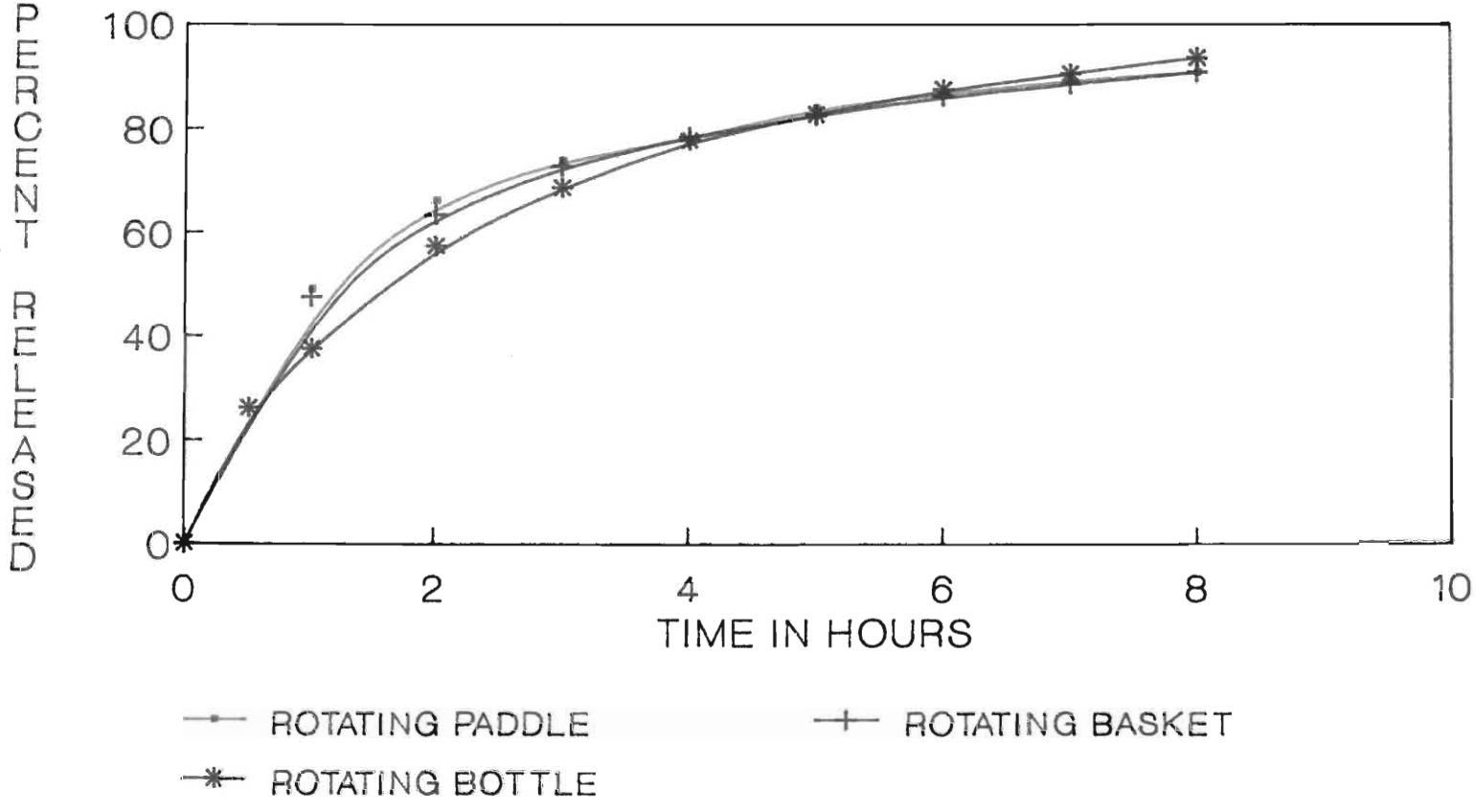
SAMPLING TIME (HR.)	DISSOLUTION METHOD		
	PADDLE*(50rpm)	BASKET*(50rpm)	BOTTLE*(30rpm)
0.5	24.71 ± 1.00	23.17 ± 0.73	26.18 ± 3.11
1	49.11 ± 2.38	47.64 ± 5.35	37.46 ± 3.42
2	66.10 ± 3.00	63.45 ± 3.71	57.25 ± 3.16
3	73.93 ± 1.21	72.88 ± 3.01	68.63 ± 2.78
4	78.59 ± 1.02	78.56 ± 1.67	77.71 ± 2.47
5	83.87 ± 0.92	82.73 ± 2.62	82.75 ± 1.77
6	86.76 ± 1.06	86.30 ± 2.29	87.13 ± 1.96
7	89.28 ± 1.78	88.70 ± 0.18	90.46 ± 1.56
8	90.87 ± 1.65	90.89 ± 1.55	93.54 ± 1.91

* Each data point represents the mean and standard deviation of six samples.

A closer examination of the drug release rates showed that the biggest difference (between methods) in release rates occurred between 0.5 and 1 hour (37.46% for the bottle as compared to 47.64 for the basket method). The profiles obtained from the rotating paddle, basket and bottle methods (Figure 6.11) revealed very similar drug release rates and although the graphs are not identical they are nearly superimposable and comparable.

The rotating paddle method was chosen for all further dissolution studies on chlorpheniramine maleate pellets as it is the official/compendial method in the USP XXII (1990).

FIGURE 6.11 : DISSOLUTION STUDIES ON PELLETS OF BATCH Q1 USING DIFFERENT DISSOLUTION TECHNIQUES



WATER (SINK CONDITIONS MAINTAINED)

6.5 DIFFERENT DISSOLUTION MEDIA

Eudragit^{R} NE 30 D is said to produce pH independent film coatings. Different media were thus used to test the pH dependency on the newly formulated pellets of Batch Q1. The dissolution rate of chlorpheniramine maleate from pellets of Batch Q1 were tested in the following media.

a) Hydrochloric acid at pH 1.5

b) Neutralised phosphate buffer at pH 4.5

c) Deionised water at pH 6.6

d) Phosphate buffer at pH 6.8

The method of preparation of the various media are presented in Appendix 5A. The dissolution studies were performed in 900ml of medium at 37°C using the rotating paddle method (50 rpm). The rates of drug release are shown in Table 6.11 and the pH profiles are presented in Figure 6.12. Individual release rates for each of the six samples used in each medium are presented in Appendix 9.

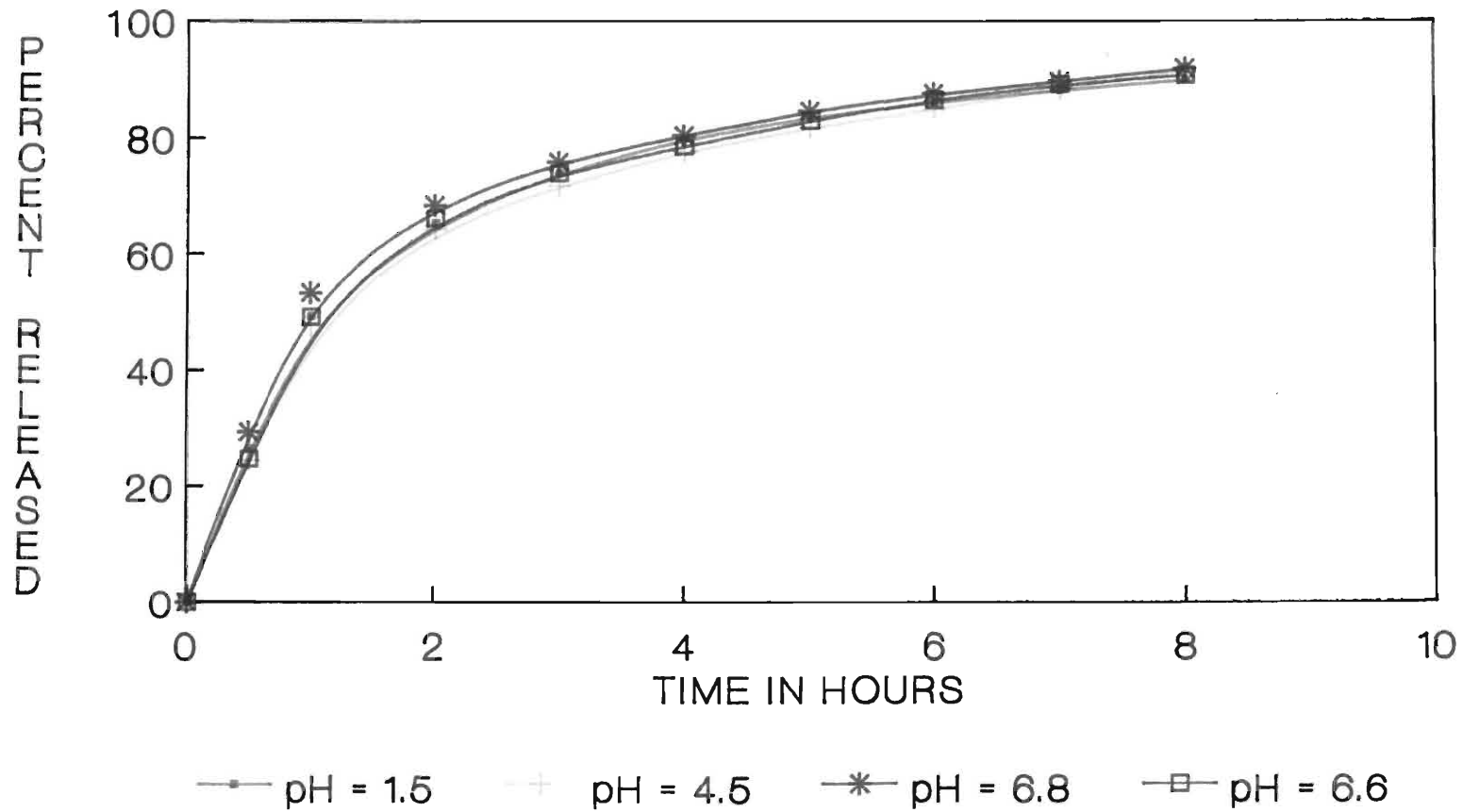
TABLE 6.11 : CUMULATIVE PERCENTAGE OF DRUG RELEASED FROM PELLETS OF BATCH Q1 USING HYDROCHLORIC ACID (pH=1.5), NEUTRALISED PHOSPHATE BUFFER (pH=4.5), DEIONISED WATER (pH=6.6) AND PHOSPHATE BUFFER (pH=6.8) AS THE DISSOLUTION MEDIUM

SAMPLING TIME (HR.)	pH OF DISSOLUTION MEDIA % CUMULATIVE RELEASE* 1.5	4.5	6.6	6.8
0.5	25.61 ± 1.00	24.52 ± 0.83	24.71 ± 1.00	29.32 ± 0.42
1	49.29 ± 0.64	47.58 ± 0.71	49.11 ± 2.38	53.19 ± 1.40
2	65.37 ± 0.84	64.36 ± 0.29	66.19 ± 3.00	68.37 ± 1.07
3	74.05 ± 0.07	71.80 ± 0.34	73.93 ± 1.20	75.88 ± 1.33
4	80.01 ± 0.36	77.79 ± 0.44	78.59 ± 1.02	80.45 ± 1.12
5	83.62 ± 0.19	81.85 ± 0.70	84.03 ± 0.92	84.63 ± 1.28
6	86.41 ± 0.56	85.09 ± 1.00	86.76 ± 1.06	87.76 ± 1.03
7	88.36 ± 0.65	88.63 ± 0.22	89.28 ± 1.78	89.71 ± 0.45
8	90.03 ± 0.66	91.45 ± 0.38	90.87 ± 1.65	91.89 ± 0.63

* Each data point represents the mean and standard deviation of six samples.

As depicted in Figure 6.12 the drug release profiles of coated chlorpheniramine pellets in hydrochloric acid, neutralised phosphate buffer, phosphate buffer and deionised water are virtually identical. These findings are consistent with those of Ghebre-Sellasie *et al.*, 1987; and Goodhart *et al.*, 1984. The largest difference between percentage released for two dissolution media at any one sampling time is 3.91% which is considered to be negligible. The standard deviations were also negligible.

FIGURE 6.12 : DISSOLUTION STUDIES ON PELLETS OF BATCH Q1 USING DIFFERENT pH's



PADDLE METHOD, 50RPM

Pellets of Batch Q1 showed sustained drug release in all three dissolution media and the release profiles were thoroughly independent of the dissolution media (Figure 6.12). These results were similar to those obtained by Takeuchi *et al.*, (1989) using Eudragit^{R} NE 30 D. This should ensure the constant release of drug *in vivo* irrespective of the various pH's encountered in the different regions of the gastrointestinal tract (Ghebre-Sellasie *et al.*, 1987). It can thus be concluded that Batch Q1 has fulfilled one of the objectives of this study as the pellets released drug in a pH independent manner.

Due to the pH independence of drug release, it was not necessary to test drug release by the half-change method.

6.6 STABILITY PROFILES

The drug release profiles and potency of chlorpheniramine maleate pellets (Batch Q1) after short term storage under various temperatures and humidity conditions are indicated hereunder.

HPLC analysis for all stored samples revealed an assay of greater than 99.5% of the initial potency of the pellets. No chemical degradation (i.e. no additional peaks in the HPLC recordings) of the drug occurred during storage under the various conditions.

6.6.1 Pellets Stored at Room Temperature (20°C ± 2°C)

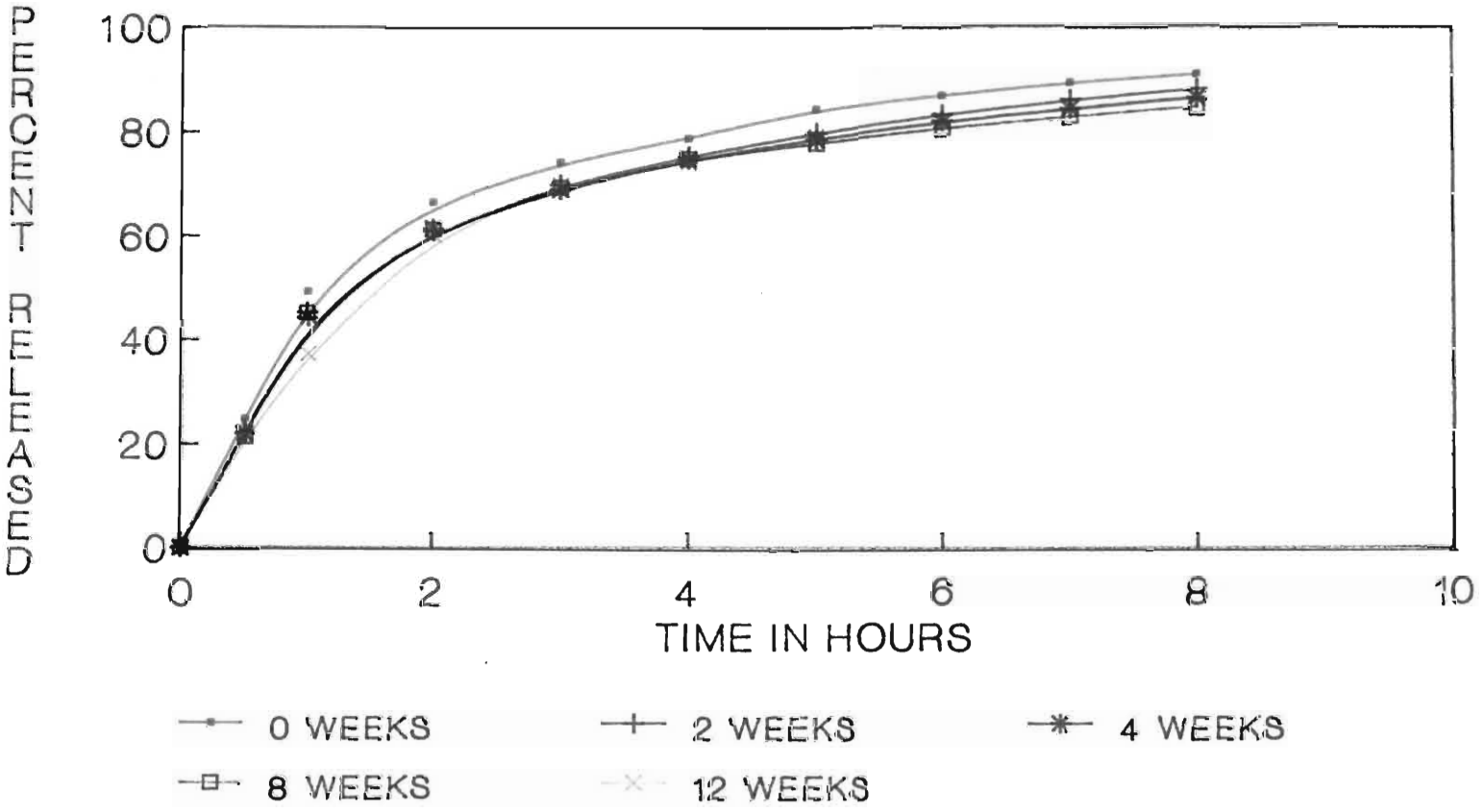
The mean rates of drug release initially (0 weeks), and after two weeks, 4 weeks, 8 weeks and 12 weeks are presented in Table 6.12 and Figure 6.13. The individual values obtained for tested samples are presented in Appendix 10.

