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THE SPRAY DRYING OF PHARMACEUTICALS

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1. INTRODUCTION

Spray drying has a wide range of applications within the chemical industry, the food industry, and the biochemical and pharmaceutical industries. For example it is commonly used to process milk, eggs, ceramics, fertilizers and several chemicals. Information pertinent to the processing of pharmaceuticals can therefore be gleaned not only from the pharmaceutical literature, but also from that of some of the aforementioned applications. Information from the food science literature and the chemical engineering literature is particularly relevant to pharmaceuticals. In this article the applications of spray drying in the pharmaceutical industry will be reviewed. These include some long established uses, such as the the production of granulations by spray drying, as well as some more novel applications which are currently under investigation. Reference will also be made to some non-pharmaceutical applications (such as food processing) when relevant to pharmaceutical uses. The basic principles of spray drying will be discussed very briefly. For further detailed discussions of the operating principles, reference is made to the large data base within the chemical engineering literature.

2. THE GENERAL PRINCIPLES OF SPRAY DRYING

The following discussion provides a brief overview of the design and operation of spray dryers and of the effect of processing variables on particle properties. For a detailed discussion of these topics, the reader is referred to the comprehensive text by Keith Masters (1985). The reader may also wish to refer to the monograph by Marshall (1954) which provides many detailed mathematical correlations covering such topics as atomization and spray dryer performance.

2.1 The Design and Operation of Spray Dryers

Spray drying converts a liquid into a powder in a one step process (Nielson, 1982). It is capable of producing fine, dustless or agglomerated powders to precise specifications (Masters, 1990). The spray drying process encompasses the following four stages (Masters, 1985):

(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 the air causes the feed to break up into a spray . Two-fluid nozzles are generally confined to laboratory

scale spray dryers (such as the Büchi 190 which is commonly used in pharmaceutical research).

Spray dryers may be designed to operate in a co-current manner, where spray and drying air pass through the dryer in the same direction or in a counter-current manner where the spray and drying air enter the drying chamber at opposite ends. Other spray dryer designs are available where the spray-air contact is intermediate between co- and counter-current. Co-current operation is preferable for the drying of heat sensitive materials since the dry product is in contact with only the coolest air. Also, the high rates of moisture evaporation enable the temperature of the dry product to be considerably lower than that of the air leaving the drying chamber. This point will be discussed in greater detail in section 3.7. 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 exiting the drying chamber. Many dryers also allow for product collection at the base of the drying chamber.

There are numerous different spray dryer designs. Spray dryers 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 (Nielson, 1982). Various dryer layouts suitable for toxic materials which operate so as to avoid air pollution have also been developed. From a pharmaceutical point of view, it is important to note that aseptic systems are available which operate to produce a sterile powder. This is achieved by filtration of the liquid feed material and the atomizing air, contamination free atomization and product collection, and careful dryer design. These systems are currently used for the production of antibiotics. Also, dryers which incorporate fluid beds into the base of the drying chamber have been designed. These are capable of producing large agglomerated powders more economically than other types of spray dryer.

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

2.2. 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). By modifying the

spray drying process, it is possible to alter and control the following properties of spray dried powders; appearance, particle size and size distribution, bulk density, particle density, porosity, moisture content, flowability, stability, dispersability, friability and retention of activity, aroma and flavor (Masters,1985; Newton, 1966). Obviously, the design of the nozzle and drying chamber will affect particle properties, and the desired powder characteristics should be borne in mind when a spray dryer design is selected.

An increase in 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 (Masters, 1985). 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, although Kata and Wayer (1985) report 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. The effect of temperature on particle size appears to be highly dependent on the material being dried (Crosby and Marshall, 1958). It was observed that for crystalline materials, such as sodium sulfate, temperature had very little effect whereas for coffee extract (a film forming material) the mean particle diameter was significantly reduced by increasing the inlet air temperature. In contrast, Newton (1966) reports a study 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 (Marshall, 1954; Masters, 1985). As a general rule, smaller particles will usually be more dense, and so the bulk density of a powder with a small particle size will be higher. Bulk density will also increase with 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 - this point will be discussed further in section 3.7. As would be expected, increased dryer outlet temperatures result in a lower final product moisture content.

3.0 THE APPLICATION OF SPRAY DRYING T0 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. In addition a number of formulation processes can be accomplished in one step in a spray dryer; these include encapsulation, complex formation and even polymerization. Spray drying is also a convenient method of drying heat sensitive pharmaceuticals, such as protein drugs, with minimal loss of activity. This is one area where the potential of spray drying has yet to be fully exploited.

3.1. Excipient Production

Spray dried lactose is by far the most commonly encountered spray dried pharmaceutical excipient, and has been available for many years. It is prepared simply by spray drying a lactose concentrate, as opposed to centrifuging and drying the concentrate, which had been the traditional method for lactose preparation. The main advantage of spray dried lactose compared to conventionally prepared lactose is that it is directly compressible (Castello and Mattocks, 1962; Gunsel and Lachman, 1963).

Gunsel & Lachman (1963) evaluated and compared a number of formulations containing traditionally prepared and spray dried lactose.

They observed superior physical properties, such as reduced friability, in most of the formulations containing spray dried lactose as opposed to conventionally processed lactose. Spray dried lactose was more susceptible to discoloration on ageing than conventionally processed lactose. The cause of this phenomenon was not fully explained by the authors.

Recent studies have shed light on the mechanism by which spray drying improves the compressibility of lactose (Vromans et al, 1987). Commercially available spray dried lactose was reported to consist of about 15% amorphous lactose and 85% crystalline α-lactose monohydrate. Lactose of this type could be produced by spray drying a dispersion of crystalline lactose in a saturated solution of lactose. The amount of lactose dissolved at the time of spray drying determines the proportion of amorphous lactose present. Lactose with varying amorphous contents was prepared by suspending crystalline lactose of a known particle size in a saturated aqueous lactose solution maintained at different temperatures. The authors concluded that the amorphous lactose acts essentially as a binder for the crystalline lactose, by coating the individual crystals. A significant increase in tablet strength was observed with a decrease in the particle size of the crystalline component; this factor seemed to be more significant than the proportion of amorphous lactose present in the product.

