CHAPTER I

INTRODUCTION

Oral controlled release products are developed in order to enhance safety and extend duration of action. These may be of great importance, especially in long term treatment. Controlled release products can decrease fluctuation of serum concentrations, resulting in reduced toxicity and sustained efficacy and also decrease frequency of dosing, resulting in improved patient compliance, reduced patient care time, and possibly reduced total amount of drug used. Drugs that are taken on a chronic or extended basis, such as cardiovascular, arthritic, respiratory, and analgesic products, often have the most potential for controlled release delivery developments (Ranade and Hollinger, 1996).

Multiparticulate dosage forms such as matrix or coated pellets or microparticles (microcapsules or microspheres) have gained interests oral controlled release formulations. Multiparticulates can be filled into hard gelatin capsules or be compressed into tablets. When filled into capsules, if the capsules dissolved, multiparticulates will be widely dispersed throughout the gastrointestinal tract. Thus, resulting in a more uniform drug absorption and reduced patient-to-patient variability. The dispersion of multiparticulates also reduce the risk of local irritation of gastric mucosa (Kramer and Blume, 1994).

Spray drying technique has been widely used in the pharmaceutical industries, including the drying of heat sensitive materials (Newton, 1966), preparing granulations for tabletting (Raff, Robinson and Svedres,1961 ; Kornblum,1969 ;

Sugimori et al.,1990), improvement in solubility of poorly water-soluble substances (Kawashima, Saito and Takenaka, 1975 ; Takeuchi, Handa and Kawashima, 1987), coating drugs with suitable polymers to produce dust-free powders (Seagar, 1977) and recently, it has been successfully employed in the preparation of microparticles for controlled release drug delivery systems. Various formulations can be accomplished in a one-step process in a spray dryer. This can both simplify the process and shorten the processing time. The structure of the microparticles obtained is different according whether the drug is dispersed or dissolved in the polymeric solution to be spray dried. Microcapsules are obtained by spraying a drug suspension in a solution of the polymeric coating, while polymeric matrices (microspheres), in which the drug is embedded, are obtained by spraying a solution of the drug and of the polymer. By modifying the spray drying process, it is possible to alter and control many properties of spray dried products (Broadhead, Rouan and Rhodes, 1992).

An aqueous-based polymeric film has been developed for pharmaceutical dosage forms instead of organic solvent-based polymeric systems in order to avoid explosion hazard and toxicity associated with solvent system. Several water dispersing polymers have become commercially available for controlled release formulations. Acrylate aqueous dispersion, such as Poly(ethylacrylate methylmethacrylate) and Ammonio methacrylate copolymer type A and type B (Eudragit® NE 30 D, Eudragit® RL 30 D and Eudragit® RS 30 D, respectively) were developed and used for controlled drug delivery systems. Eudragit® NE 30 D could be used in both oral controlled drug release and transdermal therapeutic systems. Eudragit® RL 30 D and Eudragit® RS 30D, which differ in the permeability characteristics, were used for controlled release coating. Films prepared from these polymers are swellable in water and show pH-independent permeabilities (Lehmann, 1989).

Diclofenac sodium is a non-steroidal antiinflammatory agent used for a variety of painful and inflammatory conditions. It has an adverse effect on the gastric mucosa and short biological half-lives. Thus, it is usually given two to three times daily (Reynolds et al.,1989). In order to reduce the gastric irritations, maintaining plasma drug levels within the therapeutic range for longer period and decrease frequency of dosing. Hence, controlled release of diclofenac sodium has been developed.

In this study, controlled release diclofenac sodium was developed using acrylate aqueous dispersion by spray drying technique. The physicochemical properties of spray dried products were investigated. The drug release characteristics were evaluated by in vitro dissolution test.

The objectives of this study are :

1. To study the spray drying technique in preparation of controlled release diclofenac sodium with acrylate aqueous dispersion and examine the physicochemical properties of spray dried powders.

2. To evaluate the effect of inlet air temperature that is the processing variable on physicochemical properties of spray dried product.

3. To study the effect of pH of dissolution medium on the release of drug from controlled release capsule.

4. To investigate the model of drug release from controlled release capsule.

Literature Review

1. Spray Drying Technique

Spray drying technique has been widely used in the pharmaceutical, chemical and food industries mainly for the drying of substances. However, other applications in the pharmaceutical industries include the drying of heat sensitive materials (Newton, 1966), preparing granulations for tabletting (Raff, Robinson and Svedres,1961 ; Kornblum, 1969 ; Sugimori et al., 1990), improving the solubility of poorly water-soluble substances (Kawashima, Saito and Takenaka, 1975 ; Takeuchi, Handa and Kawashima, 1987), coating drugs with suitable polymers to produce dust-free powders (Seagar,1977) and other more recent application like microencapsulation and microsphere for controlled release preparations. Spray drying technique may prove to be more useful for the preparation of microcapsules because the coated particles can be produced directly from droplets in a single process (Takenaka, Kawashima and Lin, 1980).

The General Principles of Spray Drying

Spray drying is the transformation of feed from a fluid state into a dried particulate form by spraying the feed into a hot drying medium. It is a one-step, continuous particle-processing operation involving drying. The feed can either be a solution, suspension or paste. The resulting dried product conforms to powders, granules or agglomerates, the form of which depends upon the physical and chemical properties of the feed and the dryer design and operation (Master, 1979).