TABLE 6.12 : CUMULATIVE PERCENTAGE* OF DRUG RELEASED FROM PELLETS (BATCH Q1) STORED AT ROOM TEMPERATURE

SAMPLING TIME(HR.)	% CUMULATIVE RELEASE AT				
	INITIAL	2 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	24.71±1.00	21.87±3.36	22.09±2.19	21.30±1.57	21.63±2.25
1	49.11±2.38	45.20±2.28	44.29±2.19	45.12±0.84	37.10±2.56
2	66.10±3.00	60.61±2.30	61.27±1.35	61.03±1.06	59.96±2.19
3	73.93±1.21	69.79±1.70	69.04±0.97	69.26±1.12	69.72±1.08
4	78.59±1.02	75.20±1.26	74.84±0.96	74.79±1.06	74.15±0.72
5	84.03±0.92	79.60±1.16	78.52±0.81	77.70±0.33	79.00±0.36
6	86.75±1.06	83.11±0.87	81.99±1.12	80.58±0.52	81.36±0.72
7	89.28±1.78	85.94±1.38	84.37±1.20	82.85±0.39	84.67±1.07
8	90.87±1.65	88.02±1.30	86.47±0.61	84.68±0.52	86.74±1.03

* each data point represents the mean and standard deviation of six samples.

FIGURE 6.13 : STABILITY STUDIES ON PELLETS OF BATCH Q1 STORED AT ROOM TEMPERATURE



PADDLE METHOD, WATER, 50RPM

The profiles (Figure 6.13) obtained illustrate that the pellets stored at room temperature did not show a change in the drug dissolution characteristics (Table 6.12) during the period of study. The pellets are therefore relatively stable for the period of study. Thus, the newly formulated pellets (Batch Q1) fulfil the stability requirements at room temperature (20 ± 2°C) as stated in the purpose of study.

6.6.2 Storage at Low Temperatures (5 ± 1°C)

The drug release rates of pellets stored at ±5°C and analysed after 2 weeks, 4 weeks and 8 weeks are shown in Figure 6.12. The average percentages of drug release and standard deviations are presented in Table 6.13. The actual values for the six samples analysed are shown in Appendix 11.

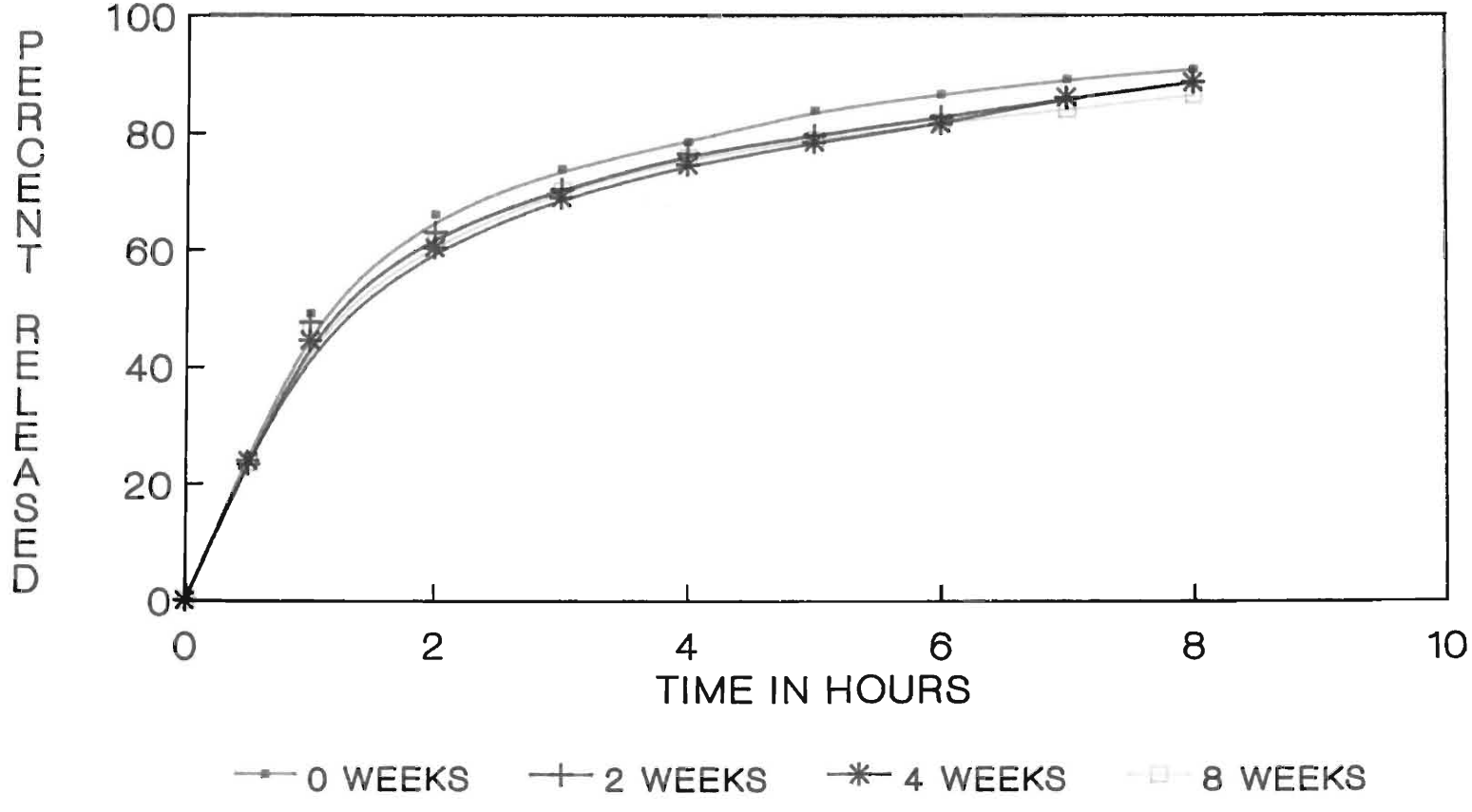
TABLE 6.13 : CUMULATIVE PERCENTAGES* OF DRUG RELEASED FROM PELLETS (BATCH Q1) STORED AT 5 ± 1°C

SAMPLING TIME(HR.)	% CUMULATIVE RELEASED			
	INITIAL	2 WEEKS	4 WEEKS	8 WEEKS
0.5	24.71 ± 1.00	23.45 ± 1.68	23.97 ± 0.77	23.70 ± 1.01
1	49.11 ± 2.38	47.71 ± 2.37	44.63 ± 0.56	46.82 ± 0.57
2	66.19 ± 3.00	63.16 ± 0.90	60.44 ± 0.66	61.54 ± 0.51
3	73.93 ± 1.21	70.56 ± 2.08	68.98 ± 0.86	70.38 ± 0.45
4	78.59 ± 1.02	76.59 ± 2.15	74.62 ± 0.57	76.01 ± 0.62
5	84.03 ± 0.92	79.87 ± 1.65	78.60 ± 0.61	79.16 ± 0.72
6	86.76 ± 1.06	83.05 ± 1.97	81.78 ± 0.99	82.20 ± 0.69
7	89.28 ± 1.78	86.15 ± 0.76	86.25 ± 0.55	84.34 ± 0.65
8	90.87 ± 1.65	88.85 ± 1.22	88.77 ± 1.10	86.75 ± 1.01

* Each data point represents the mean and standard deviation of six samples.

Pellets stored at low temperatures (5 ± 1°C) demonstrated that the drug release rate did not change appreciably. Figure 6.12 shows the drug release profiles, initially (prior to storage) and even after storage for two months, to be virtually superimposable. Thus the pellets were stable for the period of study (8 weeks).

FIGURE 6.14 : STABILITY STUDIES ON PELLETS OF BATCH Q1 STORED AT LOW TEMPERATURE (5 ± 1°C)



PADDLE METHOD, WATER, 50RPM

6.6.3 Storage at 37°C with 80% Relative Humidity

To determine the effect of elevated temperature and humidity conditions, the dissolution characteristics of Batch Q1 which was stored in a sealed amber glass bottle at 37°C with 80% relative humidity were established over a period of 8 weeks.

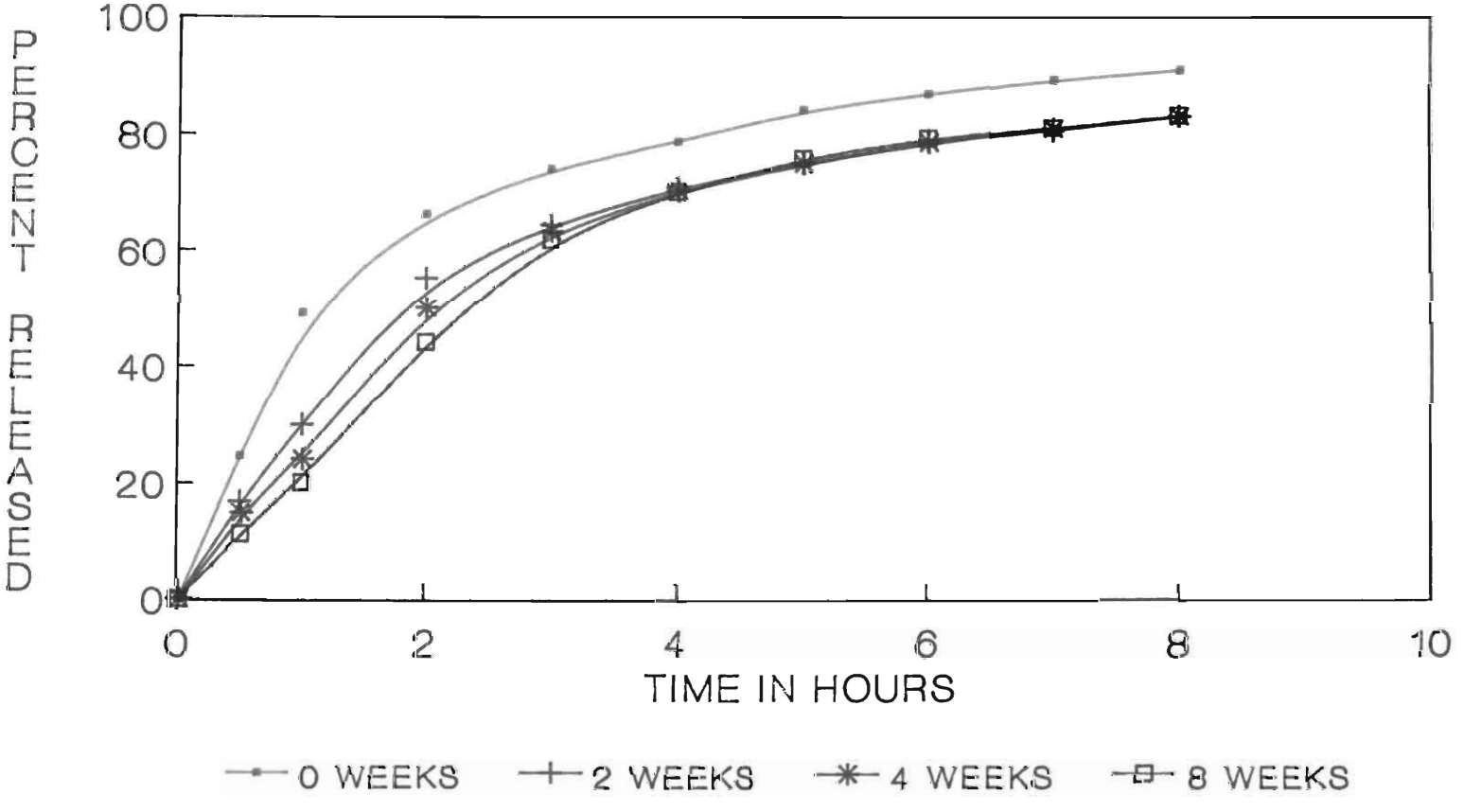
Table 6.14 and Figure 6.15 show the cumulative percent drug release and dissolution profile of pellets stored under these conditions. Individual values of drug release for each of six samples are presented in Appendix 12.

TABLE 6.14 : CUMULATIVE PERCENTAGE OF DRUG RELEASED FROM PELLETS (BATCH Q1) STORED AT 37°C WITH 80% RELATIVE HUMIDITY.

SAMPLING TIME(HR.)	% CUMULATIVE RELEASED			
	INITIAL	2 WEEKS	4 WEEKS	8 WEEKS
0.5	24.71 ± 1.00	16.86 ± 1.73	14.91 ± 1.49	11.30 ± 1.58
1	49.11 ± 2.38	29.94 ± 1.19	24.13 ± 0.74	20.18 ± 2.13
2	66.10 ± 3.00	55.16 ± 1.84	50.01 ± 0.35	44.20 ± 1.47
3	73.93 ± 1.21	64.30 ± 0.69	63.31 ± 0.34	61.84 ± 0.51
4	78.59 ± 1.02	70.77 ± 0.88	70.20 ± 0.53	70.15 ± 0.38
5	84.03 ± 0.92	74.97 ± 0.47	75.02 ± 0.57	75.89 ± 0.18
6	86.76 ± 1.06	78.93 ± 0.45	78.56 ± 1.01	79.30 ± 0.23
7	89.28 ± 1.78	80.66 ± 0.56	81.16 ± 0.82	81.28 ± 0.75
8	90.87 ± 1.65	83.15 ± 0.31	83.24 ± 0.86	83.39 ± 0.62

* Each data point represents the mean and standard deviation of six samples.

FIGURE 6.15 : STABILITY STUDIES ON PELLETS OF BATCH Q1 STORED AT 37 DEGREES CELSIUS AND 80% RELATIVE HUMIDITY



PADDLE METHOD, WATER, 50RPM

When the pellets were observed at 2 weeks after storage for dissolution analyses, the pellets appeared aggregated together in small lumps. Furthermore, as reflected in Table 6.14 and Figure 6.15 these pellets failed to maintain their original drug release profile as approximately half the drug (29.94%) was released in the first hour when compared to the initial release (49.12%). The drug release profiles at 2 weeks, 4 weeks and 8 weeks were very similar with small variations occurring in the first two hours.

It was hypothesised that the decrease in release rate can be related to the concept of further gradual coalescence as described by Gilligan and Po (1991). With time, coalescence proceeds to produce a more continuous polymer film resulting in decreased drug release rate. Storage of these pellets would allow further gradual coalescence to proceed thus providing a possible explanation for the decrease in release rate on storage at elevated temperatures.

The mechanism of further gradual coalescence is attributed to auto-adhesion and the forces that are derived from the polymer-air interfacial tension (Yang and Ghebre-Sellasie, 1990). Vanderhoff *et al.*, (1973) hypothesised the mechanism of film formation in three stages. An initial stage where the polymer particles are free to move about and drying occurs at a continuous rate; an intermediate stage in which the particles come into irreversible contact with one another and start coalescing into a continuous film, and a final stage in which the residual water escapes at a very slow rate by diffusion either through capillary channels between the spheres or through the polymer itself.

The decrease in release rates are similar to those found by Chowhan *et al.*, (1982), who also observed a large decrease in the dissolution rate when pellets were stored under high temperature and humidity conditions. These results suggest that film coated pellets of Eudragit^{R} NE 30 D should be protected from high relative humidity in order to maintain stability throughout the shelf life of the product.

