CHAPTER I

INTRODUCTION

Several types of multiparticulate system are used in order to achieve sustained release; these include various hydrophobic systems, release from which is controlled by either diffusion or erosion, and hydrophilic systems which swell in water to form a gel, from which drug is liberated primarily by diffusion. The systems that are currently employed are reviewed in many standard texts, including those of Lee and Robinson (1978) and Kydanieus (1980a, 1980b).

Multiparticulate systems are thought to have numerous advantages over single unit dose devices. These include: (i) the possibility of dispersion in the stomach, with a consequent reduction in local drug concentrations (as would be formed around a tablet), and thus less of a tendency to cause gastric irritation. Wilson and Washington (1989) have reviewed data on this subject which suggest that dispersion of the pellets will be dependent upon gastric contents; (ii) the possibility of retaining pellets in the stomach (by using either high or low density systems), and consequently further extending the duration of action of a sustained release dosage form; and (iii) the disruption of certain matrix sustained release tablets could occur (e.g., due to chewing, or due to abrasion with food in the stomach) leading to serious problems with dose dumping, however, it is considerably less likely that small pellets will be disrupted, and even if some are disrupted, it is very unlikely that all pellets will be affected, thus there is a reduced risk of dose dumping (Tapia, Buckton and Newton, 1993).

Spray drying technique has been widely used in the pharmaceutical field with various applications (Broadhead, Rouan and Rhodes, 1992). Recently it has been also successfully employed in the preparation of microparticulate drug delivery systems. The structure of the microparticles obtained is different depending on the drug is dispersed or dissolved in the polymeric solution to be spray dried. Microcapsules are obtained by spraying a suspension of drug in a solution of the polymeric coating, while polymeric matrices (microspheres), in which the drug is embedded, are obtained by spraying a solution of drug and polymer. In both cases spray drying appears to be an attractive technique as it is a fast one-step method , suitable for heat sensitive drugs (Bodmeier and Chen, 1988 ; Wan, Heng and Chia, 1992).

The use of solvents in pharmaceutical industry poses several disadvantages which have become apparent in the last 25 years due to the introduction of spray coating and spray drying systems containing large volumes of organic solvents. Pollution and solvent toxicity which have resulted in strict government regulations concerning solvent emissions together with the expense and explosion hazards of solvents have led to the renewed interest in water based polymeric systems. In the mid-seventies, scientists began to develop a new class of aqueous polymeric materials which could be more suitable for the needs of the pharmaceutical industry of the eighties and nineties (Onions, 1986). The result of this research was the introduction of aqueous colloidal dispersions for film coating and spray drying such as aqueous dispersion of ethylcellulose (Aquacoat$^{(R)}$, FMC Corp., Philadelphia, Pennsylvania; Surelease $^{(R)}$, Colorcon, Inc., West Point, Pennsylvania) and poly (metha) acrylate latices (Eudragit RL 30D, RS 30D, E 30D, L 30D and L 100-55, Rohm Pharma, Darmstadt, Germany).

An attempt has therefore been made to investigate the potential use of a spray drying technique for preparing microparticulate drug delivery systems using hydroxypropylmethylcellulose, ethylcellulose, and chitosan. The drug used was diclofenac sodium, a synthetic nonsteroidal anti-inflammatory, and analgesic compound. Frequent administration and controlled release rates are needed to maintain the drug concentration within its narrow therapeutic window. In order to improve patient compliance and controlled release of the drug, various dosage forms with controlled drug release characteristics have been generally developed. However the diclofenac sodium controlled release capsules for 24 hours prepared from spray drying technique have not been reported and developed.

The physicochemical characteristic of the spray dried powders were also studied. The suitability of spray drying technique in the manufacture of controlled release powders was investigated. The drug release patterns of the spray dried powders with various polymer to drug ratios and a commercial product (Voltaren SR) were comparatively studied.

Objectives of the study

1. To study and compare the physicochemical characteristics of diclofenac sodium microparticles.

2. To compare drug release from the capsules containing the prepared microparticles to a commercial product.

3. To investigate the pattern of drug release from the prepared microparticles.

4. To use the spray drying technique in the preparation of diclofenac sodium microparticles using aqueous polymeric systems of hydroxypropylmethylcellulose, ethylcellulose and chitosan in variable of the polymer to drug ratios.

Literature Review

1. Spray Drying Techniques

Spray drying techniques have been widely used in the pharmaceutical, chemical, and food industries. Its main use in the pharmaceutical industries include drying of heat sensitive materials (Broadhead et al., 1992), improving the drug solubility (Corrigan, Holohan and Sabra, 1984 ; Tsuda et al., 1988) or the flowability of particular excipients (Wan, Heng and Chia, 1990) and several other applications.

The following topics provide a brief overview of the spray drying operations, the properties of spray dried powders, the advantages and disadvantages of spray drying, and the applications of spray drying in pharmaceuticals.

1.1 The Spray Drying Operations

Spray drying is a one step process to convert a liquid into a powder by spraying a solution or a liquid dispersion through a nozzle in a drying chamber, where it comes in contact with hot air. The pharmaceutical industry utilized this technique to obtain powders, granules, agglomerates, and other more recent applications like microencapsulation and microsphere preparation (Broadhead et al., 1992).

The spray drying process encompasses the following four stages (Masters, 1979):

(a) Atomization of the feed into a spray

(b) Spray-air contact

(c) Drying of the spray

(d) Separation of the dried product from the drying gas

The process involves assessing of technological parameters as follows: concentration of the polymeric solution to be sprayed, inlet and outlet air temperature, spray rate of feed, air flow rate, heating, exhausing. Conte et al. (1994) studied the effect of the inlet and outlet temperatures, spray rate of feed and concentration of the starting polymeric solution on the characteristics of diazepam loaded poly-D,L-lactide microparticles. The microparticle was evaluated with respect to yield of production, shape, size, and in vitro drug release behaviour. Several technological parameters can affect the preparation and the characteristics of the microparticles obtained by spray drying method. The parameters related to the employed polymer were proven to be effective in affecting particle shape, size, and yield of production. In the tested conditions, the best results are obtained by employing the highest spray rate of feed and temperature.

Wan et al. (1990) prepared coated theophylline particles by a spray drying process. This process was carried out using an aqueous solution of hydroxypropylmethylcellulose (HPMC), 50 cps., as the coating polymer. The operation variables found to affect product properties significantly were the nozzle size and the inlet air temperature. The flow properties were improved with an increase in nozzle size or a decrease in the air to liquid diameter ratio. With an increase in inlet air temperature, there was a corresponding improvement in flow properties and a reduction in drug dissolution rate. The dissolution profiles were used as an index to determine the effectiveness of coating, with a slower dissolution rate indicating a better coat. The type of feed

used was important; a suspension feed resulted in a more sustained release and better flow properties than a solution feed. At extremely low drug to polymer ratios, the time of 50% drug released values (T50%) was high due to gelling of the polymer. The gelling hindered the dissolution of the embedded drug particles. Products of low drug to polymer ratios. (less than 1:1) have a faster release than those of higher drug to polymer ratios. The flow properties of the products improved with decreasing drug to polymer ratio. The authors reported further study on the effects of drying air flow rate, feed spray rate, and atomizing pressure (Wan, Heng and Chia, 1991). The particles that had been spray dried at a faster drying air flow rate were found to have better flowability and longer dissolution T50% values. High feed spray rates resulted in ineffective atomization, producing badly formed spray dried products. Atomizing pressure affected only the particle size of the product formed. The smaller particles had a higher dissolution T50% and were more cohesive.

Broadhead et al. (1994) evaluated the joint effects of various processing and formation variables on the properties of spray dried tilactase (beta-galactosidase). Statistically designed experiments were used to stuy the effects of product yield, residual enzymatic activity, moisture content, and particle size and appearance of spray dried tilactase. The residual enzymatic activity and product yield were significantly affected by the processing variables. The highest product yields were obtained when the drier outlet temperature was relatively high, resulting, in extensive protein denaturation. Spray drying at inlet and outlet temperature of 140 ^{0}C and 95 ^{0}C, respectively, resulted in greater than 70% yields of a fully active product with a moisture content of 2-5% and a mean particle size of 2-4 μm..

Examples of handy, small size spray dryers having a drying chamber of a diameter of about 1 m. are listed below (Kondo, 1979).

- Niro (minor unit) : centrifugal type provided with air turbine (Denmark)
- Bowen (laboratory use) : centrifugal type driven by motor (USA)
- Swenson (laboratory use) : two-fluid nozzle type (USA)
- Lurugi (model 10) : centrifugal type driven by motor (Germany)

1.2 The Properties of Spray Dried Powders

Spray dried powders are usually approximately spherical with a narrow size distribution and are usually hollow. The hollow nature imparts a low bulk density to the powders, but despite this, their spherical shape means that they are usually free flowing. By modifying the spray drying process, it is possible to alter and control the following properties of spray dried powders: appearent particle size and size distribution, bulk density, particle density, porosity, moisture content, flowability, stability, dispersability, friability and retention of activity, aroma and flavor (Newton, 1966).

