CHAPTER 2

LITERATURE REVIEWS

2.1 Probiotics

Probiotics are living microorganisms which when ingested have beneficial effects on the equilibrium and the physiological functions of the human intestinal microflora (Fuller, 1992). Probiotic bacteria, which are commensals of the human gut, have been reported to inhibit the growth of undesirable microorganisms and food poisoning bacteria, such as *Salmonella*, that can be encountered in the gastrointestinal tract (Huges and Hoover, 1991; Lim *et al*., 1993). The characteristics of a successful probiotic are acid and bile tolerance, antimicrobial activity against intestinal pathogens, and ability to adhere and colonize the intestinal tract. Beneficial effects of probiotic include alleviation of lactose intolerance, control of diarrhea, inhibition of intestinal pathogens, enhanced immune response and anticarcinogenic activity (Mishra and Prasad, 2005).

2.1.1 Health benefits of probiotic bacteria.

Experiments into the benefits of probiotic therapies suggest a range of potentially beneficial medicinal uses for probiotics. For many of the potential benefits, research is limited and only preliminary results are available. It should be noted that the effects described are *not* general effects of probiotics. Recent research on the molecular biology and genomics of *Lactobacillus* has focused on the interaction with the immune system, anti-cancer potential, and potential as a biotherapeutic agent in cases of antibiotic-associated diarrhoea, travellers' diarrhoea, pediatric diarrhoea, inflammatory bowel disease and irritable bowel syndrome (Ljungh and Wadstrom, 2009).

The effects of probiotics show here but all effects can only be attributed to the individual strain(s) tested. Testing of a supplement does not indicate benefit from any other strain of the same species, and testing does not indicate benefit from the whole group of LAB or other probiotics (Gilliland and Walker, 1990).

1. Managing lactose intolerance.

As lactic acid bacteria actively convert lactose into lactic acid,ingestion of certain active strains may help lactose intolerant individuals tolerate more lactose than what they would have otherwise (Sanders, 2000).

2. Prevention of colon cancer.

In laboratory investigations, some strains of LAB (*Lactobacillus bulgaricus*) have demonstrated anti-mutagenic effects thought to be due to their ability to bind with heterocyclic amines, which are carcinogenic substances formed in cooked meat (Wollowski *et al*., 2001). Animal studies have demonstrated that some LAB can protect against colon cancer in rodents, though human data is limited and conflicting (Brady *et al*., 2000). Most human trials have found that the strains tested may exert anti-carcinogenic effects by decreasing the activity of an enzyme called β-glucuronidase (which can generate carcinogens in the digestive system). Lower rates of colon cancer among higher consumers of fermented dairy products have been observed in some population studies (Sanders, 2000).

3. Lowering cholesterol.

Animal studies have demonstrated the efficacy of a range of LAB to be able to lower serum cholesterol levels, presumably by breaking down bile in the gut, thus inhibiting its reabsorption (which enters the blood as cholesterol). Some, but not all human trials have shown that dairy foods fermented with specific LAB can produce modest reductions in total and LDL cholesterol levels in those with normal levels to begin with, however trials in hyperlipidemic subjects are needed (Sanders, 2000).

4. Lowering blood pressure.

Several small clinical trials have shown that consumption of milk fermented with various strains of LAB can result in modest reductions in blood pressure. It is thought that this is due to the ACE inhibitor-like peptides produced during fermentation (Sanders, 2000).

5. Improving immune function and preventing infections.

LAB are thought to have several presumably beneficial effects on immune function. They may protect against pathogens by means of competitive inhibition (i.e., by competing for growth) and there is evidence to suggest that they may improve immune function by increasing the number of IgA-producing plasma cells, increasing or improving phagocytosis as well as increasing the proportion of T lymphocytes and Natural Killer cells (Reid *et al*., 2003). Clinical trials have demonstrated that probiotics may decrease the incidence of respiratory tract infections (Hatakka *et al*., 2001) and dental caries in children (Nase *et al*., 2001). LAB foods and supplements have been shown to be aid in the treatment and prevention of acute diarrhea, and in decreasing the severity and duration of rotavirus infections in children and travelers' diarrhea in adults (Reid *et al*., 2003).

6. Antibiotic-associated diarrhea

Antibiotic-associated diarrhea (AAD) results from an imbalance in the colonic microbiota caused by antibiotic therapy. Microbiota alteration changes carbohydrate metabolism with decreased short-chain fatty acid absorption and an osmotic diarrhea as a result. Another consequence of antibiotic therapy leading to diarrhea is overgrowth of potentially pathogenic organisms such as *Clostridium difficile*.

Probiotic treatment can reduce the incidence and severity of AAD as indicated in several meta-analyses. However, further documentation of these findings through randomized, double blind, placebo-controlled trials are warranted.

Efficacy of probiotic AAD prevention is dependent on the probiotic strain(s) used and on the dosage (Doron *et al*., 2008). Up to a 50% reduction of AAD occurrence has been found (Sazawal *et al*., 2006). No side-effects have been reported in any of these studies. Caution should, however, be exercised when administering probiotic supplements to immunocompromised individuals or patients who have a compromised intestinal barrier.