The Design and Operation of Spray Dryers

Spray drying consists of four process stages (Master,1979) :

I Atomization of the feed into a spray

II Spray-air contact

III Drying of the spray

IV Separation of dried product from the drying gas

The formation of a spray (atomization) and the contacting of the spray with air are the characteristic features of spray drying. The selection and operation of the atomizer is an important factor in achieving economic production of top quality of products. Atomization systems may be classified according to the nozzle design as rotary atomization, pressure atomization or two-fluid (pneumatic) atomization. In rotary atomization, the feed fluid is introduced into the drying chamber by means of a spinning disc or wheel which creates a spray of droplets. Pressure atomization occurs when the feed is fed to the nozzle under pressure which causes the fluid to be dispersed into droplets as it leaves the nozzle.

Spray-air contact is determined by the position of the atomizer in relation to the drying air inlet. Spray dryers may be designed to operate in a co-current manner, where spray and drying air pass through the dryer in the same direction or in a counter-current manner where the spray and drying air enter the drying chamber at opposite ends. Other spray dryer designs are available where the spray-air contact is intermediate between co- and counter- current. Co-current operation is preferable for the drying of heat sensitive materials since the dry product is in contact with only the coolest air. Also, the high rates of moisture evaporation enable the temperature of the dry product to be considerably lower than that of the air leaving the drying chamber. Counter-current drying, on the other hand, is a superior process in terms of heat utilization and economics, but subjects the driest powders to the hottest air stream.

As soon as droplets of the spray come into contact with the drying air, evaporation takes place from the saturated vapour film which is quickly established at the droplet surface. Different products exhibit different evaporation characteristics. Some tend to expand, others collapse, fracture or disintegrate, leading to porous, irregularly shape particles. Others maintain a constant spherical shape or an even

contact, so that the particles become denser. The extent of changes in particle shape, and hence the dried powder characteristics, are closely connected to the drying rate. To meet the desired powder characteristics, close consideration must be given to the drying-chamber design.

The final step in the spray drying process involves the separation of the product from the air stream. This is usually accomplished by means of a cyclone separator through which the air and product pass after exiting the drying chamber. Many dryers also allow for product collection at the base of the drying chamber.

There are numerous different spray dryer designs, spray dryers system are usually open cycle whereby the drying gas is discharged after use. For dryers operating in this manner, the drying gas would usually be air. In addition, however, closed cycle spray dryers are available which enable organic solvents to be used as the feed medium. In this type of dryer, the drying air is replaced by an inert gas, usually nitrogen, which is continuously recirculated. The organic solvent is also recovered. Other dryers are available which operate using air with a reduced oxygen content. This may be required if the material is extremely susceptible to oxidation or has explosive tendencies (Nielson, 1982). Various dryer layouts suitable for toxic materials which operate so as to avoid air pollution have also been developed. From a pharmaceutical point of view, it is important to note that aseptic systems are available which operate to produce a sterile powder. This is achieved by filtration of the liquid feed material and the atomizing air, contamination free atomization and product collection, and careful dryer design. These systems are currently being used for the production of antibiotics. Also, dryers which incorporate fluid beds into the base of the drying chamber have been designed. These are capable of producing large agglomerated powders more economically than other types of spray dryer.

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, Rouan and Rhodes, 1992).

Effect of processing and formulation variables on 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 (Newton, 1966). By modifying the spray drying process, it is possible to alter and control the following properties of spray dried powders; appearance, particle size and size distribution, bulk density, particle density, porosity, moisture content, flowability, stability, dispersability, friability and retention of activity, aroma and flavor (Master, 1979; Newton, 1966). Obviously, the design of the nozzle and drying chamber will affect particle properties, and the desired powder characteristics should be borne in mind when a spray dryer design is selected.

An increase in energy available for atomization (i.e. rotary atomizer speed, nozzle pressure, or air-liquid flow ratio in pneumatic atomizer) will reduce particle size (Master, 1979). The flow properties of the spray dried particles improved with decrease in the air to liquid diameter ratio of the nozzle (Wan, Heng and Chia, 1990).

The type of feed used was important, a suspension feed resulted in a more sustained release and better flow properties than a solution feed (Wan, Heng and Chia, 1992). The feed concentration or viscosity at the processing temperature influenced microparticle diameter. The viscosity is again influenced by the solid content of the feed. The yield could be increased by using a high total solid content (Broadhead,

Rouan and Rhodes,1994). Particle size is usually increased as the feed concentration or viscosity increase. If the feed rate increased, particle size will again increase (Master, 1979).

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 coffee extract (a film forming material) the mean particle diameter was significantly reduced by increasing the inlet air temperature. An increase inlet air temperature often causes a reduction in bulk density, as evaporation rates are faster, and products dry to a more porous or fragmented structure (Master, 1979), and also great effect in reducing particle size (Conte et al.,1994). In contrast, Newton (1966) reports a study where the particle size of some materials was shown to increase as the drying air temperature increase. A high inlet drying temperature produced coated particles with a slower drug dissolution rate (Wan et al., 1990).

The outlet temperature can be correlated with the moisture content of the product, increased dryer outlet temperatures result in a lower final product moisture content (Master, 1979)

The application of spray drying for controlled release system

Spray drying technique has received considerable interest as a microencapsulation process to obtain a controlled delivery systems, involved dispersing a solid or liquid core material in a coating solution and then atomizing the mixture into an airstream (Madan, 1978). Microcapsules 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 (Voellmy, Speiser and Soliva, 1977). In the spray congealing process, no solvent is used. The feed , which consists of the coating and core material, 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).