Wan, Heng and Chia (1992) used spray drying method to produce theophylline anhydrous aggregates were coated with 0.4 - 3% carboxymethylcellulose sodium (NaCMC), and the effects of polymer concentration and drug to polymer ratio on properties of the product were studied. The slowest drug release was seen for the product prepared with 1% NaCMC. This product was spherical and well-formed with improved flowability. Greater deviation of drug loading from the theorectical was seen with increasing proportion of drug in the drug to polymer ratio. The product with a drug to polymer ratio of 2:1 conformed to a biphasic first-order equation, and the other ratio conformed to single-phase order and Higuchi square root of time equations. It was concluded that NaCMC had the potential

to be a useful coating agent, forming spherical particles with a spray drying method.

Luzzi, Zoglio and Maulding (1970) reported a method for in situ preparation of nylon encapsulated sodium pentobarbitol by emulsion polymerization. The studies reported here demonstrate that interphasal polymerization can be used to prepare nylon-membrane microcapsules. It has also been shown that a free-flowing powder can be obtained by spray drying slurries of microcapsules. When the free-flowing powder was tableted, it was observed that changes in release rate could be controlled by varying hardness. It was also observed that vacuum drying yielded capsule material of different appearance and release characteristics from spray dried microcapsular material.

In addition, an increase in the energy available for atomization (i.e.rotary atomizer speed, nozzle pressure, or air to liquid flow ratio in a pneumatic atomizer) will reduce particle size(Masters, 1979). If the feed rate is increased, particle size will again increase. The effect of temperature on particle size appears to be highly dependent on the material being dried (Crosby and Marshall , 1958). It was observed that for crystalline materials, such as sodium sulfate, temperature had very little effect whereas for film forming material the mean particle diameter was significantly reduced by increasing the inlet air temperature. In contrast , Newton (1966) reported a study where the particle size of some materials was shown to increase as the drying air temperature increased. High drying air temperature also seemed to be associated with lower bulk densities (Masters, 1979). As a general rule, smaller particles will usually be more dense, and so the bulk density of a powder with a small particle size will be higher. Bulk density will also increase with a narrower particle size distribution (Newton, 1966). The outlet temperature of a spray dryer can be correlated with activity loss in the drying of

heat sensitive materials. As would be expected, increased dryer outlet temperatures result in a lower final product moisture content (Broadhead et al., 1992).

1.3 The Advantages and Disadvantages of Spray Drying

The advantages of spray drying technique are presented as follows (Masters, 1979; Mcketta, 1983).

1.3.1 Spray drying is a single step operation from liquid feed to dry product. Frequently, this eliminates such steps as precipitating or crystallizing, centrifuging or filtering , grinding , classifying , and perhaps the additional pumping , storage , and dust collecting operations associated with them.

1.3.2 The process is continuous , although it can be operated with feed from a prior batch process.

1.3.3 Adaptable to full automatic control.

1.3.4 Dried product specifications can be met through dryer design and operational flexibility :

(a) Required product form (particle as spheres, fines, agglomerates)

(b) Required properties (dusty or dustless, degree of flowability, wettability, etc.)

1.3.5 Applicable to both heat sensitive and heat resistant materials.

1.3.6 Feedstocks in solution, slurry, thixotropic paste or melted form can be handled, if pumpale.

1.3.7 Corrosive and abrasive feed stocks can be readily handled.

1.3.8 Corrosion is reduced or prevented because the material does not contact the equipment surface until it is dry. This permits selection of lower cost materials of construction.

1.3.9 Maintenance costs are low because there are few moving parts.

1.3.10 Labor costs are low because only one operator is required, even on large installations. Because the evaporation usually is done under slight vacuum, it is easy to keep the equipment and area clean.

1.3.11 Operator requirements are the same for both small and large dryers, hence spray drying is basically a high volume system with low labor cost.

1.3.12 In co-current designs, surface temperatures are low (except at the hot gas inlet) because the extremely rapid evaporation cools the inlet gas nearly to its outlet temperature a few inches from the points of atomization. This feature further restrains corrosion of the equipment.

1.3.13 Spray drying is an airborne process, hence there is very low material holdup in the equipment.

1.3.14 Designs are available to handle :

(a) Evaporation of organic solvents without explosion and fire risks
(b) Powders that form potentially explosive mixtures in air
(c) Products that create ordor during drying
(d) Toxic products
(e) Products requiring aseptic and hygienic drying conditions

The main disadvantage of spray drying for many applications is its cost, in terms of both equipment and operation. Spray dryers have poor thermal efficiency unless extremely high drying temperature are used. This is impossible for the majority of products, including pharmaceuticals, because of the heat degradation which would result. For many pharmaceuticals, however, the cost of the end product may be sufficiently high that the use of spray drying is both feasible and desirable. Thus the expense of the process must be balanced against the advantages to be gained by using spray drying instead of an alternative processing strategy, and the value of the end product (Broadhead et al., 1992).

1.4 The Applications of Spray Drying in Pharmaceuticals

Spray drying is not a new technology as far as the pharmaceutical industry is concerned, having been used successfully since the early 1940' s. It is a usuful method for the processing of pharmaceuticals since it offers a means for obtaining powders with predetermined properties, such as particle size and shape (Broadhead et al., 1992).

Recently spray drying technique has received considerable interest as a microencapsulation process to obtain a controlled delivery system. The method may offer, in comparison with the usual coating techniques , the advantage of realizing the microencapsulation process in one step (Voellymy, Speiser and Soliva, 1977; Takenaka, Kawashima and Lin, 1980; Palmieri, Wehrle and Stamm, 1994). In addition, spray dried products are also known to have improved flow properties, thus increasing the ease of incorporation into a dosage form (Wan et al., 1990).

Biodegradable microcapsules have been prepared by spray drying. Polylactic acid (PLA) microcapsules were prepared from solutions or suspensions of a number of drugs dissolved or dispersed in methylene chloride (Bodmeier and Chang, 1988). Microcapsules of progesterone-PLA were formed with diameters of less than 5 μm. The microcapsules became more spherical as the progesterone content was increased. Crystallization occurred in the aqueous phase when the microcapsules were prepared by a solvent evaporation method, but spray drying avoided this problem. The major difficulty encountered in preparing the spray dried microcapsules was the formation of polymer fibers as a result of inadeguate forces to disperse the filaments into droplets; the successful atomization into droplets was dependent on both the type of polymer used and, to a lesser extent, the viscosity of the spray solution.

Takenaka et al. (1980) prepared enteric coated microcapsules of sulphamethoxazole by spray drying an aqueous solution of drug and cellulose acetate phthalate (5%) with or without various additives, such as montmorillonite clay and colloidal silica. Particles with diameters ranging from 3.6 to 22.0 μm. were obtained. Formulations containing additives yielded smaller particles than those without additives. The addition of additives also

improved the surface texture of the spray dried products, as compared to particles prepared from non-additive formulations , which tended to have flaky surfaces. Non-additive formulations also exhibited poor flow properties and thus were not easily tableted, whereas formulations which included additives were tableted easily. All sulphamethoxazole formulations containing cellulose acetate phthalate (CAP) exhibited some conversion of the drug from crystalline form I to form II and an amorphous form during spray drying (Takenaka, Kawashima and Lin, 1981). Form II was also obtained by freeze drying or vacuum drying of sulphamethoxazole. When microcapsules were prepared by a coaccervation technique, the drug remained in form I. CAP was presumed to interact with sulphamethoxazole, since the degree of amorphism increased with an increase in the concentration of CAP in the formulation.

Further studies examined the effect of spray drying sulphamethoxazole with xanthan gum or guar gum, with and without colloidal silica or CAP (Kawashima, Lin and Takenaka, 1983). It was found that the film forming capacity of xanthan gum alone was superior to that of guar gum, but inclusion of colloidal silica or CAP made the resultant product smoother still. X-ray diffraction data showed that the presence of CAP actually caused a polymorphic change resulting in mixture of forms I, II and III (form III had been indistinguishable in the previous study which used IR analysis). When the formulation contained colloidal silica, however, the sulphamethoxazole was always present in form I, irrespective of the gum type. When reither CAP or colloidal silica was included in the formulation, the product was usually a mixture of all three forms.

An alternative technique for the preparation of microcapsules in a spray dryer was that of spray polycondensation (Voellymy et al., 1977). This was a technique whereby polyner formation formed reactive monomers,

encapsulation and product separation from the vehicle were all accomplished into one stage process. The feed consisted of a dispersion of the core material and monomers, or precondensates of relatively low molecular weight, in addition to other film forming agents and the catalyst. This technique was used by Voellymy et al. to produce microcapsules which developed slow release properties after curing.

Lin and Kao (1991) prepared diclofenac sodium enteric-coated microcapsules by a spray drying technique with Eudragit L 30D as enteric-coating material. The spray dried powder, mixed with Neocel or Flo-starch, or the mixture of Neocel and Flo-starch (weight ratio, 1:1) was directly compressed into a tablet. The spray dried powder, the mixed powder before tableting, and the tablets all exhibited enteric-coated rlease properties. The weight ratio of Neocel to Flo- starch played an important role in controlling the release of diclofenac sodium from enteric tablets. The 1:1 weight ratio of Neocel to Flo-starch was more suitable for designing the microdispersed diclofenac sodium enteric-coated tablets.

Spray drying has frequently been used for the production of slow release granulations. Kornblum (1969) reported that significantly less binder was required to achieve a given sustaining effect when compared with conventional granulation methods.