7. Reducing inflammation.

LAB foods and supplements have been found to modulate inflammatory and hypersensitivity responses, an observation thought to be at least in part due to the regulation of cytokine function (Reid *et al*., 2003). Clinical studies suggest that they can prevent reoccurrences of inflammatory bowel disease in adults (Reid *et al*., 2003), as well as improve milk allergies (Kijivainen, 2003). They are not effective for treating eczema, a persistent skin inflammation (Boyle *et al*., 2008). How probiotics counteract immune system overactivity remains unclear, but a potential mechanism is desensitization of so-called T lymphocytes, an important compenent of the immune system, towards pro-inflammatory stimuli (Braat *et al*., 2004).

8. Improving mineral absorption.

It is hypothesized that probiotic lactobacilli may help correct malabsorption of trace minerals, found particularly in those with diets high in phytate content from whole grains, nuts, and legumes (Famularo *et al*., 2005).

9. Preventing harmful bacterial growth under stress.

In a study done to see the effects of stress on intestinal flora, rats that were fed probiotics had little occurrence of harmful bacteria latched onto their intestines compared to rats that were fed sterile water (Hitti, 2006).

10. Managing urogenital health.

Several in vitro studies have revealed probiotics' potential in relieving urinary tract infections (Reid, 2001) and bacterial vaginosis (Famularo *et al*., 2001). Results have been varied on these studies, and in vivo studies are still required in this area to determine efficacy.

11. Potentially adverse effects.

While the oral use of probiotics is considered safe and even recommended by the World Health Organization (WHO) under specific guidelines, in some specific situations (such as critically ill patients) they could be potentially harmful. In a therapeutic clinical trial conducted by M. Besselink and colleagues in The Netherlands, the consumption of a cocktail containing genetically modified strains of probiotic bacteria, increased the death rate of patients with acute pancreatitis (Besselink *et al*., 2008). Probiotics have been shown to be beneficial for other types of patients (Hickson *et al*., 2007).

In a clinical trial conducted at the University of Western Australia, aimed at showing the effectiveness of probiotics in reducing childhood allergies, Dr Susan Prescott and her colleagues gave 178 children either a probiotic or a placebo for the first six months of their life. Those given the good bacteria were *more* likely to develop a sensitivity to allergens.

Some hospitals have reported treating lactobacillus septicaemia which is a potentially fatal disease caused by the consumption of probiotics by people with lowered immune systems or who are already very ill.

2.1.2 Charecteristics of a good probiotics (Triamchanchoochai, 2002).

1. Should be a strain which is capable of exerting a beneficial effect on the host e.g. increased growth or resistance to disease.

2. Should be non-pathogenic and non-toxic.

3. Should be present as viable cells, preferably in large number, although we do not know the minimum effective dose.

4. Should be capable of surviving and metabolizing in the gut environment, e.g. resistant to low pH and organic acids.

5. Should be stable and capable of remaining viable for long periods under storage and field conditions.

2.1.3 Probiotic bacteria in fermented milk

Probiotics used in fermented milk production have mostly 3 genus; *Lactobacillus*, *Enterococcus* and *Bifidibacterium*. Probiotics strains in genus *Lactobacillius* are *L. acidophilus, L. crispaths, L. amylovorus, L. gallinarum, L. gasseri, L. johnsonii, L. casei, L. paracasei, L. rhamnosus, L. reutri,* and *L. fermentum*. Both *Ec. faecium* and *Ec. faecalis* are probiotic bacteria in genus *Enterococcus.* Probiotics strains in genus *Bifidibacterium* are *B. bifidum, B. infantis, B. breve and B. longum.* Example of lactic acid bacteria used in fermented milks and lactic drinks is shown in Table 2.1.

Table 2.1 Lactic acid bacteria used in fermented milks and lactic acid drinks .

Microorganism	Function	Type of product
Lactobacilli		
Lactobacillus bulgaricus	Flavor	Yoghurt, Bulgarian milk, Kefir, Kumis, Lactic drink
L. jugutri	Flavor	Yoghurt, Lactic drink
L. acidophilus	Flavor + Health	Yoghurt, Acidophilus milk, Lactic drink
L. casei	Flavor + Health	Drinking yoghurt, Lactic drink
L. delbrueckii	Flavor	Lactic drink
Bifidobacteria		
Bifidobacterium bifidum	Healthy	Yoghurt, Lactic drink
B. infantis		
B. breve		
B. longum		
Lactic Streptococci		
S. thermophilus	Flavor	Yoghurt
S. lactis		Yoghurt, Cultured butter milk, Cultured cream
S. cremoris		Cultured butter milk, Cultured cream
Lh. citrorum		Cultured butter milk, Cultured cream

Source : Nakazawa and Hosono (1992)

2.1.4 Growth and viability of probiotic bacteria in milk

The number of viable microbial cells that should be present in a probiotic product has been the subject of much discussion, but is usually considered to be between 10^6 and 10^8 cfu/ml. Even at expiration dates, the product must contain these minimal numbers of living microbial cells. The important factors for growth and viability of probiotic microbes in milk products are summarized as followed (Tannock, 2002).