Palmieri, Wehrle and Stamm (1994) evaluated the possibility to obtain microcapsules or microspheres for controlled release by spray drying technique. Drugs of different solubilities like theophylline and sodium sulfamethazine were used. Eudragit®RS was used as coating polymer, either dissolved in an hydroalcoholic solution or suspended (pseudolatex) in water, in different weight ratios with the drug. The obtained solution or suspension was spray-dried. They found that no microencapsulation occured by spray drying a drug and polymer solution ; the spray-dried particles were simple minimatrices, that was, a fine drug dispersion in the polymer network. Even if these microparticles were not able to reduce the rate of drug release, tablets derived from their compression, were very effective as controlled release system and offer a real advantage compared with the matrix-tablets obtained by direct compression of the polymer powder or by compression of the solid dispersion powders realized by evaporation under vacuum. So, spray drying was a useful step in the formulation of controlled release matrix tablets.

Wan, Heng and Chia (1992) prepared microcapsule of theophylline by a spray drying technique using an aqueous system. Comparison was made between the use of a solution and a suspension feed. The results showed that a suspension-feed produced microcapsules with better flow properties and slower drug dissolution than the products from a solution-feed. Most of the product from the solution-feed contain drug particles on the polymer surface, resulting in a rapid drug release. The dissolution profiles of spray dried product was dependent on the type of polymer and its hydrophilicity.

The production of biodegradable microparticles by spray drying method appear to be an attractive alternative of conventional microencapsulation method. Copoly (dl-lactic/glycolic acid) microparticles for injectable sustained release of a water soluble drug (thyrotropin releasing hormone : TRH) were prepraed by a spray drying method (Takada et al.,1994 and 1995). It was seen that a higher entrapment ratio was achieved with the spray drying method than with the in-water drying method. In order to avoid agglomeration of the microparticles, a double-nozzle spray drying method was designed using mannitol as an anti-adherent. The surface of the spray-dried microparticles was coated with mannitol, and the extent of agglomeration was decreased.

Poly (lactide-co-glycolide) powders with good compaction properties can be prepared by spray drying (Avgoustakis and Nixon, 1993). The important factor for the successful spray powdering of poly (lactide-co-glycolide) polymers appeared to be the molecular weight of the polymer and not the viscosity of the sprayed solution.

Bovine serum albumin was microencapsulated into poly (D,L-lactic acid) by spray drying using single solvents and binary solvent mixtures (Gander et al., 1996). Microencapsulation was studied by a thermodynamic approach taking quantitatively into account the molecular interactions between polymer, solvent and the aqueous protein phase. Entrapment efficiency is increased and burst release is reduced if polymer-drug interaction is dominant and polymer-solvent, drug-solvent interactions are reduced.

Sutinen et al. (1995) described a new type of microspheres that control drug release with changing inner core pH. In the microspheres, micronized model drug, timolol maleate and pH adjusting agent (mono, di, and trisodium phosphate or Tris buffer) were either dry blended by mixing or coprecipitated by spray drying, and encapsulated in X7-3012 silicone microspheres using emulsion vulcanization technique. Spray drying of the drug and buffer together was the most effective in

controlling the drug release since, in this case, buffer was in the same microcompartment inside silicone and thus buffering effect was maximal.

Pavanetto et al. (1992) compared three different techniques used for the preparation of polylactide microspheres loaded with a lipophilic drug. The three methods were emulsification by solvent evaporation, emulsification by solvent extraction and spray drying. They found that spray drying achieved a highest encapsulation efficiency and shortest duration for the process of preparation. Moreover, the dissolution profile of microspheres prepared by spray drying demonstrated that more gradual release of drug was promoted.

Luzzi, Zoglio and Maulding (1970) used spray drying in order to produce a free flowing powder from a slurry containing nylon microcapsules. In this case, the spray dryer was used simply to separate the microcapsules from the vehicle. The diameter of the particles produced was approximately 10 μm. By comparison, vacuum dried microcapsules had a larger particle size and the powder was not free flowing.

Takenaka, Kawashima and Lin (1980) prepared enteric coated microcapsules of sulphamethoxazole by spray drying an aqueous solution of drug and cellulose acetate phthalate (CAP) 5%, with or without various additives, such as monmorillonite clay and colloidal silica. Particles with diameters ranging from 3.6 to 22.0 μm were obtained. Formulation 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. Formulation containing 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 sulphamethoxazole. When microcapsules were prepared by a coacervation technique the drug remained in form I. CAP was presumed to interact with the

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 cellulose acetate phthalate (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 cellulose acetate phthalate made the resultant product smoother still. X-ray diffraction data showed that the presence of cellulose acetate phthalate actually caused a polymorphic change resulting in a mixture of form 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 neither CAP or colloidal silica was included in the formulation, the product was usually a mixture of all three forms.

A spray drying method has been described for the manufacture of a drug matrix which possesses sustained action when compressed into tablets (Kornblum, 1969). The method possesses the advantages of uniformity of drug distribution and reproducibility of drug release pattern for consecutive batches. He reported that significantly less binder is 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 degrees of drug release retardation afforded by the binder seemed to be associated with the degree to which the binder encapsulated the magnesium carbonate.