Dicalcium phosphate was also spray dried from a suspension in a saturated lactose solution resulting in a surface coating of amorphous lactose around the dicalcium phosphate crystals. The tablets produced from this product also had a significantly increased crushing strength when compared to those produced from physical mixtures of the two excipients. This evidence also seemed to indicate that amorphous lactose can act as a binder for crystalline material.

3.2. Microencapsulation

A microcapsule can be either an individually coated solid particle or liquid droplet, or a matrix of wall material containing many small, fine core particles. The former type of microcapsule can be prepared by numerous methods including coacervation, coating and interfacial reaction techniques. Matrix microcapsules are usually prepared by spray drying or spray congealing. Spray drying can be used simply to separate previously prepared microcapsules from the vehicle, or for the preparation of microcapsules in a single operation (Voellmy *et al.* 1977). In the spray congealing process, no solvent is used. The feed, which consists of the coating and core materials, is fed to the atomizer in the molten state. Microcapsules form when the droplets meet the cool air in the drying chamber and congeal (Deasy, 1984).

Oil soluble vitamins, such as A and D, have been microencapsulated by spray drying an emulsion of the oil in a gum arabic or gelatin solution (Nielson, 1982). Various aromatic oils which are used in the flavoring of pharmaceuticals have also been microencapsulated by spray drying to produce a free flowing powder (Deasy, 1984). Spray drying has also been used in the preparation of polymer coated microcapsules for the purposes of taste masking (Nielson, 1982).

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

Biodegradable microcapsules have been prepared by spray drying. Polylactic acid (PLA) microcapsules were prepared from solutions or

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

Wise *et al.*(1976) prepared biodegradable microcapsules of a lactic-glycolic acid copolymer by spray drying. The core material was an anti-malarial drug. The microcapsules were subsequently suspended in carboxy methylcellulose and injected into rats for evaluation as an implantable drug delivery system.

Takenaka *et al.*(1980) prepared enteric coated microcapsules of sulphamethoxazole by spray drying an aqueous solution of drug and cellulose acetate phthalate (5%), with or without various additives, such as monmorillonite clay and colloidal silica. Particles with diameters ranging from 3.6 to 22.0μm were obtained. Formulations containing additives yielded smaller particles than those without additives. The addition of additives also improved the surface texture of the spray dried products, as compared to particles prepared from non-additive formulations, which tended to have flaky surfaces. Non-additive formulations also exhibited poor flow properties and thus were not easily tableted, whereas formulations which included additives were tableted easily. All sulphamethoxazole formulations containing cellulose acetate phthalate

(CAP) exhibited some conversion of the drug from crystalline form I to form II and an amorphous form during spray drying (Takenaka *et al.* 1981). Form II was also obtained by freeze drying or vacuum drying sulphamethoxazole. When microcapsules were prepared by a coacervation technique the drug remained in form I. CAP was presumed to interact with the sulphamethoxazole, since the degree of amorphism increased with an increase in the concentration of CAP in the formulation.

Further studies examined the effect of spray drying sulphamethoxazole with xanthan gum or guar gum, with and without colloidal silica or cellulose acetate phthalate (Kawashima *et al.* 1983a). It was found that the film forming capacity of xanthan gum alone was superior to that of guar gum, but inclusion of colloidal silica or cellulose acetate phthalate made the resultant product smoother still. X-ray diffraction data showed that the presence of cellulose acetate phthalate actually caused a polymorphic change resulting in a mixture of forms I, II and III (form III had been indistinguishable in the previous study which used IR analysis). When the formulation contained colloidal silica, however, the sulphamethoxazole was always present in form I, irrespective of the gum type. When neither CAP or colloidal silica was included in the formulation, the product was usually a mixture of all three forms.

Traue and Kala (1984) prepared phenobarbital microcapsules from aqueous polyacrylate dispersions by means of spray drying. They observed an increase in microcapsule size with an increasing viscosity of the feed dispersion, which is presumably related to the increased proportion of polymer present in the feed.

Microencapsulation by spray drying can be used to stabilize volatile compounds. Several binders were investigated in a study to evaluate the agglomeration of volatile pharmaceuticals (Kawashima *et al.* 1972). The

binders evaluated were gelatin, gum arabic, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), carboxymethylcellulose (CMC), methylcellulose and tragacanth. Formulations containing binder, salicylic acid (which sublimes at 75°C) and sodium salicylate were spray dried at an air inlet temperature of 150°C. Salicylic acid was only retained in the gum arabic and PVP products; it was presumed that these binders must have encapsulated the medicaments. As the gum arabic concentration in the slurry increased, the amount of retained salicylic acid increased.

Microencapsulation is also commonly used in the food industry to protect volatile compounds, oils and oleoresins from evaporation, oxidation and chemical reaction. Rosenberg *et al.*(1990) spray dried diluted emulsions in which volatile esters (the core material) were the dispersed phase, and the polymer coating material (gum arabic, sodium alginate or gelatin) was the continuous phase. It was found that an increase in the solids concentration of the feed solution steeply 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.

The same authors used a novel electron microscopy technique which enabled them to examine both the outer and inner surfaces of the

microcapsules (Rosenberg *et al.* 1985). They were able to identify poor wall forming materials (such as dextrin) which were characterized by deep dents pores and crack, and also to observe the exact location of the volatile materials within the microcapsules. The esters were seen to be dispersed as small droplets (0.5-2μm diameter) in the capsule walls. Large voids were seen to exist in the centers of the microcapsules, occupying most of their volume. Water soluble esters were observed to be retained less well than esters of lower polarity. This was attributed to their greater ability to diffuse through the polymer walls.

