CHAPTER I

INTRODUCTION

Spray drying is a technique widely used in the pharmaceutical field to dry materials sensible to heat, to improve the drug solubility or the flowability of particular excipients and several other applications (Broadhead et al, 1992). It is a technique allowing the instantaneous drying of solutions, suspension, or emulsion. Recently, the process received great attention in the field of microparticles for the preparation of dried liposomes, amorphous drugs (Corrigan, 1984), mucoadhesive microspheres, drying of performed microcapsule (Palmieri, 1999), gastroresistant microspheres (Giunchedi, 1995), and controlled release system (Pavenetto, 1994).

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 dispersion in a solution of 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 et al., 1992).

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 single process (Wan et al., 1991; Broadhead et al. 1994). Matrix microcapsules, a matrix of wall material contains many small, fine core particle, are usually prepared by spray drying because it can be used simply to separate previously prepared microcapsules from the vehicle (Voellmy et al., 1977). This technique has been employed for the manufacture of drug matrix that are subsequently processed into various solid dosage forms.

The use of solvents in pharmaceutical industry poses several disadvantages, which have become apparent in the last 25 years due to the introduction of spray

drying and spray drying systems containing large volumes of organic solvents. Pollution and solvent toxicity which have resulted in strict government regulations concerning solvents emissions together with the expense and explosion hazards of solvents have led to the renewed interest in water based polymeric systems. In the mid-seventies, scientists began to develop a new class of aqueous polymeric materials which could be more suitable for the needs of the pharmaceutical industry of the 1980 - 1990 (Onions, 1986).

One of the result of this research was the introduction of poly (meta) acrylate lattices. Rohm America has many products which exhibits sustain released characteristics such as Eudragit®NE30D, Eudragit®RS30D. In 1999 Rohm Pharma launched a new product Eudragit®RD100 claimed to promote the characteristics of rapid disintegration time of thirty seconds. The application is for taste masking and protective coating. It is pH independent and fast disintegrating for aqueous taste and odor masking formulation. The product is a powder combination of 91 parts dry substance of Eudragit®RL100 and 9 parts of sodium carboxymethylcellulose for the manufacture of rapid disintegration coating on tablets and active particle in coating pan and fluidized bed dryer. Since Eudragit®RL100, poly(ethylacrylate, methylmethacrylate) trimethyl ammonioethylmethacrylate chloride, is water insoluble, the ability and mechanism of rapid disintegration or fast release has not been reported and was in contrast to the known ability of sustain release. Therefore an attempt was to investigate the properties of this product and compare to the self-prepared mixture of Eudragit®RL100 and sodium carboxymethylcellulose. The objective was also to investigate the potential use of a spray drying technique for preparing microparticles using these polymers. To study the effect of formulation variable, Eudragit®RL30D was used instead of Eudragit®RL100 because the aqueous based polymeric dispersion has been developed for pharmaceutical dosage forms in order to avoid explosion hazard and toxicity associated with solvent system. Anti adherent agent was also added to improve flowability. The model drug used was diclofenac sodium, a synthetic non steroidal anti-inflammatory and analgesic compound.

In this study, the suitability of spray drying condition in the manufacture of powders was also studied. The physicochemical properties of obtained microparticles were investigated and compared. The drug release characteristics were evaluated by in-vitro dissolution test.

The objectives of the study are :

1. To prepare microparticles of diclofenac sodium with Eudragit®RD 100 or Eudragit®RL30D with sodium carboxymethylcellulose by spray drying technique.

2. To study the physicochemical properties of diclofenac sodium spray dried microparticles with Eudragit®RD100 or Eudragit®RL30 D with sodium carboxymethylcellulose.

3. To compare the drug release patterns from microparticles containing Eudragit® RD100, or Eudragit® RL 30 D and sodium carboxymethylcellulose.

4. To study the optimal spray drying condition in the manufacture of dry powders.

Literature Review

1. Spray Drying Technique

Spray drying technology has found many applications in numerous industries including the pharmaceutical industry, chemical and food industries. Mainly for the drying of substances (Masters, 1985), However, other applications in the pharmaceutical industries include the drying of heat sensitive materials (Newton, 1966), preparing granulations for (Kornblum, 1969 ; Sugimori et al., 1990), improving the solubility of poorly water-soluble substances (Kawashima et al., 1975 ; Takeuchi et al., 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 et al.,1980). It is an expensive technology requiring an investment for installation and operation. There are several reasons why this technology has been applied despite its cost. These advantages include the production of particles with consistent quality , the easy of continuous operation., the applicability of the process to heat-sensitive and heat-resistant materials, the ability to process many types of feedstock , and the flexibility in dryer design based on the product formulation.

The following topics provide a brief review of the spray drying operations, the properties of spray dried powders include effect of processing and formulation variables on the properties of spray dried powders, the advantages and disadvantages of spray drying, and the applications of spray drying in pharmaceuticals.

1.1 The Spray Drying Operations

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

(i) Atomization of the feed into a spray

(ii) Spray-air contact

(iii) Drying of the spray

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

There are a variety of atomization systems available, which 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, as the name suggests, 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. Finally, in two-fluid nozzles, the feed fluid and atomizing air are passed separately to the nozzle where they mix and air causes the feed to break up into a spray. Two-fluid nozzles are generally confined to laboratory scale spray dryers. (Broadhead et al., 1992).

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 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 (Masters, 1985).

The final step in the spray drying process involves the separation of the product from the air steam. This is usually accomplished by means of a cyclone separator through which the air and product pass after exit the drying chamber. Many dryers also allow for product collection at the base of the drying chamber (Masters, 1979).