6.6.4 Pellets Stored at 40 ± 2°C

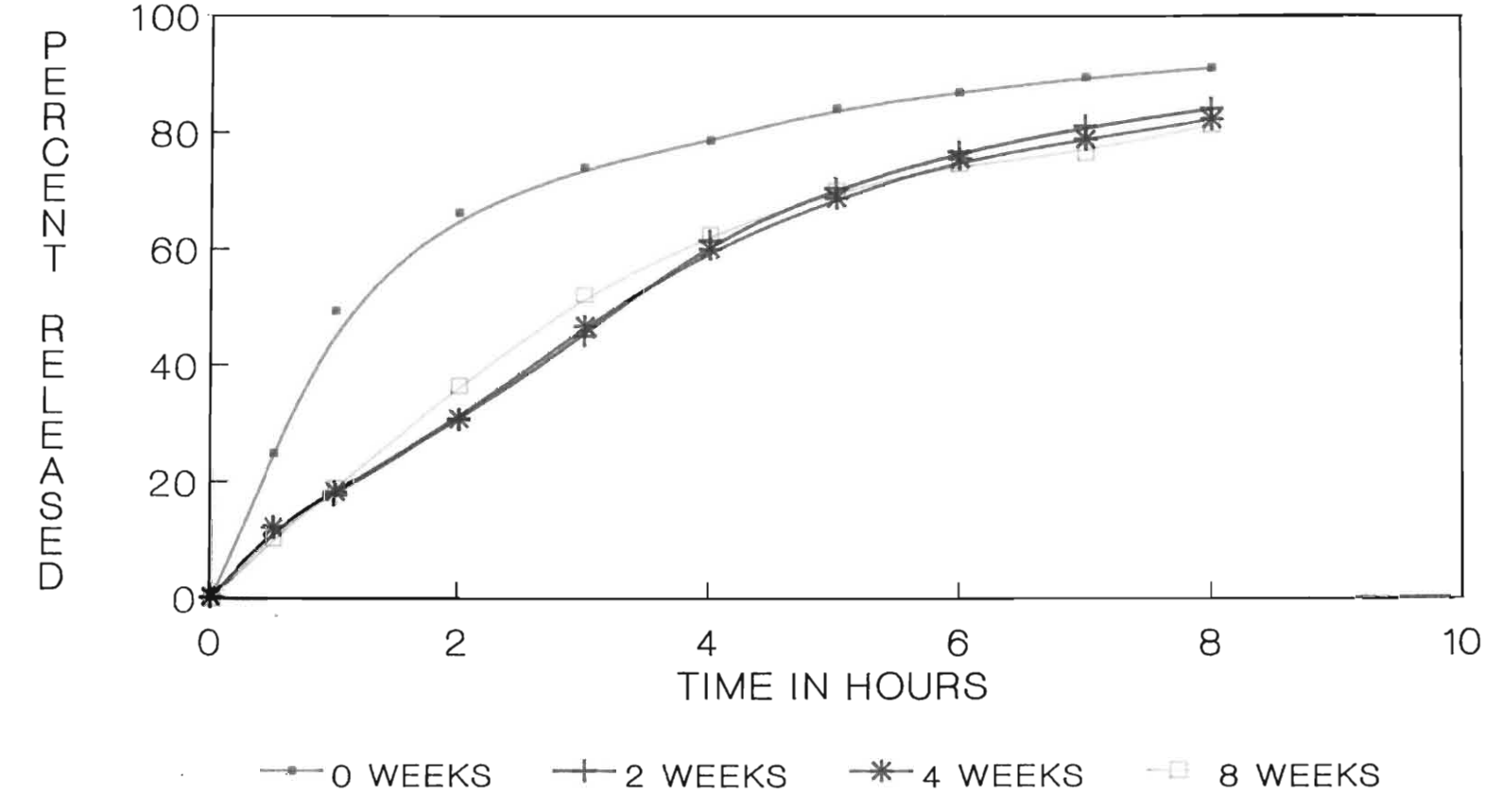
The drug release rates of pellets stored for the duration of the study are shown in Table 6.15 and Figure 6.16. Only the average percentage of drug released and standard deviations are presented in Table 6.15; actual values for the six individual samples are shown in Appendix 13.

TABLE 6.15 : STABILITY STUDY OF EUDRAGIT® NE 30 D COATED CHLORPHENIRAMINE MALEATE PELLETS STORED AT 40°C

SAMPLING TIME(HR.)	CUMULATIVE PERCENTAGE* RELEASED			
	INITIAL	2 WEEKS	4 WEEKS	8 WEEKS
0.5	24.71 ± 1.00	12.35 ± 1.43	12.08 ± 1.53	10.35 ± 2.05
1	49.11 ± 2.38	17.73 ± 0.61	18.16 ± 0.92	18.87 ± 0.82
2	66.10 ± 3.00	30.71 ± 1.00	30.69 ± 1.47	36.45 ± 1.13
3	73.93 ± 1.21	45.01 ± 1.51	46.53 ± 1.12	52.11 ± 0.90
4	78.59 ± 1.02	61.51 ± 1.12	59.94 ± 0.75	62.55 ± 0.79
5	84.03 ± 0.92	70.59 ± 1.16	68.75 ± 0.44	70.18 ± 1.64
6	86.76 ± 1.06	76.79 ± 0.81	75.45 ± 0.65	74.78 ± 0.84
7	89.28 ± 1.78	81.12 ± 1.20	78.76 ± 0.43	76.64 ± 0.81
8	90.87 ± 1.65	84.07 ± 0.88	82.14 ± 1.36	81.36 ± 0.43

* Each data point represents the mean and standard deviation of six samples.

FIGURE 6.16 : STABILITY STUDIES ON PELLETS OF BATCH Q1 STORED AT 40 DEGREES CELSIUS



PADDLE METHOD, WATER, 50RPM

On removal for massing after being stored at 40°C for 2 weeks, the pellets were agglomerated to each other. Figure 6.16 shows a release profile where there was less drug being released compared to the original study. There was an almost constant release during the first 4 hours (± 15% per hour) with the release rate of chlorpheniramine then decreasing. After 2 weeks, there appeared to be a further decrease in the release rate of the drug, with the profiles being virtually superimposable.

It is well documented that Eudragit^{R} NE 30 D coated pellets should not be stored at temperatures above 40°C. Storage of these pellets at 40°C could result in fusion of the membranes of individual adjacent pellets, resulting in a coherent film. On the emptying of the pellets from the hard gelatine capsules, the pellets remained stuck together.

In order for the newly formulated pellets to maintain their controlled release chacteristics, it is necessary to store these pellets at temperatures below 40°C. Alternatively, they should be overcoated with a membrane to reduce their tackiness and to prevent the pellets from clumping together.

6.7 SCANNING ELECTRON MICROSCOPY

6.7.1 Whole Pellets (uncoated)

Scanning electron microscopy of non-pareils (0.85-1.00mm diameter) prior to any coating revealed a porous surface as shown in Figure 6.17.

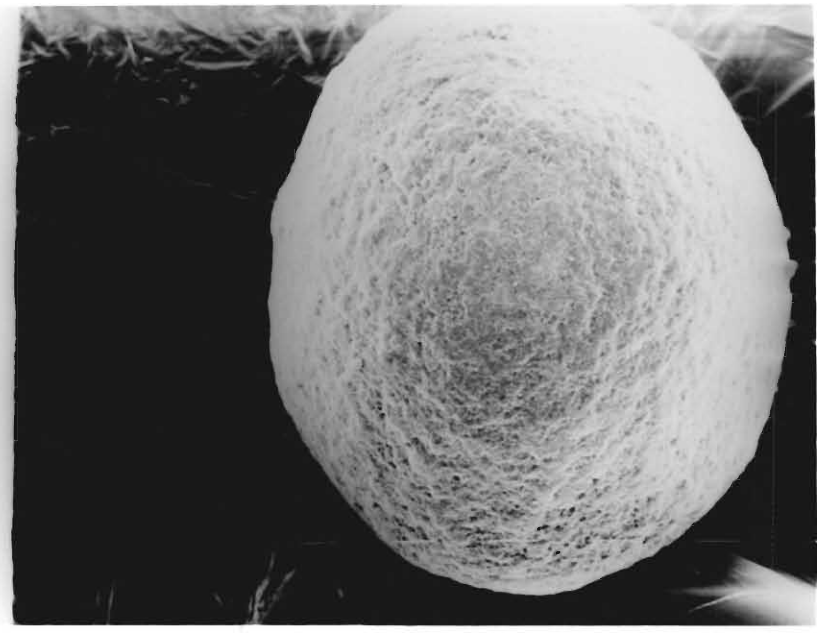


FIGURE 6.17 : SURFACE MORPHOLOGY OF A PELLET (80X MAGNIFICATION)

The surface morphologies appeared to be similar and the pellets were acceptably symmetrical. The mean diameter of pellets, measured directly, was found to be 0.93 ± 0.08mm in diameter. The core material in the pellets had identical and relatively dense structures. These results were similar to those observed by Ghebre-Sellasie *et al.*, (1985). The non-pareils also have a spherical structure that will facilitate encapsulation (in hard gelatin capsules).

6.7.2 Chlorpheniramine Maleate Coated Pellets

Pellets coated with the drug showed no drug crystals on the surface, indicating complete dissolution and intimate mixing of the drug with the binder solution (Figure 6.18 - 80 X magnification).

The external layer of the pellets which is composed of the drug and binder was loosely packed and had fewer pores when compared to Figure 6.17., particularly at the core/drug binder interface. The mean diameter of pellets coated with drug was found to be about 0.95 ±0.1mm in diameter.

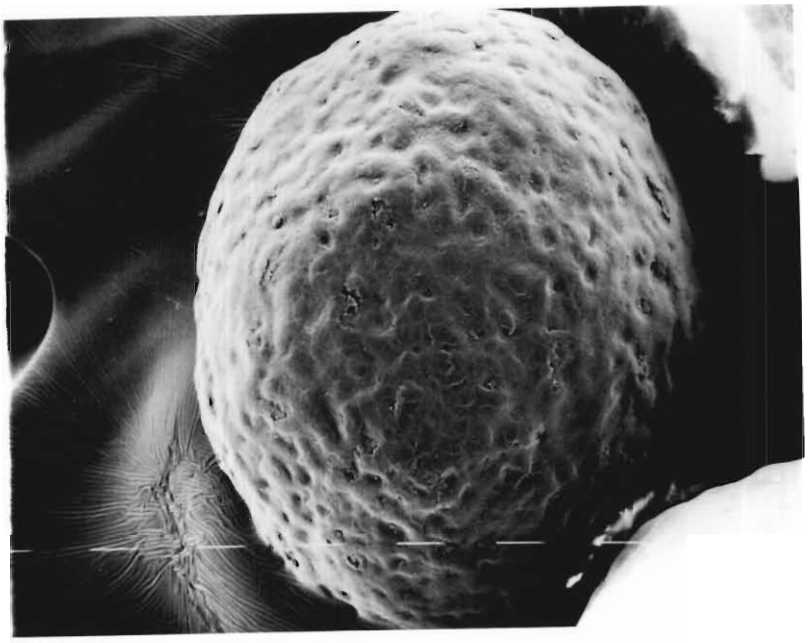


FIGURE 6.18 : CHLORPHENIRAMINE MALEATE COATED PELLETS (80X MAGNIFICATION)

6.7.3 Scanning Electron Microscopy on Final Product Batch Q1

The finally coated pellets of Batch Q1 were examined at different magnifications by scanning electron microscopy prior to stability studies being carried out. The average diameter of the pellets as measured by scanning electron microscope was found to be 1.00 $\pm$ 0.1mm. The bottom spray technique used, appeared to provide a smooth, continuous film of polymer as shown in Figure 6.19 (80 X magnification).

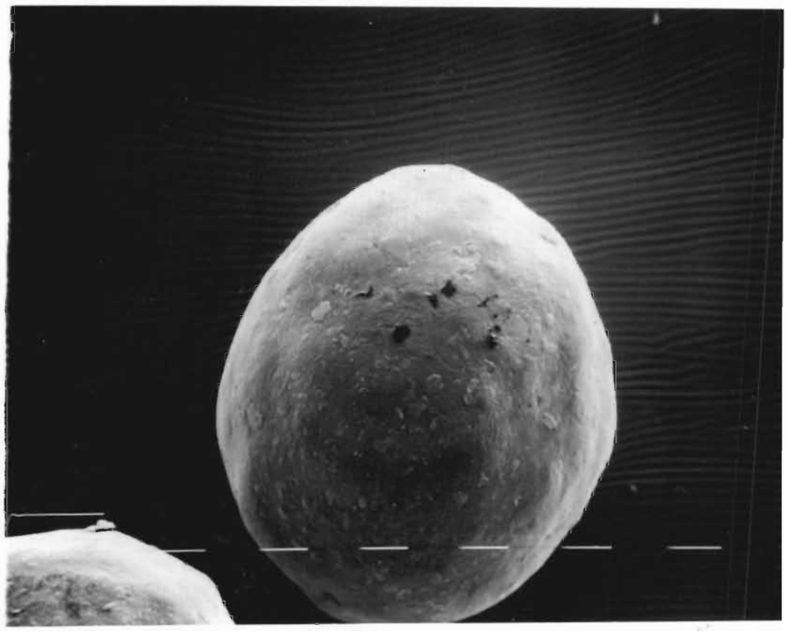


FIGURE 6.19 : COATED PELLETS OF BATCH Q1 (80X MAGNIFICATION)

The design of the Wurster process causes the pellets to be close to the spray nozzle, an arrangement that allows the droplets onto the substrate before much evaporation of solvent occurs, and the subsequent evaporation of solvent from the surface of the pellets is complete before the solvent can penetrate the pellets cores. Suspending the pellets in air keeps them discrete from one another and allows films to be applied to pellet surfaces with little or no agglomeration.

During the coating process in the fluidised bed equipment, each pellet is sprayed with only a small portion of the coating formulation randomly each time it transverses the spray path. The intermittent layering of the droplets on the surface eventually generates a film coat characterised by tortuous paths as shown in Figure 6.20 (1250X magnification). This observation is consistent with previous reports in which scanning electron microscope pictures of spray coated pellets were shown having a heterogeneous structure (Porter, 1982).

FIGURE 6.20 : SURFACE OF A COATED PELLET OF BATCH Q1 (1250X MAGNIFICATION)

The dissolution profiles of pellets stored at elevated temperatures (37°C with 80% relative humidity and 40°C) showed drug release at a slower rate compared to those stored at both room temperature and low temperature. Scanning electron microscopy was used as a means of explaining this phenomenon. The surfaces of pellets at 40°C and 37°C with 80% relative humidity, exhibited films that seemed to have further coalesced (6.6.3) (Figure 6.21-1250x magnification). These results are in agreement with those found by Chowhan *et al.*, (1982) regarding decrease in drug release rates after storage at elevated temperatures with 76% relative humidity conditions.

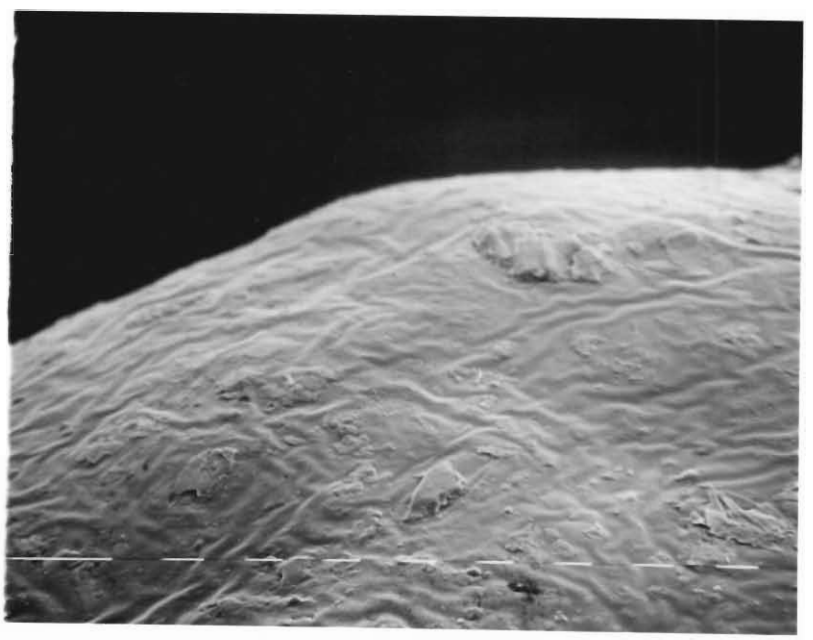


FIGURE 6.21 : 'FURTHER GRADUAL COALESCENCE' EXHIBITED BY PELLETS STORED AT ELEVATED TEMPERATURES (1250X MAGNIFICATION)

6.7.4 : Cross Sections of Pellets

Figure 6.22 shows the cross section of pellets of Batch Q1. At a magnification of 320X, the polymer membrane (A) was observed to be distinct from the core it enveloped (B). At a higher magnification (Figure 6.23-1250X magnification) it was noticed that this layering demonstrates very little (if any) solvent had penetrated the core (C).