An alternative technique for the preparation of microcapsules in a spray dryer is that of spray polycondensation (Voellmy *et al.* 1977). This is a technique whereby polymer formation from reactive monomers, encapsulation and product separation from the vehicle are all accomplished in a one stage process. The feed consists of a dispersion of the core material and monomers, or precondensates of relatively low molecular weight, in addition to other film forming agents and the catalyst. This technique was used by Voellmy *et al.*(1977) to produce microcapsules which developed slow release properties after curing.

Takenaka *et al.*(1982a) used spray polycondensation to produce smooth, spherical microcapsules of L-ascorbyl monostearate of size 1-10μm. The average size of the microcapsules increased and the drug content decreased with increasing amounts of reactive monomer; this was attributed to enhanced polymerization leading to the formation of microcapsules with thicker walls. These authors also evaluated the rheology of ointments incorporating the microcapsules, and observed an increase in the mechanical strength with an increase in the amount of reactive monomer present in the formulation. In addition, increasing amounts of reactive monomer enhanced the stability of the drug to oxidation.

Lipid micropellets in the micrometer and nanometer size range have been prepared using spray drying and spray congealing techniques (Eldem *et al.* 1991 a & b). For the spray congealing process, the lipids were melted to 10°C above their melting point and the molten feed was sprayed into air at room temperature. Spherical particles were most easily obtained using the spray congealing method, although their size distribution was wider. Calorimetric analysis showed that all spray dried and spray congealed micropellets exhibited an unstable polymorphic structure, which reverted to a more stable structure after storage for six months at elevated temperatures. The unstable form seemed to be associated with the smooth spherical structure exhibited by some pellets since conversion to a more stable form on storage was accompanied by a loss of the smooth surface structure. In some instances, the presence of lecithin retarded the conversion to the stable form, although it tended to be less effective at higher storage temperatures. The presence of steroid drugs in some cases stabilized and in other cases destabilized, the microspheres, depending on both the lipid composition of the pellets, and the drug. The unstable polymorphic structure was thought to result from the rapid crystallization which takes place during the spray processes.

Small, unilamellar phospholipid vesicles (of size 18-70μm) have also been spray dried (Hauser and Strauss, 1987). Their average size and size distribution, as well as the bilayer integrity, were preserved during spray drying-rehydration cycles when 0.3M sucrose was included in the feed medium as a stabilizer. In the absence of sucrose, the vesicles aggregated and fused and, in addition, the bilayer integrity was lost leading to an exchange of material between the internal and external compartments.

3.3. Granulation

Spray drying is a useful alternative to wet granulation for tablet

formulations that cannot be directly compressed. Slurries of up to 60% solids can be dried successfully (Newton, 1966).

Raff *et al.*(1961) described the production of a spray dried granulation from a slurry of approximately 50-60% solids by weight, composed of filler, binder, disintegrant and a coloring agent if desired. The granulation could then theoretically be mixed with up to 90% medicament prior to compression, although in the case described the drug (chlorpromazine) was present at a concentration of less than 3%. Particle size ranges of 10-70μm were obtained using a laboratory scale spray dryer, but a size range of 100-250μm was found to be most advantageous for tablet preparation on a large scale. The advantages of this method of granulation over traditional methods were reported to be; improved flowability, improved color uniformity, improved stability, improved hardness and lower lubricant requirements.

Spray drying was used to agglomerate aluminium silicate and magnesium carbonate with various binders, in order to improve flow and other tableting properties (Takenaka *et al.* 1971). The granules produced had diameters of 10-80μm as compared to 1-8μm for the original samples and were free flowing in almost all cases. The geometric mean diameter was found to be most dependent on the type of binder used, and also the binder concentration. The smallest particles resulted from the binder free formulations. The granules containing binder could all be tableted easily which the original powders could not. Formulations with higher binder concentrations had improved flow properties and resulted in tablets with the highest apparent density and hardness.

Cham *et al.*(1987) compared conventional granulation with spray drying for the production of heavy magnesium carbonate powder. They found, however, that conventional granulation imparted better flow

properties and a higher bulk density than spray drying. They attributed these results to the regular particle shape achieved by conventional wet granulation. This contrasts with observations by other authors that spray drying produces regularly shaped spherical particles with good flow properties.

Sugimori *et al.*(1990) compared high speed mixing, fluidized bed granulation and spray drying in the production of acetominophen 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. The authors pointed out, however, that spray drying is a useful method for mass production of granules, since it makes continuous granulation possible.

Seager *et al* .(1979) and Rue *et al* .(1980) compared the structure and tableting properties of acetominophen granules produced by spray drying, roller compaction and wet massing, using gelatin as a binder. They observed that in spray dried granules the binder concentrated as a shell at the surface of the spherical granules. By comparison, in wet massed granules the binder was distributed through the agglomerates in a sponge like matrix, and in roller compacted granules the binder was present as discrete particles embedded in the agglomerates.

At any given compaction pressure, the strongest tablets were produced from spray dried granules. This phenomenon was attributed to the concentration of the binder at the granule surface where it is ideally placed to form inter-granular bonds. As the binder concentration in the spray dried granules increased from 1% to 3%, tablet strength also increased, but above this, tablet strength was not influenced by binder concentration. The low tablet strengths observed at low binder

concentrations was attributed to the presence of incomplete gelatin shells around the granule. Once the binder shells are continuous, however, the area of inter-granular bonding becomes constant and hence tablet strength also reaches a plateau.

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

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

Slow release theophylline tablets were prepared by compressing spray dried microspheres containing Eudragit (Takeuchi *et al.* 1989). Depending on the amount of polymer present, the spray dried powder consisted of either agglomerated, polymer coated theophylline crystals or spherical particles of a solid dispersion of amorphous drug in a polymer base. Spray drying was also used for the production of microspheres containing paracetamol and Eudragit (Bécirevic, 1989). Spherical, aggregated particles of size 5-20μm were formed which were compressed to produce matrix tablets with slow release properties.