2.1.4.1 Strains used and interaction between different species.

Growth and survival properties vary between different bacteria strains but the combination of probiotic and traditional starter cultures is also important. Therefore the strains used in the preparation of a product must be checked carefully for compatibility. In general, lactobacilli survives better than bifidobacteria due to their greater tolerance to oxygen and low pH. The production of acetic acid by bifidobacteria can enhance the growth of *L. acidophilus* (Tannock, 2002). *L. delbrueckii* ssp. *bulgaricus* may affect the survival of bifidobacteria and *L. acidophilus* due to the amount of acid products and hydrogen peroxide that are produced. Stimulatory effects on the growth of bifidobacteria in the presence of *L. delbrueckii* ssp. *bulgaricus* have been observed and were suggested to be due to proteolytic activities of the lactobacilli which increased the availability of valine, glycine and histadine. *S. thermophilus* has not been reported to inhibit probiotic microbes to the extent as was observed with *L. delbrueckii* subsp. *bulgaricus*, and may sometimes stimulate their growth or survival due to consumption of oxygen. The study of the survival of commercial strains of *L. acidophilus* and *L. rhamnosus* GG together with a mesophilic lactococcal culture showed that the strain GG was stable in this environment, whereas the number of viable cells decreased in the case of some of the *L. acidophilus* strains (Nighswonger *et al.*, 1996).

2.1.4.2 Composition of fermentation medium.

Milk composition, and the heat treatment of the milk, is of importance for the growth of starter and probiotic strains. Addition of casein or whey protein hydrolysates, yeast extract, glucose, vitamins and minerals can stimulate the growth and survival of probiotic strains and enhance the texture of the products. However, the nature and extent of additives is regulated by law in most countries. The addition of protein increase the buffering capacity of fermented milks and hence may retard the decrease in pH and prevent further pH changes during storage, thus allowing bettersurvival of the probiotic cells. As in the case of all starter cultures, antimicrobial substances in the milk, cleaning agents, disinfectants and bacteriophages may influence the growth of probiotic microbes.

2.1.4.3 Dissolved oxygen.

Bifidobacteria are obligate anaerobes and lactobacilli are microaerophillic. Different sensitivities to oxygen have been observed among various bifidobacterial strains. De-aeration of the milk in a dairy plant before addition of probiotic microbes is important and improves the survival of both bifidobacteria and *L. acidophilus*. Packaging the product in oxygen-impermeable packages is an efficient way to achieve good survival of bifidobacteria during the shelf life of the product. This can also be of importance for lactobacilli. Incorporation of *S. thermophilus* strains that have high oxygen utilization ability lowers the level of dissolved oxygen in yoghurt and can thus improve the survival of bifidobacteria.

2.1.4.4 Size of the inoculums.

Since probiotic strains often grow poorly in milk, a relatively large inoculum, 5-10% compared to 1% for traditional starters, is usually used. The probiotic strains usually do not grow well when it is added together with a supporter culture. The addition of probiotic bacteria must be at the level required in the final product. The size of the inoculums of the supporter culture may influence the survival of probiotic bacteria.

2.1.4.5 Incubation temperature.

The optimum growth temperature for most probiotic microbes is 37°C. For yoghurt cultures 40 to 43°C is optimal for acid production. A production temperature at 37°C will therefore favour the probiotic organism.

2.1.4.6 Final acidity.

A reduced probiotic bacterial count both for lactobacilli and bifidobacteria can be caused by over acidification and accumulation of D-lactic acid in fermented products. The over acidification caused by the growth of *L. delbrueckii* ssp. *bulgaricus* at refrigerator temperature is the main factor in the death of bifidobacterial cells in milk products.

2.1.4.7 Storage temperature.

Storage temperature influences the growth and acid production of *L. delbrueckii* ssp. *bulgaricus*. Thus a low storage temperature (< 4°C) lowers the risk of over acidification and results in better survival of bididobacteria.

2.2 Spray drying

2.2.1 History

The development of spray drying equipment and techniques evolved over a period of several decades from the 1870s through the early 1900s. The first known spray dryers used nozzle atomizers, with rotary atomizers introduced several decades later. Because of the relatively unsophisticated designs of the early spray dryers and practical difficulties in operating them continuously, very little commercial use of the process was made until the 1920s.

By the second decade of the twentieth century, the evolution of spray dryer design made commercial operations practical. This process found its earliest widespread acceptance in dairy industry. Milk drying was the first major commercial application of the technology. Spray dryers to produce powdered milk, whey and baby formulas are still one of the largest applications of the technology.

Spray drying is not a new technology as far as the pharmaceutical industry is concerned, having been used successfully for producing drug substances and various excipients since the early 1940s. It was employed primarily in manufacturing of bulk pharmaceuticals and fine chemicals, such as antibiotics, analgesics, antacids, and vitamins.

Spray drying encapsulation has been used in the food industry since the late 1950s to provide flavor oils with some protection against degradation oxidation and to convert liquids into powders. Spray drying was developed as a convenient method of drying heat-sensitive biological materials, such as enzymes and pharmaceutical proteins, with minimal loss of activity.

Spray drying came of age during World War II, with the sudden need to reduce the transport weight of foods and other materials. This surge in interest led to developments in the technology that greatly expanded the range of products that could be successfully spray dried. It has been used in pharmaceutical technology studies to produce pharmaceuticals excipient with improved compressibility, such as lactose, to improve flow properties, to prepare free-flowing granules for tablet production, to improve the drug aqueous solubility and, consequently, their bioavailability. In addition, a number of formulation processes can be accomplished in one step in a spray dryer; these include complex formation and micro encapsulation. The fact that spray drying greatly reduces the labor-intensive formulation, drying and granulating of solid-dose pharmaceuticals gives cause to review the potential for this process in numerous instances. The pharmaceutical industry, however, is coming under ever-increasing pressure to reduce manufacturing cost, while still maintaining strict purity standards and highest level of quality control (Parikh, 1997).