There are numerous different spray dryer designs (Nielson, 1982). Spray dryers systems 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 being dried is extremely susceptible to oxidation or has explosive tendencies. 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 feed atomization and product collection, and careful dryer design. These systems are currently 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 designed. These are capable of producing large agglomerated powders more economically than other types of spray dryer.

1.2 The Properties of Spray Dried Powders

Spray dried powders are usually approximately spherical with a narrow

size distribution and are usually hollow. The hollow nature imparts a low bulk density to the powders, but despite this, their spherical shape means that they are usually free-flowing (Newton, 1966)

Effect of processing and formulation variables on the properties of spray dried powders

The evaluation and comparison of spray-dried materials is extremely useful during formulation development. For example, the comparison of the same formula produced using different processing parameters is often important for the definition of the final production parameters required for the product. Also, a comparison of formulations containing different levels of common ingredients aids in formulation optimization of the spray-dried product. Following initial development, in vivo testing is often performed to compaction the bioavailability of differing formulations, and stability testing is used for choosing the most stable formulation. During tableting of spray-dried materials, the compaction properties of spray-dried materials can provide an important comparison for materials to be incorporated into a final table dosage form. When the final formula has been determined a scale-up evaluation can determine the feasibility of the formula in production equipment.

Processing Parameters

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, friabuility and retention of activity, aroma and flavor (Masters,1985 ; Newton,1966). Obviously, the design of the nozzle and powder characteristics should be borne in mind when a spray dryer design is selected.

Wan et al. (1991) evaluated the effect of these and other processing parameters on coated theophylline particles. 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 temperture 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.

Master et al. (1985) reported that an increase in the energy available for atomization. (i.e. rotary , atomizer speed, nozzle pressure, or air-liquid flow ratio in a pneumatic atomizer) will reduce particle size.

Particle size is usually increased as the feed concentration or viscosity increases (Masters, 1985; Crosby and Marshall, 1958). Masters reports that surface tension has a minimal effect on particle size.

Kata and Wayer (1985) reported an 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.

Crosby and Marshall (1958) evaluated the effect of temperature on particle size appears to be highly dependent on the material being dried. 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.

Newton (1966) studied that where the particle size of some materials was shown to increase as the drying air temperature increases. High drying air temperatures also seem to be associated with lower bulk densities (Masters, 1985). As a general rule, smaller particles will usually be more dense, so the bulk density of a powder with a small particle size will be higher. Bulk density will also increase with an narrower particle size distribution (Newton, 1966; Crosby & Marshall, 1958). The outlet temperature of a spray dryer can

be correlated with activity loss in the drying of heat sensitive materials . As would be expected, increased dryer outlet temperatures result in a lower final product moisture content.

Cham (1987) evaluated the effect of processing temparature on the surface area of magnesium carbonate produced by granulation or spray drying. An experimental design using five different temperatures showed that the highest specific area was provided at lower processing temperatures and that material produced at higher temperatures wan more compressible.

Yamaguchi and co-workers (1992) studies inlet temperatures, the inlet temperature also 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 was obtained for MAT. The glassy state was confirmed by differential scanning caloriemtry (DSC) and had transition temperature of 102-103 $^{\circ}$C .

Takenaka et al.(1982) also investigated inlet temperature effects. Theophylline - ethy - enediamine complexed were formed by spray drying at varying inlet temperatures. The solubility of Theophylline was increased three to five due to the complex formation. However, solubility decreased with increasing inlet temperature and atomizer rotation speed.

Formulation parameters

Often, the effect of processing parameters is evaluated concurrently with formulation parameters. Broadhead and co-workers(1994) evaluated the effect of dryer outlet temperature on the product yield and residual enzymatic activity of beta-galactosidase. Product yield increased with increasing outlet temperature, however, extensive protein denaturation was also found at these higher temperature . Due to this denaturation,the effectiveness of four stabilizers was evaluated for their ability to maintain enzymatic stability during the spray drying process and during storage. The result of the outlet temperature and stabilizer study was a fully active final product

containing the stabilizer study was sprayed at inlet and outlet temperatures of 40°C and 90°C respectively, with a 70% yield.

While concurrent evaluation of process and formulations effects has often been done formulation effects on spray –dried variables.

The effects of eight binder excipients were evaluated following spray drying for salicylic acid and sodium salicylate using a centrifugal wheel atomizer by Kawashima et al. (1972). Sublimation of salicylic acid was found to occur during the spray-drying process for some formulations. Only granules containing gum arabic and polyvinylpyrrolidone (PVP) prevented this sublimation and only these two contained both active in gradients while all other granules contained only sodium salicylate after processing.

The authors also noted that formulation containing gelatin and polyvinyl alcohol were less free-flowing due to agglomeration. The physical properties of the particle such as diameter and true density were affected by the concentration of the binder and of sodium salicylate.

During the study of spray-drying formulation factors. Particle morphology and particle characteristics have also been studied independently of processing variables.

In one study, Takeuchi et al. (1987) studied the incorporation of two disintegrant, low-substituted hydroxypropylcellulose (L-HPC) and party pregelatinize corn starch (PCS) into spray-dried tolbutamide particles evaluated the particle formation. The particles formed L-HPC were agglomerates of disintegrant with drug on both the outside and within the particle. In contrast, PCS particles contained a single core of PCS with drug deposited only on the surface.

