CHAPTER II

LITERATURE REVIEW

I. General Principles of Spray Drying

Spray drying is a process widely used in the chemical, biochemical, paint, food, cosmetic and pharmaceutical industries. In the pharmaceutical field, spray drying is used in the preparation of heat-sensitive materials, spherical and free-flowing particles of drugs and excipients; and in granulating, microencapsulation, complex formation (Broadhead et al, 1992). Spray drying is also used to prepare the amorphous state for enhancing the dissolution rate of poorly soluble drugs (Kai et al, 1996; Yano et al, 1997 and Ueno et al, 1998), coating drugs to produce dust free powders and also to produce controlled release products (Leesawat, 1991).

1. The spray drying techique.

Spray drying provides the transformation of the feed from a fluid state into a dried particulate form by spraying the feed into a hot drying medium. Spray drying can only be done, however, when the dried final product behaves as non-sticky solid (not a liquid). The feed can either be a solution, emulsion, suspension or dispersion. It is atomized into millions of individual droplets by a nozzle or a rotary wheel. This process increases the surface area of the sprayed solution. The solvent, usually water, is vaporized immediately by the hot air.

This vaporization process rapidly removes heat so that the product is dried gently without thermally shocking it. The resulting dried product conforms to powders, granules or agglomerates within seconds, the form of which depends upon the physical and chemical properties of the feed and the dryer design and operation. Spray drying converts a liquid into a powder in a one-step, continuous particle-processing operation involving drying.

The spray drying consists of four process stages (Masters, 1985) :

i. Atomization of feed into a spray

ii. Spray-air contact (mixing and flow)

iii. Drying of spray (moisture / volatiles evaporation)

iv. Separation of dried product from the air

i. Atomization of feed into a spray

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 are of supreme importance in achieving economic production of top quality products. The atomization stage must create a spray for optimum evaporation conditions leading to a dried product of required characteristics. Rotary atomizers and nozzles are used to form sprays. With rotary atomizers centrifugal energy is utilized. There are two categorizes of rotary atomizers : (a) atomizer wheels, (b) atomizer discs. Wheel designs are available to handle feed rates up to 200 l/h. With nozzle atomization, pressure, kinetic or (less common) sonic energy is utilized.

There is a wide range of nozzle sizes and designs to meet spray drying needs. Feed capacities per nozzle are lower than per rotary atomizer, leading to nozzle duplication to meet high feed-rate requirements. The selection of the atomizer type depends upon the nature of the feed and desired characteristics of the dried product. In all atomizer types, increased amounts of energy available for liquid atomization result in sprays having smaller droplet sizes. If the available atomization energy is held constant but the feed rate is increased, sprays having larger droplet sizes will result.

The degree of atomization depends also upon the fluid properties of the feed material, where higher values of viscosity and surface tension result in larger droplet sizes for the same amount of available energy for atomization. Where a desired particle size distribution can be met by either a rotory or a nozzle atomizer, the rotary atomizer is normally selected due to its greater flexibility and use of operation. Rotary atomizers are used to produce a fine to medium-coarse product (mean size 30-120 μm). Coarser sprays can be produced , but medium-to-large industrial capacity would require a very large diameter chamber for drying. Nozzle atomizers are used to produce a coarse product (mean size 120-250 μm).

ii. Spray-air contact (mixing and flow)

The manner in which spray contacts the drying air is an important factor in spray dryer design, as this has great bearing on dried product properties by influencing droplet behavior during drying. Spray-air contac is determined by

the position of the atomizer in relation to the drying air inlet, many positions are available. The spray can be directed into hot air entering the drying chamber.

There are four types of product-air flow in spray dryers : co-current flow, countercurrent, combined co-/countercurrent and disk atomizer (rotary wheel). Product and air pass through the dryer in 'co-current' flow, i.e. they pass through the dryer in the same direction. This arrangement is widely used, especially if heat-sensitive product are involved. Spray evaporation is rapid, the drying air cools accordingly, and evaporation times are short. The product is not subject to heat degradation. Product temperature is low during the time the bulk of the evaporation takes place, as droplet temperature approximate to wet-bulk temperature levels. When the desired moisture content is being approached, each particle of the product does not rise substantially in temperature as the particle is then in contact with much cooler air. In fact low temperature conditions prevail virtually throughout the entire chamber volume, in spite of very hot air entering the chamber.

Alternatively, the spray can be contacted with air in 'countercurrent' flow. Spray and air enter at the opposite ends of the dryer. The arrangement offers dryer performance with excellent heat utilization, but it does subject the driest powder to the hottest air stream. It readily meets granular powder requirements of non-heat-sensitive products. Countercurrent flow is used with nozzle atomization, since an upward streamline flow of drying air reduces the

downward velocity of the large droplets in the spray, permitting sufficient residence time in the drying chamber for completion of evaporation.

There are dryer designs that both 'cocurrent' and 'countercurrent'.i.e., mixed flow dryers. In this type, coarse free flowing powder can be produced in dryer chambers of relatively small size, but the powder is subjected to higher particle temperature. About 'disk atomizer' flow, the material to be sprayed flows onto a rapidly rotation atomizing disk and is converted to a fine mist. The drying air flows in the same direction. The product is treated with care, just as in the cocurrent flow method.

iii. Drying of spray (moisture / volatiles evaporation)

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. The temperature at the droplet surface approximates to the wet-bulk temperature of the drying air. Evaporation takes place in two stages. At first there is sufficient moisture within the droplet maintains saturated surface conditions and as long as this lasts, evaporation takes place at a constant rate. This is termed the constant rate period or first period of drying. When the moisture content becomes too low to maintain saturated conditions, the so-called critical point is reached and a dried shell forms at the droplet surface. Evaporation is now dependent upon the rate of moisture diffusion through the dried surface shell. Thus a substaintial part of

the droplet evaporation takes place when the droplet surfaces are saturated and cool.

iv. Separation of dried product from the air

Product separation from the drying air follows completion of the drying stage, when the dried product remain suspended in the air. Two systems are used to recover the product. System (1), primary separation of dried product takes place at the base of the drying chamber. During operation, the majority of product falls to the base of the chamber, while a small fraction passes out entrained in the air and is recovered in the separation equipment. With this system, a classification of powder is achieved, as the coarse particles are recovered at the chamber base and the finer particles from the separation until.