Asker and Becker (1966) used spray drying technology to produce prolonged release sulfaethylthiadiazole (SETD) granulations. A follow-up series of papers investigated the production of slow release sulphaethylthiadiazole-wax granulations by spray congealing (Cusimano and Becker, 1968; John and Becker, 1968; Hamid and Becker, 1970). This technique had previously been used for the production of 35μm SETD-hydrogenated castor oil granules, which were used in the formulation of a

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

3.4. Complex Formation

Spray drying is a convenient method for the production of pharmaceutical complexes, since solid particulates can be produced from droplets undergoing chemical reaction in one step.

Inclusion complexes of various drugs, such as paracetamol, with β-cyclodextrin were prepared by spray drying (Lin and Kao, 1989). The drug-β-cyclodextrin complexes existed in the amorphous state, with a mean particle size of less than 10μm and a range of 3-40μm. In all cases the particle size of the complex was smaller than that of the original drug, and the particles were found to be approximately spherical. However, the powders were found to have poor flow properties and also to exhibit poor compressibility. The dissolution rate of tablets formulated from the spray dried complexes was greater than from tablets formulated from physical mixtures. This was attributed to a decrease in drug crystallinity, small particle size and complex formation.

The production of β-cyclodextrin complexes by spray drying was evaluated as a potential method for increasing the bioavailability of the poorly soluble, hydrophobic drug, diazepam (Bootsma et al, 1989).

Differential scanning calorimetry (DSC) data indicated that at levels of 5% diazepam or less, the product consisted only of complex and β-cyclodextrin, however at higher drug loading, pure diazepam was also present. Diazepam was also spray dried with lactose, with which it cannot complex, in order to ascertain the relative importance of complexation in the observed bioavailability increase. It was noted that all spray dried formulations dissolved much faster than drug/excipient physical mixtures. The authors found that at low drug levels complexation played only a minor role in the dissolution rate increase, since spray drying with lactose was equally effective. This led to the conclusion that the formation of intimate physical mixtures by spray drying with the highly soluble excipients was largely responsible for the improved dissolution profiles. However at high drug levels, β-cyclodextrin formulations had a considerably higher intrinsic dissolution rate than lactose formulations. Data obtained under conditions where the immediate microenvironment of the formulation was relatively undisturbed (such as *in vitro* data obtained at slow stirring rates) showed enhanced dissolution from β-cyclodextrin formulations even when the drug was present at low concentrations. This was attributed to the cyclodextrin increasing the diazepam solubility in the boundary layers. At high stirring rates, this effect does not occur due to the absence of thick boundary layers; the β-cyclodextrin concentration being too low to significantly increase the drug solubility in the bulk solution.

Aminophylline has been successfully prepared by spray drying a solution of theophylline and ethylenediamine (Takenaka *et al.* 1982b). DSC data indicated that the strength of the bond between the ethylenediamine and the theophylline was affected by the drying temperature. The preparation time was greatly reduced compared to that required using traditional preparative methods which involve several time consuming

stages. The packing and flow properties of the complex were found to be superior to those of the original theophylline particles, which was attributed to their particle shape.

Kawashima *et al.* (1984) investigated the possibility of spray drying theophylline and phenobarbital in order to produce directly compressible intimate physical mixtures. These authors wished to avoid complex formation since the complex has poorer bioavailability than the physical mixture. As expected, the ratio of theophylline to phenobarbital in the mixture affected the amount of complex formed. Other factors which affected the amount of complex formed were the amount of excipient (colloidal silica or methylcellulose), the pH of the feed solution and the drying temperature. Powders spray dried from aqueous slurries were physical mixtures with a small amount of molecular complex, whereas products prepared from ammonium hydroxide slurries showed extensive complexation. An increase in the drying temperature caused an increase in the degree of melting of the phenobarbital and consequently an increase in the theophylline:phenobarbital ratio in the final product.

Kawashima *et al* .(1983b) also used spray drying for the production of aminopyrine barbital complexes which were dried from feeds incorporating various excipients. In this study, drying, complexation, and agglomeration were all accomplished in one step. Again, small, spherical particles were produced, but the compressibility was found to be dependent on the particular excipient included in the formulation. When the formulation did not contain any excipient, no product could be recovered from the spray dryer. The drug content of the final product also varied depending on the excipient used, as well as on the drying temperature and the rotational speed of the rotary atomizer. Decreasing the drying temperature or increasing the rotational speed of the atomizer led to an increase in drug content.

Some oxidation of aminopyrine occurred during spray drying, the degree of which was dependent on the drying temperature, atomizer speed and on the type of excipient used in the formulation (Kawashima, 1983b). It was observed that the extent of aminopyrine auto-oxidation increased with increasing pH of the feed solution. Increasing the drying temperature increased the degree of auto-oxidation up to a maximum level at 100°C. At temperatures greater than this, oxidation was reduced, which was attributed to rapid solidification of the droplets in the dryer. The incorporation of additives into the feed solution could significantly reduce the degree of oxidation. The best additives were found to be ethylene diamine tetraacetic acid (EDTA) or glycine. This led the authors to conclude that the additives were reacting with a trace metal in the feed solution which was responsible for catalyzing the aminopyrine oxidation (Kawashima *et al.* 1983c).

3.5. Modification of Biopharmaceutical Properties

Spray drying has been used extensively to enhance the dissolution rate of poorly soluble drugs. This usually occurs as a result of a polymorphic change from a crystalline form to an amorphous form or a higher energy crystalline form during spray drying. Other factors also may be responsible for, or contribute to, the enhanced dissolution rate, such as particle size reduction and the ability to form intimate physical mixtures, or solid dispersions, with highly soluble excipients.