1.3 Advantages and Disadvantages of Spray drying

The main advantages of spray drying for many applications are continuous in operation and adaptable to full atomization (Nielsen, 1982). Dried product

specificants are met through dryer design an operational flexibility. Dried product specification are related to the properties of particle size distribution, appearance, moisture content, friability, color, aroma, taste, activity, sterility. Many kind of feed stocks (solution, slurry, thixotropic paste or melted form) can be handle, if pumpable. Corrosion and abrasion can be reduced or prevented because the material does not contact the equipment surface until it is dry. Low maintenance costs because there are few moving parts. Low labor costs because only one operator is required, even on large installation. The evaporation usually done under slight vacuum. Thus it easy to keep clean. Spray drying is an airborne process, hence threr is very low material hold up the equipment. Designs of spray drying are available to handle (Master, 1979). Spray drying is a single step operation from liquid feed to dry product. Frequently, this eliminates such steps as precipitating or crystallizing, centrifuging or filtering, griding, classifying, and perhaps the additional pumping, storage, and dust collecting operations associated with them (Master, 1985).

The disadvantage of spray drying for many applications is its cost, in terms of both equipment and operation. Spray dryers have poor thermal efficiency unless 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, 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 (Broadhead et al. 1992).

1.4 The Applications of Spray Drying in Pharmaceuticals

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

Spray Drying to produce a specific type of particle

Because of its inherent costs, spray drying is not always considered as a processing option for many conventional formulations. However, when a specialized particle type is required the active ingredient or dosage form, spray drying can become feasible alternative to more conventional manufacturing processes. Such particle types include microcapsules, controlled release particles, nanoparticles, and liposomes.

Microcapsules

The preparation of microcapsules involves the coating of particles or liquid droplets with a biodegradable polymer. This process begins with the preparaton of a three-phase immiscible system containing a liquid vehicle, the core particle, and a coating material or polymer. Several manufacturing techniques can be used to deposit the polymer around the particle and cause this coating to become rigid. These methods include phase separation, coacervation, and spray drying. In spray-drying process, the encapsulation process is achieved one step. In this step, desolvation and thermal crosslinking occur concurrently and the particle is coated. Applications for microspheres in the pharmaceutical industry include controlled release, particle coating, flavor stabilization, taste masking, physical or chemical stabilization.

Microencapsulation is a process that is often used to provide controlled release of a protein or drug. Wan et al. (1992) found theophylline release to independent on the hydrophilicity of the polymer. The hydrophiliic, sodium carboxymethylcellulose polymer gel 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 particle tended to agglomerate and delay drug release.

Two common biodegradable polymers used in microencapsulation are PLA and PLGA. The efficacy of spray drying as a method for PLA and PLGA microsphere preparation was investigated using vitamin D3 as a model lipophilic drug by Pavanetto and co-workers (1992). The spray-drying process was tailored to each polymer, and

the microspheres obtained were evaluated for shape, size, drug content, and polymer influence on there 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.

Filopo et. al., (2001) prepared of paracetamol / Eudragit®RS or RL or ethylcellulose microspheres to verify the possibility of their use in controlled-release solid dosage forms formulation and try to determine advantages and limits of the technique of such use microspheres were first characterized by scanning electron microscopy differential scanning calorimetry x-ray diffractometry, and in vitro dissolution studies and then used for the preparation of tablets. During this step, the compressibility of the spray-dried powder was also evaluated. In vitro dissolution studies were performed also on the tablets and their release control was accessed. Although powders were unable to slow down drug release, tablets obtained from microsphere compression showed a good capability of controlling paracetamol release when Eudragit®RS or ethycellulose was used even at low polymer amounts.

The same researcher and co-workers prepared microcapsules or microspheres for controlled release. Drugs of different solubilities like theophylline and sodium sufamethazine, with Eudragit ® RS as coating polymer, are chosen.

The polymer is used, either dissolved in an hydroalcoholic solution or suspended (pseudolatex) in water, indifferent weight ratios with the drug. The obtained solution or suspension is spray-dried. Scanning electron microscope analysis of the powders reveals no sigh of microencapsulation. Moreover, only a fraction of the particles has a spherical shape.

For each spray-dried powder, a part of the obtained particles is compresses into tablets and the rest is stored. Dissolution studies in distilled water at 37°C are performed on powders and tablets.

While the uncompressed microparticles do not give any controlled release. The tablets show an ability in slowing down drug delivery greater than the one obtained with the traditional methods. Wan et al. (1992) prepared microencapsulation of theophylline drug particles by a spray drying technique using an aqueous system. Comparison was made between the use of a solutoin and a suspension feed. The spray dried products obtained from a suspension feed were encapsulsted and have better flowability. Various polymers, hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylcellulose (NaCMC) were studied to evaluate their spray-coating properties. The results showed that drug release from the coated products was dependetn on the hydrophillicity of the polymer. NaCMC, wihich is more hydrophillic, gelled faster and retarded the drug release more effectively. HPMC and MC produced products with similar dissolution profiles and flow properties. Spary coating with HPMCAS was unsuccessful. The polymers also affect the size and cohesiveness of the products. Smaller size particles which are more cohesive cause agglomeration and delay release of the drug.

Takeuchi et al., (1989) prepared sustained release and enteric theophylline tablets by directly compressing spray-dried microspheres with Eudragits ® L30D, L100-55 and E30D. The spray-drying process was free from using orgainc slovent. Drug dissolution of the enteric tablet in an acidic solution (pH 1.2) was highly dependent on the polymer content of the microsphere. Completely enteric function was observed with drug-to-polymer ratio of 1:3 using Eudragit® 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. The dissolution pattern was similar to that of Theo-dur and gave a straight line in Higuchi plot. In each tablet, the contrlled drug release was attributed to continuous and well-dispersed polymer matrix formed by spray-drying and subsequent compressing process.