2.2.2 Condition of spray drying.

2.2.2.1 Type of Atomizer

. Three general types of atomizers are available (figure 2.1). The most commonly used are the rotary wheel atomizers and the pressure nozzle single-fluid atomizers. Pneumatic two-fluid nozzles are used only rarely in very special applications.

(A) Rotary atomizer (B) Pressure nozzle (C) Two fluid nozzle

Figure 2.1 The three general types of atomizer

The selection of atomizer usually means the selection between wheel atomizer or pressure nozzle because the use of the pneumatic nozzle is very limited. The selection may be based on various considerations, such as availability, flexibility, energy consumption or particle size distribution of the final dry product. The Pictures of spray dry powder using different atomizers were shown in Figure 2.2.

(a) Rotary atomizer (b) Pressure nozzle

Figure 2.2 Pictures of spray dry powder using a rotary atomizer (a) and pressure nozzle (b) (Master, 1991)

Table 2.2 Comparison of rotary atomizer and pressure nozzle

Rotary atomizer	**Pressure nozzle**
-Easy control of particle size	-Less easy control of particle size
-Large flow areas	-Small flow areas
-Single atomizer for low and high capacities	-Nozzle duplication for high capacities
-Handles slurries and crystalline feedstocks	-Fine feed filtering required
-Particle size virtually independent of feed rate	-Narrow operating feed rate range
-Capacity independent of feed rate	-Capacity proportional to square root of pressure
-Large particles dried only in large-diameter	-Large particles dried only in smaller drying chamber diameter
-Unit cost with pump comparable	-Unit cost with pump comparable
-Low-pressure feed system	-High-pressure feed system
-Fine-medium size particles individual, mean size up to 200 µm	-Coarse free-flowing particles individual, mean size up to 350µm
-Deposit tendencies on wall at wheel level	-Less tendency to deposit on wall

Source : Master (1991)

The spray drying process transforms a pumpable fluid feed into a dried product in a single operation. The fluid is atomized using a rotating wheel or a nozzle and the spray of droplets comes immediately in contact with a flow of hot drying medium, usually air. The resulting rapid evaporation maintains a low droplet temperature so that high drying air temperatures can be applied without affecting the product. The time of drying the droplets is very short in comparison with most other drying processes. Low product temperature and short drying time allow spray drying of very heat-sensitive products. Some of the spray-dried products are listed in Table 2.3 (Master, 1991).

Table 2.3 Operating parameters for some spray-dried materials.

material	Moisture content		Atomizer device	Liquid-air	Air temperature	
	Inlet(%)	Outlet(%)			Inlet (°C)	Outlet(°C)
Skim milk	48-55	4	Wheel Pressure nozzle (170-200 bar)	Co-current	<250	95-100
whey	50	4	wheel	Co-current	150-180	70-80
milk	50-60	2.5	Wheel Pressure nozzle (100-140 bar)	Co-current	170-200	90-100
Whole eggs	74-76	2-4	Wheel Pressure nozzle	Co-current	140-200	50-80
coffee	75-85	3-3.5	Pressure nozzle	Co-current	270	110
cream	52-60	4	wheel	Co-current	500-600	>110

Source : Mujumdar (1995)

2.2.2.2 Types of air-droplet contact systems

There are three basic types of air-droplet contact systems employed in spray drying processes in figure 2.3 (Master, 1991).

1. Co-current contact occurs when the droplets fall down the chamber with the air flowing in the same direction. It is the most common system with both wheel and nozzle atomization. Wheel atomizers are used when fine particles of heat-sensitive material are required; heat-sensitive coarse droplets are dried in nozzle tower chamber designs. The final product temperature is lower than the inlet air temperature.

2. Countercurrent contact is achieved when the drying air flows countercurrent to the falling droplets or particles. It is used for more heat- sensitive material that require coarse particles or special porosity or high bulk density. Nozzle atomization is usually used. The final product temperature is higher than that of the exit air.

3. Mixed-flow contact is employed when a coarse product is required and the size of drying chamber is limited. It has so far been the most economical system for a material that can withstand exposure to high temperature in dry form. How best to contact the spray cloud with drying air is dependent upon the product involved.

For example, in the countercurrent arrangement, the hottest drying air contacts the dried particles as they are about to leave the chamber. If the dried product can withstand a very hot environment, and a coarse, high bulk-density product is required, this layout is highly suitable. The product particles will be of low porosity due to the reduced tendency of the droplet to expand rapidly and fracture during, evaporation. If the particle cannot withstand such high-temperature conditions, alternative contacting methods must be employed and the co-current system may be suitable. The hottest drying air contacts droplets at their maximum moisture content. The rapid evaporation prevents high droplet temperature. However, the droplets undergoing such a high evaporation rate may expand or fracture to give non-spherical porous particles and the product will often have a low bulk density (Master, 1991)