Asker and Becker (1966) used spray drying technology to produce prolonged release sulfaethylthiadiazole (SETD) granulations. A follow-up series of papers investigated the production of slow release sulfaethylthiadiazole-wax granulations by spray congealing (Cusimano and Becker, 1968 ; John and Becker, 1968 ; Hamid and

Becker, 1970). 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 (Robinson and Swintosky, 1959). A decrease in particle size was observed with a decrease in nozzle diameter, as would be expected. The type of wax used also had a significant effect on particle size. Interestingly, these authors observed larger particle diameters with the least viscous feed solutions. This corresponding with the data of Scott et al. (1964), who observed an inverse relationship between particle size and the viscosity of the feed medium, but contrasts with most other observations of the spray drying process which indicate an increase in particle size with increasing feed viscosity.

Controlled release theophylline tablets were prepared by compressing spray dried microspheres with Eudragit® L30D, L100-55 and E30D (Takeuchi et al.,1989). Depending on the amount of polymer present, the spray dried powder consisted of either agglomerated, polymer coated theophylline crystals or spherical particles of a solid dispersion of amorphous drug in a polymer base. Completely enteric function was observed with drug-to-polymer ratio of 1:3 using Eudragit® L30D or L100-55. Tablet with Eudragit® E30D formulated at the 2-40% level showed good sustained drug release which was throughly independent of the pH of dissolution media. In each tablet, the controlled drug release was attributed to continuous and well-dispersed polymer matrix formed by spray drying and subsequent compressing process.

2. Mathematical Models for Controlled Release Kinetics

Controlled release of drugs can be achieved by incorporating solutes either in dissolved or in dispersed form in polymers. From a mathematical modeling point of view, controlled release systems may be classified according to the physical mechanisms of release of the incorporated solute. Mathematical modeling of the release kinetics of specific classes of controlled release systems may be uesd to :

(1) predict solute release rates from and solute diffusion behavior through polymer, and (2) to elucidate the physical mechanisms of solute transport by simply comparing the release data to mathematical models (Ranade and Hollinger, 1996)

Mathematical models can be categorized into three types:

1. Zero-order release model
2. Square-root-time release model
3. First-order release model

Zero-order release model

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

$$\frac{dM_t}{dt} = k \qquad (1)$$

where k is a constant, t is time, and M_t is the mass of active agent released. This model of release is called zero-order release model.

Square-root-of-time release model (Higuchi model)

The second common release model 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 :

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad (2)$$

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

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

$$Q = \left[\frac{D\varepsilon}{\tau} (2A-\varepsilon C_s) C_s t \right]^{1/2} \quad (3)$$

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 tortuosity of matrix

C_s is solubility of drug in the release medium

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

The assumption made deriving Equation are as follows :

1. A pseudo-steady state is maintained during release
2. $A >> C_s$, i.e., excess solute is present
3. The system is in perfectly sink condition in which C, is approximately to 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 (3) is usually reduced to

$$Q = k_H t^{1/2} \quad (4)$$

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 linearity if drug release

from the matrix is diffusion controlled. Although the above equation was based on release from a single face, it may used to describe diffusion-controlled release from all surface matrix.

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

$$\log Q = \log k_H + 1/2 \log t \quad (5)$$

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

First-order release model

The first-order release model 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 :

$$\frac{dM_t}{dt} = k (M_o - M_t) \quad (6)$$

where M_o is the mass of agent in the device at t = 0. On rearrangement, this gave

$$\frac{dMt}{dt} = kM_o \exp^{-kt} \quad (7)$$

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 exponential with time, Wagner (1969) suggested that drug release from most controlled-release matrices could be described by apparent first order kinetics, thus:

$$A_t = A_0 e^{-k_1 t} \quad (8)$$

where k_1 is first order release constant

A_0 is initial amount of drug

A_t is amount of drug remaining in the matrix at time t

Simplifying and taking the logarithm of Equation (8) yielded

$$\log A_t = \log A_0 - \frac{k_1 t}{2.303} \quad (9)$$

First order model 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, Bandyopadhyay and Gupta (1990) reported that the initial curvature of the plot may be obtained because of the presence of surface drugs and they suggested to 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 equation (Sa, Bandyopadhyay and Gupta, 1990)

$$\frac{dQ'}{dt} = \frac{k_H^2 S^2}{2Q'} \quad (10)$$

where Q' = Q*S (S is the surface area of matrix). The rate predicted by first-order model was given by :

$$\frac{dQ'}{dt} = kA_0 - kQ' \qquad (11)$$

where $A = A_0 - Q'$. This indicated 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.

The plots of rates of release versus 1/Q' are linear, indicating that the release is fitted with Higuchi model. If the plots of rates of release versus Q' were linear, indicating that first order model is operative.

The release model for each classes of device is illustrated in Figure 1 (Baker, 1987). the release models of Zero-Order, Square-root time, and First-Order are depicted (Equation 1, 2 and 6) respectively.

