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The development and characterisation of directly-compressible oral controlled drug delivery systems

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The Development and Characterisation of Directly–Compressible

Oral Controlled Drug Delivery Systems

submitted by

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To Sue

Summary

The principal aim of this study was to examine the feasibility of the production of oral controlled drug delivery systems by the direct compression of tablets from physical mixes of powders.

In the introduction to the work, the rationale for the controlled delivery of drugs to the body is discussed, and the routes by which this might be achieved are examined. The oral route is considered in detail, and the systems which have been proposed in the literature for use in this capacity are reviewed. The experimental work is divided into four chapters: the first dealing with an investigation of the feasibility of the use of hydrogenated vegetable oil as a tableting excipient for the production of oral controlled drug delivery systems by direct compression; the second and third with attempts to determine independently of drug release data a factor, tortuosity, which is included in the Higuchi equation describing drug release from the systems; and the fourth with the production of systems which release drug with zero-order kinetics.

Powder mixes of model drugs with hydrogenated vegetable oil and other tableting excipients were prepared and tableted. Drug release studies were performed *in vitro* and drug release from the tablets was found to be controlled by diffusion of drug through water-filled tortuous pores within the tablets. Drug release rates were found to be affected by various factors such as drug loading, hydrogenated vegetable oil concentration and particle size, drug solubility and excipient type and proportion, thus potentially providing several means of achieving desired drug release profiles.

The determination of tortuosity factors of matrix tablets was attempted in two ways. Firstly, air flow rate and pressure drop through matrices were studied using a permeametry technique, and pore surface area was determined using mercury intrusion porosimetry. An attempt was made to apply the Carman-Kozeny equation to the data, but meaningless tortuosity factors were obtained, and this was

postulated to be due to the heterogeneity of the pore size distribution within the matrix tablets. Secondly, a gaseous diffusion technique, based on Graham's law of diffusion, was used to determine the effective diffusion coefficients through the tablets of helium in air. This method yielded tortuosity factors which were found to be comparable with those obtained from drug release studies, but only after a modification which was proposed had been applied to the Higuchi equation.

The feasibility of the production of zero – order releasing oral controlled drug delivery systems was investigated by adapting the hemispherical matrix principle to tablets. Hemispherical tablets were prepared and coated with a water – impermeable material. A delivery orifice was made in the coat on the planar surface of the tablets, and *in vitro* drug release studies were performed. Zero – order drug release was observed, and the effect of reduction of hydrogenated vegetable oil content was found to increase drug release rate, with zero – order release maintained at low concentrations of hydrogenated vegetable oil. These concentrations would not be expected to be sufficient to form matrices, and a combined dissolution – diffusion mechanism was proposed to explain the drug release kinetics.

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Chapter 1

Introduction

1.1 Drug Delivery Systems

Drugs can be administered to patients in many types of dosage form and by several different routes. The aim common to all dosage forms has been to ultimately deliver the drug to its site of action in the body, and this has been achieved with varying degrees of success. The historical development of dosage forms reflects an increasing awareness of the importance of their contribution to the overall therapeutic effect of the drug. Conventional dosage forms of the single dose or bolus type include the most popular present day dosage form, the tablet, which accounts for approximately 50% of all medicines and together with capsules accounts for 65% (1). Other examples of conventional medicines available include oral liquid dosage forms, suppositories, pessaries, injections, inhalations, creams, ointments and eye, ear and nose drops. A second group of dosage forms has been the subject of great interest in recent years. This group of medicines is designed to prolong the delivery of drug to the body, preferably at a pre-determined rate. These systems have been described in a variety of ways, depending on their individual characteristics, but widely used generic terms are sustained or controlled drug delivery systems. Much research and development effort has been directed towards designing devices to be administered by the oral route either as tablets or capsules, although other novel approaches such as the transdermal route, intrauterine delivery and surgical implantation have yielded useful controlled release systems.

1.2 Rationale for Controlled Delivery of Drugs

In order to provide a rationale for the controlled delivery of drugs to the body, conventional methods of delivery will be considered first. The tablet can be taken as a typical example of a common conventional dosage form. Following administration, a tablet is designed to disintegrate rapidly in the stomach, releasing drug which dissolves and is then absorbed into the bloodstream where it is carried to its site of action in the body. However, depending on its particular

properties, the drug inevitably thus reaches most of the tissues which may require a large dose of the drug in order for it to be present at the therapeutic concentration at its site of action. Apart from being wasteful, this increases the potential for toxicity and is one of the principal reasons for interest in targeting drugs, especially highly toxic ones, to specific sites. Again, depending on the drug's individual properties, it may be metabolised and finally the drug and/or its metabolite(s) are eliminated from the body. The rates at which these processes occur will obviously be drug dependent, but can also be influenced by the performance of the dosage form e.g. the rate of disintegration of the tablet.

The ratio of the concentration of drug in blood at which serious toxicity occurs to the minimum effective concentration is termed the therapeutic index of the drug, and its magnitude varies widely between drugs. Some drugs have an extremely small therapeutic index and in such cases it is critically important that the concentration of drug does not fluctuate greatly over the desired period of activity. The concentration of drug in the bloodstream following administration in a conventional tablet formulation generally increases to a peak and then gradually falls off with time. Such a dosage form can only achieve the aim of keeping the drug concentration within the therapeutic index by delivering the correct dose at suitable intervals. This results in a "peak and trough" effect in drug concentration, which can result in both toxicity and ineffectiveness with inappropriate dosage form design. For some drugs with a small therapeutic index, this potential for serious toxicity can prevent their clinical use (2). An additional disadvantage occurs if the drug is rapidly eliminated from the body, and as a result will require administration at short time intervals if its concentration is to remain within the therapeutic index. This can be inconvenient for the patient and may lead to treatment adherence being compromised (3).

It will be apparent that a less variable and preferably constant concentration of drug in the bloodstream, which was within the therapeutic index, would be desirable and advantageous. These are the principal aims of the majority of

controlled or sustained release delivery systems, and depending on the specific characteristics of the delivery system are achieved with varying degrees of success. It has been shown that using controlled drug delivery can reduce toxicity; for example, a controlled delivery formulation containing the antiparkinsonian drug levodopa was found to eliminate drug-induced dyskinesia (4). A controlled delivery formulation of procainamide has been shown to eliminate the need for dosing with this drug every three hours (5). Also, more efficient use of drug can lead to a decreased overall dose, for example a controlled delivery formulation of tetracycline has been shown to be equally as effective as a conventional dosage form in the treatment of acne vulgaris, but using only half the dose (6). Some other advantages of controlled delivery of drugs are more difficult to quantify, but are considered to contribute to an overall improvement of disease management. It is considered that improvements in drug delivery should result in more rapid cure or control of clinical conditions, and thus might be expected to result in less time spent in hospital or consulting doctors. It is thus feasible that cost savings may be possible compared to treatment with conventional dosage forms.

One of the potential disadvantages of controlled delivery is also related to cost of treatment. A controlled delivery device is often more expensive to produce than a conventional dosage form, because it may be complex to manufacture and require investment in new technology. A second disadvantage is that "dose-dumping" may occur, that is, the entire drug load carried in the dosage form may be released rapidly if the device fails; for example, if the rate-controlling membrane surrounding a reservoir device (section 1.4.5.1 below) is ruptured. This would result in high initial concentrations of drug and, if the therapeutic index is narrow, possibly cause serious toxicity (7). This problem could also occur if the patient was not aware of the nature of the dosage form, and crushed or chewed an oral delivery system prior to ingestion. A further potential problem is concerned with accidental or intentional overdoses of oral controlled delivery products, where the slow release of drug may cause a delay before symptoms are recognised,

making it impossible to retrieve the dosage forms from the stomach (8). The oral route also poses potential problems with devices fabricated with non-biodegradable materials. A case has been reported where 98 controlled delivery tablets of ferrous sulphate became trapped proximal to a neoplastic stricture in the colon of a patient (9). The patient had discontinued taking the tablets two months before the problem was discovered. Further disadvantages of the oral delivery route will be discussed below (section 1.3.1).

1.3 Routes of Administration of Controlled Drug Delivery Devices

Several of the conventional routes of administration of drugs have also been used to deliver drugs at controlled rates. Controlled delivery has also opened up possibilities of new routes of administration e.g the transdermal route. Li *et al* (10) have discussed the influence of route of administration on the design of controlled release systems. The routes which have generated the most research interest in recent years will be discussed briefly below, with particular emphasis on the oral route.

1.3.1 The Oral Route of Controlled Drug Delivery

Controlled drug delivery via the oral route has been the subject of several reviews (e.g. 11 – 13). The advantages of the oral route make it overwhelmingly the most popular route of conventional drug administration, and this is also reflected in the numbers of oral controlled release devices in clinical use. It is widely used due to its cost, simplicity of administration and potential for the use of a variety of both solid and liquid presentations e.g. tablets, soft and hard gelatin capsules, powders, liquids, solutions, suspensions and emulsions. Solid dosage forms such as tablets in particular are relatively straightforward to manufacture in large quantities, they allow accurate and reproducible dosing, and are convenient for the patient. The convenience of the oral route for both conventional and controlled delivery dosage forms is gained at the expense of the constraints

imposed by the physiology of the gastrointestinal tract itself. Factors such as the varying pH along the tract, with particularly acidic conditions in the stomach; gastric emptying rate; intestinal motility; mucosal surface area and membrane permeability are all constraints which must be taken into account when designing oral controlled drug delivery systems. Further complications arise from the considerable inter- and intrasubject variation in these factors, in particular gastric emptying and intestinal motility, which are further affected by the absence or presence of food and/or liquid and their quantities and constituents. Some pathological conditions and many drugs (e.g. antacids) may also modify the conditions in the tract.

Recently, the technique of gamma scintigraphy has yielded much valuable information regarding the gastrointestinal transit of various types of oral controlled delivery devices. The technique and some of the results obtained using it have been reviewed by Davis (14). Differences were found between the transit times of multiparticulate devices and non-disintegrating single unit devices (15). The gastric emptying times associated with both types of device were found to be affected by the presence and quantity of food (16). The transit time of both types of device through the small intestine was found to be independent of content and shorter than was previously thought at approximately 3 hours, with little intersubject variability compared to the other regions of the tract (17). Colonic transit was found to be widely variable, but some drugs were found to be well absorbed from the colon (18). This was not previously thought to be the case – it had been thought that drugs were absorbed largely from the small intestine.

These findings have relevance in the design and administration of oral controlled delivery devices, and some general conclusions can be drawn i.e. single-unit non-disintegrating systems may be retained in the stomach for several hours by being administered after a meal; twice or even once daily dosing might be possible if the drug is well absorbed in the colon; variability in total transit time is wide and can limit the usefulness of some controlled oral delivery systems. In

recognition of the conclusion regarding the short transit time of the small intestine, several approaches have been proposed which attempt to prolong the residence time in the stomach of oral controlled delivery devices, thus extending the useful time of drug release. These will be discussed in more detail below (section 1.4.4).

A further disadvantage of the oral route is termed the "first-pass" effect. This phenomenon results from drugs which are absorbed from the gastrointestinal tract into the bloodstream being carried first into the portal circulation to the liver where they may be metabolised before reaching other tissues. In some cases the effect may result in virtually complete elimination of the drug from the circulation, but an active metabolite may be formed from some drugs. With some drugs, first-pass metabolism is less significant or does not occur at all. Variability in the extent of first-pass metabolism has also been postulated as a reason for intersubject differences in bioavailability (18).

1.3.2 Other Routes of Controlled Drug Delivery

Alternative routes of drug administration which have also been used include the parenteral, transdermal, intraocular, intrauterine, and intravaginal routes and surgical implantation. A parenteral route of administration is correctly defined as any route other than the oral route, but it is generally accepted as meaning administration by some form of injection e.g. intravenous, intramuscular, or subcutaneous. Some advantages of the parenteral route are its easy access to the systemic circulation, lack of first-pass metabolism and the rapid achievement of effective drug concentrations, with virtually instantaneous action when the intravenous route is used. This may however be accompanied by a rapid decline in blood concentrations, and several attempts have been made to prolong the release of drugs from depot-type formulations which are usually given by intramuscular injection. Various approaches have been used, including the use of polymers to complex or adsorb drug molecules in solution and/or to increase the viscosity of

the vehicle, aqueous and oil suspensions, oil solutions and emulsions of the drug (19). Further disadvantages of this route result from its invasiveness, the requirement for sterile dosage forms and usually the requirement for skilled staff to administer the preparations used.

The transdermal route of drug administration is a relatively new route for controlled drug administration and it has been reviewed recently (20 – 22). Some of its advantages include the avoidance of first–pass metabolism, a possible improvement in patient compliance and the ease of termination of treatment. Its principal limitation is the effectiveness of the skin as a barrier to drug transport, which to date has caused its application to be limited to potent drugs. Research has been conducted into ways of enhancing penetration through the skin, using both chemical (23, 24) and iontophoretic (25) methods.

The intrauterine route has been the subject of much research interest, principally because of the potential of the route for local delivery of contraceptive drugs. Intrauterine devices have been manufactured to contain either copper (26) or a steroidal hormone (27), which are released at nearly constant rates. They have been shown to have the advantages and disadvantages associated with the use of conventional intrauterine devices but combined with increased contraceptive efficacy (28).

An attempt to improve the treatment of glaucoma using drugs such as pilocarpine, has been one of the reasons for the development of intraocular controlled delivery systems. Conventional eye drops suffer from the disadvantage that drug is rapidly removed from the eye by drainage in lachrimal secretions, with only approximately 1% of the instilled dose being available for effective use (29). Also, subsequent systemic absorption of drug drained from the eye can result in toxicity (30). Polymeric ocular inserts have been developed and have been shown to be effective whilst only using one–quarter to one–eighth of the conventional dose (31). Nanoparticles with incorporated pilocarpine are another approach to ocular drug delivery which has been studied (32).

The production of systems for surgical implantation has aroused much recent research interest, with particular emphasis being placed on the production of biodegradable polymers which obviate the need for removal of the spent device when drug delivery is complete. Such systems suffer from the disadvantages that implantation is invasive and that treatment alteration or cessation is difficult. However, a significant advantage of using implants is that drug can be delivered for periods of many months (33, 34), overcoming the problem of patient compliance. Attention has therefore focused on the use of implants for example for long – term contraception (35, 36) and for the delivery of narcotic antagonists in the treatment of opiate addiction (37). Good tissue compatibility is an obvious requirement, and many polymeric substances have been investigated with regard to their toxicity when used as implants. Some examples of such classes of biodegradable polymers include polyamides, polyesters, polyorthoesters and polyanhydrides (38).

1.4 Types of Device used for Oral Controlled Drug Delivery

Many of the basic systems which have been developed for the controlled delivery of drugs have been used or adapted to deliver drugs by the oral route. Systems such as reservoir (section 1.4.5.1 below) and matrix devices (section 1.4.5.2 below) which have been used orally have also been used to deliver drugs by some of the routes discussed above. Since the studies described in later chapters are concerned with oral drug delivery, however, the systems described in the literature for use via this route will be reviewed. There are several possible ways to classify the various systems which have been developed, and a classification based upon the principal rate – controlling mechanism of the device will be used here, since several different types of system effectively utilise the same rate – controlling mechanism.

1.4.1 Dissolution Controlled Systems

Controlled delivery systems employing dissolution as the rate-controlling mechanism are in principle among the simplest to prepare. A drug which has a low intrinsic dissolution rate can have this property exploited in order to prepare a delivery system which has an inherent sustained release action but which contains only drug and which does not require any modification. For drugs with higher water solubilities and therefore higher dissolution rates, salts, other chemical derivatives or polymorphic forms can be prepared which are less soluble (11). If this approach is not possible or is unacceptable, the drug can be incorporated into a tablet containing a relatively insoluble material, and which does not contain any disintegrating agent. Several refinements to this more basic approach have been made, including development of encapsulated and matrix systems. Dissolution-controlled drug release has been used in oral controlled delivery systems, but it has been applied much more widely in systems administered via the parenteral route, where biocompatible polymeric materials which dissolve very slowly can be used as the basis for implantable systems. All dissolution controlled systems are based on the following theoretical principles.

The basic concept underlying dissolution controlled release is that the dissolution process is controlled by the rate of diffusion of drug molecules from the dissolving surface through an unstirred solvent layer to the bulk solution (39). The flux J under steady state conditions across a plane of unit area is given by the following differential equation:-

$$J \ = \ -D_i(dC/dx) \qquad\qquad .....\text{equation 1.1}$$

where $\quad D_i \quad$ = diffusion coefficient of species i

$\quad dC/dx$ = concentration gradient from the solid surface to the bulk solution

This equation represents Fick's first law of diffusion. Flux is defined as the flow of material with time (dM/dt) across a plane of area a: –

$$J = (1/a)(dM/dt) \qquad .....\text{equation 1.2}$$

If it is assumed that the concentration gradient is linear and the thickness of the diffusion layer is h_d then the concentration gradient is given by the equation: –

$$dC/dx = (C_b - C_s)/h_d \qquad .....\text{equation 1.3}$$

where C_s = concentration at the solid surface i.e. drug solubility

         C_b = concentration in the bulk solution

Combining equations 1.1, 1.2 and 1.3 results in the following equation: –

$$dM/dt = -(D_i a/h_d)(C_b - C_s) = k_d a(C_s - C_b) \qquad .....\text{equation 1.4}$$

where k_d = intrinsic dissolution rate constant

Equation 1.4 predicts that dissolution rate will be maintained constant, provided that surface area, diffusion coefficient, concentration difference and diffusion layer thickness remain constant. However, as dissolution of a solid surface proceeds, these terms may change, with surface area generally decreasing as the intact dosage form becomes depleted of drug.

The Hixson – Crowell cube – root equation (40) can be used to describe the dissolution of particles where surface area decreases during dissolution but where there is no change in overall geometrical shape. This equation arises from an integration of Fick's first law of diffusion (equation 1.1), and from the knowledge

that the surface area of a regular geometrical shape varies with the two-thirds power of its volume. It expresses this change in volume in terms of the change in mass of the particles as dissolution progresses:-

$$M_0^{1/3} - M^{1/3} = k_D t \qquad \text{.....equation 1.5}$$

where M_0 = initial mass of particle

M   = mass of particle remaining at time t

k_D = cube-root dissolution rate constant

An equation describing drug release from dissolution controlled systems which can be applied to dosage forms with various geometrical shapes has been derived by Hopfenberg (41). This equation arises from consideration of shape changes with time during dissolution and integration of the differential equations obtained:-

$$M_t/M_\infty = 1 - (1 - k_0 t/C_0 a_d)^n \qquad \text{.....equation 1.6}$$

where M_t = mass of drug released at time t

M_∞ = mass of drug released at infinite time

k_0 = constant

C_0 = concentration of drug in the device at time 0

a_d = radius of sphere or cylinder, or half-thickness of a slab

n = 1 for a slab, 2 for a cylinder, 3 for a sphere

1.4.1.1   Encapsulated Systems

Coated granules and microcapsules release drug via dissolution control. The "Spansule" type of dosage form, which was the first controlled delivery product to reach the market in the early 1950s (11), consists of individual particles or granules of drug which are coated with a slowly dissolving material, usually a

polymer. A different thickness of coat is applied separately to several individual ୳ batches of particles, and capsules containing granules from these batches having a range of thicknesses are prepared. This system exhibits a pulsed type of release pattern, with the particles having the thinnest coat dissolving first and so on, providing a fairly coarse control of release. Another way of achieving the same effect is to coat inert "seeds" with drug and then further coat them with different thicknesses of slowly dissolving substance. There have been numerous studies of the drug release characteristics of such systems (e.g. 42 − 45). As an alternative to filling capsules with the granules, compressed tablets also have been prepared, but other excipients and compaction pressure have been found to affect drug release rates, the latter sometimes causing rates to increase unpredictably due to granule fracture during the compaction process (46). Some examples of materials used in the preparation of dissolution controlled systems include beeswax, glyceryl monostearate, ethylcellulose, polyamides and acrylic resin (47).

An alternative method of achieving encapsulated dissolution controlled drug delivery is to use the process of microencapsulation. For the purposes of this discussion, a microcapsule can be considered as a discrete particle of drug or drug − loaded material which is enclosed within a coat of well − defined thickness. In contrast, microspheres generally do not possess a discrete coat, although the terms are sometimes used interchangeably. There are several methods of production of microcapsules, which result in systems which possess differing dissolution characteristics. It must be emphasised that microencapsulation does not always produce systems where dissolution is the rate − controlling mechanism of drug release, and thus microcapsules will in addition be referred to subsequently in the sections dealing with other mechanisms of release control. Furthermore, a series of papers has been published by Hoffman and co − workers (48 − 51) in which the authors warn that the drug release mechanism from microcapsules can sometimes be inferred erroneously from studies on drug release rates of heterogeneous populations of microcapsules. The authors conclude that previous workers may have drawn invalid

conclusions from such data and postulate the technique of measurement of drug release from individual microcapsules as a more reliable method of determining true drug release mechanisms.

Coacervation is one of the earliest reported and most frequently used techniques of microcapsule preparation (52). A coacervation process occurs as the result of interaction between two oppositely charged polyelectrolytes in solution to form a polymer-rich system termed a coacervate. At elevated temperature, the coacervate coats the solid or liquid drug to form the basic structure of the microcapsule. The system is cooled, causing the coating solution to gel, which is then crosslinked to form the capsule wall. Such a system consisting of gelatin and acacia has been described by Harris (53), in which water-soluble drugs can be encapsulated providing they have been previously coated with a water-impermeable material such as carnauba wax or ethylcellulose. Benita and Donbrow (54) have described the production of ethylcellulose coated microcapsules using a coacervation method from which drug release was found to be controlled by the dissolution of the coat. Further examples of microencapsulation include the interfacial polymerisation technique which involves dispersing an organic phase containing drug particles into an aqueous phase containing monomer (55). The monomers react at the liquid/liquid interface, forming a capsule wall, a process which may require a cross-linking agent. An electrostatic technique has also been described (11) which can be used when the coating material and drug are both aerosols and oppositely charged. The drug and coating substance are atomised together and cooled, and the resulting microcapsules are collected using an aerosol collection system.

1.4.1.2 Matrix Systems

The second group of dissolution controlled drug delivery systems are termed matrix systems. It should however be noted that the term matrix is also used to describe a class of systems from which drug release is controlled by diffusion

(section 1.4.5 below). Dissolution controlled matrix systems are usually formed by compressing the drug with a slowly dissolving carrier. Two methods of producing such systems for oral use were described by Becker and co-workers in a series of papers (56 - 61). The first method investigated was an aqueous dispersion technique, in which particles were prepared by pouring a heated aqueous solution of surfactant into melted wax in which drug particles had been dispersed. The mixture was then slowly cooled to room temperature whilst being stirred. The resultant drug-loaded wax particles were recovered, washed, dried and sieved into various size fractions. The second method used was spray-congealing (prilling), which involved mixing drug and surfactant in molten wax, and spraying the resultant mixture through an atomising nozzle into a collecting chamber. This also caused the production of drug-loaded wax particles. The drug release characteristics of the particles produced by both methods were found to be affected by drug loading, type of wax, type of surfactant, processing variables and size of particles produced. The mechanism of drug release was also found to vary depending on the nature of the particles produced, with dissolution control predominating for particles with a coating of drug and diffusion control predominating for particles in which drug was dispersed.

1.4.2   Ion-exchange Controlled Systems

The use of ion-exchange to control drug delivery has been reviewed by Amsel *et al* (62). Ion-exchange resins are water insoluble materials, usually polymers, which contain salt-forming groups in repeating positions on the resin chain. The functional group can be cationic (usually an amine) or anionic (usually a sulfonic or carboxylic moiety). A drug-loaded resin is prepared by exposing resin to concentrated drug solution, either by repeatedly loading a chromatography column with drug solution or simply by leaving the resin in contact with drug solution for extended periods of time. The drug-loaded resin is then washed and dried to form particles or beads. Thus appropriately charged ionic drugs bind to the functional

groups and when the resin is placed in a fresh ionic environment, eluting ions diffuse into the resin and an equilibrium is established in which drug ions are exchanged for eluting ions in solution. This situation can be described in the following manner: —

$$\text{Resin} - F^+Z^- \; + \; S^- \; \rightleftharpoons \; \text{Resin} - F^+S^- \; + \; Z^-$$

or

$$\text{Resin} - F^-Z^+ \; + \; S^+ \; \rightleftharpoons \; \text{Resin} - F^-S^+ \; + \; Z^+$$
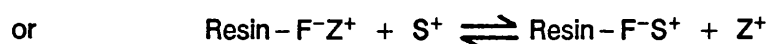
where F = functional group

Z = drug ion

S = eluting ion

The diffusion of drug ions from the resin will depend on the diffusional area and pathlength, and the amount of solvent within the resin. This will be influenced by the porosity of the resin, which in turn will be influenced by the size of the drug — loaded resin particles and the preparative conditions. Drug release from ion — exchange resins has also been modified by coating, in some cases by using the technique of microencapsulation as described above (section 1.4.1.1) (63, 64).

Ion — exchange resins have been used to prepare oral controlled delivery systems (65), but a possible disadvantage of their use is the potential variability in ionic content which might be expected to occur in the gastrointestinal tract due to differences in diet and fluid content. Also, the system is obviously limited to ionic drugs. Furthermore, in addition to the complex and time — consuming method of preparation of ion — exchange resins, it has been postulated (11) that the rate — controlling mechanism in drug release from uncoated resins is predominantly diffusion from the resin. It is therefore possible that such systems may offer no advantage over the more common matrix — type of diffusion controlled device described below (section 1.4.5.2), which also rely on this mechanism to control drug release but are generally simpler to prepare.

1.4.3 Osmotically Controlled Systems

The osmotically controlled drug delivery device is in principle a simple system which is capable of releasing drug at a zero-order rate and it was first described by Theeuwes (66). The system is fabricated by applying a rigid, semipermeable polymer membrane around a tablet core which includes drug and an osmotically active salt, or drug alone if it is itself sufficiently osmotically active. A single, microscopic orifice is made in the coat, and when the device is placed in an aqueous environment, water passes through the semipermeable membrane into the core, causing an osmotic pressure gradient to be established. Since the coat has been designed to be impermeable to drug solution, the pressure is reduced by drug solution being pumped out through the delivery orifice at a rate equal to the volume uptake of water. Thus, the drug delivery rate is controlled by the rate of water uptake, which is dependent on the osmotic pressure of the formulation. Theeuwes (66) used osmotic theory to derive the following equation to describe the drug delivery rate dQ/dt:—

$$dQ/dt = (a_m/l_m)k_f dP_O C_s \qquad \ldots\ldots\text{equation 1.7}$$

where k_f = constant

          a_m = membrane area

          l_m = membrane thickness

          dP_O = osmotic pressure of the formulation

In order to achieve a constant drug delivery rate, the hydrostatic pressure generated within the device must remain negligibly small compared to the osmotic pressure, and this can be achieved by using a delivery orifice which is larger than a minimum diameter. The orifice must not though be larger than a certain size in order to minimise the contribution to the delivery rate made by drug diffusion through the orifice. Theeuwes (66) derived equations to determine the minimum and

maximum sizes of orifice for a formulation.

Theory predicts that zero – order drug release will be maintained until the concentration of drug solution in the device falls below the drug's saturation solubility, whereafter a parabolically decreasing drug release rate will occur. Drug release rates determined experimentally *in vitro* have shown that the theoretical release profile is achieved (67, 68), with zero – order drug release occurring for approximately 70% of the total content of the device. Since drug delivery rate is controlled by rate of water uptake, the permeability to water of the material selected as the semipermeable membrane will be a rate – controlling factor in drug release, and many polymers with different water – permeabilities are available to design a system with a suitable drug release rate (11). Some examples and their water permeabilities are given below: –

Semipermeable membrane	Water permeability $(g\ cm^{-2}\ hr^{-1}\ mm^{-1})$
Polyethylene	0.134 – 0.323
Polyesters	0.538
Polycarbonate	2.15
Polyvinyl chloride, cast	2.69 – 5.38
Cellulose acetate butyrate	13.4
Polyurethane	8.07 – 40.3
Cellulose acetate	10.7 – 20.1

Many semipermeable membranes are applied by organic film coating techniques, which suffer from the disadvantages associated with the use of solvents on a large scale. Bindschaedler *et al* (69) produced osmotically controlled tablets using cellulose acetate as the semipermeable membrane, which was applied as an aqueous dispersion instead of an organic solution.

The osmotic controlled device has several potential advantages when considered for oral use. Firstly, it delivers drug at zero – order rates which can be higher

than those which are achieved with reservoir or matrix-type devices (sections 1.4.5.1 and 1.4.5.2 below respectively), and therefore higher doses can be accommodated. Secondly, drug release from the device is unlikely to be affected by conditions within the gastrointestinal tract such as variability in stationary diffusion layer thicknesses caused by differing intestinal motility, or pH variation (70). Unfortunately, the first clinically used commercial osmotic device, "Osmosin", had to be withdrawn from the market because the incidence of severe gastrointestinal toxicity due to its use was found to be increased compared to treatment with conventional dosage forms of the same drug, indomethacin (71). Subsequently the system has been used to deliver salbutamol without such side-effects being reported so far.

A more complex osmotically-driven pump system termed the generic osmotic pump has been developed to deliver liquids, solutions and suspensions of drug (72). This system consists of a drug reservoir which is separated by a flexible membrane from a compartment containing an osmotically active salt. A semipermeable membrane surrounds this compartment, which imbibes water along the osmotic pressure gradient. The influx of water compresses the flexible membrane, causing drug solution to be pumped out of the delivery orifice. A flow moderator is placed into the delivery orifice after filling: this device restricts diffusional and convective losses from the device so that the osmotic process controls the drug delivery rate. The system has been widely used as a research tool in pharmacology, since the devices are capable of delivering drug for several weeks when implanted into laboratory animals (72) and are re-usable. Several studies have reported the modification of the system to oral drug delivery requirements of shorter release periods (16, 73, 74) although the devices have the disadvantage that they are more complex than the elementary osmotic pump and therefore have only been used as simulators of the latter during pharmacokinetic studies (74).

1.4.4 Methods of Prolonging Gastric Residence Time

As discussed above (Section 1.3.1), total gastrointestinal transit time has been found to have wide inter- and intrasubject variation, with gastric residence time of oral controlled delivery systems varying from a few minutes to ten hours. Combined with the observation that small intestinal transit time is relatively constant and short at approximately three hours (17), and the fact that many drugs appear to be absorbed best in that portion of the tract, this has led to much research interest in attempting to prolong the gastric residence time of controlled delivery dosage forms. The objective of such research is to ensure that drug is only released from the device in the stomach, and is then passed to the small intestine in solution where it can be absorbed. There have been several approaches to allow these aims to be achieved, one utilising materials termed mucoadhesives which adhere to the wall of the stomach, and another in which the density of formulations is manipulated so that the delivery systems float on the gastric contents. Other approaches have included using pellets with high density, and administering dosage forms with saturated fat (75) to inhibit gastric motility.

1.4.4.1 Methods using Mucoadhesion

The term bioadhesion can be used to describe any form of adhesion to biological surfaces, whereas the term mucoadhesion is used specifically to describe reversible adhesion to mucous membranes (75). However, in the literature concerning the applicability of various adhesive systems to controlled drug delivery the terms have been used interchangeably. The principles of the use of mucoadhesion in controlled drug delivery have been reviewed recently (75, 76). Since adhesion is required to be reversible, the bonding forces are weak in nature, for example hydrogen bonds or van der Waals forces. Hence mucoadhesive materials for controlled drug delivery must be capable of both bonding the delivery system to the mucous membranes and of releasing drug at the required rate.

The gastrointestinal mucosa secretes a gel termed mucus which is highly

viscous and whose physiological function is to protect the mucosal cells from damage. The principal component of mucus, apart from water, is a glycoprotein with a high molecular weight (approximately 2×10^6 daltons), and which causes a gel structure to form due to intermolecular associations, the exact nature of which is unclear (75). Several polymeric materials have been studied as potential mucoadhesives for use in controlled delivery systems (76 – 83), and the conclusions which have been drawn regarding the ideal properties of such polymers are as follows. Firstly, the polymer should possess strong hydrogen – bonding groups such as hydroxyl or carboxyl functions; secondly, it should be anionic in nature; thirdly, the polymer should be sufficiently flexible to penetrate the mucus gel structure; fourthly, it should have surface tension characteristics suitable for wetting mucus and/or mucosal tissue and lastly it should have a high molecular weight. Polymers which have been found to best satisfy these requirements include sodium carboxymethylcellulose, polyacrylic acid and hydroxypropyl cellulose, although many others have been investigated (75).

Several techniques have been used to study the phenomenon of mucoadhesion and the adhesive strength of polymers to mucosa. Gurny *et al* (84) used a system involving the separation of two perspex discs which had mucoadhesive material placed between them. Stress was recorded as a function of elongation of the material using a tensile tester. Smart *et al* (85) used a technique based on the Wilhelmy plate method of measuring surface tension. A thin glass plate coated with the polymer was dipped into a preparation of purified mucin and removed slowly at a constant rate. The force exerted on the plate was measured with a microforce balance and compared to the force exerted on an uncoated glass plate. Park and Robinson (78) used a technique which examined the change in fluorescence of a probe molecule attached to the lipid bilayer of the cell wall of a mucous membrane caused by the compression of the bilayer when mucoadhesion to the membrane occurred. The same authors (81) also developed a tensiometer method to measure the force required to remove a mucoadhesive polymer from a section of rabbit stomach mucosa. More

recently Ponchel et al (86 - 88) have used a similar method to study mucoadhesion to bovine sublingual mucosa.

Oral controlled drug delivery systems based on mucoadhesive polymers have been investigated for the release of chlorothiazide and metronidazole (80, 88). The chlorothiazide delivery system, a multiparticulate dosage form based on polyacrylic acid, was found to release drug in vitro over a period of approximately eight hours. Gastrointestinal transit was investigated in rats, and it was found that 90% of the particles remained in the stomach six hours after ingestion. In addition, bioavailability of the drug was almost doubled compared with a non-mucoadhesive control formulation. The metronidazole mucoadhesive system, also based on polyacrylic acid, was found to be capable of delivering drug in vitro over a period of eight hours, but no in vivo studies were performed. The technique of gamma scintigraphy described above (section 1.3.1) has been used recently to investigate the gastrointestinal transit of a mucoadhesive dosage form in humans (89). A multiparticulate dosage form again based on polyacrylic acid was used, but the gastric emptying of the particles was found to be no different from control particles which did not contain mucoadhesive. Clearly, more research needs to be performed to demonstrate clearly whether mucoadhesive systems can achieve clinically their intended function of prolonged gastric residence.

1.4.4.2 Methods using Altered Density of Formulations

The density of particles has been reported to affect their gastrointestinal transit (90), with an increase in relative density from 1.0 to 1.6 resulting in an increase in mean gastrointestinal transit time from 7 to 25 hours. These results were obtained in ileostomy patients and further studies (91) were unable to repeat the findings in patients with normal gastrointestinal tracts. An alternative approach is to prepare dosage forms with a relative density of less than 1 which float on the stomach contents. This has been accomplished using hydrophilic polymers which form gels and swell on contact with water. Sheth and Toussounian

(92) described a device which they termed a hydrodynamically balanced system consisting of a capsule of a gel-forming hydrocolloid. Drug dissolved on hydration of the hydrocolloid and then diffused through it before being released from the surface of the swollen gel. Stockwell *et al* (93) investigated alginate gel formulations which included sodium bicarbonate, the intention being that the effervescent release of carbon dioxide which occurred on contact of the formulation with gastric fluid would become entrapped in the gel network producing a buoyant system. This concept was carried further by Ingani *et al* (94), who produced both tableted and encapsulated floating dosage forms and compared the bioavailability *in vivo* of a riboflavin derivative as determined by urinary excretion of a metabolite with that from a non-floating controlled release dosage form. It was found that the bioavailability of the floating dosage forms was increased compared to the standard controlled release dosage form, and it was concluded from this indirect evidence that gastric retention time of the floating dosage forms was increased compared to the standard formulation. Park (95) synthesised swelling polymers which increased in mass several hundred times on gelation, and which were digestible by enzymes present in the gastrointestinal tract. The intention was that the dosage form would swell to such a degree that it could not be passed through the pylorus to the small intestine, but that once drug delivery was complete, the gel would be broken down by enzymatic activity. This would eliminate any possibility of the gastrointestinal tract becoming blocked by the dosage form.

A gamma scintigraphy study of the gastrointestinal transit of floating dosage forms (96) yielded results which indicated that there was no difference in gastric emptying time between a floating dosage form and a non-floating, non-disintegrating tablet. This may be due to an inherent disadvantage of the system, which is that for such a dosage form to float on the stomach contents, the stomach must contain fluid over the period during which drug is released. This requirement would not be satisfied if the dosage form was administered on an empty stomach, and even if taken after food and/or fluid, may require the repeated ingestion of further fluid.

This would obviously be inconvenient for the patient, with non-compliance possibly rendering the system inefficient.

1.4.5 Diffusion Controlled Systems

Diffusion controlled devices constitute the most widely investigated systems for the controlled delivery of drugs. There are two principal classes of diffusion controlled device, reservoir devices and monolithic devices. Monolithic devices can be further subdivided into dissolved systems, dispersed systems, inert porous systems and hydrophilic swelling systems. Polymers have been widely used in the manufacture of these types of device, and thus diffusion of drugs in polymers has been a subject of wide research interest (97 - 99)

1.4.5.1 Diffusion Controlled Reservoir Systems

Diffusion is the process by which a concentration difference of a molecular species across a volume is reduced by the flow of material from a region of high concentration to a region of low concentration. This process is described by Fick's first law of diffusion described above (equation 1.1). If steady-state conditions are assumed, equation 1.1 can be integrated to give the following equation:-

$$ J = -D_i (\Delta C/l_c) \qquad \text{.....equation 1.8}$$

where ΔC = concentration gradient

l_c = distance over which the concentration gradient exists

A diffusion controlled reservoir device consists essentially of a core of drug surrounded by a water-insoluble coat through which drug must diffuse. The rate of drug release is given by a modified form of equation 1.8:-

$$ dQ/dt = a_m D_i K \Delta C/l_c \qquad \text{.....equation 1.9}$$

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

In this case, l_c is the diffusional pathlength, which in ideal conditions can be assumed to be the thickness of the membrane, and ΔC is the concentration difference across the membrane. In order for zero-order drug release to be achieved from a reservoir device, examination of equation 1.9 shows that the surface area, diffusional pathlength, concentration difference, diffusion coefficient and partition coefficient must remain constant. In some reservoir devices this may not be possible, and zero-order release is not achieved. Also, it is possible that *in vivo* an unstirred boundary layer of release medium may exist immediately adjacent to the membrane. This situation has been analysed by Baker and Lonsdale (100), who proposed the following equation to describe the situation:-

$$Q = \frac{C_s K D_m D_b t}{(K D_m l_m + D_b l_b)} \qquad .....equation\ 1.10$$

where   Q   = cumulative amount of drug released at time t per unit of surface area

D_m = diffusion coefficient of the drug in the membrane

D_b = diffusion coefficient of the drug in the boundary layer

l_b = thickness of the boundary layer

The evaluation of polymers as potential reservoir device coating materials has been the subject of numerous investigations. The diffusion of various model drugs in films of ethylcellulose was studied by Donbrow *et al* (101, 102). Polymer films were prepared by the solvent casting method, which involved dissolving the powdered polymer and drug in a suitable organic solvent and evaporating the solvent from the solution. Drug release from the films was found to be controlled by diffusion. Similar results were obtained by Adel El Egakey and Speiser (103), who studied the release of model drugs from cast films of a series of poly(alkyl)cyanoacrylates,

which have the added advantage of being biodegradable. The methyl– and ethyl– substituted polymers were found to release drug over periods potentially useful for oral controlled delivery devices. Borodkin and Tucker (104) prepared films cast from varying proportions of a hydrophobic polymer, polyvinyl acetate and a hydrophilic additive, hydroxypropyl cellulose. Drug release rates were found to increase with increasing proportion of hydroxypropyl cellulose.

Although studies of polymer permeability to drugs are of vital importance to the design of controlled delivery devices, the drug release kinetics of true reservoir devices are not modelled by release from drug–loaded cast films, since no drug reservoir is present. Borodkin and Tucker (105) extended their study of polyvinyl acetate–hydroxypropyl cellulose to the reservoir situation by laminating a film which did not contain drug to a drug–loaded film. The latter acted as a drug reservoir, and the former as the rate–controlling membrane, and zero–order drug release was observed. Li and Peck (106 – 108) studied films of silicone elastomer modified with polyethylene glycols. They prepared coated tablets using chlorpheniramine maleate as a model drug (108) and measured drug release rates, which were found to be zero–order and which increased with increasing proportion of polyethylene glycol in the film. It was hypothesised that this additive, because of its water–solubility, was leached from the membrane coat, leaving water–filled channels through which drug diffused from the core. Similar conclusions were reached by Ritschel and Udeshi (109) after studies on tablets coated with a methacrylate polymer which included dextrose as a water–soluble additive in the coat, although zero–order release was also obtained without including dextrose.

Multiparticulate reservoir systems have also been investigated as oral controlled drug delivery systems. The technique of microencapsulation by coacervation discussed above (section 1.4.1.1) was used to prepare coated microcapsules of clofibrate (110). Drug release was found to decrease with increasing coating membrane thickness, as predicted by equations 1.9 and 1.10. The Wurster air–suspension coating technique was used to coat particles of aspirin with

a mixture of ethylcellulose and methylcellulose (111, 112). Drug release was found

to be affected by the ratio of methylcellulose to ethylcellulose, with rates

increasing with increasing methylcellulose content. This was hypothesised to be due

to the methylcellulose dissolving in the dissolution medium and leaving water –

filled pores in the ethylcellulose coat for drug to diffuse through. An acrylic

polymer was investigated as a coating material for a multiparticulate system, and

was applied in a fluidised bed granulator (113). It was concluded that diffusion

through water – filled pores was the rate – controlling mechanism of drug release in

this case also.

One of the problems associated with the use of reservoir devices is that zero –

order drug release can only be maintained if the concentration of drug in the core

reservoir is maintained constant. As drug is depleted from the core, this condition

may not be met and the release rate may therefore decrease with time. With

reservoir systems for long term drug administration it may be possible to maintain

constant concentration in the core for the majority of the drug release period by

preparing the core as a highly saturated solution of drug. The problem of

maintaining the same concentration gradient in an oral system was overcome by

Laghoueg *et al* (114) who utilised a slowly dissolving coating material consisting

of a mixture of polyglyceride fatty esters. As the drug reservoir became depleted,

the coating membrane was synchronously eroded, effectively becoming thinner and

presenting less diffusion resistance. By selection of a suitable initial coat

thickness, it was found that zero – order release was possible for up to

approximately 70% of the total amount of drug released. A further problem which may

be encountered with reservoir devices is the phenomenon of dose – dumping, which

occurs if the rate – controlling membrane fails to function correctly, leading to the

immediate or inappropriately rapid release of the entire dose. This could occur

with an oral device if it was crushed or chewed before it was ingested. Since oral

controlled delivery devices generally carry a greater drug load than their

conventional counterparts, this could result in an overdose.

1.4.5.2 Diffusion Controlled Matrix Systems

Matrix systems have been widely used as controlled drug delivery systems and earlier systems have been reviewed by Cardinal (115, 116). The theoretical treatment of drug release from such devices depends on such factors as the solubility of the drug in the matrix material, its concentration in the device, the method of manufacture and the choice of matrix material. Depending on how these parameters are manipulated, matrix systems can be classified into one of four different types. If the matrix material does not interact with the dissolution medium, the drug is soluble in the matrix material and present at a concentration in the device below its solubility, then the system is termed a dissolved system, and drug is released from the device by diffusion through the matrix material itself. If in a similar device, the drug is present at a concentration greater than its solubility in the matrix material, the system is termed a dispersed system, and only dissolved drug diffuses through the matrix material. As drug is removed the concentration of drug in the device decreases, and dispersed drug is able to dissolve and diffuse out. A third type of system occurs where the drug is present at a concentration above its solubility in the matrix material, but where the dissolution medium is able to enter through pores in the matrix. Drug dissolves in the dissolution medium and diffuses out of the device through the liquid-filled pores. This type of system is termed a porous device. A fourth class of system is where the matrix material interacts with the dissolution medium, usually by hydration, becoming swollen and forming a gelled system in which drug can dissolve and diffuse out. These devices are usually termed hydrophilic matrices.

The first classes of matrix to be subjected to investigation from the pharmaceutical standpoint were the dissolved, dispersed and porous systems. These were first analysed by W. I. Higuchi and T. Higuchi who extended work concerned with drug delivery from ointments (117 - 120) to dispersed and porous matrices (121). The case of the dissolved system had already been treated by Barrer (122), who proposed the following equation describing drug release from a planar surface:-

$$Q = hC_0[1 - (8/\pi)\Sigma^{\infty}_{m=0} \; 1/(2m + 1)^2 \exp\{-D_M(2m + 1)^2\pi^2t/4h^2\}] \quad \ldots\ldots\text{equation 1.11}$$

where   h   =   thickness of the device

         D_M =   diffusion coefficient of drug in the matrix material

         m   =   an integer between 0 and ∞

When the percentage of the drug load released from a dissolved matrix system is less than approximately 30%, the following simplified form of equation 1.11 was proposed:-

$$Q = 2C_0(D_Mt/\pi)^{\frac{1}{2}} \qquad\qquad \ldots\ldots\text{equation 1.12}$$

Higuchi (119) proposed a moving boundary model to describe drug release from a dispersed matrix system, where the amount of drug present per unit volume of matrix is substantially greater than the solubility of the drug in the matrix material. He postulated that drug was first removed from the surface layer of the matrix; after this layer had been depleted to the saturation level, removal was initiated at the next layer, leading to a concentration discontinuity at a boundary. This model is based on the so-called pseudo steady-state assumption, that the concentration profile in the extracted region is always at steady state with respect to the movement of the extraction boundary. This implies that the rate of movement of the extraction front must be much slower than the rate of removal of drug from the device. The model is therefore restricted to devices where the drug loading A is greater than solubility of drug in the matrix C_d by a factor of approximately 3. The second assumption is that the dissolution of the drug in the matrix material does not influence the rate of release i.e. release is diffusion controlled with dissolution being relatively rapid. Finally, it is assumed that the medium to which drug is delivered acts as a perfect sink.

Figure 1.1 is a representation of a concentration profile existing after a

time t in such a system. The solid line in the diagram represents the concentration gradient in the system normal to the surface of the matrix. The concentration gradient shows a sharp discontinuity at a distance h from the surface. The gradient to h from the surface is constant, which follows only if A is significantly greater than C_d, as in the diagram. This linearity follows from Fick's first law of diffusion described above (equation 1.1). The change in concentration gradient after a time δt is depicted as a dotted line, and corresponds to the extension of the depleted zone by a distance δh. Based on this diagram, the amount dQ depleted by the movement of the front by dh is given by the following equation:-

$$dQ = Adh - \tfrac{1}{2}C_d dh \qquad \text{.....equation 1.13}$$

According to Fick's first law of diffusion:-

$$dQ/dt = D_M C_d / h \qquad \text{.....equation 1.14}$$

Combining equations 1.13 and 1.14 results in:-

$$Adh/dt - \tfrac{1}{2}C_d dh/dt = D_M C_d / h \qquad \text{.....equation 1.15}$$

Equation 1.15 can be rearranged to give:-

$$\{(2A - C_d)h/2D_M C_d\}dh = dt \qquad \text{.....equation 1.16}$$

Both sides of equation 1.16 can be integrated to give:-

$$t = (2A - C_d)(h^2/4D_M C_d) + K_I \qquad \text{.....equation 1.17}$$

where $\quad K_I$ = integration constant
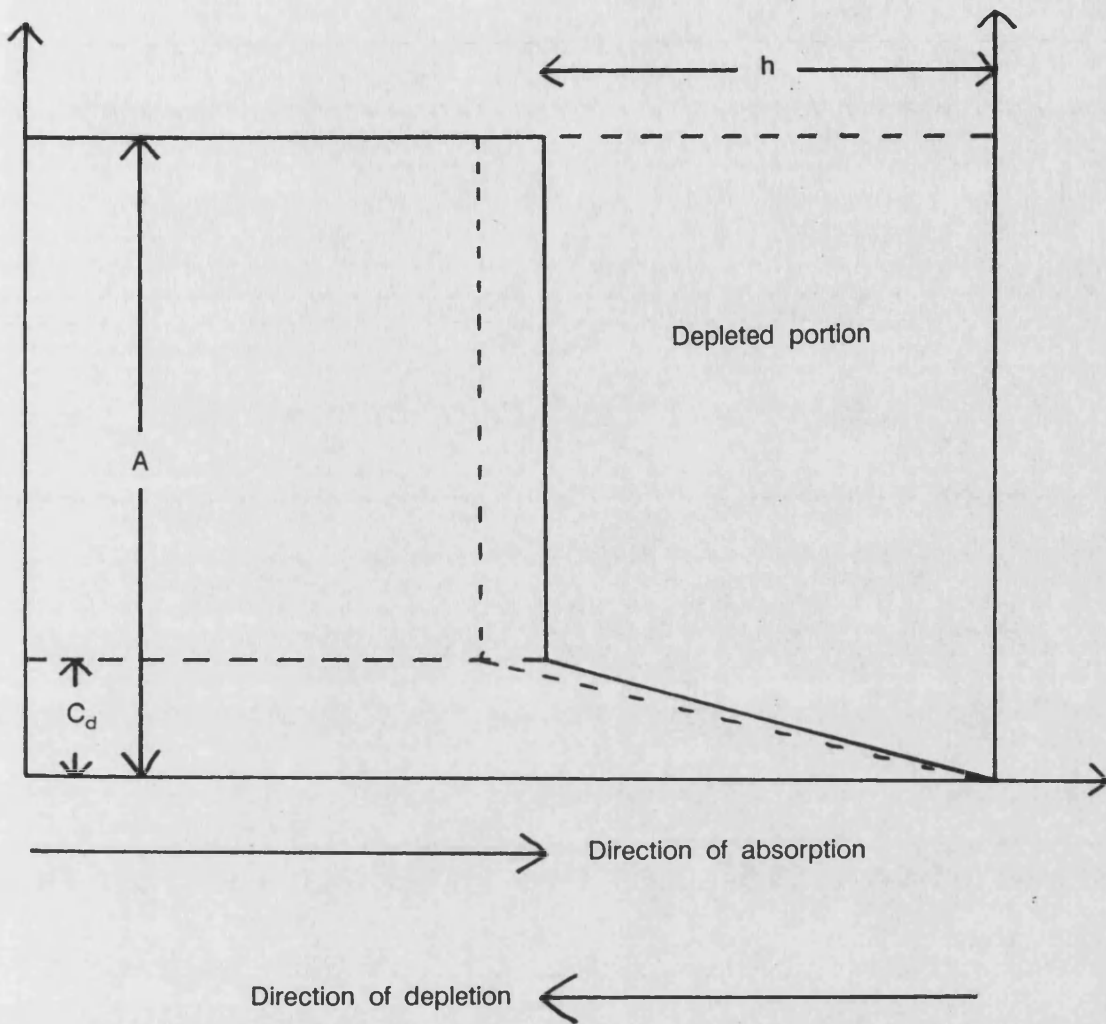
Figure 1.1   Concentration profile existing at time t in a dispersed matrix

The constant K_I equals 0 when t Is measured from 0, therefore:-

$$t = (2A - C_d)(h^2/4D_MC_d) \qquad \ldots\text{equation 1.18}$$

Equation 1.18 can be rearranged to make h the subject:-

$$h = 2\{(D_MC_dt)/(2A - C_d)\}^{\frac{1}{2}} \qquad \ldots\text{equation 1.19}$$

From the diagram it can be seen that the amount of depletion Q at time t is:-

$$Q = hA - hC_d/2 \qquad \ldots\text{equation 1.20}$$

Substitution of equation 1.19 in equation 1.20 gives:-

$$Q = (A - C_d/2)2\{(D_MC_dt)/(2A - C_d)\}^{\frac{1}{2}} \qquad \ldots\text{equation 1.21}$$

Rearrangement of equation 1.21 gives the following equation:-

$$Q = \{D_MC_d(2A - C_d)t\}^{\frac{1}{2}} \qquad \ldots\text{equation 1.22}$$

This is one form of the relationship which has become known as the Higuchi equation. It is evident that a plot of amount of drug released versus time will not be linear and hence zero-order, but a linear relationship will exist between amount released and the square root of time. The relationship can be simplified in the case where A » C_d to give the following equation:-

$$Q = (2AD_MC_dt)^{\frac{1}{2}} \qquad \ldots\text{equation 1.23}$$

The Higuchi pseudo steady-state analysis only applies to unidimensional

diffusion from a single planar surface. Baker and Lonsdale (100) extended the analysis to three dimensions for devices of cylindrical geometry and also analysed the case of spherical geometry. As described immediately above, because of the pseudo steady-state assumption, the Higuchi analysis is restricted to cases where the drug loading A is greater than the solubility C_d by a factor of approximately 3. As A tends to the value of C_d, the model becomes more approximate, and an exact analysis by Paul and McSpadden (123) which did not make the pseudo steady-state assumption has been proposed for all values of A greater than C_d. This analysis was simplified by Lee (124) in a model which results only in small errors as A tends to C_d.