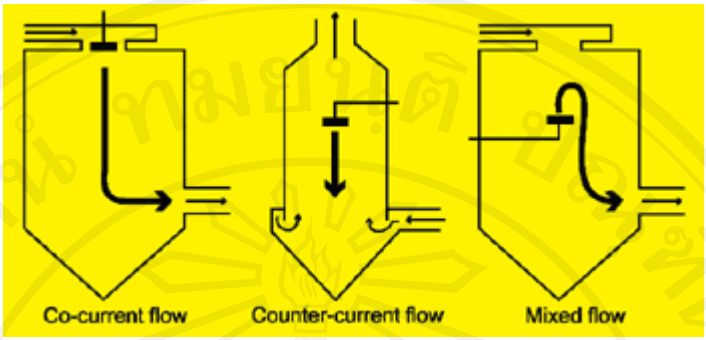

Figure 2.3 Three basic types of air-droplet contact systems employed in spray dryer. source : http://www.gpo.or.th/rdi/htmls/spray.html

2.2.3 Spray drying process

Spray drying consists of four process stages.

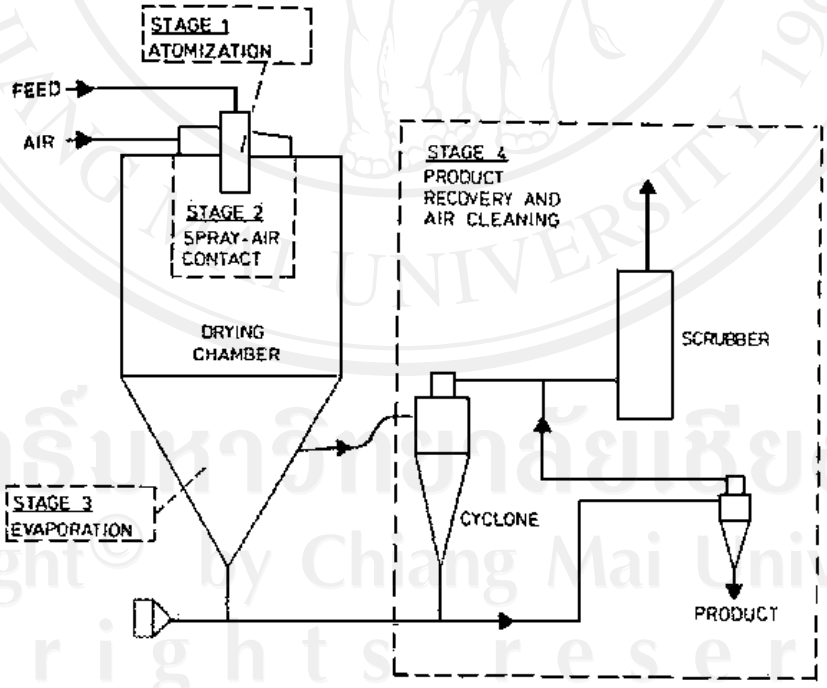

Figure 2.4 The process stages of spray drying illustrated by the open-cycle co-current layout (Master, 1991).

2.2.3.1 Atomization of feed into a spray

Atomization is the most important operation in the spray drying process. The type of atomizer not only determines the energy required to form the spray but also the size and size distribution of the drops and speed, on which the final participle size depends. The chamber design is also influenced by the choice of the atomizer. The drop size establishes the heat transfer surface available and thus the drying rate. Existing spray drying systems provided various forms of the dry product- from fine powders to granules. The typical ranges of the disintegrated droplets and particle sizes of various products in a spray dryer are listed in Table 2.3 (Master, 1991).

Table2.4 Range of droplet and particle sizes obtained in spray dryers (μm)

Rotating wheels	1-600
Pressure nozzles	10-800
Pneumatic nozzles	5-300
Sonic nozzles	5-1000
Milk	30-250
Coffee	80-400
Pigments	10-200
Ceramics	30-200
Pharmaceutics	5-50
Chemicals	10-1000

Source : Master (1991)

2.2.3.2 Spray-air contact (mixing and flow)

2.2.3.3 Drying of spray (moisture/volatiles evaporation)

As soon as droplets of the spray come into contact with the drying air, evaporation takes place from the saturated vapor film which is quickly established at the droplet surface. The temperature at the droplet surface approximates to the wet-bulb temperature of the drying air. Evaporation takes place in two stages. At first there is sufficient moisture within the droplets to replenish that lost at the surface. Diffusion of moisture from within the droplet maintains saturated surface conditions and as long as this lasts, evaporation takes place at a constant rate. This is termed the constant rate period or first period of drying. When the moisture content becomes too low to maintain saturated conditions, the so-called critical point is reached and a dried shell forms at the droplet surface. Evaporation is now dependent upon that of moisture diffusion through the dried surface shell. The thickness of the dried shell increases with time, causing a decrease in the rate of evaporation. This is termed the falling rate period or second period of drying (Master, 1991).

2.2.3.4 Separation of dried product from the air

During operation, the majority of product falls to the base of the chamber, while a small fraction passes out entrained in the air and is recovered in the separation equipment. Such equipment is usually cyclones as the dry collector is followed by wet scrubbers as the final wet collector. Alternative dry collectors are bag filters and electrostatic precipitators. The choice of equipment is dependent upon the powder loading of the air leaving the drying chamber and acceptable efficiencies of recovery. With this system, a classification may be useful, but normally the two powder off-takes are combined and conveyed to a single discharge area. Separation of dried product from the air influences powder properties by virtue of the mechanical handling involved during the separation stage. Excessive mechanical handling can produce powders having a high percentage of fines (Master, 1991).