Kawashima and Takenaka (1974) prepared slow release magnesium carbonate granulation by spray drying. They observed that the degree of drug release retardation afforded by the binder seemed to be associated with the degree to which the binder encapsulated the magnesium carbonate.

Takeuchi, Handa and Kawashima (1989) prepared sustained release and enteric theophylline tablets by directly compressing spray dried microspheres with Eudragit L 30D, L100-55 and E 30D. The spray drying process was free from using organic solvents. Drug dissolution of the enteric tablet in an acidic solution (pH 1.2) was highly dependent on the polymer content of the microsphere. Completely enteric function was observed with drug to polymer ratio of 1:3 using Eudragit L 30D or L100-55. Tablets with Eudragit E 30D formulated at the 2 - 40 % level showed good sustained drug release which was thoroughly independent of the pH of dissolution media. The dissolution pattern was similar to that of Theo-dur and gave a straight line in Higuchi plot. In each tablet, the controlled drug release was attributed to continuous and well dispersed polymer matrix formed by spray drying and subsequent compressing process.

Asker and Becker (1966) used spray drying technology to produce prolonged release sulphaethylthiadiazole (SETD) granulations. A follow-up series of papers investigated the production of slow release SETD-wax granulations by spray congealing (Cusimano and Becker, 1968; John and Becker, 1968; Hamid and Becker, 1970). In a series of papers by Cusimano and Becker; John and Becker, certain details of spray congealing process for SETD were investigated, such as the composition of the coating wax, the nozzle size of the atomizer, and the presence of surfactant in the wax matrix. Both decreasing nozzle size and increasing surfactant concentration tended to produce products with a faster rate of drug release in acid pepsin or alkaline pancreatin media. However, dissolution behavior was most affected by the type of wax coating material used. White beeswax, glyceryl tristearate, carnauba wax, hydrogenated castor oil, cetyl alcohol and glyceryl monostearate were examined. In subsequent paper by Hamid and Becker, the in vitro dissolution patterns of some spray congealed SETD wax products in tablet form were

studied. Tabletting caused a decrease in the rate of drug release. This technique had previously been used for the production of 35 μm. SETD-Hydrogenated castor oil granules, which were used in the formulation of a slow release suspension. The researcher prepared particle of SETD by mixing them with molten hydrogenated castor oil at 110 ^{0}C; the suspension was then spray congealed into an air-cooled chamber using a centrifugal wheel atomizer. The spherical microcapsules obtained were observed to consist of finely divided drug particles uniformly dispersed throughout a matrix of hydrogenated castor oil and to have a uniform film of the oil over the surface of each microcapsule.

Conte et al. (1994) prepared poly-D,L-lactide microspheres containing tolmetin by emulsification solvent evaporation or by spray drying. The microspheres were evaluated in vitro and in rats. Spherical shaped particles with a size of 3.5 - 7.5 μm. and drug content of 4.5 - 9.5% were obtained. The dissolution of microspheres was dependent on the method of preparation, with drug release being slower from spray dried microspheres. Biological evaluation showed the suitability of a microparticulate system for chronic administration of the drug. The anti-inflammatory effect of tolmetin-loaded microspheres in rat models of acute and chronic inflammation was comparable to that of free drug but significantly sustained. It was concluded that poly-D,L-lactide microspheres could be used for the sustained release of tolmetin.

2. Microparticulate Systems

2.1 Matrix Microspheres

The literature about the matrix system was well reviewed by Baker (1987). A matrix system, as the name implies, consists of drug distributed homogeneously throughout a polymer matrix as represented in Figure 1.

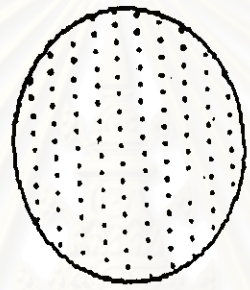


Figure 1 Matrix Microsphere.

When the term "matrix device" is used without qualification, it typically means that the polymer contained does not chemically disintegrate. If the polymer does erode, the device-although actually a type of matrix device is referred to as an erodible, bioerodible, or biodegradable system.

Matrix systems have the advantage of generally being easier and less expensive to produce than reservoir systems. In addition, because they do not have a polymer covering that can suddenly break, there is no danger of an abrupt release of a large amount of drug.

There are two principal categories of matrix devices. If the active agent is dissolved in the polymer medium, the device is called a matrix

solution. A device of this kind is often used when the active agent is a liquid, some polymers can easily dissolve up to 20% or more of these liquids. If the active agent has a more limited solubility in the polymer medium, then only a portion of agent is dissolved in the polymer medium and the remainder is dispersed as small particles throughout the polymer. A device of this type is called a matrix dispersion.

2.1.1 Matrix solution

One method of preparing a matrix device containing dissolved active material is to equilibrate it with the material : for example, the device may be soaked in neat liquid or a concentrated solution. If the active constituent is dissolved homogeneously in the polymer matrix and it is assumed, for simplicity, that one planar surface was available for release, the amount of drug delivered will be obtained by solving Fick's second law of diffusion.

2.1.2 Matrix dispersion

The second type of matrix system consists of a dispersion of solid active agent in a rate-limiting polymer matrix. The characteristics of matrix dispersion system are listed in Table 1 (Grass IV and Robinson, 1990). Matrix dispersion systems are of three types, which will be described latter, depending on the volume fraction of the agent in matrix.

Table 1 Characteristics of matrix diffusion systems.

Description	-Homogeneous dispersion of solid drug in a polymer mix
Advantages	-Easier to produce than reservoir devices
	-Can deliver high-molecular-weight compounds
Disadvantages	-Cannot obtain zero-order release
	-Removal of remaining matrix is necessary for implanted system

At low loading levels of agent (0-5 volume percentage), the release of the compound involves dissolution of the agent in the polymer medium followed by diffusion to the surface of the device. We will call these devices simple matrix dispersions.

At slightly higher loading levels (5-10 volume percentage), the release mechanism is more complex, since the cavities remaining from the loss of material near the surface are filled with fluid imbibed from the external environment , and these cavities provide preferred pathways for the escape of material remaining within the device. At those loading levels, the cavities are not connected to form continuous pathways to the surface, but they may increase the overall apparent permeability of the agent in the device. We will call these devices complex matrix dispersions.

When the loading of dispersed agent exceeds 20 volume percentage , the cavities left by the loss of material are sufficiently numerous to from a continuous channel to the surface of the matrix. In this case, the majority of all of the active agent is released by diffusion through these channels. We will call these type of device monolithic matrix systems or simply

matrix systems. The solubility and diffusivity of the dispersed agent in the fluid filling the channels determines its rate of release.

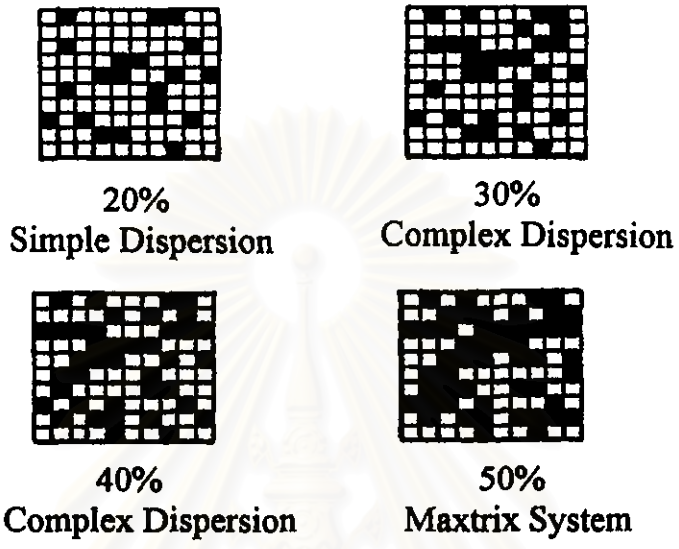


Figure 2 A two-dimentional representation of a random distribution of agent particles (filled squares) in a polymer matrix.
Agent loading of 20, 30, 40, and 50% are shown (Baker,1987).

Release from these matrix dispersion systems can be described by percolation theory. The concept behind percolation theory can be conveniently illustrated in a two-dimentional grid in which some of the sites are randomly occupied, as show in Figure 2 (Baker,1987). The empty sites represent the polymer matrix while the filled sites are the active agent particles. At low loading, as in the simple dispersion case, the active agents are well separated. At higher loading, as in the complex dispersion case, some small islands of interconnected particles grow, while at even higher loading these islands grow in size and are connected to form extended pathways. At loadings above a certain critical value, continuous channels permeate the grid, and almost all the agent particles are connected to the channels. This is the matrix system. For the

two-dimensional grid illustrated in Figure 2, the critical value at which almost all particles are in contact with one another is an agent volume fraction of 0.45, but in three-dimensional matrix the critical loading value above which a continuous network formed in only 0.15 (Zaller, 1979, cited by Baker, 1987).