This form of powder classification may be useful, but normally the two powder off-takes are combined and conveyed to a single discharge area. System (2), total recovery of dried product takes place in the separation equipment. This system places great importance on the separation efficiency of the equipment, but the system is often utilized, as it does not need a product-conveying system. Separation of dried product from the air influences powder properties by virtue of the mechanical handling involved during the separation stage. Excessive mechanical handling can produce powders having a high percentage of fines.

2. Effects of processing parameters

To meet the requirement of the dried product, close attention must be given to all four stages, since each stage affects the properties of the product to some degree. Atomization technique and feed properties have a bearing on particle size distribution, bulk density, appearance, and moisture content. Many operation variables associated with atomization and the drying operation offer means of altering the characteristics of the dried product. The optimization of the physical and chemical characteristics of spray dried materials often involves the comparison of the processing parameters such as inlet temperature, air volume, or nozzle. The effect of these and other processing parameters on coated theophylline particles was studied by Wan, Heng and Chia (1991).

The parameters varied included spray nozzle size, inlet drying temperature, drying air flow rate, feed spray rate, and atomizing pressure. Results showed that the properties of coated theophylline particles were affected by these parameters. A decrease in the air-to-liquid diameter ratio of the nozzle, faster air flow rate, and increased inlet temperature improved particle flow properties. High inlet air temperature produced particles with a slower dissolution rate, and high feed spray rates produced poorly formed particles due to ineffective atomization. An increase in the energy available for atomization will reduce particle size. Particle size is usually increased as the feed concentration or viscosity increase (Masters, 1985). Masters reported that surface tension has a minimal effect on particle size, although reported on increase in particle size with an increase in feed surface tension and density as

well as with concentration and viscosity. If the feed rate is increased, particle size will again increase.

The effect of inlet temperature was also studied by Yamaguchi et al. (1992), it was found to affect glass formation of amorphous 4-0-(4-methoxyphenyl) acetyltylosin (MAT). By changing the inlet temperature of the spray dryer, different kinds of glassy state were obtained for MAT. Inlet temperature has also been used to compare spray-dried microsphere formulation. In the work performed by Bitz and Doelker (1996), the decrease of inlet temperature from 60^{o}C to 50^{o}C led to increased residual methylene chloride concentration for polylactide (PLA) and polylactide-co-glycolide (PLGA) microspheres Takena et al. (1982), also investigated inlet temperature effects. Theophylline-ethylenediamine complexes were formed by spray drying at varying inlet temperatures. The solubility of theophylline was increased three-to-five fold due to the complex formation. However, solubility decreased with increasing inlet temperatures and atomizer rotation speeds.

3. Applications of spray drying

Spray drying is useful for the processing of pharmaceuticals since it offers a means for obtaining powders with predetermined properties, such as particle size and shape. Spray dried powders are usually approximately spherical with a narrow size distribution and are usually hollow. 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, porosity, moisture content, flowability, stability, dispensability, friability and retention of activity (Master, 1985). In addition a number of formulation processes can be accomplished in one step in a spray dryer; these include encapsulation, complexation and even polymerization.

Microencapsulation is often used to provide controlled release of a protein or drug. Several studies have utilized spray drying as a method for controlled release microencapsulation. Wan, Heng and Chia (1992), found theophylline release to be dependent on the hydrophilicity of the polymer. The most hydrophilic polymer, carboxymethylcellulose, sodium carboxymethylcellulose, gelled faster and retarded the drug release the most. The size and cohesiveness of the particles were also a function of the polymer and affected drug release. Smaller, more cohesive particles tended to agglomerate and delay drug release.

Controlled release solid dispersion formulation of diclofenac sodium containing either ethylcellulose, Eudragit RS100, chitosan, hydroxypropylemethylcellulose (HPMC) or carbomer 934 as a single carrier and ethylcellulose-chitosan as combined carriers were spray dried. Among the combinations evaluated, the slowest dissolution was attained with the chitosan solid dispersion containing 3:7 drug:carrier ratio, and the combined carrier showed dissolution than either polymer alone.

Broadhead, Edmond and Rhodes (1992) spray dried diluted emulsions in which volatile ester (the core material) were the dispersed phase, and the coating material (gum arabic, sodium alginate or gelatin) was the continuous phase. It was found that an increase in the solid concentration of the feed solution steply increased the retention of the volatile components. This could be explained by a reduction in the time for a crust to form around the drying droplet. Increasing the emulsion viscosity also increased retention up to a maximum beyond which it decreased again.

The explanation for this phenomenon was that initially increasing viscosity slows the movement of the volatiles to the surface of the drying microcapsules and reduces internal mixing, thereby minimizing the loss of volatiles. However a further increase in viscosity decreases retention due to an increased residence time in the atomizer and difficulties in droplet formation from a viscous solution. Retention also increased by increasing the air inlet temperature which could be due to a reduction in the time taken for capsules to form and hence in the time for losses to occur.