Takenaka et al. (1981) prepared enteric coated micropapsules of Sulfamethoxazole with cellulose acetate phthalate and talc, colloidal silica, or montmorillonite clay by a spray-drying techinque. The surface opography of the

products varied with the type of excipient used and the pH of the suspending medium. The products without the excipient were coated with flake like crusis, while the products containing the excipient tended to become well-rounded spheres. In addition, the crystalline form of sulfamethoxazole converted from Form I to and amorphism and Form II during the spray-interaction of cellulose acetete phthalate with sulfamethoxazole. In creasing the concentration of cellulose acetate phthalate in the formulation increased the attainment of amorphism. Form II aws also obtained by freeze and vacuum drying. Talc was the only excipient that contributed to polymorphism, which occurred in the alkaline suspensiion medium. Montmorillonite products prepared from the acidic medium exhibited an exothermic differential scanning calorimetry thermogram, which might be interpreted in terms of adsorption ofth efused sulfamethoxazole with the internal surface of montmorillonite.

Controlled Release

Controlled release can also be attained without producting microcapsule suing the spray-drying process. A bilayer tablet containing fast release and slow release nifedipine was formulated by Wan et al (1991). With both layers containing spray-dried material. For the fast –release layer, poorly water-soluble nifedipine was spray dried with hydroxypropyl-beta-cyclodextrin and a nonionic surfactant. For the slow release layer, hydroxypropylcelluloses of different viscosity grades were combined with the drug. Following an initial burst of rapid dissolution provided by the spray-dried material, the final tablet provided a sufficient slow release of the drug over a wide pH range.

Nanoparticles

Recently, much interest has been generated by colloidal drug delivery systems such as nanocapsules because of the possibilities for controlled release, increased drug efficacy, and reduced toxicity after parenteral adminisration. Nanocapsules of poly-ε-caprolactone and Eugratit S90® were prepared by C.R. Muller et al. (2000). However, these systems provent physicochemical instability. To dry these nonocapsules suspensions with the view of obtaining a solid form, the spray-drying proces was sued.

Spray-dried powders of nanocapsules of poly-ε-caprolactone and and Eugratit S90® were prepared by atomization in a Buchi 190 Minii-spray dryer using colloidal silicon dioxide as a technological carrier. The morphological analysis of the surface at the powders showed that nanocapsules remain intact, and no change in particle size was detected after the spray-drying process. These results suggest that this method can be an interesting alternative to dry nanocapsule suspensions.

Liposomes

Another particle type that can be produced by spray drying is liposomes. Traditional preparation of liposomes begins with the preparation of a solution containing the lipid to be used in a volatile organic slovent mixture. Following filtration of the solution, the slovent mixture is removeed under conditions that ensure phase separation does not occur. The dry lipid mixture is then hydrated by and aqueous mixture containing the drug to be entrapped and subsequently dried. Spray drying is another method of preparation avilable fro accomplishing one or both of these drying steps.

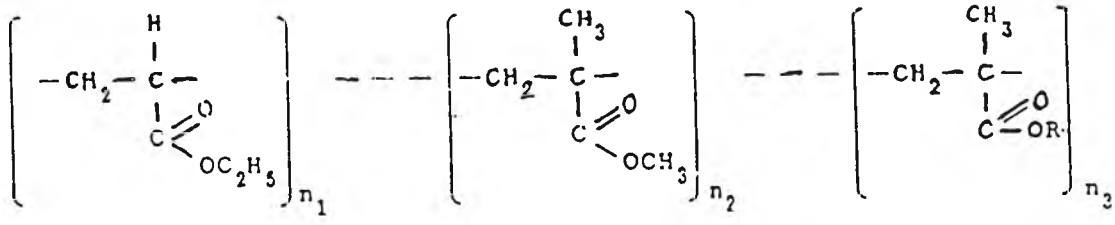
N.Skalko-Basnet et al. 2000 prepared of liposomes containing drug and cyclodextrin (CD). Spray-dried lecithin liposomes, entrapping metroniddzole or verapamil alone or together with hydroxypropyl-β-cyclodextrin (HPβCD), were characterized for morphology, size distribution, and drug entrapment effciency. The main factor influencing the liposomal size was the volume of aqueous medium used of hydration of the spray-dried product. No differences in size for entrapment between liposimes prepared by immediate hydration of fried powder or by hydration after 1 year of powder storage at 4°C were observed. All liposomes we're taste for their serum stability. The most stable liposomes (still retaining about 10% of the originally entrapped drug even after 24 hr incubation with scrum) were liposomes prepared by the direct spray-drying of the mixture of lipid. drug, and HPβCD.

2. Eudragit® RL 30D

Eudragit® RL 30D is copolymers synthesized from acrylic and methacrylic

acid esters with a low content of quaternary ammonium group. The molar compositions of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride are 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 neatral (meth) acrylates is 1:20 (Lehmann, 1989).

Films made of Eudragit® RL 30D are readily permeable to water and dissolved active substances, so that active substance diffusion is only slightly delayed. Eudragit® RL 30D is 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 may stimulate the dispersing process by stabilizing new surfaces formed and repelling the small dispersed particles. The effect of the quaternary ammonium 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 (Lehmann, 1989).