As discussed above (section 1.4.5.1), a factor which cannot be influenced by the characteristics of a controlled delivery device, but which may have a considerable influence on the release rate from it, is the possible existence *in vivo* of a hydrodynamic diffusion boundary layer at the releasing surface. The boundary layer acts as an extra diffusional resistance and restricts transport of drug from the surface of the device. The models described so far have not included the influence of such a layer, each one assumes that the drug is released into a well-agitated sink. Roseman and Higuchi (35) extended the pseudo steady-state model to include the effects of a boundary layer on a planar device, and also examined the case of a device with cylindrical geometry. Paul and McSpadden (123) also extended their exact model to include boundary layer effects.

Higuchi (121) extended the pseudo steady-state moving boundary analysis for dispersed systems to porous matrix devices, and proposed the following equation:-

$$Q = D\in/\tau(2A - \in C_s)C_s t^{\frac{1}{2}}$$

.....equation 1.24

where $\in$ = porosity of the matrix after leaching of drug

τ = tortuosity factor

D = diffusion coefficient of drug in dissolution medium

Equation 1.24 can be reduced to the following form: –

$$Q = k_H t^{\frac{1}{2}}$$ .....equation 1.25

where k_H = Higuchi constant

It can be seen that equations 1.24 and 1.25 are analagous to equation 1.22, which is the Higuchi equation for drug release from dispersed matrices. In the modified form applicable to porous matrices, the diffusion coefficient of the drug is altered from that in the matrix material to that in the dissolution medium. It is then further modified by multiplying it by the porosity (or volume fraction) of the leached matrix and dividing by a correction factor, tortuosity, to account for the increased diffusional pathlength caused by the heterogeneous nature of the pore structure. Tortuosity is hence defined as the ratio of the length of the average diffusional path to the thickness of the device, and according to Higuchi could be expected to be of the order of 2 – 3 (121). The same model was also used by Higuchi (121) to describe drug release from porous spherical matrices and Roseman and Higuchi (35) applied the model to cylindrical porous matrices. Cobby et al (125, 126) derived a cubic equation in t which utilised k_H and various adjustable parameters to allow it to be applied to different geometrical shapes: –

$$f_t = G_1 K_r t^{\frac{1}{2}} + G_2 (K_r t^{\frac{1}{2}})^2 + G_3 (K_r t^{\frac{1}{2}})^3$$ .....equation 1.26

where f_t = fraction of the drug load released at time t

G_{1-3} = constants dependent on the geometry of the device (125)

K_r = $1/Aa_d K_H^{\frac{1}{2}}$ where a_d is the radius of the device (sphere, cylinder)

More recently, Peppas and co–workers (127 – 130) proposed a simple exponential relationship to describe drug release from controlled release devices of various

geometrical shapes and regardless of drug release mechanism:−

$$f_t = k_e t^n \qquad \qquad .....\text{equation 1.27}$$

where $\quad k_e$ = constant

$\qquad \quad$ n = exponent which is characteristic of the release mechanism and device geometry

The equation is valid for values of f_t up to 0.6. For porous matrices where Fickian diffusion is the rate−controlling mechanism, it is evident from comparison with equation 1.25 that k_e equals the Higuchi constant k_H. It also follows that the exponent n for a planar surface equals 0.5, and for cylinders and spheres Ritger and Peppas (130) showed n to equal 0.45 and 0.43 respectively.

Fessi *et al* (131) examined the case of a porous matrix where the drug concentration A is less than $\in C_s$. Again assuming pseudo steady−state conditions they proposed the following equation:−

$$Q = A(Dt)^{\frac{1}{2}} \qquad \qquad .....\text{equation 1.28}$$

Equation 1.28 predicts that in this case drug release is independent of solubility and porosity, but that it is still dependent on the square-root of time. An alternative approach has been taken by Miller and Peppas (132), who treated cases where values of A were both greater than and less than C_s with an approach which did not require the pseudo steady−state assumption.

Although of little relevance to oral delivery systems at present, Langer (133) has described the use of porous polymers for the delivery of macromolecules where drug release does not conform to square-root of time kinetics. Peppas and co−workers (134, 135) have developed a dissolution−diffusion model to account for the zero−order release kinetics observed with these systems.

A complete analysis of diffusion in a particular porous system would require the exact mathematical description of the pore space, which would require precise knowledge of its structure, which in turn is unlikely. Rowe *et al* (136) proposed a model in which instead of modifying the diffusion coefficient with porosity and tortuosity factors as in the Higuchi equation (equation 1.24), the pore structure of the matrix was taken into account in the following manner. A bimodal model pore structure was assumed, with the length and radius of one pore taken to be the mean diameter and radius respectively of the drug particles and those of a second pore taken as the mean distance between drug particles in the matrix and the mean pore diameter as determined by mercury porosimetry. Experimentally determined drug release rates agreed reasonably with rates predicted using this model. More recently, mathematical simulations based on a probabilistic approach to diffusion, the so-called "random walk" interpretation of diffusion (137) have been proposed. These have included the application of percolation theory to drug release from porous matrices (138) and also a stochastic approach based on a mathematical technique termed "Monte Carlo" simulations of pore structure (137).

The remaining class of monolithic diffusion controlled systems is termed the hydrophilic matrix. Roorda *et al* (139) have reviewed the properties and use of hydrophilic polymers as matrix systems. The interaction of certain polymers termed hydrogels with water is used as the basis for the system. If a glassy polymer is thermodynamically compatible with water, on hydration the polymer's glass transition temperature may be lowered below the ambient temperature. The polymer subsequently undergoes a transition to a rubbery, gel state during which the volume of the polymer increases. In this swollen gel state, the polymer chains are more mobile than in the glassy state and allow the drug to diffuse out of the device through the gel region. Lapidus and Lordi (140, 141) utilised hydroxypropylmethylcellulose as a hydrophilic polymer and prepared compressed tablets containing this material and a model drug. Sustained drug release over several hours was achieved and drug release was found to be linear with square-root

of time. The authors therefore concluded that the rate-controlling mechanism was diffusion, and that the system was analogous to a non-swelling porous matrix. Further investigation of the rate-controlling mechanism in hydrophilic matrices was performed by Bamba *et al* (142), who found that drug release was controlled by the rate of water penetration and the rate of diffusion of the drug through the swollen gel. Square-root of time kinetics were also found with the various natural polymers used in this study. As further research was performed on hydrophilic matrices 'by other workers (e.g. 143), it became clear that square root of time kinetics were not always followed, with approximately zero-order kinetics observed for a system consisting of a copolymer of 2-hydroxyethylmethacrylate and N-vinyl-2-pyrrolidone. A distinction emerged between two different rate-controlling mechanisms, depending on the properties of the particular polymer chosen. This was described by Peppas (144), who attributed the zero-order kinetics to a non-Fickian transport phenomenon. The release process was envisaged as progressing in the following manner. As water enters the glassy polymer, an interface separating the swollen gel region from the glassy core develops and moves into the matrix as gelatinisation proceeds. Release occurs by diffusion from the the gel region; however, the diffusivity is governed by the "macromolecular relaxation" phenomenon of the polymer chains in this region and is not dependent solely on the concentration gradient. Depending on the rate of polymer relaxation at the interface, the drug release behaviour may either be Fickian or described as Case-II. If the rate of relaxation is very slow compared to the rate of drug diffusion then the rate of relaxation controls the release and a time-independent, Case-II drug release process occurs. This type of system is usually termed a swelling-controlled system, as opposed to the swollen, diffusion controlled system described immediately above. However, drug release behaviour from some polymers may not accord with either of these two extremes (145), with both Fickian and and Case-II transport occurring synchronously, such transport being described as anomalous. The approach of Peppas described above to the analysis of drug release from polymers, where equation 1.27

was used to indicate the release mechanism, has also been applied to hydrophilic matrices (145 – 147). If the exponent n in equation 1.27 equals 0.5, then the release mechanism is considered to be Fickian diffusion. In cases where the exponent equals 1 then Case – II transport is considered to occur and the system is swelling controlled. A value of n between 0.5 and 1 indicates anomalous transport. Fan and Singh (137) recently reviewed the more fundamental models which have been proposed to describe drug release from hydrogels.

Numerous polymers have been investigated for use as hydrophilic matrices, and many studies using them as oral controlled delivery systems have been published. Amongst the first were investigations of sodium carboxymethylcellulose, hydroxypropylmethylcellulose and carboxypolymethylene (148, 149). Different release kinetics ranging from first– to zero–order were observed for the different polymers. Hydroxypropylmethylcellulose was further investigated by Ford *et al* (150), who examined the effect of various formulation factors on drug release from matrices prepared with this material. Drug solubility was found to have an effect on drug release mechanism, with anomalous diffusion predominating for drugs of medium to high water solubility. Relatively insoluble drugs were found to undergo largely Case – II transport, with near zero – order release profiles. Both soluble and insoluble tableting diluents were found to increase drug release rate only when included at high initial concentrations in a formulation. A linear relationship was found to exist between release rate and initial tablet surface area. Other materials including hydroxypropyl cellulose (151), α–starch (152), some modified starches (153) and various natural gums such as carrageenan, locust bean gum, guar gum, gum tragacanth and sodium alginate (154) , have also been investigated as hydrophilic matrices for use in oral controlled drug delivery. Zero–order drug release was found when an anionic polymer such as sodium carboxymethylcellulose and the non–ionic hydroxypropylmethylcellulose were mixed in certain ratios and with certain drug loadings (155 – 157). A further phenomenon exhibited by swelling polymers was discussed and modelled by Lee and Peppas (158). This was the

dissolution of some polymers after the swelling process was complete. This phenomenon could be made use of in oral delivery systems, since a device which is bioerodible after it has delivered drug cannot lodge in the gastrointestinal tract.

Shah *et al* (159) found that some grades of hydroxypropylmethylcellulose appeared to dissolve after swelling, causing a sigmoidal drug release pattern with the latter portion of release being faster than the earlier portion. An interesting but rather complex approach to obtaining zero-order release from hydrogel matrices was proposed by Kuu and Yalkowsky (160). A water- and drug-impermeable membrane was laminated to a diffusion controlled, hydrophilic, swollen-type matrix, and several hemispherical cavities were made in the surface of the device. The number, size and arrangement of the cavities was discussed and an optimum arrangement for zero-order drug release was predicted. Pywell and Collett (161, 162) extended the analysis to the practically simpler case of planar holes in the membrane and predicted that zero-order release would not be achieved. *In vitro* drug release studies from such devices showed that zero-order drug release was achieved, and a modified model was proposed.

1.4.5.2.1 Porous Matrix Systems

Both porous and hydrophilic matrix systems have been widely used as oral controlled delivery devices. Since the work to be described in subsequent chapters is concerned with porous matrices, the properties and use of these types of device will be reviewed here.

Subsequent to the original work concerned with the proposal of the Higuchi equation (121), Higuchi and co-workers in a series of papers (163 - 167) attempted to validate the equation by measuring each of the variables in the equation and assessing their effect on *in vitro* drug release rates. They studied the release of various drugs from single faces of matrices containing polyethylene and polyvinyl chloride. Drug release was found to be proportional to the square root of time from polyethylene matrices, but a sigmoidal shaped curve was obtained with polyvinyl

chloride matrices. This latter result was attributed to the incomplete removal of air from the matrices during the release process. The effect of increasing initial drug concentration, and of increasing drug solubility, was in both cases found to cause an increase in drug release rate. The increases in drug release rate were not however found to be directly proportional to the increases in drug concentration and solubility, and it was concluded that tortuosity was also affected. The tortuosity factors determined from slopes of release data and from an independent technique were generally less than 10, except for sulphanilamide release into water from polyethylene matrices, where slightly sigmoidal release profiles were obtained and tortuosity factors several orders of magnitude greater were found. This was also hypothesised to be due to the incomplete removal of air from the matrix due to the low wettability of polyethylene. Drug release studies from the same matrices in surfactant solutions yielded tortuosity values of less than 10, which was considered to support this hypothesis. Further evidence was provided by an experiment in which the air in a sulphanilamide – loaded polyethylene matrix was evacuated and water allowed to enter the matrix under the pressure difference caused by the vacuum in the pores. Drug release into water from such a matrix was found to be linear with square-root of time and tortuosity values of less than 3 were obtained. It was concluded from these results that in practice, matrix tablets may not always conform to the Higuchi model, since it effectively assumes a totally interconnected pore structure within the matrix which is immediately wetted by dissolution medium. Further studies (168 – 171) on the release of mixtures of non – interacting and mutually interacting drugs, and of acidic and amphoteric drugs into various media, were also performed to extend the Higuchi equation to a wider range of practical situations.

In addition to the plastic materials used in the studies described, Higuchi and co – workers also investigated the use of waxes as matrix materials (172). A matrix composed of equal parts of propylene glycol monostearate and hydrogenated castor oil was prepared by suspending or dissolving drug in the molten wax mixture,

which was then cooled whilst being stirred. The solidified mixture was granulated and compressed into tablets. Drug release was found to be linear with square–root of time, but the data was also found to fit a first–order model. A data analysis technique to determine which model was appropriate was developed which involved evaluating the change in drug release rate with amount released, and the square–root of time, diffusion controlled model was found to be the model which was applicable to the data obtained. A further study (173) using the same wax matrix but using sulphanilamide as the drug was conducted to investigate the system mentioned above where tortuosity factors of the order of 1000 had been found. It was hypothesised that at low drug concentrations, drug diffusion out of the pores which had been created by dissolving drug was a limiting factor in drug release, due to the low incidence of interconnecting pores. An equation for $\bar{z}$ the determination of permeability in two–phase systems, the Bruggeman equation, was used to analyse the results, with the pores due to dissolved drug being regarded as one phase and the interconnecting pores as the other phase. Reasonable agreement between theory and experimental results was found.

Goodhart *et al* (174) investigated release of phenylpropanolamine hydrochloride from wax matrix tablets prepared from a granulation, but no details of the wax, diluent or the method of granulation were given. Drug release was found to be linear with square–root of time. Penetration of dissolution fluid into the matrices was also investigated by removing tablets from dissolution fluid at intervals and measuring the thickness of the wetted portion of the tablet. Dissolution fluid uptake was found to take approximately seven hours, and was also found to be proportional to the square root of time. Dakkuri and co–workers (175 – 177) examined various drug–wax combinations by differential scanning calorimetry and found that there was no significant interaction between the drugs and wax which could be detected using this technique, and concluded that drug release was influenced only by the physico–chemical interaction of the matrix with dissolution fluid. They also investigated the effect on drug release rate of the incorporation of various

surfactants and polyvinyl pyrrolidone into the matrix during preparation. Approximately zero-order release was found to occur in some cases, and this was explained by the existence of a channeling effect caused by the surfactants which increased the porosity during the drug release process. This explanation does not account for the fact that the porosity term in the Higuchi equation is the porosity of the leached matrix, and one possible alternative explanation is that the surfactants solubilised part of the matrix, causing drug release to be due to a combination of diffusion and erosion.

Groves and Galindez (178) prepared wax matrix tablets by a heat granulation process. Brompheniramine was used as the drug and the matrices were composed of a mixture of carnauba wax, cetostearyl alcohol and glyceryl monostearate. Drug release was found to be linear with square-root of time and it was concluded that the diffusion controlled model was applicable to this system. Drug release into buffers of acid and alkaline pH was also studied, and it was found that there was no effect on drug release, other than what would be expected from the change in solubility of the drug with changing pH. Najib and Suleiman (179) prepared matrices of beeswax by two different methods. Firstly the drug was suspended in molten wax and the resultant mixture cooled whilst being stirred. The solidified mixture was then granulated, though the granulation methods and conditions were not specified. Secondly, a simple physical mixture of the drug and beeswax was prepared in a mortar and tablets were compressed directly with this mixture. Drug release from both types of matrix was found to conform to the Higuchi diffusion model, with the release rate exhibited by the directly-compressed matrix being greater than from the matrix prepared from granules. This was attributed to differences in porosity and tortuosity between the two formulations, but these parameters were not measured.

Kopcha and Lordi (180) prepared spray-dried powders of oil-in-water emulsions of castor wax and a commercial wax "Durkee 07". The spray-dried emulsion powders were then mixed with drug and an aqueous dispersion granulation technique was used

to prepare granules for tableting. Drug release in artificial gastric and [c] intestinal fluids was found to conform to the Higuchi diffusion model, although short lag times were noticed before drug release began, followed in intestinal fluid by a burst effect. The burst effect was attributed to the dissolution of drug present on the tablet surface. Trigger *et al* (181) prepared matrices containing concentrations of glyceryl stearate in the range 0.48 – 14.69%, using a granulation process which was not specified. The exponential equation of Peppas (equation 1.27) was applied to the drug release data to elucidate the mechanism of drug release, and it was found that at low glyceryl stearate concentrations drug was released predominantly by an erosion mechanism, but at higher concentrations, drug release was predominantly diffusion controlled.

Polymers have also been widely investigated as materials for preparation of porous matrices. In a series of papers, Farhadieh and co-workers (182 – 184) investigated drug release from matrices of methyl acrylate-methyl methacrylate copolymer. The Higuchi model was found to apply, and tortuosities were determined from drug release data. Tortuosity values up to 18.8 were found for [c] matrices prepared with sodium pentobarbital, methapyrilene hydrochloride and dextromethorphan hydrobromide as model drugs, but values exceeding 30 were found with ephedrine hydrochloride. This was attributed to the particle size range of this drug, which had a median particle size larger than the others investigated. It was also found (183) that exposing the matrices to acetone vapour caused a decrease in drug release rate proportional to the amount of acetone absorbed. This decrease was attributed to an increase in tortuosity, with values up to approximately 200 being obtained. No hypothesis for the mechanism by which acetone vapour increased tortuosity was proposed. The effect on drug release rate of the inclusion of the tableting excipients sodium chloride and dextrose was also investigated (184), and drug release was found to be explained by the equation postulated by Singh *et al* (168) for the release of non-interacting mixtures of solutes from porous matrices. The effect on drug release of including tableting excipients in porous matrices was

further investigated by Kristofferson and Hannula (185), who examined the effect of microcrystalline cellulose on release from matrices of copolymers of acrylic/methacrylic esters. Matrix tablets were prepared in three ways. Firstly a direct compression mix of polymer, drug and microcrystalline cellulose in the ratio 1:4:1 was prepared; secondly the same mix was granulated using a 1:1 mixture of isopropyl alcohol and acetone; and thirdly granules of the drug and polymer in the ratio 4:1 were prepared in the same manner and microcrystalline cellulose was mixed with the dried granules to produce the same overall ratio of the constituents as in the previous formulations. Drug release from the direct compression mix was found to be 90% complete within 3 hours, with the tablets also disintegrating in this period. Drug release from tablets of the formulation containing intragranular microcrystalline cellulose was found to be slower than from tablets of the formulation containing intergranular microcrystalline cellulose. It was hypothesised that these results could be explained by the disintegrant action of microcrystalline cellulose, which although insoluble in water, exerted a disruptive effect as a result of uptake of water destroying hydrogen bonds formed during tablet compaction between adjacent cellulose micro–crystals. In tablets containing intragranular microcrystalline cellulose, less hydrogen bonds were able to form on compaction and therefore there was less disintegrant action during the drug release process.

The kinetics of liquid penetration into matrices was investigated by Carli and Simioni (186), who prepared matrices from several different polymers. They measured contact angle of water on the matrices, and the volumetric uptake of water with time into the matrices. Matrices of polyvinyl chloride and a vinyl chloride–vinyl acetate copolymer were found to be saturated within tens of seconds, whereas a period of approximately 2.5 hours was required for matrices of an acrylic polymer, and of a mixture of the vinyl chloride–vinyl acetate copolymer and polytetrafluoroethylene, to become saturated. Water was not found to enter matrices of polyethylene. Contact angles of greater than 90° (i.e. non–wetting) were found

for the matrices of polyethylene and the mixture of copolymer and polytetrafluoroethylene, and of less than 90° (i.e. wetting) for the other matrices. The fact that water penetrated the matrix prepared from the polymer mixture, but exhibited a non-wetting contact angle on the surface of that material, was explained on the basis that since the drug and one of the components of the mixture had wetting contact angles, the non-wetting polymer surface contact angle was not representative of the actual wetting conditions at some pore walls within the matrix. Pore size distributions were determined by mercury porosimetry and drug release studies were performed, but no attempt was made to relate the wetting phenomena to a quantitative application of the Higuchi equation to the release data.

A co-precipitation method was used to prepare matrices of polymers of the "Eudragit" type (187). Drug and polymer were dissolved together in an appropriate solvent, either ethanol or acetone, and the solvent evaporated off. A particle size fraction of 200 – 500 µm of the resulting powder was collected and tablets were compacted directly from the granules. Drug release was found to be linear with square-root of time. Jambhekar and Cobby (188) showed that pH-independent release from porous matrices of a drug whose solubility changed with pH was possible using a matrix composed of a mixture of polyvinyl chloride and polyethylene. This was attributed to the buffer capacity of the buffer solutions used as dissolution media being exceeded within the matrix. The drug solution in the microenvironment within the matrix would hence not be properly buffered and solubility would not be affected. This is an advantage which is particularly useful for oral controlled delivery systems, where the varying pH conditions along the gastrointestinal tract would not affect drug release. It is also possible that although drug would be released from the device in solution, it may precipitate in the bulk solution of the gastrointestinal contents, whose buffer capacity might not be exceeded. The effect of compaction pressure on drug release from matrices prepared using two different methods was studied by Fassihi (189). Matrices were prepared by dispersing drug in

molten polymer mixtures, and casting the molten mixture onto cold glass plates. The solid mixture was then milled and compressed into tablets. Direct compression of powder mixes in the same ratios was also used to prepare tableted matrices. Compaction pressure was found to exert a significant effect on drug release rates from the matrices prepared by fusion, with matrices produced using higher compaction pressures exhibiting decreased release rates. This was considered to be due to the decreased porosity of the matrices produced using higher compaction pressures. The same effect was not observed with the matrices produced using direct compression, with only a slight decrease in release rate being observed. No explanation was proposed for this observation. Diffusion controlled drug release was found in porous matrices composed of polyhydroxybutyrate-valerate copolymers (190). These were prepared by direct compression of powder mixes which included either microcrystalline cellulose or lactose, two tableting excipients which are used in direct compression tableting. Drug release rate was found to increase with increasing concentration of both microcrystalline cellulose and lactose, which was attributed to the wicking into the matrix of water caused by the insoluble microcrystalline cellulose and the increase in porosity caused by the dissolution of lactose, respectively. An added advantage of these copolymers was that they are biodegradable, and devices would therefore not potentially become lodged in the gastrointestinal tract.

1.4.6 Other Systems for Oral Controlled Drug Delivery

Several systems for oral controlled delivery have been described in the literature which do not fall readily into the categories discussed above. Also, certain geometrical modifications to diffusion controlled matrices in order to obtain zero-order release will be discussed in chapter 5 (section 5.1 below).

Farah and co-workers (191, 192) have prepared a system which was termed a dry adsorbed emulsion. This was prepared by dissolving drug in water and producing an oil-in-water emulsion. A hydrophilic silica was then added to the emulsion and the

mixture stirred at the very high rate of 12000 rev min^{-1}. A hydrophobic silica was

then added, with stirring at 5000 rev min^{-1}, which produced a dry, particulate

mass. Drug release rate from these particles was found to decrease with time, and

the rate controlling mechanism was found to be diffusion. de Haan and Lerk (193 —

195) proposed a system which was described as megaloporous. It was prepared from

tableted mixtures of two granulations, one termed the housing phase, and the other

the restraining phase. The housing phase controlled the rate of liquid penetration

into the device, producing large pores within the device, and the restraining phase

controlled the release of drug into the pores and thus out of the device. Drug

release was found to be zero – order from such a system, and independent of

compaction pressure above a certain value. A capsule dosage form was described by

Jain et al (196) which simply comprised a water – insoluble capsule filled with drug

and a soluble excipient, and which was sealed to prevent fluid ingress. A number of

holes were drilled in the capsule with a laser and drug release studies showed a

zero – order release profile. Lee (197) proposed a matrix system where the drug

loading was non – uniform, and predicted suitable concentration profiles for zero –

order and other drug release kinetics for various geometrical shapes of polymers

where drug release was either diffusion or dissolution controlled.

Chapter 2

Investigation of the use of Hydrogenated Vegetable Oil as a Directly – Compressible

Controlled Release Tableting Excipient.

2.1 Materials

Potassium chloride: Analar grade, Lot 991713OF, supplied by BDH Chemicals, Poole, Dorset, U.K.

Potassium phosphate, monobasic: Analar grade, Lot 9822033f, BDH Chemicals

Magnesium stearate: GLR grade, Lot 9595340E, BDH Chemicals

Amaranth: Technical grade, Lot 8549670P, BDH Chemicals

Sodium salicylate: GLR grade, Lot 516109OJ, BDH Chemicals

Theophylline, anhydrous: Lot 70, supplied by Boehringer Ingelheim, Ingelheim, FRG.

Lactose, hydrous NF: "Fast–Flo", Lot 3RG504 supplied by Foremost Whey Products, Wisconsin, U.S.A.

Hydrogenated vegetable oil: "Emvelop", Lot V4317E, supplied by Edward Mendell Co., Inc., Carmel, NY 10512, U.S.A.

Dicalcium phosphate dihydrate: "Emcompress", Lot 9101, Edward Mendell Co.

Microcrystalline cellulose: "Emcocel", Lot 5115, Edward Mendell Co.

Sodium hydroxide: Lot MU4093, supplied by May and Baker, Dagenham, U.K.

Hydrochloric acid: Lot MU4060, May and Baker

"Slow–K" Tablets 600 mg: Lot PA16577, supplied by Ciba Laboratories, Horsham, U.K.

Potassium chloride and sodium salicylate were each milled in an end–runner mill and the sieve diameter fraction < 355 µm was collected and used. The same size fractions of hydrogenated vegetable oil (unless otherwise stated) and theophylline were collected and used. All other materials were used as received.

2.2 Methods

2.2.1 Apparatus and Techniques for Drug Release Studies

In this part of the study the feasibility of producing controlled release oral

devices by direct compression tableting of hydrogenated vegetable oil (HVO) was examined. HVO is refined cottonseed oil which is hydrogenated, then prilled to produce the final powder form. It is widely used in the food industry and is also available as a pharmaceutical excipient. It has official status in the National Formulary (198) and is hence generally regarded as safe for human use. It has been used pharmaceutically as a tableting lubricant at levels of approximately 0.5 – 2% w/w (199). Use of HVO as a lubricant led to the suggestion that it might be capable of delaying drug release from conventional tablets, a property which is possessed by other lubricants such as magnesium stearate (MS) (200). Unlike magnesium stearate, HVO has been found not to reduce tablet crushing strength (201). The ability of HVO to be capable of tablet lubrication and its potential for delaying drug release as a result of its water insoluble, waxy and therefore hydrophobic nature, together with its ability to flow uniformly, suggested that the material may be useful as a directly – compressible controlled release tableting excipient. A direct compression excipient vehicle with such wide properties is not currently available and the overall aim of these initial studies was to assess the feasibility of using HVO, possibly in combination with other excipients, as a vehicle for producing oral solid dosage forms which would release drug over therapeutically significant periods.

Potassium chloride (KCl) was chosen as a model drug for these initial studies for several reasons. Firstly, it is freely soluble in water (approximately 1 part KCl in 3 parts water at 20°C (202)) and hence provides a rigorous test of the ability of a given system to control drug release. Secondly, it is conveniently assayable in solution by measurement of specific conductance. Lastly, it is used clinically for the treatment of hypokalaemia and commercial controlled release formulations are available for comparison with any HVO – based systems produced.

2.2.1.1 Preparation of Tablets

Powder mixes for direct compression were prepared by weighing 100.0 g of each

formulation into a cylindrical polythene bottle of approximately 300 cm^3 internal volume. Each formulation was blended for 15 minutes by attaching the container with rubber bands to the powder container of a cube blender (Model AR400, Erweka GMBH, Frankfurt, F.R.G.). When magnesium stearate was included in a formulation, it was added to the mix after this blending stage and the final mix was blended for a further 3 minutes. Tablet compaction was performed volumetrically using a single punch tableting machine (Model F3, Manesty Machines, Speke, U.K.), which was fitted with 12.7 or 10 mm diameter flat-faced punches according to the formulation. The target mass was adjusted according to that required for a specific formulation, as given below. Compaction pressure was set to produce tablets with a diametral crushing strength in the range 59 – 78 N (6 – 8 kPond), which was measured on a tablet strength tester (Model 2E, K. Schleuniger and Co., Switzerland). This was achieved by producing a small number of tablets at one compaction pressure, measuring the diametral crushing strength of 5 tablets and adjusting the compaction pressure accordingly, repeating the process if necessary until tablets were produced of a crushing strength within the desired range.

2.2.1.2 Assay of Potassium Chloride using Specific Conductance Measurements

A series of aqueous solutions of increasing concentrations of KCl in the range 0.1 – 0.5 mg cm^{-3} was prepared by dissolving the appropriate amount of KCl in distilled water followed by equilibration of the solutions at 20°C in a water bath (Grant Instruments, Cambridge, U.K.). Specific conductance of solutions was measured with a conductivity meter and cell (Models PW9505 and PW9514/60 respectively, Philips, Eindhoven, Holland) which had been factory calibrated to measure at that temperature. The specific conductance measured was corrected for conductance due to distilled water in which the solutions were prepared by measuring the specific conductance of the water and subtracting the value obtained from each test measurement.

In order to establish whether any interference in the assay would be caused by

excipient which might dissolve from tablets during dissolution testing, solutions containing excipients used in a formulation were prepared. 500 mg of each excipient was added to 1000 cm³ of water to provide excess ions available in comparison with those available from a tablet, and stirred overnight on a magnetic stirrer. Any insoluble matter remaining was filtered out by passing the solution through qualitative filter paper in a filter funnel and the specific conductance of the resulting solution was measured.

2.2.1.3 Measurement of Release Characteristics of Potassium Chloride by Dissolution Testing using a Manual Sampling Technique

The release of KCl from tablets was measured with time using the rotating paddle method of tablet dissolution testing described (as Apparatus 2) in the United States Pharmacopoeia, (198). This method was chosen in preference to the rotating basket method since the tablets produced were denser than water and formulations generally remained discrete throughout the period of release. The test was performed using a tablet dissolution test apparatus equipped with 6 individual dissolution vessels (Model 6ST, G. B. Caleva, Basingstoke, U. K.) on 6 tablets of each formulation, and with the temperature of the dissolution fluid maintained at $37 \pm 0.5\,^{\circ}C$. Dissolution fluid was degassed prior to use by bubbling helium through 2 dm³ batches for at least 10 minutes. Except where otherwise stated, the volume and type of dissolution fluid used was 1000 cm³ of freshly distilled water in each vessel and paddle stirring rate was 50 revolutions per minute (rev min⁻¹). 10 cm³ samples of dissolution fluid were removed using 10 cm³ volume plastic syringes from each of the 6 vessels at pre-determined times via the standard sampling tubes fitted in compliance with the USP test method (198). Samples were then transferred to measuring cylinders of 50 cm³ volume and covered with plastic film (Nescofilm, Nesco, Japan) to prevent evaporation, before being placed in a water bath maintained at 20°C. Equilibrated samples were diluted to 25 cm³ with water at 20°C and their specific conductance was measured as described in section 2.2.1.2 above.

After each sample had been removed, 10 cm³ volumes of water were replaced in each dissolution vessel in order to maintain the same volume of dissolution fluid throughout the test.

2.2.2 Effect of Drug Loading on Drug Release Characteristics

N.B. The work described in this section had already been performed (203), and is repeated here for completeness. In order to obtain an initial indication of the ability of HVO to sustain drug release, tablet formulations containing the following proportions of drug and HVO were prepared as described in section 2.2.1.1 using 12.7 mm flat-faced punches to produce tablets having a target mass of 600 mg: –

Formulation	Composition
2A	KCl 80% / HVO 20%
2B	KCl 70% / HVO 30%
2C	KCl 60% / HVO 40%

Note 1: Information relating to the composition of all formulations used in this chapter is given in table 2.1 at the end of the chapter.
Note 2: All percentages stated are on a weight in weight basis.

KCl release rate was determined by subjecting tablets to dissolution testing as described in section 2.2.1.3 above, except that in this initial ranging study, 2 tablets from each formulation instead of 6 were tested.

2.2.3 Effect of Microcrystalline Cellulose Content on Drug Release Characteristics

The effect of microcrystalline cellulose (MCC) content on drug release characteristics was studied by preparing tablets of the following formulations using 10 mm diameter flat-faced punches (which were used for all further

formulations unless otherwise stated) to a target mass of 500 mg and subjecting them to dissolution testing: --

Formulation	Composition	
2D	KCl 40% / HVO 20% / MCC 39% / MS 1%	
2E	KCl 40% / HVO 30% / MCC 29% / MS 1%	
2F	KCl 40% / HVO 40% / MCC 19% / MS 1%	
2G	KCl 40% / HVO 50% / MCC 9% / MS 1%	

2.2.4   Effect of Different Types of Inert Directly – Compressible Diluents on Drug Release Characteristics

The effect on drug release characteristics of replacing MCC with direct compression forms of either spray – dried hydrous lactose (HL) or dicalcium phosphate dihydrate (DPD) was investigated by preparing tablets of the following formulations and subjecting them to dissolution testing: --

Formulation	Composition
2H	KCl 40% / HVO 40% / HL 19% / MS 1%
2I	KCl 40% / HVO 40% / DPD 19% / MS 1%

2.2.5   Measurement of Drug Release Characteristics of a Commercially – Available Controlled Release Formulation of Potassium Chloride

6 "Slow – K" Tablets, each nominally containing 600 mg of KCl, were obtained and subjected to dissolution testing using the method described above for tablets containing HVO.

2.2.6 Effect of Drug Solubility on Drug Release Characteristics

The effect of drug solubility on drug release characteristics was investigated by replacing KCl in a suitable formulation with model drugs of different

solubility. Sodium salicylate was chosen because it was more soluble than KCl (approximately 1 part in 1 part water at 20°C (202)) and theophylline because it was relatively insoluble (approximately 1 part in 120 parts water at 20°C (202)).

2.2.6.1 Assay of Sodium Salicylate using Ultra–Violet Spectrophotometry

A series of aqueous solutions of increasing sodium salicylate concentration in the range 5 – 100 mg dm^{-3} was prepared. A scan of 30 nm on either side of the wavelength of maximum absorption at 294 nm (202) was performed using a double beam ultra–violet/visible spectrophotometer (Model CE954, Cecil Instruments, Cambridge, U.K.) and 1 cm pathlength quartz cuvettes. This procedure was carried out in order to determine the exact wavelength of maximum absorption for sodium salicylate on that particular instrument. The absorbance of the sodium salicylate solutions was determined at 296 nm wavelength against a blank of distilled water.

Excipient solutions were prepared as described above in section 2.2.1.2 and any absorbance was also determined.

2.2.6.2 Assay of Theophylline using Ultra–Violet Spectrophotometry

A series of aqueous solutions of increasing theophylline concentration was prepared and a UV scan performed as described above (section 2.2.6.1) around the wavelength of maximum absorption for theophylline at 270 nm (202). The maximum concentration at which absorbance at the wavelength of maximum absorption was accurately measurable was found to be approximately 35 mg dm^{-3}. This concentration corresponded to a maximum possible theophylline content in any formulation of 35 mg. Given that the drug concentration in a formulation was likely to be 40% of the total tablet mass, this would result in tablets weighing only 87.5 mg, if the automated dissolution testing system described immediately below was to be used. Tablets of this mass having a diameter of 10 mm were unacceptably thin for practical purposes. For this reason, in order to maintain tablet diameter constant for comparability between formulations, a larger theophylline mass was required. To allow more theophylline to be incorporated and assayed accurately, the absorbance

at a wavelength of 290 nm, i.e. on the shoulder of the absorption peak was therefore determined for a series of concentrations of theophylline. This procedure allowed theophylline to be assayed over a wider measurable concentration range.

The absorbance of theophylline solutions in buffers of pH 2.0 and 6.0 was also determined. (For details of buffer formulae see section 2.2.8 below). Excipient solutions were prepared as described immediately above both in water and in each of the buffers and any absorbance was determined against the appropriate blank solution.

2.2.6.3 Measurement of Release Characteristics of UV–Assayable Drugs using an Automated Dissolution Testing Technique.

In order to automate the dissolution testing procedure, a cell controller attachment with motorized cell changer (Model CE830, Cecil Instruments) and 6 flow–through quartz cuvettes of 1cm pathlength (Cecil Instruments) were obtained for the UV spectrophotometer. Solutions were pumped out of the 6 dissolution vessels and through the appropriate cuvettes in the cell changer via 3.2 mm internal diameter plastic tubing using a peristaltic pump (Model 502S, Watson Marlow, Falmouth, U.K.). Vinyl peristaltic tubing (Type 980–0279–000, Watson Marlow) was used at the pump head. Both inlet and outlet tubing was inserted into the vessels to the same depth of 10 cm as used for the manual sampling tubes, so that fluid was always removed from and returned to the same points in each vessel. The pumping rate used was 39% of the maximum rate attainable by the pump. At this rate, dissolution fluid took 110 s to circulate through the UV cells and back to the dissolution vessels. This was considered appropriate considering the need to minimise both turbulence in the dissolution vessels caused by returning fluid and pump wear, and to maximise peristaltic tubing life. The cell changer was programmed to move each cell into the beam at the required time intervals and the resulting absorbance reading was relayed to a microcomputer (BBC Model B, Acorn Computers, Cambridge, U. K.) which

was interfaced with the spectrophotometer. A "Basic" programme (listed in Appendix 1) was written to record the absorbance readings, which were then converted to concentration values according to data obtained from calibration curves. Dissolution profiles were determined by calculating the cumulative percentage drug released with time and these data were then saved on disc for subsequent analysis. It was possible to record for each tablet a minimum of 1 and a maximum of 20 sample analyses per hour, up to a maximum of 25 sample analyses per test.

The effect of drug solubility on dissolution characteristics was investigated by preparing tablets of formulations containing the following concentrations of drug and excipients, and subjecting them to automated dissolution testing as described immediately above:–

Formulation	Composition
2J	Sodium Salicylate 40% / HVO 40% / MCC 19% / MS 1%
2K	Theophylline 40% / HVO 40% / MCC 19% / MS 1%

The target mass for formulation 2J was 220 mg and for 2K, 180 mg. This allowed the full range of UV absorbance to be used in the assay for each drug.

2.2.7 Determination of Release–Controlling Mechanism for Tablets Containing Hydrogenated Vegetable Oil

2.2.7.1 Effect on Drug Release Characteristics of Paddle Stirring Speed

The effect of paddle stirring speed was studied by preparing tablets of the following formulation to a target mass of 180 mg and subjecting them to dissolution testing at paddle stirring speeds of 50, 100 and 150 rev min^{-1}.

Formulation	Composition
2L	Theophylline 40% / HVO 30% / MCC 29% / MS 1%

2.2.7.2 Measurement of Tablet Thickness

In order to assess whether HVO – containing tablets underwent significant dimensional changes as the result of swelling or erosion during the dissolution test period, the diameter and thickness of tablets of formulation 2L were measured with a digitally – reading micrometer (Model 601 – 906, RS Components, Corby, U. K.) both before and after the dissolution test which was performed at a paddle stirring speed of 50 rev min^{-1}. The latter measurement was performed after rinsing the tablets with a small volume of distilled water and removing excess moisture from the tablet surfaces by blotting with tissue paper.

2.2.7.3 Data Analysis

Drug release data from formulation 2L was transferred to a statistics software package written for BBC computers (Instat, University of Reading, U.K.) and analysed according to zero – order, first – order and square – root of time kinetic models to further elucidate the release controlling mechanism.

2.2.7.4 Qualitative Assessment Of Water Penetrability of Tablets containing Hydrogenated Vegetable Oil

The water penetrability of HVO – based tablets was studied qualitatively by observing whether a dye dissolved in dissolution fluid entered the tablets during the drug release process. An aqueous solution of amaranth which appeared deep red in colour was prepared (at a concentration of approximately 0.5 g dm^{-3}). Two tablets of formulations 2F, 2H and 2I were each placed in 1 dm^3 of dye solution in the dissolution apparatus. A dissolution test was carried out as described in section 2.2.1.3 except that no samples were removed or analysed. After 12 hours, the tablets were removed from the vessels, rinsed with a small volume of water and excess water was removed from their surfaces by blotting with tissues. The tablets were then cut in half with a scalpel blade and examined visually for ingress of the dye.

2.2.7.5 Scanning Electron Photomicrography of Tablet Surfaces

The outer flat tablet faces and diametral fracture surfaces of tablets produced from formulation 2l which had been recovered after dissolution testing had been performed on them, were examined using a scanning electron microscope (Model JSM T330, Japanese Electron Optics Ltd., Tokyo, Japan). The samples were mounted on 10 mm diameter cylindrical aluminium stubs of approximate thickness 5mm using colloidal graphite adhesive. A layer of gold was deposited onto the sample surface using a sputter coater (Model S150B, Edwards High Vacuum, Crawley, U.K.). Sputter coating was carried out for 5 minutes using a voltage of 1.4 kV and a current of 20 mA applied across specimen stubs held in a vacuum of approximately 100 µm Hg. The coated samples were then examined at various magnifications using a working distance of 39 mm and an electron beam potential of 5 keV. Higher potentials were used but were found to cause overheating which led to sample degradation.

2.2.7.6 Fitting of Drug Release Data to the Higuchi Square – Root of Time Kinetic Model

The drug release data obtained were fitted to the Higuchi square – root of time model using least squares regression analysis of the linear portions of the dissolution curves.

2.2.8 Effect of pH of Dissolution Medium on Drug Release Characteristics

A study was carried out to examine the effect on drug release rate of dissolution testing in solutions having a pH approximating to that which would be experienced by tablets in the stomach and the small intestine. Values of pH 2.0 and 6.0 were selected for use in the present study and buffers were prepared to the following U.S.P. formulae (198): –

pH = 2.0:	0.2 M Potassium chloride solution	250 cm^3
	0.2 M Hydrochloric acid solution	65 cm^3
	Distilled water	to 1000 cm^3

pH = 6.0:	0.2 M Potassium phosphate,monobasic	250 cm^3
	0.2 M Sodium hydroxide solution	28 cm^3
	Distilled water	to 1000 cm^3

Dissolution testing was performed on tablets produced using formulation 2L in both of the buffers described above. This formulation was chosen because the solubility of theophylline has been shown not to vary significantly in the pH range 2 - 7 (204).

2.2.9 Effect of Hydrogenated Vegetable Oil Particle Size on Drug Release Characteristics

HVO was sieved into 2 size fractions; (a) < 125 μm and (b) 125 - 355 μm. Tablets produced using formulation 2L were prepared from these two size fractions and subjected to dissolution testing as described above.

2.3 Results and Discussion

2.3.1 Apparatus and Techniques for Drug Release Studies

2.3.1.1 Preparation of Tablets

Some general observations regarding the preparation of tablets produced using formulations containing HVO will be discussed here. The principal problem encountered was that of adhesion of formulations to the punches of the tablet machine, in particular the upper punch. At low HVO concentrations the problem was slight, however at the HVO concentrations required to produce sustained drug

release the problem was more evident. For this reason, formulations prepared after the initial binary mixes containing KCl and HVO (section 2.2.2) included magnesium stearate at a proportion of 1% w/w as an anti-adherent. The punch diameter was also reduced from 12.7 to 10.0 mm at this stage in order to reduce the overall surface area of the punches in contact with the formulation during compression. In addition, the target tablet mass was reduced to 500 mg. The problem of adhesion was considered to be caused by melting of HVO as a result of increased friction at point contacts at the punch face during tablet compression; HVO has a relatively low melting point of 61 – 66 °C (199). The formulations were found to be well lubricated in terms of achieving acceptable ejection forces, even when not containing magnesium stearate. This result was not unexpected since all formulations contained at least 10 times the proportion of HVO considered to be suitable for use as a tablet lubricant. All the formulations were found to produce tablets of the required diametral crushing strength and it was concluded that HVO was capable of producing tablets by direct compression with mechanical strength suitable for general handling.

2.3.1.2 Assay of Potassium Chloride using Specific Conductance Measurements

The measured specific conductance of the solutions prepared was plotted against their concentration (figure 2.1) and a linear relationship between the variables was considered to exist. Least squares regression analysis of this data produced the following statistics: –

Slope $= 1.842 \times 10^{-3}$ S cm^{-1} / g dm^{-3}

Intercept $= -1.429 \times 10^{-6}$ S cm^{-1}

$r^2 = 0.9996$

These results were considered to show that the assay was appropriate for analyses in the concentration range measured.
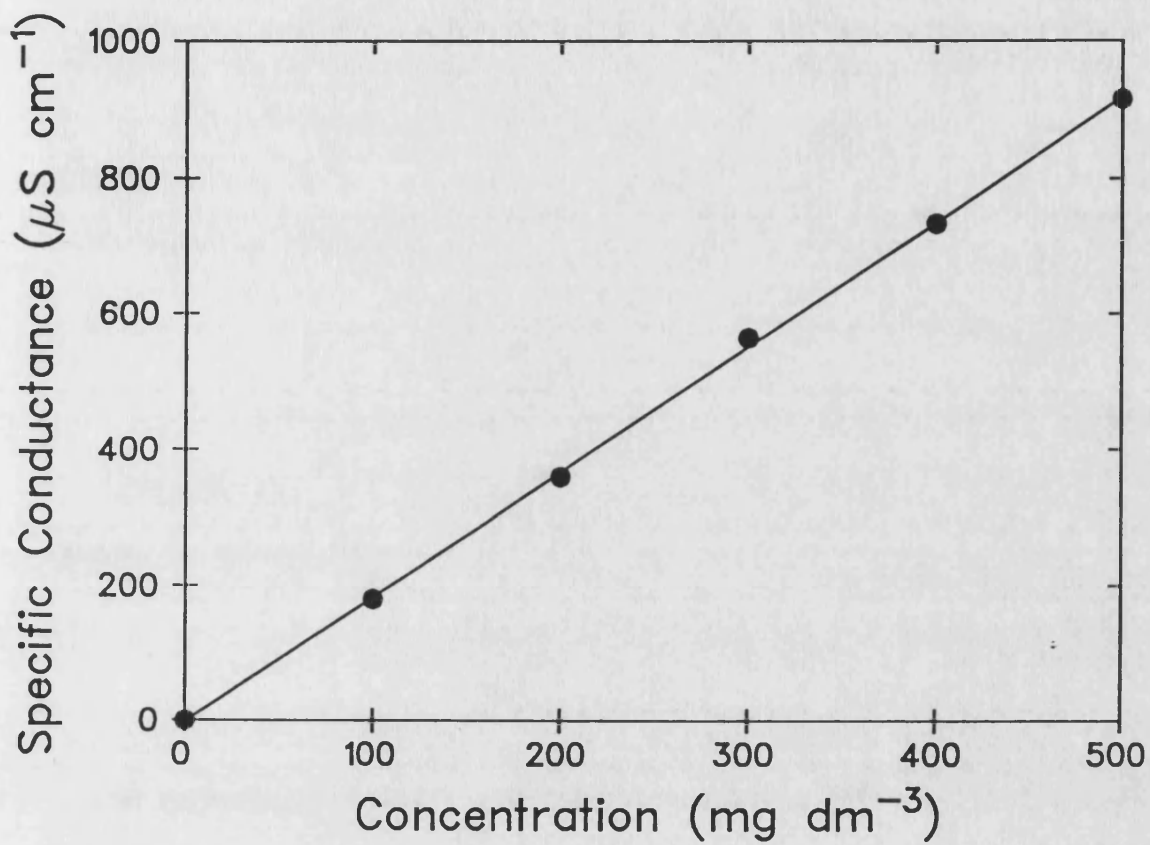
Figure 2.1   Calibration curve of specific conductance versus concentration of

potassium chloride in water

2.3.1.3   Measurement of Release Characteristics of Potassium   Chloride   by
Dissolution Testing using a Manual Sampling Technique

The amount of KCl released from each tablet at the first time point was calculated in the following manner. Given that the measured conductivity at time t = S_t, then the conductivity of the dissolution medium S_d = 2.5 x S_t. This was converted to a concentration value C_t in g dm^{-3} using the calibration curve constructed in section 2.3.1.2:−

$$C_t = (S_d - \text{intercept}) / \text{slope} \qquad \dots\text{equation 2.1}$$

Letting the mass of drug in the tablet at time 0 = M_z gram, then the percentage released R_x was calculated as:−

$$R_x = (C_t / M_z) \times 100 \qquad \dots\text{equation 2.2}$$

At each subsequent time point t_i, the value C_t had to be corrected for the amount of KCl withdrawn at each previous time point $t_{(i - 1)}$, and was calculated in the following manner:−

$$R_x = \{[C_t + \Sigma^n_1(C_{t(n)} / 100)] / M_z\} \times 100 \qquad \dots\text{equation 2.3}$$

where   n = (total number of samples taken − 1)

This calculation procedure was incorporated into a "Basic" programme (listed in Appendix 1) which was run on a BBC microcomputer. This allowed each conductivity reading to be entered into the computer and the corresponding percentage released values to be calculated and displayed. The data was then stored on disc for subsequent analysis.

2.3.2 Effect of Drug Loading on Drug Release Characteristics

Figure 2.2 (reproduced with data from reference 203) shows the mean cumulative percentage KCl released versus time for the three formulations 2A – 2C (table 2.1). It can be seen that HVO causes a sustaining in the time over which KCl is released from tablets and that increasing drug loading results in an increased release rate. Tablet formulations containing 20 and 30% HVO both released all their drug within approximately 2 and 4 hours respectively, whereas the formulation containing 40% HVO shows that drug was released over approximately 8 hours. In terms of clinical usage, this latter result is a potentially useful sustained release profile.