In a study comparing air attrition and spray drying of poorly water soluble quinazoline compounds, the dissolution rate of the spray dried powders was found to be much more rapid than that of powders prepared by air attrition, even though the spray dried particles were larger and had a lower specific surface area. This was attributed to the tendency of the particles micronized by air attrition to form large aggregates which

slowed their dissolution. When the particles were pelletized, however, the differences in dissolution between spray dried particles and those prepared by air attrition were eliminated (Kornblum and Hirschorn, 1970).

Takeuchi *et al.* (1987a) used spray drying to prepare spherical particles loaded with fine drug crystals (tolbutamide). A much greater drug to core ratio was achieved compared to a conventional ordered mix or solvent deposition system . It was found that when efficient disintegrating agents were used as the core material, the particles had good dissolution properties despite the high drug loading.

Solid dispersions of tolbutamide with enteric coating polymers and with colloidal silica were also prepared by spray drying (Takeuchi *et al.* 1987b). In both cases spherical particles containing amorphous drug resulted, with improved dissolution properties compared to the original drug. In the case of the polymer containing dispersions, the increased solubility was attributed to the improved wettability of the particles, rather than a change in the drug's crystallinity. However, with the colloidal silica dispersions, the increase in dissolution rate was attributed to both reduced drug crystallinity and increased wettability.

The solubility of non steroidal anti-inflammatory drugs can be substantially improved by spray drying, due to an alteration in the predominant polymorphic form. Indomethacin, which has a melting point of around 160°C (the exact value depending on the polymorph in question) was spray dried as an ethanolic solution in the presence and absence of polyvinyl pyrrolidone (PVP) (Corrigan *et al.* 1985). In the absence of PVP, a glassy amorphous phase formed on the wall of the cyclone separator which became crystalline within a week. In the presence of PVP an amorphous phase was still formed but the conversion to a crystalline phase was significantly retarded. When the PVP concentration was

increased above 20% an amorphous powder formed in the collecting vessel. A physically stable amorphous form of the drug was considered desirable because of its greater solubility. Ketoprofen and ibuprofen could also be converted to stable amorphous solid products when spray dried in the presence of 50-75% PVP. These drugs have an increased PVP requirement due to their lower melting points. In the absence of PVP the products were liquids.

The same authors investigated the effect of spray drying on various thiazide diuretics. When hydroflumethiazide was spray dried from an alcoholic system containing 20% PVP, the solubility was increased to 4-5 times that of the corresponding physical mixture. This compared with a solubility increased by a factor of only 1.6 when pure drug was spray dried, even though the pure spray dried drug was amorphous. Also, when pure drug was spray dried, it converted to a crystalline form within about 12 days. Spray drying in the presence of 10% PVP resulted in a solubility about 2.5 times that of the crystalline drug. The authors therefore proposed the existence of two amorphous states, with the pure drug amorphous phase still having considerable structure despite the absence of crystallinity. The degree of disorder was proposed to increase with increasing PVP content as evidenced by thermodynamic studies (Corrigan and Holohan, 1984a; Corrigan *et al.* 1983).

Several other thiazide diuretics have been prepared by spray drying from ethanolic solutions. It was observed that lower molecular weight thiazides, such as chlorthiazide, hydrochlorthiazide and hydroflumethiazide formed amorphous phases less readily, and when formed, these phases had poor physical stability with only moderate solubility enhancements. Spray dried hydrochlorthiazide was stable for only 24 hours and chlorthiazide failed to form an amorphous phase at all unless PVP was included in the

formulation. In contrast, however, the larger molecular weight compounds, such as bendrofluazide and cyclopenthiazide gave amorphous phases on spray drying (without PVP) which were physically stable (even after twelve months) and considerably more soluble than the crystalline material (Corrigan *et al.* 1984b).

Spray drying of the poorly soluble drug, mefruside, with 50% PVP 30 also resulted in enhanced dissolution, when compared to a physical mixture of micronized drug with PVP (Junginger, 1984). The crystal form of several other drugs has been reported to be altered during spray drying, with the nature of any additives present significantly affecting the predominant form.

Spray drying salicylic acid with acacia increased the drug solubility and dissolution rate. This was partly due to a decrease in drug crystallinity. Formulations with low weight ratios of salicylic acid to acacia appeared to be amorphous, however an increase in the ratio of salicylic acid to acacia led to an increase in the crystallinity of the product. If the ratio is increased above a certain point, the salicylic acid is not completely encased, and thus may sublime and recrystallize in the collector which would result in an apparent increase in crystallinity of the spray dried product. The authors concluded that although spray drying did reduce drug crystallinity, it was the greatly improved wettability of the product due to the incorporation of the acacia that was mainly responsible for the improved solubility.

The temperature at which spray drying is carried out can have a significant effect on the predominant crystal form of a drug. Kawashima *et al.*(1983) in preparing a pyrabarbital complex observed a greater degree of amorphism when the feed was dried at a temperature of 145°C as opposed to 85°C. This was attributed to the more rapid evaporation which occurs at higher temperatures. Spray drying a solution of phenylbutazone in

methylene chloride resulted in differences in the predominant polymorphic form depending on the drying temperature (Matsuda *et al.* 1980; Matsuda *et al.* 1984). The authors observed that high drying temperatures allowed the formation of the most stable form (δ). As the drying temperature was reduced, more of form β was present. When the drying temperature was lowered below 60°C, increasing amounts of a third form (ε) were present, which was presumed to be associated with the slower rate of solvent evaporation. This form also exhibited a significantly higher solubility than that of any other known crystalline form.

3.6 Dry Powder Aerosol Formulation

The use of spray dried powders in dry powder aerosol formulation is an area which has not been extensively investigated to date, but is one where spray drying would seem to have a great deal of potential because of its ability to produce powders to predetermined specifications.