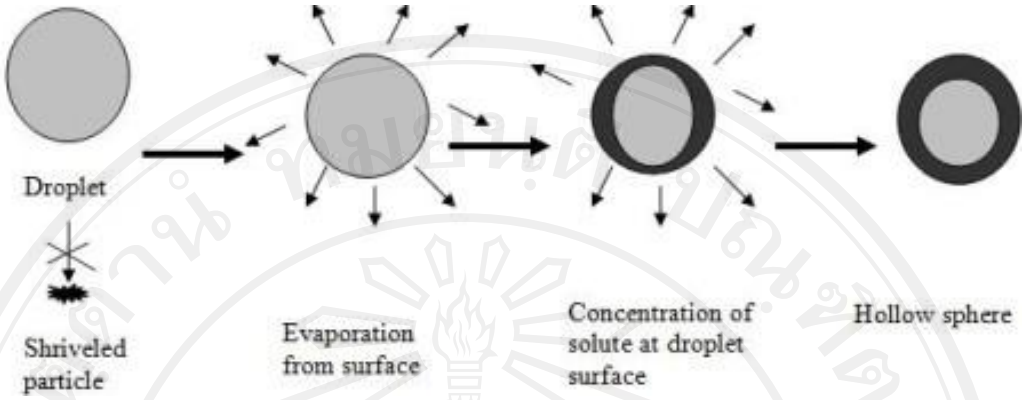

Figure 2.5 Formation of product in spray drying

http://www.acmefil.co.in/spraydryer.html/ accessed on November 11, 2008

2.2.4 Advantages and disadvantages of spray drying

There are many positive aspects that have led to establishing spray drying as a most important industrial drying system today. For example:

1. The specification or powder quality remains constant throughout the entire dryer operation irrespective of the length of the dryer run when drying conditions are held constant.

2. Spray dryer operation is continuous and easy, operation is adaptable to full automatic control, response times are fast. One operator can handle more than one automatically controlled spray dryer if located together in one complex.

3. A wide range of dryer designs are available. Product specifications are readily met through selection of the appropriate spray dryer design and its operation.

4. Spray drying is applicable to both heat-sensitive and heat-resistant materials.

5. Feedstock in solution, slurry, emulsion, paste or melt form can be handled if pump able, whether or not they be corrosive or abrasive.

6. Spray dryers can be designed to any individual capacity requirement. The largest spray dryer absorber complex in operation today handles over five million cubic meters of flue gas per hour.

7. There is extensive flexibility in spray dryer designs. Designs are available to handle:

(a) Evaporation of organic solvent-based feedstocks without explosion and fire risks;

(b) Evaporation of aqueous feedstocks that form powders that are potentially explosive when mixed in air;

(c) Evaporation of aqueous feedstocks where the drying process gives odour discharge;

(d) Drying of toxic materials

(e) Drying of feedstocks that require handling in aseptic/hygienic drying condition;

(f) Drying of feedstocks to granular, agglomerated and non-agglomerated powder.

Spray drying is disadvantaged by high installation costs. Industrial units are physically larger per unit powder output than other dryer types. This makes spray dryers expensive to fabricate. Furthermore their large diameter or tall drying chambers require expensive buildings and/or supporting strictures. However, the latest designs with integrated fluid beds in drying chambers have decreased space requirements significantly (Master, 1991).

2.2.5 Spray dry applications

2.2.5.1 Spray drying technology is applied in pharmaceutical.

1. Granulation and tabletting

When compared with other granulation methods, spray drying stands out as unique in several ways. Because the feed to a spray dryer is a homogenous liquid, it eliminates the concern over blending of dry components with liquids.

Although it is the application of shear forces in the centrifugal atomizer that creates a spray, this form of energy generally will not destroy microencapsulated material as can happen in high shear granulators. Spray drying technique has been used for granulating, for slow-release granulations of magnesium carbonate, theophylline and acetaminophen (Parikh, 1997).

The spherical composite particles consisting of amorphous lactose and sodium alginate were prepared by spray drying their aqueous solutions using rotary atomizing spray-dryer. The SD composite particles had good compactibility and excellent micrometric properties as filler for direct tableting of controlled release matrix tablets (Hirofumi *et al*., 1998)

2 Micro particles

Recently, the process received great attention in the field of micro Particles (Palmieri *et al*., 1994) for the preparation of dried liposomes, amorphous drugs, mucoadhesive microspheres, drying of preformed microcapsules, Gastroresistant microspheres, and controlled-release systems.

Comprehensive studies have been performed on the preparation of microspheres by spray drying techniques for different purposes, like modification of biopharmaceutical properties, formulation of dry emulsions, spray dried phospholipids, nanoparticle-loaded microspheres, for drug delivery, spray-dried powders formulated with hydrophilic polymers, biodegradable microspheres, and spray-dried silica gel microspheres. Eudragit RL microspheres (Espositoa *et al*., 2002) containing vitamin C were prepared by Spray drying method.Spray-drying was useful for the preparation of Paracetamol encapsulating Eudragit RS/RL or Ethylcellulose microspheres (Palmieri *et al*., 2001).