2.3.3 Effect of Microcrystalline Cellulose Content on Drug Release Characteristics

It was decided that in view of the problems with adhesion which occurred when formulations containing high concentrations of HVO were compressed into tablets (section 2.3.1.1) and in order to improve the ultimate compressibility of the system, it would be of interest to examine the effect on release rate of including another directly – compressible inert diluent in some HVO – based formulations. The excipient microcrystalline cellulose was chosen initially because it is one of the most compressible insoluble inert diluents available. Figure 2.3 shows the release data obtained for formulations 2D – 2G (table 2.1). It can be seen that drug release rate increased with increasing MCC content and concomitantly decreased with increasing HVO content. Visual observation of the tablets containing 29 and 39% MCC showed that the tablets did not remain discrete throughout the dissolution process. A split in the tablets containing 29% MCC occurred around the tablet edge, giving the appearance that the tablet had capped. Those tablets containing 39% MCC were found to have partially disintegrated into several fragments by the end of the dissolution test. The reason for these effects was considered to be due to the interaction of MCC with water. Although it is insoluble, MCC is hydrophilic and draws water into a tablet by wicking or capillary suction potential. As a result of compaction during tableting, adjacent MCC particles are considered to undergo

-76-
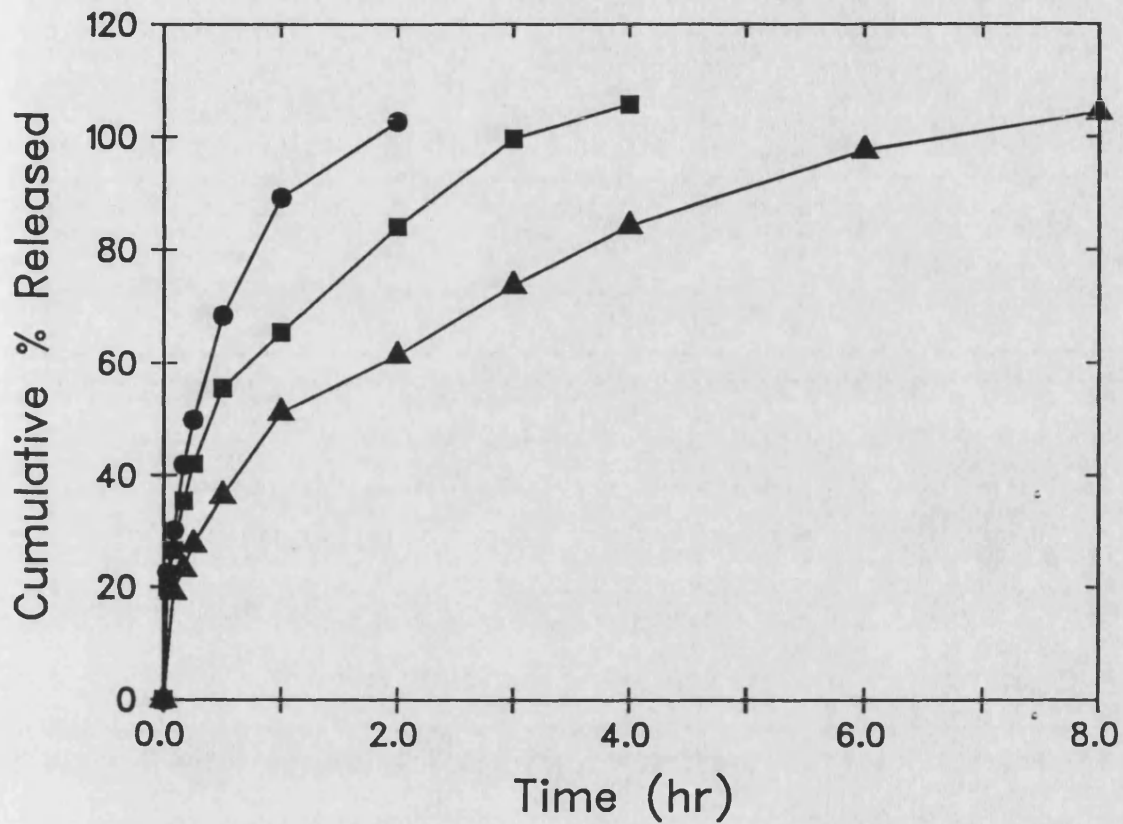
Figure 2.2   Effect   of   drug concentration on release from formulations   2A   —   2C

(table 2.1)

Key: ● = KCl 80% / HVO 20%

■ = KCL 70% / HVO 30%

▲ = KCl 60% / HVO 40%
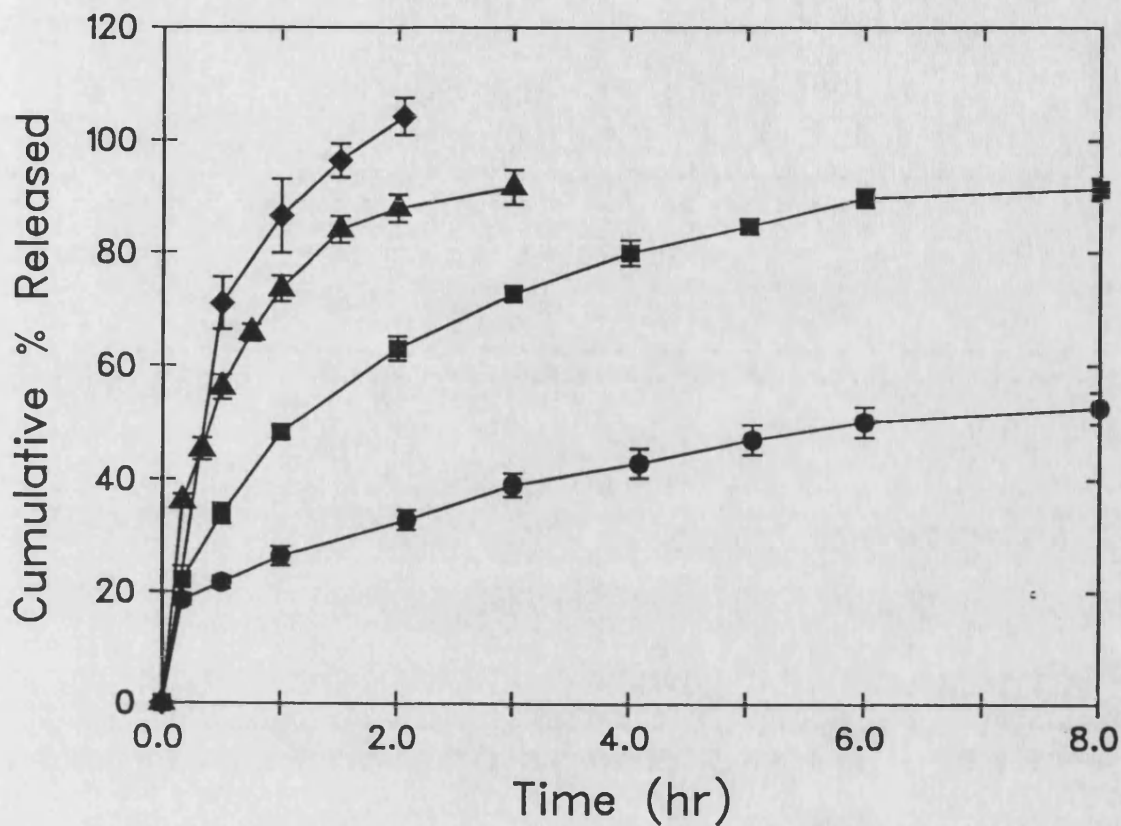
Figure 2.3 Effect of microcrystalline cellulose concentration on drug release from formulations 2D – 2G (table 2.1). (N. B. Error bars on this and all subsequent plots are 95% confidence intervals)

Key: ● = 9% MCC / 50% HVO

■ = 19% MCC / 40% HVO

▲ = 29% MCC / 30% HVO

◆ = 39% MCC / 20% HVO

hydrogen bonding between the hydroxyl groups on the polymeric cellulose chains. Since water is thought to disrupt these bonds, causing the crystals to separate (205), this may account for the loss of tablet integrity at higher concentrations of MCC. If there is sufficient MCC in a tablet it will hence effectively act as a disintegrant and this was concluded to be the case when it was included in HVO-based formulations, with the effect increasing with increasing proportion of MCC.

Formulations containing 40 and 50% HVO both exhibited potentially useful release kinetics and it was decided to prepare further formulations containing 40% of HVO, as this appeared to represent a suitable compromise between useful sustaining of release and minimal adhesion to the punch faces.

2.3.4 Effect of Different Types of Inert Directly-Compressible Diluents on Drug Release Characteristics

The effect on drug release characteristics of tablets prepared from formulation 2F (KCl 40% / HVO 40% / MCC 19% / MS 1%) of replacing MCC with DPD or HL was examined. The reason for studying this was that these excipients may be required in a formulation in order for example to improve its flow characteristics, or because of chemical incompatibility of particular drugs with a specific excipient. DPD was chosen because it is an example of a directly-compressible diluent which like MCC is insoluble but unlike MCC does not possess any intrinsic disintegrant action, and HL because it is soluble. The release data obtained are shown in figure 2.4. It can be seen that the formulation containing MCC has the highest release rate, the one containing HL an intermediate rate and the formulation containing DPD the slowest rate. These results will be discussed in the light of further analysis in section 2.3.7 below.

2.3.5 Measurement of Drug Release Characteristics of a Commercially-Available Controlled Release Formulation of Potassium Chloride

The drug release data obtained for "Slow-K" tablets are shown in figure 2.5
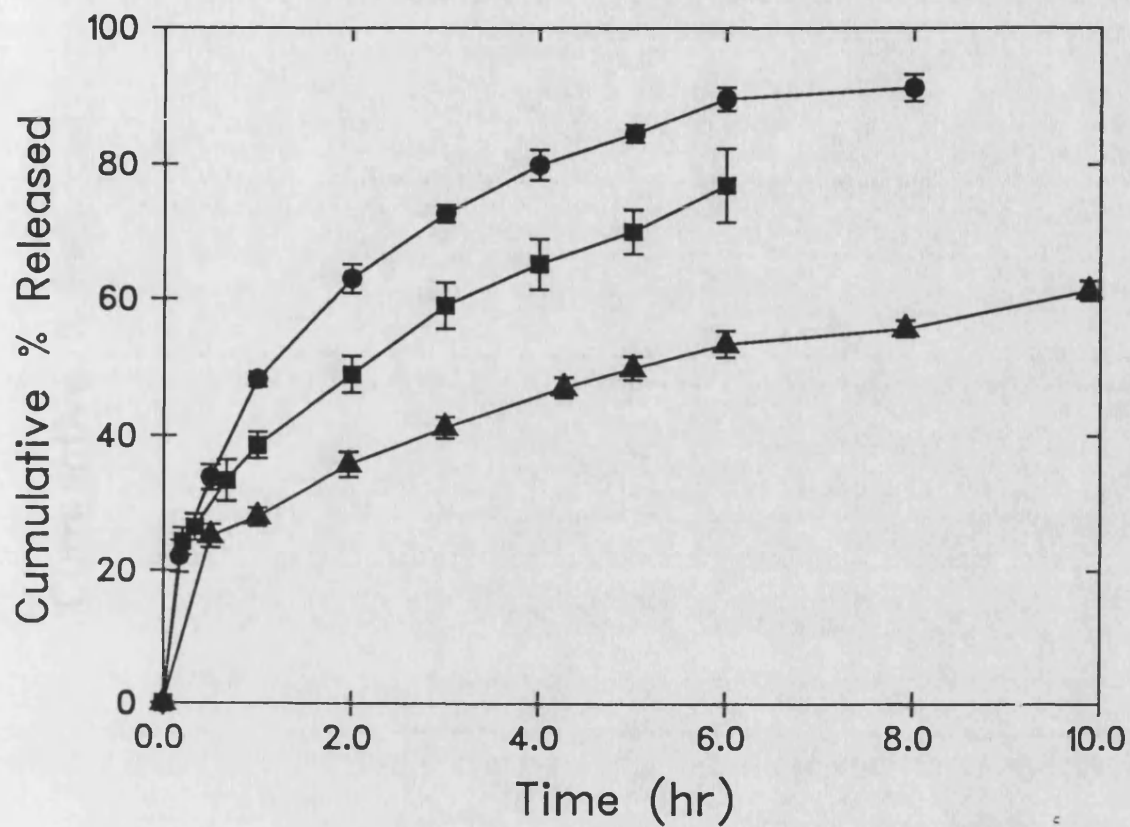
Figure 2.4   Effect   of different types of directly – compressible diluents   on   drug

release from formulations 2F, 2H and 2I (table 2.1)

Key: ● = 2F (microcrystalline cellulose)

              ■ = 2H (spray – dried hydrous lactose)

              ▲ = 2I (dicalcium phosphate dihydrate)
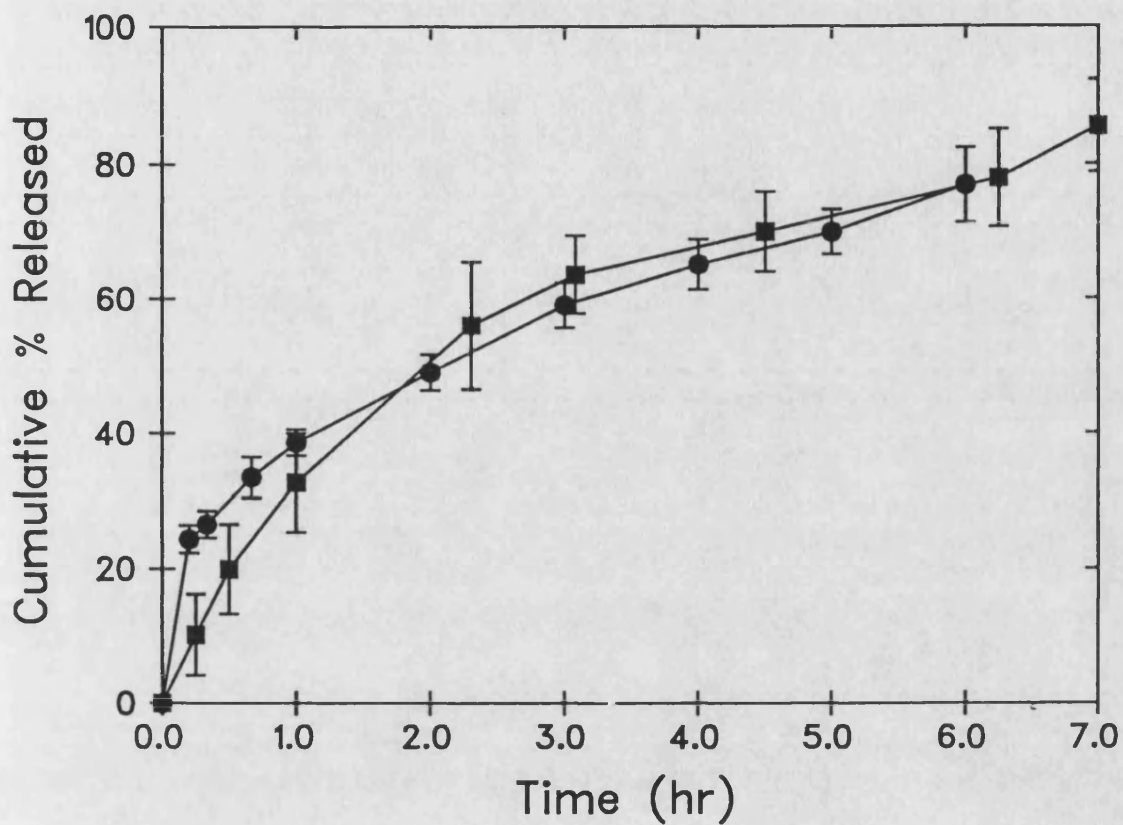
Figure 2.5   Drug release profile of "Slow – K" tablets in comparison with drug release profile of formulation 2H (table 2.1)

Key: ● = formulation 2H
            ■ = "Slow – K" tablets

with the corresponding drug release data for tablets from formulation 2H (table 2.1) for comparison. It can be seen that tablets prepared from the HVO formulation had drug release profiles which were similar to those for the commercial formulation. Visual observation of the "Slow – K" tablets during the release process showed that an initial dissolution of the coat occurred followed by a slow swelling of the core and in the final stages of release, some evidence of core disintegration. It was concluded that "Slow – K" was a hydrophilic matrix type of device. The release rate of "Slow – K" is slower than that of the HVO formulation at first, probably reflecting the fact that initial coat dissolution must occur before release begins. Towards the end of the release period there is evidence of a burst effect which was probably caused by the breaking up of the swollen core. The similarity of the HVO formulation's release kinetics showed that HVO – based systems possess some potential as oral controlled delivery systems, especially in view of the fact that the HVO system was prepared using direct compression technology. It is unlikely that the system could be used for KCl, however, because the drug loading of the formulation exhibiting a similar release profile to "Slow – K" was only 40%, whereas the "Slow – K" tablets had a loading of 80%. A therapeutic dose of 600 mg of KCl would hence result in a tablet mass of 1.5 g for the HVO formulation, which is probably unacceptably high. The system may hence be limited to more potent drugs where high drug loading would not be necessary.

2.3.6   Effect of Drug Solubility on Drug Release Characteristics

2.3.6.1   Assay of Sodium Salicylate using Ultra – Violet Spectrophotometry

The wavelength of maximum absorbance of sodium salicylate in aqueous solution was found to be 296 nm. The measured absorbance of the solutions prepared was plotted against their concentration (figure 2.6) and it was considered that a linear relationship existed between the variables. Least squares regression analysis was performed on the data and it produced the following statistics: –
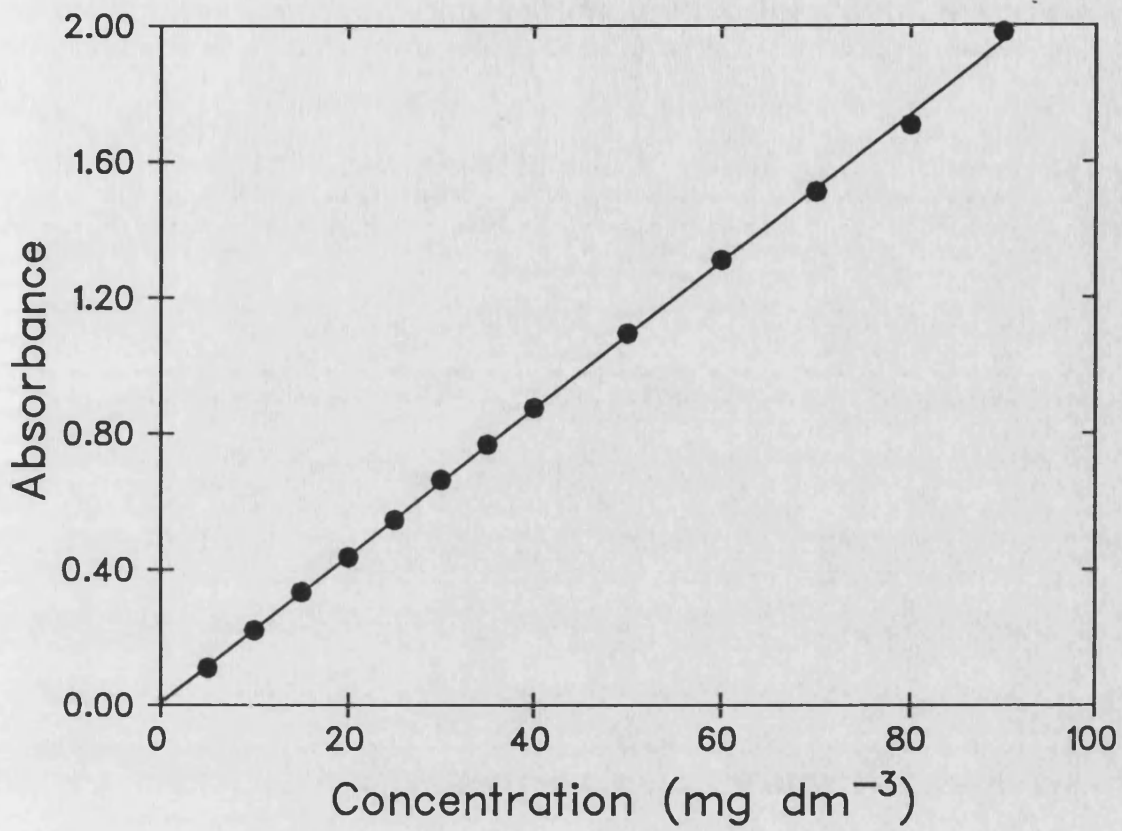
Figure 2.6   Calibration   curve of UV absorbance at 296 nm versus concentration   of

sodium salicylate in water

Slope $= 21.68$ (g $dm^{-3})^{-1}$

Intercept $= 0.01095$

$r^2 = 0.9999$

These results were considered to show that the use of this assay was appropriate for analyses in the concentration range measured.

No significant difference in absorbance was noted between any of the excipient solutions prepared and a blank of distilled water and it was concluded that any dissolved excipient did not interfere with the assay.

2.3.6.2 Assay of Theophylline using Ultra-Violet Spectrophotometry

The measured absorbance of the solutions prepared in water and buffers of pH 2.0 and 6.0 was plotted against concentration (figure 2.7) and it was considered that linear relationships existed between the variables in each case. Least squares regression analysis was performed on the data and it produced the following statistics: -

Water: Slope $= 10.32$ (g $dm^{-3})^{-1}$

Intercept $= 0.02426$

$r^2 = 0.9996$

Buffer pH 2.0:   Slope $= 9.873$ (g $dm^{-3})^{-1}$

Intercept $= 0.01405$

$r^2 = 0.9996$

Buffer pH 6.0   Slope $= 10.54$ (g $dm^{-3})^{-1}$

Intercept $= 0.01347$

$r^2 = 0.9997$

These results were considered to show that the use of these assays was appropriate for analyses In the concentration range measured.
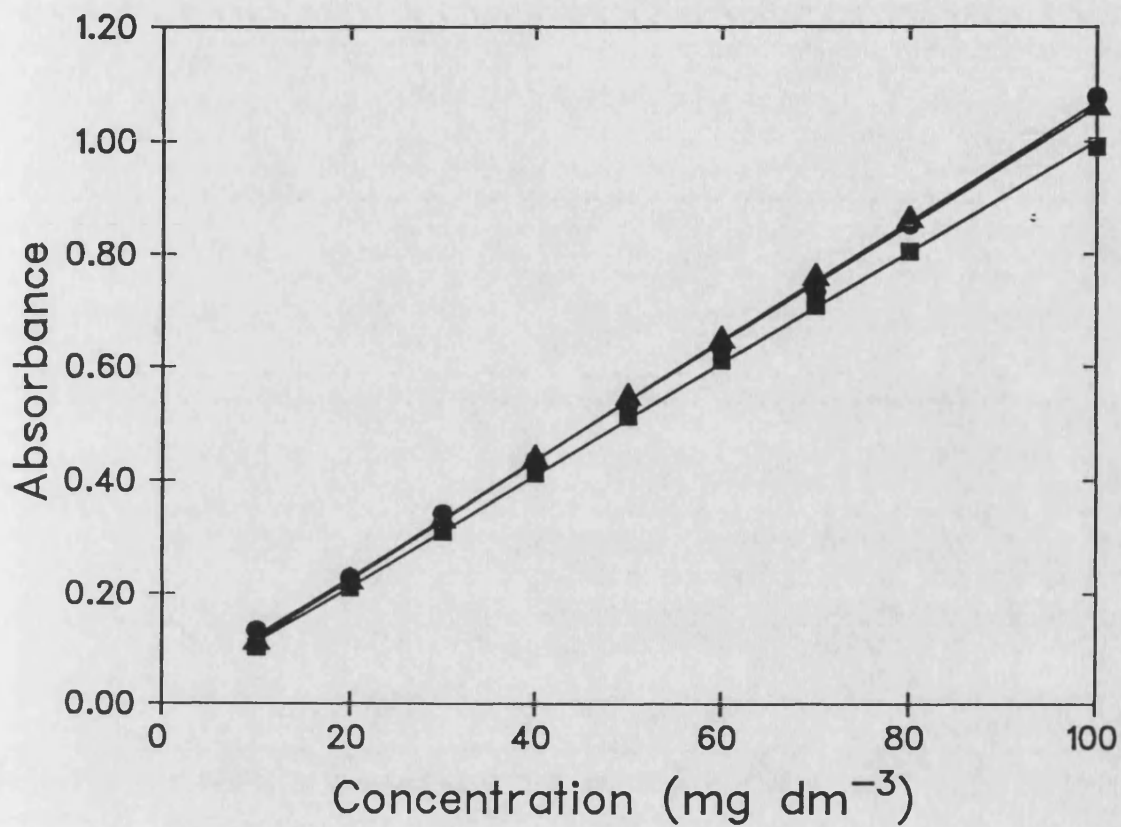
Figure 2.7 Calibration curve of UV absorbance at 290 nm versus concentration of theophylline in water and buffers of pH 2.0 and pH 6.0

Key: ▲ = water

■ = buffer pH 2.0

● = buffer pH 6.0

No difference in absorbance was noted between any of the excipient solutions prepared in water and buffers and their respective blanks and it was concluded that any dissolved excipient did not interfere with the assay.

2.3.6.3 Measurement of Release Characteristics of UV Assayable Drugs using an Automated Dissolution Testing Technique

The release profiles of the sodium salicylate and theophylline formulations measured by the automated system and the corresponding KCl formulation are shown in figure 2.8. It can be seen that the effect of increasing drug solubility whilst maintaining the other proportions of the formulation constant was to produce an increase in drug release rate. These results will be discussed in the light of further analyses in section 2.3.7 immediately below.

2.3.7 Determination of Release – Controlling Mechanism for Tablets Containing Hydrogenated Vegetable Oil

In order to be able to quantify the release kinetics from HVO – based systems, the data was analysed according to various models. As can be seen from the release profiles shown above in section 2.3.4 – 6, the zero – order model does not apply to drug release from HVO tablets, since release is not linear with respect to time. It was concluded from the general shape of the profiles obtained in sections 2.3.4 – 6 that either a first – order or a square – root of time model could possibly describe the release process and the data was therefore fitted to these models. Other tests described below were also performed to further elucidate the model of best fit for the data produced using HVO – based systems.

2.3.7.1 Effect on Drug Release Characteristics of Paddle Stirring Speed

If the release process was dissolution controlled, then the agitation conditions during the release process would be expected to have a significant effect on drug release rate. For this reason, the effect of increasing paddle stirring speed on the release profile of formulation 2L (table 2.1) was studied,
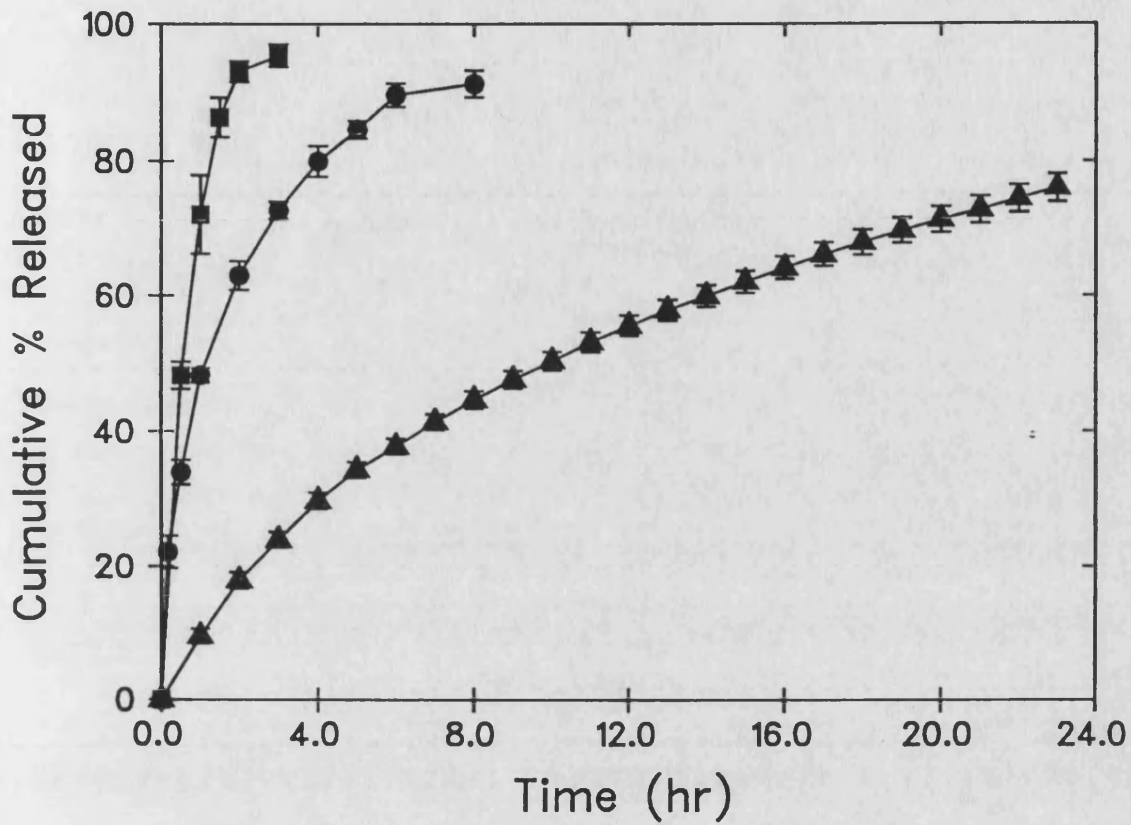
Figure 2.8   Effect   of drug solubility on drug release profile of formulations   2F,

2J and 2K (table 2.1)

Key: ■   = sodium salicylate

●   = potassium chloride

▲   = theophylline

and the data obtained are shown in figure 2.9. It was found that the effect on drug release rate of increasing the paddle stirring rate from 50 to 100 and 150 revolutions per minute was negligible. Furthermore, no simple relationship between drug release rate and paddle stirring speed was evident, since drug release for the test carried out with a paddle speed of 150 rev min^{-1} was slightly slower than that at 100 rev min^{-1}, although both are faster than at 50 rev min^{-1}. These results provide evidence that the release process is not erosion controlled.

Visual examination of this formulation during the release process showed that tablets remained whole throughout, indicating that the extent of the disintegrant action of MCC found in formulations containing KCl, was not based on an absolute MCC concentration, but rather, it also varied with other formulation factors. For example, formulation 2L contained MCC at a concentration of 29% w/w, which at the same concentration in formulation 2E (table 2.1) had caused "capping" to occur during the release process (section 2.3.3).

2.3.7.2   Measurement of Tablet Thickness

When examined visually, HVO – based tablets did not appear to swell or erode during the release process. Quantitative evaluation was carried out by measuring both tablet diameter and thickness for formulation 2L before and after dissolution testing at 50 rev min^{-1}. No consistent increase or decrease was found, with a difference of no greater than 0.008 mm in thickness and 0.003 mm in diameter being recorded. This represents percentage changes of 0.38% and 0.03% respectively and was taken as further evidence that the release process was neither swelling nor erosion controlled.

2.3.7.3   Data Analysis

Since all the drug release profiles obtained conformed to the pattern of apparently exponentially decreasing cumulative drug release with increasing time it was decided to analyse the data according to first – order and square – root time
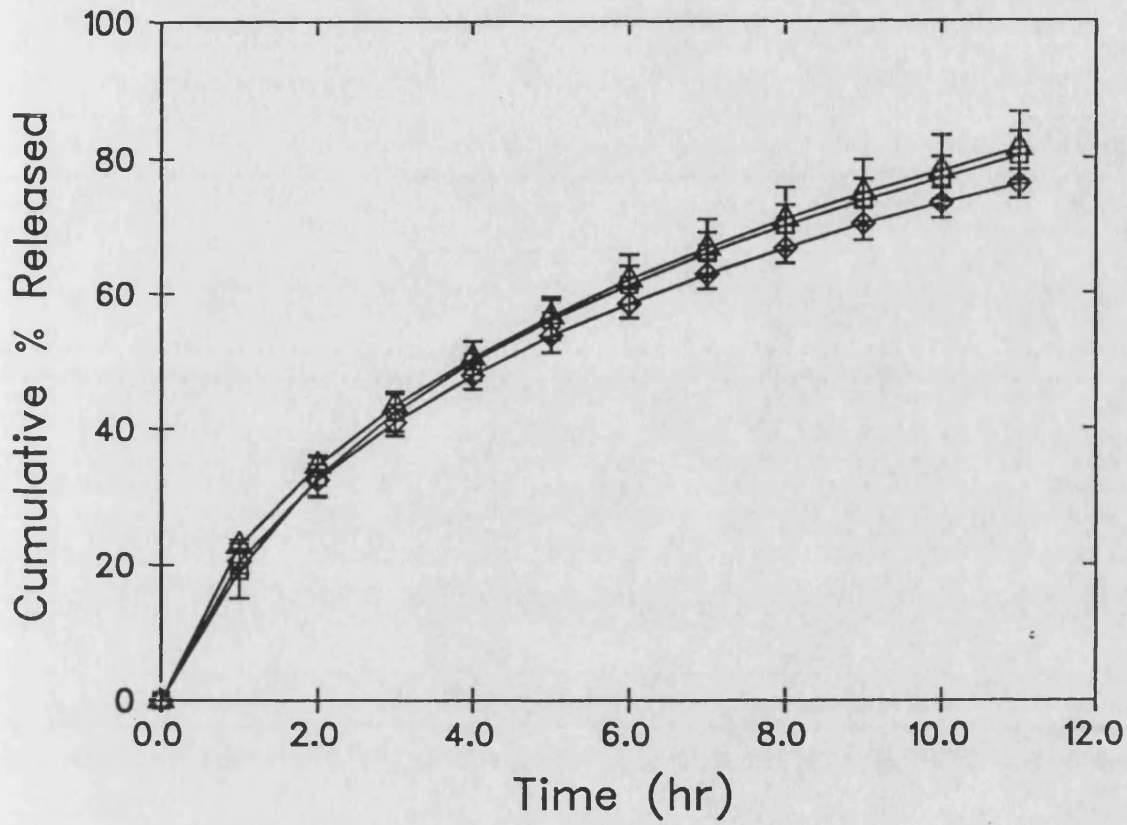
Figure 2.9 Effect of paddle stirring speed on drug release profile of formulation

2L (table 2.1)

Key: ◇ =   50 rev min^{-1}

          △ = 100 rev min^{-1}

          □ = 150 rev min^{-1}

models, since both models could be expected to give such release profiles. The release data from formulation 2L (table 2.1) was analysed according to a first–order model using the following relationship:–

$$\log_{10} M = \frac{K_1 t}{2.303} + \log_{10} M_o \qquad .....\text{equation 2.4}$$

where K_1 = first–order rate constant

    M   = mass of drug remaining at time t

    M_0 = initial mass of drug

For drug release from a tablet according to this first–order model a plot of $\log_{10} M$ versus time would produce a straight line having a slope $-(K_1/2.303)$. Data for formulation 2L was plotted according to this relationship except that percentage remaining was used in place of mass remaining (figure 2.10).

The data was also analysed according to the square–root of time model using the simplified form of the Higuchi equation (section 1.4.5.2 above):–

$$Q = k_H t^{\frac{1}{2}} \qquad .....\text{equation 1.25}$$

A plot of Q versus $t^{\frac{1}{2}}$ should therefore give a linear plot having slope k_H, and the data is plotted according to this relationship in figure 2.11 except that cumulative percentage released is used instead of mass. Examination of these two plots indicate that both are approximately linear, with slight curvature observed after a lag period in figure 2.11 and hence both models appeared to be potentially applicable to the data. The method of further analysing the data to distinguish between the two models which was described above (section 1.4.5.2.1) was therefore employed. It involves differentiating the above equations with respect to time in order to examine the time dependency of release rate.
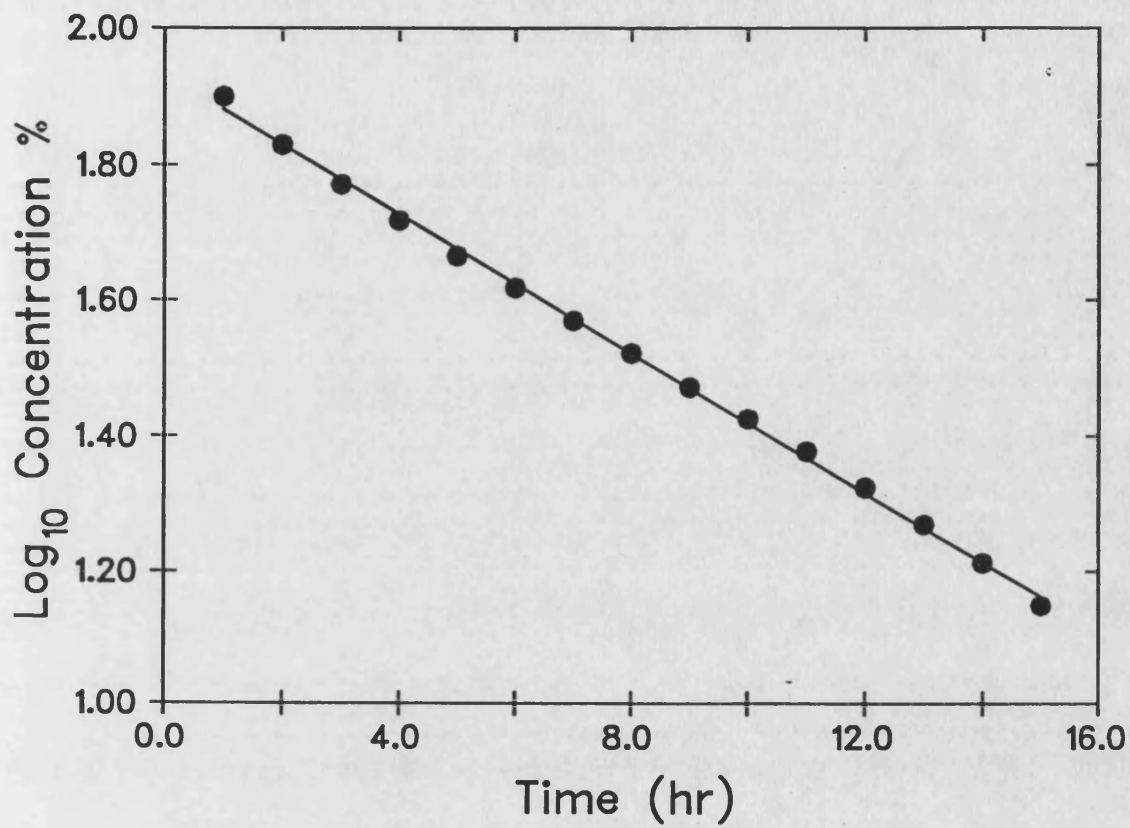
Figure 2.10 Log_{10} percentage original drug concentration remaining versus time for

formulation 2L (table 2.1)
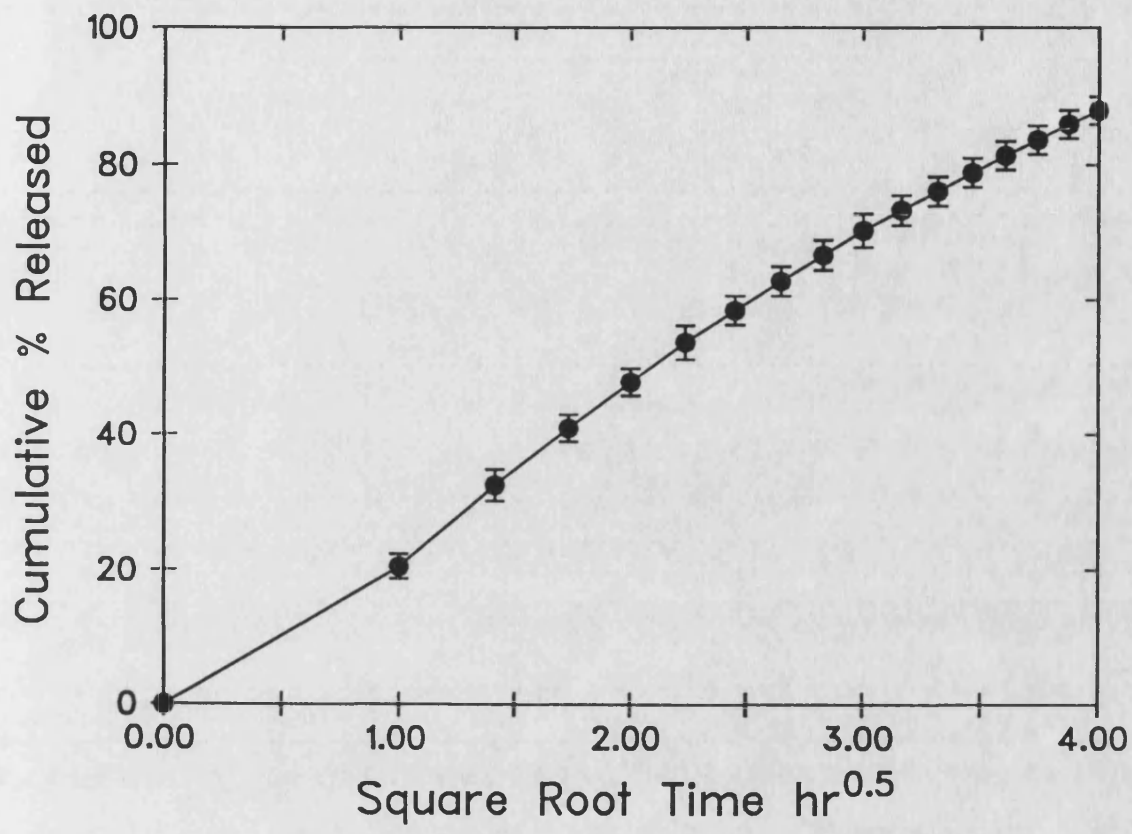
Figure 2.11   Cumulative   percentage drug released   versus   square – root   time   for

formulation 2L (table 2.1)

Differentiation of equation 2.4 gives:-

$$\frac{dQ}{dt} = kM_0 - kQ \qquad \text{.....equation 2.6}$$

since

$$M = M_0 - Q \qquad \text{.....equation 2.7}$$

and

$$-\frac{dM}{dt} = kM = \frac{dQ}{dt} \qquad \text{.....equation 2.8}$$

Differentiation of equation 2.2 gives:

$$\frac{dQ}{dt} = \frac{k^2}{2Q} \qquad \text{.....equation 2.9}$$

Hence the first-order model predicts that rate is proportional to Q and the square-root model predicts that rate is proportional to $1/Q$. The data was analysed according to these latter two equations in the following manner: the rate of release at each time point t_i on the cumulative percent drug released versus time curve (i.e. the derivative) was approximated by use of the equation given below:-

$$\text{slope} = \frac{Q(t_{i+1}) - Q(t_{i-1})}{t_{i+1} - t_{i-1}} \qquad \text{.....equation 2.10}$$

where $Q(t_i)$ = cumulative amount released at time t_i

Figure 2.12 shows the slopes (i.e. rates) obtained using equation 2.10 plotted against drug released and figure 2.13 shows the same data plotted against $1/Q$. It is clear that only the second plot is approximately linear, proving that the square-root time model is the most appropriate description of the release profiles obtained.

Since drug release from HVO tablets was found to conform to the Higuchi model, drug release was concluded to be controlled by diffusion. As discussed above in section 1.4.5.2, devices from which release conforms to Higuchi model kinetics are
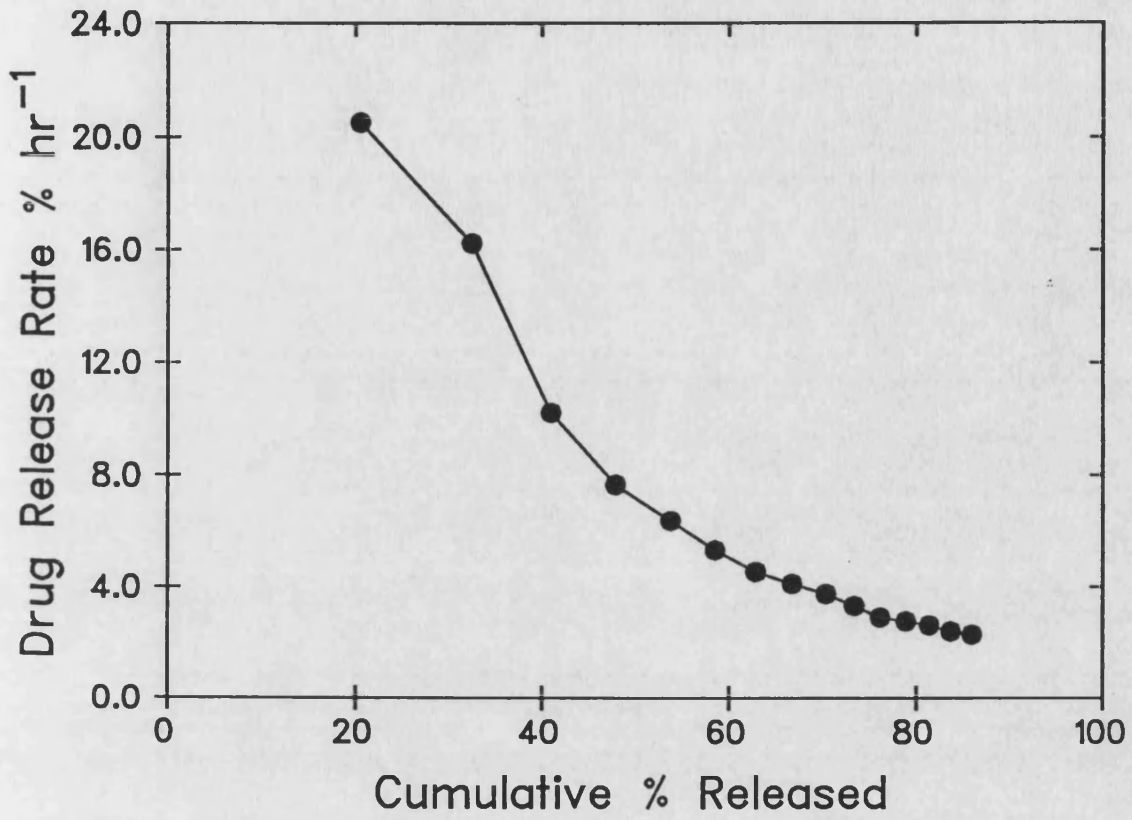
Figure 2.12   Drug   release   rate versus cumulative percentage   drug   released   for

formulation 2L (table 2.1)
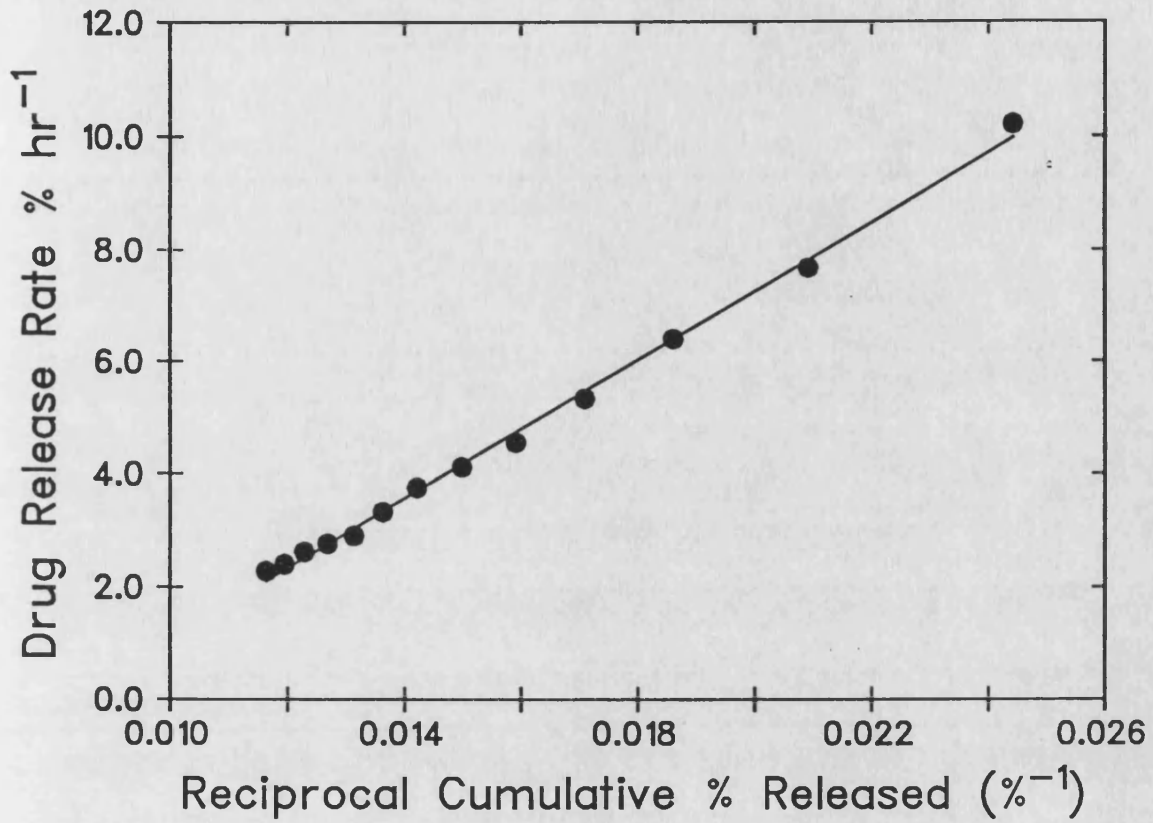
Figure 2.13 Drug release rate versus reciprocal cumulative percentage drug released for formulation 2L (table 2.1)

termed matrices, of which there are several types. There are two types where ⸱ the drug is dispersed in the matrix phase at a concentration in the delivery system above its solubility in the matrix phase – dispersed systems and porous systems. In dispersed systems drug release occurs via a diffusion process through the matrix material itself, and the matrix remains unpenetrated by the dissolution medium. This process is described by equation 1.22. In porous systems the matrix is penetrated by the dissolution medium and drug diffusion occurs along the fluid – filled channels within the matrix, a process which is described by equation 1.24. It was postulated that the second process was likely to be the predominant mechanism controlling drug release from HVO matrices for the following reasons. Firstly, drug release from dispersed systems generally takes place over periods of days rather than hours (35). This substantial prolongation of drug release occurs because the diffusion coefficient of a drug solute molecule in a solid is several orders of magnitude smaller than that of a drug solute molecule in water. Secondly, the process of matrix production by compression of powdered drug and matrix material is unlikely to produce a system which is compressed to such a low porosity that the drug is effectively completely dispersed in a continuous matrix phase. Thirdly, since matrices containing a high proportion of MCC have been observed to disintegrate to some degree during the release process, and this has been explained by the disintegrant effect of MCC caused by its interaction with water, this indicates that water penetrates HVO – based matrices containing MCC. The fourth reason was the results of the qualitative examination of leached matrices described immediately below.

2.3.7.4   Qualitative Assessment of Water Penetrability of   Hydrogenated   Vegetable
Oil – based Tablets

After removal from the amaranth solution, tablets produced from formulations containing HL and MCC were found on sectioning to be coloured red throughout. A small, uncoloured portion was found in the centre of the tablets containing DPD but

the majority of the sectioned surface of the tablets was coloured red. This confirmed that water penetrated HVO tablets during the release process and that the porous model was applicable.

2.3.7.5 Scanning Electron Photomicrography of Tablet Surfaces

Photomicrographs of the flat and diametral fracture surfaces of tablets are shown in figure 2.14. Clefts or pores can be seen on the surfaces of the tablets and a pore structure is also evident within the tablet itself. This is further evidence that a pore structure is formed which can be penetrated by dissolution medium.