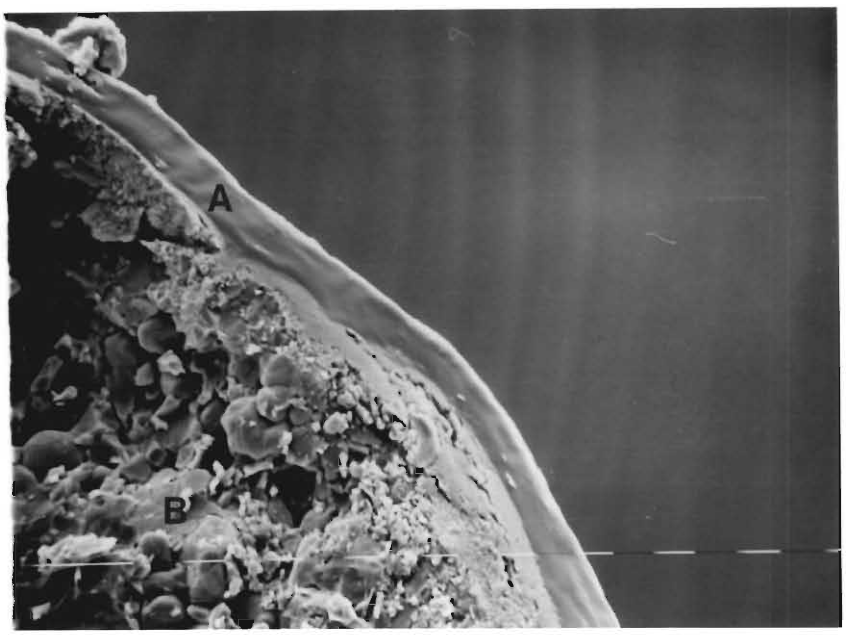


FIGURE 6.22 : CROSS SECTION OF A PELLET OF BATCH Q1 (320X MAGNIFICATION)

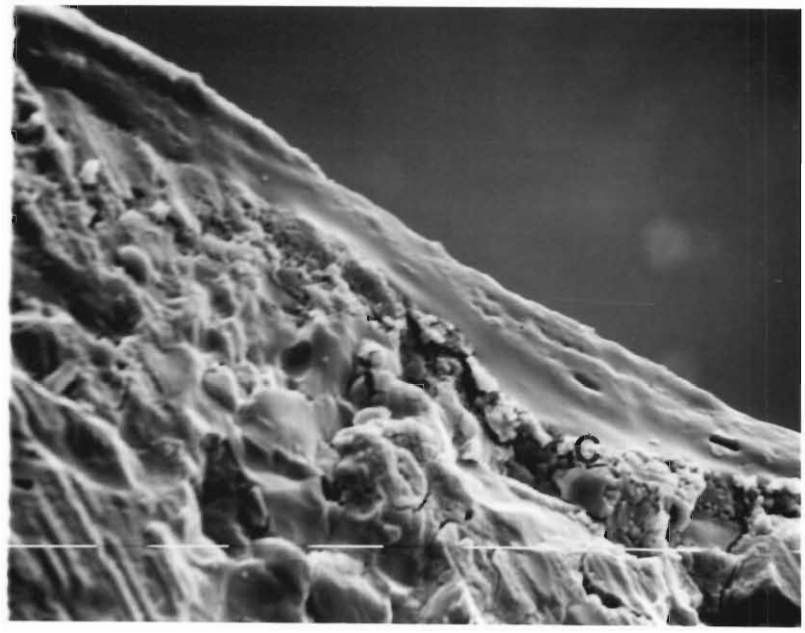


FIGURE 6.23 : CROSS SECTION OF A PELLET OF BATCH Q1 (1250X MAGNIFICATION)

Cross sections of pellets from Batch X (18% coating) and Batch K (5% coating) revealed a thicker level of coating for the former as compared to Batch K (Figures 6.24 and 6.25 respectively). There were distinct layers (A) at both levels of coating. This is in agreement with their dissolution profiles where the rate of drug release was much slower from Batch X than Batch K.

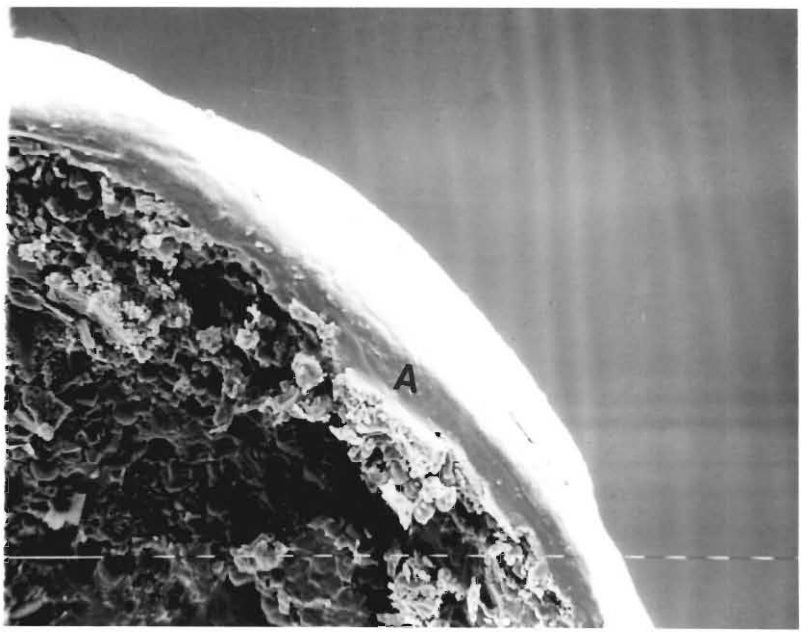


FIGURE 6.24 : CROSS SECTION OF PELLET OF BATCH X (18% COATING - 80X MAGNIFICATION

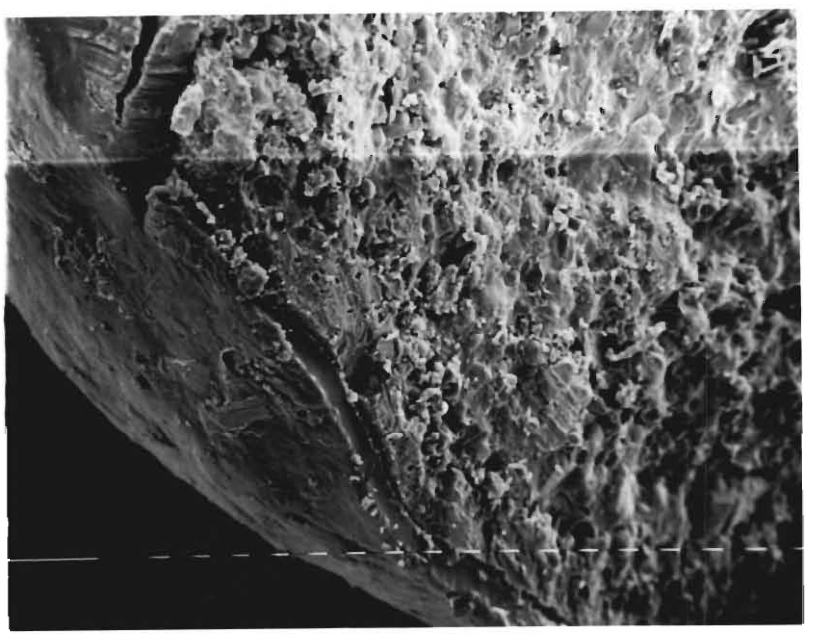


FIGURE 6.25 : CROSS SECTION OF PELLET OF BATCH K (5% COATING - 80X MAGNIFICATION

6.7.5 Polymer Coat during Dissolution

The surface morphology of pellets of Batch Q1 was examined initially (6.7.2) at 0.5 hours, 1 hour and after the dissolution test was completed (i.e. 8 hours).

The structure of pellets withdrawn after 0.5 and 1 hours were spherical, with many more pores observed on the surface of the latter (1 hour) than on the former. (Figures 6.26 and 6.27).

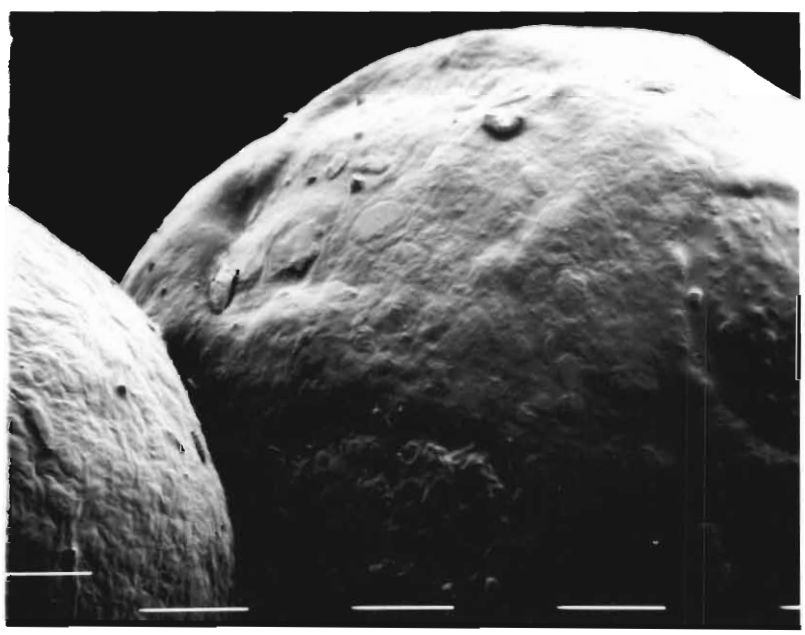


FIGURE 6.26 : SURFACE OF PELLETS 0.5 HOURS AFTER DISSOLUTION (320X MAGNIFICATION)

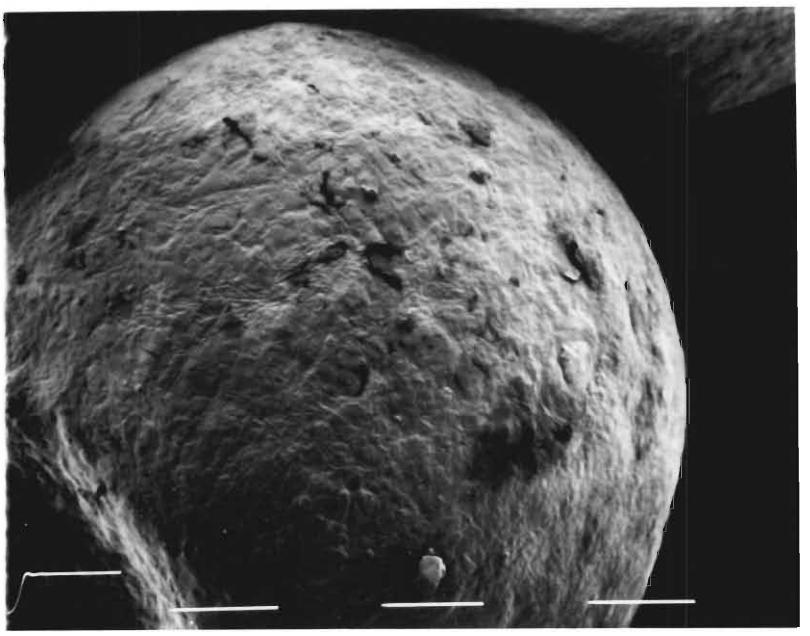


FIGURE 6.27 : SURFACE OF PELLET 1 HOUR AFTER DISSOLUTION (320X MAGNIFICATION)

The spherical shape of the pellets recovered from the dissolution system was found to be unchanged (intact) and without disintegration, but numerous macro pores and voids were observed in the polymer film as illustrated in Figure 6.28. These findings are consistent with those obtained by Kawashima *et al.*, (1989).

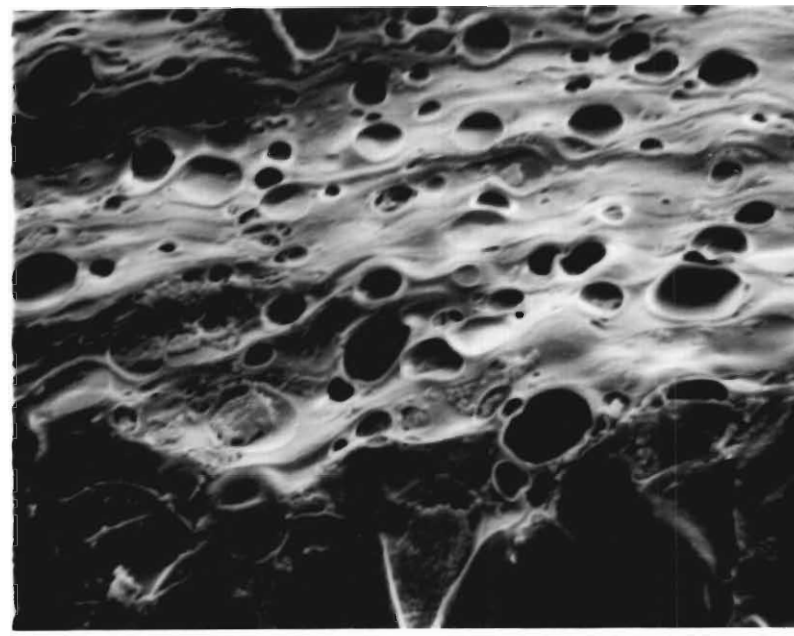


FIGURE 6.28 : SURFACE OF PELLETS 8 HOURS AFTER DISSOLUTION (320X MAGNIFICATION)

6.8 DETERMINATION OF THE ORDER OF RELEASE

For the purposes of describing the kinetics of the release process of drugs formulated in controlled release preparations, various techniques are normally used. For example, the zero order rate equation which describes the systems where the release rate is independent of the concentration of the dissolving species. The first order equation (Schwartz *et al.*, 1968; Buckton *et al.*, 1988) describes the release from systems where the dissolution rate is dependent on the concentration of the dissolving species.

The order of a reaction may be determined by several approaches (Martin *et al.*, 1983) as shown in Appendix 14.

For this study we will use the graphical method. If a straight line results when concentration remaining [i.e. (a-x)] is plotted against time (t), the reaction is **zero order**. The reaction is **first order** if log (a - x) versus t yields a straight line , and is **second order** if 1 / (a - x) versus t gives a straight line.