Two common biodegradable polymers used in microencapsulation are PLA and PLGA. The efficiency of spray drying as a method for PLA and PLGA microsphere preparation was investigated using vitamin D_3 as a model lipophilic drug by Pavanetto et al. (1993). The spray drying process was tailored to each polymer, and the microspheres obtained were evaluated for shape, size, drug content and polymer influence on these characteristics. Polymer type, polymer molecular weight, and polymer concentration were

shown to be the greatest contributing factors to these characteristics. In vitro dissolution testing revealed different release profiles depending on polymer type and microsphere morphology.

Non-crosslinked and crosslinked chitosan microspheres were prepared by a spray drying method. The microspheres so prepared had a good sphericity and a smooth but distorted surface morphology. They were positively charged. The particle size ranged from 2 to 10 μm. The size and zeta potential of the particles were influenced by the crosslinking level. With decreasing amount of crosslinking agent (either glutaraldehyde or formaldehyde), both particle size and zeta potential were increased. Preparation conditions also had some influences on the particle size. DSC studies revealed that the H_2–antagonist drug cimetidine, as well as famotidine was molecularly dispersed inside the microspheres, in the form of a solid solution. The release of model drugs (cimetidine, famotidine and nizatidine) from these microspheres was fast, and accompanied by a burst effect (He, Davis and Illum, 1999).

Sugimori et al. (1990) compared high speed mixing, fluidized bed granulation and spray drying in the production of acetaminophen and ascorbic acid granules. In both cases, spray drying produced the smallest granules. The tensile strength of tablets produced from the different types of granules was found to be more dependent on the amount of water used in granulation than on the granulation method. However the spray drying is useful method for mass production of granules, since it makes continuous granulation possible.

Acrylic resin was use for the preparation of spray dried controlled release microcapules containing theophylline anhydrous or sulfamethazine sodium as model drugs with dibutylphthalate being used as the plasticizer. Dissolution results of tablets compressed from the microcapsules showed successful controlled release with advantages over a matrix system. Takeuchi et al. (1989) prepared sustained release and enteric theophylline tablets by directly compressing spray dried microcapsules produced using different types of Eduragit resins. Complete enteric properties were observed for tablets made from Eudragit L-30D or L100-55 microcapsules at a drug:polymer ratio of 1:3 while a sustained release profile was observed for tablets made from microcapsules containing 2% - 40% Eudragit E-30D.

4. Advatages of spray drying

Spray drying has many advantages, which are as follows :

1. Continuous in operation.
2. Adaptable to full automatic control.
3. Dried product specifications met through dryer design and operational flexibility.
4. Applicable to both heat-sensitive and heat-resistant materials.
5. High thermal efficiency, especially at high inlet drying temperatures and large temperatures drops over drying chamber.
6. Feedstocks in solution, slurry, thixotropic paste or melt form can be handled if pumpable.
7. Corrosive and abrasive feedstocks can be readily handled.

8. Individual dryer sizes are availble to meet capacity demands of a few kg/h feed to 150 tonnes / h or more feed.
9. Operator requirement the same for both small and large dryers, hence spray drying is basically a high-volume system with low labour cost.
10. One operator can handle more than one automatically controlled spray dryer, if located together in one complex.
11. Designs are available to handle (a) evaporation of organic solvents without explosion / fire risks, (b) powders that form potentially explosive mixtures in air, (c) products that create odour during drying, (d) toxic products, (e) products requiring aseptic / hygienic drying conditions.

II. Controlled release delivery system

Controlled release technology can solve a variety of problems that have in common the application of an active compound to a system in such a way to accomplish a specific purpose while avoiding certain other possible responses. An optimally formulated and bioavailable controlled release product can produce effective concentrations of drug in blood or plasma over an extended time period. To achieve and maintain the drug concentration in the body within the therapeutic range required for a medication, it is often necessary to take this type of drug delivery system several times a day.

A number of technical advancements have been recently made in developing new techniques for drug delivery. These techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the delivery of drug to a tissue. These advancements have already let to the development of several novel drug delivery systems that could provide one or more of the following benefits :

1) Controlled administration of a therapeutic dose at a desirable delivery rate.
2) Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment.
3) Maximization of efficacy-dose relationship.
4) Reduction of adverse side effects.
5) Minimization of the needs for frequent dose intake.
6) Enhancement of patient compliance.

1. Technical advancements in controlled release delivery system

The technical advancements can be categorized as follows :

i. Controlled release by diffusion process

1) Membrane permeation-controlled drug delivery
2) Matrix diffusion-controlled drug delivery

3) Microreservoir dissolution-controlled drug delivery

ii. Controlled release by modulation process

1) Osmotic pressure-modulated drug delivery

2) Hydrodynamic pressure-modulated drug delivery

3) Vapor pressure-modulated drug delivery

4) Mechanical force-modulated drug delivery

5) Magnetics-modulated drug delivery

6) Ultrasonic wave-modulated drug delivery

7) Iontophoresis-modulated drug delivery

8) pH-modulated drug delivery

9) Ion-modulated drug delivery

10) Swelling-modulated drug delivery

11) Hydrolysis-modulated drug delivery

12) Enzyme-modulated drug delivery

The following discussion provides a brief overview only controlled release by diffusion process.

2. Controlled release by diffusion process

1) Membrane permeation controlled drug delivery

In this type of controlled-release drug delivery system, a drug formulation is totally or partially encapsulated in a drug reservior compartment whose drug-releasing surface is covered by a rate-controlling polymeric

membrane. The drug reservior can be drug solid particles, a dispersion of drug solid particles, or a concentrated drug solution in a liquid or solid type dispersing medium. The polymeric membrane can be fabricated from a homogeneous or a heterogeneous nonporous polymeric material or a microporous or semipermeable membrane. The encapsulation of drug formulation inside the reservoir compartment can be accomplished by molding, capsulation, microencapsulation, or other techniques. Different shapes and sizes of drug-delivery system can be fabricated.