2.3.7.6 Fitting of Drug Release Data to the Higuchi Square−Root of Time Kinetic Model

Data and information obtained in sections 2.3.7.2 *et seq* above showed that the form of the Higuchi equation applicable to HVO matrices was equation 1.24, which is repeated here:−

$$Q = D\in/\tau(2A - \in C_s)C_s t^{\frac{1}{2}} \qquad \text{.....equation 1.24}$$

where Q = mass of drug released per unit surface exposed to dissolution medium

        D = diffusion coefficient of drug in the dissolution medium

        $\in$ = void fraction or porosity of the fully leached matrix

        C_s = solubility of the drug in the dissolution medium

        A = initial mass of drug in the matrix per unit volume

        τ = tortuosity factor of the matrix

        t = time

From a comparison of equation 1.24 with equation 1.25 it can be seen that the constant k_H in equation 1.25 is hence equal to the term $(D\in/\tau)(2A - \in C_s)C_s$, each

Figure 2.14 (Overleaf). Scanning electron photomicrographs of outer flat surface

(upper photomicrograph) and diametral fracture (lower photomicrograph) surface of

tablets of formulation 2I (table 2.1)

5KU X75 100μm 000911

5KU X75 100μm 000910
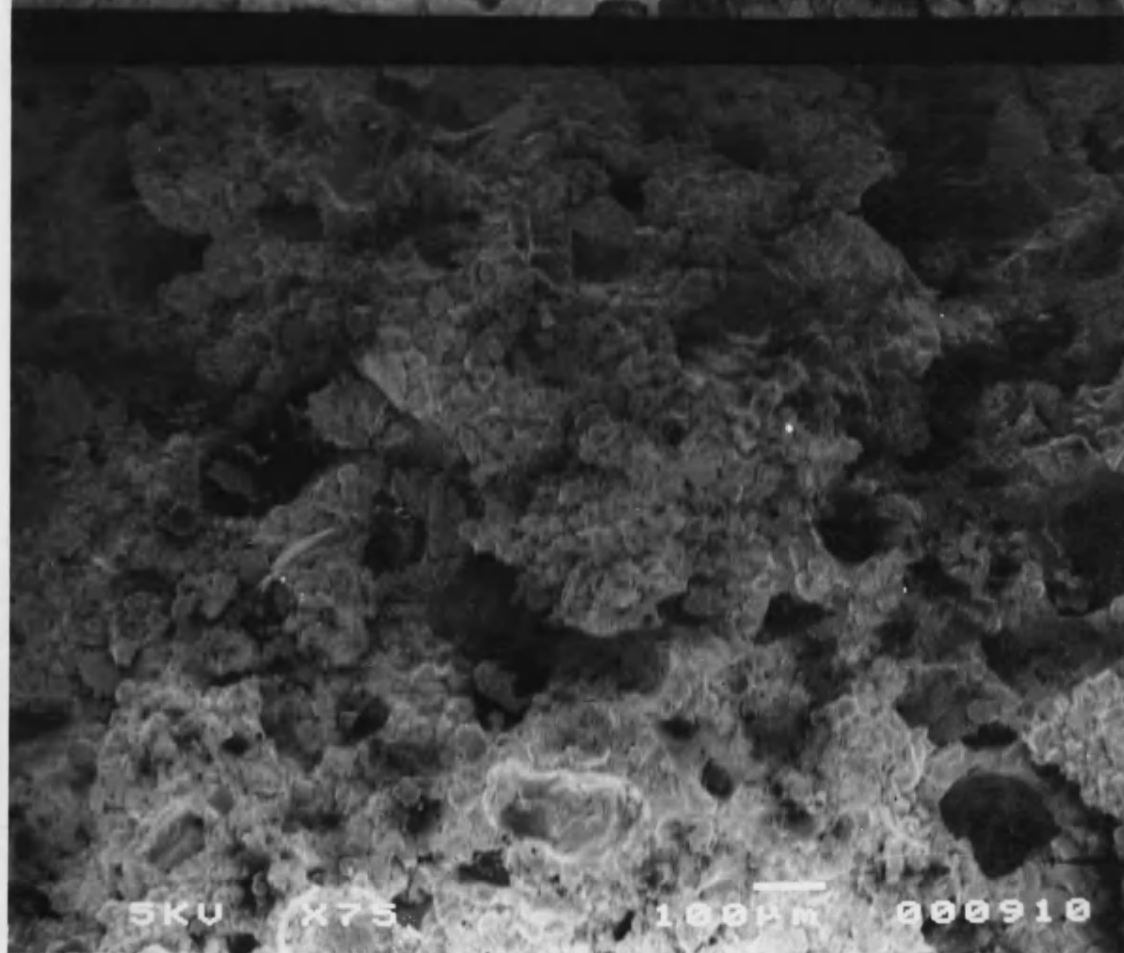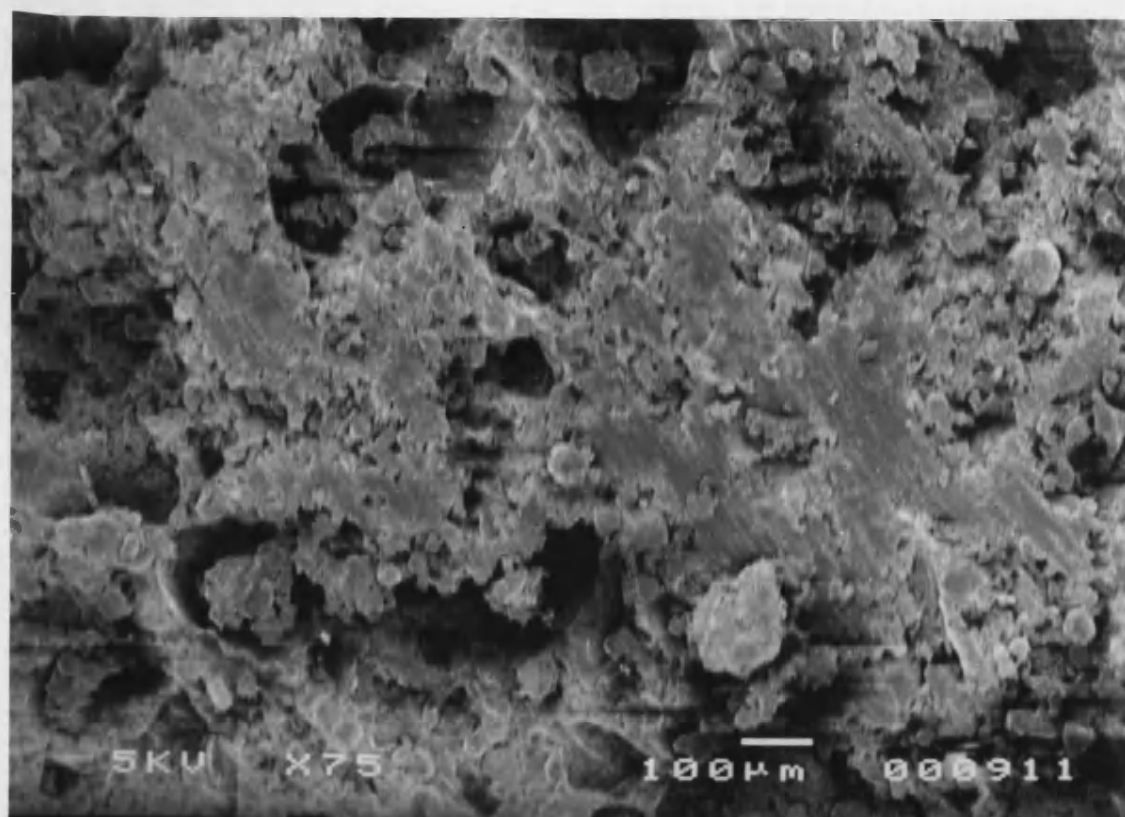
factor of which is constant. This indicates that a change in any of these constants would alter Q, thereby providing several factors which could potentially be used to regulate drug release characteristics.

Application of the porous Higuchi model for drug release may be useful in explaining different release rates observed with the HVO formulations studied above. All the release data obtained above were re-analysed according to the Higuchi model and plotted against square-root time. Those formulations for which almost complete release was measured showed some tailing off in the latter stages of release (e.g. figure 2.11). This can be explained by the fact that the Higuchi model is not applicable during the latter stages of release, above approximately 60% released. This is because the pseudo-steady state assumption cannot be made when drug is no longer present in the tablet as a solid. The slight curvature of the data was also attributed to the fact that drug release studies were performed on whole tablets rather than from single planar faces, which as discussed above (section 1.4.5.2) would cause a slight deviation from linearity. Least squares regression analysis was performed on only the linear portion of each release profile (i.e. up to less than approximately 60% released) to obtain slope and intercept values for each formulation. These data are tabulated in table 2.2.

For many of the formulations, a positive intercept was obtained. This can be explained by the presence of drug on the surface of the tablet which dissolved when the tablet was first immersed in dissolution fluid. For the theophylline formulation however, a negative intercept was obtained, reflecting the existence of a lag time of approximately 1 hour before a constant, higher slope was achieved.

In section 2.3.2, the effect of drug loading was investigated and examination of the slopes of formulations 2A – 2C indicated that drug release rate increased with drug loading. This follows from the Higuchi equation since an increase in the A factor, which will also result in an increased porosity, will cause an increase in release rate.

In section 2.3.3 the effect of MCC content was investigated. Examination of

the slopes indicates that drug release rate increased with increasing MCC concentration (and concomitantly decreasing HVO) concentration. In this case the A factor remains approximately the same. The differences between the formulations must therefore be explained on the basis of differences in either porosity and/or tortuosity. Although linear portions of the profiles for tablet formulations which did not remain discrete throughout the release process were obtained, the Higuchi equation could not be applied quantitatively to the data since the surface area for release would not remain constant during the release process.

Formulation	Slope ($\%hr^{-\frac{1}{2}}$)	Intercept (%)	r^2
2D	70.3	8.19	0.9982
2E	64.6	9.42	0.9974
2F	42.0	4.49	0.9925
2G	15.9	10.9	0.9963
2H	26.4	12.0	0.9990
2I	15.2	14.4	0.9951
2J	74.1	-3.49	0.9972
2K	18.3	-7.61	0.9926
2L (50 rev min^{-1})	25.2	-3.40	0.9987
2L (100 rev min^{-1})	28.3	-7.74	0.9936
2L (150 rev min^{-1})	26.5	-2.93	0.9974

Table 2.2   Least squares regression analysis of drug release data for formulations 2C – 2L

(table 2.1)

In section 2.3.4 the effect of different inert directly – compressible diluents on drug release was examined, whilst the drug:HVO ratio was maintained constant at

1:1. Examination of the slopes indicates that the formulation containing MCC exhibited the fastest release rate, that containing HL exhibited the next fastest and the formulation containing DPD exhibited the slowest release rate. As before, the A factor for these tablets is approximately similar, but since HL is soluble, the porosity of this formulation was higher than for the other two formulations and the drug release rate consequently higher. This explains the difference in drug release rates when comparing the HL formulation with the formulation containing DPD but does not explain why the formulation containing MCC exhibits the fastest release rate of the three formulations. This apparently anomalous result can probably be explained in terms of the disintegrant action of MCC discussed above (section 2.3.3). However it is also possible that the MCC causes water to be drawn into the tablet when first immersed in water much more rapidly than would be the case with either HL or DPD. As discussed above (section 1.4.5.2.1), slow wetting has been shown to be a factor in decreasing release rate from matrix systems and since HVO is known to be considerably hydrophobic and hence slow to wet, release from HVO matrices may be decreased as a result of this mechanism. Further evidence to support this hypothesis is the fact that when the water penetrability experiment was performed (section 2.3.7.4), an uncoloured and therefore unwetted section was found in the centre of the tablet containing DPD after 12 hours in amaranth solution, indicating that the wetting process was not complete.

The effect of drug solubility was investigated in section 2.3.6 above and it was found that increasing drug solubility increased release rate, which was reflected in the slopes of the appropriate curves and can be explained by the increase in the C_s term in the Higuchi equation. The lag time which was found to occur with the theophylline formulation was taken as further evidence that wetting of the matrix takes place slowly.

It is interesting to note that the Higuchi equation assumes that the entire matrix is wetted at time = 0 and hence contains no factors to account for any wetting phase which may occur during a portion of the release process. If slow

wetting does have an influence on release rate as the data above suggests, then the Higuchi equation can only reflect this by using a falsely high value for the matrix tortuosity factor, which would not be an accurate representation of the true matrix pore structure.

2.3.8 Effect of pH of Dissolution Medium on Drug Release Characteristics

Since an HVO matrix would encounter different pH environments during release *in vivo*, the effect on release rate from the system was studied by performing dissolution testing in buffers of pH 2.0 and 6.0. The drug release data obtained are shown in figure 2.15. Least squares regression analysis of the linear portions of the release data yielded the following statistics:

Buffer pH = 2.0   Slope   = 24.9% $hr^{-\frac{1}{2}}$

                    Intercept = -1.11%

                    r^2 = 0.9982

Buffer pH = 6.0   Slope   = 22.4% $hr^{-\frac{1}{2}}$

                    Intercept = 1.84%

                    r^2 = 0.9947

Water   Slope   = 25.2% $hr^{-\frac{1}{2}}$

                    Intercept = -3.40%

                    r^2 = 0.9987

It can be seen that the difference between the drug release rate in water and that in buffer solution of pH = 2.0 is small but that there is a slightly larger difference in drug release between that in water and buffer of pH = 6.0. A test was hence required to determine whether there was a statistically significant difference between the slopes. A suitable test is to calculate the slope of each one of the 6 tablets in a release rate determination and calculate mean and
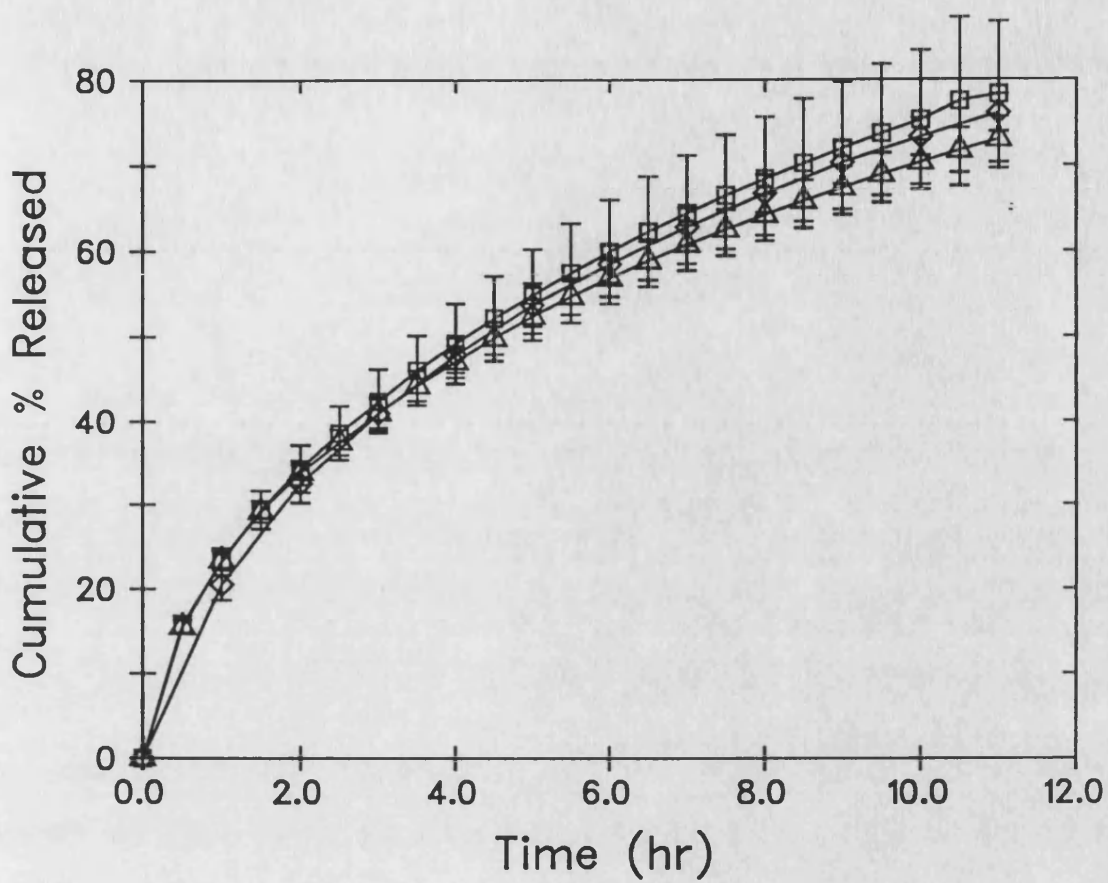
Figure 2.15 Effect of pH of dissolution medium on drug release profile of

formulation 2L (table 2.1) in comparison to drug release profile in water

Key: □   = water

         ◇   = buffer pH 2.0

         △   = buffer pH 6.0

standard deviation values. A Student–t test can then be used to test for significant difference between the mean slopes calculated in this way. The mean and standard deviations of the slopes of the release data in water and the two buffers were hence calculated and the following statistics obtained: –

Buffer pH = 2.0   Mean slope (s.d.) = 24.9% $hr^{-\frac{1}{2}}$ (2.96)

Buffer pH = 6.0   Mean slope (s.d.) = 22.4% $hr^{-\frac{1}{2}}$ (0.672)

Water   Mean slope (s.d.) = 25.2% $hr^{-\frac{1}{2}}$ (0.837)

Student–t values for the comparison between the mean slope for water and those for the two buffers were calculated. The value of t for the difference between water and buffer at pH = 2.0 was 0.274 and the result is hence not significant (p = 0.7856). The value of t for the difference between water and buffer at pH = 6.0 was 6.43 and this result suggests that a small but significant difference between release rates in water and buffer at pH = 6.0 exists (p < 0.0001). Since HVO is composed of saturated hydrocarbons, it was considered unlikely that dissolution medium pH would affect it chemically. One possible explanation is that the diffusion coefficient of theophylline was decreased in phosphate buffer compared with in water, and it was also hypothesised that the difference might be due to changes in the wicking and disintegrant behaviour of MCC in phosphate buffer compared with in water.

2.3.9 Effect of Hydrogenated Vegetable Oil Particle Size on Drug Release Characteristics

The drug release data obtained from the two batches of formulation 2K (table 2.1) prepared from two different sieve size fractions of HVO are shown in figure 2.16. The data were analysed by least squares regression of each individual slope and the following statistics were obtained: –

Size fraction < 355 µm   Slope (s.d.) = 25.2% $hr^{-\frac{1}{2}}$ (0.837)

                                       Intercept   = – 3.40%
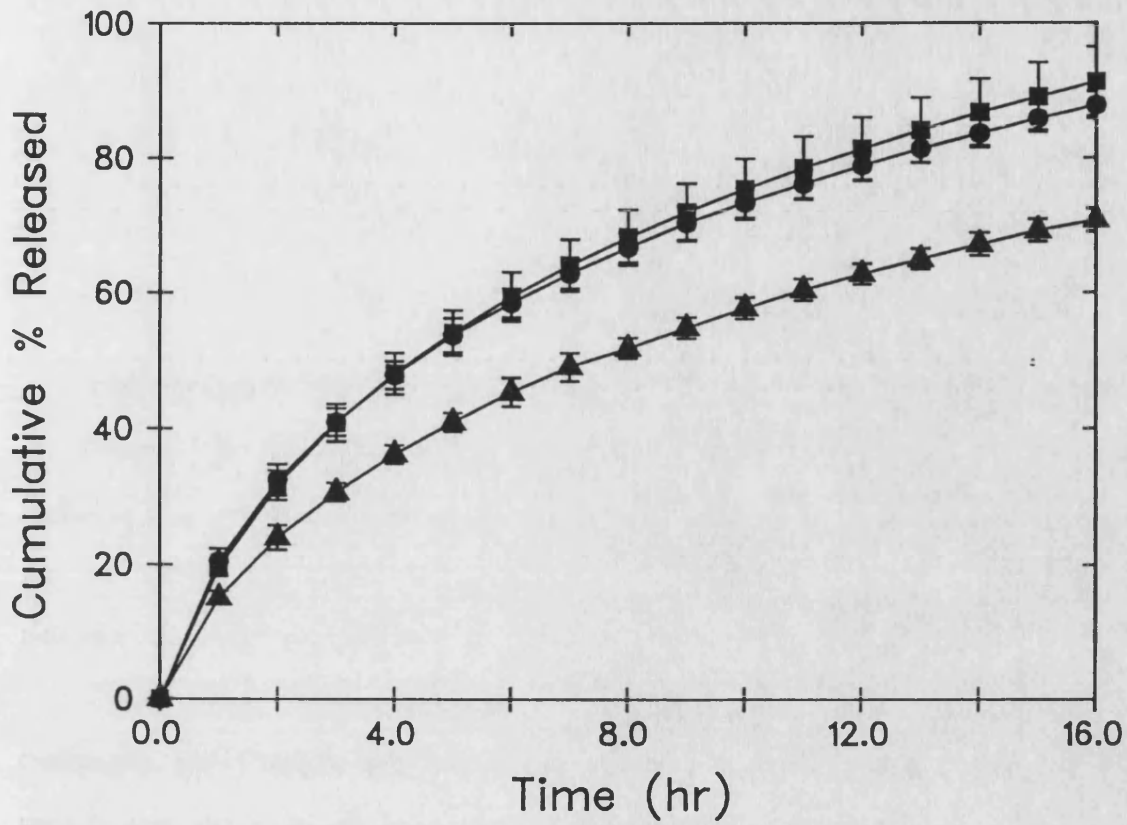
Figure 2.16 Effect of particle size of hydrogenated vegetable oil on drug   release

profile of formulation 2L (table 2.1)

Key: ● = < 355 µm

■ = 125 – 355 µm

▲ = < 125 µm

$$r^2 \quad = 0.9987$$

Size fraction 355 – 125 μm Slope (s.d.) = 27.1% $hr^{-\frac{1}{2}}$ (1.51)

Intercept = –1.76%

r^2 = 0.9961

Size fraction < 125 μm Slope (s.d.) = 19.7% $hr^{-\frac{1}{2}}$ (0.228)

Intercept = –2.14%

r^2 = 0.9986

Comparisons of the mean slopes of the release data of the < 355 μm and the 355 – 125 μm size fractions using a t–test yielded a t value of 2.80, which is indicative of a significant difference ($p = 0.019$). The same test on the < 355 μm and the < 125 μm size fraction release data yielded a t value of 17.9 which is also indicative of a significant difference in drug release ($p < 0.0001$).

These results indicate that drug release rate decreased significantly with decreasing HVO particle size fraction, with the decrease caused by removal of particle sizes above 125 μm being particularly marked. Since the formulations were identical apart from HVO size fraction the only factors in the Higuchi equation which could be changed to account for the differences in release rate are porosity and tortuosity. Porosity would not be expected to vary widely between these formulations and it was thus concluded that a smaller particle size fraction of HVO resulted in the formation of matrices with higher apparent tortuosity than with larger size fractions. This increase in tortuosity may either be due to physical differences in the way the matrices were formed during compaction and/or may be due to differences in rates of matrix wetting, as described in section 2.3.7.6 above.

These differences could be usefully exploited during formulation of an HVO–based delivery system, since release rate could be adjusted to some extent by varying the size fraction of the HVO used to produce tablets of a given formulation.

Formulation	Composition
2A	KCl 80% / HVO 20%
2B	KCl 70% / HVO 30%
2C	KCl 60% / HVO 40%
2D	KCl 40% / HVO 20% / MCC 39% / MS 1%
2E	KCl 40% / HVO 30% / MCC 29% / MS 1%
2F	KCl 40% / HVO 40% / MCC 19% / MS 1%
2G	KCl 40% / HVO 50% / MCC 9% / MS 1%
2H	KCl 40% / HVO 40% / HL 19% / MS 1%
2I	KCl 40% / HVO 40% / DPD 19% / MS 1%
2J	NaS 40% / HVO 40% / MCC 19% / MS 1%
2K	THE 40% / HVO 40% / MCC 19% / MS 1%
2L	THE 40% / HVO 30% / MCC 29% / MS 1%

Table 2.1   Composition of tablet formulations prepared in chapter 2

Key: KCl = potassium chloride

HVO = hydrogenated vegetable oil

MCC = microcrystalline cellulose

MS = magnesium stearate

HL = hydrous lactose

DPD = dicalcium phosphate dihydrate

NaS = sodium salicylate

THE = theophylline

Chapter 3

Determination of Tortuosity Factors I: Measurement of Air Flow Rate and Pressure

Drop through Matrices

3.1   Materials

Silica gel: self–indicating, lot 5735980P, supplied by BDH Chemicals   Ltd.,
Poole, U.K.

Sodium dodecyl sulphate: specially pure, lot 5201860J, BDH Chemicals

Polyvinyl chloride: high molecular weight (approximately 200,000), GLR grade,
lot 4573670G, BDH Chemicals

White Beeswax BP: lot OFQ2968, supplied by Evans Medical Ltd., Speke, U.K.

LR White Resin: medium grade, lot R1281/3, supplied by Agar Aids Ltd.,
Stansted, U.K.

Molecular Sieve: supplied by Silica Gel Ltd., London, U.K.

Acetone: lot 5313410J, supplied by Fisons Scientific Apparatus Ltd.,
Loughborough, U.K.

Mercury: triple–disilled, supplied by Belgrave (Mercury) Ltd., London,   ·
U.K.

Helium: supplied by British Oxygen Company, Brentford, U.K.

Air: British Oxygen Company

Vacuum Grease: "Apiezon–N", supplied by Apiezon Products, London, U. K.

Polyacrylic Adhesive: "Uhu", supplied by Beecham UHU, Brentford, U.K.

Epoxy Resin Adhesives: "Araldite" and "Araldite Rapid", supplied by Ciba–Geigy
Plastics, Duxford, U.K.

3.2   Methods

3.2.1   Determination of Tortuosity Factors from Drug Release Data

It was hypothesised in Chapter 2 that some of the differences in drug release
profiles which were observed between a number of different formulations of HVO–
based matrices were due to differences in tortuosity of the tablet cores. It was
proposed to test this hypothesis by quantitative application of the Higuchi
equation to release data from HVO matrices to allow tortuosity values to be

determined. This would also allow further exploration of a second hypothesis, that release from some HVO-based matrices may be decreased by a wetting phase. As discussed in section 2.3.7.6 above, if wetting of matrices was a significant factor controlling drug release, then the Higuchi equation (equation 1.24) can only account for this phase by indicating a falsely high value for the tortuosity factor. Hence if the tortuosity values calculated from release data were too high to be physically realistic (i.e. greater than approximately 10) as discussed above (section 1.4.5.2.1), this would provide evidence that a wetting phase may be the true practical reason for decreased release rates. Further evidence to support this hypothesis would be provided by the determination of tortuosity factors by a method which was completely independent of drug release data, for comparison with those calculated from release data.

In order to apply the Higuchi equation quantitatively, release kinetics must be measured from one single planar surface of a matrix. The release data described in chapter 2 were obtained from all faces of the tablet matrices and hence equation 1.24 could not be used to determine tortuosity values.

As described above (section 1.4.5.2), modifications of the Higuchi equation have been proposed (equations 1.26 and 1.27) which describe drug release from cylindrical matrices. The use of equation 1.26 or 1.27 would allow analysis of the release data in chapter 2 to be performed, and would also enable calculation of tortuosity factors. However, the aqueous solubilities and diffusion coefficients of the drugs used would have to be accurately known, and in the case of equation 1.26, a method of non-linear regression employed to determine the constant K_r. It was decided that a simpler and more accurate approach would be to prepare some model HVO-based formulations and perform drug release studies from one planar surface, thus allowing the direct application of the Higuchi equation to the release data. The drug chosen was sodium salicylate, since values for aqueous solubility and diffusion coefficient have been already determined by Desai et al (164) in some of the original experimental work performed on porous matrices.

Equation 3.16 is thus substituted back into equation 3.12, which is then modified in the same way as equation 3.14 by the inclusion of (L/L_e) to give:-

$$u = (L/L_e)^2 \frac{\in^3 \delta P}{2S^2 vL} \qquad \text{.....equation 3.17}$$

Since L_e/L is equivalent to tortuosity τ, the Carman – Kozeny equation can be re-written as:-

$$u = \frac{\in^3 \delta P}{2\tau^2 S^2 vL} \qquad \text{.....equation 3.18}$$

The factor B_0 in equation 3.8 can therefore be defined as:-

$$B_0 = \in^3/(2\tau^2 S^2) \qquad \text{.....equation 3.19}$$

The Carman – Kozeny equation thus constitutes a relationship which includes a tortuosity factor. It has been used to predict flow rates with applied pressures and *vice versa* by measurement of B_0. One of its other main uses has been in the determination of specific surface area of porous media, whether "unconsolidated" such as packed samples of powder or "consolidated" such as rocks or concrete. Matrices can hence be regarded as porous media for the purposes of this equation. When the Carman – Kozeny equation is used to measure specific surface area a value for tortuosity must be either assumed or determined.

The product $2\tau^2$ is often referred to as the Kozeny constant K_K, and is further defined as:-

$$K_K = k_x(L_e/L)^2 \qquad \text{.....equation 3.20}$$

where k_x = factor dependant on the cross – sectional shape of a pore (which equals 2.0 for a pore of circular cross – section)

Hence, pore cross-sections with shapes other than circular can be accounted for. Other values range from 1.67 to 2.65 for pores having equilateral triangular cross-sectional shape and rectangular (with the longest side greater than the shortest by a factor of 10) cross-sectional shape respectively. Experimental determinations showed that for unconsolidated media, i.e. powder beds, K_K generally equals 5.0. Carman (207) observed the path of a coloured streamline through a loosely packed bed of glass spheres. The streamline appeared to adopt an average direction at an angle of $45°$ to the direction of flow and therefore he took L_e/L as $1/\cos 45°$ or 1.414. This agreed well with experimental data on K_K, giving a shape factor of approximately 2.5.

Tortuosity has been determined more directly by the measurement of conductivity of fluid-filled porous media (208). If the pore space is filled with an electrically-conducting solution such as an aqueous solution of sodium chloride, then the specific conductance of a unit cube of the medium will be less than that of the solution itself (assuming that the porous medium itself is a non-conductor). The fluid-filled cross-section of the medium available to pass current will be equal to the total cross-section multiplied by the porosity $\in$. The current must follow a tortuous path which is longer than the length of the sample, further reducing the conductance. Hence the ratio J_c of apparent specific conductance to true specific conductance (i.e. in solution) will be:-

$$J_c = \in/q \qquad .....\text{equation 3.21}$$

where q = a tortuosity factor greater than 1.

A similar relationship should exist between the apparent diffusion coefficient of a gas in air-filled porous medium, and the true diffusion coefficient of the gas in air. Specific conductance and diffusion measurements hence provide methods for determining the tortuosity factor q directly. The relationship of q to L_e/L is

given by (209):-

$$q = (L_e/L)^2 \qquad\qquad \ldots\ldots\text{equation } 3.22$$

This relationship will be discussed further in chapter 4. Values of q determined by conductance and diffusion measurements on unconsolidated media have been found to be in the range 1.1 to 2, with many values around 1.5 (208). These agree reasonably well with the observed value of 5 for the Kozeny constant, since some variability of the shape factor k_x would also be expected. Values of q have also been determined for consolidated media, and have been found to be higher than those for unconsolidated media, with values up to 22 being recorded (210).

Where matrices are concerned, the method of measuring tortuosity by specific conductance could not be used, since the porous medium must be completely saturated with conducting solution. Since it was hypothesised that drug release is decreased by slow or incomplete wetting, this method cannot be used in the present study. This leaves the diffusion method which will be investigated in chapter 4. It was considered that it may be possible to use the Carman−Kozeny equation itself to determine tortuosity, providing that matrix specific surface area was known or could be determined using an independent method.

3.2.2.2 Development of a Constant Pressure Air Permeameter

As discussed in the above section, the Carman−Kozeny equation has been used as a basis for determining the specific surface area of powder samples, by assuming that the Kozeny constant always equals 5. One of the most common types of apparatus used to perform these kinds of measurement is the constant pressure air permeameter, which is often known as the Lea and Nurse permeameter, after its originators (211). A schematic diagram of the Lea and Nurse apparatus is shown in figure 3.1. Air at constant pressure above atmospheric is applied to the upper surface of the sample; the pressure drop across the sample is measured using the
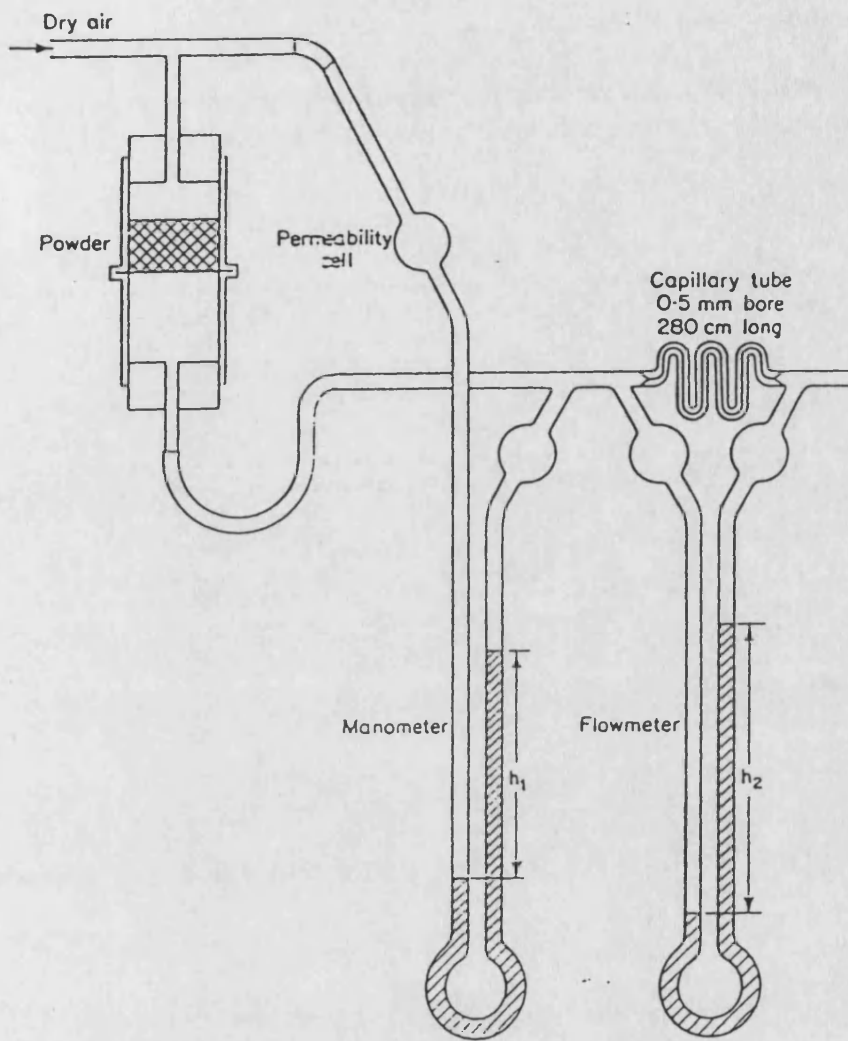
Figure 3.1   Schematic diagram of Lea and Nurse constant pressure air permeameter

first manometer, and the volume rate of flow is calculated using the second manometer.

A modified version of the Lea and Nurse apparatus, including a sample cell, was designed and constructed using mild steel for the cell. A schematic diagram of the cell is shown in figure 3.2. Air was supplied from a bottled compressed source, fitted with coarse and fine head valves to allow small adjustments of pressure to be made. The air was dried by passing it through a packed column of length 50 cm and diameter 0.95 mm containing "Molecular Sieve" gas drying agent, which was dried periodically by leaving the column overnight in a fan oven at approximately 80°C. The column was connected at one end to the compressed air cylinder with copper tubing having an internal diameter of 6.4 mm using "Simplifix" screw connectors and at the other end to the sample cell using plastic tubing having an internal diameter of 1 cm. A branch was taken off the line between the drying column and the sample cell by means of a T–piece connector and connected to a glass manometer of length 1 m (Gallenkamp Ltd., Loughborough, U.K.). The manometer was attached to a mounting board using clips and secured in a vertical position. An air flow–meter ("Sho–Rate" Model 1350/1/A, Brooks Instrument Division, Stockport, U.K.) with a measuring range of 0.2 – 4 dm^3 hr^{-1} was obtained. The flow meter was connected to the bottom of the sample cell using 6.4 mm internal diameter nylon tubing, and clamped vertically to a retort stand. Hose clips were used to secure all plastic tubing joints.

All the joints in the system were checked for leaks by smearing a film of detergent solution on them, and observing for the appearance of soap bubbles when the system was under pressure. Any leaks were rectified by tightening the appropriate joints or clips. A sample tablet was attached to the top of the tube in the sample holder with adhesive PVC tape and the inlet and outlet parts of the holder were secured to the main section of the cell using hexagonal headed screws. A dilute aqueous solution of amaranth was used as the manometer fluid to facilitate the location of the meniscus position against the white mounting board.

Inlet tube

O – ring

Bolt

Tablet

O – rings

Outlet tube
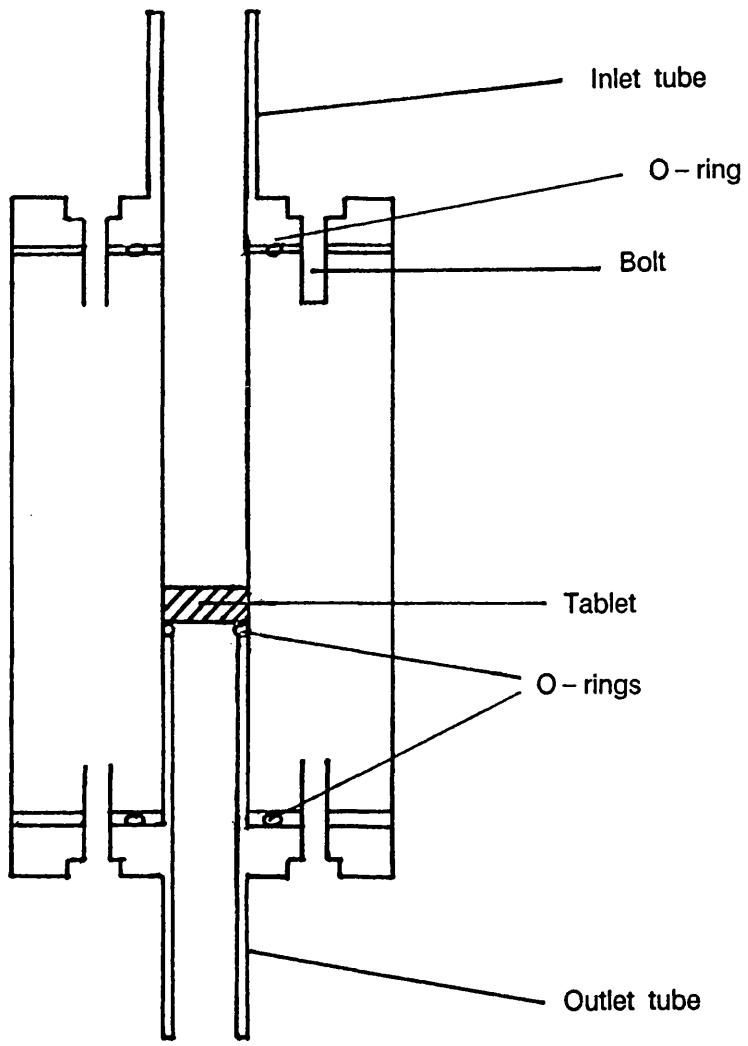
Figure 3.2 Schematic diagram of original permeametry cell: scale 1 cm = 1 cm

Permeametry was performed by application of pressure in small increments to the upper surface of the tablet in the holder and noting the flow rate as measured by the flow meter at each pressure. Equation 3.23 was used to calculate the pressure drop δP between the upper and lower faces of the tablet from the measurements of height increase caused in the manometer:—

$$\delta P = h_m \sigma g \qquad \ldots\ldots\text{equation 3.23}$$

where h_m = height increase

σ = density of manometer fluid

g = acceleration due to gravity

The density of the amaranth solution used as the manometer fluid was determined by equilibrating it at $20°C$ in a water bath, pipetting 100.0 cm^3 into a tared beaker and noting the mass. The density was calculated by dividing the mass of the amaranth by its volume.

Unfortunately, initial trials of the system using formulation 3A (table 3.1) indicated that repeatable results using the same tablet might not be obtainable. Apparently linear relationships between pressure drop and flow rate were obtained, but when a repeat series of measurements was performed, the flow rate at each pressure increased. It was considered that this might be due to allowing insufficient time for the flow rate to equilibrate at each pressure and for this reason the system was left under pressure for 24 hours, and the pressure and flow rate noted at intervals of time. This exercise was repeated using increased pressures. It was found that at lower pressures, flow rate equilibrium was reached within one minute, but that at higher pressures, the flow rate tended to increase with time. This suggested that an air leak was occurring at the higher pressures, and it was concluded from these trials that the seal formed around the tablet by the adhesive PVC tape was not robust and that higher pressures were liable to cause

the tape to separate from the tablet surface, breaking the seal around the tablet.

It was evident that some modification of the sample cell was required, in order to ensure that an air–tight seal was obtained around the sides of the tablet, even at high pressures. A piece of apparatus which had been previously used to measure the gas permeability of tablet coating films was modified according to the design shown in figure 3.3. The plastic tubing used with the first cell between the drying column and the cell was replaced with copper tubing and re–tested for air–tightness. The space in the cell for the tablet sample was circular with a diameter of 21 mm and depth 5 mm. It was decided that a good seal around the tablets might be achieved either by setting them in a resin mould shaped to fit this space or by gluing them into suitable holders. Sealing around the sides of such moulds or holders would be achieved by the pressure on the O–rings above and below them caused by the bolting down of the lid of the cell directly onto the upper O–ring. This arrangement was tested for air–tightness by obtaining a cylindrical piece of mild steel having similar dimensions to the sample holding space – 21 mm in diameter with a thickness of 5 mm. The metal cylinder was sealed in the sample holding space as described above; the O–rings were lightly greased with vacuum grease prior to insertion. The manometer used to measure the pressure drop was disconnected from the system, and the pressure gradually increased up to a reading of approximately 100 psi (690 kPa) as measured using the compresed air cylinder head gauge. This pressure was approximately 70 times the maximum used with the previous cell and no flow was registered at this pressure. It was concluded that the modified sample holding arrangement provided a good seal around the holder. The whole system was also re–checked for leaks at the same time, using the method described above.

A chemically–cured resin used for holding samples for microscopy was obtained and a circular mould of diameter 6 cm and thickness 6 mm with a circular hole of diameter 21 mm was constructed from mild steel. Initial experimentation indicated that the optimum ratio of curing agent to resin for a suitably rapid curing time

Inlet tubes

O – ring

Bolt

Sample holder

Tablet

O – ring

Outlet tube
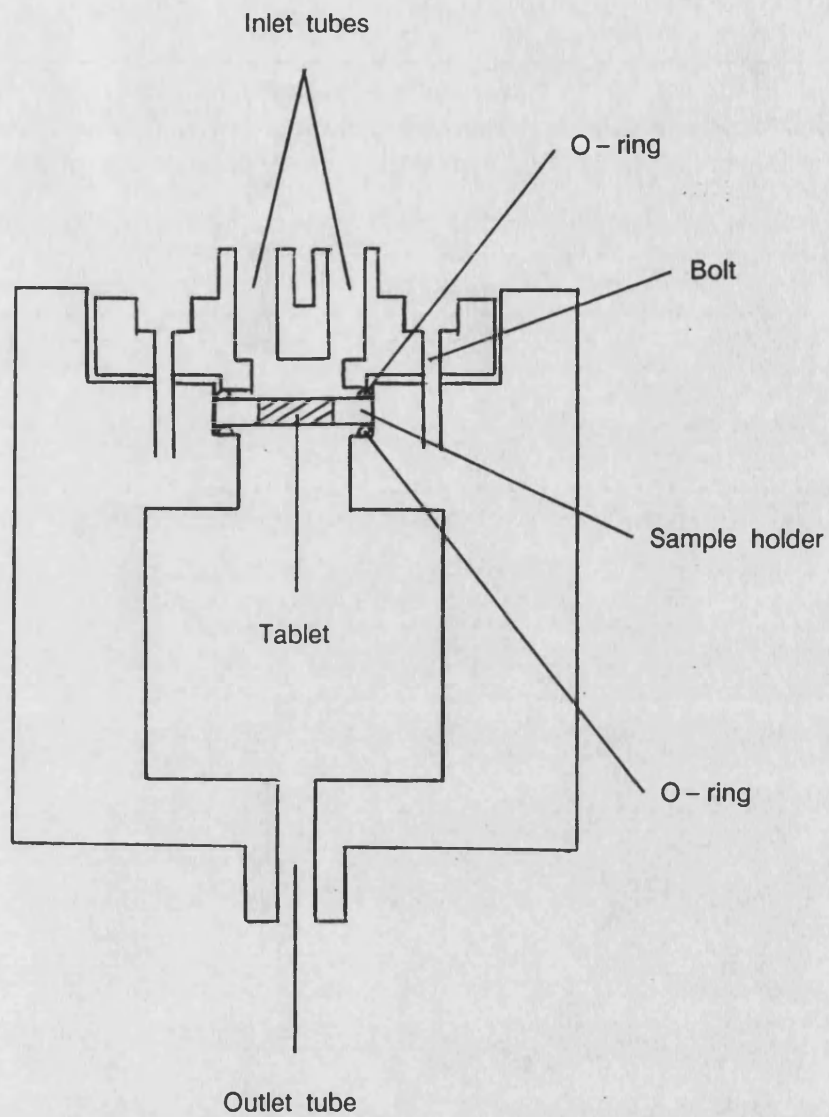
Figure 3.3 Schematic diagram of modified permeametry cell: scale 1 cm = 1 cm

was 3 drops to 5 cm^3 respectively. This hardened quickly enough to hold the tablet in the centre of the hole in the mould. The mould was lined with double-sided adhesive tape without the backing paper removed from the side in contact with the resin. This facilitated removal of the cured resin from the mould. The mould was placed on a steel plate supported on ice in a suitable container, in order to prevent heat from the exothermic curing reaction causing melting of any HVO in the matrices. The resin was prepared and pipetted into the mould around the tablet and allowed to cure for 15 minutes, after which time it was solid enough to be removed from the mould and was then allowed to cure completely overnight. Following trials using several tablets it was found that some could be pushed out from the resin after curing and it was considered that the air pressure in the permeameter would have the same effect.

For this reason it was decided to glue tablets into modified sample holders and holders were manufactured to the following design using stainless steel. In order to fit into the sample space in the cell described above, the modified sample holders were made cylindrical with a diameter of 21 mm, a thickness of 5 mm and with a central hole of diameter 10.4 mm to accommodate the tablet. This hole was slightly larger than the tablet diameter of 10.0 mm so as to allow space for a glue bond between the tablet and the wall of the sample holder. It was decided to test the air-tightness of the bonds formed by various types of glue between the tablet and the sample holder by gluing a piece of steel of the same dimensions as a tablet into a sample holder. The three glues tested were the epoxy resins "Araldite" and "Araldite Rapid" and the polyacrylic adhesive "UHU" and were allowed to set overnight. It was found that no flow was registered at pressures up to 690 kPa at the cylinder head gauge with any of the three glues. It was decided to utilise the polyacrylic adhesive as this was the simplest to use, since the mixing of two components did not have to be performed as it did with the two epoxy resins.

Initial trials of the system using tablets of formulation 3A (table 3.1) glued into holders with polyacrylic adhesive showed that no flow was observed at

3.2.1.1   Determination of True Density of Drugs and Excipients using Helium – Air Comparison Pycnometry

In order to measure the porosity of matrices, it was necessary to determine the true density of the matrix components. A helium – air comparison pycnometer (Model 1302, Micromeritics Instrument Corporation, Norcross, U.S.A.) was used for these measurements, connected to a helium source and a vacuum pump (Model E2M2, Edwards High Vacuum, Crawley, U.K.). Samples of drug and excipient were dried by placing them in a vacuum oven (Model OVL570, Gallenkamp, Loughborough U.K.) over dry silica gel; applying a vacuum of approximately 100 μm Hg for at least four hours with the vacuum pump attached to the oven and then leaving overnight under vacuum at room temperature. Following this treatment, samples were removed from the oven and immediately transferred to a desiccator containing dry silica gel. Samples were only removed from this container immediately before analysis and the desiccator was immediately re – sealed. The instrument was checked each morning with one of the standard masses supplied (a steel sphere of volume 8.58 cm^3). It was found that the instrument could take 30 – 60 minutes to give an accurate reading for this standard and so the machine was left switched on overnight before measurements were commenced each morning. It was also found that temperature fluctuations affected the precision of the measurements, and for this reason the instrument was situated in a position as isolated as possible from air currents originating from windows and doors. The sample container and standards were transferred to and from the instrument using forceps and a magnet respectively and the machine was not handled any more than was absolutely necessary.

Once an accurate reading for the standard had been established, measurements on the various samples were carried out until three results with a coefficient of variation of less than 3% had been obtained.

3.2.1.2   Production Of Model Matrices and Drug Release Studies

Tablets of the following formulations were prepared: –

3A: Sodium salicylate 20%/ HVO 40%/ DPD 39%/ MS 1%

3B: Sodium salicylate 10%/ HVO 40%/ DPD 49%/ MS 1%

3C: Sodium salicylate 5%/ HVO 40%/ DPD 54%/ MS 1%

Key: HVO − hydrogenated vegetable oil

DPD − dicalcium phosphate dihydrate

MS   − magnesium stearate

Note 1:   Information relating to the composition of all formulations used in   this

chapter is given in table 3.1 at the end of the chapter.

The reasons for choosing DPD as the filler were as follows: firstly, since DPD

was insoluble it would remain in the matrix during the drug release process and

therefore would not affect the final porosity of the matrices.   Secondly, DPD would

not prevent the application of the Higuchi application unlike the soluble filler

HL, since HL would dissolve and therefore act as a second diffusing species in

addition to drug, which cannot be taken into account by the Higuchi equation in its

basic form. Thirdly, it had not been found to exert any disintegrant action, unlike

MCC, and therefore would not potentially disrupt the matrix during the drug release

process.

The tablets were produced as described above in section 2.2.1.1, apart from

the following differences. In order to make the matrices of a particular

formulation as similar to each other as possible, tablets were produced manually

from pre−weighed powder samples instead of under power using the normal volumetric

filling system.   Individual powder samples of 500 ± 1 mg were weighed into glass

sample tubes and subsequently transferred to the tablet die.   The powder was then

compacted by actuating the tablet punches manually using the flywheel. This

procedure was performed at approximately the same speed each time, in order to

ensure that the compaction event was as reproducible as possible.

In these experiments, formulations were all prepared to approximately the same initial porosity rather than to the same diametral crushing strength, in order to minimise variability between formulations. The tablets of the first HVO formulation were prepared to a diametral crushing strength in the range 59 – 78 N and their diameter and thickness measured with a micrometer. The mean porosity of 10 tablets was calculated and the other formulations were prepared to approximately this porosity by adjusting die depth and compaction pressure accordingly. Porosity was calculated using the following equation: –

$$\in \ = \ 1 \ - \ (V_m/V_t) \qquad\qquad .....\text{equation 3.2}$$

where V_m = volume occupied by each component of the matrix

V_t = volume occupied by the matrix itself

V_m was calculated from the mass of the tablet and from a knowledge of the true density of each component (section 3.2.1.1). V_t was calculated from the geometrical formula for the volume of a cylinder using tablet radius and tablet thickness measurements.

In order to further test the hypothesis that slow wetting may decrease release rate from HVO – based matrices, it was also decided to prepare a matrix system which had been shown to wet rapidly when placed in dissolution fluid. This would allow comparison of release data and hence tortuosity factors. Matrices produced using polyvinyl chloride (PVC) have been shown by Carli and Simioni (186) to wet completely in 40 s. Tablets were therefore prepared using the following formulation in order to examine the influence of wetting on drug release from matrices: –

3D: Sodium salicylate 10%/ Polyvinyl chloride 90%

Magnesium stearate has been shown to inhibit penetration of liquid into

conventional tablets (200), although the time for uptake of 0.1 cm^3 of water only increased from 55.5 s to 80 s when magnesium stearate was included in a previously unlubricated formulation at a proportion of 1%. Nevertheless, it was decided not to include magnesium stearate in formulation 3D, since any inhibition of wetting was considered undesirable. Die wall lubrication was achieved by brushing with a suspension of magnesium stearate in acetone at a concentration of 5% w/v. The acetone was allowed to evaporate prior to tableting and the operation was repeated before each tablet was compacted. The tablets prepared in this manner were removed from the tablet machine and stored with the face which had been in contact with the upper punch of the tablet machine uppermost. This procedure was adopted because the lower punch was also covered with magnesium stearate when the die wall was lubricated which inevitably contaminated the lower surface of the tablet with lubricant. The uncontaminated upper tablet face was hence used as the surface from which drug release was studied.

Drug release studies from single planar faces of matrices have generally been achieved by forming some type of water–impermeable barrier around the other surfaces (163). This was accomplished in these experiments by melting approximately 30 g of white beeswax in a porcelain evaporating dish using an electric heating mantle and allowing it to cool to just above its melting point. A tablet from which release was to be studied was then carefully lifted by its upper surface using suction applied through a glass pasteur pipette attached by a flexible hose to a vacuum pump, and placed in the cooling wax so that the lower planar and cylindrical surfaces were immersed. It was then immediately removed, which resulted in a solid coat of wax being deposited on the immersed surfaces. This process was repeated rapidly three further times, which resulted in the build up of a wax coat approximately 2 mm thick. The wax was allowed to cool to room temperature before drug release studies were commenced.

An advantage of coating with this material was that since the white beeswax was slightly malleable at room temperature, it was found that it could easily be

removed from a tablet by making a small incision in the coat with a scalpel blade and peeling the coat off. This property was desirable in order to allow studies of leached matrix cores to be carried out.

In order to confirm that the wax coat was impermeable to water and drug, 6 tablets of formulation 3A (table 3.1) were coated in the manner described except that all their faces were covered in the wax. The small hole left by the suction pipette was sealed using a small drop of molten wax applied from a pasteur pipette. A dissolution test was then carried out for 24 hours as described in section 2.2.6.3 above. No release of sodium salicylate was detected and it was concluded that this method produced a suitable water- and drug-impermeable barrier coat.

The partially-coated tablets were attached to metal discs of diameter 20 mm and thickness 2 mm with a small amount of molten white beeswax which was allowed to cool. This procedure ensured that the uncoated surface of the tablet could be placed in a reproducible orientation in the bottom of the dissolution vessel, i.e. parallel to the plane of rotation of the paddle. Dissolution testing was carried out as described above in section 2.2.6.3.

Desai et al (167) have shown that drug release rate from some porous matrices can be increased in the presence of surfactant dissolved in the dissolution medium. This was attributed to one or both of the following two effects. Firstly, the incomplete removal of air from the matrix when dissolution is performed in water and hence the incomplete wetting of the available pore space. This could result in a falsely high porosity being used in the Higuchi equation and consequently inaccurate tortuosity values would be obtained. Secondly, in the presence of surfactant the rate of permeation of the matrix could be increased, indicating that slow wetting was decreasing release rate.

It was consequently decided to

perform release studies in surfactant solutions. The surfactant selected for use in the present study was sodium dodecyl sulphate (SDS). Desai et al (167) found no

change in sodium salicylate solubility, diffusion coefficient or the absorbance versus concentration curve in the presence of SDS at a concentration of 0.2% w/v. For this reason SDS solution was used at this concentration and dissolution testing was performed on formulations 3A – 3C (table 3.1) using this solution as the dissolution medium. The drug release profiles obtained were compared with those obtained using water as the dissolution medium.