The three types of matrix dispersion are:

(i) Simple matrix dispersion

When the active agent concentration is in the range of 0-5 volume percent, the release rate from these systems can be described by a simple Higuchi model (Higuchi, 1961). This model assumes that solid agent in the surface layer of the device dissolves in the polymer matrix and diffuses from the device first. When the surface layer becomes exhausted of agent, the next layer begins to be depleted. The interface between the region containing dispersed agent and the region containing only dissolved agent thus move into the interior as a front. The release kinetics for such a system have been solved, and the appropriate equation is as follows:

$$\frac{dMt}{dt} = \frac{A}{2}\left(\frac{2DCs(m)Co}{t}\right)^{1/2} \qquad (1)$$

for $Co >> Cs(m)$

where Mt is the mass of drug released at time t

A is the total area of the slab (both sides)

D is agent diffusion coefficient

t is time

Cs(m) is the solubility of the agent in the polymer matrix

Co is the total concentration of agent (dissolved plus dispersed) initially present.

The release is proportional to the square root of time.

(ii) Complex matrix dispersion

The Higuchi model is generally a good predictor of agent released for matrix polymer dispersions containing low level (<5%) of active material. However, at higher loading, deviations from the expected release profile occur. The rate of release is still proportional to the square root of time but has a higher value than the model predicts. As described earlier, this is due to the presence of fluid-filling cavities created by dissolution of particles near the surface, which increases the system's permeability to most substances. At high loading doses, the drug can form a continuous capillary network throughout the polymer and release is governed by drug leaching through this region. Thus Equation 1 may be modified for the complex matrix dispersion to

$$\frac{dMt}{dt} = \frac{A}{2}\left(\frac{2DCs(m)}{t} \cdot \frac{1+2Co/\rho}{1-Co/\rho}\right)^{1/2} \qquad (2)$$

where ρ is the density of permeant.

(iii) Monolithic matrix systems

At loading of active agent above approximately 15-20 volume percentage, all the agent particles dispersed in the polymer matrix are in contact with one another. The active agent is released by diffusion through the water-filled pores that are formed as water is imbibed from the surface of the device to replace the active agent that leaches out.

The mathematical descriptical of release from this type of system exactly matches Equation 1 previously derived for simple matrix dispersions, the only difference being substitution of the appropriate expression for the permeability term DK in this equation. In this case, release is through the pores formed by dissolution of the agent, and thus the appropriate substitution for the partition coefficient is

$$K = \varepsilon \qquad (3)$$

to reflect the fact that, although the filled inside the membrane pores is the same as the surrounding solution, only a volume fraction ε of the membrane is filled with this fluid.

The appropriate substitution for the diffusion coefficient is

$$D = \frac{Dw}{\tau} \qquad (4)$$

where Dw is the diffusion coefficient of the agent in the fluid filling the matrix pores and τ (tortuousity) is a term reflecting the entire distance the agent must on average diffuse to escape from the device. Thus, the Higuchi model expression for release from a monolithic slab is

$$\frac{dMt}{dt} = \frac{A}{2}\left(\frac{2Dw\,\varepsilon\,CsCo}{\tau t}\right)^{1/2} \qquad (5)$$

2.2 Matrix Microcapsules

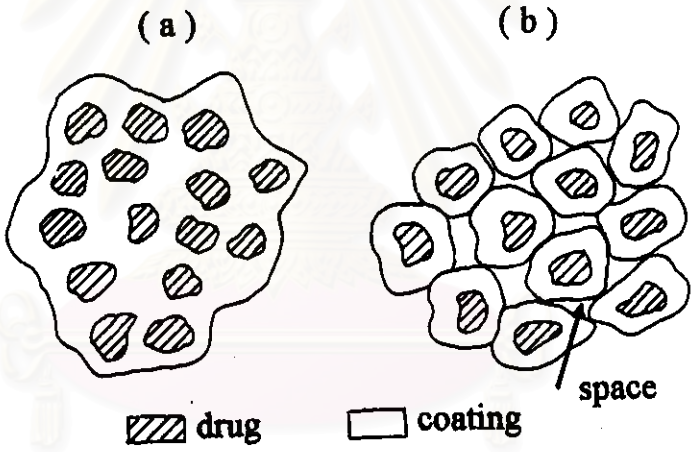


Figure 3 Homogeneous (a) and granular (b) matrices.

A microcapsule can be either an individually coated solid particle or liquid droplet, or a matrix of wall material containing many small, fine core particles. The former type of microcapsules can be prepared by numerous methods including coacervation, coating and interfacial reaction techniques. Matrix microcapsules are usually prepared by spray drying or spray congealing.

Spray drying can be used simply to separate previously prepared microcapsules from the vehicle, or for the preparation of microcapsules in a single operation (Voellymy et al., 1977). In the spray congealing process, no solvent is used. The feed, which consists of the coating and core materials, is fed to the atomizer in the molten state. Microcapsules form when the droplets meet the cool air in the drying chamber and congeal (Deasy, 1984).

Release of drug from matrix microcapsules is a mass transport phenomenon involving diffusion of drug molecules from a region of high concentration in the dosage form to a region of low concentration in the surrounding environment. Drug molecules are transported through one or more polymeric membranes comprising the coating material, understanding of how core substances are released from microcapsules. The coating normally acts as a barrier, the resistance of which is influenced by factors such as the identity of the film former, its degree of crystallinity, the inclusion of plasticizers and fillers, its thickness, the occurrence of pores, and the presence of a stagnant diffusion layer in contact with the outer coating surface. Drug transport through such coating material is a very complex subject and will be considered primarily in terms of passive diffusion, where factors that influence transport, such as electrochemical and thermal gradients, and active transport, are considered to be negligible. The coating material may be considered as consisting of one or more homogeneous barriers that offer resistance to the transport of a drug substance in the direction of the flux vector.

Matrix microcapsules are multinuclear or are composed of aggregates of smaller microcapsules so that their release kinetics do not follow that expected of a reservoir type device but rather that of a monolithic device. Because of the diversity of inclusion and lack of homogeneity of many polymeric coatings, the following review of mathematical approaches that have

been used to quantify drug release in vitro from microcapsules is of interest primarily for indicating those factors that influence drug release. By identifying these factors it is possible to vary them to achieve greater control over core release from these products.

Luzzi et al. (1970) reported the formation of clusters in nylon coated phenobarbitone sodium microcapsules recovered by a spray drying process. The approximately spherical units formed are usually composed of solid drug particles dispersed in the coating material, and because of the relatively small number of irregularly joined nuclei they contain, their uniformity of drug dispersion is usually lower than that produced by microparticle production procedures. Obviously a portion of the drug (Cm) may dissolve in the membrane material, but if this is assumed to be very small compared to the total drug loading (Ctot), then the expected drug release has been mathematically derived from Higuchi (1961) by Baker and Lonsdale (1974) for a homogeneous spherical matrix as follows:

$$\frac{d(Mt/M\infty)}{dt} = \frac{3CmD}{r^2_0 Co}\left(\frac{(1 - Mt/M)^{1/3}}{1-(1-Mt/M\infty)^{1/3}}\right) \qquad (6)$$

where r_o is the outside radius.

The assumption that Ctot >>Cm is usually valid for most polymeric drug dispersions containing greater than 1% drug. This model (see Figure 3a) assumes that the solid drug dissolves from the surface layer first, and when this layer has become exhausted the next layer begins to dissolve. Obviously, from Equation 6 it is not possible to express the release rate as a single function of time. Accordingly, the release rate from a slab geometry is often used to

approximate drug release from such irregularly shaped matrix microcapsules. The relevant equation is:

$$\frac{dM}{dt} = \frac{A}{2}\left(\frac{DCm}{t}(2Ctot - Cs)\right)^{1/2} \qquad (7)$$

Which upon integration gives

$$Q = \frac{M}{A} = \left(DCm\,(2\,Ctot - Cs)\,t \right)^{1/2} \qquad (8)$$

where Q is the mass of drug released per unit area of surface at time t. The value for Ctot should preferably be at least 10 times that of Cs. Assuming that the diffusion coefficient and other parameters of Equation 8 remain constant during release, this equation may be expressed as

$$Q = k_1 t^{1/2} \qquad (9)$$

where k is a constant.

Higuchi (1963) subsequently presented the following equation for the steady state drug release from the planar surface of a granular type matrix as might be observed with a cluster of microcapsules shown in Figure 3b, where geometry is usually very irregular:

$$Q = \left(\frac{D\varepsilon}{\tau} (2Ctot - Cs)\, Cst \right)^{1/2} \qquad (10)$$

where ε is the porosity of the leached portion of the matrix

τ is the tortuousity of the matrix or degree of nonlinearity of the formed capillaries.

It was assumed that Ctot >> Cs, that the noninteractant, uniformity of dispersed drug particles were much smaller than those comprising the matrix, and that perfect sink conditions prevailed. As the tortuousity factor is often assumed to be about 3, Equation 10 is valid provided that Ctot is greater than Cs by a factor of 3 or 4. In reality, matrix microcapsules contain drug loadings not greatly in excess of the drug solubility, and the application of Equations 8 and 10 to such products is questionable. More recently, Fessi et al. (1982) have shown that a similar square root equation of the form

$$Q = Ctot\, (Dt)^{1/2} \qquad (11)$$

also applied to matrix formulations where Ctot < ε Cs.

3. The Analysis of Dissolution Data of Controlled Release System

Mathematical models used to describe the kinetics of drug release from microcapsules or microparticles are usually based on drug release from macromatrix devices. Because of the size difference, drug release from the microdosage forms tends to attain a steady state more quickly that is of shorter duration (Deasy, 1984).