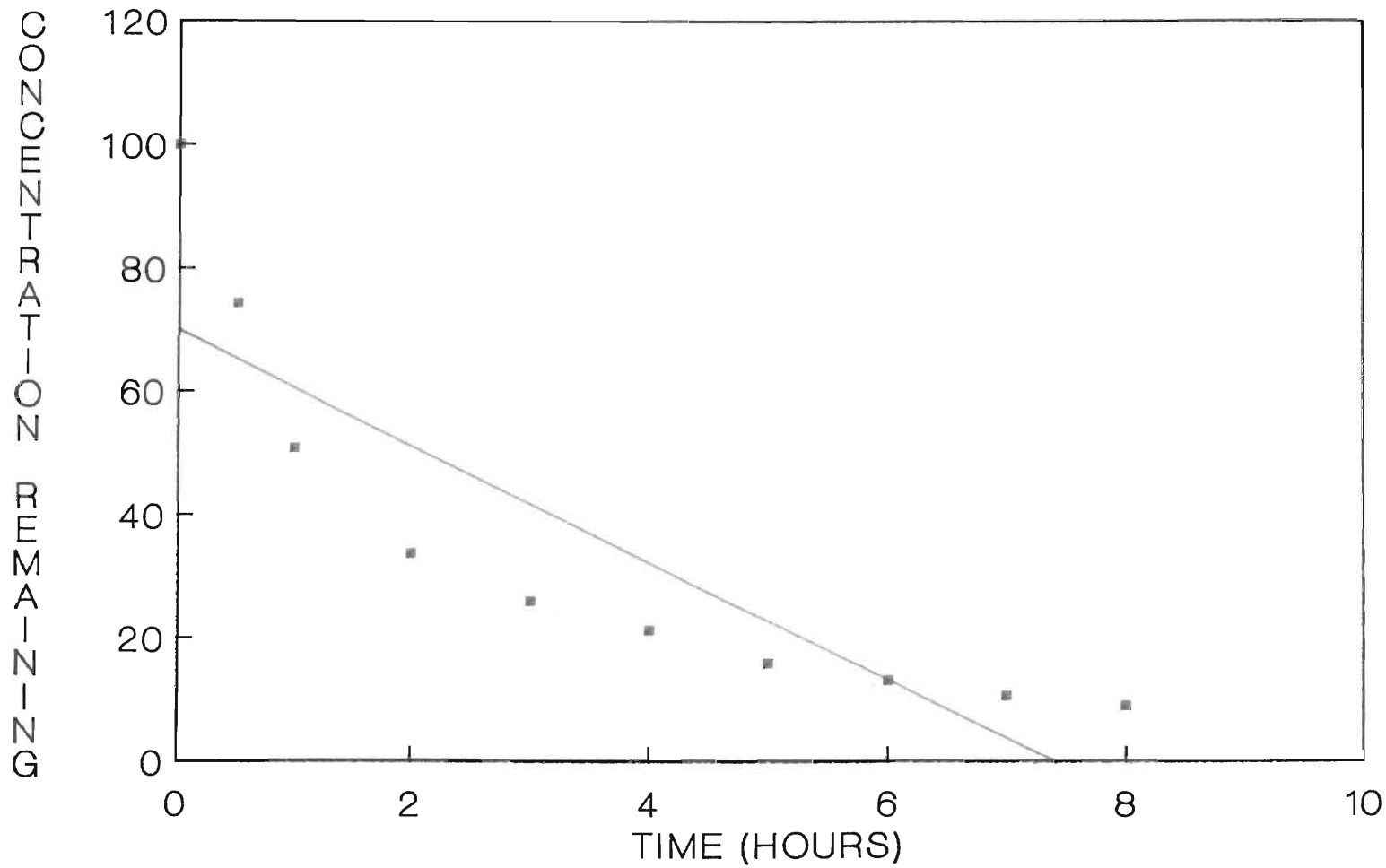
TABLE 6.16 : DETERMINATION OF THE ORDER OF DRUG RELEASE

TIME	a	a - x	Log (a -x)	1/(a - x)
0	0.00	100	2.00	0.0100
0.5	25.60	74.40	1.87	0.0134
1	49.12	50.88	1.70	0.0196
2	66.10	33.90	1.53	0.0294
3	73.92	26.08	1.41	0.0393
4	78.59	21.41	1.33	0.0467
5	84.03	15.97	1.20	0.0626
6	86.75	13.25	1.12	0.0754
7	89.28	10.72	1.03	0.0932
8	90.87	9.13	0.96	0.1095

Note : 100% = 40mg of chlorpheniramine maleate in 900ml dissolution medium.

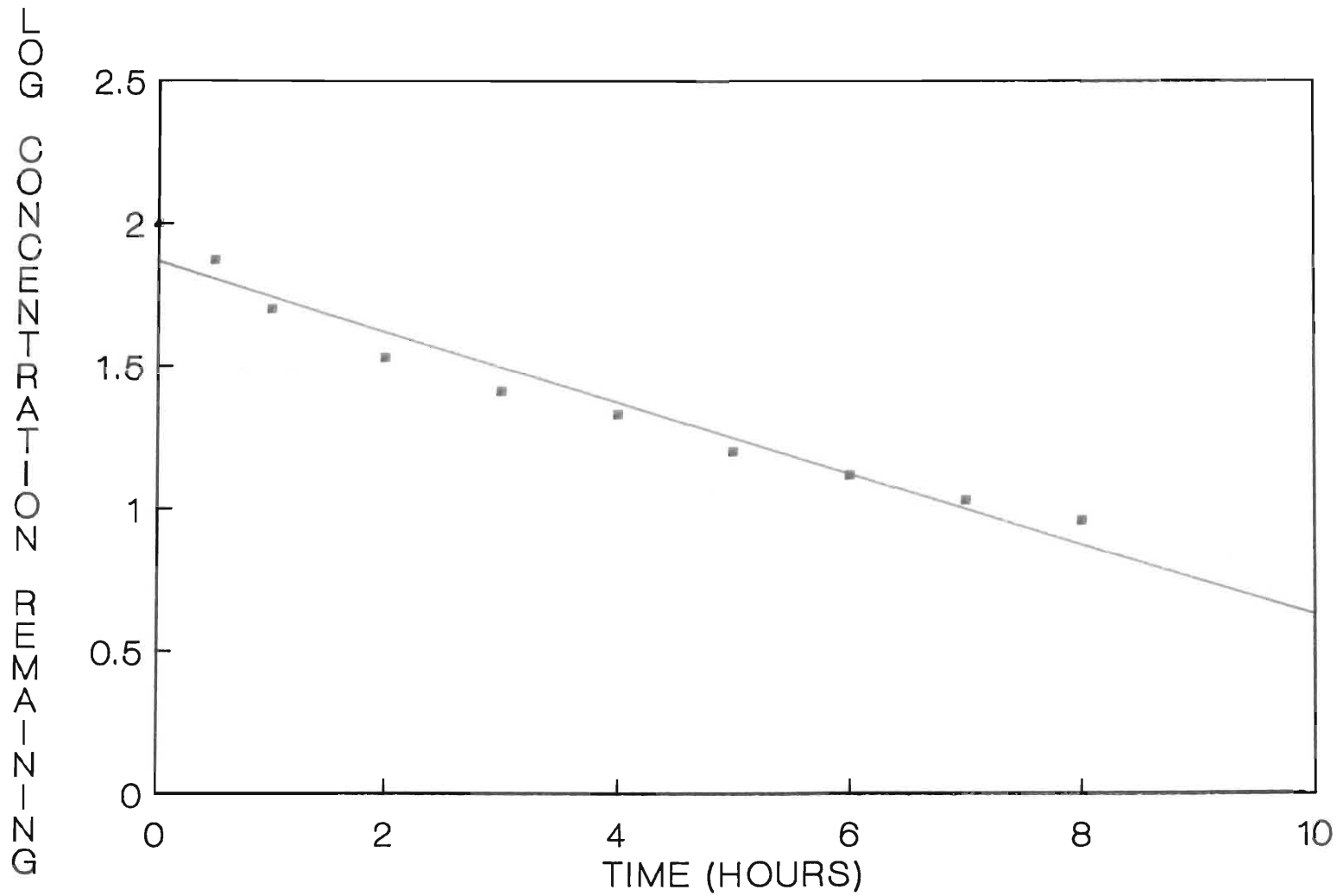
The analysis of the dissolution data was carried out by the application of the zero order (Figure 6.29), first order (6.30) and second order (6.31) equations.

FIGURE 6.29: DETERMINATION OF THE ORDER OF DRUG RELEASE : ZERO ORDER



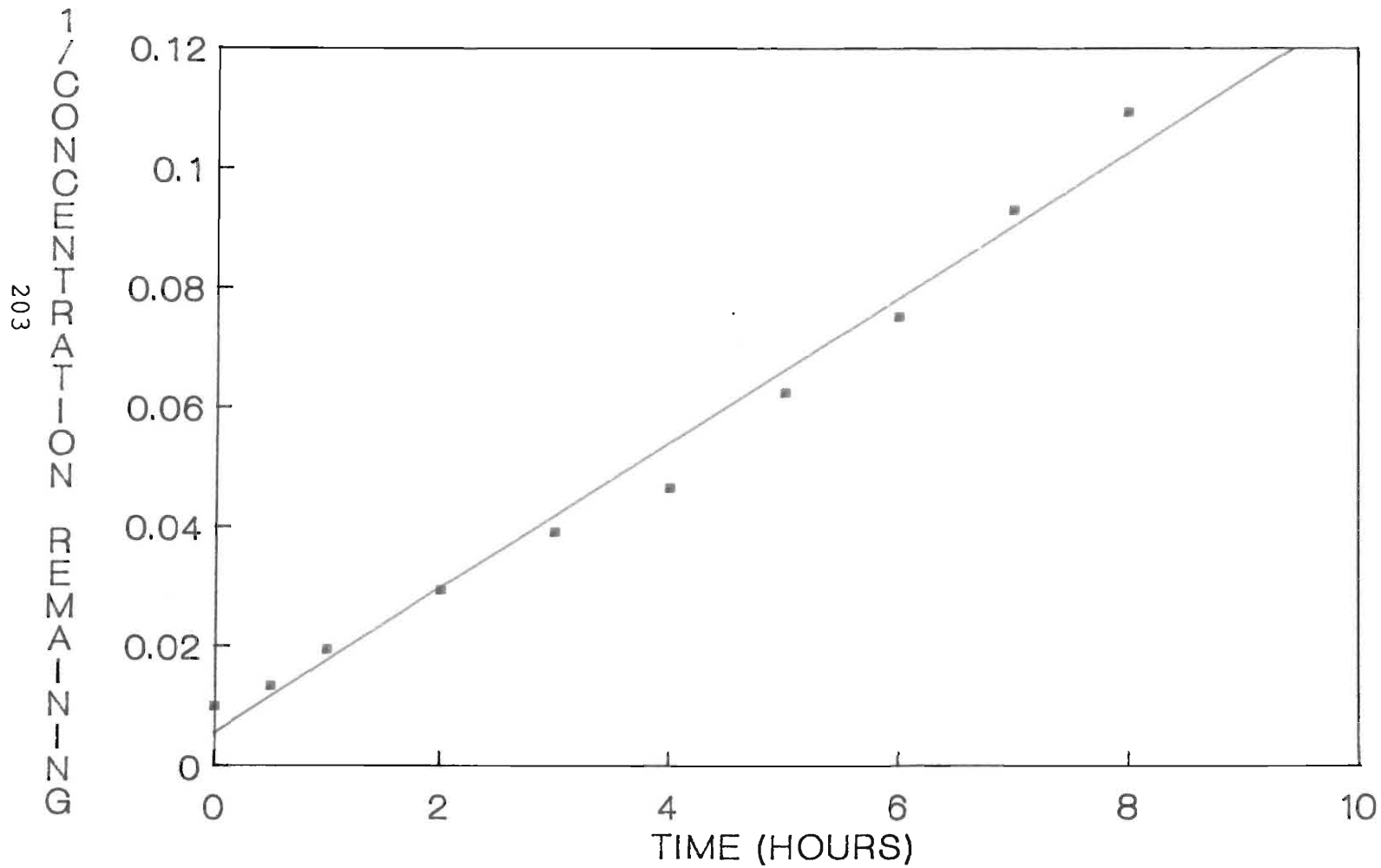
R SQUARE = -0.87

FIGURE 6.30: DETERMINATION OF THE ORDER OF DRUG RELEASE : FIRST ORDER



R SQUARE = 0.992

FIGURE 6.31: DETERMINATION OF THE ORDER OF DRUG RELEASE : SECOND ORDER



R SQUARE = -0.977

The dissolution data obtained in deionized water was plotted in a accordance with the zero order equation i.e. percent dissolved as a function of time (Figure 6.29). It was evident from Figure 6.29 that the plot was curvilinear suggesting the process was not zero order in nature. This indicated that the dissolution rate of the drug was dependent on the amount of drug available for dissolution and diffusion from the core.

The dissolution data were plotted in accordance with the first order equation i.e. the logarithm of the percent remaining as a function of time (Figure 6.30). It was evident from Figure 6.30 that a linear relationship was obtained showing that release was an apparent first order process. This indicates that the amount of drug released is dependent on the pellet drug load.

The inapplicability of the zero order equation to the dissolution data showed that the release process was indeed dependent on the matrix drug load. The applicability of the first order equations showed that the release process was diffusion and dissolution controlled.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

In vitro dissolution tests were used to evaluate the drug release characteristics of newly formulated controlled release pellets of the antihistamine, chlorpheniramine maleate in the present study. The design of this product involved the logical development of a formulation until a desirable product was achieved.

7.1 FORMULATION OF DRUG-COATED NON-PAREILS

Chlorpheniramine maleate as a 6.75% alcoholic solution was coated onto non-pareils (0.85 - 1.00mm diameter). Povidone was found to increase the adherence of drug to the non-pareils by about 75% and was therefore employed at a 0.25% concentration as a binder in all formulations.

7.2 METHACRYLATES AS COATING POLYMERS

Eudragit^{R} NE 30 D when used without any excipients, caused agglomeration of the pellets. In an attempt to overcome this, talc was incorporated into the membrane. However, talc was only effective when low concentrations of polymer

were employed (5% Eudragit^{R} NE 30 D). At higher levels of coating (6.6% Eudragit^{R} NE 30 D) the non-pareils were very tacky and the coating process was inefficient due to the long time taken to coat the polymer onto the non-pareils.

7.3 EFFECT OF POLYETHYLENE-GLYCOL 6000 ON DRUG RELEASE

The inclusion of polyethylene glycol 6000 (PEG 6000) was found to decrease the tackiness and reduce the time taken to coat the polymer onto non-pareils. A proportionate increase in the release rate of drug from the pellets was found with the use of PEG 6000. Several batches of pellets were then formulated with various amounts of Eudragit^{R} NE 30 D (2 - 20%) in combination with talc (0.5 - 2%) and PEG 6000 (0.25 - 2%). The drug release profiles of the batch coated with 8.3% Eudragit^{R} NE 30 D, 0.5% talc and 1% PEG 6000 (BATCH Q) was found to resemble that of Dykatuss^{R} Capsules (controlled release 8mg chlorpheniramine maleate pellets in a hard gelatin capsule) which was used as the reference standard. The formulation was subsequently subjected to various tests in order to evaluate the suitability of the chosen formulation. The formulation was shown to exhibit predictable and reproducible drug release characteristics.

7.4 EFFECT OF DISSOLUTION TECHNIQUE OR DISSOLUTION MEDIUM ON RELEASE PROFILES

Dissolution studies using other dissolution methods (rotating bottle, rotating basket) showed no appreciable difference in drug release profiles.

Dissolution studies in different media also showed that the release rates of pellets were independent of the pH of the dissolution medium. The pH independence of the film coat ensures the development of modified release products that are not affected by the variable pH that prevails in the gastrointestinal tract.

7.5 STABILITY PROFILES

The drug release characteristics were unchanged when stored for three months at room temperature and two months at low temperature. However, the pellets (Batch Q1) stored at 37°C with 80% relative humidity and at 40°C were shown, using scanning electron microscopy to undergo 'further gradual coalescence' with consequently slower drug release rates.

7.6 SCANNING ELECTRON MICROSCOPY (SEM)

The SEM studies showed the smooth continuous film in both the newly prepared pellets as well as of the pellets stored for three months at room temperature and two months at low temperature. The occurrence of 'further gradual coalescence' on the surface of pellets stored at 37°C with 80% relative humidity and 40°C was also observed. The cross sections of pellets showed the distinct layer of coating applied to these pellets. The presence of pores on the polymer membrane after dissolution was measured to have an average diameter of 10um. Hence scanning electron microscopy appears to be a very effective tool for evaluating film coatings that have been applied to non-pareils. Examination of pellets under the scanning electron microscope can provide researchers involved in formulation, processing and quality control with an efficient tool for product development.

7.7 CHARACTERISTICS OF DRUG RELEASE

Drug release was shown to occur by a first order process and is primarily controlled by diffusion.