Vidgrén *et al.* have published a series of papers comparing the inhalation properties of spray dried and mechanically micronized sodium cromoglycate (Vidgrén *et al.* 1987a; Vidgrén *et al.* 1988a; Vidgrén *et al.* 1989). They observed superior *in vitro* deposition (using the cascade impaction model) in the therapeutically important area of the simulated respiratory tract from dry powder aerosols than from metered dose aerosols with both spray dried and mechanically micronized drug (Vidgrén *et al.* 1988a).

The accepted optimum size range for locally acting inhaled drug particles is about 0.5-7.0μm. The range 3.3-7.0μm represents deposition in the bronchioles, and the range 0.5-3.3μm represents deposition in the alveoli. Because of inter-particulate cohesive forces which tend to cause small particles to agglomerate, dry powder aerosols are generally formulated as drug mixtures with lactose particles as a carrier.

Spray drying was found to convert sodium cromoglycate to spherical particles of an amorphous nature. This contrasted with the small, irregularly shaped crystals obtained by micronization. The mean size of the spray dried product was slightly smaller (mean diameter 2.81μm as opposed to 3.81um for the micronized material), and the size distribution was also a little narrower.

Both methods of powder preparation resulted in about the same proportion of material (approximately 40%) having an acceptable particle size (i.e. 0.5-7.0μm). However, in the case of the spray dried material, approximately 2/3 of this was in the range 0.5-3.3μm, whereas less than 1/3 of the therapeutically relevant micronized drug was in this range (Vidgrén *et al.* 1987a). Whilst this difference is not really important for locally acting drugs such as sodium cromoglycate, it could be extremely important if the pulmonary route was to be used as a means of delivering drugs systemically since deposition in the alveolar region is required for absorption. In this instance, spray drying would seem to be a better method for particle size reduction than mechanical micronization.

The *in vitro* deposition behaviour of spray dried and commercially available sodium cromoglycate, from two dry powder devices was compared using the cascade impaction model. Significantly more of the spray dried material was retained in both devices compared to the commercially available micronized material (Vidgrén *et al.* 1988b). The authors proposed that this was due to the more cohesive nature of the spray dried material because of its smaller particle size or more activated particle surface.

One potentially serious problem that was observed with spray dried sodium cromoglycate was the high hygroscopicity which it exhibits. No changes in crystalline structure were observed provided the material was

stored at a relative humidity of less than 60%, however the crystal structure clearly changed at humidity levels greater than this. Spray dried particles were observed to recrystallize, and large aggregates formed. This had an extremely deleterious effect on the *in vitro* inhalation properties of the spray dried drug. After storage at 80% relative humidity for twenty days, only 8% of the drug was in the size range 3.3-7.0μm and only 0.4% was in the range 0.5-3.3μm. In contrast, the particle size of mechanically micronized drug was virtually unaffected by storage at high humidity (Vidgrén *et al.* 1989). This effect may place limitations on the use of spray dried amorphous sodium cromoglycate in dry powder aerosols.

These authors also used spray drying to produce ^{99m}Tc-labelled sodium cromoglycate particles for *in vivo* deposition studies in humans (Vidgrén *et al.* 1987b). This strategy made it possible to carry out tracer studies using actual drug as opposed to inert particles which have been used in the past.

3.7 Heat Sensitive Materials

Spray drying is a recognized method for the processing of heat sensitive materials. It can be used for materials of this nature since the cooling effect caused by the solvent evaporation means that the temperature of the dried product does not rise above its wet bulb temperature. As the feed droplets come into contact with the hot air, the liquid begins to evaporate. A skin forms at the surface of the droplets and as it thickens it restricts further moisture evaporation. At this time (the falling rate drying period) particles form, their temperature begins to rise and thus they become more heat sensitive. Large scale degradation is prevented, however, since the evaporated moisture absorbs most of the available heat. Generally the particles reach a maximum temperature which is 15-20°C

below the outlet temperature of a co-current dryer (Masters, 1990). The extent of destruction of thermolabile materials is particularly dependent on the temperature-time combinations that they encounter during the process as well as the inherent thermolability of the material in question (Daemen and van der Stege, 1982). Typically, the time period of exposure to elevated temperatures is only 5-30 seconds (Deasy,1984).

3.7.1 Food Proteins

A number of protein products in the food industry are processed by spray drying and there is an abundance of information in the food science literature concerning the spray drying of milk, eggs and proteins from various other sources. Much of the information presented here is of limited relevance to the drying of pharmaceutical proteins, since food scientists are more concerned with the functional properties of the product (e.g. dispersability) rather than activity. Nevertheless, since the spray drying of pharmaceutical proteins is a relatively new area of interest, it is useful to first briefly review the drying of food proteins since this may provide useful clues as to how the spray drying process affects macromolecules.

Rao and Mathur (1987a & b) investigated the effect of processing changes (prewarming and spray drying) on the properties of infant milk powder. They observed evidence of several inter and intra molecular interactions induced by the thermal processing. Electrophoretic studies seemed to indicate the presence of large molecular aggregates not present in the raw material. Gel chromatography pinpointed noticeable differences between infant formula spray dried at 95°C and that spray dried at 110°C. For example, one fraction of α-lactoglobulin was completely absent from the sample dried at the higher temperature indicating a greater degree of denaturation. The authors also observed a loss in reconstitution

characteristics of the proteins on storage. This was thought to be partly due to the coalescence of fat globules leading to increased hydrophobicity and therefore decreased wetting, and partly due to the formation of protein aggregates.

Omar and Smietana (1986) observed that the addition of calcium chloride to skimmed milk prior to pasteurization and spray drying improved the wettability and solubility of the dried milk and reduced the level of whey protein denaturation during heat treatment. Calcium ions were reported to form a calcium linked complex between the whey protein and the casein whilst reducing denaturation because of the increased heat resistance of the complex.