Scientific Name	n:n:n	MW	Behavior in digestive juices	Eudragit type	Marketed form
Poly(ethylacrylate Methylmethacrylate) trimethylammonio ethylmethacryalte chloride	1:2:0.2	150000	Insoluble films of high permeability	RL30D RL100	30%aqueous dispersion Granules

* R: CH_2-CH_2-$N(CH_3)_3Cl$

Figure 1 Structural formular of methacrylate ester copolymers

The minimum film forming temperature (MFT) of thses 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 films are pH-independent, thus the active substance release takes place largely independetn 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, diethy phthalate, triacetin and 1,2 propylene glycol.

Eugragit® RL 30D is 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.

Bodmeier and Paeratakul (1990) prepared polymeric films containing propanolol HCl by dissolving the drug in the aqueous colloidal polymer dispersion, Eudragit ® RS 30D, before casting and drying. The release of propranolol HCl was studied as a function of drug content, Eudragit RS 30D/RL 30D ratio, plasticizer content, method of film preparation and storage humidity. The addition of the more hydrophilic Eudragit ® RL 30D increased the permeability of the films. The amount of water-soluble plasticizer, triethyl citrate, added had a pronounced effect on drug release. The release was rapid at low and high plasticizer concentrations because of incomplete coalescence of the latex and leaching of the plasticizer. The drug release from latex-cast films was faster when compared to that from solvent-cast films.

Amighi and Moes (1995) improved processing and film formation form acrylic polymers with poor film forming properties and /or to obtain sustained – release film coated pellets with optimal barrier properrties according to the physico-chemical and pharmacokinetic requirements of the active substance.

Heterogeneous film structures are generally obtained from blends containing an association of hard acrylic polymers (Eudragit RS30D, S100) with the soft Eudragit NE30D when the drying temperature is lower than the minumum 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 theses blends which are generally characterized by two individual glassy transitions.

On the other hand, 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 RL30D in association with the less permeable Eudragit RS30D in order to obtain pH-independent permeability membrane, or by mixing the anionic methacrylic acid copolymers (L30D, S100) with the neutral NE30D in order to obtain pH-dependent permeability film coated pellets showing higher dissolution release rates at intestinal pH values.

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. It was observed that the release rates of drugs decreased by increasing the amount of Eudragit® RL 30D in the formulation, on the other hand, increasing 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, 1980).

3. Eudragit ® RD 100

Eudragit® RD 100 is a powder combination of 91 parts dry substance of Eudragit® RL 100 and 9 parts sodium carboxymethylcellulose for the manufacture of rapidly disintegrating coatings. When stirred into water, Eudragit® RD 100 forms a dispersion that can be processed in the usual manner it is pH independent and fast disintegrating for aqueous taste &odor marking formulations.

Dispersibility:

100 g of water was filled into a 250 ml beaker and dissolved 3 mg of Polysorbate 80 therein, using a magnetic stirrer. Then 15 g of Eudragit® RD 100 was added slowly stirring and continue for another 30 minutes. The dispersion was passed thus was obtained through a steel wire cloth with a mesh size of 0.4 mm and rinse the cloth with water until the filtrate is clear. There should be no major residues.

Table 1 Processing properties of Eudragit ® RD 100.

Processing properties	Data
Minimum film-forming temperature (DIN 53 787)	< 10 °C with 20% Polysorbate80
Glass transition temperature (DSC method Tgm)	approx. 26 °C with 20 % Polysorbate 80
Decomposition temperature	> 130 ° C

Application

Rapidly disintegrating coatings on tablets and active particles in coating pans and fluidized bed equipment.

For medium-sized tablets, a polymer weight of 1 mg/cm^2 is usually sufficient for a coherent coating. In special cases, e.g. for effective taste masking, higher quantities may be required. Owing to the excellent pigment-binding capacity, even very dark cores can be provided with light-colored coatings at low polymer requirement. Surface textures, e.g. engravings, are reproduced and recognizable after coating.

Tablets and particles can be coated in conventional equipment according to known techniques. The process parameters to be selected are the same as for working with aqueous dispersions. Polysorbate 80 serves as a plasticizer and reduces the minimum film-forming temperature.

Table 2 Colored coating on quinidine sulfate tablets in the Accela Cota 10.

Equipment	Material	Formulation
Accela Cota 10 Manesty spray gun Peristaltic pump with Silicone tube Magnetic stirrer	10 kg of quinidine sulfate tablets, 3.9 mm in height 305 mg in weight (w), tablet surface(S)= 280mm^2 polymer requirement (l) = 2.0 mg/cm^2 Coating weight = s*l / w = 1.84 % polymer	Eudragit ® RD 100 = 183.0 g Polysorbate 80, 33% in water = 112.0 g Polyethylene glycol 6000, 33% in water = 55.0 g Talc = 92.0 g Titanium dioxide = 22.0 g Iron oxide yellow= 22.0 g Water = 2007.0 g

Preparing the spray suspension

The spray suspension was prepared with 670 g of water and add the Polysorbate 80 solution after that stir in Eudragit ® RD 100 within 5 minutes (propeller stirrer) avoiding lump formation for another 30 minutes.

The other excipients in the remaining water was homogenized by using an Ultra-Turrax or a toothed colloid mill and then add them with stirring to the Eudragit ® RD 100 dispersion. Stirring the finished mixture to prevent solids from settling.