Thus a stable controlled release chlorpheniramine maleate formulation can be prepared by coating drug-loaded nonpareils with an appropriate amount of Eudragit^{R} NE 30 D, and appropriate types and amounts of pharmaceutical additives via a Wurster process.

Although chlorpheniramine maleate controlled release pellets have been successfully formulated and prepared, the following **recommendations** may be considered for future studies:

1. Solvent-based acrylic polymers have been used in the pharmaceutical industry for coating purposes for over 30 years. Recently, however, the toxicity and environmental concerns associated with the use of organic solvents coupled with the long term projected rise of the cost of solvents have forced the pharmaceutical industry to explore alternative procedures. Aqueous film coating is rapidly becoming the method of choice and this in turn has led to the development of much more efficient coating units and low viscosity water soluble and water dispersible polymers. Thus I would recommend that all similar future studies utilise aqueous coating rather than organic solvent.

2. *In vitro* dissolution studies have proved to be important tools for formulation, development and monitoring of the quality of solid preparations. The use of *in vitro* dissolution data for prediction of clinical effects requires a correlation between the *in vitro* dissolution tests and the *in vivo* clinical response parameter. Thus an *in vitro-in vivo* correlation for controlled release chlorpheniramine maleate pellets could be considered/ developed.

3. Agglomeration of pellets to form soft lumps upon storage at or above room temperature was observed for pellets coated with Eudragit^{R} formulations. Although the lumps are broken easily at lower temperatures and generally appear to have no effect on dissolution profiles, their formation can be totally prevented by the application of an overcoat that is composed of a water soluble, hydrophilic film former like HPMC (Li *et al.*, 1991; Rekhi *et al.*, 1989; Ghebre-Sellasie *et al.*, 1988). Thus, it is suggested all future studies employ an overcoat to overcome this inherent tackiness associated with Eudragit^{R} NE 30 D.

4. Excellent sustained release preparations can be manufactured by compressing coated pellets into matrix tablets e.g. Peltabs^{R}. The rate of release can be adjusted as required not only by varying the amount of lacquer permeability but also by varying the amount of lacquer and the choice of fillers. Thus the compressing of pellets into a Peltab^{R} is a future avenue for research.

5. The numerous possibilities for the further processing of such pellets into drug tablets, matrix structures etc., plus the possibility of their combination with other drugs or ancillary substances, open new ways to produce formulations for a given drug of optimal convenience, design and therapeutic effect.

6.Due to the low glass transitional temperature(T_g) Eudragit^{R} NE 30 D has been used for the purpose of lowering the T_g of other polymers. Thus there exists the possibility of combination with other methacrylate polymers such as Eudragit^{R} RS 30 D to enable the researcher to coat the polymer at lower temperatures (i.e. 35°C rather than > 60°C).

7. The monitoring of the water content at high relative humidity conditions could shed some light on the decrease in release rates of drug under these conditions. Therefore, I would recommend that for all future studies using similar conditions, that the water content of the pellets be closely monitored.

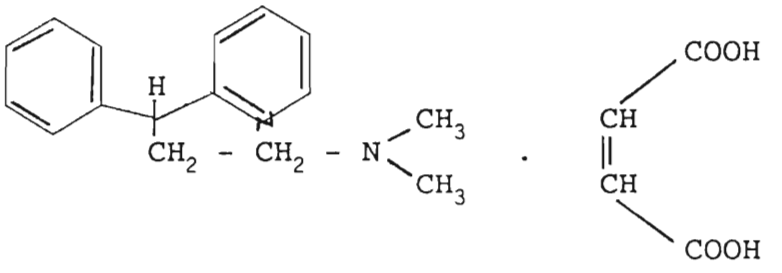
Technology in the field of controlled drug delivery is moving forward at a rapidly accelerating pace, leading to new products and helping to overcome most of the limitations which at present accompany some of the controlled drug delivery systems. Future developments and especially clinical acceptance of new drug delivery systems will move forward step by step and will strongly need the close multidisciplinary collaboration of biomedical engineering, pharmacological, pharmaceutical and clinical scientists.

Nowadays, instead of the traditional search for new pharmacologically active agents, the strategy of many pharmaceutical companies and research institutes is focusing on the development of new drug formulations which achieve optimal therapeutic effect not solely on the basis of the drug itself, but also on the basis of the principles of release and absorption.

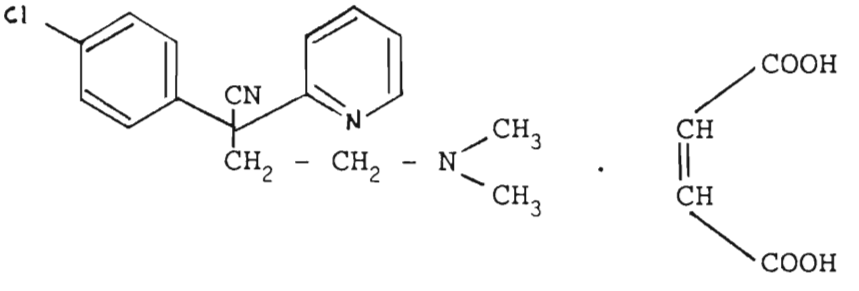
APPENDIX 1

POTENTIAL IMPURITIES

a) Pheniramine maleate, 0.25% maximum.



b) 2-(4-Chlorophenyl)-2-(2-pyridyl-4-dimethylamino-butyronitrile maleate salt, 0.05% maximum



C) 1-(2-Chlorophenyl)-1-(2-pyridyl)-3-dimethylamino-propane maleate salt, 0.4% maximum

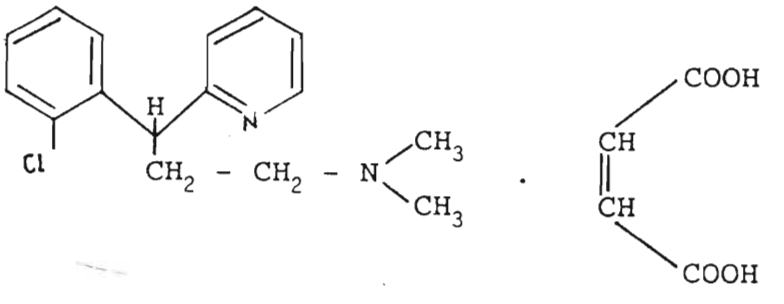
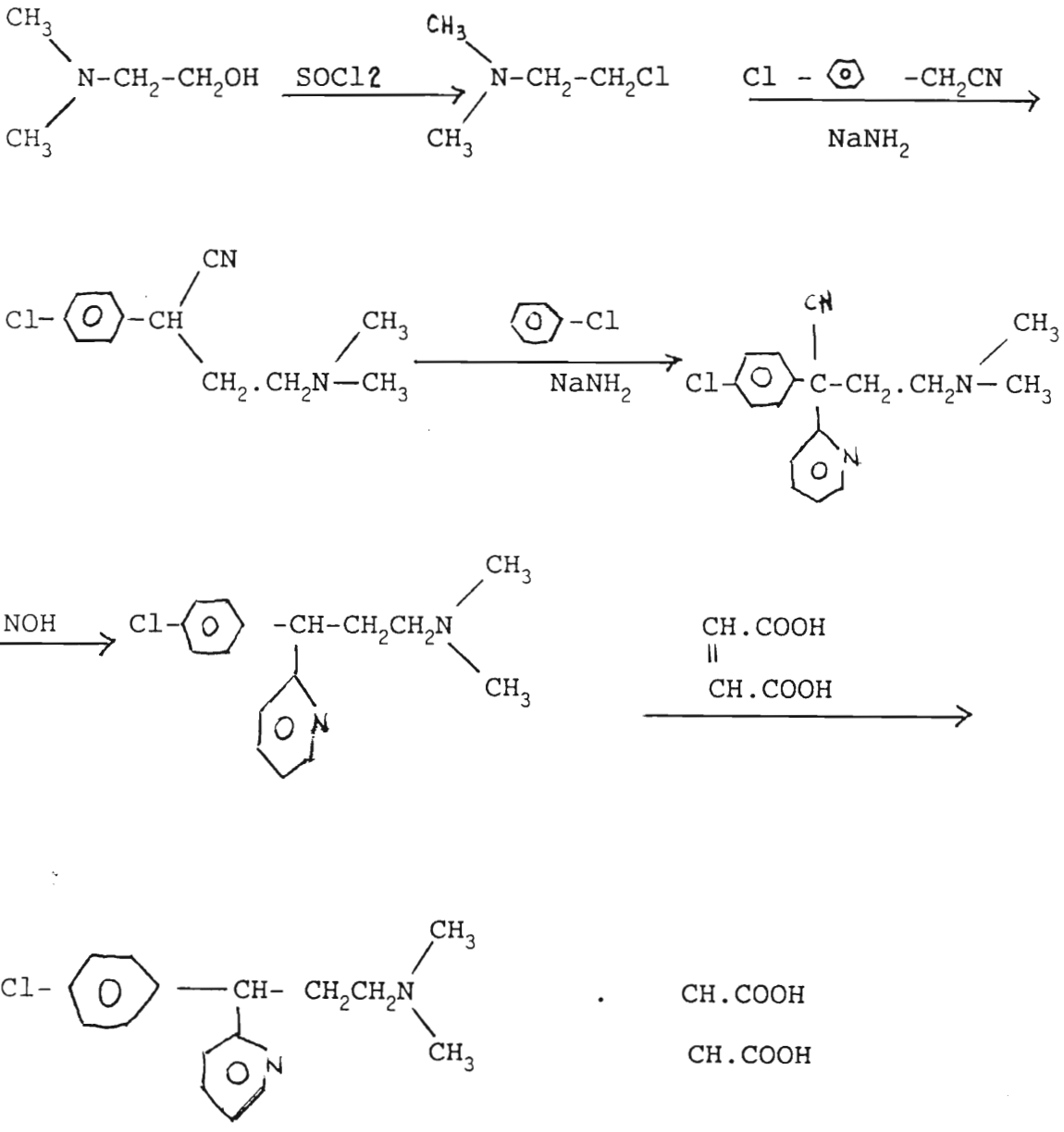
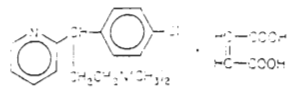


DIAGRAM OF THE SYNTHESIS OF CHLORPHENIRAMINE MALEATE:



CHLORPHENIRAMINE MALEATE

Chlorpheniramine Maleate



$C_{16}H_{19}ClN_2 . C_4H_4O_4$ 390.87

2-Pyridinepropanamine, γ-(4-chlorophenyl)-*N*,*N*-dimethyl-, (*Z*)-2-butenedioate (1:1).

2-[*p*-Chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) [*113-92-8*].

» Chlorpheniramine Maleate contains not less than 98.0 percent and not more than 100.5 percent of $C_{16}H_{19}ClN_2 . C_4H_4O_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Chlorpheniramine Maleate Reference Standard*—Dry at 105° for 3 hours before using.

Identification—The infrared absorption spectrum of a potassium bromide dispersion of it exhibits maxima only at the same wavelengths as that of a similar preparation of USP Chlorpheniramine Maleate RS.

Melting range ⟨741⟩: between 130° and 135°.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

Related compounds—

Test preparation—Dissolve about 200 mg of Chlorpheniramine Maleate in 5 mL of methylene chloride, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 1.2-m × 4-mm glass column containing 3 percent phase G3 on support S1AB. The column temperature is maintained at about 190°, and the injection port and detector temperatures are both maintained at about 250°. The carrier gas is dry helium, flowing at a rate adjusted to obtain a retention time of 4 to 5 minutes for the main peak. Chromatograph the *Test preparation*, record the chromatogram, and determine the peak area as directed under *Procedure:* the tailing factor for the chlorpheniramine maleate peak is not more than 1.8.

Procedure—Inject a volume (about 1 μL) of the *Test preparation* into the chromatograph. Record the chromatogram for a total time of not less than twice the retention time of the chlorpheniramine peak, and measure the areas of the peaks. The total relative area of all extraneous peaks (except that of the solvent peak) does not exceed 2.0%.

Assay—Dissolve about 500 mg of Chlorpheniramine Maleate, accurately weighed, in 20 mL of glacial acetic acid. Add 2 drops of crystal violet TS, and titrate with 0.1 *N* perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* perchloric acid is equivalent to 19.54 mg of $C_{16}H_{19}ClN_2 . C_4H_4O_4$.

APPENDIX 3

Chlorpheniramine Maleate Tablets

» Chlorpheniramine Maleate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{16}H_{19}ClN_2 . C_4H_4O_4$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Chlorpheniramine Maleate Reference Standard*—Dry at 105° for 3 hours before using.

Identification—Disperse a portion of powdered Tablets, equivalent to about 25 mg of chlorpheniramine maleate, in about 20 mL of dilute hydrochloric acid (1 in 100). Dissolve about 25 mg of USP Chlorpheniramine Maleate RS in 20 mL of dilute hydrochloric acid (1 in 100). Treat each solution as follows: Render alkaline, to a pH of about 11, with sodium hydroxide solution (1 in 10). Extract with two 50-mL portions of solvent hexane, collect the extracts in a beaker, and evaporate to dryness. Prepare a mineral oil dispersion of the residue so obtained and determine the infrared absorption spectrum of the preparation in the region between 2 μm and 12 μm: the spectrum of the test preparation exhibits maxima only at the same wavelengths as that of the Standard preparation.

Dissolution ⟨711⟩—

Medium: water; 500 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_{16}H_{19}ClN_2 . C_4H_4O_4$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 262 nm in filtered portions of the solution under test, suitably diluted with 3 *N* hydrochloric acid, in comparison with a Standard solution having a known concentration of USP Chlorpheniramine Maleate RS in the same medium.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{16}H_{19}ClN_2 . C_4H_4O_4$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—Using a portion of powdered Chlorpheniramine Maleate Tablets equivalent to 4 mg of chlorpheniramine maleate, proceed as directed under *Salts of Organic Nitrogenous Bases* ⟨501⟩, but using dilute hydrochloric acid (1 in 100) instead of the dilute sulfuric acid (1 in 350), and dilute sulfuric acid (1 in 70), and using solvent hexane instead of the ether, and diluting 10 mL of the *Assay preparation* with dilute hydrochloric acid (1 in 100) to 25.0 mL to prepare the solution employed for the determination of the absorbance, A_U, at 264 nm. For the determination of A_S, prepare a solution containing about 40 mg of USP Chlorpheniramine Maleate RS, accurately weighed, in 200.0 mL of dilute hydrochloric acid (1 in 100), and treat 20.0 mL of this solution the same as the solution in dilute hydrochloric acid (1 in 100) of the portion of Tablets taken. Calculate the quantity, in mg, of $C_{16}H_{19}ClN_2 . C_4H_4O_4$ in the portion of Tablets taken by the formula:

$$C(A_U/A_S),$$

in which *C* is the weight, in mg, of USP Chlorpheniramine Maleate RS in the 20.0-mL portion of the *Standard preparation.*

APPENDIX 4

Chlorpheniramine Maleate Extended-release Capsules

» Chlorpheniramine Maleate Extended-release Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Chlorpheniramine Maleate Reference Standard*—Dry at 105° for 3 hours before using.

Identification—The retention time of the chlorpheniramine peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation*, as obtained in the *Assay*.

Uniformity of dosage units ⟨905⟩—meet the requirements.

Change to read:

Identification—

■A:■ The retention time of the chlorpheniramine peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation*, as obtained in the *Assay*.

■B: Transfer the contents of 1 Capsule to a 10-mL volumetric flask, add 5 mL of methanol, and insert the stopper into the flask. Sonicate this solution for 10 minutes, dilute with water to volume, mix, and filter. Apply separately 10 µL of this solution and 10 µL of a solution of USP Chlorpheniramine Maleate RS in a mixture of methanol and water (1:1) containing about 1.2 mg per mL to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩), coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of ethyl acetate, methanol, and ammonium hydroxide (100:5:5) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, allow the solvent to evaporate, and examine the plate under short-wavelength ultraviolet light: the R_f value of the principal spot observed in the chromatogram of the solution under test corresponds to that obtained from the Standard solution.■

Change to read:

Assay—

Mobile phase—Dissolve 2.0 g of sodium perchlorate in 350 mL of water. Add 650 mL of methanol and 2.0 mL of triethylamine, and mix. Filter, and degas this solution prior to use. Make adjustments if necessary (see *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Chlorpheniramine Maleate RS in ■dilute hydrochloric acid (1 in 100)■ to obtain a solution having a known concentration of about 0.12 mg per mL.