2) Matrix diffusion controlled drug delivery

In this type of controlled release drug delivery system, the drug reservoir results from the homogeneous dispersion of drug particles in either a lipophilic or a hydrophilic polymer matrix. The drug dispersion in the polymer matrix is accomplished either by (1) blending a dose of finely ground drug particles with a viscous liquid polymer or a semisolid polymer, followed by crosslinking of polymer chain or (2) mixing drug solids with a melted polymer at an elevated temperature. The resultant drug-polymer dispersion is then molded or extruded to form drug-delivery devices of various shapes and sizes designed for specific application. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation in a mold at an elevated temperature an/or under vacuum.

3) Microreservoir dissolution controlled drug delivery

In this type of controlled release drug delivery system, the drug reservoir is a suspension of drug solid particles in an aqueous solution of water-miscible polymer, such as polyethylene glycol. This forms a homogeneous dispersion of many discrete, unleachable, microscopic drug reserviors in biocompatible polymer, such as silicone elastomer. The microdispersion is accomplished by high-energy dispersion technique. Different shapes and sizes of drug delivery devices can be fabricated from this microreservoir-type drug delivery system by molding or extrusion techniques. Depending upon the physicochemical properties of drugs and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and the rate of drug release.

2. Applications of controlled drug release system

In controlled release systems, a drug or other bioactive agent is incorporated into a carrier, generally a polymeric material. The rate of release of the substance is determined by the properties of the polymer itself as well as environmental factor (such as the pH of body fluids). Beten and Moes (1994) obtained controlled release dosage forms of dipyridamole as a model drug practically insoluble in pH 5. The coevaporates were prepared by the solvent method using enteric and insoluble acrylic polymers as well as their mixtures in different proportions. The in vitro dissolution test results were dertermined by

the USP XXII paddle method at different pH values during a period of 8 h. These results showed that the progressive pH-dependent release of dipyridamole could only be achieved by blending enteric and insoluble polymers. Dipyridamole formed a molecular dispersion with Eudragit S. The dissolution profiles of coevaporates prepared with Eudragit S , L and L 100-55 showed that it was possible to inhibit to a great extent the dissolution of dipyridamole in acidic medium and to enhance it in fluid media of higher pH values despite its low solubility at these pH values. In contrast, Eudragit RL and RS had no effect whatsever on drug release. On the other hand, it was shown that the S/L, S/L 100-55, RS/S/L 100-55 ratios could be optimized to modulate the release profile of dipyridamole.

The release of the drug from solid dispension which was prepared by evaporation after dissolving or suspending a water-soluble drug into an organic solvent was studied. Oxprenolol hydrochloride was used as a model water soluble drug. Eudragit RS, methylcellulose, ethylcellulose, polyvinylpyrrolidone, hydroxypropyl cellulose and pullulane were used as the polymers. The polymers and oxprenolol hydrochloride were suspended in or dissolved into ethanol under heating, and then ethanol in these solutions was evaporated to solid dispersion.

Solid dispersion granules were prepared by grinding and sieving the solid dispersion obtained. As a result, it was clarified that in a solid dispersion granules composed of 25% oxprenolol hydrochloride, 70% ethylecellulose and

5% hydroxypropyl cellulose, the dissolution behavior of oxprenolol hydrochloride from the granules was of a leaching type for the matrix and was not affected by pH. Furthermore, various dissolution behaviors could be obtained by changing the particle size and the ratio of the polymer in the granules. These results suggested that this granulating method by the evaporation of the solvent was useful in preparing a sustained release preparation (Yuasa et al., 1991).

Yuasa et al. (1993) prepared the solid dispersion by the evaporation of ethanol after dissolving into ethanol a water soluble oxprenolol hydrochloride (OXP), four grades of water soluble hydroxypropyl cellulose (HPC), both having different molecular weights. The precise control of the release rate of a water soluble medicine by applying the difference in the molecular weight of polymer was attempted. The pore size distribution in solid dispersion granules was measured before and after the dissolution test to clarify the mechanism of medicine release from the granules when the molecular weights of polymers were different. The release rate of OXP from the granules of the OXP-HPC system decreased as the molecular weight of HPC increased. The release behavior of OXP in the OXP-EC system was scarcely affected by the molecular weight of EC. However, in the OXP-EC-HPC system, the release rate markedly decreased with a larger molecular weight of EC. The decrease in the release rate of OXP in the OXP-EC-HPC system was caused by the increase in the ratio of OXP dissolving via the latter route, occurring with a larger molecular weight of EC. These results suggested that it is feasible to precisely control the release of EC. These results suggested that it was feasible to precisely control the

release of a water soluble medicine by varying the molecular weight of the polymers in the solid dispersion.The development of a loading method of a water-soluble drug using aqueous binding solution to produce microgranules that were then coated with an aqueous ethylcellulose dispersion to sustain drug release was described. The results , in terms of drug , showed that besides the fluidized bed parameters, the amount of drug dissolved in the binder solution played an important role in obtaining a satisfying result during the spraying process. Thus, it seemed necessary to determine the critical concentration above which the materials started to adhere to the interior of the fluidization column, and the possibility of drug layering onto carrier material is aggravated. ANOVA of the time parameter for release of 63.2% of total drug (td) value showed significant influence of ethylcellulose (Aquacoat ECD-30) and dibutylsebacate concentration on diphenhydramine hydrochloride release. The dissolution rate decreased with an increase in polymer concentration.