3.2.1.3   Calculation of Tortuosity Factors

Least squares regression analysis was performed on the linear portions of the drug release data. The slope thus estimated was equal to the constant term in the Higuchi equation: –

$$slope = \{(D \in C_s / \tau)(2A - \in C_s)\}^{\frac{1}{2}} \qquad .....equation\ 3.3$$

Rearrangement of equation 3.3 to make tortuosity the subject results in: –

$$\tau = \{D \in C_s (2A - \in C_s)\}/slope^2 \qquad .....equation\ 3.4$$

The term A (initial concentration of drug in the tablet), was calculated from a knowledge of the proportion of sodium salicylate in the tablet and the volume of the tablet calculated from its radius and thickness. The porosity term $\in$ was calculated, assuming that 100% of the drug had been leached out of the tablet, by adding the porosity caused by drug removal to the initial porosity. The values used for aqueous solubility C_s and diffusion coefficient D of sodium salicylate were those determined by Desai *et al* (164), as mentioned in section 3.2.1. Tortuosity factors for the various formulations could hence be calculated and compared.

3.2.2   Rationale for Determination of Tortuosity Factors Independently of Drug Release Data

A serious limitation of use of the Higuchi equation is that the tortuosity
factor can only be calculated indirectly, by means of drug release studies. It is'
therefore impossible to determine every parameter of the Higuchi equation prior to
drug release studies, and thus produce matrices which will release drug at a
particular desired rate. For the same reason, it has not been possible to
quantitatively validate the Higuchi equation by the fully independent determination
of each of its factors. Desai *et al* (165) developed a method to measure tortuosity
which involved the complete leaching of drug from matrices, followed by re –
saturation with drug in solution, and finally immersion in fresh dissolution medium
and re – measurement of drug release. It was postulated that drug release from this
solution – saturated matrix could be described by the following relationship: –

$$Q \quad = \quad 2 \in C_r (Dt/\pi)^{\frac{1}{2}} \qquad .....\text{equation 3.5}$$

where C_r = concentration of drug solution used to re – saturate the matrix

It is possible to determine tortuosity from the slope of the solution release
data, by rearrangement of this equation.

This method suffered from the disadvantage that it required the completely
leached matrices to be resaturated with drug solution, a process which took 2 – 3
weeks to accomplish. It also relied on further drug release studies. Measurement of
tortuosity by a method independent of release studies was hence desirable. If such
a method could be developed, then the effect of various formulation parameters on
tortuosity could be studied and matrix formulations produced which would exhibit
desired drug release profiles. It would also enable a test of the validity of the
Higuchi equation, since it would be possible to measure every parameter
independently of release data, predict a release rate for a given matrix and hence

test the equation against the experimentally determined rate.

3.2.2.1 Theory of Gas Flow Under Pressure through Porous Media

Darcy's law describes the basic relationship governing fluid flow in pipes or cylindrical tubes and permeability. It states that the rate of flow is directly proportional to the pressure gradient causing flow. If a volume V flows in time t across a cross sectional area A_x the apparent linear flow velocity u is given by:-

$$u = V/A_x t \qquad \qquad .....\text{equation 3.6}$$

Darcy's law further defines u in terms of the pressure drop δP across a sample of thickness L and a permeability coefficient B_1:-

$$u = (B_1 \delta P)/L \qquad \qquad .....\text{equation 3.7}$$

If it is assumed that the flow is entirely viscous streamline in nature i.e. the fluid is incompressible and does not interact in any way with the medium it is flowing through, then flow rate will be inversely proportional to the viscosity v of the fluid. The permeability coefficient can be modified:-

$$u = (B_0 \delta P)/(vL) \qquad \qquad .....\text{equation 3.8}$$

where B_0 = specific permeability coefficient for viscous flow

In order to be able to calculate pressures required to achieve certain flow rates, it has been attempted to quantify B_0 in terms of measurable parameters of porous media. The Carman–Kozeny equation is an attempt to achieve this and is derived from Poiseuille's law which describes flow through a tube of circular cross–section. It is assumed that the pore space can be modelled as a set of cylindrical tubes arranged in parallel. Poiseuille's law states:-

$$u_t = \frac{d_t^2 \delta P}{32 v L_t} \qquad \qquad \text{.....equation 3.9}$$

where d_t = diameter of the tube

             u_t = flow velocity in the tube

             L_t = length of the tube

The problem of defining a pore diameter is surmounted by using the concept of hydraulic radius. For a tube of complex cross-section hydraulic radius is defined as the cross-sectional area normal to flow divided by the wetted perimeter. If the tube is of uniform cross-section throughout its length, hydraulic radius will be equal to the volume filled with fluid divided by the wetted surface area. For a tube of circular cross-section, the hydraulic radius is the diameter divided by 4. A porous medium can be considered to have a fractional free cross-section equal to its porosity $\in$ and if this pore space is assumed to be a single tube of complex cross-section, then using the concept of hydraulic radius:-

$$r_h = \in / S \qquad \qquad \text{.....equation 3.10}$$

where r_h = hydraulic radius

           S = surface area of the pore space

Substituting hydraulic radius for diameter in Poiseuille's equation (3.9) gives:-

$$u = \frac{(4r_h)^2 \delta P}{32 v L} \qquad \qquad \text{.....equation 3.11}$$

Substituting equation 3.10 into equation 3.11 gives:-

$$u = \frac{\in^2 \delta P}{2 S^2 v L} \qquad \qquad \text{.....equation 3.12}$$

It was realised by Dupuit (206) that the actual velocity in the pore space was larger than the apparent linear velocity of flow. He deduced that the relationship between the two factors was: −

$$u_e = u/\in$$

.....equation 3.13

where u_e = effective velocity in the pore space

If this relationship is substituted into equation 3.12, since the velocity term in that relationship is describing the velocity in the pore space, we get: −

$$u = \frac{\in^3 \delta P}{2S^2 vL}$$

.....equation 3.14

Kozeny further assumed that the path through the porous medium would be tortuous, with an average effective pore length L_e greater than than the thickness of the medium L. Equation 3.14 can hence be re−written in terms of L and L_e: −

$$u = \frac{L \in^3 \delta P}{L_e 2S^2 vL}$$

.....equation 3.15

The ratio L_e/L is termed the tortuosity factor. It was noted by Carman (207) that if a tortuosity factor is to be introduced, then the Dupuit relationship (equation 3.13) must be modified. This is because if the path of fluid flow is tortuous, the velocity in the pore must be larger than than the equivalent linear velocity of flow. He deduced that the time taken to pass through a tortuous path of length L_e at a velocity u_e corresponded to the time taken to pass through a distance L at a velocity $u/\in$. The velocity u_e was hence defined as: −

$$u_e = \frac{uL_e}{\in L}$$

.....equation 3.16

−120−

pressures measurable with amaranth solution as the manometer fluid i.e. up to approximately 10 kPa. Higher pressures up to approximately 130 kPa were applied and measured using mercury as the manometer fluid. (The density of mercury at $20°C$ (13546 kg m^{-3}) was obtained from tables (212)). No flow was recorded. These trials confirmed that the results obtained with flow at low pressures with the first sample cell were erroneous, but it was clear that higher pressures than were measurable with a manometer would be required before there would be a possibility of achieving measurable flow through the tablets.

Trials were conducted using tablets of formulation 3D (table 3.1), since these had been produced to a slightly higher porosity than tablets of formulations 3A – 3C (table 3.1) and hence might have been expected to be more permeable. It was found that flow was achieved at pressures measurable with mercury as the manometer fluid and that linear relationships between pressure drop and flow rate could be obtained. Again though, these were not found to be consistently repeatable on the same tablet, and wide variability was found between different tablets. Also it was sometimes not possible to achieve a linear relationship; in these cases a gradually increasing slope of gas flow with pressure was obtained. As well as measuring the change in flow rate as pressure was increased, changes in flow were also measured as pressure was decreased and in some cases a hysteresis effect was found with the flow at a given pressure always being higher in the decreasing pressure cycle.

A digital – reading pressure meter (Model KM5007 I.S., Kane – May, Welwyn Garden City, U.K.) was obtained and incorporated into the permeameter in place of the manometer so that the two could be interchanged as necessary. The meter was capable of measuring pressures up to a maximum of 700 kPa. Tablets of formulation 3A were subjected to pressure up to 700 kPa, however, inconsistent results were again obtained. Out of a total of 10 tablets tested, no flow was registered with 5; low flow rates of less than 0.4 dm^3 hr^{-1} were registered at approximately 600 kPa and above with 3 tablets and with 2 tablets flow was registered at low pressures of approximately 5 and 10 kPa.

These results further suggested that the seal formed between the tablet and the holder was leaking in some cases and this was confirmed by examining the tablets which had been subjected to high pressures. Several had been partially forced downwards out of the sample holders, indicating that the polyacrylic adhesive bond was insufficiently strong to withstand high pressure. The tests were repeated with tablets glued into the holders with "Araldite Rapid" epoxy resin adhesive and no flow was registered at pressures up to 700 kPa with any tablets of formulation 3A (table 3.1). All future tests were hence carried out on tablets glued into holders with this adhesive.

It was concluded that the problem of no flow being registered with HVO matrices of formulation 3A (table 3.1) was due to the low initial porosity of the matrices (section 3.3.1.2 below), which suggested the absence of sufficient continuous paths through the matrix for enough flow to be measurable at the pressures used. For this reason it was decided to carry out permeametry on matrices which had been completely leached of drug. Using leached tablets also effectively allowed measurement of the tortuosity of the path taken by a dissolved drug molecule, since the space which dissolved drug particles left would contribute to the final porosity of the matrix.

Air permeametry was therefore performed as described on matrices produced from formulations 3A – 3D (table 3.1), which had been leached of drug using the method described in section 3.2.2.3 immediately below. A further modification to the permeameter which was carried out at this stage was the replacement of the original flow meter with a more accurately calibrated capillary flow meter (Model "Meterate" RS1/GF/P AIR, Glass Precision Engineering, Hemel Hempstead, U.K.), which measured flow over the range 2 – 50 cm^3 min^{-1} (0.12 – 3.0 l hr^{-1}).

3.2.2.3 Preparation of Leached Matrices

Matrices were leached of drug in the following manner. A dissolution test was carried out on 6 tablets each of formulations 3A – 3D (table 3.1). Instead of

removing the matrices from the dissolution apparatus after the test had finished they were left in the dissolution vessels with the paddles stirring and the pump circulating fluid to the spectrophotometer. The matrices were left in these conditions until the absorbance readings from each sample were constant. These readings were noted and the matrices removed from the vessels. The time taken from the start of the test until constant readings were reached was also noted. Leached matrices were gently rinsed with distilled water and excess water was removed from their surfaces by blotting with tissues. The matrices were then dried by placing them in a vacuum oven over silica gel; a vacuum of approximately 100 μm Hg was maintained for at least four hours and then the leached matrices were left under vacuum overnight at room temperature. The wax coat was then removed from the tablets as described in section 3.2.1.2. Data from these experiments were then used to establish a leaching method which did not require prolonged use of the dissolution apparatus.

Two shaking water baths were obtained and each fitted with 12 conical flasks of 100 cm^3 capacity sealed with ground glass stoppers. 100.0 cm^3 of water was pipetted into each flask and allowed to equilibrate to 37°C. Matrices were set in white beeswax as described in section 3.2.1.2 and one matrix was placed in each flask. Although the volume of water in each flask was only 1/10th that in the dissolution vessels, this still represented sink conditions for the drug used. Sink conditions are defined as being at least 5 to 10 times the volume required to dissolve the total amount of drug in the matrix (213). The solubility of sodium salicylate is 0.65 g cm^{-3} (164) and the maximum amount of drug present in a matrix is 100 mg. Sink conditions would hence be achieved by ((100 ÷ 650) x 10) = 1.54 cm^3. The volume of 100 cm^3 was hence well in excess of that required.

The shaking water baths were set to 40 strokes per minute and each formulation was left for the same amount of time as it had taken for the absorbance readings to become constant as described above. 10.0 cm^3 aliquots were then removed from the relevant flasks, diluted to 100.0 cm^3 and their absorbance measured. In cases where

the concentration of drug leached from a matrix was the same as that found when the

formulation was leached in the dissolution apparatus, the tablets were removed from

the flasks and dried as described above. When leaching was found to be incomplete,

10.0 cm^3 of water was replaced in the flasks and the tablets were left for a

further 24 hours. The process was repeated until complete leaching had been

achieved.

3.2.2.4   Determination of Specific Surface Area of Leached Matrices using   Mercury Intrusion Porosimetry

As discussed in section 3.2.2.1, the Carman – Kozeny equation could only be used

to determine   tortuosity values if an independent method of   determining   specific

surface   area   was employed.   It was decided that the method of   mercury   intrusion

porosimetry would be the most appropriate, since it would give a value for specific

surface area which had effectively been wetted by mercury. This would in a sense be

analogous to the surface area term in the Carman – Kozeny equation, since that

relationship was derived from the concept of hydraulic radius which is defined   in

terms of wetted surface area. The other method of specific surface area

determination considered was gas adsorption,   but this was rejected on the   grounds

that it might give a value which included surface which effectively took no part in

the process of viscous flow.

The technique of mercury porosimetry is based on the   law   governing liquid

penetration into capillaries.   Mercury is a non – wetting liquid for   virtually   all

solid   surfaces i.e.   its contact angle is greater than 90° and   external   pressure

must   be   applied to enable it to enter a capillary in a   solid.   The   relationship

governing penetration is: –

$$d = -(1/P)4y\cos\theta \qquad\qquad .....equation\ 3.24$$

where   d = capillary diameter, assuming cylindrical geometry

P = pressure required to achieve penetration

y = surface tension of mercury

θ = contact angle of mercury on the pore surface

This relationship and the related expression describing the penetration of a wetting liquid into pores, the phenomenon known as capillarity, were first described by Washburn (214) and are often referred to by his name.

The instrument used for the porosimetry analyses (Model "Poresizer 9310", Micromeritics Instrument Corporation, Norcross, U.S.A.) provided manual low pressure (i.e. hypobaric) and automated high pressure (i.e. hyperbaric) control, up to a maximum pressure of 30,000 psia (approximately 2×10^5 kPa). Data on intruded volume at each pressure was recorded and subsequent data manipulation performed by an IBM compatible microcomputer (running proprietary software written by Micromeritics), which was linked to the instrument via a serial interface connector. In order to carry out a pore size analysis, a porous sample was first evacuated and then brought into contact with mercury. Hypobaric analysis was carried out by allowing mercury to flow into any macropores as pressure was allowed to rise in increments to atmospheric. For hyperbaric analysis, external pressure was applied to the mercury and the volume of mercury forced into any meso- and micro-pores was recorded. The pore diameter equivalent to a particular applied pressure was then calculated using equation 3.24. The pressure was then further increased and the volume intruded at each new pressure recorded; in this way a complete analysis of pore diameters present in a sample was obtained. The pore surface area was calculated from the pore diameter and the intruded volume at each pressure, assuming cylindrical pore geometry. From a knowledge of the sample mass, a measure of the intruded specific surface area was obtained.

The intruded pore specific surface areas of matrices from formulations 3A – 3D (table 3.1) which had been leached of drug as described in section 3.2.2.3 were determined in the manner described.

The leached matrices were stored under vacuum in a desiccator over silica gel

prior to pore surface area analysis to prevent any adsorbed water from entering the porosimeter. This was because the presence of adsorbed water can adversely affect the ultimate vacuum achievable and hence the accuracy of the measurements. The analyses were carried out on 3 samples from each formulation and a mean value for specific surface area was calculated. The data produced by the instrument also provided an analysis of pore size distribution and these data were also recorded.

3.2.2.5 Calculation of Tortuosity Factors from the Carman–Kozeny Equation and Comparison with Tortuosity Factors Calculated from Drug Release Data

The Carman–Kozeny equation predicts a linear relationship between pressure drop and flow rate for viscous flow through a porous medium. As noted in section 3.2.2.1, the equation takes the form:–

$$u = \frac{\in^3 \delta P}{2\tau^2 S^2 vL} \qquad .....\text{equation 3.18}$$

Equation 3.18 can be presented in the form $y = sx$, where s is the slope of the line. By rearrangement:–

$$s = \frac{\in^3}{2\tau S^2 vL} \qquad .....\text{equation 3.25}$$

Rearrangement of equation 3.25 gives:–

$$\tau = (\in^3/(2S^2 vLs))^{\frac{1}{2}} \qquad .....\text{equation 3.26}$$

Tortuosity was calculated using this relationship from the data obtained and the values were compared with those calculated from the drug release data.

3.3 Results and Discussion

3.3.1 Determination of Tortuosity Factors from Drug Release Data

3.3.1.1 Determination of True Density of Drugs and Excipients using Helium-Air Comparison Pycnometry

The true densities of the drug and excipients used in the preparation of matrices from formulations 3A – 3D were measured. The results are shown below in table 3.2.

Material	True Density kg m^{-3} x 10^3				
	Rep 1	Rep 2	Rep 3	Mean	% C.V.
Sodium Salicylate	1.59	1.58	1.59	1.59	0.36
Hydrogenated Vegetable Oil	0.99	1.03	1.00	1.01	2.07
Dicalcium Phosphate Dihydrate	2.24	2.34	2.35	2.31	2.63
Magnesium Stearate	1.11	1.07	1.05	1.08	2.84
Polyvinyl chloride	1.48	1.47	1.47	1.47	0.39

Table 3.2 True density of sodium salicylate and excipients as measured by helium-air comparison pycnometry

3.3.1.2 Production of Model Matrices and Drug Release Studies

The mean initial porosities of the matrices prepared were found to be:-

Formulation 3A: Mean porosity ± 95% C.I. = 0.11 ± 0.0055 (n = 10)

Formulation 3B: " " " " " = 0.12 ± 0.0060 "

Formulation 3C: "   "   "   "   "   = 0.13 ± 0.0064   "

Formulation 3D: "   "   "   "   "   = 0.15 ± 0.0072   "

The drug release profiles of formulations 3A – 3D in water are shown in figure 3.4, and the drug release profiles of formulations 3A – 3C in 0.2% w/v sodium dodecyl sulphate solution in figure 3.5. It can be seen that increased drug loading results in increased release rate, as might be expected. It can also be seen that a lag phase occurs before a constant slope is achieved, which may be due to the existence of an initial wetting period. A comparison of the release profiles of drug from formulations 3A – 3C occurring in water and surfactant shows that no marked increase in release rate was evident when surfactant solution was used to replace water as the dissolution fluid. These results appear to provide evidence against the hypothesis that slow wetting was a mechanism which may be responsible for decreasing the release rate of drugs from HVO – based matrices.

The drug release rate from a PVC matrix was faster than that from an HVO matrix containing the equivalent proportion of drug. This appears to provide evidence for the hypothesis, since if PVC was wetted instantaneously and HVO more slowly, then the release rate from the PVC matrix might be expected to be faster than that from the HVO – based matrix.

3.3.2.3   Calculation of Tortuosity Factors

The mean slopes of the linear portions of the release curves were calculated and are shown in table 3.3. Also shown in this table are the values for the A and $\in$ terms calculated for use in the Higuchi equation for each formulation. Student – t tests were performed to test for significant difference between the release rates in water and surfactant.
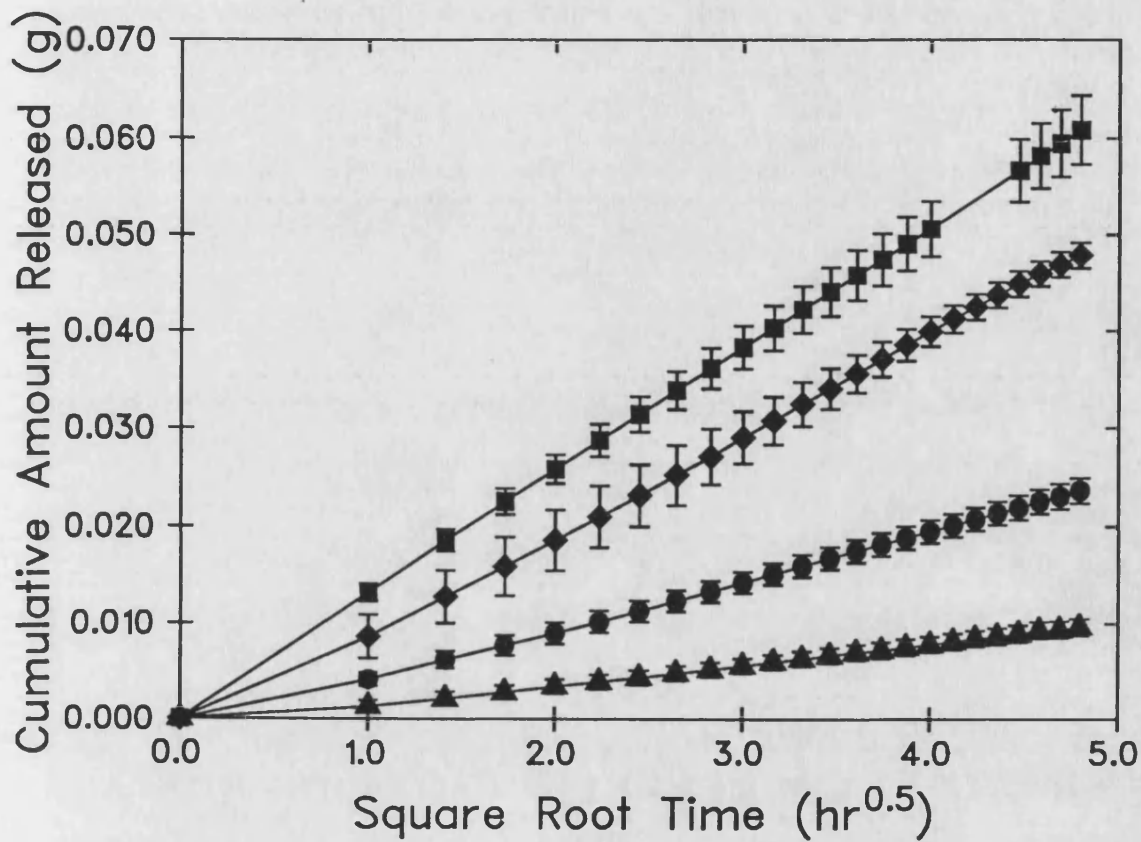
Figure 3.4 Drug release profiles in water of formulations 3A – 3D (table 3.1)
— effect of drug loading   :

Key: ■   = formulation 3A   NaS 20% / HVO 40%

        ●   = formulation 3B   NaS 10% / HVO 40%

        ▲   = formulation 3C   NaS 5% / HVO 40%

        ◆   = formulation 3D   NaS 10% / PVC 90%
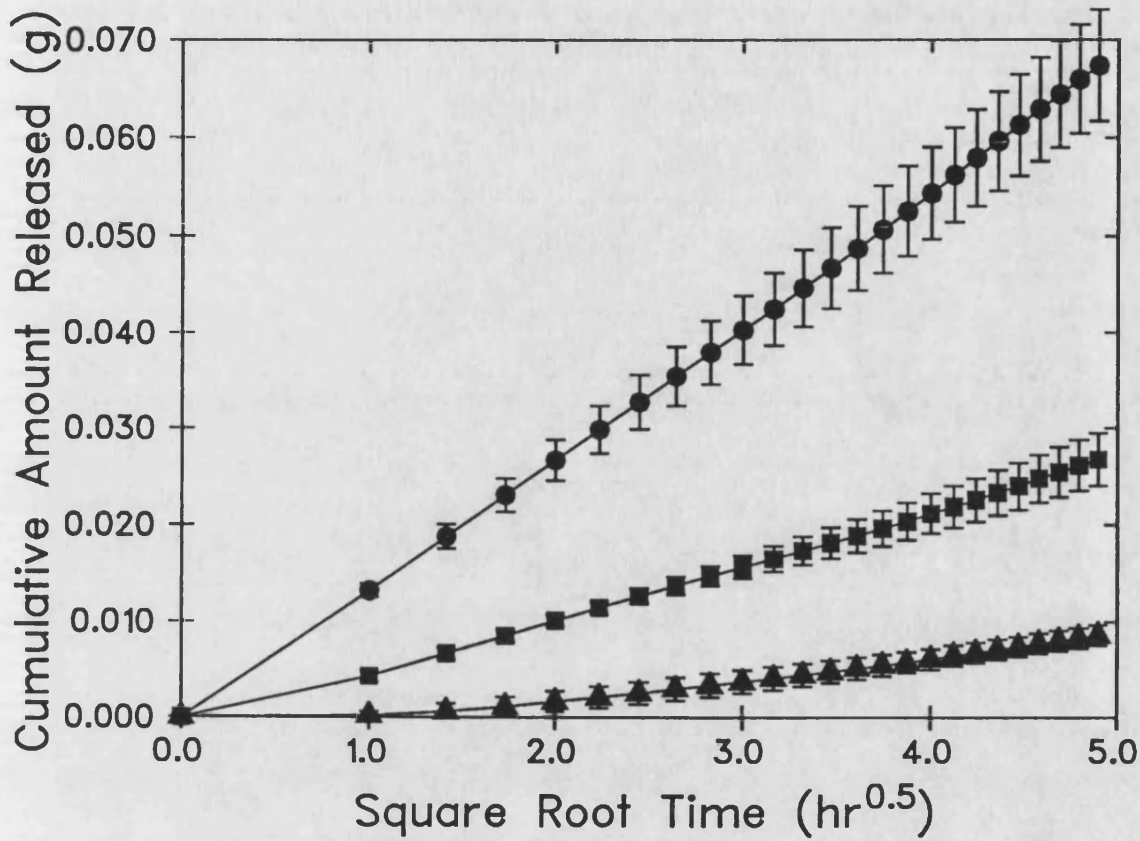
Figure 3.5   Drug release profiles in sodium dodecyl sulphate solution of

formulations 3A – 3C (table 3.1)

– effect of drug loading

Key: ● = formulation 3A   NaS 20% / HVO 40%

■ = formulation 3B   NaS 10% / HVO 40%

▲ = formulation 3C   NaS 5% / HVO 40%

Release Parameter	Formulation			
	3A	3B	3C	3D
A g cm^{-3}	0.259	0.134	0.067	0.127
Porosity $\in$	0.273	0.203	0.168	0.229
Mean slope (in water) g $s^{-\frac{1}{2}}$ cm^{-2}	2.10×10^{-4}	8.67×10^{-5}	3.73×10^{-5}	1.83×10^{-4}
95% C.I.	1.34×10^{-5}	3.58×10^{-6}	2.63×10^{-6}	1.04×10^{-5}
Mean Tortuosity τ	32.1	55.4	45.6	12.2
95% C.I.	3.86	4.47	6.86	2.4
Mean slope (in SDS) g $s^{-\frac{1}{2}}$ cm^{-2}	2.31×10^{-4}	9.45×10^{-5}	4.03×10^{-5}	–
95% C.I.	2.10×10^{-5}	1.32×10^{-5}	9.95×10^{-6}	–
Mean Tortuosity τ	26.7	48.4	43.7	–
95% C.I.	4.60	12.0	28.5	–

Table 3.3   Release parameters for formulations 3A – 3D in water and formulations

3A – 3C in surfactant (0.2% w/v SDS) solution

The t values obtained by performing this test on the mean release rates obtained in water and surfactant for formulations 3A – 3C are shown below with the relevant probabilities (p): –

Formulation 3A: t value = 2.21 (p = 0.0516)

Formulation 3B: t value = 1.69 (p = 0.123)

Formulation 3C: t value = 0.990 (p = 0.346)

None of these results are significant at the 5% level. This shows that there is no statistically significant difference between drug release rates in water and surfactant for any of the three HVO–based formulations.

The mean tortuosity values for the four formulations were calculated from the release data in water, using the values of Desai et al (164) for aqueous solubility (0.65 g cm^{-3}) and diffusion coefficient (2.31 x 10^{-5} cm^2 s^{-1}) of sodium salicylate. They are shown in table 3.2 and repeated below:-

Formulation 3A: Mean tortuosity ± 95%C.I. = 32.1 ± 3.9

Formulation 3B: "   "   "   = 55.4 ± 4.5

Formulation 3C: "   "   "   = 45.6 ± 6.9

Formulation 3D: "   "   "   = 12.2 ± 2.4

It can be seen that the tortuosity values for the three HVO – based formulations are higher than those obtained by Higuchi and co-workers (163 – 167), as discussed above (section 1.4.5.1.2). The tortuosity factors obtained by these workers were generally less than 10, and were taken to be physically realistic indicators of the pore structure. Tortuosity values several orders of magnitude higher were found by these workers for some matrices and incomplete removal of air was hypothsised to be the reason. Since the tortuosity factors obtained in this study for HVO matrices were greater than 10 but less than one order of magnitude greater than this figure, it was not clear whether these figures could be regarded as physically realistic, or whether an artefact caused them to be increased. The PVC based formulation has a tortuosity value which is only slightly higher than 10, with a 95% confidence interval which includes this value. It was therefore thought possible that slow or incomplete wetting was decreasing release rate from HVO – based matrices and effectively increasing tortuosity values. However, this conclusion appeared to contradict the results from studies of drug release rates in water and surfactant, which were not significantly different.

There are several possible explanations for this apparent incongruity. Firstly, it may be possible that the high tortuosities determined are physically

realistic, and that the rate of wetting of HVO matrices may not decrease release rate. Secondly, the porosity in the HVO – based matrices may not be completely available even to dissolution media containing surfactant i.e. the compaction process results in some voids or pores being completely enclosed by matrix material and hence being inaccessible to dissolution fluid. A related explanation is that the capillary network of the matrix may not be completely interconnected or continuous and hence air may become trapped in "blind" capillaries. Desai *et al* (167) postulated that surfactant effectively prevents this effect by removing air more efficiently, but it is possible that it may not do so completely. This would also result in a decreased effective porosity. A reduction in effective porosity could hence account for high tortuosities, since according to the Higuchi equation a decrease in effective porosity would have to be accompanied by a decrease in tortuosity to describe the same release rate.

3.3.2 Rationale for Determination of Tortuosity Factors Independently of Drug Release Data

The results obtained from the drug release studies indicated that it was not possible to determine whether the high tortuosity factors calculated were physically realistic or were an artefact of other processes which could not be accounted for in the Higuchi equation. The independent determination of tortuosity would hence be useful in the further exploration of these phenomena.

3.3.2.1 Theory of Gas Flow Under Pressure through Porous Media

3.3.2.2 Development of a Constant Pressure Air Permeameter

The final development of the permeameter technique of determining pressure drop and flow rate through leached matrices was found to give reproducible results using the same tablet. There was also found to be no flow rate hysteresis effect at the same pressure when pressure was being increased or decreased. The measurements were made using 6 leached samples from each of formulations 3A – 3D and the results

are shown in figures 3.6 - 3.9. The data are plotted as pressure drop versus volume

flow rate and it can be seen that two linear phases are evident for the curves

obtained with the HVO-based formulations, with the second phase having a steeper

slope than the first. This effect is not seen with the PVC-based formulation. It

was postulated that the reason for the two phases results from the nature of the

flow changing from viscous streamline to turbulent at a certain flow rate dependent

on the nature of the capillary structure of the pore space in each matrix. If the

capillaries are assumed to be circular in cross-section, then a dimensionless

number termed the Reynolds number R_e can be defined as:-

$$R_e = d\sigma_f u/v \qquad\qquad .....\text{equation 3.26}$$

where σ_f = density of the fluid

At a certain value of R_e, termed the critical Reynolds number R_c the flow

becomes turbulent in nature and for a circular capillary R_c is equal to 2.1. For a

particular fluid passing through a given capillary R_e will hence be dependent on

flow rate. This explains why the inflexions on the curves occur at approximately

similar flow rates for samples of one formulation but vary between formulations. It

is not possible to confirm quantitatively whether the effective Reynolds number for

a matrix is above the critical value at a particular flow rate because the

effective pore radius is unknown. It is not therefore possible to confirm this

hypothesis.

Figure 3.10 shows a comparison of a curve representative of each formulation.

It can be seen that the PVC-based formulation is more permeable than any of the

HVO-based formulations. The permeabilities of the latter increase with increasing

amount of leached drug and hence final porosity, which is as expected because the

initial porosities were all similar.

The slopes of the initial linear portions of the two-phase curves and the

whole of the single-phase curves were estimated by least squares regression

analysis. This was in order to be able to apply equations 3.18 and 3.19 to

Figure 3.6   Air flow rate versus pressure drop for 6 tablets of formulation 3A
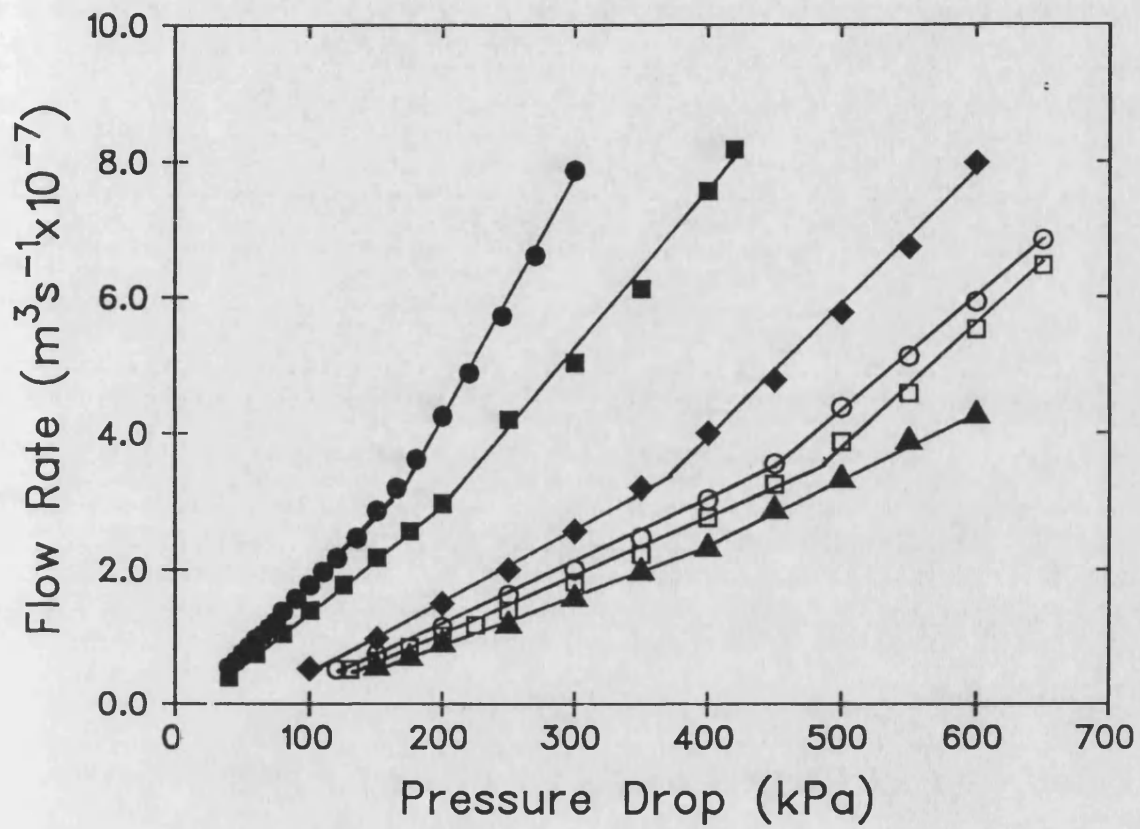
(table 3.1)

Figure 3.7   Air   flow rate versus pressure drop for 6 tablets   of   formulation   3B
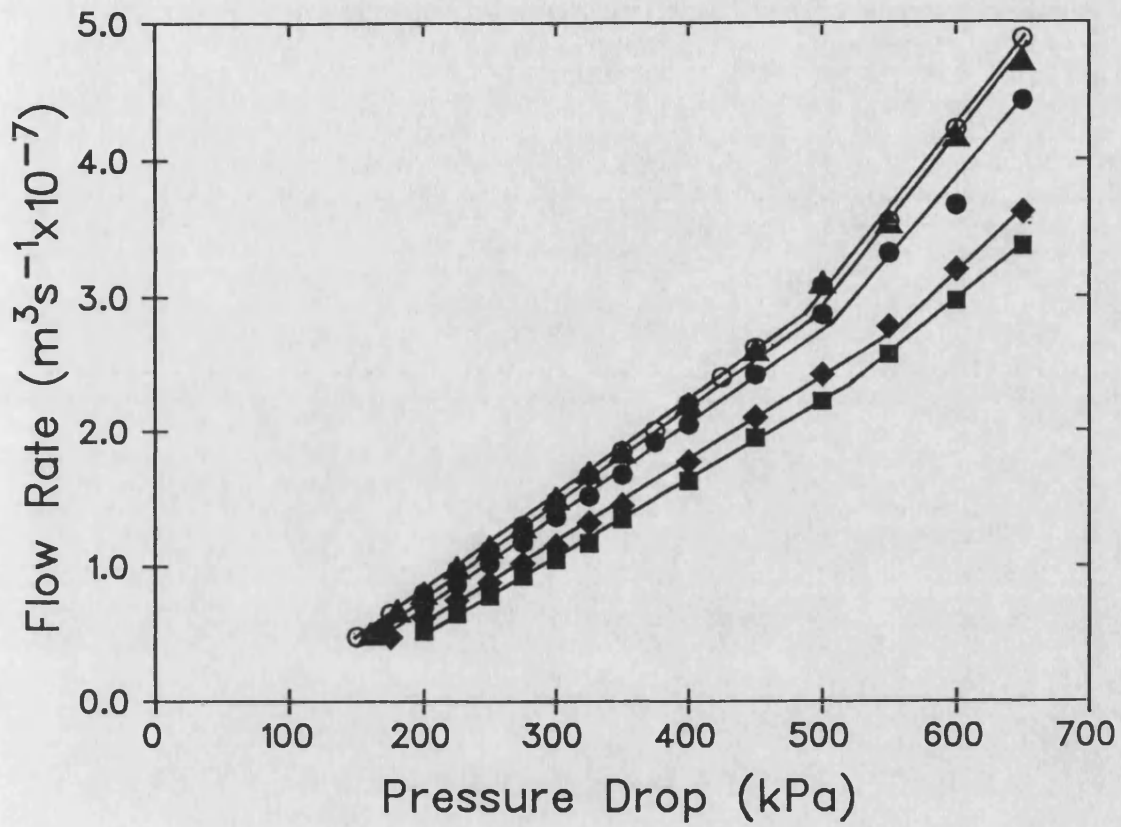
(table 3.1)
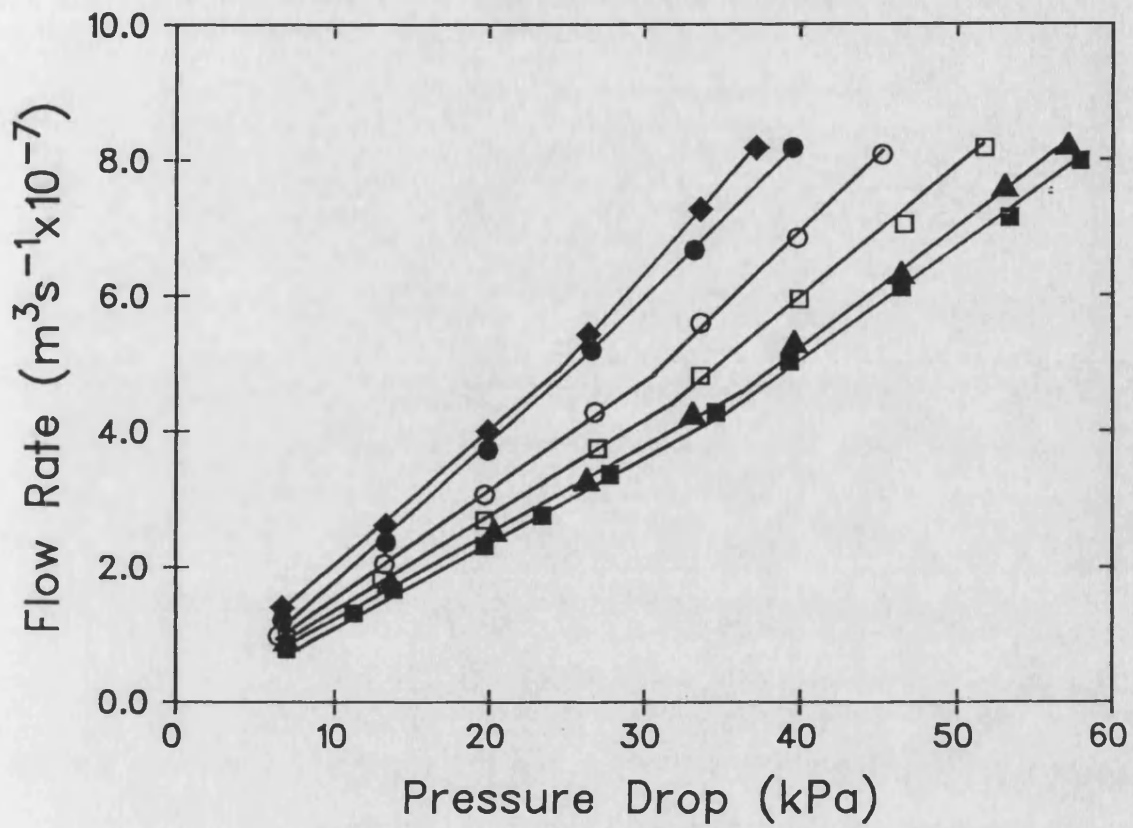
Figure 3.8   Air flow rate versus pressure drop for 5 tablets of formulation 3C
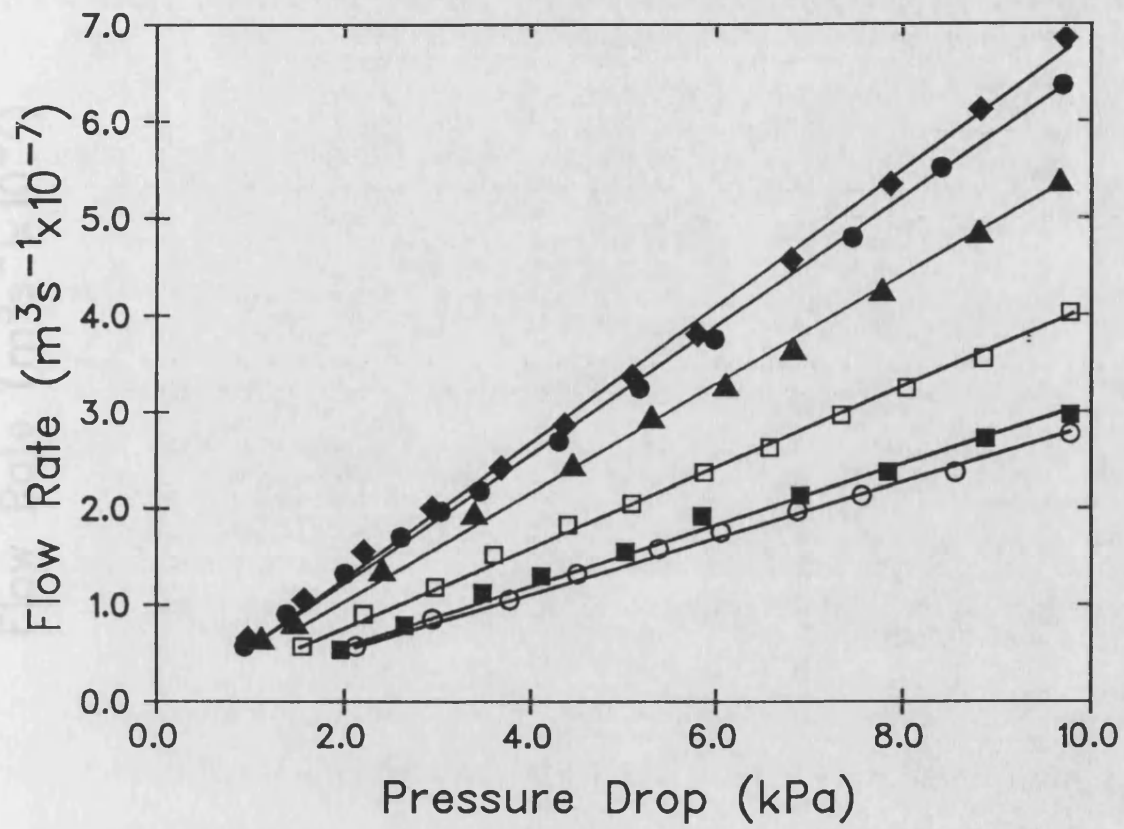
(table 3.1)

Figure 3.9   Air flow rate versus pressure drop for 6 tablets   of   formulation 3D
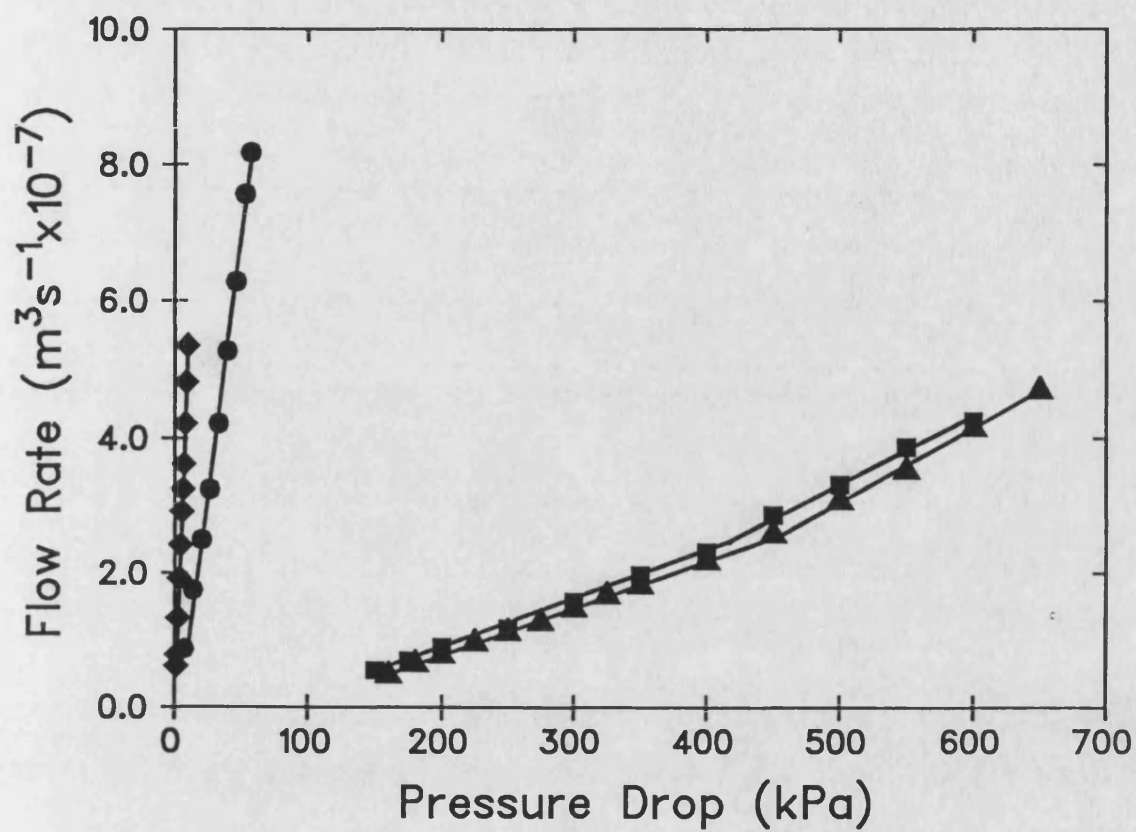
(table 3.1)

Figure 3.10   Air flow rate versus pressure drop for 1 tablet each of   formulations

3A – 3D (table 3.1)

Key: ● = formulation 3A

■ = formulation 3B

▲ = formulation 3C

◆ = formulation 3D

calculate tortuosity when the values for specific surface area had been determined. The values of the slopes thus calculated are shown below:-

Formulation 3A: Mean slope ± 95% C.I. = $1.79 \times 10^{-7} \pm 0.45 \times 10^{-7}$ m s^{-1} Pa^{-1}

Formulation 3B: "   "   " " = $1.29 \times 10^{-8} \pm 0.55 \times 10^{-8}$ m s^{-1} Pa^{-1}

Formulation 3C: "   "   " " = $7.50 \times 10^{-9} \pm 1.24 \times 10^{-9}$ m s^{-1} Pa^{-1}

Formulation 3D: "   "   " " = $6.15 \times 10^{-7} \pm 2.51 \times 10^{-7}$ m s^{-1} Pa^{-1}

3.3.2.3 Preparation of Leached Matrices

The times taken to reach a constant absorbance for each of the formulations and the corresponding cumulative percentage of drug released from matrices for the two methods used to obtain leached matrices are shown in table 3.4. It can be seen that more than approximately 92% was released from all four formulations studied. It was concluded that these figures indicated that all the drug had been leached from the matrices, with the variability from 100% release being within what would be expected to result from inhomogeneity in the powder mixes and experimental error.

Formulation	Method of Leaching			
	Dissolution Apparatus		Shaking Water Bath	
	Time to constant Absorbance hr	Mean % Released	Time to constant Absorbance hr	Mean % Released
3A	96	>94.8	168	>94.8
3B	116	96.3	168	91.8
3C	168	93.4	264	93.4
3D	96	94.3	168	100.3

Table 3.4 Time for complete release of drug and mean percentage released from formulations 3A – 3D in dissolution apparatus and shaking water bath

It can be seen that leaching in the shaking water baths took longer than in the dissolution apparatus and this was attributed to the differences in the hydrodynamics of the two systems. For example, the paddle method might be expected to remove any leached drug from the region at the surface of the matrix more effectively than the shaking method, thus reducing the diffusion boundary layer thickness. In the shaking method, drug would have to diffuse through a thicker boundary layer at the surface, consequently increasing the time for complete release.