Assay preparation—Weigh and mix the contents of not less than 20 Chlorpheniramine Maleate Extended-release Capsules. Transfer an accurately weighed portion of the mixture, equivalent to about 120 mg of chlorpheniramine maleate, to a 200-mL volumetric flask. Add about 100 mL of ■dilute hydrochloric acid (1 in 100)■ bring to a boil on a hot plate, and continue boiling moderately for 5 minutes. Cool, dilute with ■dilute hydrochloric acid (1 in 100)■ to volume, mix, and filter. Transfer 10.0 mL of the filtrate to a 50-mL volumetric flask, dilute with ■dilute hydrochloric acid (1 in 100)■ to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 261-nm detector and a 3.9-mm × 15-cm column that contains 10-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the column efficiency is not less than 900 theoretical plates, the tailing factor is not greater than 2.0, and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ in the portion of Capsules taken by the formula:

$$(1000C)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Chlorpheniramine Maleate RS in the *Standard preparation*, and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

APPENDIX 5

⟨711⟩ DISSOLUTION

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form, except where the label states that the tablets are to be chewed. Requirements for *Dissolution* do not apply to soft gelatin capsules unless specified in the individual monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. Of the types of apparatus described herein, use the one specified in the individual monograph.

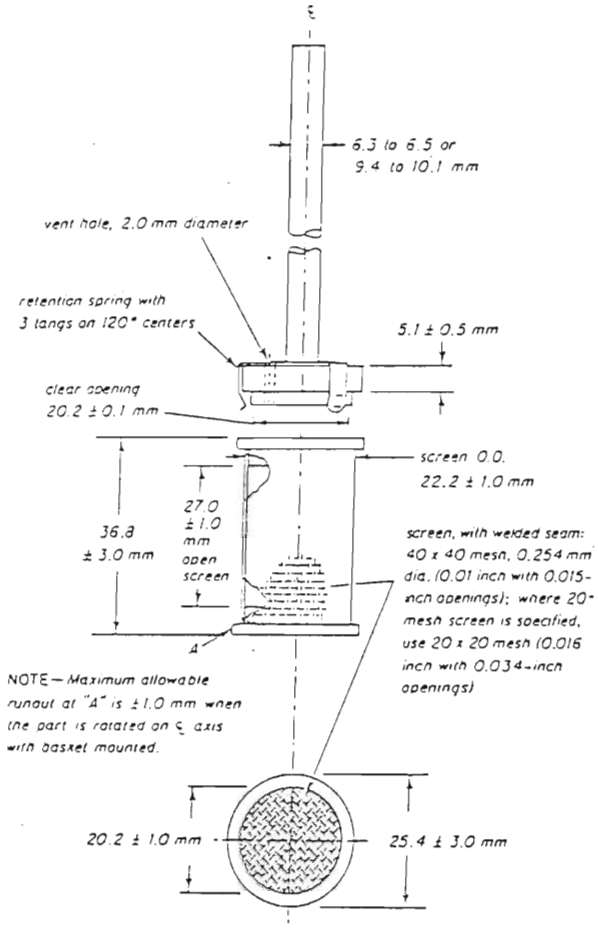
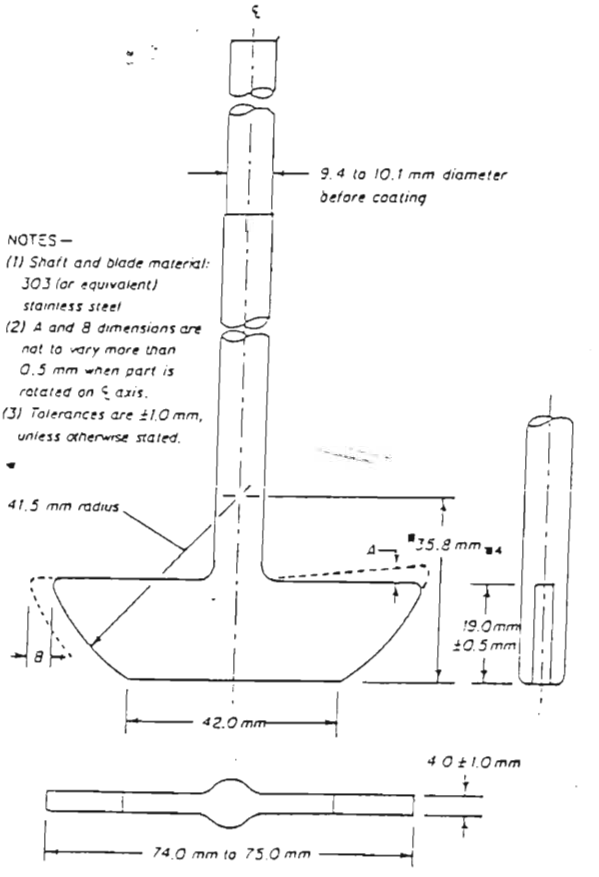


Fig. 1. Basket Stirring Element.

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 mm to 175 mm high, its inside diameter is 98 mm to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 μm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.



Apparatus 2—Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel, and rotates smoothly without significant wobble. The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float.

APPENDIX 5A

PREPARATION OF HYDROCHLORIC ACID (pH = 1.5) (USP XXII, 1990)

Potassium chloride solution (2.5 litres x 0.2M) was placed in a 10 litres flask. Hydrochloric acid (1.55 liters x 0.2M was added. Deionised water was added to volume. The pH of the buffer was 1.5 $\pm$ 0.05.

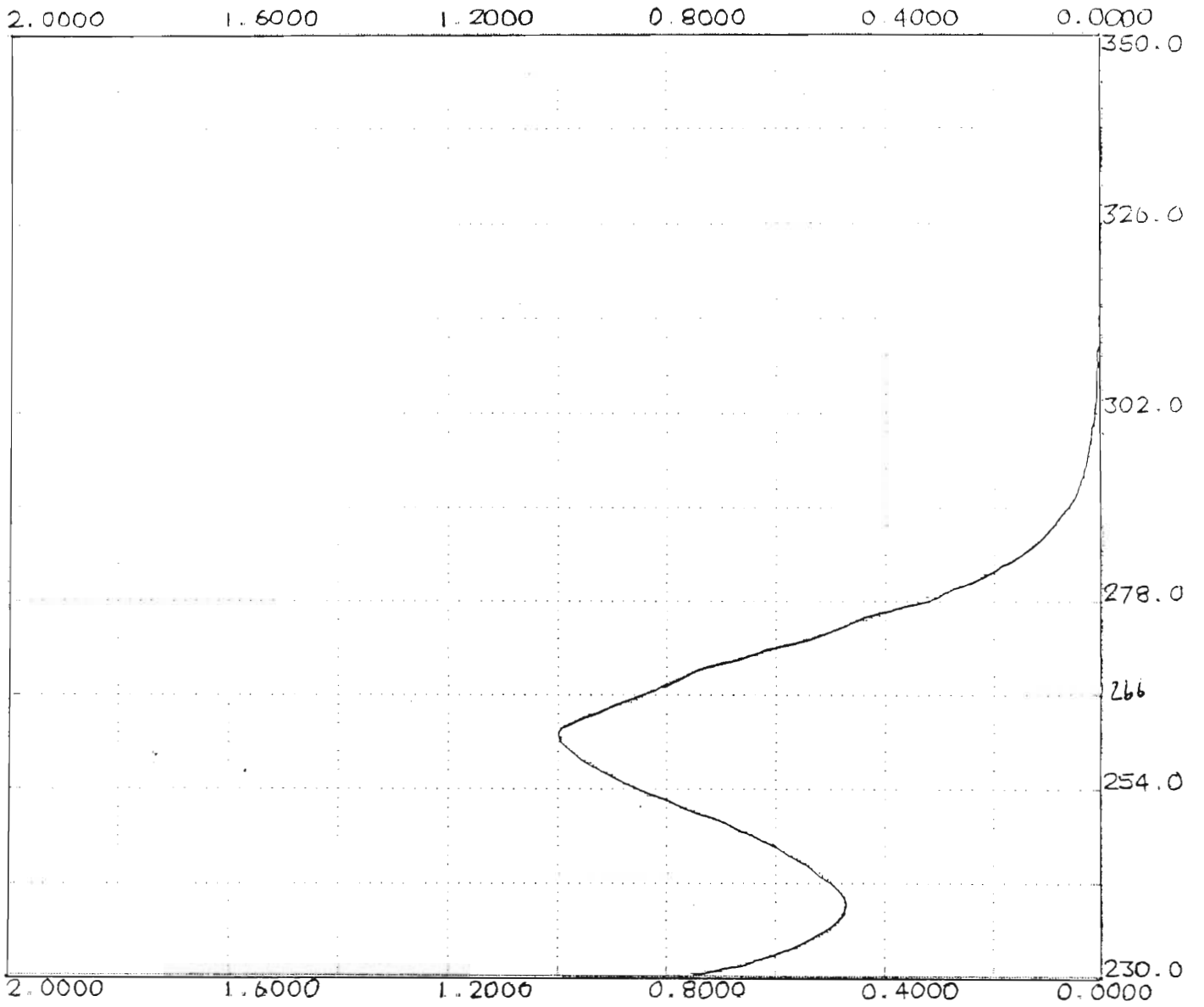
PREPARATION OF PHOSPHATE BUFFER (pH = 6.8) (USP XXII, 1990)

Monobasic potassium phosphate solution (2.5 litres x 0.2M) was placed ina 10 litre flask. Sodium hydroxide (840ml x 0.2M was added. Deionised water was added to volume. The pH of the solution was 6.8 $\pm$ 0.05.

PREPARATION OF NEUTRALISED PHOSPHATE BUFFER (pH = 4.5) (BP 1988)

136.1g of potassium dihydrogen orthophosphate was dissolved in 7.5 litres of water, and adjusted to pH 4.5 with 0.1M hydrochloric acid and then diluted to 10 litres with water.

APPENDIX 6



Scan Speed: 500 mm/min

APPENDIX 7

Cumulative percent of drug released from pellets coated with 6.6% Eudragit^{R} NE 30D, 0.5% talc and 0.5% PEG 6000 cured for 24 and 48 hours.

CURING TIME (HOURS)	SAMPLING TIME (HOURS)	CUMULATIVE PERCENT RELEASED				MEAN ± SD
24	1	48.39	53.31	53.01	54.58	52.32±2.35
	2	67.66	67.64	69.31	69.22	68.46±0.81
	3	76.00	77.11	79.59	81.75	78.61±2.23
	4	81.42	85.23	85.26	84.58	84.12±1.58
	5	85.97	88.56	89.37	88.90	88.20±1.32
	6	89.78	92.71	92.02	92.54	91.76±1.17
	7	90.01	94.09	94.00	94.01	93.03±1.74
	8	94.31	95.69	95.11	95.08	95.05±0.49
48	1	51.45	52.82	53.31	52.92	52.63±0.70
	2	68.49	71.61	71.03	72.31	70.86±1.44
	3	77.65	79.44	79.33	78.96	78.85±0.71
	4	83.62	85.02	84.13	83.94	84.18±0.52
	5	88.00	87.54	87.74	89.03	88.08±0.57
	6	89.52	91.31	90.63	91.43	90.72±0.76
	7	92.88	94.58	93.69	93.89	93.76±0.61
	8	93.93	95.65	94.74	94.94	94.81±0.61

APPENDIX 8

Cumulative percent of drug released from Batch Q1 using the rotating paddle, rotating basket and rotating bottle methods

METHOD	SAMPLING TIME	CUMULATIVE PERCENT RELEASED						MEAN ± S.D
Rotating paddle	0.5	23.72	23.72	23.72	25.61	25.61	25.90	24.71±1.00
	1	50.60	47.14	45.18	49.59	49.59	52.56	49.11±2.38
	2	63.54	62.28	64.56	67.00	69.25	70.51	66.19±3.00
	3	74.07	74.64	73.27	74.67	71.63	75.30	73.93±1.21
	4	79.11	79.08	77.85	79.51	76.65	79.36	78.59±1.02
	5	85.18	84.15	83.15	81.52	84.57	84.62	83.87±0.92
	6	87.01	86.35	87.18	86.18	88.64	85.18	86.76±1.06
	7	89.01	85.90	88.59	90.04	91.07	91.09	89.28±1.78
	8	90.42	88.14	90.62	92.05	93.53	90.47	90.87±1.65
Rotating paddle	0.5	22.27	22.54	22.54	23.72	23.97	23.97	23.17±0.73
	1	42.42	46.94	43.63	43.02	54.28	55.54	47.63±5.35
	2	60.23	62.51	61.03	59.77	68.65	68.48	63.45±3.72
	3	76.48	72.19	69.50	69.07	76.75	73.27	72.88±3.01
	4	80.26	78.48	76.35	76.37	80.36	79.53	78.56±1.67
	5	80.84	83.09	80.39	80.36	87.71	83.97	82.73±2.62
	6	84.47	86.13	84.45	84.17	90.32	88.26	86.30±2.29
	7	86.88	88.56	87.06	87.66	91.95	90.07	88.70±1.80
	8	89.31	90.77	89.29	90.09	93.38	92.50	90.89±1.55
Rotating bottle	0.5	28.25	24.75	20.25	28.55	29.50	25.80	26.18±3.11
	1	43.00	35.00	35.25	35.00	35.00	41.50	37.46±3.42
	2	56.50	57.25	56.50	58.00	63.00	52.25	57.25±3.16
	3	71.75	66.50	71.50	70.75	67.75	63.50	68.63±2.78
	4	82.25	74.75	77.50	77.75	78.75	75.25	77.71±2.47
	5	86.50	81.00	82.50	82.00	82.75	81.75	82.75±1.77
	6	86.25	85.50	84.75	89.75	89.75	86.75	87.13±1.96
	7	90.25	90.45	89.00	92.50	92.30	88.25	90.46±1.56
	8	96.50	91.75	90.75	93.75	95.00	93.50	93.54±1.91

APPENDIX 9

Cumulative percent of drug released from Batch Q1 using deionised water (pH = 6.5), hydrochloric acid (pH = 1.5), neutralised phosphate buffer (pH = 4.5) and phosphate buffer (pH = 6.8) as the dissolution medium.

MEDIUM	SAMPLING TIME	CUMULATIVE PERCENT RELEASED						MEAN ± SD
Deionised water	0.5	23.72	23.72	23.72	25.61	25.61	25.90	24.71±1.00
	1	50.60	47.14	45.18	49.59	49.59	52.56	49.11±2.39
	2	63.54	62.28	64.56	67.00	69.25	70.51	66.19±3.00
	3	74.07	74.64	73.24	74.67	71.63	75.30	73.92±1.21
	4	79.11	79.08	77.85	79.51	76.65	79.36	78.59±1.02
	5	85.18	84.15	83.15	81.52	84.57	87.62	84.37±0.92
	6	87.01	86.35	87.18	86.18	88.64	85.18	86.76±1.06
	7	89.01	85.90	88.59	90.04	91.07	91.09	89.28±1.78
	8	90.42	88.14	90.62	92.05	93.53	90.47	90.87±1.65
Hydrochloric acid	0.5	26.81	26.81	24.37	24.37	25.63	25.66	25.61±1.00
	1	50.23	50.23	49.05	49.06	48.58	48.59	49.29±0.69
	2	65.02	65.25	66.51	66.51	64.43	64.51	65.37±0.85
	3	74.00	74.09	73.98	74.07	73.98	74.18	74.05±0.07
	4	79.69	79.80	79.67	79.87	80.51	80.51	80.01±0.36
	5	83.59	83.31	83.49	83.58	83.87	83.87	83.62±0.19
	6	87.04	87.13	86.38	86.46	85.71	85.71	86.41±0.56
	7	89.31	89.20	88.02	88.13	87.69	87.78	88.36±0.65
	8	90.80	90.69	90.29	89.06	89.28	90.04	90.03±0.66
Neutralised phosphate buffer	0.5	25.62	25.62	23.61	23.63	24.33	24.33	24.52±0.83
	1	48.56	48.56	47.29	47.28	46.86	46.93	47.58±0.71
	2	64.61	64.85	64.13	64.28	63.99	64.28	64.36±0.29
	3	71.72	72.51	71.50	71.50	71.79	71.80	71.80±0.34
	4	78.08	78.22	77.17	77.17	78.03	78.08	77.79±0.44
	5	82.51	82.29	80.78	80.95	82.22	82.34	81.85±0.70
	6	85.86	85.86	83.68	83.68	85.66	85.81	85.09±1.00
	7	88.98	88.40	88.49	88.73	88.37	88.80	88.63±0.22
	8	91.98	91.32	91.17	91.17	91.07	91.98	91.45±0.38
Phosphate buffer	0.5	35.94	35.64	34.57	35.31	35.16	35.31	35.32±0.42
	1	54.26	53.81	53.01	55.20	51.44	51.44	53.19±1.40
	2	69.04	69.54	68.96	68.89	66.99	66.79	68.37±1.07
	3	76.22	75.57	74.42	78.61	75.22	75.22	75.88±1.33
	4	80.03	80.03	79.71	82.95	80.00	80.00	80.45±1.12
	5	83.77	83.27	84.37	87.31	84.52	84.52	84.63±1.28
	6	87.66	87.01	86.81	89.95	87.46	87.66	87.76±1.03
	7	89.60	89.30	89.00	90.15	89.95	90.25	89.71±0.45
	8	91.94	90.97	91.12	92.17	92.57	92.54	91.89±0.63

APPENDIX 10

Cumulative percentage of drug released from Batch Q1 after storage at room temperature (20±2°C).