Coevaporates of paracetamol and rifampicin with Eudragit polymer of different natures were prepared (Ammar and Khalil, 1997). Determination of dissolution rate of these coevaporates in dissolution media simulating those of the gastrointestinal tract (GIT) revealed that the release rate of paracetamol was retarded from all the coevaporates studied. In this respect, Eudragit L100-55 showed the highest sustainment of drug release, while Eudragit E100 showed the lowest. Conversely, the release of rifampicin from its coevaporated with the anionic Eudragit S100 polymer was more retarded than the corresponding coevaporate with zwitterionic Eudragit RL100 or from coevaporates with equal

mixtures of the two polymers. Increasing the polymer weight fraction in rifampicin coevaporates with Eudragit S100 up to 0.5 resulted in a corresponding decrease in the dissolution rate. However, beyond this weight fraction, the polymer effect on the dissolution rate of the drug becames minimized. The results confirmed that the process of dissolution of the two drugs from their coevaporates was diffusion-controlled release process.

Lin and Kao (1991) prepared sodium diclofenac coated microcapsules by a spray drying technique with Eudragit L30D 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 tabletting, and the tablets all exhibited enteric-coated release properties. The weight ratio of Neocel to Flo-starch plays an important role in controlling the release of sodium diclofenac from enteric tablets. The 1:1 weight ratio of Neocel to Flo-starch was more suitable for designing the microdispersed sodium diclofenac enteric coated tablets.

The authors reported further study about the effect of different coating polymer by spray drying process (Wan, Heng and Chia, 1992). Various polymers; hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylecellulose (NaCMC) were evaluated for their spray-coating properties. The drug release from the coated products was dependent on the

hydrophilicity of the polymer. NaCMC, which was more hydrophilic, gelled faster and retarded the drug release more effectively. HPMC and MC produced products with similar dissolution profiles and flow properties. Spray coating with HPMCAS was unsuccessful. The polymer also affected the size and cohesiveness of the products.

Controlled release theophylline matrices containing cellulose derivative (ethylcellulose, hydroxypropylmethyl cellulose, hydroxy propylmethyl cellulose phthalate) were also prepared by spray drying technique (Leesawat, 1991; Kulvanich and Leesawat, 1991). The types and amounts of matrix additives affected the physical properties of co-spray dried powders. The matrix of theophylline 300 mg. With 3% ethylcellulose and 25% lactose exhibited the most satisfactory release profiles.

III. The release mechanisms of controlled release

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

1) Zero-order release mechanism
2) First-order release mechanism
3) Square-root-time release mechanism

3.1 Zero-order release mechanism

An ideally controlled release device is one that 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 the mass of active agent release is M_t. This mechanism of release is called zero-order release model.

3.2 First-order release mechanism

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

$$\frac{dM_t}{dt} = k_1(M_0-M_t) \qquad (2)$$

Where M_0 was the mass of agent in the device at t=0. On rearrangement, this gives the following :

$$\frac{dM_t}{dt} = kM_0 \exp^{-k_1 t} \qquad (3)$$

In first-order mechanism, 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 suggested that drug release from most controlled release matrices could be described by apparent first order kinetics, thus :

$$A_t = A_o e^{-k_1 t} \qquad (4)$$

Where k_1= first order release constant

A_o= initial amount of drug

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

Simplifying and taking the logarithm of Equation 8 yielded

$$\text{Log } A_t = \log A_0 - \frac{k_1 t}{2.303} \qquad (5)$$

First order mechanism can be predicted by ploting the logarithm of the percentage of drug remaining against time. If first order mechanism, linear relationships were obtained. The initial curvature of the plot may be indicated that first order mechanism was operative.

3.3 Square-root-time release mechanism (Higuchi model)

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

$$\frac{dM}{dt} = \frac{k}{t^{1/2}} \qquad (6)$$

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

The release mechanism of this type can be described by Higuchi equation as (Higuchi T., 1963)

$$Q = \frac{[D\varepsilon(2A-\varepsilon C_s)C_s t]^{1/2}}{\tau} \qquad (7)$$

Q = weight in grams of drug release per unit surface area

D = diffusion co efficient of drug in the release medium

ε = porosity of the matrix

τ = tortuosity of matrix

C_s = solubility of drug in the release medium

A = centration of drug in the tablet, expressed as g/ml

The assumption made deriving from Equation 3 is as follows :

1. A pseudo-steady state is maintained during the release.
2. $A >> C_s$, i.e., excess soluble is present.
3. The system is in a 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

$$Q = k_H t^{\frac{1}{2}} \qquad (8)$$

Where k_{H} was 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 the release from a single face, it may be used to desired diffusion-controlled release from all surface matrix. In order to verify further that the release followed the Higuchi model, Higuchi equation was converted into logarithmic form as

$$\text{Log } Q = \log k_H + \tfrac{1}{2} \log t \qquad (9)$$

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

IV. Nifedipine

1. Pharmaceutical properties of nifedipine

Chemical structure :

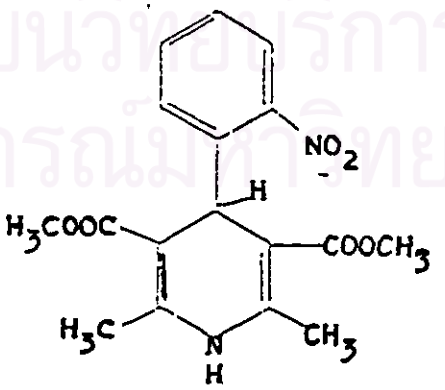

Figure 1 : Nifedipine structure

Empirical formula : $C_{17}H_{18}N_2O_6$

Molecular weight : 341.34

Chemical name : Dimethyl 1,4-dihydro-2,6 –dimethyl 1-4 –
(2- nitrophenyl) –3,5 –pyridine dicarboxylate
: 3,5 –pyridinedicarboxylic acid 1,4-dihydro-2,6
dimethyl-4-(2-nitrophenyl)-dimethyle ether

Description : A yellow crystalline powder

Melting point : 171 ^{o}C to 175 ^{o}C

Solubility : Easily soluble in acetone , chloroform , less soluble in ethanol, practically insoluble in water. Very light sensitive in solution (Windholz et al., 1983).