Coating instructions

The rotational speed of the pan was reduced (approx. 4 rpm) and preheat the tablets to 30°C. This temperature was maintain throughout the coating process. Warm air (approx. 40 to 50°C) was supplied continuously while increasing the pan speed (approx. 10 rpm). The spray gun was directed at the upper third of the cascading cores, A fine spray pressure was pressured of 0.5 bar (air volume 44 L/min). The spray suspension was delivered from the peristaltic pump at a rate of approx. 25 to 30 g per minute.

If the cores should become too moist in between, the spraying process was interrupted and allow a few minutes for drying. Spraying being completed, post-dry the coated tablets for 5 minutes in the slowly rotating pan and then dry for an additional 6 hours at 40°C on trays.

Table 3 Disintegration test of uncoated and film – coated tablet.

	Water	0.1 N HCL
Uncoated	12-20 min	13-20 min
Film – coated tablets		
1.0 mg/cm	18-21 min	18-23 min
2.0 mg/cm	19-23 min	18-21 min
3.0 mg/cm	21-24 min	18-23 min

4. Sodium carboxymethylcellulose

Sodium carboxymethylcellulose is widely used in oral and topical pharmaceutical formulations primarily for its viscosity increasing properties. Viscous aqueous solutions are used to suspend powders intended foe either topical application or oral and parenteral administration. It may also be used as a tablet binder and disintegrant, and to stabilize emulsion. Higher concentrations, usually 4-6 % ,of the medium viscosity grade is used to produce gets which can be used as the base for applications and pastes ; glycerin is often included in such gels to prevent drying out.

Sodium carboxymethylcellulose is additionally one of the main ingredients of self-adhesive ostomy wound care and dermatological patches where it is used to absorb wound exudate or transepidermal water and sweat.

It is also used in pharmaceutical industries such as coating agent, tablet and capsule disintergrant, tablet binder, stabilizing agent, suspending agent, viscosity-increasing agent and is used in cosmetics and food products (Wade and Weller, 1994).

Table 4 Application of sodium carboxymethylcellulose in pharmaceutical.

Use	Concentration (%)
Emulsifying agent	0.25 – 0.1
Gel-forming agent	4.0-6.0
Injections	0.05-0.75
Oral solutions	0.1-1.0
Tablet binder	1.0-6.0

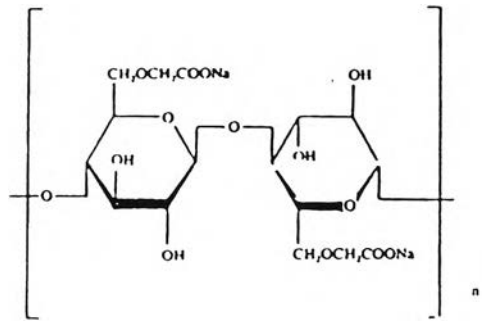


Figure 2 Structure formula of sodium carboxymethylcellulose

Various grades are commercially available which have differing aqueous viscosities ; aqueous 1% w/v solutions with viscisities of 5-4000 mPas (5-4000 cf) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity. Viscosities of various grades of sodium carboxymethylcellulose are shown in this Table 5.

Table 5 Viscosity of carboxymethylcellulose sodium solutions at 25°C.

Grade	Concentration(%w/v)	Viscosity (mPas)
Low viscosity	4	50-200
Medium viscosity	2	400-800
High viscosity	1	1500-3000

Sodium carboxymethylcellulose is a stable though hygroscopic material. Under high conditions carboxymethylcellulose sodium can absorb a large quantity (> 50%) of water. In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time.

Aqueous solution are stable between pH 2-10; below pH2 precipitation can occur while above pH 10 solution viscosity rapidly decrease. Generally , solutions exhibit maximum viscosity and stability at pH 7-9 (Wade and Weller, 1994).

It may be sterilized in the dry state by maintaining it at a temperature of 160°C for 1 hour. However,this process results in a significant decrease in viscosity and some deterioration in the properties of solutions prepared from the sterilized material.

Aqueous solutions may similarly be sterilized by heating although this also results in some reduction in viscosity. After autoclaving, viscosity is reduced by about 25% although this reduction is less marked than for solutions prepared from material sterilized in the dry state. The extent of the reduction is dependent on the molecular weight and degree of substitution; higher molecular weight grades generally undergo a greater percentage reduction in viscosity. Sterilization of solutions by gamma irradiation also results in a reduction in viscosity.

Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative. The bulk material should be stored in a well-closed container in a cool, dry, place.

Sodium carboxymethylcellulose is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury and zinc; it is also incompatible with xanthan gum. Precipitation can occur at pH < 2 and when mixed with ethanol (95%).

Sodium carboxymethylcellulose also forms complex coacervates with gelatin and pectin. It additionally forms a complex with collagen and is capable of precipitating certain positively garged proteins.

Va'zquez et al. (1995) characterized two varieties of HPMC, two varieties of NaCMC and various HPMC/NaCMC mixtures with the aim of providing a sound basis for the selection of appropriate mixtures to use as gelling agents in controlled-release

tablets for hydrosoluble drugs. For both HPMC and NaCMC, one variety was of high and the other of low nominal viscosity.

Va'zquez (1995) also investigated possible relationships between the rheological properties of HPMC/NaCMC mixtures and atenolol release from tablets prepared with such mixtures. The mean molecular weights of each polymer variety were estimated on the basis of determination of their intrinsic viscosities in aqueous dispersions. Rotational viscosimetry of 2% aqueous dispersions of the polymers and polymer mixtures revealed rheological synergism in some mixtures. Drug dissolution trials were carried out in water and 0.1 N HCI. Dissolution medium, gelling agent composition and proportion of gelling agent in the data for dissolution in water indicated zero-order dissolution kinetics for all formulations. For tablets prepared with the most viscous HPMC variety, 8-hour dissolution efficiency was closely correlated with the apparent viscosity (shear rate 0.5 s) of the aqueous dispersion of the polymer mixture used as gelling agent. Assays of tablet erosion rates indicated that the erosion mechanism may contribute to the observed zero-order dissolution kinetics, but that other factors are probably also involved.