PERIOD OF STORAGE (WEEKS)	SAMP-LING TIMES (HOURS)	CUMULATIVE PERCENT RELEASED						MEAN±SD
0	0.5	23.72	23.72	23.72	25.61	25.61	25.90	24.71±1.00
	1	50.60	47.14	45.18	49.59	49.59	52.56	49.11±2.38
	2	63.54	62.28	64.56	67.00	69.25	70.51	66.19±3.00
	3	74.07	74.64	73.24	74.67	71.63	75.30	73.92±1.21
	4	79.11	79.08	77.85	79.51	76.65	79.36	78.59±1.02
	5	85.18	84.15	83.15	82.51	84.57	84.62	84.02±0.92
	6	87.01	86.35	87.18	86.18	88.64	85.18	86.75±1.06
	7	89.01	85.90	88.59	90.04	91.07	91.09	89.28±1.78
	8	90.42	88.14	90.62	92.05	93.53	90.47	90.87±1.65
2	0.5	26.65	18.22	21.02	18.83	26.22	20.28	21.87±3.36
	1	48.24	42.50	44.75	42.50	47.84	45.36	45.20±2.28
	2	61.78	57.19	60.53	58.47	61.38	64.29	60.61±2.30
	3	71.91	67.30	69.63	67.97	71.51	70.41	69.79±1.70
	4	76.10	73.34	75.22	73.99	77.13	75.42	75.20±1.26
	5	80.94	78.78	79.06	77.78	80.96	80.06	79.60±1.16
	6	84.60	81.82	82.49	83.27	83.60	82.87	83.11±0.87
	7	88.86	84.82	85.28	85.10	86.29	85.30	85.94±1.38
	8	89.44	86.83	86.68	86.83	89.81	88.51	88.02±1.30
4	0.5	26.65	22.34	21.48	21.71	20.28	20.08	22.09±2.19
	1	46.81	44.38	44.13	43.12	46.81	40.47	44.29±2.19
	2	63.64	61.13	61.33	60.33	59.27	61.91	61.27±1.35
	3	69.35	68.98	68.98	68.58	67.55	70.81	69.04±0.97
	4	74.87	74.82	76.46	74.67	73.17	75.02	74.84±0.96
	5	78.88	78.86	78.28	78.41	77.00	79.66	78.52±0.81
	6	81.26	83.70	81.89	82.04	80.19	82.87	81.99±1.12
	7	84.30	85.90	85.00	85.28	82.32	83.42	84.37±1.20
	8	86.30	87.31	86.25	87.08	86.45	85.43	86.47±0.61
8	0.5	20.28	20.88	19.65	20.08	23.57	23.34	21.30±1.57
	1	45.16	45.16	44.95	43.50	45.78	46.18	45.12±0.84
	2	60.73	60.30	60.93	59.87	63.21	61.15	61.03±1.06
	3	68.58	69.60	69.80	68.15	67.77	71.06	69.16±1.12
	4	74.42	73.79	75.22	74.59	73.82	76.90	74.79±1.06
	5	77.80	77.40	78.36	77.38	77.63	77.65	77.70±0.33
	6	80.81	80.21	81.64	80.39	80.21	80.24	80.58±0.52
	7	83.02	82.82	83.62	82.59	82.62	82.44	82.85±0.39
	8	85.03	84.37	85.45	85.05	84.00	84.20	84.68±0.52

PERIOD OF STORAGE (WEEKS)	SAMP-LING TIMES (HOURS)	CUMULATIVE PERCENT RELEASED						MEAN±SD
12	0.5	19.65	21.52	23.21	22.54	18.02	24.82	21.63±2.25
	1	36.13	41.04	34.70	33.57	38.39	38.81	37.11±2.56
	2	58.62	60.50	57.57	59.85	58.85	64.39	59.96±2.19
	3	70.16	69.13	68.53	68.53	70.56	71.43	69.72±1.08
	4	74.54	73.14	74.02	74.79	75.02	73.37	74.15±0.70
	5	79.41	78.98	78.53	79.01	78.58	79.46	79.00±0.36
	6	82.62	80.92	81.39	82.65	80.99	81.23	81.63±0.72
	7	85.43	83.80	84.00	84.85	83.40	86.53	84.67±1.07
	8	87.23	85.60	86.40	86.46	86.00	88.76	86.74±1.03

APPENDIX 11

Cumulative percent released from Batch Q1 after storage at low temperature (5 ± 1°C)

PERIOD OF STORAGE (WEEKS)	SAMP-LING TIMES (HOURS)	CUMULATIVE PERCENT RELEASED						MEAN±SD
0	0.5	23.72	23.72	23.72	25.61	25.61	25.90	24.71±1.00
	1	50.60	47.14	45.18	49.59	49.59	52.56	49.11±2.38
	2	63.54	62.28	64.56	67.00	69.25	70.51	66.19±3.00
	3	74.07	74.64	73.27	74.67	71.63	75.30	73.92±1.21
	4	79.11	79.08	77.85	79.51	76.65	79.36	78.59±1.02
	5	85.18	84.15	83.15	81.52	84.57	84.62	84.02±0.92
	6	87.01	86.35	87.18	86.18	88.64	85.18	86.75±1.06
	7	89.01	85.90	88.59	90.04	91.07	91.09	89.28±1.78
	8	90.42	88.14	90.62	92.05	93.53	90.47	90.87±1.65
2	0.5	26.42	23.14	22.94	22.92	24.37	20.88	23.45±1.68
	1	51.93	47.24	46.80	45.58	49.59	45.13	47.71±2.37
	2	61.78	63.21	62.81	64.24	64.31	62.61	63.16±0.90
	3	73.54	71.26	66.57	70.23	71.28	70.46	70.56±2.08
	4	78.00	77.73	71.76	76.75	77.35	77.35	76.49±2.15
	5	80.16	81.34	77.60	78.25	82.39	80.06	79.97±1.65
	6	81.31	84.57	81.44	80.76	86.03	84.17	83.05±1.97
	7	85.58	86.58	84.75	86.55	87.03	86.40	86.15±0.76
	8	87.18	90.82	88.51	88.16	88.41	90.04	88.85±1.22
4	0.5	24.19	24.80	23.14	23.77	25.00	22.94	23.97±0.77
	1	44.78	45.58	44.35	44.98	44.15	43.93	44.63±0.56
	2	60.95	60.57	60.53	60.35	61.15	59.07	60.44±0.67
	3	69.40	69.83	70.01	67.97	68.96	67.75	68.99±0.87
	4	74.24	75.25	75.05	73.59	74.54	75.02	74.62±0.57
	5	78.03	78.63	79.28	77.80	79.46	78.41	78.60±0.61
	6	80.81	83.30	82.87	80.61	81.50	81.61	81.78±0.99
	7	85.50	86.53	87.16	86.50	85.70	86.08	86.25±0.56
	8	87.08	90.79	88.54	88.11	88.34	89.74	88.77±1.10
8	0.5	25.43	24.28	23.75	23.73	22.48	22.55	23.70±1.01
	1	46.55	46.34	46.75	46.14	47.58	47.58	46.82±0.57
	2	61.47	60.82	61.90	61.03	62.32	61.67	61.54±0.51
	3	69.72	71.19	70.34	70.34	70.11	70.55	70.38±0.45
	4	75.30	76.74	75.69	75.30	76.33	76.74	76.01±0.62
	5	78.34	80.22	78.78	78.98	78.57	80.06	79.16±0.72
	6	81.86	82.89	81.86	82.04	81.25	83.30	82.20±0.69
	7	83.66	84.95	83.89	84.51	83.66	85.36	84.34±0.65
	8	86.13	85.54	85.93	86.77	88.45	87.65	86.75±1.01

APPENDIX 12

Cumulative percent of drug released from Batch Q1 after storage at 37°C with 80% relative humidity.

PERIOD OF STORAGE (WEEKS)	SAMPLING TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED						MEAN ±SD
0	0.5	23.72	23.72	23.72	25.61	25.61	23.90	24.71±1.00
	1	50.60	47.14	45.18	49.59	49.59	52.56	49.11±2.38
	2	63.54	62.28	64.56	67.00	69.25	70.51	66.19±3.00
	3	74.07	74.64	73.24	74.67	71.63	75.30	73.92±1.21
	4	79.11	79.08	77.85	79.51	76.65	79.36	78.59±1.02
	5	85.18	84.15	83.15	81.52	84.57	84.62	84.02±0.92
	6	87.01	86.35	87.18	86.18	88.64	85.18	86.76±1.06
	7	89.01	85.90	88.59	90.04	91.07	91.09	89.28±1.78
	8	90.42	88.14	90.62	92.05	93.53	90.47	90.87±1.65
2	0.5	15.57	14.54	15.37	18.43	18.63	18.63	16.86±1.73
	1	30.16	29.96	28.53	28.33	31.21	31.44	29.94±1.19
	2	57.52	57.54	53.66	53.68	53.03	55.51	55.16±1.84
	3	64.16	64.16	63.34	63.76	65.19	65.19	64.30±0.69
	4	70.38	70.36	69.95	69.98	71.66	72.26	70.77±0.88
	5	74.62	74.59	74.57	74.80	75.42	75.82	70.97±0.47
	6	78.81	78.81	78.36	78.58	79.33	79.68	78.93±0.45
	7	79.98	79.98	80.56	80.79	81.44	81.21	80.66±0.56
	8	82.79	82.79	82.97	83.45	83.45	83.45	83.15±0.30
4	0.5	14.94	13.51	12.91	14.74	17.40	15.97	14.91±1.49
	1	24.64	23.19	22.99	24.42	24.67	24.84	24.13±0.74
	2	50.75	49.69	49.92	49.74	49.97	49.97	50.01±0.35
	3	63.49	62.68	63.28	63.28	63.31	63.81	63.31±0.34
	4	70.31	69.08	70.51	70.31	70.21	70.76	70.20±0.53
	5	75.55	74.52	75.32	75.32	75.55	73.87	75.02±0.57
	6	78.73	77.10	78.03	78.10	80.34	79.07	78.56±1.01
	7	80.94	80.09	80.84	81.31	80.96	82.80	81.16±0.82
	8	82.94	81.87	83.12	83.32	83.37	84.80	83.24±0.86
8	0.5	13.32	13.51	10.85	10.85	9.62	9.62	11.30±1.58
	1	22.99	23.00	19.69	19.68	17.85	17.85	20.18±2.13
	2	44.83	40.92	44.80	45.10	44.78	44.76	44.20±1.47
	3	61.76	62.78	61.18	61.38	61.96	61.96	61.84±0.51
	4	70.23	70.46	69.65	69.65	70.23	70.66	70.15±0.38
	5	76.12	76.12	75.87	75.87	75.67	75.70	75.89±0.18
	6	79.41	79.73	79.08	79.31	79.13	79.11	79.30±0.23
	7	80.89	81.51	80.86	81.29	80.36	82.74	81.28±0.75
	8	82.89	83.09	83.07	83.27	83.27	84.75	83.39±0.62

APPENDIX 13

Cumulative percent of drug released from Batch Q1 after storage at 40°C.

PERIOD OF STORAGE (WEEKS)	SAMP-LING TIMES (HOURS)	CUMULATIVE PERCENT RELEASED						MEAN ± SD
0	0.5	23.72	23.72	23.72	25.61	25.61	25.90	24.71±1.00
	1	50.60	47.14	45.18	49.59	49.59	52.56	49.11±2.38
	2	63.54	62.28	64.56	67.00	69.25	70.51	66.19±3.00
	3	74.07	74.64	73.24	74.67	71.63	75.30	73.93±1.21
	4	79.11	79.08	77.85	79.51	76.65	79.36	78.59±1.02
	5	85.18	84.15	83.15	81.52	84.57	84.62	84.03±0.92
	6	87.01	86.35	87.18	86.18	88.64	85.18	86.76±1.06
	7	89.01	85.90	88.59	90.04	91.07	91.09	89.28±1.78
	8	90.42	88.14	90.62	92.05	93.53	90.47	90.87±1.65
2	0.5	12.28	10.23	10.90	14.11	12.68	13.91	12.35±1.43
	1	18.88	17.02	17.25	17.67	18.07	17.47	17.73±0.61
	2	32.09	29.81	30.01	29.83	32.09	30.44	30.71±1.00
	3	46.16	44.93	44.93	42.12	46.99	45.13	45.04±1.51
	4	61.33	61.50	60.90	59.87	63.59	61.86	61.51±1.12
	5	71.03	70.78	70.58	68.53	72.46	70.18	70.59±1.16
	6	77.28	76.85	76.45	75.17	77.50	77.48	76.79±0.81
	7	81.11	80.24	80.44	79.63	83.17	82.12	81.12±1.20
	8	84.32	83.45	83.67	82.84	85.58	84.55	84.07±0.88
4	0.5	12.08	11.68	11.05	11.68	15.34	10.63	12.08±1.53
	1	18.58	18.48	17.05	18.10	19.70	17.05	18.16±0.92
	2	31.69	31.06	30.04	30.66	32.72	27.98	30.69±1.47
	3	46.99	46.33	44.93	45.33	47.81	47.79	46.53±1.12
	4	60.33	60.08	58.80	59.20	60.10	61.10	59.94±0.75
	5	68.98	69.15	67.90	68.68	68.63	69.18	68.75±0.44
	6	75.82	76.22	74.34	74.92	75.42	75.97	75.45±0.65
	7	79.03	79.26	78.36	78.93	78.03	78.96	78.76±0.43
	8	81.67	83.04	80.96	82.17	80.44	84.55	82.14±1.36
8	0.5	10.86	9.42	7.57	10.03	9.84	14.35	10.35±2.05
	1	19.68	17.65	18.45	18.65	18.65	20.13	18.87±0.82
	2	38.84	36.35	36.15	35.58	35.38	36.40	36.45±1.13
	3	53.78	51.90	52.10	51.27	51.07	52.55	52.11±0.90
	4	63.64	62.08	63.21	61.76	61.55	63.04	62.55±0.79
	5	71.11	69.60	68.40	69.20	69.40	73.37	70.18±1.64
	6	75.10	75.45	73.42	73.82	75.45	75.45	74.78±0.84
	7	79.31	79.88	77.43	78.08	78.28	78.88	78.64±0.81
	8	81.49	81.04	81.01	80.81	81.87	81.92	81.36±0.43

APPENDIX 14

Determination of the order of release

1. *Substitution method.* The data accumulated in a kinetic study may be substituted in an integrated form of the equations that describe the various orders. When the equation is found in which the calculated k values remain constant within the limits of experimental variation, the reaction is considered to be of that order.

2. *Half-life method.* In a zero order reaction, the half-life is proportional to the initial concentration, a. The half-life of a first order reaction is independent of a, and for a second order reaction, in which $a = b$, is proportional to $1/a$.

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