3.3.2.4 Determination of Specific Surface Area of Leached Matrices using Mercury Intrusion Porosimetry

Examples of the cumulative volume of mercury intruded and extruded versus pore diameter curves are shown for each of the formulations 3A – 3D (table 3.1) in figures 3.11 – 3.14. It can be seen that the extruded volume is always greater at a given diameter than the intruded volume. This indicates that at any given pressure less mercury is extruded than was intruded at the same pressure. This hysteresis effect is seen with many different porous media, and it has been postulated to be due to several different effects. It is found that the hysteresis loop does not close even when the pressure is reduced to zero, which indicates that some mercury is entrapped in the pores. If subsequent pressurisation – depressurisation cycles are performed, no additional entrapment usually occurs. It has been shown that during a cycle when no entrapment is occurring, the hysteresis disappears if the contact angle is adjusted to take account of the fact that the intrusion contact angle is different to the extrusion contact angle, the former always being the greater (215). The hysteresis due solely to entrapment has been postulated as being due to some pores being "ink – bottle" shaped, i.e. with a narrow neck and a wide internal cavity. Thus the mercury becomes trapped in the pore until a lower pressure is reached allowing extrusion. A second theory involves the concept of a "pore potential" (216) and requires that molecules can "fall" into a potential field at

Figure 3.11   Cumulative mercury intrusion volume per gram versus $\log_{10}$ pore

diameter for formulation 3A (table 3.1)

Key: O = intruded volume
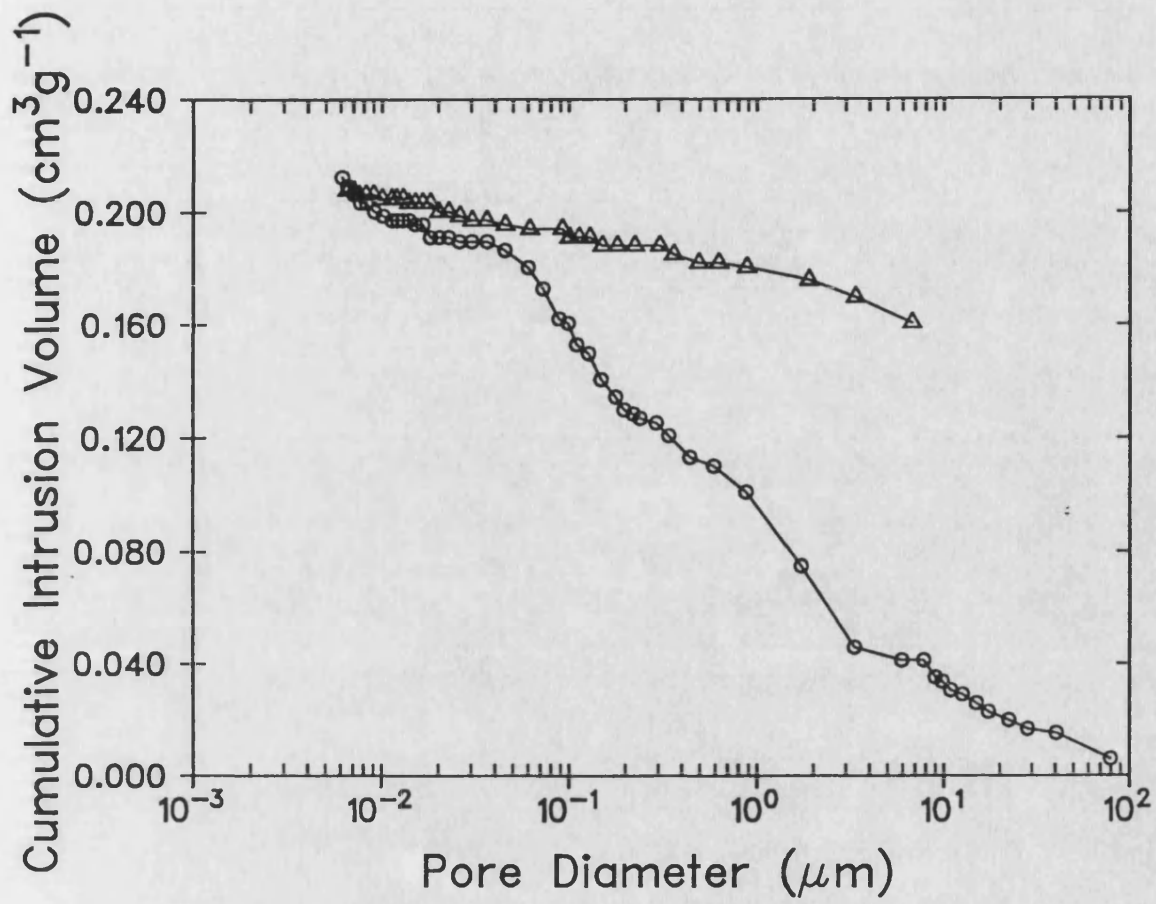
          △ = extruded volume

Figure 3.12 Cumulative mercury intrusion volume per gram versus $\log_{10}$ pore diameter for formulation 3B (table 3.1)

Key: O = intruded volume
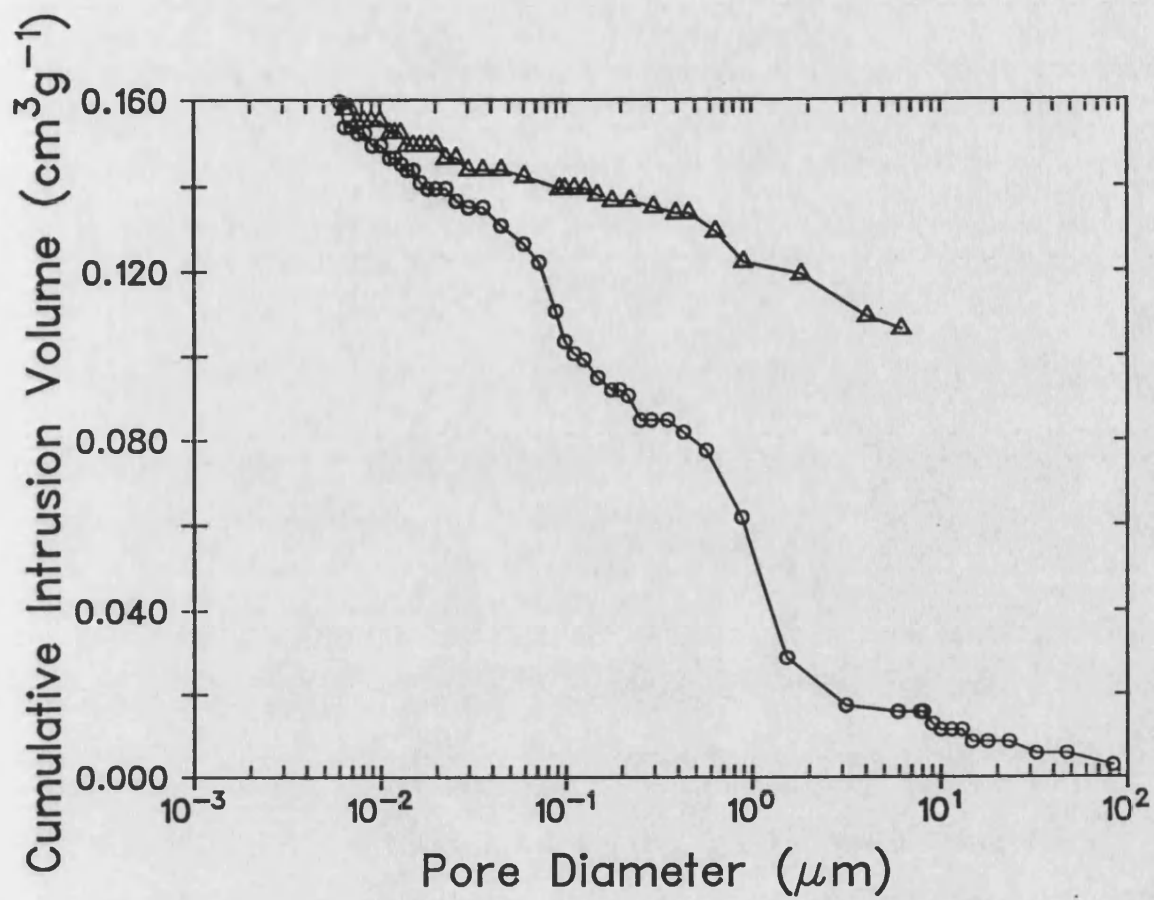
△ = extruded volume
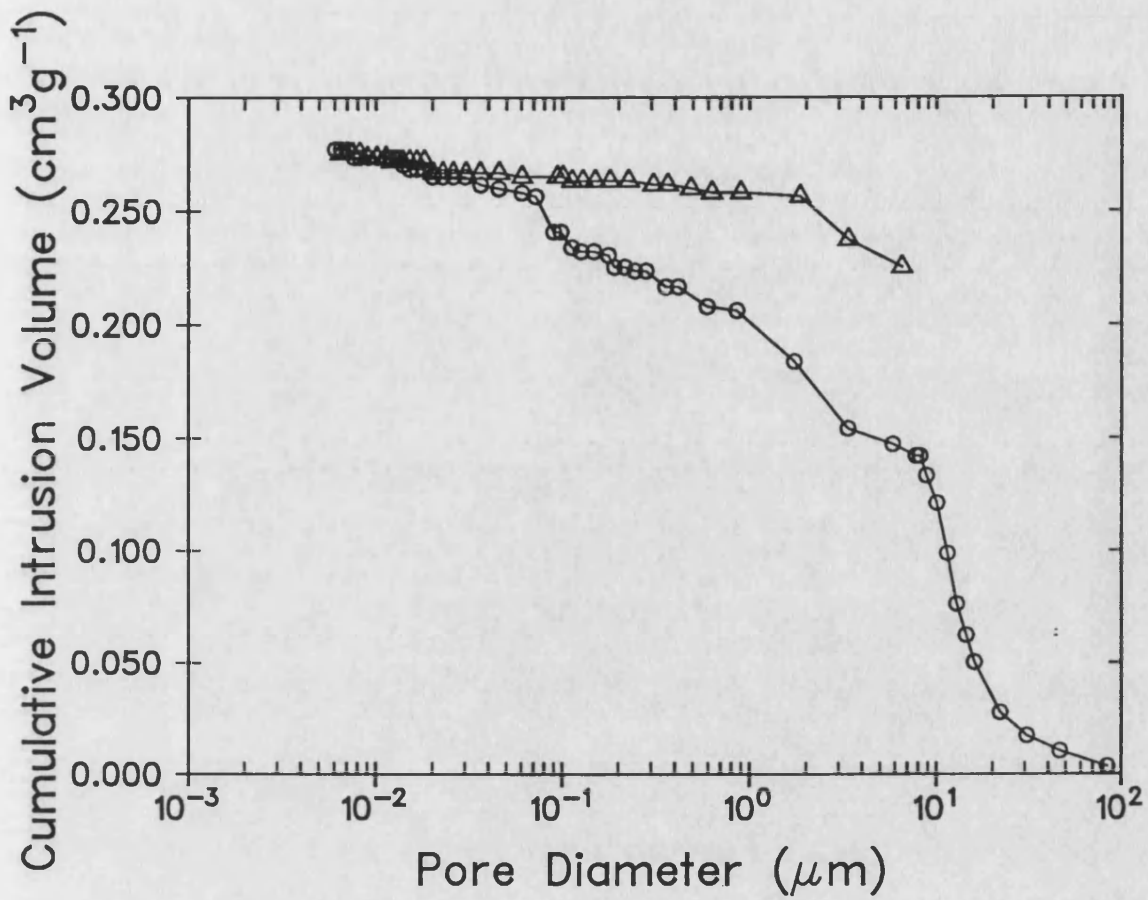
Figure 3.13   Cumulative mercury intrusion volume per gram versus $\log_{10}$ pore
diameter for formulation 3C (table 3.1)

Key: O   =   intruded volume
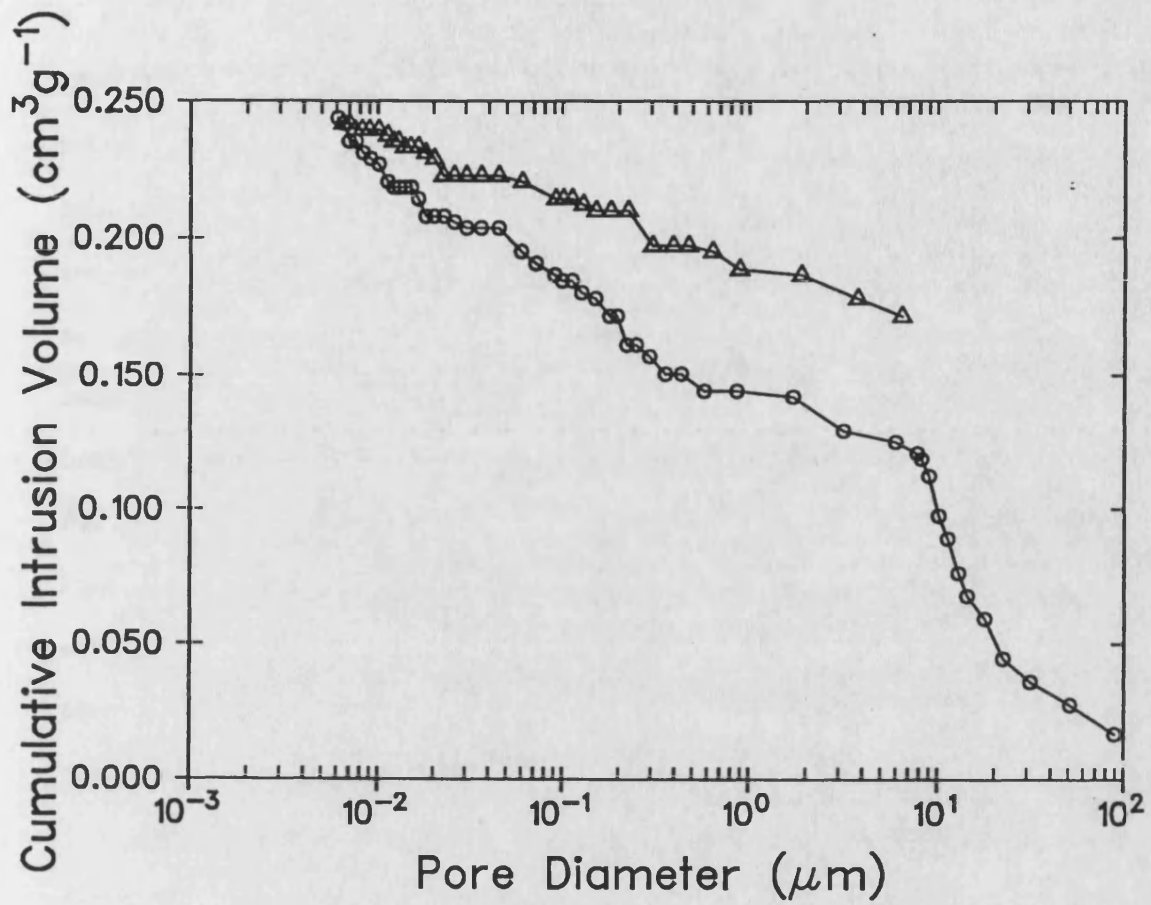
        △   =   extruded volume

Figure 3.14   Cumulative mercury intrusion volume per gram versus $\log_{10}$ pore

diameter for formulation 3D (table 3.1)

Key: o = intruded volume

△ = extruded volume

the surface of a solid. This effect would be enhanced in a narrow pore and it was proposed that this causes a pore potential which prevents extrusion of mercury from a pore until a pressure smaller than the intrusion pressure is reached. This effectively causes entrapment of mercury in the pores, resulting in less mercury being extruded at any given pressure than was intruded. The postulators of the pore potential theory discount the ink–bottle model as a universal explanation for entrapment for the following reasons (217). Firstly, they suggest that all porous samples show hysteresis, implying that they all without exception possess ink–bottle pores. Secondly, hysteresis curves would always be the same shape if ink–bottle pores were present, which is not the case. Thirdly, hysteresis occurs over the entire range of pore sizes, indicating that all pores are ink–bottle shaped. Fourthly, hysteresis occurs in samples of regularly packed spheres, where the pore entrances are wider than the cavities. Lastly, the ink–bottle model does not account for the energy needed to break the column of mercury in order for the pore entrance to empty while the cavity remains filled.

The results obtained in the present study were also plotted in the form of incremental intrusion volume per gram of sample versus pore diameter. This gives a representation of the cumulative pore size distribution within the samples. Typical examples for each of the formulations are shown in figures 3.15 – 3.18. It can be seen that a wide pore size distribution exists within all the samples of all the four formulations. Formulation 3A shows a bimodal distribution centred on 12.3 µm and 1.72 µm, while formulation 3B shows a more unimodal distribution centred on 1.05 µm. Formulation 3C shows a distinctly unimodal distribution centred on 0.82 µm whereas the PVC–based formulation 3D appears to have a polymodal distribution. The significance of these results will be discussed in section 3.3.2.5 in the light of the permeametry data.

The results obtained for specific surface area of the four formulations are shown in table 3.5. It can be seen that results showing wide variability were obtained with 3 of the 4 formulations. It was unfortunately not possible to perform
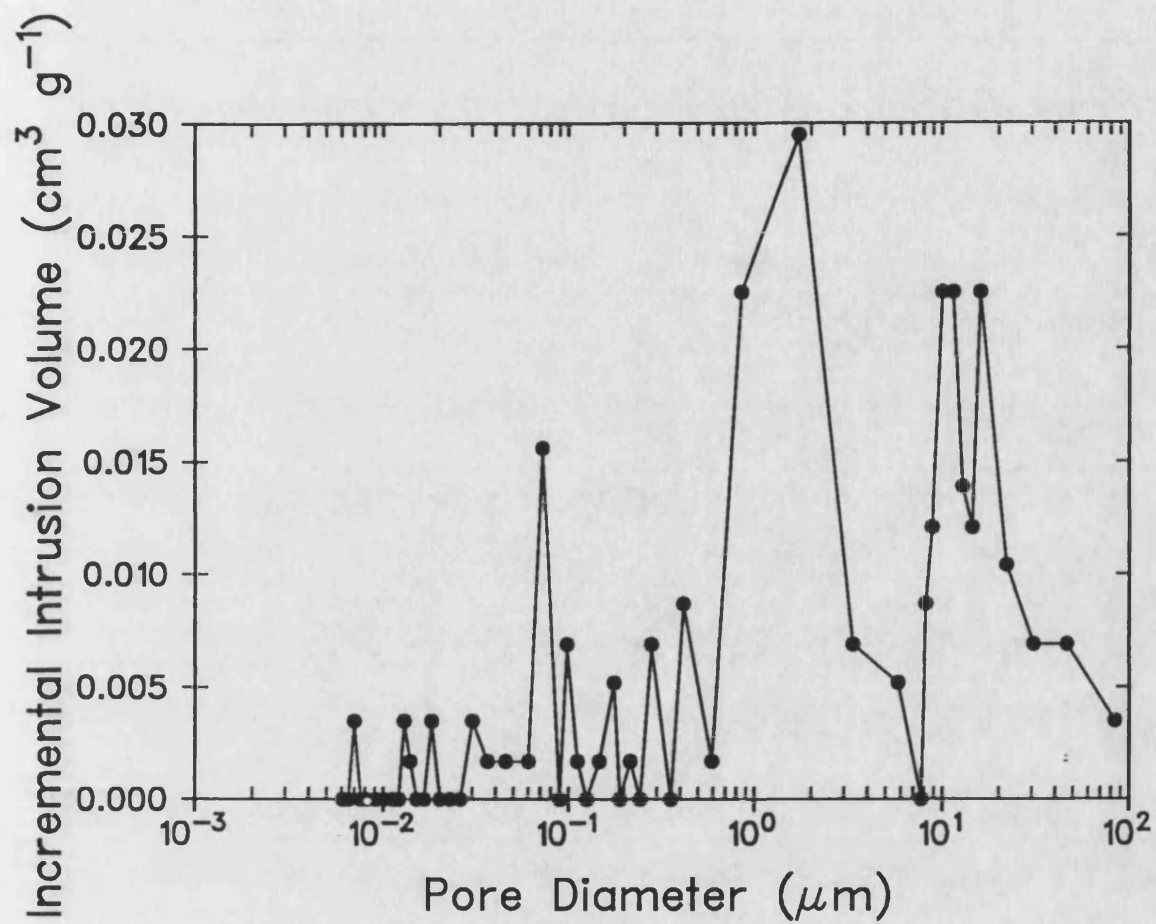
Figure 3.15   Incremental   mercury   intrusion volume per   gram   versus $\log_{10}$ pore

diameter for formulation 3A (table 3.1)
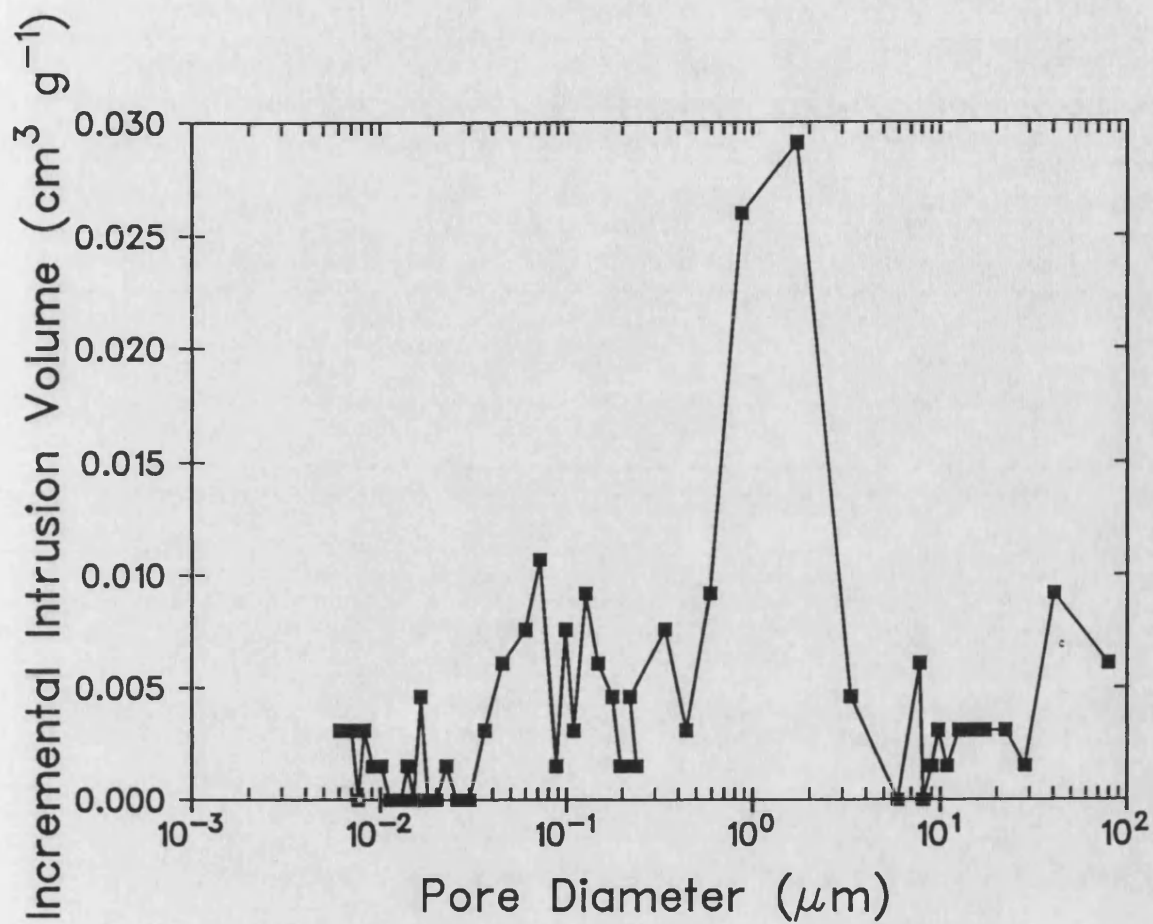
Figure 3.16   Incremental   mercury   intrusion volume per   gram   versus $\log_{10}$ pore

diameter for formulation 3B (table 3.1)
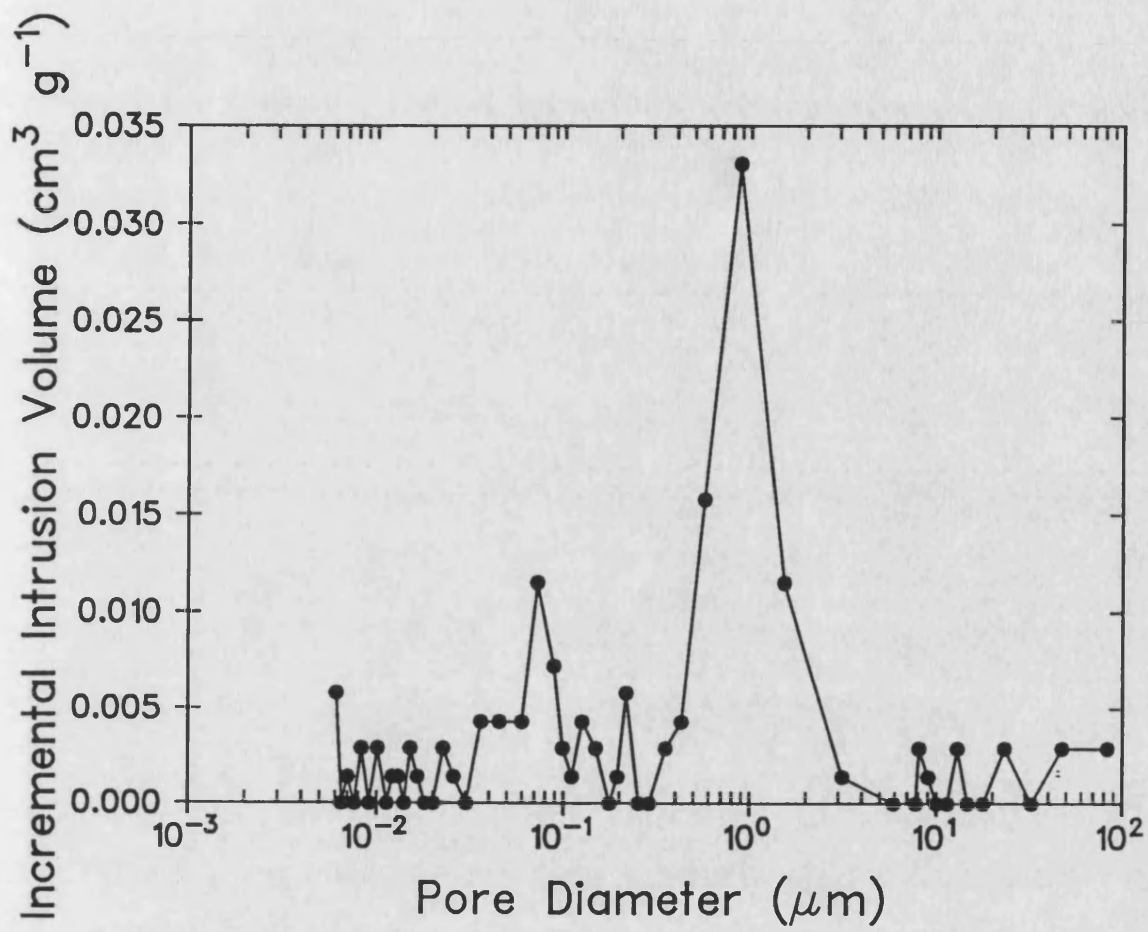
Figure 3.17   Incremental mercury intrusion volume per gram versus $\log_{10}$ pore diameter for formulation 3C (table 3.1)
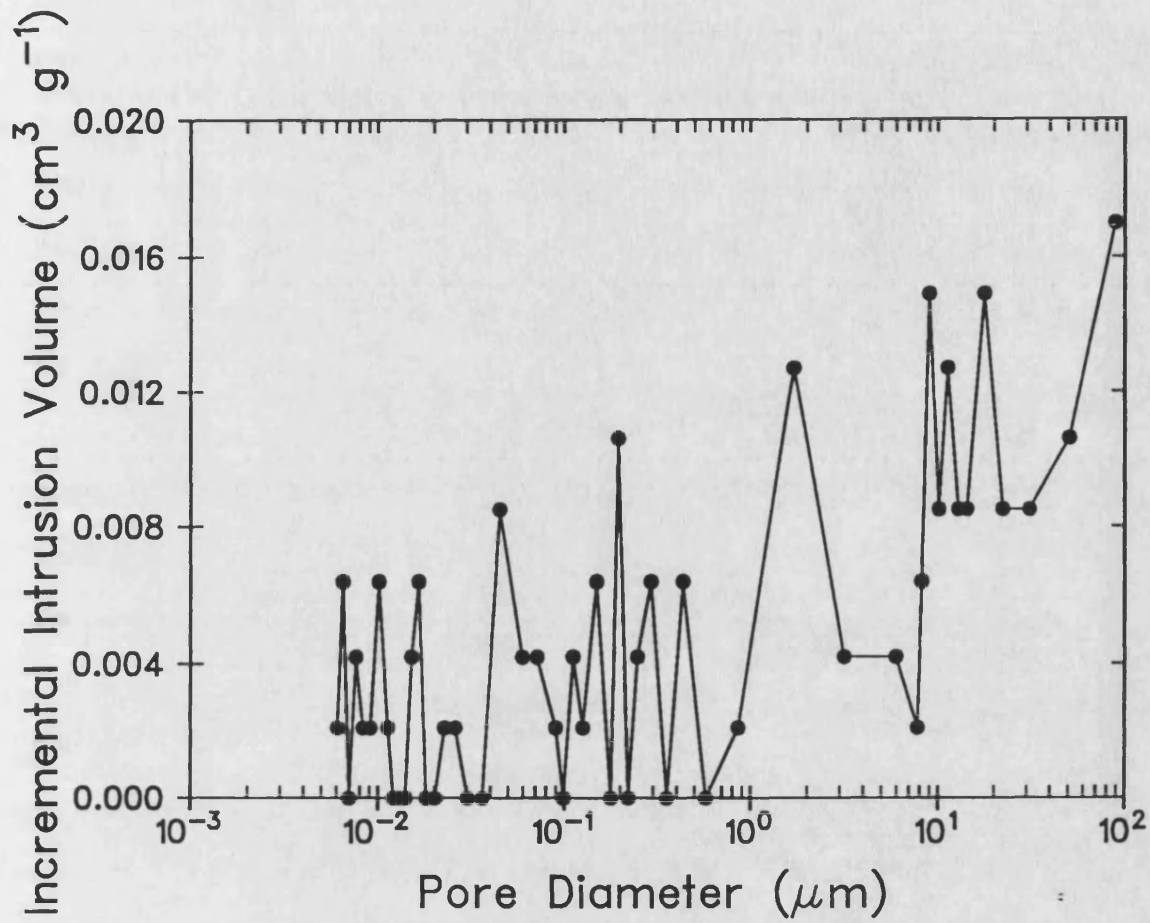
Figure 3.18 Incremental mercury intrusion volume per gram versus $\log_{10}$ pore diameter for formulation 3D (table 3.1)

further determinations to enable a more accurate estimate of the mean specific surface area for each formulation to be determined, and hence the mean values calculated must be viewed with some caution. In addition, the instrument used was only capable of applying pressures up to a maximum of 30,000 psia whereas the upper limit actually measurable with some instruments is reached at a pressure of 60,000 psia. (N.B. 1 psia = 6896 Pa therefore 60,000 psia = 414 MPa). If pores were present which were smaller than would be penetrated at a pressure of 30,000 psia (I.e. 6 nm diameter) then their surface area would not be accounted for.

The variability in the values for specific surface area between samples of the same formulation is due to small variations in volume intruded at the highest pressures, which result in large variations in surface area, since the pores with the smallest diameters account for a large proportion of the surface area.

Formulation	Specific Surface Area $m^2 g^{-1}$				
	1	2	3	Mean	95% C.I.
3A	17.78	6.58	14.64	13.00	14.34
3B	12.98	12.37	7.77	11.04	7.07
3C	11.78	12.14	11.23	11.72	1.14
3D	17.47	11.85	17.43	15.58	8.03

Table 3.5   Specific surface area of three replicate leached samples of formulations 3A – 3D measured by mercury intrusion porosimetry

3.3.2.5   Calculation of Tortuosity Factors from the Carman–Kozeny Equation and comparison with Tortuosity Factors Calculated from Drug Release Data

Tortuosity factors were calculated from equation 3.26 using the mean slopes obtained from the permeametry experiments and the mean specific surface areas determined by mercury porosimetry. The value for the viscosity of air at 20°C was

obtained from tables (1.81 x 10^{-5} N s m^{-1} (212)). The tortuosity values obtained were: –

Formulation 3A: 0.0479

Formulation 3B: 0.132

Formulation 3C: 0.123

Formulation 3D: 0.0167

It is clear that the tortuosity factors determined in this fashion are meaningless, since they are consistently less than 1, and tortuosity factors must by definition be greater than or equal to 1.

The reason for the failure of this technique to determine tortuosity factors was considered to arise from the wide pore size distributions exhibited by the matrix formulations, which were observed from the mercury porosimetry data. A limitation of the Carman – Kozeny equation is that uniformity of pore size is implied (218). The equation assumes that the pore space can be represented by a bundle of capillaries of one hydraulic radius, hence if the pore space consists of capillaries of widely varying radius, a mean hydraulic radius is irrelevant. Viscous flow through porous media with a wide pore size distribution will predominantly occur through the larger capillaries, since these offer the path of least resistance. Hence the flow through the larger capillaries will effectively swamp the flow through the smaller ones. The surface area over which the flow occurs will therefore only be a very small portion of the actual surface area within the matrix. This is because the smaller capillaries will contribute disproportionately largely to the overall surface area, while contributing little to the "flow" surface area. The value for specific surface area determined by mercury porosimetry is hence irrelevant to the surface area term in the Carman – Kozeny equation, explaining the failure to calculate valid tortuosity factors.

Formulation	Composition
3A	NaS 20% / HVO 40% / DPD 39% / MS 1%
3B	NaS 10% / HVO 40% / DPD 49% / MS 1%
3C	NaS 5% / HVO 40% / DPD 54% / MS 1%
3D	NaS 10% / PVC 90%

Table 3.1   Composition of all formulations used in chapter 3

Key: NaS = sodium salicylate

HVO = hydrogenated vegetable oil

DPD = dicalcium phosphate dihydrate

MS = magnesium stearate

PVC = polyvinyl chloride

Chapter 4

Determination of Tortuosity Factors II: Measurement of Effective Diffusion

Coefficients of Gases in Matrices

4.1 Theory of Gaseous Interdiffusion

The failure of the permeametry method to enable meaningful tortuosity factors of matrices to be determined, necessitated the use of an alternative method for measurement of tortuosities. For this reason, the diffusion technique mentioned briefly in section 3.2.2.1 above was studied further. As previously described, the diffusion coefficient of a single gaseous species through a porous medium filled with air is related to the diffusion coefficient of the gas in free air by the following relationship: –

$$D_{eff} = D_a \in / q \qquad \qquad .....\text{equation 4.1}$$

where D_{eff} = effective diffusion coefficient of the gas in the porous medium

D_a = diffusion coefficient of the gas in free air

$\in$ = porosity of the medium

q = tortuosity factor

A method of estimating D_{eff} has been described by Evans *et al* (219). It is based on the application of Graham's law of diffusion, which states that when two gases interdiffuse at uniform pressure, their fluxes are in the inverse ratio of the square-roots of their relative molecular masses. Graham's original experiments (220) utilised an apparatus which was described as a "diffusion tube". As the gas diffuses out of the tube through the porous material, the liquid level in the tube rises or falls depending on whether the gas is lighter or heavier than air, respectively. Constant zero pressure difference across the porous material is maintained, and the ratio of the diffused gas and air volumes is given as a function of the ratio of their overall fluxes. Graham performed the experiment with several gases and found that the law held on a general basis described by the relationship: –

$$J_{gas} / J_{air} = (M_{r(air)} / M_{r(gas)})^{\frac{1}{2}} \qquad \ldots\ldots\text{equation 4.2}$$

where J_i = flux of species i where i is a diffusing gas

            $M_{r(i)}$ = relative molecular mass of species i

Evans *et al* (219) used this principle in the determination of effective diffusion coefficients of gases through air–filled porous media. A differential equation was derived which related the rate of change of volume in the diffusion tube to the effective diffusion coefficient and by using the published values for the true diffusion coefficients in air of the gases investigated, they calculated the ratio $\in/q$ using equation 4.1. In the present study, the porosities of the matrices had already been determined, therefore allowing the determination of tortuosity factors from effective diffusion coefficient measurements.

4.2 Materials

Light liquid paraffin: (Lot 32043), supplied by J.M. Loveridge, Southampton, U.K.

4.3 Methods

4.3.1 Construction and Validation of A Graham's Law Diffusion Tube Apparatus

A diagram of the apparatus is shown in figure 4.1. A graduated burette was modified by being shortened to a length of approximately 35 cm and by having a portion of the tubular section above the zero mark removed so that the latter was as close to the top of the tube as possible. A sample holder was made from glass and a diagram of it is also shown in figure 4.1. An indentation was made in the outer surface of the tubular portion of the holder as a seating for an O–ring. When the holder was pushed into the top of the burette, the O–ring was lightly greased with vacuum grease to seal the holder into the tube to prevent gas from leaking out
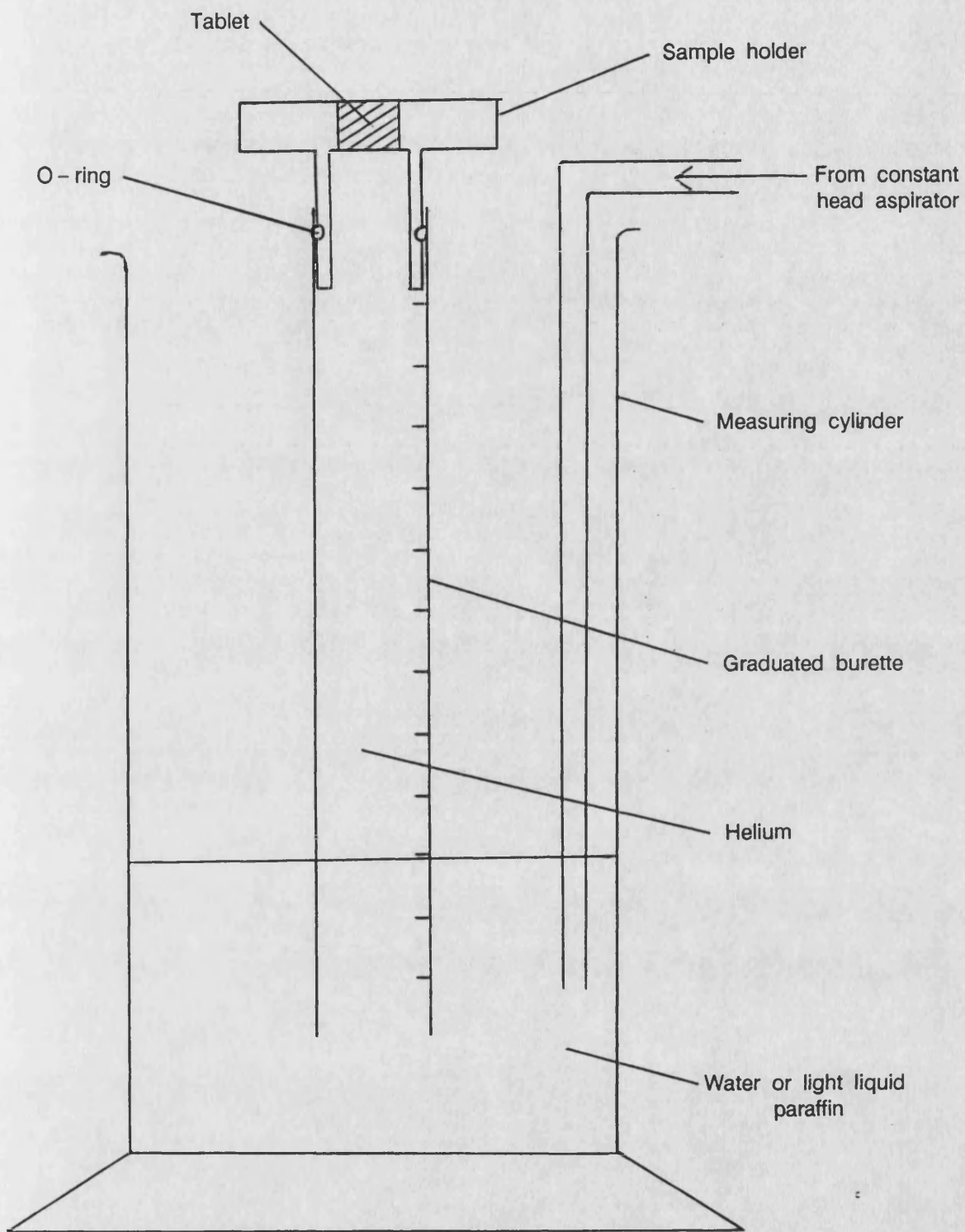
Figure 4.1   Schematic diagram of diffusion tube apparatus

through the joint. The sample holder had a circular hole of diameter 10.4 mm drilled in the upper cylindrical section, and the remaining upper surface was prepared to a ground finish. A cylindrical piece of glass of the same diameter as the sample holder was made with a ground finish on one planar surface and with a piece of solid glass tubing of diameter 10mm protruding at right angles from the opposite surface. This was used to seal the tube immediately above the sample whilst the tube was being filled with gas, the two ground glass surfaces being made gas-tight by light greasing prior to closure.

In order to ensure firstly that the sample holder sealed into the top of the burette and secondly that the sealing piece was itself sealed onto the sample holder, the following tests were conducted. A piece of steel of the same dimensions as those of a tablet matrix was glued into a sample holder using epoxy resin adhesive, which was allowed to set overnight. A vacuum was applied to the top of the sample holder using a vacuum line attached to a vacuum pump. No change in the water level in the tube was observed, indicating that the sample to holder bond was air-tight at these pressures. Secondly, the water level in the tube was made to rise by applying the vacuum line to the top of the tube without the sample holder in place. When the level had reached the top of the tube the vacuum line was removed and the sample holder with the steel test sample was quickly sealed into the top of the tube. The water level in the tube was recorded and the apparatus left overnight. The level was found to have remained unchanged, indicating that the sample holder to burette joint was air-tight.

The steel test piece was then replaced with a leached matrix and the following tests performed. The vacuum line was applied to the top of the sample holder, drawing the water up the burette to the zero mark. The sealing piece was then sealed onto the sample holder and the apparatus again left overnight. No change in the water level was observed, indicating that the sample holder to sealing piece joint was air-tight. This was further confirmed by filling the measuring cylinder almost full with water, placing the sample holder with the sealing piece sealed

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onto it in the burette, and bubbling helium into the burette. The water level was allowed to fall almost to the bottom of the burette then the helium was turned off. The water level was noted and the apparatus left overnight, thus leaving the helium in the tube under pressure. No change in the water level was noted, further indicating that the system was adequately gas–tight.

Experiments were conducted in the following manner. A leached matrix was glued as described into the sample holder which was then inserted into the top of the diffusion tube. This was placed inside the measuring cylinder and clamped in a perpendicular position. The water level in the measuring cylinder was adjusted using the constant head aspirator so that the lower end of the diffusion tube was below it. A vacuum was applied to the top of the sample holder using a vacuum line in order to draw the water level in the diffusion tube up to slightly above the zero mark. The vacuum line was removed and the water level allowed to fall to the zero mark when it was prevented from falling further by sealing off the tube above the sample with the ground glass–faced sealing piece. Helium was then bubbled into the tube, displacing water until the tube was nearly full of the gas; the water level in the measuring cylinder was adjusted to the same level as in the burette tube and the burette reading noted. At time zero, the sealing joint was removed from the top of the diffusion tube and the change of the level of water in the burette recorded with time. Development of a pressure difference across the sample was prevented by synchronously increasing the water level in the measuring cylinder with the rise in water level in the diffusion tube as the helium diffused out, using the constant head aspirator. Readings were taken until no further change was observed. Since the helium became partially saturated with water vapour whilst passing through the water in the measuring cylinder, the air diffusing into the tube was also humidified by placing a cone of wet filter paper on the sample holder at the start of the experiment, taking care to ensure that no droplets of water fell onto the sample.

The reproducibility of the technique was assessed by performing this procedure

five times on the same matrix sample. The applicability of Graham's Law to the system was determined by calculating the ratio of the volume of helium diffused out of the tube to the volume of air diffused in. i.e. the initial burette reading divided by the final reading. Graham's Law states that this ratio should be equal to the square-root of the inverse ratio of the relative molecular masses. This ratio for the helium / air system is 2.69 (219). It was found that the law was obeyed to within 10% on only three of the five occasions, the percentages of the volume change in each case which would have given the theoretical ratio of 2.69 being found to be 95.7, 100.0, 101.7, 86.3 and 82.4%. The test was repeated on a further sample and the percentages obtained were 94.5, 91.2, 86.3, 81.0 and 87.4%.

It was clear that the technique appeared to be giving results which were generally below what would be expected, even accounting for experimental error. Tests of the validity of Graham's Law (221) have indicated that it is obeyed to within a few percent. If this is taken to be $\pm$ 5% and experimental error is taken to be the same figure, then a maximum variability of 10% from the theoretical volume change would be acceptable. The results described immediately above indicated that only half of the tests which had been performed satisfied this requirement. It was considered that the reason for this was the variability in water vapour content between the helium and air. The theoretical ratio of 2.69 assumes that both the helium and the air were dry. If the helium (relative molecular mass $\approx$ 4) contained water vapour (relative molecular mass $\approx$ 18) this effectively increased its relative molecular mass. Similarly if the air (effective relative molecular mass $\approx$ 28) contained water vapour, this effectively decreased its relative molecular mass. Since the ratio is calculated as $(M_{r(air)} / M_{r(He)})^{\frac{1}{2}}$, water vapour present in either or both the gases effectively decreased the ratio, explaining the generally consistently low results obtained.

The same argument also appeared to explain the variability in the results obtained. The degree of saturation of the helium would be a function of the rate at which it was passed through the water in the measuring cylinder, the amount it was

passed through and their respective temperatures. The degree of saturation of the air would depend on the temperature and the relative humidity of the air in the laboratory at the time of each experiment. (The dampened cone of filter paper placed immediately above the sample was not able to saturate the air totally). The variability of these factors appeared consistent with the observation that when tests were performed on the same day, the results of the percentages of the ratio which were obtained were reasonably consistent. In order to eliminate variability as much as was practicable, it was decided to ensure that the helium was consistently dry and to use non-humidified air. Data from experiments resulting in a variability in ratios of greater than 10% from the theoretical ratio of 2.69 was not used.

In the modified experimental procedure, helium was dried by passing it through a column of "Molecular Sieve" drying agent (as described in section 3.2.2.1) and prevented from passing through water by replacing the water in the measuring cylinder and the constant head aspirator with light liquid paraffin. Data obtained using the modified method was found to be more consistent.

4.3.2   Determination of Effective Diffusion Coefficient

A differential equation for determining diffusion coefficient from the data obtained was derived by Evans *et al* (219):–

$$\frac{dV(t)}{dt} = -D_{eff}\frac{A_x}{L}\ln\left\{\frac{V(t) + V_0}{V(\infty) + V_0 + [(1 - \delta_1)(V(t) - V(\infty)]}\right\} \quad .....equation\ 4.3$$

where $V(t)$ = burette volume at time t

$V(\infty)$ = burette final volume

V_0 = dead-space volume between the zero mark and lower face of the sample

The factor δ_1 is derived from the following equation:–

$$\delta_1 = D_K / (D_K + D_{eff}) \qquad \text{.....equation 4.4}$$

where D_K = Knudsen diffusion coefficient of the diffusing gas

Equation 4.3 predicts an exponentially decreasing rate of change of volume with time and the results of the validation tests performed were found to conform to this pattern. Leached samples of formulations 3A – 3D were prepared as already described above (section 3.2.2.3) and the experiment was performed in duplicate on three samples of each formulation. The effective diffusion coefficient was calculated by estimating the slope of the curves obtained by plotting {V(0) – V(t)} versus time at each time point t_i using the following formula: –

$$\frac{dV(t_i)}{dt} = \frac{V(t_{i+1}) - V(t_{i-1})}{t_{i+1} - t_{i-1}} \qquad \text{.....equation 4.5}$$

The value V_0 in equation 4.3, i.e. the dead–space volume between the zero mark on the diffusion tube and the lower surface of the sample was determined by fixing a piece of steel of approximately the same dimensions as a matrix into the sample holder using epoxy resin adhesive. The assembly was then inserted into the diffusion tube which was inverted and clamped, and a burette of 10 cm³ volume was placed above it. The upper burette was filled with water and a piece of plastic tubing narrow enough to fit into the diffusion tube was attached to its tip. The diffusion tube was then filled with water from the second burette so that the space between the lower surface of the sample and the zero mark was filled. The dead–space volume V_0 was equal to the volume of water added from the second burette and this value was recorded.

4.3.3 Estimation of δ_1 and Permeability Coefficient K_p

The factor δ_1 is a measure of the relative contributions of continuum and free–molecule (Knudsen) diffusion to the uniform pressure diffusive flux through

matrices at atmospheric pressure. The more it deviates towards zero from a value of 1.00, the greater the contribution to the flux from the free-molecule component, and hence the larger the correction factor to account for it in equation 4.3. The true Knudsen diffusion coefficient D_K can be determined accurately by flux measurements at a series of pressures below atmospheric pressure, which necessitates the use of a complex apparatus. However, Evans et al (219) estimated D_K and hence δ_1 using an iterative technique which utilised effectively the same principle as the tablet permeability experiments described above in chapter 3. Air was forced under pressure through the porous sample at a pressure difference which was small compared to atmospheric pressure. Instead of performing steady-state pressure measurements as described in chapter 3 though, a pressure decay technique was used. This involved placing the diffusion tube with the porous sample at one end into the measuring cylinder which was full of water, to a depth which allowed the end of the tube which contained the porous sample to protrude just above the surface of the water. The pressure difference caused the air to be forced out of the tube through the porous sample until the water level in the tube reached that in the measuring cylinder. The rate of change of volume decayed exponentially with time and the permeability coefficient K_p (equation 4.8 below) was calculated from this data.

The factor δ_1 was estimated in the following way. The rate of change of volume at time t in the pressure decay experiment is related to the volume reading V(t) by the following equation:-

$$\frac{dV(t)}{dt} = -C_p V(t) \qquad \qquad .....\text{equation 4.6}$$

where C_p = constant

Integration of this equation gives:-

$$V(t) = V(0)e^{-C_p t} \qquad \qquad .....\text{equation 4.7}$$

A plot of ln V(t) versus t should hence give a straight line of slope C_p. The permeability constant K_p is calculated from the following equation:−

$$C_p = \frac{\sigma_w g A_x K_p}{P a_x L} \qquad \qquad .....\text{equation 4.8}$$

where σ_w = density of water

   a_x = cross − sectional area of diffusion tube

   P   = atmospheric pressure

The factor δ_1 was calculated using the relationship in equation 4.4 by taking the value obtained for K_p as an estimate of D_K. A trial value of D_{eff} was calculated from equation 4.3 assuming that $\delta_1 = 1$. This gave the upper bound for δ_1, since K_p is always greater than D_K, and hence indicated whether a significant portion of the flux was in the Knudsen flow regime. If δ_1 was found to be significantly less than 1.00 then the calculation of D_{eff} was performed a second time using the new value of δ_1.

In order to estimate δ_1 for matrices, the pressure decay experiment was performed on leached samples of formulations 3A − 3D, using the technique described immediately above. The diffusion tube with sample holder was sealed above the sample with the sealing piece and placed in a perpendicular position in the measuring cylinder. At time zero the sealing piece was removed from the holder and the volume readings recorded with time.

4.3.4   Calculation of Tortuosity Factors from Diffusion Data and Comparison with Tortuosity Factors Calculated from Drug Release Data

The value of the $\in/q$ ratio was calculated using equation 4.1, using the values of D_{eff} which were obtained and the published value for the diffusion coefficient

of helium in air (222) quoted by Evans *et al* (219). An empirical correction factor to the $\in/q$ ratio was applied to account for the resistance to diffusion which occurs in the diffusion tube rather than in the porous sample (219). This was achieved by calculating an effective "diffusion resistance" by assuming that the "conductance" of a section of tube or porous sample is proportional to the area over which diffusion can occur divided by the diffusional length: -

$$\frac{1}{(DA_x/L)_{total}} = \frac{1}{(DA_x/L)_{tube}} + \frac{1}{(D_{eff}A_x/L)_{sample}} \quad \text{.....equation 4.9}$$

The $\in/q$ ratio was then multiplied by the ratio of total diffusion resistance to sample diffusion resistance. The true tortuosity L_e/L was calculated from the corrected $\in/q$ ratio using equation 3.22. The tortuosity factors thus calculated were compared with the values obtained from the leaching data (section 3.3.1.3).

4.4 Results and Discussion

4.4.1 Construction and Validation of a Graham's Law Diffusion Tube Apparatus

The results obtained for the change of burette reading V(t) with time for samples of formulations 3A – 3D are shown in figures 4.2 – 4.5. Of the experiments performed using dried helium, it was found that approximately 80% yielded a volume change within 10% of the theoretical figure of 2.69. The mean (± 95% C. I.) percentage of the theoretical volume change of these experiments was found to be 94.3% ± 1.48 (n = 24).