Billon et al. (1999) evaluated the effects of cellulose derivatives and additives in the spray-drying preparation of acetaminophen delivery systems.

Microcrystalline cellulose (MCC), sodium carboxymethylcellulose (NaCMC), hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), and ethylcellulose(EC) were used for the production of time-controlled acetaminophen delivery systems using a spray-drying technique. The influence of factors such as polymer concentration of the polymer, with the highest values being reached from feeds containing 1% MCC and EC. Parameters of 1% polymer concentration and an inlet temperature of 140% oC gave rise to optimal processing conditions.

Singh (1992) evaluated the effect of sodium carboxymethylcelluloses on the disintegration, dissolution and bioavailability of Lorazeparn from tablet. A new range of sodium carboxymethylcelluloses (i.e. Nymcel types ZSB-10, ZSB-16 and ZSD-16)

were included into lorazepam tablet formulations to improve the disintedration, dissolution and bioavailability in mongrel dog in comparison to tablets of the other batches.

Hussain et al. (1994) evaluated the effect of blending a nonionic and an anionic cellulose ether polymer on drug release from hydrophilic matrix capsules. Blends of hydroxyethylcellulose (HEC) and sodium carboxymethylcellulose (NaCMC) were used to achieve zero order release of chlorpheniramine maleate (CM) from hydrophilic matrix capsules. Dynamic swelling/erosion and response measurements were made to provide an insight into the drug release behavior. The drug to total polymer and the HEC to NaCMC ratio influence the rate of drug release. NaCMC appears to influence water uptake and erosion of the matrix mixture. The factors which zero-order drug achieves release may include synchronization of the rates of water uptake and polymer erosion even though a constant diffusion pathlength may not be maintained. The combined mixture factorial design presented in this study allows for the characterization and optimization of the drug release profiles.

5. Colloidal silicon Dioxide (SiO_2)

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products. Its small particle size and large specific surface area give it desirable flow characteristics, which are exploited to improve the flow properties of dry powers in a number of processes, e.g. tableting.

Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agents in gels and semisolid preparation. With other ingredients of similar refractive index transparent gets may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity (Wade and Weller, 1994).

In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling and minimize the clogging of spray nozzles.

Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent-dispersing agent for liquids in powders or suppositories.

Table 6 Use of colloidal silica in pharmaceutical.

Use	Concentration(%)
Aerosols	0.5-2
Emulsion stabilizer	1-5
Glidant	0.1-0.5
Suspending and thickening agent	2-10

Colloidal silicon dioxide is hygroscopic, but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH between 0-7.5 colloidal silicon dioxide is effective in increasing the viscosity increasing properties of colloidal silicon dioxide are reduced and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container. It is incompatible with diethylstilbestrol preparations

Vecchio (1995) studied that among the additives used in formulation techniques, talc, that was normally utilized as an antiadherent and polishing agent, presents some problems connected with its tendency to form sedimentation. For this reason, during the film coating operation, the dispersion must be always kept under constant and proper agitation. However, the danger of blocking the piping and the spraying system of the equipment employed could not be completely avoided.

On the bases of these observations, the aim of Vecchio's research work was to evaluate the possibility of substituting talc with colloidal silica as separating agent in aqueous dispersion of film acrylic resins, normally used in the preparation of prolonged release systems.

Results concerning fluidized bed coating processes of pellets prepared by extrusion spheronization technique have been reports, with particular attention to usable concentration of colloidal silica and to possible influence of these of these on the drug release characteristics of the systems obtained.

Takenaka et al.(1980) prepared enteric-coated microcapsules for tableting by a spray-drying technique and the drug release behavior from the tabulated microcapsules was investigated using a disintegration apparatus and a new in vitro method of simulating the GI tract. As a model system, ammonium solutions of sulfamethoxazole and cellulose acetate phthalate were spray dried using a centrifugal wheel atomizer at 140°C. Additives such as colloidal silica, montmorillonite clay, and talc were included in the formulations for spray drying. The influence of the additives on the particle diameter, density, packing properties and compressibility of the product and on the release characteristics of the resultant tablet vitro were investigated. The additives in the formulations greatly improved the flow properties of the spray-dried products, which could be tabulated easily. Product form the nonadditive formulations could not be tabulated due to their poor flowability. The hardness and disintegration rate of the tablet increased with increasing concentration of additives in the formulations.

Peter York (1991) evaluated effect of glidants on flowability of cohesive pharmaceutical powders, lactose and calcium hydrogen phosphate, using the flow factor as the flowabiity parameter. Fine silica, magnesium stearate, and purified talc were investigated as glidants; for each host power-glidant mixture, an optimum concentration of gilding was observed beyond which no further increase in flowability occurred. The order of efficiency of glidants for both host powders was fine silica> magnesium stearate> purified talc.

Johansson (1985) investigated of the film formation of magnesium stearate by applying a flow through dissolution technique. The effect of mixing time, lubricant surface area, and the additional of colloidal silica was studied. The film formation increased by increasing mixing time. The final level reached was independent of the specific surface area of the lubricants, but granular magnesium stearate gave a lower surface coverage than the powdered lubricants. The lubricating effect was independent of mixing time and specific surface area of the lubricants. Colloidal silica was found to interact primarily with the free fraction of magnesium stearate.