Spray drying was found to adversely affect the nutritional value of lactose hydrolyzed milk under conditions which were acceptable for normal milk (inlet temperature 185°C, outlet temperature 85°C) (Burvall *et al.* 1977). Spray drying caused a 35-40% loss in biologically available lysine (as determined by a protein utilization assay in growing rats), which was attributed to Maillard reactions occurring between the lactose derived sugars and the proteins. These reactions particularly affect lysine which constitutes more than 90% of all free amino groups in a protein. This problem did not occur when hydrolyzed milk was freeze dried or when non-hydrolyzed milk was spray dried. The lysine loss was not associated with any visible browning. The authors concluded that considerably milder conditions, or other drying processes, must be employed for lactose hydrolyzed milk. Rawson and Mahoney (1983) also observed only a small loss in reactive lysine (<10%) when lactose hydrolyzed milk was freeze dried; the total lysine was unchanged so the small loss in reactive lysine was attributed to early Maillard reactions. When the milk was spray dried, there was a fall of about 18% in reactive lysine and a similar fall in total

lysine and nutritional quality of the protein. This indicated advanced Maillard reactions in which the lysine moiety is destroyed. The difference between their data and the 35-40% loss observed by Burvall *et al.*(1977) may have been due to differences in process conditions and equipment. The milk powders were stored at 30°C under different humidity levels, and it was observed that the losses in reactive lysine, total lysine and nutritional value were much greater during storage than during processing; both freeze dried and spray dried powder lost reactive lysine at approximately the same rate. It seemed that the fall in protein quality correlated well with the loss in reactive lysine. The authors concluded that both spray dried and freeze dried lactose hydrolyzed milks need to be stored at very low humidities to avoid deterioration.

Galyean and Cotterill (1979) investigated the effect of spray drying on the chromatographic and electrophoretic behaviour of egg white. The egg white was spray dried from feed solutions varying in pH from pH 4 to pH 10, at a dryer inlet temperature of 137°C and an outlet temperature of 65-68°C. There were only slight alterations in the chromatographic peaks of these components, and the authors proposed that spray drying caused small changes, possibly in the secondary or tertiary structure of the proteins, without causing large scale denaturation. It had previously been observed (Hill *et al.* 1965) from electrophoretic evidence that conalbumin did undergo denaturation when spray dried. Denaturation was observed to be greater when the feed pH was 5.5-6, which is close to the isoelectric point of the protein (pH 6.0). The globulin constituents of the egg white underwent considerable denaturation during spray drying at all pH's, and could not be rehydrated. This was thought to be due to denaturation by foaming resulting from the shear forces applied to the protein during atomization.

Parkinson (1977) observed a high degree of stability of egg white towards the spray drying process. A partial reduction in the content of ovalbumin, ovomucoid and conalbumin was observed, but the addition of milk to the egg before spray drying resulted in a marked increase in the stability of these three proteins.

3.7.2. Enzymes and Pharmaceutical Proteins

A variety of heat sensitive biological materials are currently spray dried. These include enzymes, sera, plasma, micro-organisms and yeasts. In addition a number of heat sensitive, biologically active pharmaceutical materials can be processed in this manner, such as antibiotics, vaccines and, very recently, macro-molecular drugs.

The spray drying of enzymes is particularly interesting from a pharmaceutical point of view. Some macromolecular drugs are enzymes (e.g. streptokinase), and enzymes are frequently used as model protein drugs (for example, in lyophilization studies) due to the ease with which their activity can be determined.

Enzymes, such as amylase, β-galactosidase and renin, are currently spray dried in large and small quantities for use mainly in the food and chemical industry. The activity losses encountered during the spray drying process are obviously dependent on the enzyme in question, and can usually be reduced by the incorporation of additives, such as sugars and salts. Masters (1985) reports that activity losses in extremely heat sensitive enzymes can be prevented by drying a mixture of enzyme and salts containing water of crystallization, such as $Na_2SO_4.10H_2O$. Low outlet temperatures are required which result in a product with a high moisture content. This can be reduced, however, by passing the spray dried product through a fluid bed dryer for further drying. Spray dried enzymes can be

mixed with waxes and spray cooled to produce powders with reduced dustiness.

In a patent held by the Rohm and Haas Company (1980), the spray drying of various enzymes is described. Water insoluble salts, such as tribasic calcium phosphate, and water insoluble suspenders and thickeners, such as corn starch were added to the feed concentrate. The best inlet and outlet temperature ranges were 155-165°C and 75-83°C respectively. The products containing additives were generally free-flowing and retained their good flow properties on storage, whereas those without additives tended to become lumpy on storage.

Shah (1963) carried out an extensive study of the effect of spray drying on the enzyme rennet. He evaluated the effect of various additives on both the activity retention and storage stability of spray dried rennet. Gelatin and dextrin were found to be the best additives in terms of both activity recovery and storage stability. Other substances which improved activity recovery were succinate, oxalate, lysinate, sodium tartrate, sucrose and galactose. Generally, the additives which were beneficial during drying were also beneficial during storage, but some exceptions were observed, such as oxalate which reduced the storage stability of rennet. The reducing sugars (lactose and glucose) had no effect on activity recoveries and adversely affected the storage stability due to the occurrence of Maillard-type browning reactions.

The influence of dryer operating parameters on the activity recovery of rennet was also evaluated. Only the dryer temperature had a major influence and it seemed that outlet temperature was much more important than inlet temperature. The moisture content of the spray dried material was in the range 0.5-3.5% but could not be correlated to any dryer variables. The author proposed that it was a function of the humidity of the drying air.

Daemen and van der Stege (1982) examined the effect of spray drying on the activity retention of a number of enzymes. They observed that when the dryer outlet temperature was kept constant (by feed rate adjustment) throughout a series of experiments conducted at different inlet temperatures, the variation in inlet temperature had only a slight effect on the degree of activity loss. However, if the feed rate was kept constant while the inlet temperature was varied, so that the outlet temperature also changed, the effect of varying inlet temperature seemed to be much more significant. These observations again indicated that the dryer outlet temperature was more important in terms of activity retention than the inlet temperature. This was confirmed by the steep slopes observed when the residual activity was plotted against the outlet temperature.