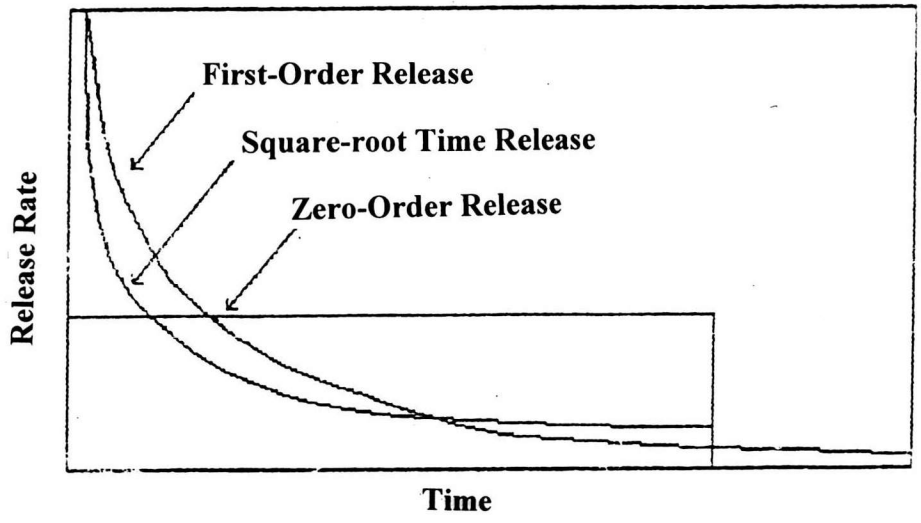


Figure 1 Zero-order, first- order, and square-root time release models from devices containing the same initial active agent content.

3. Matrix Devices

A matrix device, as the name implies, consists of drug dispersed homogeneuosly throughout a polymer matrix as represented in Figure 2.

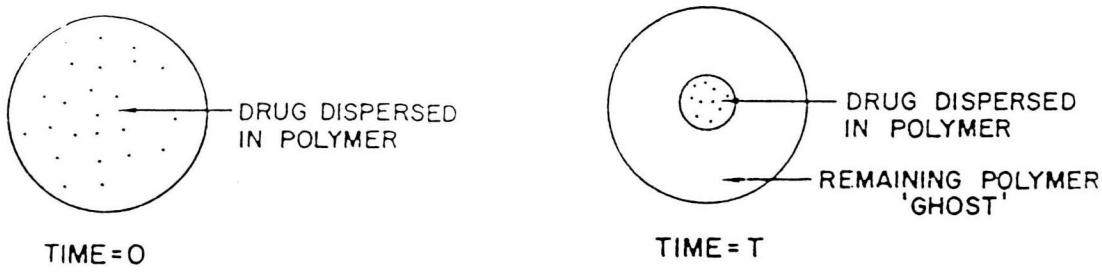


Figure 2 Matrix diffusional system before drug release (time = 0) and after partial drug release (time = t)

In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. Obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions (Grass and Robinson, 1990) : (1) a pseudo-steady state is maintained during drug release ; (2) the diameter of the drug particles is less than the average distance of drug diffusion through the matrix ; (3) the bathing solution provides sink conditions at all time ; (4) the diffusion coefficient of drug in the matrix remains constant (i.e., no change occurs in the characteristics of the polymer matrix).

The equation presented below, which describe the rate of release of drugs dispersed in an inert matrix system, have been derived by Higuchi. The following equation can be written based on Figure 3 :

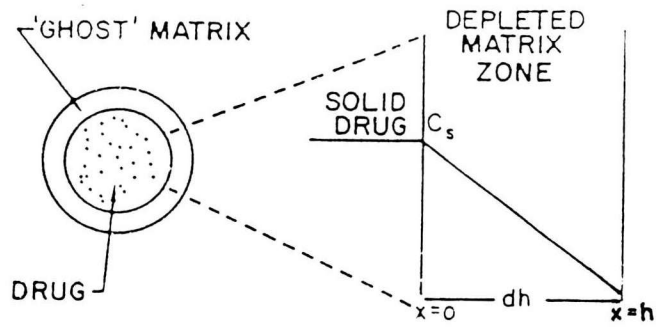


Figure 3 Schematic representation of a matrix release system. C_s is the saturation concentration of drug controlling the concentration gradient over the distance, h, of the remaining ghost matrix.

$$\frac{dM}{dh} = C_0 dh - \frac{C_s}{2} \tag{12}$$

where dM is change in the amount of drug released per unit area

dh is change in the thickness of the zone of matrix which has been depleted of drug

C_0 is total amount of drug in a unit volume of the matrix

C_s is saturated concentration of the drug within the matrix

From diffusion theory,

$$dM = \frac{D_m C_s}{h} dt \tag{13}$$

where D_m is the diffusion coefficient in the matrix. Equating Equation (12) and (13), integration, and solving for h gives

$$M = [C_s D_m (2C_0 - C_s) t]^{1/2} \tag{14}$$

When the amount of drug is in excess of the saturation concentration, that is, $C_0 >> C_s$

$$M = (2C_sD_mC_0t)^{1/2} \quad (15)$$

which indicates that the amount of drug released is a function of the square root of time. In a similar manner, the drug release from a porous or granular matrix can be described by

$$M = [\, D_s\, C_a \frac{P}{T} (2C_0 - pC_a)\, t]^{1/2} \quad (16)$$

where P is porosity of the matrix
T is tortuosity
C_a is solubility of the drug in the release medium
D_s is diffusion coefficient in the release medium

This system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid-filled channels and does not pass through the polymer directly.