4.4.2 Determination of Effective Diffusion Coefficient

The value V_0 was found to be 3.20 cm^3. Plots of V(0) – V(t) versus time for samples of formulation 3A are shown in figure 4.2. It can be seen that the rate of change of volume decreases exponentially with time and the results from all samples of formulations 3A – 3D were found to take this form. Values for effective

Figure 4.2   V(0) – V(t)   versus time from diffusion tube experiment   performed   on
leached matrices of formulation 3A (table 3.1)

Key: ○ = tablet 1, rep. 1   ◇ = tablet 1, rep. 2

            ▲ = tablet 2, rep. 1   ◆ = tablet 2, rep. 2

            △ = tablet 3, rep. 1   □ = tablet 3, rep. 2
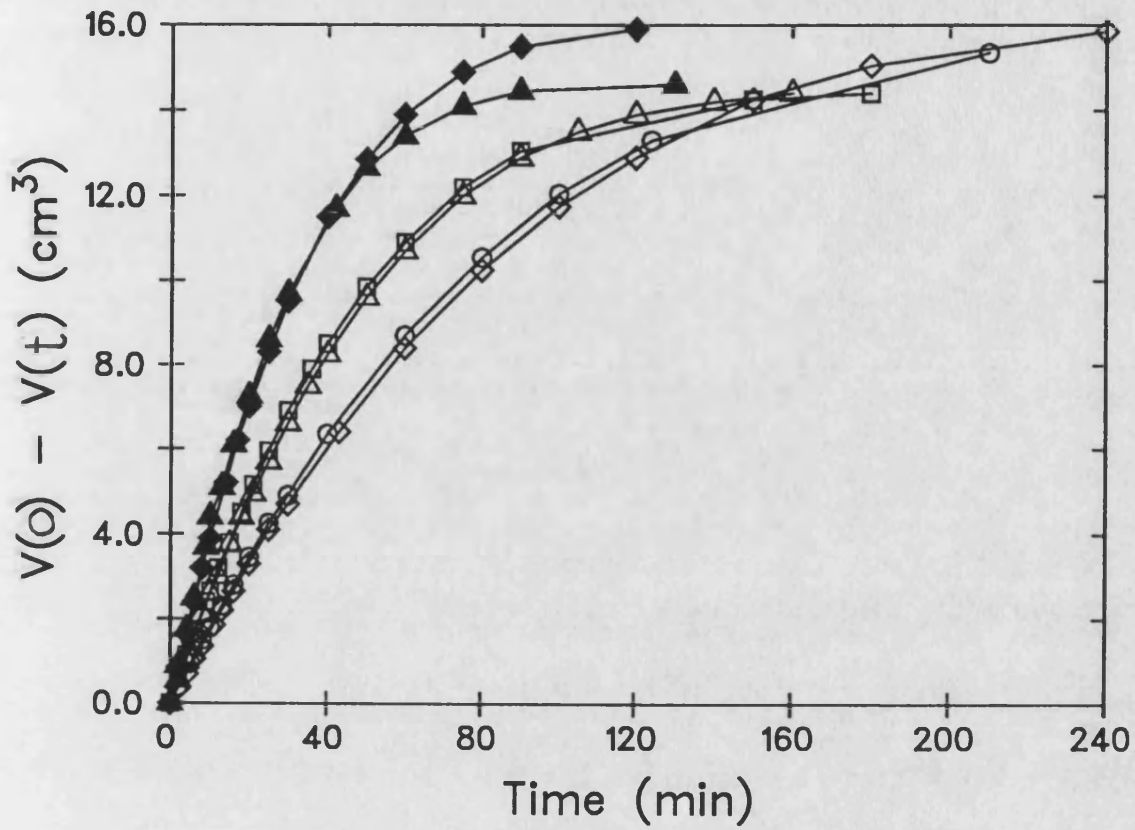
Figure 4.3   V(0) – V(t) versus time from diffusion tube experiment performed on

leached matrices of formulation 3B (table 3.1)

Key: ◇ = tablet 1, rep. 1   ○ = tablet 1, rep. 2

□ = tablet 2, rep. 1   △ = tablet 2, rep. 1

▲ = tablet 3, rep. 1   ◆ = tablet 3, rep. 1
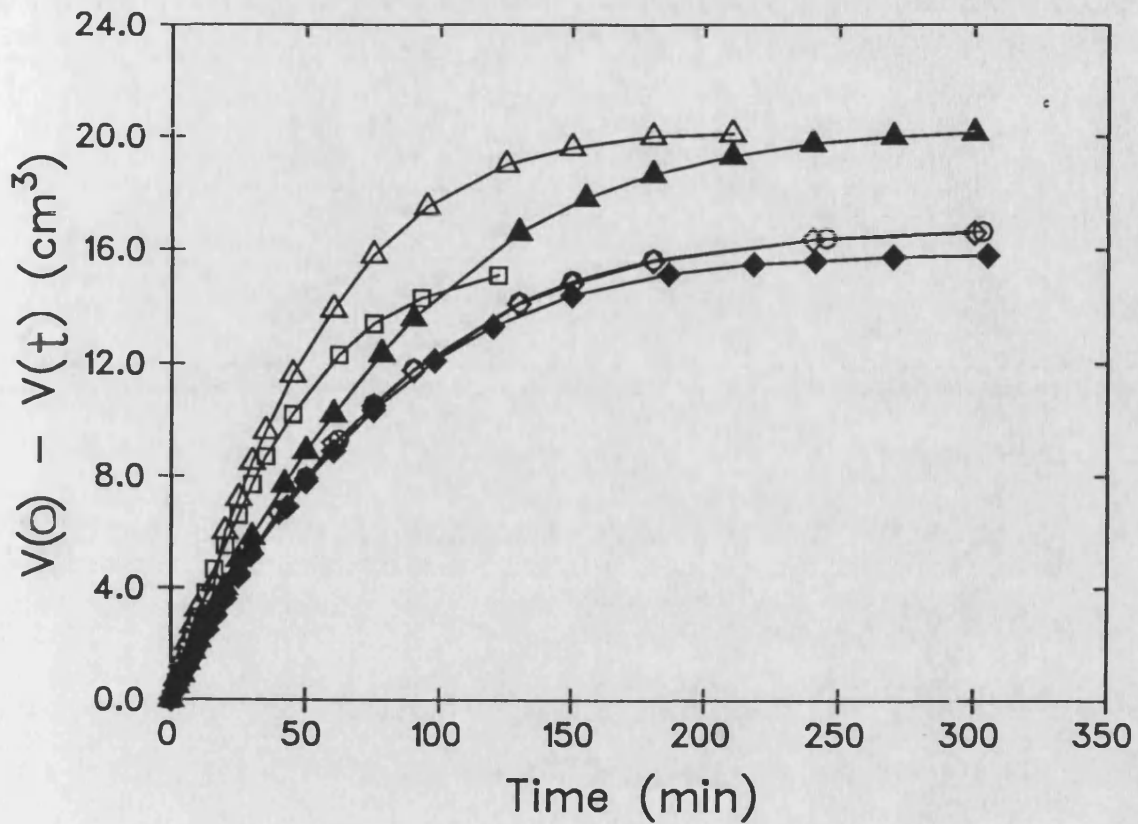
Figure 4.4   V(0) – V(t)   versus time from diffusion tube experiment   performed   on

leached matrices of formulation 3C (table 3.1)

Key: △   = tablet 1, rep. 1   □ = tablet 1, rep. 2

         ▲   = tablet 2, rep. 1   ◆ = tablet 2, rep. 1

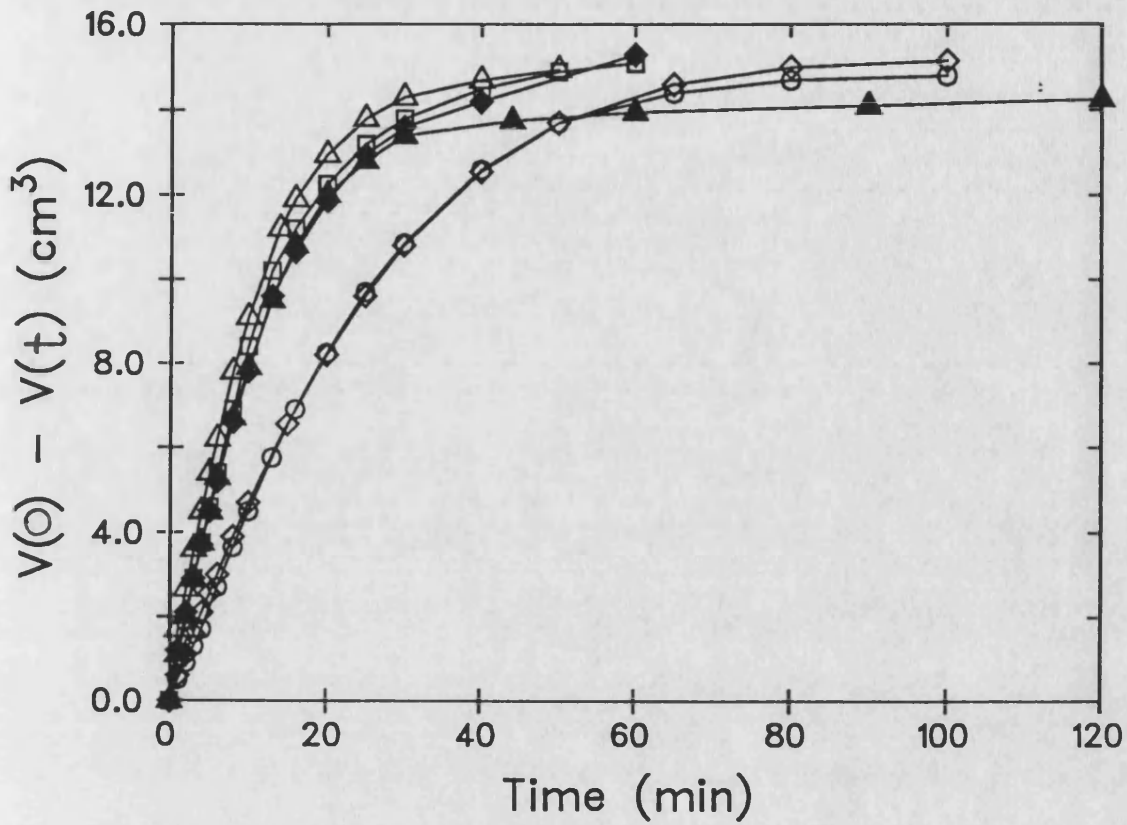   ○   = tablet 3, rep. 1   ◇ = tablet 3, rep. 1
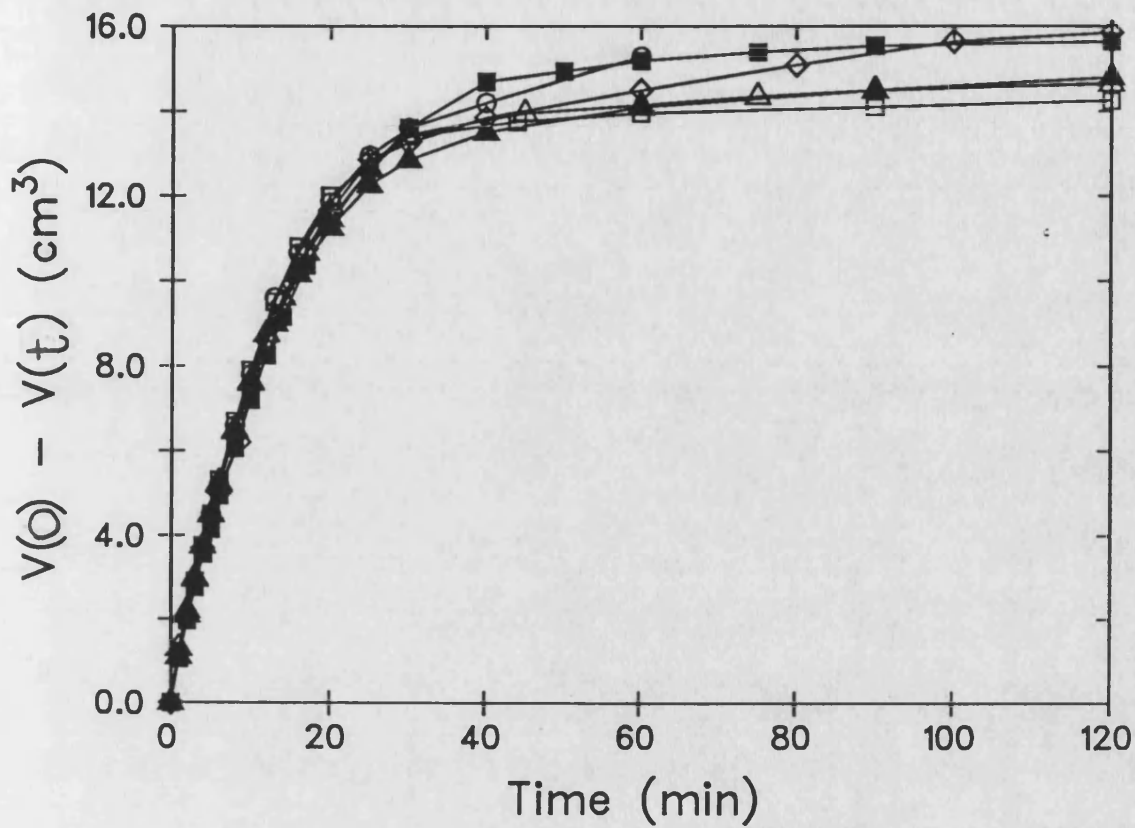
Figure 4.5   V(0) – V(t)   versus time from diffusion tube experiment   performed   on

leached matrices of formulation 3D (table 3.1)

Key: ◇ = tablet 1, rep. 1   ○ = tablet 1, rep. 2

■ = tablet 2, rep. 1   △ = tablet 2, rep. 1

□ = tablet 3, rep. 1   ▲ = tablet 3, rep. 1

diffusion coefficient were calculated by estimating the slope of the plots at each

time point using equation 4.5 and substituting the value obtained into equation

4.3. This method of calculating D_{eff} was found to give consistent values from

approximately the first two-thirds of the complete curve. Values calculated from

slopes estimated from the latter third of the curve were less consistent due to the

error introduced by using equation 4.5 to estimate shallow slopes where the time

interval $\{t_{i+1} - t_{i-1}\}$ was large. For this reason only the values of D_{eff}

calculated from slopes estimated from approximately the first two-thirds of each

curve were used to obtain a mean value. The value for δ_1 used in equation 4.3 was

determined as described in the section immediately below. A mean value for D_{eff}

was determined for each sample and the results obtained are shown in table 4.1.

Sample Number   Mean Effective Diffusion Coefficient of Helium in air in Matrices

$$cm^2 \ s^{-1} \ x \ 10^{-3} \ (\pm 95\% \ C. \ I.)$$

(Rep. Number)	Formulation			
	3A	3B	3C	3D
1 (1)	8.11 (0.816)	1.60 (0.066)	2.02 (0.092)	10.9 (1.50)
1 (2)	6.90 (0.576)	1.71 (0.135)	1.99 (0.080)	9.77 (1.02)
2 (1)	7.06 (0.596)	2.66 (0.225)	1.47 (0.076)	11.2 (1.12)
2 (2)	6.36 (0.522)	2.48 (0.069)	1.38 (0.102)	10.0 (1.23)
3 (1)	6.32 (0.402)	1.26 (0.031)	1.28 (0.057)	9.97 (1.05)
3 (2)	6.43 (0.374)	1.15 (0.057)	1.35 (0.063)	11.3 (1.08)
Overall Mean ($\pm$ 95% C.I.)	6.86 (0.716)	1.81 (0.658)	1.58 (0.350)	10.5 (0.719)

Table 4.1   Effective diffusion coefficient of helium in air in leached matrices of

formulations 3A - 3D (table 3.1)
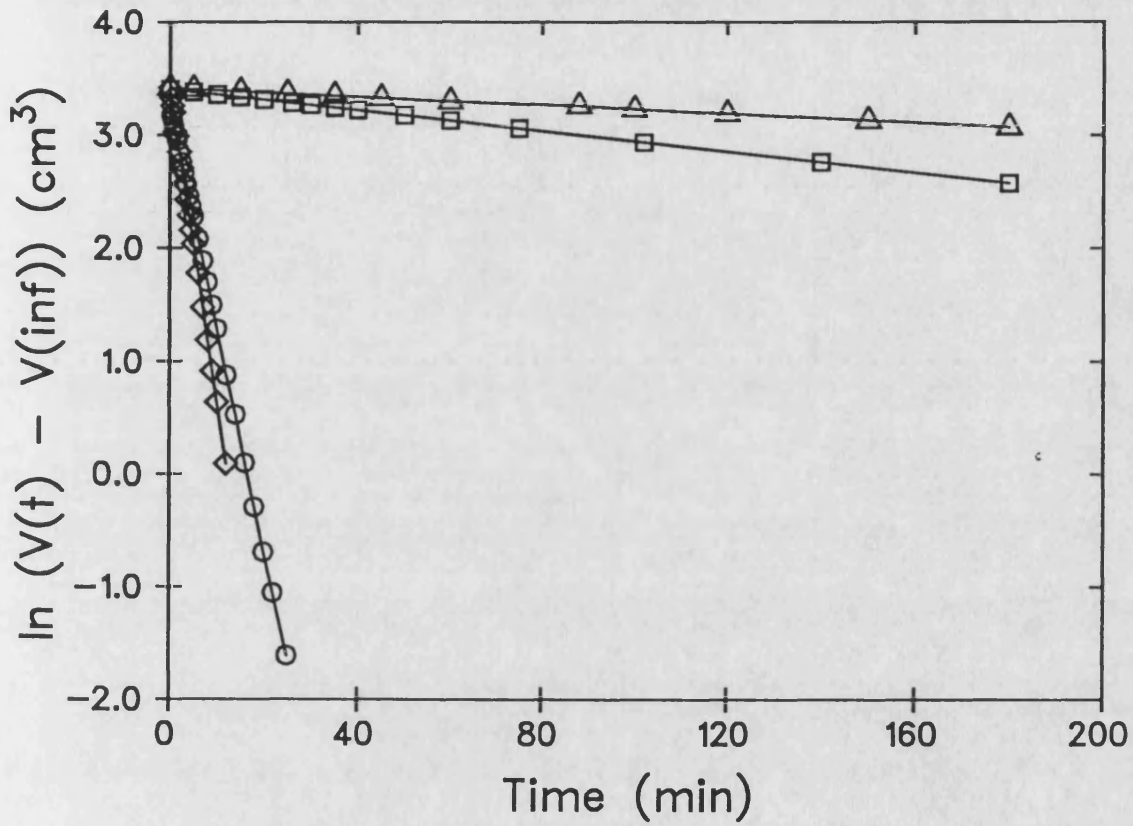
Figure 4.6 ln {V(t) − V(∞)} versus time from pressure decay experiment of leached

matrices of formulations 3A − 3D (table 3.1)

Key: ○ = formulation 3A

        □ = formulation 3B

        △ = formulation 3C

        ◇ = formulation 3D

4.4.3 Determination of δ_1 and Permeability Coefficient K_p

Typical plots of ln V(t) versus t are shown for one sample each of formulations 3A – 3D In figure 4.6. Examination of the plots indicated that linear relationships could be considered to exist between the variables and least squares regression analysis was employed to estimate the slopes of the lines which were equal to the factor C_p in equation 4.6. The permeability constant K_p was hence calculated from C_p using equation 4.8 and the values of δ_1 were subsequently calculated from equation 4.4, using K_p as an estimate of the upper bound of D_K. These values are shown in table 4.2. It can be seen that δ_1 only varies significantly from 1.00 for formulation 3C, and it was therefore concluded that this formulation was the only example amongst the four matrix formulations investigated through which uniform pressure diffusion at approximately 1 atmosphere pressure, occurred in the transition region between free–molecule and continuum diffusion.

Formulation	C cm^4 s^{-1}	r^2	K cm^2 s^{-1}	δ_1
3A	3.26×10^{-3}	0.9994	0.886	0.99
3B	4.64×10^{-3}	0.9991	1.35	1.00
3C	3.31×10^{-5}	0.9996	8.90×10^{-3}	0.88
3D	4.51×10^{-3}	0.9997	2.61	1.00

Table 4.2 Slope C of V(0) – V(t) versus time plot from pressure decay experiments, permeability coefficient K and δ_1 for formulations 3A – 3D

4.4.4 Calculation of Tortuosity Factors from Diffusion Data and Comparison with Tortuosity Factors Calculated from Drug Release Data

The factor q was calculated from equation 4.1 using the published value for

the true diffusion coefficient of helium in air of 0.691 cm^2 s^{-1} (222). The tortuosity L_e/L was calculated from q using equation 3.22. Mean values for tortuosity for each formulation were calculated and these are shown in table 4.3 with the tortuosity values calculated from the drug release data (section 3.3.2.3). It can be seen that the tortuosity values obtained from the diffusion experiments were an order of magnitude lower than those obtained from drug release data, and can all be considered to be physically realistic i.e. greater than 1 and less than approximately 10, a range which as discussed above (section 1.4.5.2.1) could be considered reasonable. These results would appear to be evidence to support the hypothesis that tortuosity values obtained from drug release data were inaccurately high indicators of the true tortuosity of the pore structure of the matrices and that an artefact which the Higuchi equation was unable to account for such as slow or incomplete wetting caused them to be increased to such high values.

However, in the Higuchi equation, the true diffusion coefficient of the drug solute molecules in bulk solution is modified by the inclusion of the porosity and tortuosity terms, which is exactly the same model used to modify the diffusion coefficient of one gaseous species in another in equation 4.1. Hence the factor q is equivalent to the tortuosity factor τ, and therefore τ is also equal to the square of the true tortuosity L_e/L. If it was assumed that $\tau = L_e/L$, when actually $\tau = (L_e/L)^2$, this would lead to the assumption of an incorrectly low figure for the physically realistic upper bound of τ. For example, if the upper bound of L_e/L is taken as 10, then the upper bound of τ and hence q becomes 100. The values of τ obtained from drug release data were therefore all square-rooted in order to obtain L_e/L values, which were then compared to the equivalent values obtained from the diffusion experiments. The figures obtained are shown in table 4.3. It can be seen that the values for L_e/L obtained from the diffusion experiments are comparable with the modified square root of τ values obtained from the drug release experiments. It was therefore concluded that the modified tortuosity values determined from drug release data, were confirmed by the diffusion experiments as

physically realistic estimates of the tortuosity of the pore structure of the matrices. It was also concluded that slow or incomplete wetting did not limit drug release rates from HVO – based matrices.

| Mean Parameter | Formulation | | | |
(± 95% C.I.)	3A	3B	3C	3D
Corrected $\in/q$ ratio x 10^{-3}	13.5 (0.258)	2.95 (1.20)	2.52 (0.671)	20.5 (1.75)
q	21.2 (3.52)	78.1 (29.5)	70.6 (16.9)	11.5 (0.998)
τ from Drug Release Studies	32.1 (3.9)	55.4 (4.5)	45.6 (6.9)	12.2 (2.4)
L_e/L	4.58 (0.408)	8.70 (1.70)	8.36 (1.21)	3.38 (0.188)
$\sqrt{\tau}$ from Drug Release Studies	5.67 (2.0)	7.44 (2.1)	6.75 (2.6)	3.49 (1.6)

__Table 4.3__ Mean corrected $\in/q$ ratio, q, and L_e/L determined from diffusion tube experiments and τ and $\sqrt{\tau}$ from drug release studies

These conclusions indicated that the Higuchi equation ought to be modified by having the tortuosity term squared. In the work concerned with the original validation of the Higuchi equation (163 – 167) it was found that tortuosity values up to approximately 10 with one value of 18 were obtained from drug release data from polyethylene and polyvinyl chloride matrices. This would indicate that the actual tortuosity factors of these matrices would be less than 4.25, which is less than the figures obtained from HVO – based matrices. A tentative explanation for these differences can be tendered by considering the method of preparation of the matrices. The polyethylene and polyvinyl chloride were compressed with heating, which might be expected to produce a less tortuous pore structure than direct compression of the HVO – based matrices, which included dicalcium phosphate dihydrate, an excipient which is known to undergo brittle fracture during

compaction.

The ability of the diffusion method to determine tortuosity factors independently of drug release data indicated that this technique might be usefully employed to determine tortuosity factors during formulation of porous matrices for the delivery of drugs at desired rates. It may also be possible to use it to determine whether any relationship existed between tortuosity and formulation variables such as drug and excipient concentration or particle size, or compaction pressure. This might enable the effects of formulation variables on tortuosity and hence drug release rate to be predicted, making further formulation a simpler process.

Chapter 5

Investigation of the Feasibility of Production of Hemispherical, Zero-order Drug

Releasing HVO-based Matrices for Oral Use

5.1 Theory

When matrix devices from which drug release is diffusion controlled are used clinically they suffer from the potentially significant disadvantage that the amount of drug released is proportional to the square-root of time and hence drug release rate constantly decreases during the period of delivery. Zero-order kinetics would result in a drug release profile which would be more desirable i.e. drug release rate would always be constant since the amount of drug released would be a linear function of time. One means of altering the characteristic release profile of drug loaded matrices is to alter the geometry of the device. Several such geometrical shapes have been proposed and they have been shown to release drug with approximately zero-order kinetics. Diagrams of these devices are shown in figure 5.1. A device with hemispherical geometry (type 1, figure 5.1) has been described (223, 224). A matrix is coated completely with a water-impermeable barrier and a small hemispherical cavity is made in the centre of the planar surface of the device, exposing the matrix material. As drug is released, the section of the device depleted of drug becomes hemispherical in shape and constantly increasing in radius. This concomitantly increases the area of drug available for diffusion and thus compensates for the increase in diffusion distance to the exposed surface. Drug is therefore released at a constant rate. In release from a cylindrically shaped matrix, or from a single planar surface of a matrix, it is the increase in diffusion distance without a corresponding increase in area which is responsible for the constantly decreasing release rate. Devices with other geometries which operate on the same principle include a cylindrical device (type 2, figure 5.1) which is coated with a water-impermeable barrier and which has a narrow circular central hole drilled laterally through the device (225). Another type of device (226) consists of a wedge-shaped section of a circular cylinder (type 3, figure 5.1), which is coated with a water-impermeable barrier except on the narrow end of the "wedge", which is exposed to dissolution medium. A related device (227) (type 4, figure 5.1), consists of an inwardly tapered disc which is

Type 1.
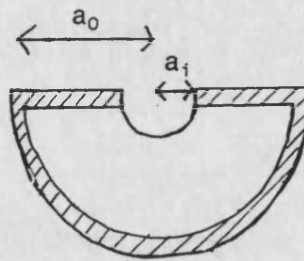
Type 2.
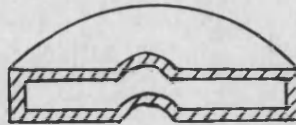
Type 3.
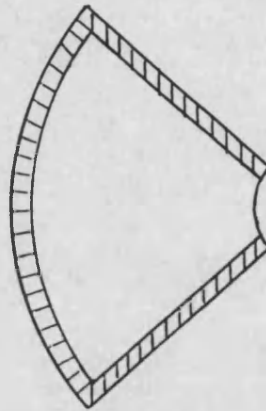
Type 4.
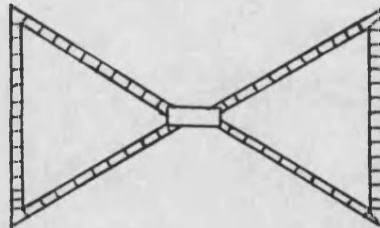
Type 5.
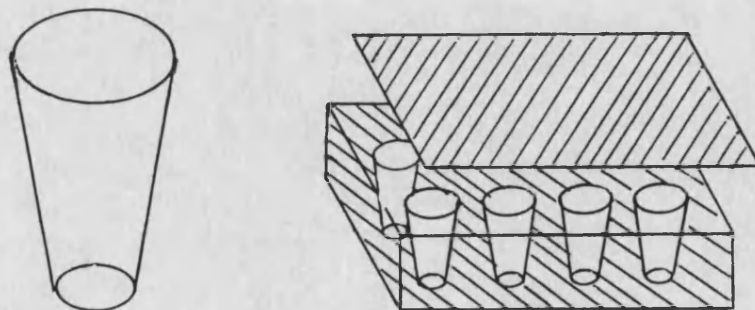
Figure 5.1   Geometrical configuration of zero – order drug releasing matrix devices

(Hatched areas indicate water – impermeable barriers)

coated with a water – impermeable barrier, except for a circular shaped portion in the centre of disc, from which drug release occurs. A further device reported (228) (type 5, figure 5.1) consists of an array of sections of cones, the exact geometrical shape being described as a frustrum of a cone. The frustra are enclosed in a water – impermeable slab with a water – impermeable backing, with the narrow ends of the frustra exposed to dissolution medium.

The composition and methods of preparation of the matrices used in the devices described varied and only the cylindrical device with the drilled hole was produced by tableting. It was found with this system that drug release over periods which were useful for oral devices could be obtained without including any matrix – forming material in the tablets. Drug was hence able to be blended with just a soluble inert diluent and tableted using direct compression technology. This system was therefore of potential clinical use, because it had the advantage that it could be prepared with conventional tableting and coating technology, with the one extra step required being the drilling of the hole. It was found though, that the system was not suitable for highly water – soluble drugs, which were released too rapidly.

Since drug release from all the types of device described is affected by the surface area of the core exposed to dissolution medium it was considered that a device which might be useful for delivering highly water – soluble drugs with zero – order kinetics would be the hemispherical system. It was considered that the exposed matrix surface area would be small and easily adjusted and secondly that this shape would be the simplest of those described to produce, both in terms of the feasibility of the production of the devices by direct – compression tableting, and the opening of the cavity in the coat. As described for the cylindrical system, if a device with the desired zero – order drug release profile could be produced more simply than is presently possible, and mostly by using conventional production technology, this would potentially be a clinically useful system.

An equation describing drug release from hemispherical matrices was derived by Rhine et al (223) and takes the following form: –

$$Q = 2\pi C_s Da_i\{R/(R - a_i)\}t \qquad \ldots\ldots\text{equation 5.1}$$

where a_i = radius of the cavity

R = radial distance to the interface between dissolved and dispersed drug within the matrix

Note 1: the diffusion coefficient D is that of the drug in the matrix, and for a porous matrix will become the diffusion coefficient of the drug in the release medium multiplied by the porosity/tortuosity factor $\in/\tau$ as in equation 1.24.

Note 2: The equation only applies if the radius of the device is at least three times that of the radius of the cavity a_i.

Examination of this equation indicates that drug release rates could be modified by altering drug solubility, porosity, tortuosity, and the radius of the cavity.

It was therefore decided to investigate the production of hemispherical shaped drug delivery devices by tableting, evaluate suitable methods of coating and assess the effect of various formulation factors on drug release profiles.

5.2 Materials

Chlorpheniramine maleate: micronised, Lot 39MI, was supplied by Schutz and Co., D-2000, Hamburg 11, F.R.G.

Carnauba Wax: GLR grade, Lot 9862950F, BDH Chemicals

Ethylcellulose: viscosity grade - 14 cP at 25°C in 80 : 20 toluene : ethanol by weight, Lot 5105962H, BDH Chemicals

Polyvinyl pyrrolidone: K-90 grade, sample, was supplied by Midland Dykem Chemicals, Leicester, U.K.

Toluene: Analar grade, lot 5762780B, BDH Chemicals

Industrial methylated spirit: GPR grade, Lot 5066400H, BDH Chemicals

Diethyl phthalate: Lot 6336680, BDH Chemicals

Dichloromethane: HPLC grade, Lot T2306, Fisons Scientific Apparatus, Loughborough, U.K.

Lactose Ph. Eur.: Direct compression grade – "Tablettose", Lot 227773, was supplied by Meggle, D–8090 Wasseburg, F.R.G.

Ethylcellulose coating suspension: "Ethocel AQ", Lot MM880622, was supplied by Colorcon, Orpington, U.K.

Colloidal silicon dioxide: "Aerosil 200", Lot 0494 was supplied by Degussa AG, D–6000, Frankfurt 1, F.R.G.

5.3 Methods

5.3.1 Assay of Chlorpheniramine Maleate Using UV Spectrophotometry

A model drug which was highly water–soluble and which preferably could be assayed by UV spectrophotometry was required for this study. Chlorpheniramine maleate (CHL) was selected, having a water solubility at $20\,^{\circ}C$ of approximately 1 part in 4 parts water (202) and a maximum UV absorbance at a wavelength of approximately 265 nm (202). The following procedures were carried out as described above (section 2.2.6.1). A series of aqueous solutions of increasing chlorpheniramine maleate concentration in the range 5 – 140 mg dm^{-3} was prepared; the wavelength of maximum absorption was determined and the absorbance of the solutions was measured at this wavelength. Excipient solutions were also prepared as described above (section 2.2.1.2) and any UV absorbance was determined.

5.3.2 Preparation of Hemispherical Matrices using Tableting

The target mass of all tablets prepared in this part of the study was 350 mg. The matrix tablets produced for the initial studies were prepared as described above (sections 2.2.1.1 and 3.2.1.2). Compaction was carried out manually using 12.7 mm diameter, flat–faced punches to produce tablets with a diametral crushing strength in the range 59 – 78 N according to the following formulation:–

Formulation	Composition
5A	CHL 40% / HVO 40% / MCC 19% / MS 1%

Note 1: Information relating to the composition of all formulations used in this chapter is given in table 5.1 at the end of the chapter.

Tablets were also prepared as described above using a 12.7 mm diameter flat-faced lower punch and a 12.7 mm diameter deep concave upper punch according to the following formulations 5B – 5E.

Formulation	Composition
5B	CHL 40% / HVO 30% / SDL 29% / MS 1%
5C	CHL 40% / HVO 10% / SDL 49% / MS 1%
5D	CHL 40% / HVO 5% / SDL 54% / MS 1%
5E	CHL 40% / HVO 2.5% / SDL 56.5% / MS 1%

An upper punch of 10 mm diameter having a hemispherical radius of curvature and a flat-faced lower punch were also used to prepare tablets from formulations 5B – 5E and from formulations 5F and 5G:–

Formulation	Composition
5F	CHL 40% / SDL 59% / MS 1%
5G	CHL 40% / SDL 60%

A problem which occurred during the process of pan–coating of hemispherical tablets with sprayed ethylcellulose films, which is described below (section 5.3.3.2), was that tablets of several of the formulations described split along the plane where the hemispherical portion of the tablet met the small cylindrical portion. This was considered to be due to inadequate mechanical strength and for

this reason granulations of powder mixes of further formulations were prepared in an attempt to improve the compactibility of powder mixes. Formulations 5H – 5M were prepared using a polymeric binder (polyvinyl pyrrolidone – K90 grade (PVP)) dissolved in the granulating fluid and the drug content was reduced from 40% to 29.4%:–

Formulation	Composition
5H	CHL 29.4% / HVO 29.4% / SDL 38.7% / PVP 2% / MS 0.5%
5I	CHL 29.4% / HVO 19.6% / SDL 48.5% / PVP 2% / MS 0.5%
5J	CHL 29.4% / HVO 9.8% / SDL 58.3% / PVP 2% / MS 0.5%
5K	CHL 29.4% / HVO 4.9% / SDL 63.2% / PVP 2% / MS 0.5%
5L	CHL 29.4% / HVO 2.5% / SDL 65.6% / PVP 2% / MS 0.5%
5M	CHL 29.4% / SDL 68.1% / PVP 2% / MS 0.5%

The granules were prepared using a pestle and mortar and the wet granules were screened through a 20 mesh sieve followed by tray–drying in a fan oven at 35°C for 12 hours. The dried granules were re–screened through a 22 mesh sieve and subsequently mixed with magnesium stearate at a concentration of 0.5% w/w for 3 minutes, using a cube blender as described above (section 2.2.1.1). Tablets of formulations 5H – 5M were prepared as described above except that they were prepared to approximately the same initial porosity. This was achieved in the following manner.

The true densities of CHL and PVP were determined using helium – air comparison pycnometry as described above (section 3.2.1.1). The dimensions of a hemispherical tablet were determined using a micrometer to measure the thickness of the whole tablet, and digitally–reading calipers (Model 600–880, RS Components) to measure the thickness of the small cylindrical portion. The volume of the cylindrical portion was calculated as described above (section 2.2.7.2). The remaining portion of the tablet was not a complete hemisphere because the rim of the upper punch which had hemispherical curvature had a finite thickness, and

therefore only allowed tablets to be produced which had the shape of part of a hemisphere. The shape of the punch and the actual tablet shape produced are shown in figure 5.2. The volume V of the partial hemisphere portions of tablets was determined using the following equation: –

$$V = \pi H^2 \{r - (H/3)\} \qquad \ldots\text{equation 5.2}$$

where   H = distance from the centre of the planar surface to the furthest point on the curved surface

                r = radius of curvature of the partial hemisphere portion of the tablet

Having determined the total volume occupied by the tablets, the porosity was calculated using equation 3.2. Tablets of formulation 5H were prepared to a high diametral crushing strength in the range 157 – 176 N (16 – 18 kPond). A mean porosity of 10 tablets was determined as described immediately above and tablets of further formulations were prepared to a similar porosity by adjusting compaction pressure accordingly.

5.3.3 Coating of Hemispherical Tablets

In order to achieve a water – impermeable barrier around the tablets, except for the opening through which drug release would occur, two methods of tablet coating were employed. In initial studies, the tablets were dip – coated using molten wax. The second method used pan – coating to apply either organic solutions or aqueous suspensions of ethylcellulose by spraying onto tablet cores.

5.3.3.1 Dip – Coating of Tablets in Molten Carnauba Wax

Initial studies were carried out using tablets prepared from formulations 5B – 5E having one deep concave and one flat surface, and hemispherical tablets prepared

A. Cross – section of tablet

H mm

(5 – H) mm

r

= 5 mm
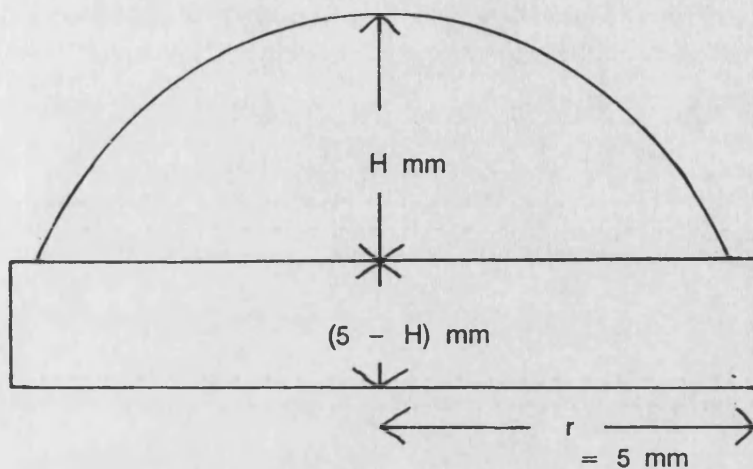
B. Cross – section of hemispherical tablet machine punch

10 mm

5 mm
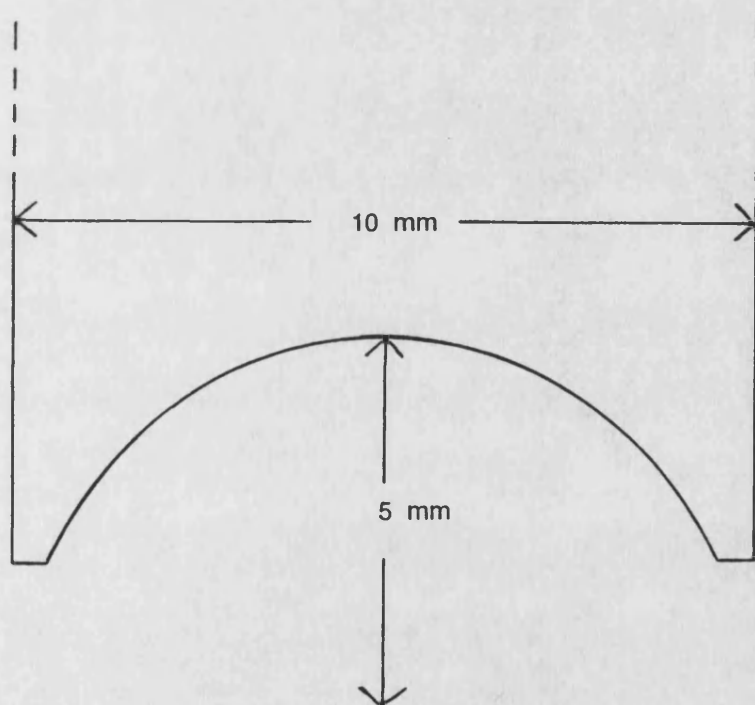
Figure 5.2   Cross – sections of tablet machine punch having hemispherical   curvature

and the shape of a tablet produced therefrom

from formulations 5F and 5G. These tablets were dip-coated in molten carnauba wax using the following technique. The tip of a needle mounted on a wooden handle was heated in a bunsen flame and inserted into the centre of the planar face of a tablet to a depth just sufficient to allow the needle to be picked up with the tablet attached. The tablet was then dipped five times into in an evaporating dish on a heating mantle containing the molten wax which had been allowed to cool to just above its melting point. This procedure caused a solid wax coat to be progressively built up on the tablet surface. The mounted needle was then removed, leaving a hole in the coat. This was used as a guide to make a larger hole in the coat using an appropriate bit in a high speed drill mounted perpendicularly on a drill stand. In the case of the 12.7 mm diameter tablets the hole diameter was 4.0 mm and with the 10 mm diameter tablets, 3.2, 4.0, 4.8 or 5.6 mm according to the experiment. The tablet was held in place manually and the hole was drilled through the coat until the tablet surface was reached.

The permeability of the coat to water was tested on six tablets which had not had holes drilled in them. The small hole left by removal of the mounted needle was sealed with a drop of molten carnauba wax. The tablets were then subjected to dissolution testing as described above (section 2.2.6.3) for 24 hours to determine whether any drug was released.

5.3.3.2 Organic and Aqueous Film-Coating of Tablets with Ethylcellulose

The batch of tablets of formulations 5B – 5G prepared with the 10 mm diameter hemispherical upper punch was coated with a film coat of ethylcellulose applied by spray-coating in a brass coating pan. Ethylcellulose film-coats have been used to control drug release from tablets and microspheres, and factors affecting drug release rates were found to be the thickness of the coat, and the percentage of water soluble additives in the coat (101, 102). Hence if no water-soluble additives are included and a thick enough coat is applied, a water-impermeable barrier should be formed. In order to obtain such a barrier, it was considered that a percentage

gain in tablet mass of at least 15% was required. This was estimated from previous work (201) which had established that drug release occurred through coats of a thickness resulting from an increase in mass of up to 12%. The following coating solution was used and was prepared by dissolving the ethylcellulose in the mixed organic solvents and then adding the plasticiser diethyl phthalate:—

Material	Amount
Ethylcellulose	4 g
Diethyl phthalate	1 g
Dichloromethane	57 g
Industrial methylated spirit	38 g

In order to reduce the likelihood of the "twinning" of hemispherical tablets i.e. the adhesion of the planar faces of two tablets with coating solution, the solvent of which then evaporates leaving the tablets held together with a film of coating material, the tablets were coated along with other tablet cores. These had convex faces to prevent twinning, did not contain drug and were prepared in the following manner. 5 kg of powder mix was prepared according to the formulation described immediately below by blending the lactose and the microcrystalline cellulose in a laboratory blender (Model KM/502, Kenwood, Havant, U.K.) for 15 minutes. Magnesium stearate was added and the final mix was blended for a further 3 minutes.

Material	Amount
Lactose	697.5 g
Microcrystalline cellulose	297.5 g
Magnesium stearate	5.0 g

Tablets were produced volumetrically using 9 mm diameter shallow concave tooling fitted to a rotary tablet machine (Model B, Manesty Machines), with a diametral crushing strength in the range 98 – 118 N (10 – 12 kPond).

Hemispherical tablets of formulations 5B – 5G were identified with combinations of coloured dots applied to the hemispherical surfaces with felt–tipped pens. A total tablet load of approximately 3 kg was coated in a brass coating pan of approximately 10 dm^3 capacity with the coating solution sprayed onto them via a peristaltic pump (Model Minipuls 2, Gilson, 95400 Villiers Le Bel, France) and using a spray head (Model L910, Binks Bullows, London, U.K.) attached to a compressed air source. Coating solution and air flow rates were adjusted to give a suitable spray pattern. This was ascertained by holding a piece of paper approximately 20 cm from the nozzle of the spray head and adjusting the pump speed and air flow rate until a circular pattern of approximately 10 cm diameter was produced from which coating liquid did not run. Solvent evaporation was aided by employing a domestic hairdryer. The even coating of the tablets was aided by taping two intersecting pieces of rubber tubing of diameter 5 mm onto the inner surface of the pan, which facilitated tumbling of tablet cores during coating.

This system proved satisfactory at producing the desired type of coat, (section 5.4.3.2 below), but suffered from the disadvantages that it required a large total amount of tablets and large quantities of coating material in order to coat a small number of hemispheres. Coating with ethylcellulose also necessitated the use of organic solvents, whose toxicity and potential flammability were undesirable in a laboratory environment. A smaller version of the coating equipment was therefore constructed and a water–based coating formulation of ethylcellulose obtained. A small coating pan was constructed from the lower part of a flat–bottomed flask having two pieces of square perspex with dimensions indicated in figure 5.3 glued to its base. A screw of length 40 mm was driven perpendicularly through the centre of one of the pieces of perspex so that it protruded from the opposite surface, and the other piece of perspex was glued to the side opposite to
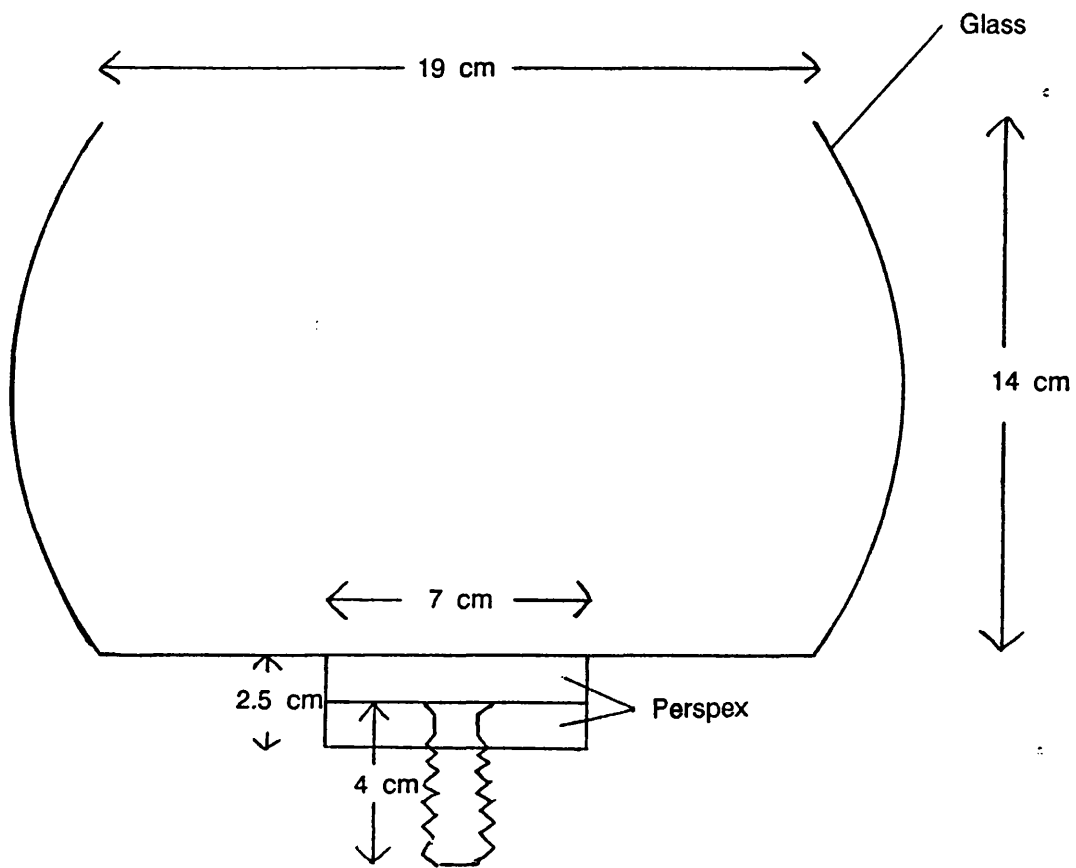
Figure 5.3   Small scale coating pan

the protruding screw. This effectively fixed the position of the screw in the perspex and provided a means of attaching it to a variable drive motor (Model KQ/506, Citenco Ltd., Boreham Wood, U.K.). The motor and bowl assembly was clamped into a suitable position and the motor speed adjusted to rotate the bowl at 15 rev min^{-1}.

Coating suspension was pumped to a spray–head using a peristaltic pump. The spray–head was clamped into a suitable position and the spray pattern was adjusted in the manner described immediately above. Drying air was provided by a domestic hair–dryer, in this case used on the low heat setting. Trials established that a suitable load for the pan was approximately 100 tablet core hemispheres in a total mass of 250 g of tablet cores. This load ratio minimised the occurrence of twinning of the planar faces of hemispheres. The coating suspension was prepared using the following formula by dispersing the colloidal silica in the ethylcellulose suspension (Ethocel AQ) by gentle stirring using a magnetic stirrer and then diluting to volume with water:–

Material	Quantity
Ethylcellulose coating suspension (Ethocel AQ)	100 g
Colloidal silicon dioxide	1.25 g
Distilled water	135 cm^3

The coating process was carried out until the hemispheres showed an increase in mass of at least 15%, in comparison with the uncoated cores. It was found that the most reproducible method of opening a hole in the film coat through which drug release could occur was to use a circular cork borer of the appropriate size (diameter 3.2 mm). Using this, it was possible to cut out and remove a disc–shaped section of the coat without damaging the tablet surface. Circular apertures were produced in this manner in the centre of the planar faces of the hemispherical tablets. This technique did not produce a hemispherical cavity in the planar

surfaces, but it was considered that a simple and reproducible method of producing such a cavity was not available, and that such a technique would only be worth developing if the lack of a such a cavity was found to have a significantly detrimental effect on zero-order drug release kinetics.

As described above (section 5.3.3.1) with the wax-coated tablets, tablets without a hole were subjected to dissolution testing to ascertain whether drug was released through the intact coat.

5.3.4 Determination of Drug Release Characteristics of Hemispherical Tablets

Drug release rates were determined as described above (section 2.2.6.3). It was found that when tablets were first placed in dissolution fluid, an air bubble sometimes lodged on the tablet surface in the hole in the coat. This occurred with both wax and ethylcellulose coated tablets and air bubbles were removed by aspiration using a pasteur pipette.

5.4 Results and Discussion

5.4.1 Assay of Chlorpheniramine Maleate Using UV Spectrophotometry

The wavelength of maximum absorbance of chlorpheniramine maleate (CHL) in aqueous solution was found to be 261 nm. The absorbance data obtained was plotted against concentration, and is shown in figure 5.4. It was considered that a linear relationship existed between concentration and absorbance and least squares regression analysis was used to estimate the relationship between the variables. It yielded the following parameters:-

$$\text{Slope} \quad = \quad 14.33 \ (\text{g dm}^{-3})^{-1}$$

$$\text{Intercept} \quad = \quad -0.0015$$

$$r^2 \quad = \quad 0.9999$$
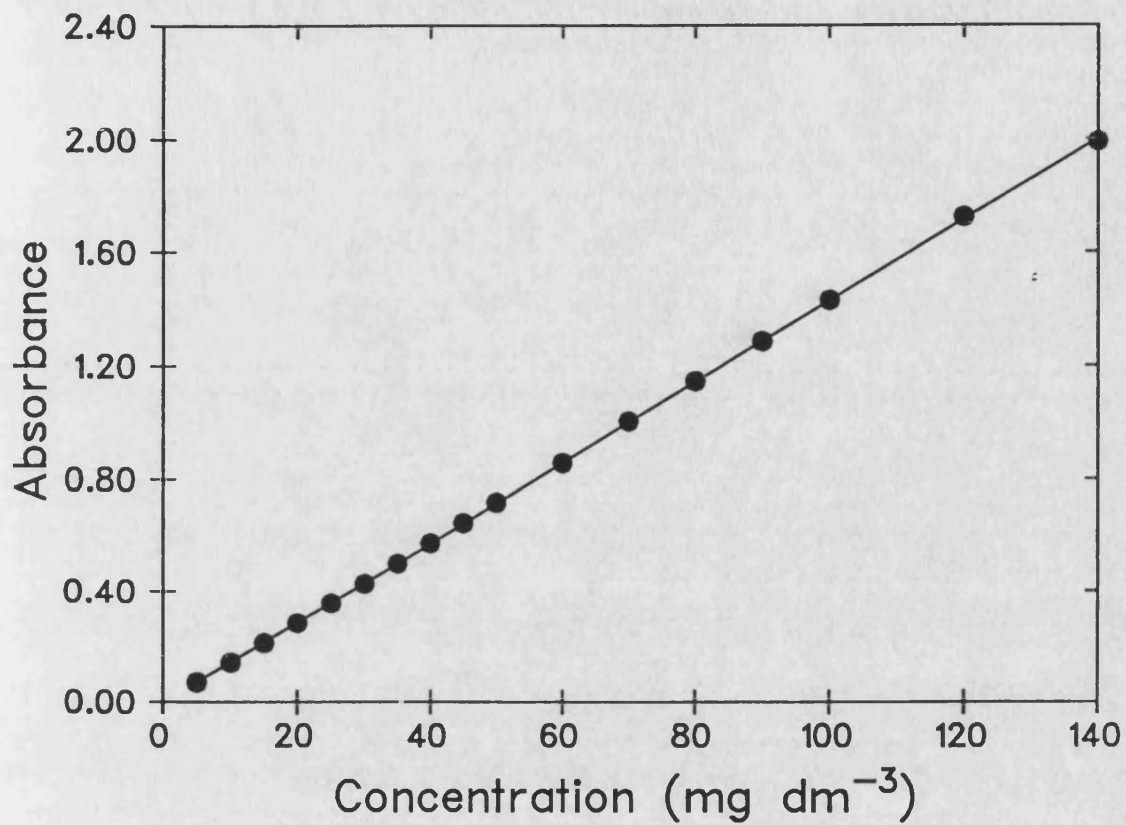
Figure 5.4   Calibration curve of UV absorbance at 261 nm versus   concentration   of

chlorpheniramine maleate

The results were considered to show that the assay was appropriate for analyses in the concentration range measured. No significant difference in absorbance was noted between any of the excipient solutions prepared and a blank of distilled water and it was concluded that any dissolved excipient did not interfere with the assay.