Nifedipine, an oral calcium-blocking agent is widely used clinically as a coronary vasodilator and for the treatment of hypertension, angina pectoris and other cardiovascular disorders (Sorkin, Clissold and Brogden, 1985). It shows very slightly water solubility (11 mcg/ml at 37 ^{o}C in distilled water) and exhibits poor dissolution characteristics (Kohri et al., 1987). Oral dose of nifedipine soft capsules is rapidly absorbed from the GI tract approximately 90%. Only 65-75% of the oral dose reaches systemic circulation as unchanged drug since nifedipine is metabolized on first pass through the liver. Peak serum concentrations are reached within 0.5-2 hours after oral administration. The therapeutic range in plasma is 25-100 mcg/l.

2. Photostability of nifedipine

Nifedipine is a relatively sensitive compound, it has an aromatic nitro group which is often photoactive, degraded rapidly in sunlight. The nitro group is reduced to nitroso while the ring is oxidised. The oxidizing agents yield predominantly two degradation products after exposure to sunlight (A) as shown in Figure2 but under UV irradiation the nitroso group is reoxidized to give B.

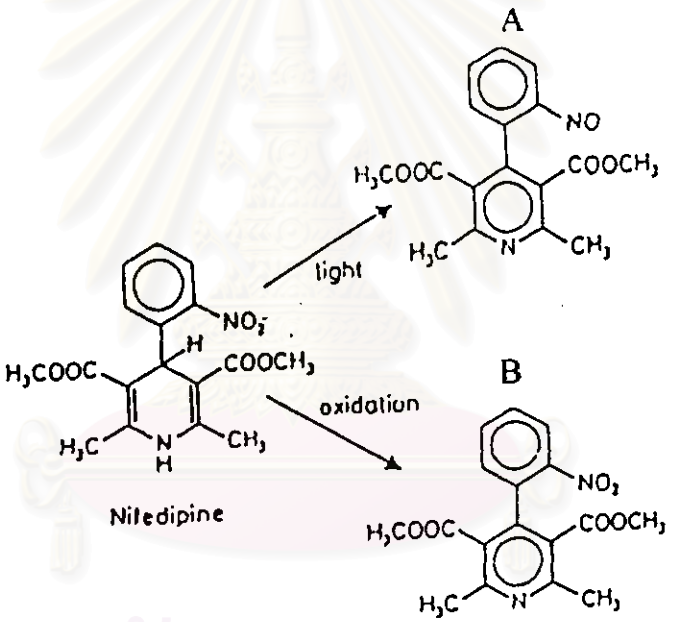

Figure 2 Nifedipine degradation under exposure to sunlight and UV light.

The decomposition of nifedipine in solutions under the influence of light intensity is remarkably high. This makes it impossible to work with the nifedipine solution in daylight on account of considerable decomposition. Therefore all experimental work with nifedipine solutions should be performed

under red light. Yellow light of sodium lamp is also suitable, as yellow or redlight are not absorbed by nifedipine and consequently has no influence on its decomposition.

Nitrosophenylpyridine and nitrophenylpyridine derivatives are photodegradation products from exposure of nifedipine solution to daylight. Nifedpine crystals are more stable than solutions, because the light effect is a surface phenomenon. There was a report on which photodegradation of nifedipine in the crystalline state and in solution were compared. Within 40 minutes, 20% of the crystalline nifedipine decomposed. During the next 80 minutes no further degradation, but nifedipine solution decomposed completely during this period (Thoma and Klimak, 1991). In terms of the influence of the wavelength to absorption spectrum of nifedipine, shows that the solution is stable down to a wavelength of 475 nm. Photolysis starts exactly at the point where nifedipine absorption begins at 450 nm. Photoysis increases considerably up to about 400 nm. Nifedipine is thus completely degraded by light in the rather long–wavelength region within 10 minutes.

3. Modification of nifedipine release

Nifedipine exhibits limited water solubility; as a result, it shows poor bioavailability (Sugimoto et al., 1982; Kohri et al., 1987). Moreover, because of short elimination half-life of 3.43 hrs (Foster et al., 1983), the plasma nifedipine levels fluctuate markedly following administration and its

antihypertensive effect lasts only for a few hours. It is, therefore, important to improve the dissolution and develop a sustained release form of nifedipine to improve the therapeutic efficacy.

Nifedipine–polyethylene glycol solid dispersion were prepared by melting or fusion method in order to improve nifedipine solubility in the aqueous body fluids. The dissolution rate of the drug was markedly increased in these solid dispersion systems. The increase in dissolution was a function of the ratio of drug to polyethylene glycol used and the molecular weight of polyethylene glycol. The dissolution rate was compared with 10% w/w physical mixture of drug with polyethylene glycol (Save and Venkitachalam, 1992).

β-cyclodextrin and its family have also shown an improvement of nifedipine dissolution rate. Acarturk, Kislal and Celebi, 1992 studied that interaction of nifedipine with water soluble gelatin, egg albumin and β-cyclodextrin in solid state prepared by kneading method. β-cyclodextrin and water soluble gelatin were found significantly increased in the dissolution rate of nifedipine from the system. This may be caused by the solubility effect. It was reported that the inclusion complex of nifedipine and β-cyclodextrin had not been completely formed in the solid state.