3.1 The Release Mechanism of Controlled Release System

In order to analyze the mechanism of the drug released from the matrices, the dissolution data may be analyzed using the semi-empirical equation of Peppas (1985) given below

$$\frac{Mt}{M\alpha} = kt^n \qquad (12)$$

where $Mt / M\alpha$ is the fraction of drug released up to time t

t is the release time

k is a constant incorporating structural and geometric characteristics of the controlled device

n is the diffusional release exponent indicative of the mechanism of release.

The determination of the exponent n is valid for the first 60% of the total released drug ($Mt/M\alpha \leq 0.6$), which also applied only to the early times of release.

Clearly, a desirable mechanism for many applications is that which leads to n equals 1, which characterizes zero-order release behavior. Table 2 summarizes the general dependence of n on the diffusional mechanism (Peppas, 1985).

Table 2 Interpretation of diffusional release mechanisms from drug release data from thin polymer film .

Release Exponent (n)	Drug Transport Mechanism	Rates as a Function of Time
0.5	Fickian Diffusion	$t^{0.5}$
$0.5 < n < 1.0$	Anomalous (non-Fickian) Transport	t^{n-1}
1.0	Case - II Transport	Zero-order (Time-Independent) Release
$n > 1.0$	Super Case - II Transport	t^{n-1}

The empirical Equation 12 could be modified for application to non-planar geometries. The relationship between the diffusional exponent n and the corresponding release mechanism is clearly dependent upon the geometry employed as shown in Table 3 (Ritger and Peppas, 1987 a).

In non-swellable matrices, the values of n are 0.45 and 1.00 for Fickian and Case-II transport, respectively. Case-II transport is a special case readily identified and characterized by the constant velocity of the moving solvent front and the resulting linear weight gain with time. However, its characteristics are not as well understood, nor are they as fundamental in origin as those of Fickian diffusion. When the value of n is > 0.45 and <1.00, the release was said to be non-Fickian (Ritger and Peppas, 1987 a). A value of n=1,

however, means that the drug release is independent of time, regardless of the geometry. Thus, zero-order release can exist for any geometry.

Table 3 Diffusional exponent and mechanism of diffusional release from various non-swellable controlled release systems.

Diffusional Exponent (n)			Drug Release Mechanism
Thin film	Cylindrical Sample	Spherical Sample	
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.00	0.45<n<1.00	0.43<n<1.00	Anomalous (Non-Fickian) Transport
1.0	1.0	1.0	Zero - order Release

In swellable controlled release systems, Case-I (Fickian diffusion) and Case-II solute release behaviors are unique in that each can be described in terms of a single parameter. Case-I transport is described by a diffusion coefficient, while Case-II transport was described by a characteristic relaxation constant. Non-Fickian behavior, by comparison, required two or more parameters to describe the coupling of diffusion and relaxation phenomena.

In swellable matrices, when the system do not swell more than 25% of its original volume, the values of n are 0.45 and 0.89 for Fickian and Case-II transport, respectively. When the value of n is > 0.45 and <0.89, the release is said to be non-Fickian .When the value of n was greater than that of the Case-II transport, the release was said to be Super Case-II transport. Table 4 summarized the range of value of diffusional exponent n, and the related transport mechanism for each geometry (Ritger and Peppas, 1987b). A value of n=1, mean that the drug release was independent of time, regardless of

geometry. Thus, zero-order release can exist for any geometry; only for slabs did this release coincide with Case-II transport.

Table 4 Diffusional exponent and mechanism of drug from various swellable controlled release systems.

Diffusional Exponent (n)			Drug Release Mechanism
Thin Film	Cylindrical Sample	Spherical Sample	
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.00	0.45<n<0.89	0.43<n<0.85	Anomalous (Non-Fickian) Transport
1.0	0.89	0.85	Case-II Transport

Hogan (1989) examined the dissolution curves of the drugs promethazine hydrochloride, aminophylline and propranolol hydrochloride with differing HPMC quantity and concluded that as the polymer fraction increased, the dissolution of the drug decreased. The kinetics of drug release can be investigated by using Equation 6. The promethazine and diazepam matrices appear to have slightly higher values of n at low HPMC content. The values of n are similar (0.65-0.71) for highly soluble drugs promethazine hydrochloride, aminophylline and propranolol hydrochloride and additional theophylline (0.64). The values of n for these drugs are close to the values predicted for diffusional release. The n values for the two poorly soluble drugs are 0.82 and 0.9 for diazepam and indomethacin, respectively. Thus the values of n obtained for indomethacin and diazepam merely emphasize that release for these drugs is not Fickian-controlled and indicates large contribution of tablet erosion to drug release. The anomalous behavior for tetracycline matrices with a value of n=0.45 emphasized the complexity of release of this drug. Peppas (1985) did not interpret n values of $n < 0.5$ but stated that such occurrences

were an indication of statistical analysis problems or were due to diffusion through a polymeric network where diffusion occurred partially through a swollen matrix and partly through water-filled pores. It is possible that tetracycline hydrochloride undergoes a complexation reaction with HPMC in the gel state in the hydrating matrix, thus retarding its release.

3.2 The Release Pattern of Controlled Release System

The pattern of delivery achieved by a controlled release system can vary over a wide range, but most release profiles are categorized into three types.

3.2.1 Zero-order model

An ideal controlled release device is one which can deliver the drug at a constant rate until the device is exhausted of the active agent. Mathematically, the release rate from this device is given as

$$\frac{dMt}{dt} = k \qquad (13)$$

where k is a constant

t is time

Mt is the mass of active agent released.

This pattern of release is called zero - order release model.

3.2.2 Square root of time model (Higuchi model)

The second common release pattern is frequently referred to as square root of time or $t^{1/2}$ release, providing compound release that is linear with the reciprocal of the square root of time. The release rate is then given as:

$$\frac{dMt}{dt} = \frac{k}{t^{1/2}} \qquad (14)$$

In contrast to first-order release, the release rate here remains finite as the device approaches exhaustion.

The release pattern of this type can be described by Higuchi equation (Higuchi, 1963)

$$Q = \left(\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right)^{1/2} \qquad (15)$$

where Q is weight in grams of drug released per unit surface area

D is diffusion coefficient of drug in the release medium

ε is porosity of the matrix

τ is tortuousity of matrix

Cs is solubility of drug in the release medium

A is concentration of drug in the tablet, expressed as g./ml. .

The assumptions made in deriving Equation 15 are as follows:

1. A pseudo-steady state is maintained during release.
2. A>> Cs, i.e., excess solute is present.
3. The system is in perfectly sink condition,in which C is approximately zero at all time.
4. Drug particles are much smaller than those in the matrix.
5. The diffusion coefficient remains constant.
6. No interaction between the drug and the matrix occurs.

For purposes of data treatment, Equation 15 is usually reduced to

$$Q = k_H t^{1/2} \qquad (16)$$

where k_H is Higuchi constant.

Therefore, the plot of amount of drug released from matrix versus the square root of time should be increased linearly if drug release from the matrix is diffusion controlled. Although the above equation was based on release from a single face, it may be used to describe diffusion controlled release from all surface matrix.

In order to further verify that the release follows Higuchi model, Higuchi equation is converted into logarithmic form as:

$$\log Q = \log k_H + \frac{1}{2} \log t \qquad (17)$$

The plot of log Q versus log t must not only yield a straight line, but must have a slope of 0.5.

3.2.3 First - order model

The first-order pattern is the third common type of the release model. The release rate in this case is proportional to the mass of active agent contained within the device. The rate is then given as

$$\frac{dMt}{dt} = k\,(Mo - Mt) \qquad (18)$$

where Mo is the mass of agent in the device at t=0.

On rearrangement, this gave

$$\frac{dMt}{dt} = kMo\,\exp^{-kt} \qquad (19)$$

In first-order model, therefore, the rate declined exponentially with time, approaching a release rate of zero as the device approached exhaustion.

On the assumption that the exposed surface area of matrix decreased exponentially with time, Wagner (1969) suggested that drug release from most controlled release matrices could be described by an apparent first-order kinetic, thus:

$$At = Aoe^{-k_1 t} \qquad (20)$$

where k_1 is first-order release constant

Ao is initial amount of drug

At is amount of drug remaining in the matrix at time t.

Simplifying and taking the logarithm of Equation 20 yields:

$$\log At = \log Ao - \frac{k_1 t}{2.303} \qquad (21)$$

First-order pattern can be predicted by plotting the logarithm of the percentage of drug remaining against time. If the release pattern follows first-order model, linear relationship is obtained. Sa, Bandayyopadhyay and Gupta (1990) reported that the initial curvature of the plot may be obtained because of the presence of surface drugs and they suggested it be ignored.

Since both the square root of time release and first-order release plots are linear, as indicated by correlation coefficient, it is necessary to distinguish between the models. The treatment has been based upon use the differential forms of the first-order and square root of time equations (Schwartz, Simonelli and Higuchi, 1968).

For Higuchi model, the rate will be inversely proportional to the total amount of drug release in accordance with the equation (Sa, Bandayyopadhyay and Gupta, 1990)

$$\frac{dQ'}{dt} = \frac{k^2_H S^2}{2Q'} \qquad (22)$$

where Q′ is Q*S (S is the surface area of matrix).