Varthalis (1977) studied the action of colloidal silicon dioxide as a glidant for lactose, paracentmol, oxytetracycline and their mixtures. Anomalies are observed in some of the physical and mechanical properties of mixtures of lactose, paracetamol and oxytetracycline when small amounts of colloidal silicon dioxide are added to them. Owing to its differing propensities to coat the particles of the host powders, the silicon dioxide acts as a glidant for the lactose and paracetamol, but as an antiglidant for the oxytetracycline.

Moura et al. (1996) studied the thermal constraint. Temperature variation in the spray dying method has no effect on the ascorbic acid molecule. No chemical interaction between the colloidal silica and the ascorbic acid could be determined, but a physicochemical interaction "absorption" was determined. Colloidal silica improved the final yield of spray drying in proportion to its concentration. No polymorphs forms couldbe determined in the spray-dried ascorbic acid. Drug release from the ascorbic acid spray dried was found to be dependent on the Aerosol content: highest release rates were obtained with Aerosol.

Kawashima et al. (1983) studied polymorphism and drug release behavior of spray-dried microcapsules of sulfamethoxazole with polysaccharide gum and colloidal silica. Sulfamethoxazole microcapsules with polysaccharide gum, i.e. xanthan gum and guar gum, were prepared by employing a spray drying technique. The aqueous or the ammonium hydroxide solution of the gum containing the drug with or without colloidal silica was atomized with a centrifugal wheel atomizer rotated at 40000 rpm into a drying chamber held at $140\pm10^{\circ}C$.

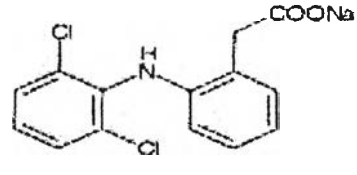
By formulation with colloidal silica, particle size of the resultant product increased, leading to improve the flowability and packability for the tableting. Polymorphs sulfamethoxazole mixture of Form I, II and III was produced in the formulation with cellulose acetate phthalate. Xanthan gum product prepared from both aqueous and ammonium hydroxide solution and guar gum product from ammonium hydroxide solution also contained the polymorph mixture. In the formulations with colloidal silica, the crystalline form of all the products was Form I.

A dissolution test of the product compressed into a table with microcrystalline cellulose was undertaken using a disintegration apparatus and a flow-type GI tract simulator. The product prepared from the aqueous solution ad prolonged drug release rate, while the product prepared from ammonium hydroxide solution exhibited rapid drug release due to improve tablet disintegration. Colloidal silica in the product enhance the drug dissolution rate of the product from the aqueous solution, but decreased that from the product made from the ammonium hydroxide solution. In the flow-type simulator, the drug release from the product was pH independent.

6. Diclofenac sodium

Diclofenac sodium is a synthetic, non-steroidal anti-inflammatory and analgesic compound. It is widely used for relief of pain and inflammation. Its formula and molecular weight are presented below.

Diclofenac Sodium



$C_{14}H_{10}Cl_2NNaO_2$ 318.1

Figure 3 The structural formula of diclofenac sodium.
Empirical formular " $C_{14}H_{10}C_{12}NO_2Na$ " (MW.=318.13)

The chemical name of diclofenac sodium is 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.

Diclofenac sodium powder is odorless, white to off-white crystalline, slightly hygroscopic powder. The powder was melted , when heated at about 283 to 285 °C.

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 (Adeyeye and Li, 1990).

The presence of cations (sodium ions or potassium ions) markedly affects the solubility of diclofenac sodium. The addition of sodium or potassiumchloride to the dissolution decreased the solubility of diclofenac sodium and slowed the dissolution rate, with the effect of sodium chloride being greater .

The equilibrium solubility performed in various solvents at the room temperature (RT) are shown in Table 7 (Adeyeye and Li, 1990).

Table 7 The solubility of diclofenac sodium

Solvent	Temperature	Solubility(mg/ml)
Deionized water(pH5.2)	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

Dissociation Constant (pKa) and Partition Coefficient

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

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

Stability

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

Muller and Kolter (1991) investigated the effects of beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin and hydroxy-gamma-cyclodextrin on the solubility and stability of diclofenac sodium, indomethacin and piraxicam. The influence of beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin on the stability of diclofenac

solutions with and without oxygen at a stress temperature of 71 °C showed that the cyclodextrin derivative had the most stabilizing effect. At room temperature the decrease in degradation was not significant, even when the solutions without cyclodextrin were physically unstable due to recrystallization of the drug. In contrast to indomethacin and diclofenac, the cyclodextrins had a destabilizing effect on the stability of piroxicam.

Uses and Administration (Reynolds et al., 1989)

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

The drug is used for the relief of pain and inflammation in conditions such as rheumatoid arthritie, osteoarthritis, ankylosing spondylitis, acute gout and following some surgical procedures. The usual dose by mouth is 75 to 150 mg. daily in divided doses. It may also be given reactally as a suppository in a usual dose of 100 mg. Each evening. Dictofenac sodium may also be given by intramuscular injection in a dose of 75 mg. Once daily or, if required in severe conditions, 75 mg. Repeated once after 30 minutes if necessary. In chicken the suggested dose by mouth or reactally for juvenile chronic arthritis is 1 to 3 mg./ kg. Body weight daily in divided doses.

Adverse Effects

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

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