Wang et al. (1992) designed a double-layer tablet to modify the release rate of nifedipine. Amorphous nifedipine powders prepared by spray drying with 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD) and nonionic surfactant

HCO-60 were employed as a fast release portion to attained on initial rapid dissolution of nifedipine. Hydroxypropylcelluloses (HPC) with different viscosity grades (type L, M, and H) were used for a slow-release portion to provide and appropriate sustained-release. Taking into account of the physiological conditions of the gastrointestinal tract (pH and motility), an optimal formulation of the double layer tablet was obtained by changing the mixing ratios of each component. For example, the tablet consisting of HP-β-CyD with 3% HCO-60 / (HPC-L:HPC-M) in the weight ratio 1/2 (1:1) provided a sufficient slow release of the drug over a wide pH region following an initial rapid dissolution. The present results suggest that a combination of HP-β-CyD, HCD-60 and HPC can serve as a modified-release carrier for poorly water soluble nifedipine.

Nifedipine loaded albumin microspheres were prepared by a chemical cross-linking method to develop a sustained release form. Albumin microspheres prepared with different amounts of cross-linking agent (glutaraldehyde) indicated different release kinetics. Increasing the glutaraldehyde concentration decreased the release rate of nifedipine from albumin microspheres as a result of formation of greater structural strength and more slightly texture. Besides, albumin microspheres gave an adequate fit to either zero order or spherical matrix model, depending on the extent of cross-linking reaction (Chauo et. al, 1996).

Guyot and Fawaz (1998) prepared nifedipine–loaded microspheres of cellulosic polymers by a solvent evaporation method. It appeared from obtained results that mean diameter of microspheres increased with the viscosity of the dispersed organic phase. Drug incorporation efficiency in ethylcellulose microsphres decreased when organic phase viscosity was increased. In the other hand, it was noted that drug loading efficiency could be enhanced by decreasing ethylcellulose/hydroxypropyl cellulose (EC/HPC) or ethylcellulose/hydroxypropyl methylcellulose (EC/HPMC) ratios. DSC thermograms and X-ray diffraction patterns indicated that nifedipine was incorporated in an amorphous state in the microspheres. Microspheres formulation exhibited slow and S-shaped release profiles with poor dissolution efficiency.

However, release from microspheres of EC/HPC and EC/HPMC was slower but more regular than that from microspheres of EC. It was also found that drug release was related to organic phase viscosity. Thus, in the case of EC, the higher was the viscosity of the organic phase, the slower was the release kinetic. Whatever the microspheres formulation, release pattern did not exhibit any burst effect indicating the absence of free nifedipine of crystals on the surface of the microspheres. Nifedipine release from microspheres was well described by combined kinetics (zero-and first-order kinetics or zero-order and Higuchi square-root kinetics).

Nifedipine and its solid dispersion in polyvinylpyrrolidone-microcrystalline cellulose (PVP-MCC), hydroxypropyl cellulose-microcrystalline cellulose (HPC-MCC) were microencapsulated with cellulose acetate (Chowdary and Ramesh, 1995). Hydroxypropylmethyl cellulose-microcrystalline cellulose (HPMC-MCC) were microencapsulated with Eudragit RLPM (Chowdary and Sankar, 1997) by emulsion solvent evaporation method. The microcapsules are spherical, discrete and free flowing. Nifedipine as such and its microcapsules gave very slow release because of its highly crystalline nature and poor solubility. Solid dispersions in PVP-MCC, HPC-MCC and HPMC-MCC gave fast and rapid dissolution of nifedipine. When solid dispersions were microencapsulated, a slow controlled complete release over a period of 12 hours was observed from the resulting microcapsules. Drug release depended on the proportion of PVP-MCC, HPC-MCC and HPMC-MCC in the solid dispersion used as core, coat:core ratio and size of the microcapsules and the release was pH independent. Drug release was governed by diffusion rate and followed first-order kinetics

V. Polymethacrylates

1. Pharmaceutical properties

Nonproprietary Name:USP/NF:Ammonio methacrylate copolymer

Synonyms : Eudragit ; polymeric methacrylate

Chemical Name : -Poly (ethylacrylate, methylmethacrylate, trimethyl ammonioethyl methacrylate chloride) 1:2:0.2 (Eudragit RL 100)

-Poly (ethyl acrylate, methyl methacrylate, trimethyl ammoniocthyl methacrylate chloride) 1:2:0.1

(Eudragit RS 100)

Empirical Formula :Type A (Eudragit RL)

Type B (Eudragit RS), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymer of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups.

Molecular Weight : approximate 150,000

Structural Formula :

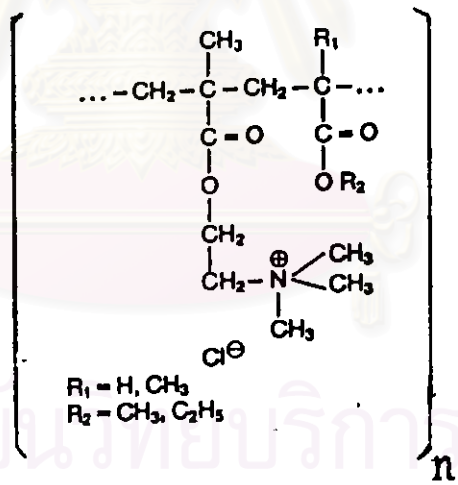

Figure 3 Eudragit structure

Description : Eudragit RL and RS copolymer synthesized from acrylic acid and methacrylic acid esters with Eudragit RL (type A) having 10% of functional quaternary ammonium groups and Edragit RS (type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as

salts and give rise to pH-independent permeability of the polymers. Both polymers are water insoluble, and films prepared from Eudragit RL are freely permeable to water, whereas films prepared from Eudragit RS are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propane-2-ol/acetone (60:40). Solution are colorless or slightly yellow in color, and may be clear or slightly turbid ; they have an odour characteristic of the solvents. Solvent-free granules (Eudragit RL100 and Eudragit RS 100) contain $\geq$ 97% of the dried weight content of the polymer.