The rate predicted by first-order model is given by :

$$\frac{dQ'}{dt} = kAo - kQ' \qquad (23)$$

where A is Ao-Q′.

This indicates that rate will be proportional to Q′. The rates of release are determined by measuring the slopes at different points on the percentage of drug release versus times curves. If the plots of rates of release versus Q′ are linear, they indicate that first-order model is operative.

The release patterns for each class of device are illustrated in Figure 4 (Baker, 1987). The release of patterns of zero-order, square root time and first-order are depicted (Equations 13, 14 and 18) respectively.

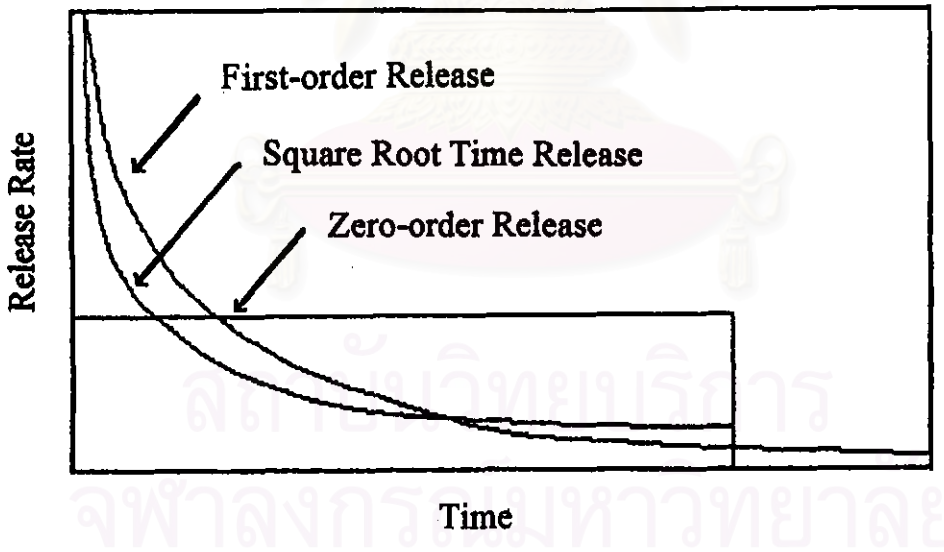
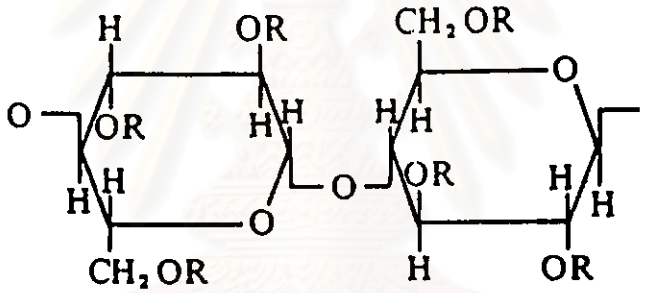


Figure 4 Zero-order, first-order and square root time release patterns from devices containing the same initial active agent content.

4. Hydroxypropylmethylcellulose

An application of hydroxypropylmethylcellulose (HPMC) for film coating have become popular, taking the place of the classic sugar coating of tablets, since they give a superior appearance, act as protective coatings for fragile tablets and can mask color and unpleasant taste. The main reason that HPMC is preferred as a film coating in the initial stage is that it dissolves in both organic solvents and water over the entire biological pH range. This means that film coating can be done using an organic solvent system and the film formed is expected to dissolve in the digestive juices, leading to complete release of the active ingredients.



R = H - , CH_3- or $CH_3CH(OH)CH_2$ -

Figure 5 Chemical structure of HPMC.

The chemical structure of HPMC is shown in Figure 5. HPMC is classified according to its substituent groups, composition and viscosity. HPMC of lower viscosity (less that 15 cps.) is commonly used in film coating and is produced by depolymerization of higher viscosity HPMC. Commercially available brands of HPMC for film coating widely used throughout the world are Pharmacoat 615, 606 and 603 (Shin-Etsu Chemical Co., Ltd., Japan) and Methocel E 15, E 5 and E 3 (Dow Chemical Co., Ltd., USA). Figure 6 illustrate relationships between the concentrations of various viscosity types of HMPC

and their solution viscosities. The viscosity required for aqueous film coating is commonly less than 100 cps., the maximum concentrations of 3, 6 and 15 cps. types correspond to approximately 14, 7.5 and 4.5 % respectively. Thus, the maximum concentrations available depend greatly upon the viscosity type of HPMC used, though there are other factors that should be taken into consideration in practical applications.

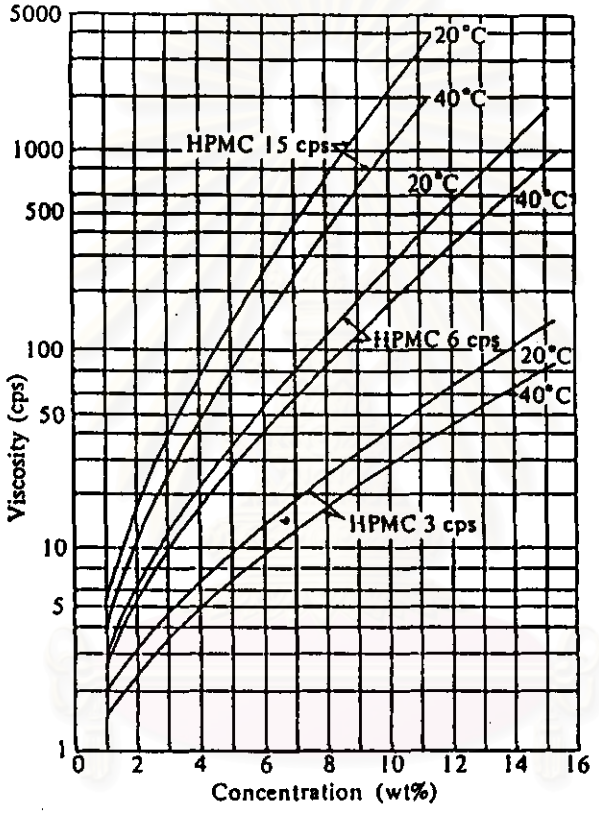


Figure 6 Effects of concentration and viscosity type on viscosity of aqueous solutions of HPMC.

HPMC is cellulose ethers which may be used as the basis for hydrophilic matrices for controlled release oral delivery. HPMC is an odorless, tasteless white or creamy-white fibrous or granular powder. It is soluble in cold water, forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform but soluble in mixture of methylalcohol and methylene chloride. HPMC is very stable in dry conditions. Solutions are stable at pH 3.0-11.0. It is unstable in

extreme pH conditions and incompatible with oxidizing materials. Human and animal feeding studies have shown to be safe. HPMC can be used as film former, thickening agent, protective colloid, emulsifier, suspending agent and stabilizer. High viscosity grades are used to retard the release of water soluble drugs.

Lapidus and Lordi (1966, 1968) investigated drug release from compressed hydrophilic matrix of HPMC 15,000 cps.Water-soluble drugs (chlorpheniramine maleate, sodium salicylate) and water-insoluble drugs (benzoic acid, benzocaine) were used as model drugs. The dissolution profiles when plotted against square root of time were linear. In addition, the effects of temperature, added diluent and type of polymer on release patterns measured from plane surfaces and whole tablets were also reported.

Dissolution studies of indomethacin controlled release tablets showed that for a poorly water soluble drug, not only was the polymer to drug ratio important in controlling the release, but both viscosity grade of HPMC and particle size of the drug were to be recognized more eritically than the water soluble drugs. Furthermore, erosion of the HPMC matrix was suggested to be the only mechanism by which poorly soluble drugs were released from HPMC matrix (Ford, Rubinstein and Hogan, 1985a).

For a formulation containing cetperazine as active drug, aerosil 200, CMC and HPMC in the ratio of 1: 0.7: 4.4 gave a linear release for about 12 hours, both in vitro and in vivo studies. The release of drug from this formulation was found to be independent of hardness of tablet and pH of the dissolution medium (Beveja and Rao, 1986).

HPMC was used to produce hydrophilic matrix of propranolol hydrochloride, aminophylline and promethazine hydrochloride. It was found that a plot of percentage drug dissolved against square root of time produced a straight line and the major factor controlling drug release was the drug : HPMC ratio (Ford, Rubinstein and Hogan, 1985b,1985c).

Wan, Heng and Wong (1990) studied the drug release profile of ibuprofen-HPMC matrices with different polymer to drug ratios using HPMC of various molecular weights. Increase in the polymer to drug ratio decreased the release rate in a nonlinear manner. HPMC altered the drug release profile by forming a gel layer, its composition being dependent on polymer content and the molecular weight. Erosion of this gel layer led to enhanced drug release from matrix by increasing the surface area exposed to the dissolution medium. The polymer that formed a gel which was least susceptible to surface erosion and dissolution showed greatest retardation in drug release. In systems where the polymer gel remained intact, the drug diffused through the gel, and the release pattern was linear with the square root of time. Thus, the rate of the dissolution medium entering the compressed matrix, the rate of formation of the gel layer, the rate of diffusion of drug in the gel, the thickness and the integrity of gel would influence the drug release pattern.