5.4.2 Preparation of Hemispherical Matrices using Tableting

Mean values for the true densities of CHL and PVP were found to be 1.30 g cm^{-3} (C. V. = 1.82%, n = 3) and 1.18 g cm^{-3} (C. V. = 2.53%, n = 3) respectively, using helium – air comparison pycnometry. The mean porosities of tablets of formulations 5H – 5M are given in table 5.2.

Formulation	Mean Porosity %	95% Confidence Interval
5H	3.92	0.15
5I	3.81	0.17
5J	4.53	0.15
5K	4.88	0.06
5L	5.61	0.27
5M	5.55	0.18

Table 5.2 Mean porosity and 95% confidence interval for tablets prepared from formulations 5H – 5M

5.4.3 Coating of Hemispherical Tablets

5.4.3.1 Dip – Coating of Tablets in Molten Carnauba Wax

No drug release was found to occur from the tablets completely coated with wax which were subjected to dissolution testing. This confirmed that the wax coat was

impermeable to water and continuous.

A disadvantage of wax coating which was found, apart from the need to coat each tablet individually, was the irreproducibility of both the thickness of the coat applied, and the depth to which the hole through the coat could be drilled, The drilling process also sometimes caused part of the coat immediately adjacent to the hole to split away from the tablet, due to the brittleness of the solid wax. These factors caused significant variability in the drug release data which was obtained (section 5.4.4 below). It was for these reasons, in addition to the fact that coating by this method could not be easily employed in large scale production, that film – coating with ethylcellulose was also studied.

5.4.3.2 Organic and Aqueous Film – Coating of Tablets with Ethylcellulose

No drug release was found to occur from tablets completely coated with ethylcellulose which were subjected to dissolution testing. This confirmed that a gain in mass of 15% was sufficient to render the coat continuous and impermeable to water over 24 hours, when applied to tablets of the size and shape used. This method of coating and the method of opening an aperture in the coat with a cork borer was found to produce devices from which the drug release rates were less variable than from the tablets dip – coated with carnauba wax.

5.4.4 Determination of Drug Release Characteristics of Hemispherical Tablets

In order to ascertain the period over which CHL would be released from an HVO – based matrix, tablets of formulation 5A were subjected to dissolution testing. The drug release profile obtained is shown in figure 5.5, and the tablets were found to have released approximately 90% of their drug content after 8 hours. It was considered that coated hemispheres of this formulation might release drug .too slowly for potential oral use and thus the HVO concentration was reduced in the first formulation from which hemispheres were produced. Coated tablets of formulation 5B were hence subjected to dissolution testing and uncoated hemispheres
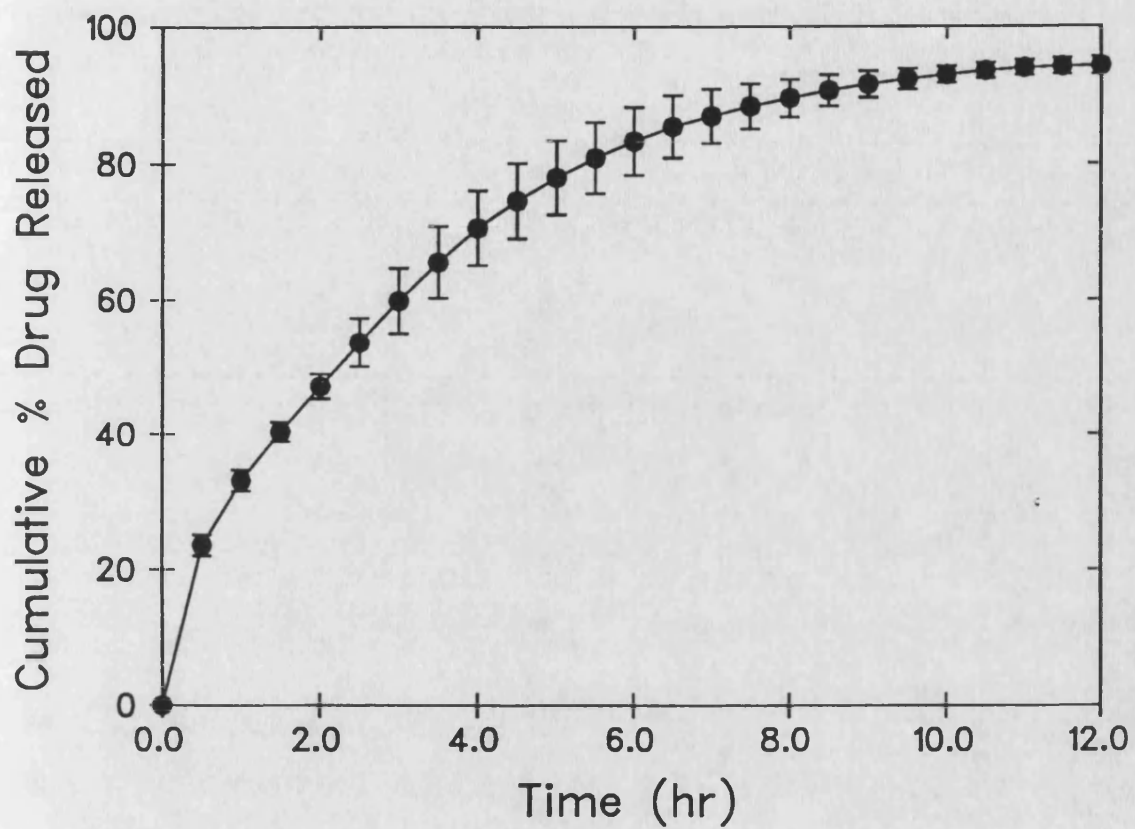
Figure 5.5   Drug release profile for formulation 5A (table 5.1)

were also subjected to dissolution testing for comparison. The release profiles obtained are shown in figure 5.6. It can be seen that the uncoated tablet shows a rapid non-linear release profile, but that the coated tablet releases drug with an initially slightly decreasing rate over approximately 10 hours, then a constant zero-order phase. Least squares regression on the linear phase of release was performed and the results are given in table 5.3 at the end of the chapter. This shape of release profile is characteristic of a hemispherical matrix (224), but it is interesting to note that the tablets from which it was derived were not truly hemispherical in shape. They had been produced with a punch having deep concave curvature, not hemispherical curvature. They also had a small cylindrical portion (figure 5.2). This indicated that true hemispherical curvature appeared not to be an absolute requirement for zero-order release characteristics.

Since the coated tablets of formulation 3B had only released approximately 25% of their drug content over 23 hours, it was decided to investigate the effect of further reducing the HVO content of tablets, in order to attempt to attain complete drug release over a shorter time. Formulations containing 10%, 5%, and 2.5% HVO (formulations 5C – 5E) were therefore prepared as described above (section 5.3.2) and subjected to dissolution testing. The drug release profiles exhibited by tablets of these formulations together with the formulation containing 30% HVO are shown in figure 5.7.

Examination of these plots indicated that HVO proportion appeared not to have a consistent effect on drug release rate, with the formulation containing 10% HVO exhibiting a faster drug release rate than the formulation containing 5% HVO. The large 95% confidence interval bars, which overlap for all the four formulations, indicate that it is not possible to distinguish statistically between the drug release rates exhibited by any of these formulations. The slopes of the linear, zero-order portions of the release profiles are given in table 5.3.

Since the inclusion of only 2.5% HVO in a formulation resulted in a drug release rate which was not significantly different from a formulation containing
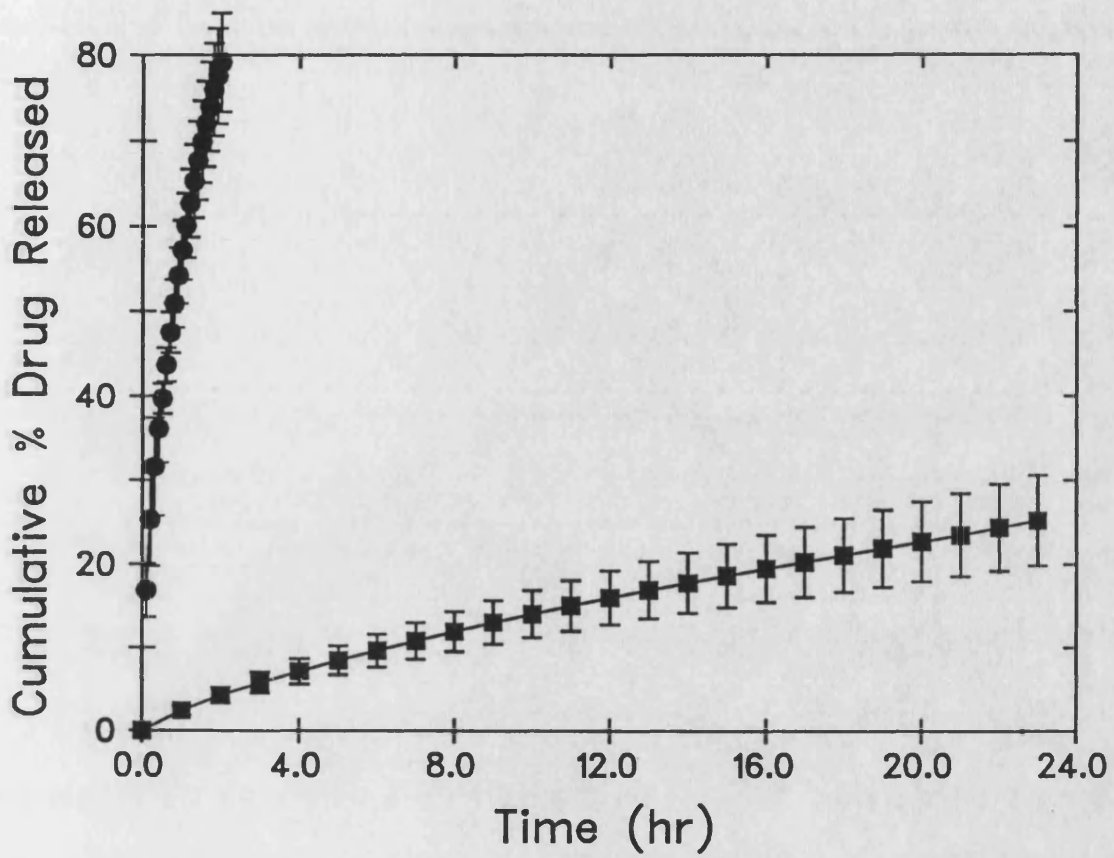
Figure 5.6   Drug release profiles for formulation 5B (table 5.1), ● uncoated   and

■ coated hemispheres
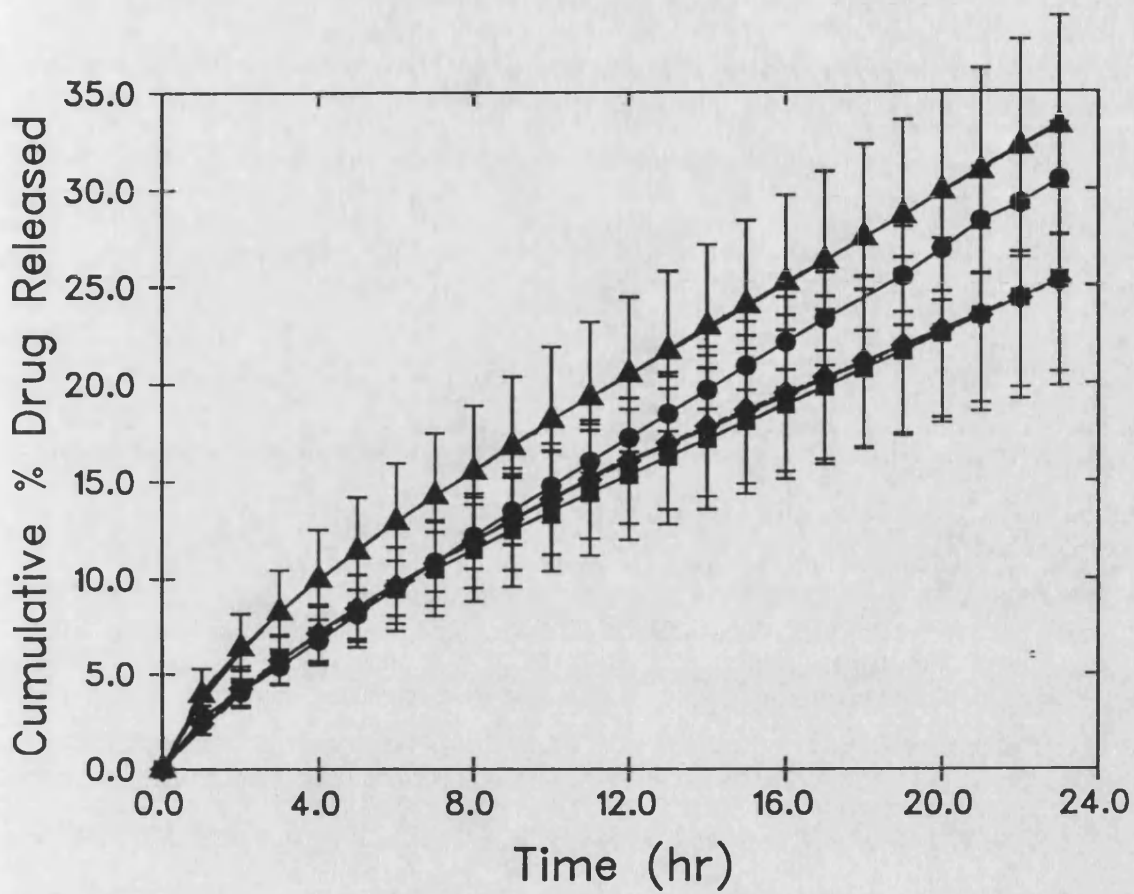
Figure 5.7   Effect of hydrogenated vegetable oil concentration on drug release

profile from wax – coated hemispheres

Key: ▲ = 2.5% HVO

           ◆ =   5% HVO

           ● =   10% HVO

           ■ =   30% HVO

30% HVO, this indicated that the formation of a porous matrix structure was not necessary for prolonged zero-order release characteristics. It was decided to investigate the effect on drug release rate of removing HVO completely from a formulation and also the effect of not including magnesium stearate in a formulation. This was because the proportions of HVO which appeared to prolong drug release were low enough to be considered as only having a lubricant effect, and since magnesium stearate was also a lubricant, its presence may have affected drug release rate. At this point of the study, a tablet machine punch with hemispherical curvature had been obtained and tablets of formulation 5G and 5H were prepared using it. They were subjected to dissolution testing and the drug release profiles obtained are shown in figure 5.8.

The drug release profiles obtained indicated that the exclusion of HVO from a formulation did not result in a marked increase in release rate compared to formulations containing HVO. The shape of the release profile was altered, with an initial lag period rather than a burst phase observed. The exclusion of magnesium stearate from a formulation resulted in a slight increase in release rate, but the variability in the data indicated that no statistically significant difference could be distinguished between the two release profiles. The shape of the steady-state portions of the release curves indicated that zero-order drug release was exhibited by the truly hemispherical tablets, as well as those which were prepared having deep convex curvature. The slopes of the zero-order phases of drug release are given in table 5.3.

The results obtained indicated that the system was capable of releasing drug with predominantly zero-order kinetics, but that the period of drug release was too long to be of potential clinical use. In an attempt to increase drug release rate from hemispherical tablets, the effect of increasing hole size was examined. Tablets of the formulation containing no HVO (5G) were prepared with holes of 4.0, 4.8 and 5.6 mm diameter and subjected to dissolution testing. The drug release profiles obtained are shown in figure 5.9, with the profile for the tablets with
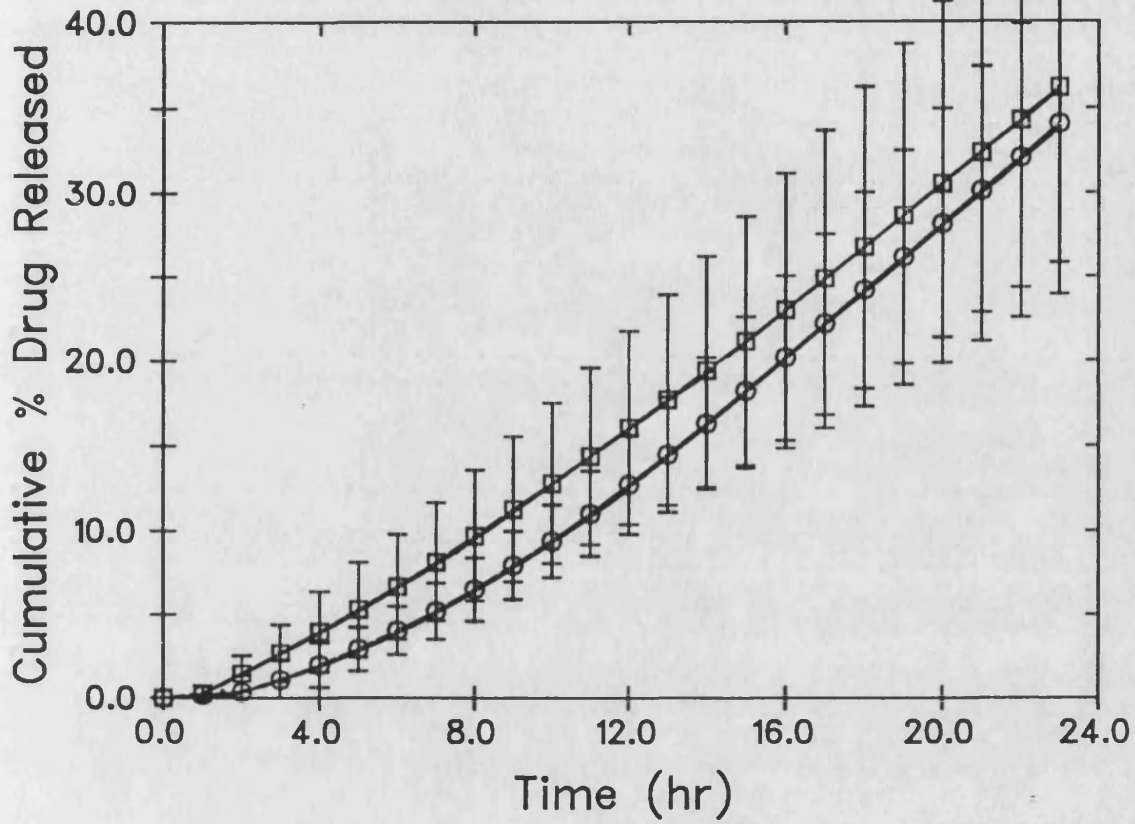
Figure 5.8   Effect of magnesium stearate on drug release   profile   of   wax – coated

hemispheres not containing hydrogenated vegetable oil

Key: □ = 0% magnesium stearate

            O = 1% magnesium stearate
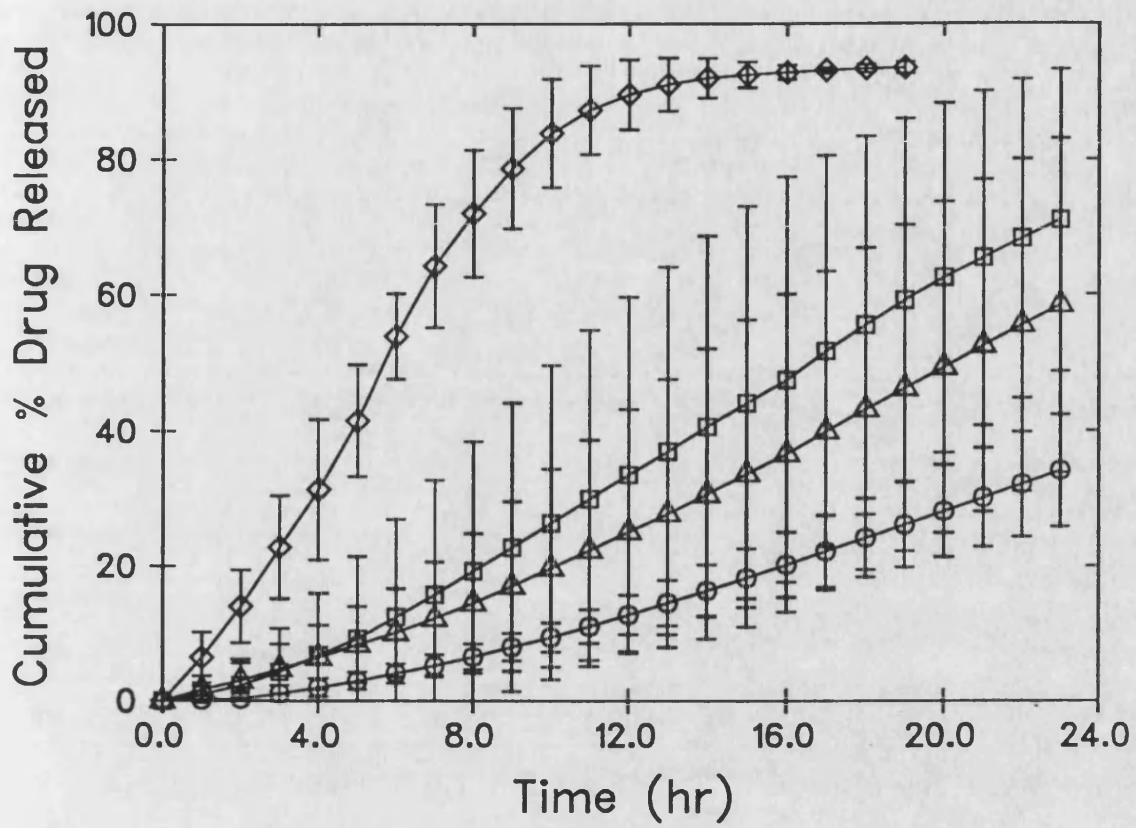
Figure 5.9   Effect   of delivery hole diameter on drug release   profile   from   wax –

coated hemispheres of formulation 5G (table 5.1)

Key: O   = 3.2 mm

          △   = 4.0 mm

          □   = 4.8 mm

          ◇   = 5.6 mm

3.2 mm diameter holes also shown for comparison.

Examination of these plots indicated that increasing hole size resulted in an increased drug release rate. The 95% confidence intervals indicated that no statistically significant difference could be distinguished between tablets with holes of 3.2, 4.0 and 4.8 mm, but that tablets with a 5.6 mm diameter hole released drug at a significantly greater rate than tablets with each of the three smaller holes. The shape of the release profiles indicated that after a lag period, drug release still conformed to approximately zero – order kinetics. One of the original requirements for the hemispherical matrix system was that the hole in the coat was no greater in diameter than one – third of the diameter of the hemisphere. The holes of diameter greater than 3.2 mm were greater than one – third of the diameter of the hemispheres, and the results indicated that with hemispheres not containing matrix – forming material, hole diameter could be increased beyond this limit without altering the zero – order release characteristics. The slopes of the linear phases of the drug release profiles are given in table 5.3.

It was considered that the inconsistency and variability in the results obtained were due to the method of coating and of drilling the hole in the coat, which resulted in the disadvantages described above (section 5.4.3.1). For these reasons, it was decided to investigate the method of spray – coating with ethylcellulose films. This technique would be more likely to deposit a coat of reproducible thickness and hence the holes would be of reproducible dimensions.

Tablets of formulations 5B – 5G were prepared and coated with ethylcellulose as described above. As mentioned in section 5.3.2 above, a problem which occurred during the film – coating process was that tablets of some of the formulations split into two pieces, and unfortunately only enough intact tablets from formulations 5B and 5C were recovered on which to perform dissolution studies. The drug release profiles obtained are shown in figure 5.10. These profiles showed that the formulation containing 30% HVO released drug with the characteristic pattern of a hemispherical matrix but that the formulation containing 10% HVO exhibited a
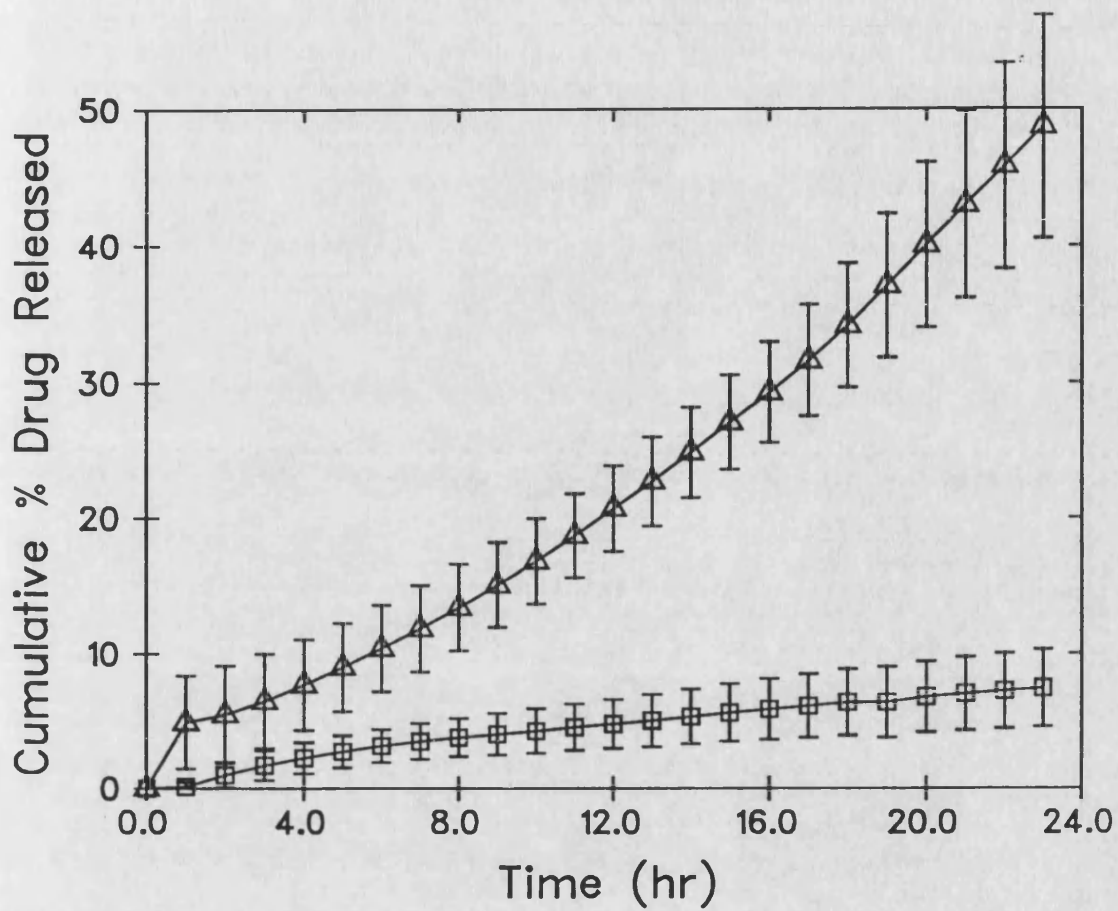
Figure 5.10   Drug   release   profiles   of   ethylcellulose – coated   hemispheres   of

formulations 5B and 5C (table 5.1)

Key: □ = formulation 5B

△ = formulation 5C

gradually increasing release rate. It was considered that this was due to small radial cracks surrounding the hole which had appeared in the coat on the planar surface of tablets of this formulation. This suggested that the coat was not adequately plasticised, and constituted a further reason to replace the organic-based ethylcellulose coating solution with the water-based suspension, which produced a less brittle coat.

In order to further investigate the effect on drug release profile of HVO content, tablets from other formulations (5H – 5M) were prepared using granulated powder mixes of drug and excipients in order to increase the mechanical strength of tablets and increase the probability of their surviving the film-coating procedure. It was found that tablets from all the formulations produced using powder mixes which had been granulated were sufficiently strong to withstand the coating process and they were therefore subjected to dissolution testing. The dissolution profiles obtained for tablets from these formulations are shown in figure 5.11. Examination of these data confirmed that increasing HVO content resulted in decreasing release rate. A decrease in HVO content from 29.4% to 19.6% and from 19.6% to 9.8% was found to only slightly increase drug release rate. However, there was a comparatively large increase in release rate when HVO content was decreased from 9.8% to 4.9% and from 4.9% to 2.5%, although a smaller increase in release rate was found when HVO content was reduced from 2.5% to 0%. Wide variability in drug release rate was found between tablets of the same formulation of both the formulation containing 2.5% HVO and the one containing no HVO. In comparison, excellent reproducibility was found between drug release rates of individual tablets from formulations containing 29.4%, 19.6%, and 9.8% HVO, with the tablets from the formulation containing 4.9% HVO showing a variability in drug release rate intermediate between the two extremes.

Apart from the formulation which did not contain HVO, whose drug release profile was slightly sigmoidal in shape, the shapes of the drug release profiles showed that the tablets delivered drug with the predominantly zero-order profile
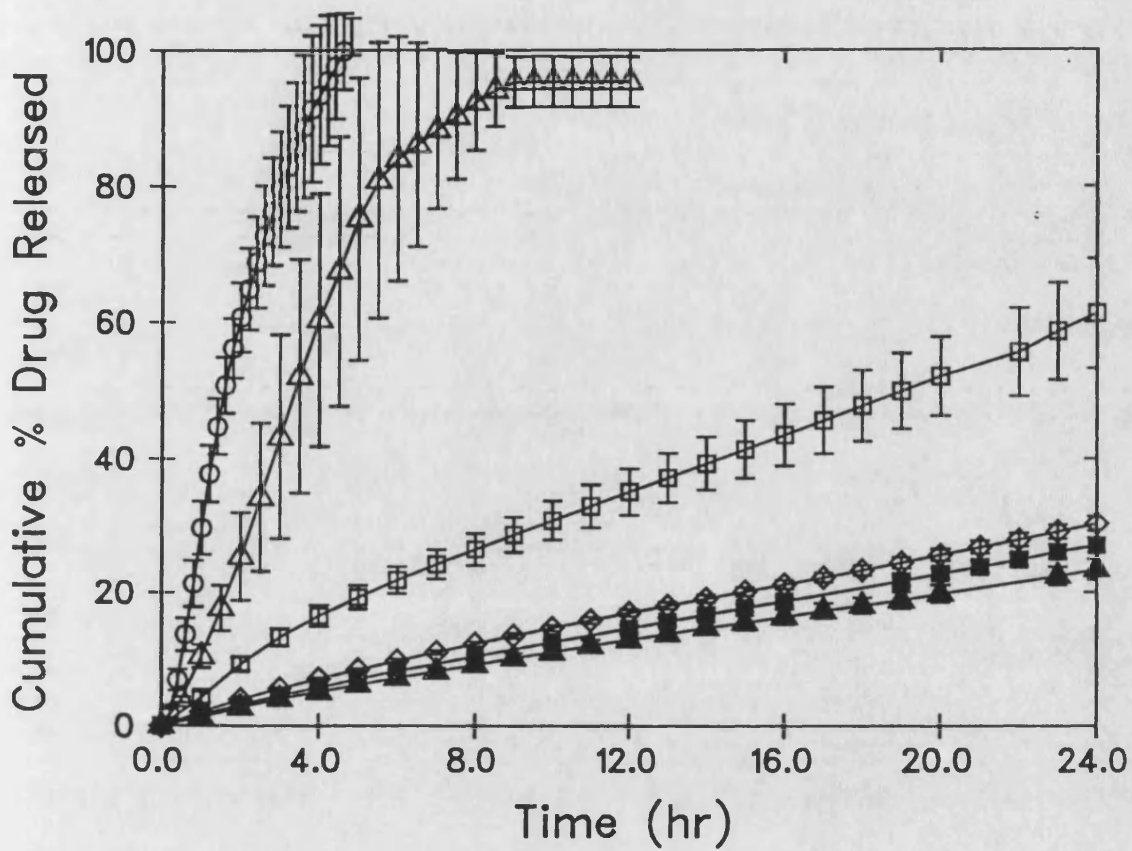
Figure 5.11   Effect of hydrogenated vegetable oil concentration on drug   release

profile from ethylcellulose – coated hemispheres

Key: O =   0% HVO

△ = 2.5% HVO

□ = 4.9% HVO

◇ = 9.8% HVO

■ = 19.6% HVO

▲ = 29.4% HVO

characteristic of a hemispherical matrix, even when there was apparently insufficient HVO in a tablet to form a porous matrix. The slopes of the linear phases of the release profiles are given in table 5.3.

In an attempt to elucidate the mechanism by which drug was released with zero-order kinetics from hemispherical tablets containing low concentrations of HVO, tablets from formulations 5H – 5M were recovered after dissolution testing had been performed and were immediately cut into two sections along a diameter of the planar faces. This enabled visual examination of any material remaining within the coat. With the tablets of the formulations containing 19.6%, 9.8% and 4.9% HVO, it was found that a hemispherical portion of the tablet had been removed, and the remaining material appeared to have taken up water and could best be described as being a thick slurry. The very bottom of the tablets of the formulation containing 29.4% HVO appeared dry and the remainder of the space within the coat of tablets was still completely filled with material. The amount of slurry remaining appeared to increase with increasing HVO content, which would be expected since HVO is insoluble. No material was found to be remaining within the coat of tablets of the formulations containing 2.5% HVO and containing no HVO.

It was considered that these observations, and the drug release data which was obtained, could be explained in the following manner. In tablets prepared from a formulation containing 29.4% HVO a porous matrix would be expected to form on compaction and would remain within the coat during the drug release process allowing drug to diffuse through water-filled pores to the opening in the coat. As the proportion of HVO decreased in a formulation, the amount of insoluble material present decreased to a level insufficient to form a continuous porous matrix. The amount of water entering the tablet was not sufficient to dissolve the soluble components of the tablet, and hence a thick suspension or slurry was formed. This can be deduced from a knowledge of the volumes of the tablets which were determined during the porosity measurements. A typical tablet volume was found to be approximately 0.275 cm³ and since each tablet contained a nominal CHL content of

140 mg, (aqueous solubility approximately 250 mg cm^{-3}), this mass of drug would require 0.56 cm^3 water to completely dissolve. The presence of the soluble excipient (approximate aqueous solubility 200 mg cm^{-3} (229)), would effectively further reduce the amount of water available to dissolve drug. This suspension would effectively act as a form of porous matrix, with drug solute molecules having to diffuse around suspended particles of HVO and undissolved drug and soluble excipient. After some drug and excipient had dissolved and diffused out of the device through the hole in the coat, there would be sufficient water present to dissolve all the drug and excipient which would diffuse out around the remaining suspended HVO particles. As the HVO concentration was reduced further, to 4.9% and 2.5%, drug release would become controlled increasingly by the dissolution rate of drug and excipient within the device, rather than diffusion through a suspension. Zero−order kinetics were maintained because the concave surface area of the dissolving compact increased with time, compensating for the increased diffusional distance which drug solute molecules must traverse through the unstirred solvent layer within the coat. In a formulation containing entirely soluble components, e.g. formulation 5M, drug release was considered to be controlled by the intrinsic dissolution rate of the drug and excipient, and the subsequent diffusion of solute molecules through the static solvent layer within the hemisphere.

It therefore appeared that the rate−controlling mechanism of drug release changed with decreasing HVO content from an entirely diffusion controlled system, to a system where intrinsic dissolution rate was a significant factor governing drug release. It is not possible to determine unequivocally from the drug release data at what, if any, concentration of HVO, dissolution rate becomes the rate−controlling factor in drug release. However it may be hypothesised that the large increase in drug release rate which was found when HVO concentration was decreased from 9.8% to 2.5%, occurred because the rate of drug release changed from being diffusion controlled to dissolution controlled.

The drug release data obtained showed that this method of impermeable coating

of tablets was capable of delivering highly water-soluble drugs for periods suitable for oral use with predominantly zero-order kinetics. Drug release rates could be altered by choice and proportion of soluble and insoluble excipients, and hole dimensions. Providing a formulation could be found which exhibited the required drug release rate, it would be possible, if tablets could be prepared with sufficient mechanical strength to withstand the film-coating process, to prepare hemispherical tablets using direct compression technology. If a reproducible method of opening a hole in the tablet coat could be adapted to a production process, the system would represent a reasonably simple means of producing oral drug delivery devices which released drug with zero-order kinetics, using established excipients and production processes. The initial data which was obtained from tablets which were not truly hemispherical in shape, also indicated that hemispherical geometry appeared not to be an absolute requirement for zero-order drug release, possibly making tablet production simpler.

Formulation	Composition
5A	CHL 40% / HVO 40% / MCC 19% / MS 1%
5B	CHL 40% / HVO 30% / SDL 29% / MS 1%
5C	CHL 40% / HVO 10% / SDL 49% / MS 1%
5D	CHL 40% / HVO 5% / SDL 54% / MS 1%
5E	CHL 40% / HVO 2.5% / SDL 56.5% / MS 1%
5F	CHL 40% / SDL 59% / MS 1%
5G	CHL 40% / SDL 60%
5H	CHL 29.4% / HVO 29.4% SDL 38.7% / PVP 2% / MS 0.5%
5I	CHL 29.4% / HVO 19.6% / SDL 48.5% / PVP 2% MS 0.5%
5J	CHL 29.4% / HVO 9.8% / SDL 58.3% / PVP 2% / MS 0.5%
5K	CHL 29.4% / HVO 4.9% / SDL 63.2% / PVP 2% / MS 0.5%
5L	CHL 29.4% / HVO 2.5% / SDL 65.6% / PVP 2% / MS 0.5%
5M	CHL 29.4% / SDL 68.1% / PVP 2% / MS 0.5%

Table 5.1   Composition of tablet formulations prepared in Chapter 5

Key: CHL = chlorpheniramine maleate

HVO = hydrogenated vegetable oil

MCC = microcrystalline cellulose

SDL = spray-dried hydrous lactose

MS = magnesium stearate

PVP = polyvinyl pyrrolidone

Formulation	Slope % hr^{-1}	Intercept %	r^2
5B	0.823	6.27	0.9997
5C	1.16	6.54	0.9999
5D	0.912	4.34	0.9999
5E	1.26	1.89	0.9993
5F	1.96	− 11.0	0.9998
5G	1.81	− 5.76	0.9992
5H	0.902	1.82	0.9990
5I	1.05	1.95	0.9998
5J	1.14	2.97	0.9991
5K	2.14	9.33	0.9995
5L	16.9	− 11.8	0.9989

Table 5.3 Slopes, intercepts and correlation coefficients obtained using least squares regression analysis of linear portions of drug release profiles of tablets prepared from formulations 5B – 5L

Conclusions

Direct compression of powder mixes of hydrogenated vegetable oil with drug and inert excipients was found to produce tablets from which drug release was sustained for periods of several hours. Drug release rates were found to be affected by drug loading, type of inert excipient, concentration of microcrystalline cellulose, drug solubility and hydrogenated vegetable oil particle size. It was found that the rate – controlling mechanism in drug release from HVO – based tablets was diffusion, with drug release conforming to the Higuchi square – root of time kinetic model. It was concluded that drug release occurred through water – filled tortuous pores within a tablet matrix. Differences in drug release rate observed between different formulations were postulated to be due to differences in porosity and tortuosity between the tablets prepared from different formulations. Drug release into dissolution medium of acidic pH was found to be unchanged compared to drug release into water, but a small decrease in drug release rate was found when drug release studies were performed in medium of alkaline pH.

Tortuosity factors determined according to the Higuchi equation from drug release data from single planar faces of hydrogenated vegetable oil – based matrices were found to be in the range 32 – 55, compared to 12 for a polyvinyl chloride matrix. Drug release rates from hydrogenated vegetable oil – based matrices in surfactant solution were found to be not significantly different from release rates in water, and it was concluded that slow or incomplete wetting was not a factor affecting release rates. A permeametry technique based on the application of the Carman – Kozeny equation to air flow under pressure through matrices which had been leached of drug was used to determine matrix tortuosity factors, but tortuosity factors of less than 1 were obtained. Since tortuosity factors must by definition be greater than or equal to 1, this indicated that the results were meaningless. Mercury porosimetry of matrices which had been leached of drug showed that a wide pore size distribution existed within the matrices, and this was concluded to account for the failure of the Carman – Kozeny equation in this case.

An experiment based on the application of Graham's law of gaseous

interdiffusion was used to determine the effective diffusion coefficient of helium in air through matrices which had been leached of drug. Tortuosity factors calculated from this data were found to be greater than 1, but approximately one order of magnitude lower than tortuosity factors calculated from drug release data. However, when the tortuosity factors obtained from drug release data were square-rooted, in the same manner as those obtained from the diffusion data, the tortuosity factors became comparable. It was concluded that the tortuosity factor in the Higuchi equation should be square-rooted in order to give a realistic indication of the nature of the pore structure within a matrix. The diffusion technique was concluded to be a valid method of the determination of tortuosity factors, independently of drug release data.

Drug release from hemispherical, hydrogenated vegetable oil-based matrix tablets coated with a water-impermeable barrier and with a delivery orifice in the centre of the planar face was investigated, and it was found that zero-order drug release could be obtained. However, release rate of a highly water-soluble drug was found to be too slow for potential oral use. Coat thickness and delivery orifice dimensions were found to be factors which affected the reproducibility of drug release data, and a pan-coating system involving the spraying of aqueous suspensions of ethylcellulose was found to give a coat of reproducible thickness in which suitable delivery orifices could be made. The effect of reduction of hydrogenated vegetable oil content on drug release profile was investigated and increased drug release rates were obtained. Small increases in release rate were found on reduction of hydrogenated vegetable oil concentration from 29.4% to 19.6% and to 9.8%, but a larger increase was found on further reduction to 4.9%. A further large increase was found on reduction to 2.5%, and a smaller increase when hydrogenated vegetable oil was excluded completely. A combined diffusion/dissolution model was proposed to explain the drug release behaviour, and it was hypothesised that the rate-controlling mechanism changed progressively from diffusion to dissolution with decreasing hydrogenated vegetable oil concentration.

```
10 FACTOR = 1
20   ON ERROR GOTO 130
30 REM AUTO DISSOL
40 REM  SAB(0,X) = TIME,SAB(1 – 6,X) = REPS  1 – 6,SAB(7,X) = MEAN,SAB(8,X) = STD  DEV,SAB
(9,X) = SE,SAB(10,X) = TEMPSTORE  FOR  REP,X,  SAB(1 – 6,0) = TAMTAB
50 DIM SAB(10,25),Z(6)
60 PROCINIT
70 PROCCLEAR
80 PROCDESC
90 PROCMENU
100 FL% = 1
110 PROCKEY
120 ON FL% GOTO 110,90,60,150
130 PROCEND
140 PRINT ERR,ERL
150 PROCEND
160 STOP
170 DEF PROCMENU
180 CLS
190 PRINT"f0    –    CALIBRATE/ZERO'"
200 PRINT"f1    –    CONTINUE WITH RUN'"
210 PRINT"f2    –    PRINTOUT RESULTS'"
220 PRINT"f3    –    SAVE DATA ON DISC'"
230 PRINT"f4    –    START ANOTHER RUN'"
240 PRINT"f5    –    FINISHED'"
250 ENDPROC
260 DEF PROCKEY
270 IF INKEY(– 33) = – 1 PROCCALIB
280 IF INKEY(– 114) = – 1 PROCRUN
290 IF INKEY(– 115) = – 1 PROCPRINT
300 IF INKEY(– 116) = – 1 PROCSAVE
310 IF INKEY(– 21) = – 1 FL% = 3
320 IF INKEY(– 117) = – 1 PROCEND
330 ENDPROC
340 FL% = 1
350 DEF PROCRUN
360 CLS
370 INPUT"ENTER NUMBER OF REPS "K%
380 INPUT"ENTER RUN TIME h "TM
390 INPUT"ENTER SAMPLE FREQUENCY (NO. OF SAMPLES PER HOUR "JJ%
400 PRINT"ENTER TOTAL AMOUNT IN TABLET"
410 FOR I% = 1 TO K%
420 PRINT I%
430 INPUT SAB(I%,0)
440 NEXT
450 J% = (JJ%*TM) + 1
460 PRINT"TO START DATA COLLECTION RUN PRESS SPACE"
470 @% = &20306
480 IF GET < > 32 THEN 480
490 FOR N% = 1 TO J%
500 SAB(0,N%) = (TM/(J% – 1)*(N% – 1))
510 I% = 0
520 PROCWAIT
530 FOR I% = 1 TO K%
540 IF I% = 1 THEN 560
```

```
550 PROCWAIT
560 PRINT"SAMPLE "N%
570 PRINT"REP. "I%
580 PROCAV
590 SAB(I%,N%) = ((AV%*2.82E – 5) + 0.019)*A1
600 IF N% = 1 THEN Z(I%) = SAB(I%,N%)
610 SAB(I%,N%) = SAB(I%,N%) – Z(I%)
620 IF SAB(I%,N%) < .02 THEN SAB(I%,N%) = 0.0184
630 IF PR1% = 1 THEN 650
640 VDU2
650 PRINT SAB(I%,N%)
660 VDU3
670 NEXT
680 NEXT
690 @% = 10
700 IF PR1% = 1 THEN 720
710 VDU2
720 FOR N% = 1 TO J%
730 FOR I% = 1 TO K%
740 PRINT SAB(I%,N%)" ";
750 NEXT
760 PRINT
770 NEXT
780 VDU3
790 FOR I% = 1 TO K%
800 FOR N% = 1 TO J%
810 SAB(I%,N%) = SAB(I%,N%) – 0.0184
820 SAB(I%,N%) = SAB(I%,N%)/0.0212:REM CONC IN1000
830 SAB(I%,N%) = SAB(I%,N%)/SAB(I%,0)*100
840 NEXT
850 NEXT
860 PROCMSD
870 PROCT
880 FL% = 2
890 ENDPROC
900 DEF PROCPRINT
910 IF PR% = 1 THEN 930
920 VDU2
930 TI% = 2
940 FL% = 2
950 IF SAB(0,J%) > 12 THEN TI% = 1
960 PRINT"SAMPLE "SC$
970 PRINT DESC$"
980 PRINT"        TIME";
990 FOR I% = 1 TO 6
1000 PRINT"  REP ";I%;
1010 NEXT
1020 PRINT"   MEAN     SD      SE"
1030 PRINT"AM.TAB       ";
1040 @% = &20206
1050 FOR I% = 1 TO 9
1060 PRINT SAB(I%,0)" ";
1070 NEXT
1080 PRINT
1090 FOR N% = 1 TO J%
1100 PRINT"     ";
1110 FOR I% = 0 TO 9
1120 PRINT SAB(I%,N%)" ";
```

```
1130 NEXT
1140 TT% = TIME
1150 PRINT
1160 NEXT
1170 IF SK% = 1 THEN 1200
1180 PRINT"T50  =  "T50
1190 PRINT"T90  =  "T90
1200 @% = 10
1210 VDU3
1220 ENDPROC
1230 DEF PROCCLEAR
1240 FOR I% = 0 TO 10
1250 FOR N% = 0 TO 25
1260 SAB(I%,N%) = 0
1270 NEXT
1280 NEXT
1290 ENDPROC
1300 DEF PROCINIT
1310 CLS
1320 SK% = 0
1330 VDU15
1340 PRINT"WILL YOU HAVE A PRINTER AT THE END ? Y/N"
1350 Z% = GET
1360 IF Z% > 90 THEN Z% = Z% - 32
1370 IF Z% < > 78 AND Z% < > 89 THEN 1350
1380 IF Z% = 78 PR% = 1
1390 IF Z% = 89 PR% = 0
1400 PRINT"DO YOU HAVE A PRINTER DURING THE RUN ? Y/N"
1410 Z% = GET
1420 IF Z% > 90 THEN Z% = Z% - 32
1430 IF Z% < > 78 AND Z% < > 89 THEN 1410
1440 IF Z% = 78 PR1% = 1
1450 IF Z% = 89 PR1% = 0
1460 *FX15,1
1470 INPUT"SET REQUIRED ABSORBANCE .5 OR 1 OR 2  "A1
1480 FG% = 0
1490 *FX229,1
1500 *FX16,2
1510 ENDPROC
1520 DEF PROCMSD
1530 FOR N% = 0 TO J%
1540 FOR I% = 1 TO K%
1550 SAB(7,N%) = SAB(7,N%) + SAB(I%,N%)
1560 NEXT
1570 SAB(7,N%) = SAB(7,N%)/K%
1580 NEXT
1590 FOR N% = 1 TO J%
1600 FOR I% = 1 TO K%
1610 SAB(8,N%) = SAB(8,N%) + ((SAB(I%,N%) - SAB(7,N%))^2)
1620 NEXT
1630 SAB(8,N%) = SQR(SAB(8,N%)/(K% - 1))
1640 SAB(9,N%) = SAB(8,N%)/(SQR(K%))
1650 NEXT
1660 ENDPROC
1670 DEF PROCDESC
1680 INPUT"ENTER SAMPLE CODE "SC$
1690 INPUT"ENTER DESCRIPTION (MAX 80 CHRS) "DESC$
1700 ENDPROC
```

```
1710 DEF PROCT
1720 C50%=0:C90%=0
1730 T50=-1:T90=-1
1740 FOR N%=1 TO J%-1
1750 IF SAB(7,N%)>=50 THEN 1780
1760 C50%=N%+1
1770 GOTO 1800
1780 IF SAB(7,N%)>=90 THEN 1800
1790 C90%=N%+1
1800 NEXT
1810 IF C50%=0 THEN T50=0
1820 IF T50=0 THEN 1870
1830 P50D=SAB(7,C50%)-SAB(7,(C50%-1))
1840 P50=(SAB(7,C50%)-50)/P50D
1850 TI50=SAB(0,C50%)-SAB(0,(C50%-1))
1860 T50=SAB(0,C50%)-(P50*TI50)
1870 IF C90%=0 THEN T90=0
1880 IF T90=0 THEN 1930
1890 P90D=SAB(7,C90%)-SAB(7,(C90%-1))
1900 P90=(SAB(7,C90%)-90)/P90D
1910 TI90=SAB(0,C90%)-SAB(0,(C90%-1))
1920 T90=SAB(0,C90%)-(P90*TI90)
1930 ENDPROC
1940 DEF PROCSAVE
1950 FL%=2
1960 INPUT"ENTER FILENAME"FLNM$
1970 FLNML$=LEFT$(FLNM$,7)
1980 X%=OPENIN(FLNML$)
1990 IF X%=0 THEN 2120
2000 CLOSE# X%
2010 PRINT"FILENAME ALREADY IN USE"
2020 PRINT"RENAME FILE ? Y/N"
2030 Z%=GET
2040 IF Z%>90 THEN Z%=Z%-32
2050 IF Z%=89 THEN 1960
2060 IF Z%<>78 THEN 2030
2070 PRINT"THIS OPTION OVERWRITES THE FILE OK ? Y/N"
2080 Z%=GET
2090 IF Z%>90 THEN Z%=Z%-32
2100 IF Z%=78 THEN 1960
2110 IF Z%<>89 THEN 2080
2120 X%=OPENOUT (FLNML$)
2130 PRINT"CODE "SC$
2140 PRINT"DESCRIPTION "DESC$
2150 PRINT# X%,SC$,DESC$,K%,J%,T50,T90
2160 FOR I%=0 TO 10
2170 FOR N%=0 TO J%
2180 PRINT# X%,SAB(I%,N%)
2190 NEXT
2200 NEXT
2210 CLOSE# X%
2220 ENDPROC
2230 DEF PROCWAIT
2240 IF I%=0 AND N%=1 THEN 2260
2250 IF ?&FC00=254 THEN 2250
2260 IF INKEY(-113)=-1 THEN FG%=1
2270 IF FG%=1 THEN 2290
2280 IF ?&FC00=255 THEN 2260
```

```
2290 ENDPROC
2300 ENDPROC
2310 DEF PROCAV
2320 AV%=0
2330 TT%=TIME
2340 FOR M%=1 TO 100
2350 AV%=AV%+ADVAL(2)
2360 IF TIME<TT%+5 THEN 2360
2370 TT%=TIME
2380 NEXT
2390 AV%=AV%/100
2400 ENDPROC
2410 DEF PROCCALIB
2420 CLS
2430 PRINT"ABSORBANCE ON SPEC SHOULD BE "A1
2440 PRINT"DWELL TIME MUST BE AT LEAST 10 SECONDS"
2450 PRINT"PRESS SPACE TO CONTINUE "
2460 IF GET<>32 THEN 2460
2470 FOR L%=1 TO 6
2480 PROCWAIT
2490 IF FG%=1 THEN 2550
2500 PROCAV
2510 IF FG%=1 THEN 2550
2520 @%=&20306
2530 CAL=((AV%*2.82E-5)+.019)*A1
2540 PRINT CAL;
2550 NEXT
2560 PRINT
2570 IF FG%=1 THEN 2590
2580 GOTO 2470
2590 @%=10
2600 FL%=2
2610 FG%=0
2620 ENDPROC
2630 DEF PROCEND
2640 CLOSE #X%
2650 *FX229,0
2660 FL%=4
2670 ENDPROC
```

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