2. Pharmaceutical applications of Eudragit RL and RS 100

Furosemide-Eudragit RL100 sustained release microcapsules were prepared using phase separation technique (Al Gohary and Al Gamal, 1991). In Sorensen phosphate buffer pH 7.4, a good sustained release was indicated. Increasing drug to polymer ratio resulted in a decrease in the release, while increased release obtaine by increasing the pH of the dissolution medium. On the other prepared sulphamethizole loaded Eudragit RL100 microspheres by emulsification solvent evaporation technique. Drug release dependent on pH of the dissolution medium pH-dependent release from pH 1.1 to 4.6 was rationalized by the solubility differences of the drug. Although drug-polymer interaction and drug degradation were not evident in the microspheres dosage form, significant drug-polymer interaction occurred in dissolution medium having pH 7.4 leading to retarded drug release.

Sustained release tablets of indomethacin were prepared using Eudragit RS. Two types of formulation were considered, one was a directly compressed powder mixture which produced a matrix system, and the other was prepared by granulation, such that the drug was to some extent scaled within a cast film of the polymer. The drug release from the matrix was directly proportional to the concentration of the polymer that was used. Drug release from the granulated system was much slower than from the directly compressed matrix (Efentakis and Buckton, 1990).

El-Mahrouk et al. (1993) developed a controlled release oral drug delivery system of indomethacin by using nonpareil seeds as a matrix system. These seeds were coated with different concentrations of drug release controlling materials via Eudragit RL 100 and Eudragit RS 100, and beeswax. The particle size of the seeds and the concentration as well as the type of the drug release controlling Eudragits has a pronounced effect on the release rate profiles. All types of formulation showed release rate patterns which can be described by both first-order and diffusion controlled mechanisms.

A polymeric matrix system for controlled drug release was developed employing the model drug, salicylic acid and chlorpheniramine maleate with Eudragit RL and RS. The presence of an interaction between the drug and polymer was found. Eudragit polymers interacted with acidic compounds in a manner similar to ion exchange resins which contain quaternary ammonium groups, as found in these polymers. No evidence of new covalent chemical

bond formation between the drug and polymer was shown. The dissolution release profiles were directly correlated to the drug-polymer interaction. Decreases in pH or increase in ionic strength which minimized ionization of the anionic drug resulted in decreased drug sorption and increase drug release from the matrix films (Jenquin and McGinity, 1994).

VI. Povidone

1. Pharmaceutical properties

Nonproprietary Names : Povidone

Synonyms : Kollidon; Plasdone ; poly [1-(2-oxo- pyrrolidinyl) ethylene]; polyvidone, polyvinylpyrrolidone; PVP; 1- vinyl–2 pyrrolidinone polymer.

Chemical Name : 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula : $(C_6H_9NO)_n$

Molecular Weight : 50,000

Structural Fomula :

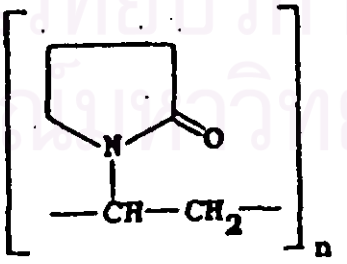

Figure 4 Povidone structure

Description : Povidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

2. Pharmaceutical applications of povidone

Solid dispersion of CI-987 (5-{ [3,55 bis (1,1-dimethylethyl)-4-hydroxy-phenyl]-methylene}-2,4-thiazolidinedione) having varying concentration of polyvinylpyrrolidone (PVP K 28-32), were prepared in an attempt to improve the dissolution rate of CI-987. The dissolution rate can be significantly increased by increasing the weight fraction of PVP. The maximum dissolution rate occurred with the solid dispersion having a PVP weight fraction of 0.81 (Kearney et al. 1994).

Gohel, Patel and Patel (1996), prepared solid dispersion containing PVP and PEG inclusion complex with beta cyclodextrin (β-Cyd), and kneaded mixtures with hydrophilic adjuvants such as water soluble gelatin (WSG) and microcrystalline cellulose (MCC) were prepared in order to enhance the dissolution rate of nifedipine in simulated gastric fluid.

The dissolution rate of nifedipine from solid dispersion increased in the order of PVP K-30 > PEG 6000 > PEG 4000 > pure drug. About a threefold increase in solution of nifedipine was observed from nifedipine-β-Cyd inclusion complex. The drug was released at a quicker rate from hard gelatin capsules containing physical mixtures of inclusion complex of nifedipine-β-Cyd and

WSG and also from tablets. WSG promoted wetting of nifedipine by reducing surfacc tension.

VII. Methods for solid state of spray dried powders characterization

1. X-ray powder diffraction

The diffraction method is the most powerful tool in solid state studies especially for studying the physical nature of solid dispersion. A diffractogram serves as the drug's fingerprint which markedly different from these of the compound or complex formation. In this method, the intensity of the X-ray diffraction from a sample is measured as a function of diffraction angles. Various studies of solid dispersion has been used this mothod (Guyot et al., 1995 ; Portero, Remunan-Lopez and Vila-Jato, 1998)

2. Differential scanning calorimetry (DSC)

DSC has proved a powerful tool in evaluating the drug-carrier interaction. The physical or chemical changes are automaticaly recorded as a function of temperature or time as the substance is heated at a uniform rate. Ageing characteristics and stability problems may also be predicted from this method (Ford and Timmins, 1989).

3. Infrared (IR) spectrophotometry

Infrared spectrophotometry is the method of determination between the interaction of drug and carrier in solid dispersion system. If the IR band does not deviate from the drug, it suggests that there is no interaction between drug and carrier. If the band is broaden and different from the pure drug, it indicates that there might be some interaction such as complex formation, hydrogen bond.

4. Scanning electron microscopy (SEM)

This is the method where sample was scanned under microscopy. It can actually see what appearances of particles. This method is often used to characterize morphology, particle size, shape, surface and appearance.