The spray drying technique has been widely applied to prepare micro-particles of drug with polymer. When a drug crystal suspension of a polymer solution is spray-dried, microcapsulated particles are prepared, whereas spray drying of solution of polymer containing dissolved drug leads to formation of drug-containing microspheres in which the drug can be dispersed in a molecular state or as micro crystals. In both cases, the particles tend to have a spherical shape and are free

flowing. These properties are preferable pharmaceutical manufacturing process such as tabletting and capsule filling.

Controlling microsphere size is an important process variable that can affect product performance. Scanning Electron microscope (SEM) is used to characterize the size of microspheres (figure 2.6). The conventional method of sizing involves periodic sampling and subsequent analysis using off-line techniques, but these have limitations such as late feedback response times, sampling errors and lacks the sensitivity required for it to be used in the detection of fluctuations. Using PAT as an in-process monitor during spray drying could offer better process control and improved product quality resulting in products of greater value. Thus, PAT serves as a useful tool to provide real time information about process and product size (Hui *et al*., 2008).

Micro particles of diltiazem hydrochloride with ethyl cellulose (EC) were prepared by using spray drying technique. Drug was dispersed in benzene solution of EC or dissolved in methanol solution of EC with 1:1-1:5 drug EC ratio, followed by spray drying. A microcapsule structure was obtained in the suspension system, while a microsphere structure, while the drug was in an amorphous state, was formed in the solution system.

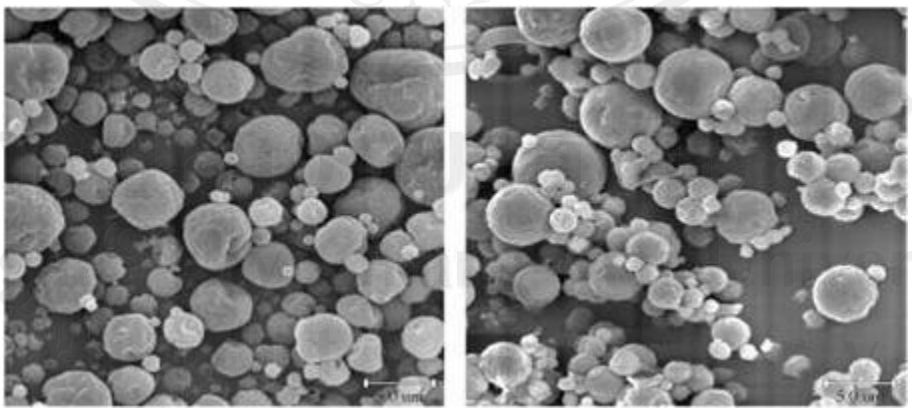

Figure 2.6 Scanning electron microscopic photographs of spray-dried chitosan microspheres; a) Uncross-linked, b) cross-linked with d,l-glyceraldehyde.

3 Coating applications

Spray drying has proved extremely useful in the coating and encapsulation of both solids and liquids. Spray-dried micro particles of theophylline were prepared with a coating polymer (Lachman *et al*., 1991) in an aqueous system. Hydroxypropyl methylcellulose (1.25%w/v) and the drug (0.25w/v) were dissolved in water and spray-dried using a laboratory spray dryer equipped with a two-fluid pressure nozzle.

The spray drying method can produce discrete particles coated with an aqueous coating solution or dispersion from spray droplets of the aqueous solution or suspension of drug and coating polymer when sprayed into a drying chamber. As the solvent is evaporated the coating material envelops the suspended particle. The coating provides such valuable characteristics as taste and odour masking, improvement in stability, enteric coating and sustained release. Oily liquids may be encapsulated by emulsification in water with the aid of a gum such as acacia, or starch, and subsequent spray drying. As the water evaporates, the oil is entrapped in a shell of the gum. This process is used for the preparation of "dry" flavor oils (Steven *et al*., 1997).

4 Dry emulsions and dry elixirs

Dry emulsions (Christensen *et al*., 2001) were prepared by spray drying various liquid o/w emulsions containing fractionated coconut oil dispersed in aqueous solutions of HPMC (solid carrier). Flurbiprofen (FP) dry elixir (Kim *et al*., 1995) prepared by the spray-drying technique showed good flowability and was spherical in shape, having a geometric mean diameter of about 13 μm. Dry elixir is a solid form of microcapsules simultaneously containing ethanol and drug in water-soluble polymer shell. The dry elixir was produced when a solution of water-soluble dextrin and drug dissolved in an ethanol-water co-solvent system was spray-dried. The final solutions were delivered to the nozzle at a flow rate of 5 ml/min using a peristaltic pump and thereafter spray-dried.

Inlet and outlet temperatures were maintained at 90 and 55°C respectively. The poorly water-soluble drugs encapsulated in the dry elixir are readily dispersed and dissolved in aqueous media as a result of the co-solvent effect of ethanol, resulting in enhanced dissolution rate & bioavailability.