For purpose of data treatment, equation (15) or (16) can be reduced to

$$M = kt^{1/2} \quad (17)$$

where k is a constant, so that a plot of amount of drug released versus the square root of time will be linear, if the release of drug from the matrix is diffusion controlled. If this is the case, then by the Higuchi model, one may control the release of drug from a homogeneous matrix system be varying the following parameters : (1) initial concentration of drug in the matrix, (2) porosity, (3) tortuosity, (4) polymer system forming the matrix, and (5) solubility of the drug.

Matrix systems offer several advantages. They are, in general easy to make and can be made to release high-molecular-weight compounds. Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although on some cases, cracking of the matrix material can cause unwanted release. The primary disadvantages of this system are that the remaining matrix "ghost" must be removed after drug has been released. Also, the release rates generated are not zero-order since the rate varies with the square root of time. A substantial sustained effect, however, can be produced through the use of very slow release rates, which in many application are indistinguishable from zero-order.

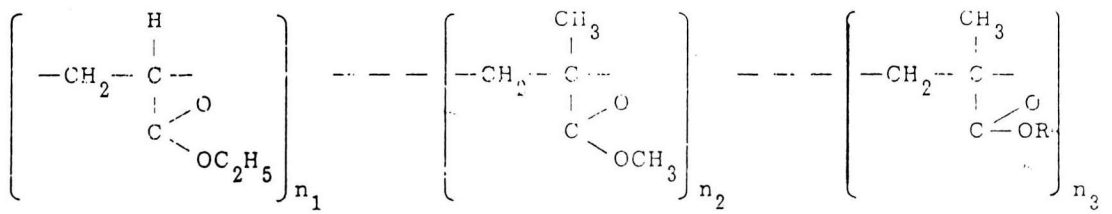
4. Acrylate Aqueous Dispersion

The acrylic polymers Eudragit® RL 30D, Eudragit® RS 30D and Eudragit® NE 30D were developed for pH-independent, controlled release of active ingredients from oral dosage forms. The release of the active ingredients in the digestive tract controlled by swellable, permeable coatings and matrix structures. Eudragit matrices provide dosage forms of good mechanical strength and control the diffusion of the embedded active ingredients through pores and channels (Lehmann, 1989).

Eudragit® NE 30D

Eudragit® NE 30D is produced as an aqueous latex by emulsion polymerization, which contain 30% solid including some emulsifier. The molecular weight is amount 800,000. Eudragit® NE 30D is a neutral ester dispersion without any functional groups that form water-insoluble films. It is consists of neutral copolymers of ethyl acrylate and methyl methacrylate (2:1) esters that are insoluble in pure water, dilute acids, buffer solutions, or digestive fluids over the entire physiological pH range. A sticky solid can be prepared by freeze-drying or other

Methacrylate ester copolymers



Scientific name	$n_1:n_2:n_3$	MW	Behavior in digestive juices	Eudragit type	Marketed form
Poly(ethylacrylate. methylmethacrylate)	2:1	800,000	Insoluble films of medium permeability	NE 30 D	30% aqueous dispersion
Poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride R: $CH_2—CH_2—N^+(CH_3)_3Cl^-$	1:2:0.2	150,000	Insoluble films of high permeability	RL 30 D	30% aqueous dispersion
				RL 100	Granules
Poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride) R: $CH_2—CH_2—N^+(CH_3)_3Cl^-$	1:2:0.1	150,000	Insoluble films of low permeability	RS 30 D	30% aqueous dispersion
				RS 100	Granules

Figure 4 Structural formula of methacrylate ester copolymers.

drying processes but is not commercially available. Films prepared from this latex swell in water and show a medium degree of permeability. Permeability is independent of pH. Eudragit® NE 30D was described in the Federal Register as safe for use as a food-contact surface for articles intended for packaging and holding food including the heating of prepared food.

Films prepared from this latex swell in water and show a medium degree of pH-independent permeability. The polymer is used mainly for sustained release and transdermal drug formulations. The minimum film forming temperature (MFT) is around 5°C, and a soft, flexible film is formed at room temperature without any plasticizer. The addition of plasicizer will cause undesirable sticking effects in film-coating processes. Normally no reactions or absorptive effects are observed when the polymer comes in direct contact with drug substances, so it is a very useful material for embedding drugs, for granulation processes, and also for protective coatings. Changes in pH do not alter the properties of the polymer, and the latex is not very sensitive to incorporation of drugs or excipients. Drug particles are dispersed throughout the polymer matrix, which, first control the penetration of digestive fluid into the matrix and later diffusion of the dissolved drug through the pores, channels, and capillaries of the matrix.

Eudragit® RL 30D and Eudragit® RS 30D

Eudragit® RL 30D and Eudragit® RS 30D were copolymers synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar compositions of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride were 1:2:0.1 for Eudragit® RS 30D and 1:2:0.2 for Eudragit® RL 30D. The quaternary ammonium group in molecules are responsible for the permeability of the films. Films prepared from Eudragit® RL 30D that molar ratio of ammonium groups to the neutral (meth)acrylates is 1:20, show higher permeability than Eudragit® RS 30D, which a molar ratio of ammonium groups

to the neutral (meth)acrylates is 1:40. Films made of Eudragit® RL 30D are readily permeable to water and dissolved active substances, so that active substance diffusion is only slightly delayed. In contrast, low permeability lacquer films made from Eudragit® RS 30D are much less permeable to water, and therefore used exclusively to manufacture retard coatings giving pH-independent release of active substance from small particles such as granulates, crystals, powders or pellets. Eudragit® RL 30D and Eudragit® RS 30D are contain 30% solid including 0.25% sorbic acid as a preservative, but no emulsifier. The disaggregation is enhanced by the water uptake and the additional softening effect of water as a plasticizer-dispersing agent. Furthermore the quaternary ammonium groups with their positive charges many stimulate the dispersing process by stabilizing new surfaces formed and repelling the small dispersed particles. The effect of the quaternary ammonim groups in the polymer on hydrophilicity, swelling properties, and particle stabilization is so great that no emulsifier or high shear forces are needed in the emulsification process.