For two of the enzymes and one of the bacteria investigated by Daemen and van der Stege, an increase in denaturation was observed with increasing total solids content of the feed. For one bacteria the reverse was true, however, and for renin a maximum activity retention was observed at a total solids content of around 20%, with levels above and below this showing reduced activity retention. This data did not agree with that of Shah (1963), who reported no effect of total solids content, at levels between 6 and 12%, on the activity retention of renin. It is therefore difficult to draw firm conclusions about the effect of total solids content of the feed, based on the information available to date.

Wijlhuisen *et al.*(1979) used a theoretical model in an attempt to explain enzyme inactivation during spray drying. According to their theory, for solid spheres, thermal degradation occurs to a greater extent in the interior of the spray dried droplet. This is because at the time when the temperature of the droplet begins to rise there is relatively little water near the surface of the particle and so the reaction rate here is relatively slow,

whereas at the center of the particle the moisture level is higher and the reaction rate is faster. Thus enzyme activity at the particle surface is retained but drops to zero further into the drop interior. When the authors used a hollow sphere model, they predicted a less steep gradient in enzyme activity due to a more uniform water content.

These authors offered explanations for the experimentally observed effects of processing parameters on activity retention. The increase in destruction with increasing outlet temperature was explained by the higher air temperature causing steeper water concentration profiles within the droplet. The end of the constant rate drying period is reached sooner and the surface layer in which the enzyme is protected from thermal degradation, due to low water content, is thinner. This effect, plus the faster temperature rise, increases degradation. Increasing the total solids content was predicted to lead to a small increase in thermal degradation because of an increase in droplet size and hence longer drying times.

Shah (1963) carried out some single drop studies in his investigation of the inactivation of renin. He also observed that enzyme inactivation occurs mainly during the period when the temperature of the drops rose from the saturation temperature (i.e. the falling rate drying period). Yamomoto *et al.*(1984) confirmed this observation in their study of the drying of single enzyme droplets. These authors measured residual activity, drop moisture content and drop temperature as a function of time. The inactivation of glucose oxidase was observed to be a simple first order process. The rate constant of this inactivation could be reduced by the presence of sucrose. The pH of the drop solution seemed to be important in determining activity retention, and in enzymes containing sulfydryl groups, the presence of the reducing agent, dithiothreitol, resulted in higher residual activities, indicating that oxidation was contributing significantly

to activity loss. As would be expected, the residual activity decreased with increasing drying air temperature. Also, small droplets were observed to exhibit a higher degree of activity retention than large droplets. This agrees with the observations of Shah. The authors developed mathematical models which allowed them to predict enzyme inactivation behaviour, drop temperature and moisture content during drying, from experimentally determined inactivation rate constants and diffusivities. However, these models could only be applied when the effects of pH and oxidation on inactivation were negligible.

Hemoglobin has been successfully spray dried at the laboratory scale with the inclusion of 0.25M sucrose as a protector (Labrude *et al.* 1989). Without a protector, approximately 50% of the hemoglobin was oxidized, even when the inlet and outlet temperatures of the dryer were only 60°C and 30°C respectively. However, when 0.25M sucrose was included in the formulation, the temperatures could be increased to 100°C and 70°C, with 97% of the hemoglobin remaining in the reduced form. At the higher drying temperature, the moisture content of the product was only 2.7%, compared to 4.7% at an inlet temperature of 60°C. Additionally, these drying conditions increased the product yield and improved its storage stability. The authors used their experience in lyophilization to assist in the selection of potential stabilizers. The stabilizers were generally more effective in freeze drying than spray drying; only sucrose was highly efficient in both. One disadvantage of sucrose, however, is its high hygroscopicity.

The authors used circular dichroism spectroscopy and electron spin resonance spectroscopy to study the oxidation of the hemoglobin, and they observed similar spectral changes when hemoglobin was either freeze dried or spray dried without protection.

The use of spray drying for the processing and formulation of macromolecular drugs is a very recent development, and as yet there is very little published information available which discusses this topic. American Cyanamid Company have recently patented a bovine somatotrophin formulation for the stimulation of milk production in dairy cows (Cady *et al.* 1989; Eur. Patent, 1987). Bovine growth hormone is initially spray dried from an ammonium hydroxide solution which also includes stabilizers, such as sodium benzoate, and non-ionic surfactants, such as a block copolymer of ethylene oxide and propylene oxide. A molten mixture of the spray dried material and a fat and/or wax is then spray congealed to form microspheres of 45 to 180 microns in size, which are then suspended in a suitable vehicle prior to administration. The authors found that by optimizing the hydrophobicity of the microsphere/vehicle formulation, they were able to achieve the desired sustaining effect.

4. SUMMARY

As this review indicates, spray drying has a number of applications in pharmaceutical formulation. It is an extremely useful technique for producing powders to predetermined specifications, since by modifying and optimizing both process and formulation variables, one can exert considerable control over the properties of the final product.

A number of formulation techniques, such as complexation and microencapsulation, can be accomplished in a single step in a spray dryer. This can both simplify the process and shorten the processing time.

The production of powders for dry powder aerosols by spray drying, and the spray drying of pharmaceutical proteins are two areas where it seems that the full potential of the process has yet to be exploited.

Spray drying may be a useful alternative to lyophilization for the drying of pharmaceutical proteins, since spray dried powders are often much more amenable to further processing than are lyophilized powders.

The main disadvantage of spray drying is the cost of both the equipment and the process. This may outweigh the advantages for some applications. However, as far as the formulation of pharmaceutical proteins is concerned, lyophilization is also an expensive process and so spray drying may be an economically viable alternative, particularly since the end product will generally be of very high value.

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