Sheu et al. (1992) studied the effect of parameters on the dissolution of diclofenac sodium from Voltaren SR and HPMC based matrix tablets. The results indicated that addition of sodium or potassium chloride to the dissolution medium decreased the solubility of the drug and slowed the dissolution rate, with the effect of sodium chloride being greater. The dissolution of the drug was studied in a medium which simulated the changing pH of the pathway followed by the drug as it passes from the stomach to the intestine. Dissolution was found to be inversely related to the rate at which the

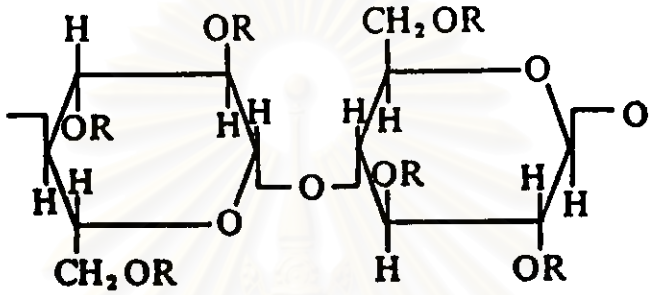
pH was changed.This may be caused by the deposition of an insoluble drug layer when contact is made with an acid medium. When higher viscosity grades of HPMC are used, slower release rates result . Drug release from Voltaren SR is best described as non-Fickian in an aqueous medium irrespective of whether salt is added; however, a zero-order dependence became evident in pH-changing media. The release of diclofenac sodium from the hydrophilic HPMC matrices follows a non-Fickian transport in all media.

5. Ethylcellulose

Ethylcellulose (EC) is an inert, hydrophobic polymer and has been extensively used as a pharmaceutical vehicle in a number of dosage forms: as a tablet binder, in preparing microcapsules and microspheres (Benita and Donbrow, 1982; Benita et al., 1988) as a coating material for tablets and granules (Sarisuta and Sirithunyalug, 1988) and as film forming and matrix forming materials for sustained release dosage forms (Donbrow and Friedman, 1974).

EC is the ethyl ether of cellulose and can contain 44.0 and 51.0 percentage of ethoxy groups. EC is resistant to alkali, both dilute and concentrated and also to salt solutions. It can withstand dilute acids for a limited period of exposure. It is subject to oxidative degradation in the present of sunlight or ultraviolet light at elevated temperatures. EC is incompatible with paraffin wax and microcrystalline wax. It is presented as a non-toxic substance. EC is insoluble in water, glycerin and propylene glycol, but soluble in varying degrees in certain organic solvents, depending upon the ethoxyl content.

Aquacoat(R) aqueous polymeric dispersion is a liquid product designed for use by the pharmaceutical industry for the aqueous film coating of solid dosage forms-beads, granules and tablets. Formulators employ Aquacoat(R) in conjunction with suitable plasticizers to form continuous, strong and flexible films on the substrate surface. The dispersion appears as a milky white liquid with the characteristics odor of EC.



R = H- or CH_3CH_2-

Figure 7 Chemical structure of ethylcellulose.

Table 5 Aquacoat(R) specifications.

Component or Property	Specification*
Total solids	29-32 %
Ethylcellulose	24.5-29.5 %
Sodium lauryl sulfate	0.9-1.7 %
Cetyl alcohol	1.7-3.3 %
pH	4.0-7.0 %
Viscosity	NMT 150 cps.
Heavy metals	NMT 10 ppm
Total aerobic microbial count	NMT 100 cfu/g
Total yeast and mold count	NMT 20 cfu/g

* NMT = not more than

Aquacoat(R) consists primarily of EC (National Formulary grade). In addition to EC, smaller amounts of cetyl alcohol (National Formulary grade), sodium lauryl sulfate (National Formulary grade) and Anti-Foam A (a food grade antifoaming agent consisting of dimethylpolysiloxane and silica gel) are also present. It contains 29-32 % total solids. Sodium lauryl sulfate and cetyl alcohol are included as stabilizers. Their concentrations are in the range of 0.9-1.7 % and 1.7-3.3 % , respectively. EC is present in the dispersion as spherical particles in the size range of 0.1-0.3 μm. The pH of the dispersion ranges from 4.0 to 7.0 and the specific gravity ranges from 1.025 to 1.040. These properties are tabulated in Table 5 (Harris and Ghebre-Sellassie, 1989).

The dispersion is stable and has a shelf life of 12 months when stored at room temperature; it will rarely settle upon standing because of the colloidal nature of the dispersed solids. As a precaution, however, the manufacturer's label suggest that the dispersion be shaken before use. Since the dispersion has properties similar to those of an emulsion, the normal precautions associated with emulsions should be exercised with Aquacoat(R).

Gilligan and Po (1991) prepared sustained release pellets of dextromethorphan. The system used consisted of drug coated sugar spheres which were then overcoated with the rate controlling membrane. The membrane was produced by spray coating with an aqueous dispersion of EC containing HPMC. It was shown that adequate post-coating conditioning was important to ensure consistency of release rate. Drug release could be made pH-independent by a choice of proper formulation.

EC used in combination with HPMC and corn starch produce a sustained release granule of nifedipine, and a linear relationship up to above 40% release is obtained based on the Higuchi equation(Kohri et al., 1987).

6. Chitosan

Chitin is the most plentiful natural polymer next to cellulose and it is widely distributed in nature. Chitin is synthesized by some unicellular organisms, for instance, diatoms, chrysoflagellates and protozoa, especially ciliates. Chitin is a cell-wall constituent of most fungi, molds and yeasts. Chitin is also present in cuticular or exoskeletal structures of most invertebrates and echinoderms. The amount of chitin with respect to total dry weight is the highest in crustaceans, mainly decapods. Crab and shrimp shells contain approximately 15-20 and 15-30 % chitin on a dry weight basis, respectively. This observation may explain the use of crustacean shells as the main source of chitin by most chemical industries.

Chitin is a cellulose like polymer which contains hydroxyl, amino and acetyl groups on a polysaccharide chain. It's structure is a crystalline polysaccharide. Like cellulose , chitin is a beta-(1-4)-linked glucan, but is composed of 2-acetamide-2-deoxy-D-glucose (N-acetylglucosamine), as shown above. Although there is no clear distinction between chitin and chitosan, it is generally accepted that chitin is extensively acetylated, while chitosan is virtually deacetylated (Filar and Wirick,1978).

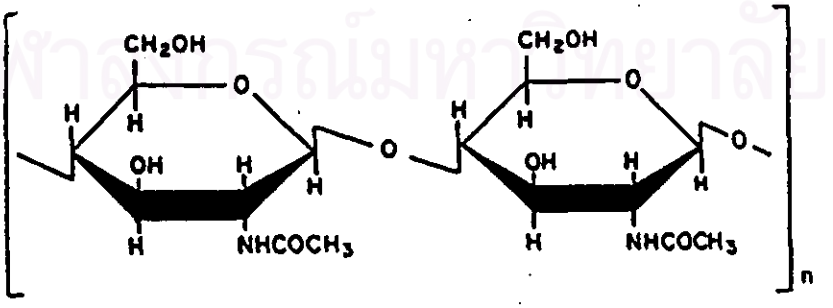


Figure 8 N-acetyl-D-glucosamine repeating unit.

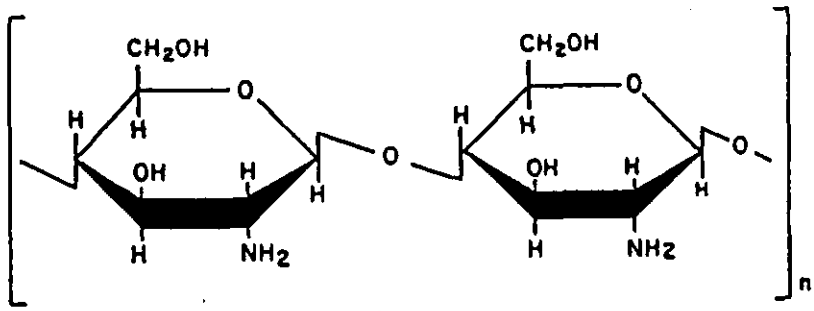


Figure 9 D-glucosamine repeating unit.

Chitosan is a polysaccharide obtained by partial or complete deacetylation of chitin, and its molecular structure and properties are largely affected by the degree of deacetylation. Chitosan is composed primarily of glucosamine,2-amino-2-deoxy-D-glucose, the structure is shown above. For this reason, it is needed to determined exactly the degree of deacetylation. the mole fraction of deacetylated units defined as the degree of deacetylation will usually range from 70-90 %.

The average molecular weight of chitin exceeds 1 million. Since chitosan is prepared from chitin by alkaline deacetylation, it has a lower average molecular weight. The chitosan product consists of a mixture of different polymer sizes (The average molecular weight of chitosan typically ranges from about 50,000 to 4 million). The range of sizes or polydispersity of the molecular weight distribution is influenced by variables such as time, temperature, concentration and atmospheric conditions employed in the deacetylation reaction. The molecular weight of a polymer has been considered to be one of the most important characteristics affecting functions of the polymer. Thus methods for determination of the molecular weight of chitosan samples have been developed, but the average molecular weight of chitosan is certainly the most difficult parameter to obtain with precision.