The minimum film forming temperature (MFT) of these dispersions are between 40 and 50°C and addition of 10-20% plasticizer is necessary to reduce the MFT below 20°C. Films of these copolymers are water-insoluble and in digestive fluids, though they are swellable and permeable, this means that the active ingredients are released by diffusion. The permeabilities of Eudragit® RL/RS films are pH-independent, thus the active substance release takes place largely independent of individual fluctuations in the pH-conditions of the digestive tract. The permeability of films is influenced to some extent by the added plasticizer. Suitable plasticizers are citrates, dibutyl phthalate, diethyl phthalate, triacetin and 1,2 propylene glycol.

The addition of talc, colloidal silica or kaolin were recommended to reduce the tendency to stick during the spraying process. Colloidal silica was also added to improve the flow of small particles. Vecchio, Fabiani and Gazzaniga (1995) evaluated the possibility of substituting talc with colloidal silica as separating agent in aqueous dispersion of film acrylic resins. The resulting shown that the spraying of acrylic

dispersion coating (Eudragit® RL 30D and RS 30D) using colloidal silica instead of talc was performed without problems of sedimentation, which made vigorous agitation unnecessary while it is usually indispensable when talc is employed. Moreover, no sticking tendency and pellet aggregation was observed during the application of the film. From the morphological point of view, no differences between the films obtained from dispersion containing talc or colloidal silica as separating agents.

Eudragit® RL 30D and Eudragit® RS 30D are used mainly for the manufacture of oral dosage forms with controlled drug release. Both polymers can be mixed with one another in any desired ratio; this means that it is possible to vary the release rates between wide limits.

Lehmann and Dreher (1988) reported that mixing of aqueous dispersion in sometimes a very urgent request for the following reasons: (i) improved processing and better film properties. (ii) optimization of drug release profile. Aqueous dispersion of methacrylic acid copolymer with anionic porperties (Eudragit® L 30D) can be mixed together and are also miscible with dispersions of neutral methacrylate esters (Eudragit® NE 30D) in any proportion. Such mixtures show reduced film forming temperature, films are softer and exhibit graded solubility in intestinal fluid. Hydrophilic, slightly cationic poly (meth)acrylate dispersions (Eudragit® RL 30D and Eudragit® RS 30D) are also miscible with each other and with neutral dispersions. Addition of emulsifier is recommended for stabilization. These mixed films show graded pH-independent permeability. Anionic dispersions can be mixed in limited amounts to hydrophilic poly (meth)acrylate dispersions if a solution of methacrylic acid copolymer in salt form and emulsifier are added. The resulting films show increasing permeabiility above pH 5.5. Mixing of dispersions opens a variety of applications for dosage forms with controlled drug release.

Polymeric films containing propanolol HCl were sucessfully prepared from acrylic colloidal polymer dispersions (Bodmeier and Paeratakul, 1990). Eudragit® RS and RL 30D were mixed in various proportions to study the drug release from mixed films as a function of Eudragit® RS/RL ratio. The mixed films had intermediate release patterns when compared to those of pure films. Propanolol HCl-Eudragit® RL 30D formed films which swelled rapidly and later disintegrated in the dissolution medium. The higher proportion of quaternary ammonium groups in Eudragit® RL films resulted in rapid hydration and drug release. Otherwise, they found that unplasticized Eudragit® RS 30D did not form continuous and flexible films upon drying. They required the addition of plasticizer for film formation because the minimum film forming temperature was above the drying temperature.

Amighi and Moes (1995) formulated sustained release film coated theophylline pellets and evaluated film forming properties of acrylic aqueous polymer dispersion blends. They reported that aqueous acrylic polymer dispersions were blended in order to improve processing and film formation from acrylic polymers with poor film forming properties and/or to obtain sustained release film coated theophylline pellets with optimal barrier properties according to the physico-chemical and pharmacokinetic requirements of the active substance. Heterogeneous film structure are generally obtained from blends containing an association of hard acrylic polymers (Eudragit® RS 30D, S 100) with the soft Eudragit® NE 30D when the drying temperature is lower than the minimum film forming temperature (MFT) of the hard acrylic polymers. The Tg and MFT values of the hard acrylic polymers are not modified in the presence of the soft polymer as shown by the thermograms of these blends which are generally characterized by two individual glassy transitions. Otherwise, a wide range of drug dissolution profiles can be obtained from film coated pellets either by using, in different proportions, the insoluble but readily permeable Eudragit® RL 30D in association with the less permeable Eudragit® RS 30D in order to obtain pH-independent permeability membrane.

Aqueous polymeric dispersion of Eudragit® RS 30D and Eudragit® RL 30D were used as the inert carriers to develop extended-release solid dispersion of nonsteroidal antiinflammatory drugs (Ho and Hwang, 1992). It was observed that the release rates of drugs decreased by increasing the amount of Eudragit® RS 30D in the formulation, on the other hand, increasing the amount of Eudragit® RL 30D in the solid dispersion would increase the release rate of drugs.

Toxicity of Acrylic Aqueous Dispersions

The polymeric substances are not absorbed from the digestive tract due to their high molecular weight. No acute toxicity is found by oral application even with the highest doses that could be applied. In feeding studies, daily dose of more than 200 mg/kg were tolerated for 6 months. The normal dose of polymer applied with a controlled release drug is in the range of 10-250 mg/day, which is only 0.1-4 mg/kg body weight in adult humans (Lehmann,1989).

Special Precautions in Application

During application of latexes, high shearing forces must be prevented. This mean that solid additives should be dispersed so that during mixing with the latex, only gentle stirring will be necessary ; high speed mixers are not suitable (Lehmann, 1989).

5. Diclofenac sodium

Diclofenac sodium is a synthetic, non-steroidal antiinflammatory and analgesic compound. It is widely used for relief of pain and inflammation.

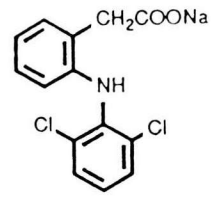


Figure 5 The structural formula of Diclofenac sodium.

Empirical formula $C_{14}H_{10}Cl_2NO_2Na$

Molecular weight 318.13

Chemical name
1. 2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid monosodium salt
2. [O-(2,6- dichloroanilino)phenyl]acetic sodium salt
3. Sodium[O-[(2,6-dichlorophenyl)amino]phenyl]acetate

Description odorless, white to off-white crystalline, slightly hygroscopic powder.

Melting point diclofenac sodium melts at 283 to 285°C.

Dissociation Constant (pKa) and Partition Coefficient

The pKa of diclofenac sodium in water is 4 and the partition coefficient in n-octanol/aqueous buffer pH is 13.4 (Adeyeye and Li, 1990).

Solubility

The aqueous solubility of diclofenac sodium is dependent on pH ; solubility is poor at low values of pH but when the pH rises above the pKa, rapid increases in solubility occur (Maitani, Nakagaki and Nagai, 1991 ; Herzfeldt and Kummel,1983).

The presence of cations (sodium ions or potassium ions) markedly affects the solubility of diclofenac sodium (Maitani, Nakagaki and Nagai, 1991). The addition of sodium or potassium chloride to the dissolution decreased the solubility of diclofenac sodium and slowed the dissolution rate, with the effect of sodium chloride being greater (Sheu et al., 1992).

The equilibrium solubility performed in various solvents at the room temperature (RT) are shown in Table 1 (Adeyeye and Li, 1990).

Table 1 The solubility of diclofenac sodium

Solvent	Temperature	Solubility (mg/ml)
Deionized water (pH 5.2)	RT	>9
Methanol	RT	>24
Acetone	RT	6
Acetonitrile	RT	<1
Cyclohexane	RT	<1
pH 1.1	RT	<1
pH 7.2 (phosphate buffer)	RT	6

Stability

Diclofenac sodium tablets film coated with polymers like acrylate and hydroxypropylcellulose were reported to be stable after storage for one week at 30°C in 80% relative humidity. 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 can be frozen for at least two weeks without degradation (Adeyeye and Li, 1990).

Buffered solution (pH 7.4) that contained diclofenac sodium dissolved in either β-cyclodextrin(β-CD) or hydroxypropyl-β-cyclodextrin (HP-β-CD) were prepared either in the presence or absence of oxygen and stored in the dark (Backensfeld et al.,1991). Solution from which oxygen had been removed were claimed to be more stable than those with oxygen. Although precipitation was observed in solutions without β-CD or HP-β-CD during a short storage time at 21°C, no loss of diclofenac sodium was reported after 520 days. At 71°C, in solutions (without oxygen) that contained diclofenac sodium alone, or with β-CD or with HP-β-CD, 24.7%, 30.4%, and 34.6% diclofenac sodium remained, respectively, after 207 days.

Use and Administration (Reynolds et al., 1993)

Diclofenac has analgesic, antipyretic, and anti-inflammatory properties; it is an inhibitor of cyclooxygenase.

Diclofenac is used mainly as the sodium salt for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, renal colic, acute gout, and following some surgical procedures. The usual dose by mouth is 75 to 150 mg of diclofenac sodium 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 per kg body-weight daily in divided doses.

Adverse Effects (Reynolds et al., 1993 ; Adeyeye and Li, 1990)

Due to the activity of inhibit cyclooxygenase, the most frequent adverse effects occuring with diclofenac sodium are gastro-intestinal disturbances; reactions range from abdominal discomfort, nausea and vomiting, and abdominal pain to serious gastro-intestinal bleeding or activation of peptic ulcer. Cyclooxygenase, PGE_2 has a cytoprotective effect on the gastric mucosa by inhibiting gastric acid secretion and by helping to maintain the gastric mucosa barrier. Other adverse effects include CNS-related side-effect; headache, dizziness, nervousness, tinnitus, depression, drowsiness and insomnia. Hypersensitivity reaction may occur occasionally and include fever and rashes.