The viscosity of chitosan is related to the average molecular weight affected by many factors in deacetylation process. Not only the molecular weight but the viscosity of chitosan solution of its concentration, and the particular acid and its concentration used as a solvent as well.

Filar and Wirick (1978) defined the molecular weight ranges of chitosan in terms of solution viscosity. These viscosity types were selected as representative of readily be produced on a commercial scale from shrimp shell. The viscosity ranges are :

High	: > 1000 cps., 1 % polymer in 1 % acetic acid
Medium	: 100-250 cps., 1 % polymer in 1 % acetic acid
Low	: 25-70 cps., 2 % polymer in 2 % acetic acid

The term " chitosan " may be considered as referring to a family of polymers derived from chitin that has been deacetylated to provide sufficient free amino groups to render the polymer soluble in certain aqueous acid systems. The exact degree of deacetylation required to render the polymer soluble is not readily determined, and it undoubtedly varies with such factors as polymer molecular weight, temperature and concentration and nature of the acid species. In general, solubilization begins at about 60 % , usually about 75 % deacetylation depending on the molecular weight of chitosan formed. Chitosan samples with 75 % or more deacetylation dissolve readily in dilute organic acids to give clear, homogeneous and viscous solutions. For practical purposes, chitosan is insoluble in sulfuric acid and phosphoric acid, while a certain solubility exists for other mineral acids like hydrochloric acid, nitric acid and perchloric acid. Compared with the more common organic acids,the solubility in inorganic acids seems more limited concerning the concentration ratio of chitosan to acid. The solubility of chitosan in some organic acids is up

to 50 %, for example in acetic acid, lactic acid, formic acid and propionic acid. (The standard solvent commonly used for solution property measurement is acetic acid.)

Chitosan displays a wide range of viscosities in diluted acid media which depend on the molecular weight. Chitosan dissolves in diluted acid solutions, and only chemically treated or acid hydrolyzed chitin forms viscous solutions. This insolubility of chitin is the main reason for considering chitosan for sustained release application. Citric acid not only forms a complex with chitosan but also results in a viscous gel (Nigalaye, Adusumilli and Bolton, 1990). Since chitosan is a cationic polyelectrolyte which forms a gel structure in acidic pH, it is different from commercial high molecular weight hydrocolloids which are generally neutral or polyanionic.

Chitin and especially chitosan can be used effectively in oral sustained release dosage forms. Although many of the studies have developed novel applications for chitin and chitosan in theory, few have been practically feasible from an industrial standpoint.

Preparations of direct compression matrix tablets of both water soluble and water insoluble drugs were prepared by using chitosan as a vehicle. In the case of water soluble drugs, propranolol hydrochloride tablets (Sawayanagi, Nambu and Nagai, 1982) and chlorpheniramine maleate tablets (Brine, 1989) were prepared, and zero-order and pseudo-zero-order drug release patterns were obtained, respectively.

In another case of poorly soluble drug, a hydrocolloidal matrix system containing theophylline and chitosan was prepared and evaluated by Nigalaye, Adusumilli and Bolton (1990). It was found that chitosan when used alone in a

tablet formulation, did not impart sustained release properties at low concentration (10%) and when it was used in concentration of 50 % of tablet weight, a non-erosion type matrix system was formed. In order to produce a 24-hour sustained release tablet, the combination with both carbomer-934P and citric acid was needed.

In the case of matrix tablets produced by wet granulation, only water soluble drug was investigated. Aspirin was a model drug in this case. Prolonged release tablets of aspirin with chitosan were first prepared by Kawashima et al. (1985) where the granules were dried in a fluidized bed dryer. After that, Brine (1989) prepared the granules in the similar fashion but dried them in vacuum oven. Wet granulation formulation for aspirin was modified and optimized in the later study and zero-order drug release was obtained.

7. Diclofenac Sodium

Diclofenac sodium is a synthetic, nonsteroidal anti-inflammatory and analgesic compound.

7.1 Formula , Name, Formula Weight (Reynolds et al., 1989; Budavari, 1989; Adeyeye and Li, 1990)

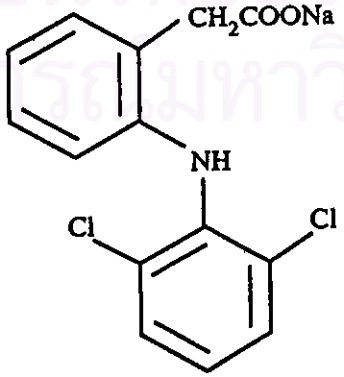


Figure 10 Diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$)., Formula weight 318.13

Diclofenac sodium is also described under the following chemical names :

(1) 2-[(2,6-Dichlorophenyl) amino] benzeneacetic acid monosodium salt
(2) [0-(2,6-dichloroanilino) phenyl] acetic acid sodium salt
(3) sodium [0-[(2,6-dichlorophenyl) amino] phenyl] acetate
(4) sodium [2-(2,6-dichloroanilino) phenyl] acetate

7.2 Appearance , Color and Odor

Diclofenac sodium is an odorless, white to off-white crystalline, slightly hygroscopic powder (Adeyeye and Li, 1990).

7.3 Solubility

The equilibrium solubility performed in various solvents at room temperature are shown in Table 6 (Adeyeye and Li, 1990).

Table 6 Solubility of diclofenac sodium at room temperature.

Solvent	Solubility (mg/ml)
Deionized water (pH 5.2)	> 9
Methanol	> 24
Acetone	6
Acetonitrile	< 1
Cyclohezane	< 1
pH 1.1 (Hydrochloric acid)	< 1
pH 7.2 (Phosphate buffer)	6

7.4 Dissociation Constant (pKa) and Partition Coefficient

The dissociation constant (pKa) of diclofenac sodium is 4.0 and the partition coefficient in n-octanol/aqueous buffer pH is 13.4 (Adeyeye and Li, 1990).

Maitani, Nakagaki and Nagai (1991) investigated the pKa of diclofenac sodium in ethanol-water mixtures, in connection with percutaneous absorption, using the titration method. The pKa of the drug was decreased by the increase in the concentration of ethanol in the aqueous solution. Results were interpreted in terms of solvent polarity. It is suggested that ethanol, which is used as an enhancer for percutaneous absorption, assumes another role by increasing the proportion of unionized form of the drug and forming ion pairs in low dielectric media. The partition coefficients for the drug were measured in n-octanol to water or buffer system over the pH range from 3 to 8. The distribution behavior of diclofenac is dramatically affected in the presence of added cations. Above pH 7, ion pair formation promotes the distribution of the drug into lipophilic environment.

7.5 Stability

Diclofenac sodium tablets film coated with polymers like acrylate hydroxypropylcellulose were reported to be stable after storage for one week at 30 ^{0}C in 80 % relative humidity (Adeyeye and Li, 1990). A suppository formulation was also analyzed for stability using thin layer chromatography and ultraviolet spectroscopy. The formulation was stable for 24 months at room temperature. Stability in biological fluid (serum) was determined and the results demonstrated that diclofenac sodium could be frozen for at least two weeks without degradation.

Backensfeld, Muller and Kolter (1991) investigated the effects of beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin and hydroxy-gamma-cyclodextrin on the solubility and stability of diclofenac sodium, indomethacin and piroxicam. The influence of beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin on the stability of diclofenac solutions with and without oxygen at a stress temperature of 71° C showed that the cyclodextrin derivative had the most stabilizing effect. At room temperature the decrease in degradation was not significant, even when the solutions without cyclodextrin were physically unstable due to recrystallization of the drug. In contrast to indomethacin and diclofenac, the cyclodextrins had a destabilizing effect on the stability of piroxicam.

7.6 Uses and Administration (Reynolds et al., 1989)

Diclofenac sodium has analgesic, antipyretic and anti-inflammatory properties; it is an inhibitor of prostaglandin synthetase (cyclo-oxygenase).

The drug is used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout and following some surgical procedures. The usual dose by mouth is 75 to 150 mg. daily in divided doses. It may also be given rectally as a suppository in a usual dose of 100 mg. each evening. Diclofenac sodium may also be given by intramuscular injection in a dose of 75 mg. once daily or, if required in severe conditions, 75 mg. twice daily. It is also used intramuscularly in renal colic in a dose of 75 mg. repeated once after 30 minutes if necessary. In children the suggested dose by mouth or rectally for juvenile chronic arthritis is 1 to 3 mg. / kg. body weight daily in divided doses.

7.7 Adverse Effects

The most frequent adverse effects occurring with diclofenac sodium are gastro-intestinal disturbances (Reynolds et al ., 1989). Peptic ulceration and gastro-intestinal bleeding have been reported. Other side effects include headache, dizziness, nervousness, skin rash, pruritus, tinnitus, edema, depression, drowsiness, insomnia, and blurred vision and other ocular reactions.

In order to eliminate the gastro-intestinal adverse effect of diclofenac sodium, effective enteric coated products have been developed and commercialized (Lin and Kao, 1991). They may allow a drug dosage form to pass through the acid environment of the stomach without irritation, to disintegrate in the upper small intestine, and to release the drug.