2.2.5.2 Spray drying technology is applied with probiotic bacteria.

Gardiner *et al*.(2000) reported that Spray drying of skim milk was evaluated as a means of preserving *Lactobacillus paracasei* NFBC 338 and *Lactobacillus salivarius* UCC 118, which are human-derived strains with probiotic potential. An air outlet temperature of 80 to 85°C was optimal for spray drying; these conditions resulted in powders with moisture contents of 4.1 to 4.2% and viable counts of 3.2×10^9 cfu/g for NFBC 338 and 5.2×10^7 cfu/g for UCC 118. Thus, *L. paracasei* NFBC 338 survived better than *L. salivarius* UCC 118 during spray drying; similar results were obtained when we used confocal scanning laser microscopy and LIVE/DEAD *Bac*Light viability staining. In addition, confocal scanning laser microscopy revealed that the probiotic lactobacilli were located primarily in the powder particles. Although both spray-dried cultures appeared to be stressed, as shown by increased sensitivity to NaCl, bacteriocin production by UCC 118 was not affected by the process, nor was the activity of the bacteriocin peptide. The level of survival of NFBC 338 remained constant at ;1×10^9 cfu/g during 2 months of powder storage at 4°C, while a decline in the level of survival of approximately 1 log (from 7.2×10^7 to 9.5×10^6 cfu/g) was observed for UCC 118 stored under the same conditions. However, survival of both *Lactobacillus* strains during powder storage was inversely related to the storage temperature. Our data demonstrate that spray drying may be a cost-effective way to produce large quantities of some probiotic cultures.

Gillian *et al*. (2002) reported that spray-dried probiotic milk powder was produced at pilot scale from 300 L of 20% (w/v) reconstituted skim milk containing a rifampicin resistant variant of the probiotic *Lactobacillus paracasei* NFBC 338 (Rif^r).During powder manufacture, air inlet and outlet temperatures of

175°C and 68°C, respectively, were used, which yielded a probiotic survival of 84.5%. The powder, which contained 1×10^9 cfu/g of *Lb. paracasei* NFBC 338 Rif^r was used as an adjunct inoculum (at 0.1% w/v) during probiotic Cheddar cheese manufacture. Probiotic numbers were 2×10^7 cfu/g in the cheese on day 1 and grew to 7.7×10^7 cfu/g after 3 months of ripening, without adversely affecting cheese quality. The data demonstrate that probiotic spray-dried powder is a useful means of probiotic addition to dairy products, as this example for Cheddar cheese manufacture shows.

Bielecka and Majkowska (2000) reported that a synergistic set of the strains *L. delbrueckii* ssp. *bulgaricus* 151 and *S. thermophilus* MK-10 was preserved with a method of spray drying. Studies were performed on the effect of outlet air temperature in the range of 60-80°C upon the survival of yoghurt cultures, as well as the moisture content and sensory properties of yoghurt powder. Survival of yoghurt cultures was the highest at 60 and 65°C, but excessive moisture (10.2%) of yoghurt powder had a negative effect on its texture. The moisture content of the powder was lower at 80°C (4.4%), unfortunately sensory faults appeared at this temperature, and survival of bacteria cultures decreased considerably. Temperatures within the range of 70-75°C ensured satisfactory survival of yoghurt cultures (*L. delbrueckii* ssp. *bulgaricus* 13.7- 15.8% and *S. thermophilus* 51.6-54.7%), maintained the proportion of yoghurt strains (*L. bulgaricus* : *S. thermophilus* = 1:3), a satisfactory moisture content (5.1-6.3%), and good sensory properties of yoghurt powder.

Kim and Bhowmik (1990) reported the survival of *Streptococcus salivarius* sub.sp. *thermophilus* and *L. delbrueckii* sub.sp. *bulgaricus* was determined under various processing conditions for spray drying. Numbers of both microorganisms decreased with increased outlet or inlet air temperature and atomizing air pressure. Outlet air temperature was a major parameter affecting the number of survivors. Suitable conditions were an inlet air at 160°C, an outlet air at 60°C, an atomizing at pressure 98 kPa, a hot air flow of 0.28 m^3/min and a feed temperature at 30°C. The spray dried yoghurt powder showed lower survival for *S. thermophilus* but

a similar survival for *L. delbrueckii* ssp. *bulgaricus* as compared to freeze-dried powder.

Lian *et al*, 2002 investigated the survival of bifidobacteria after spray-drying with different carrier media. Among the test organisms, B. *longum* B6 exhibited the least sensitivity to spray-drying and showed the highest survival of 82.6% after drying with skim milk. The effect of carrier concentrations revealed that spray-drying at 10% (w/w) gelatin, gum arabic or soluble starch resulted in the highest survival of bifidobacteria. The highest survival after spray-drying was at air outlet temperature of 50 ^{o}C.

Wang *et al*, 2004 investigated the viability of lactic acid bacteria (*S. thermophilus* and *L. acidophilus*) and bifidobacteria (*B. longum* and *B. infantis*) in fermented soymilk which was subjected to freeze drying and spray-drying. The air outlet temperature of spray-drying were 60, 75 and 90 ^{o}C. It was found that lifting the air outlet temperature resulted in the reduced viability. After freeze drying, both lactic acid bacteria and bifidobacteria exhibited the higher percent of survival than spray-drying and survived better when stored at 4^{o}C than 25^{o}C in laminated pouch which was the best packaging material resulted in the highest survival tested in this study. The optimum temperature for rehydration was 35-50 ^{o}C for freeze dried and 20 ^{o}C for spray dried fermented soymilk.

2.3 Packaging material

Food packaging is packaging for food. It requires protection, tampering resistance, and special physical, chemical, or biological needs. It also shows the product that is labeled to show any nutrition information on the food being consumed. (Brody and Marsh, 1997)

2.3.1 Packaging has several objectives.

1. Physical protection - The food enclosed in the package may require protection from, among other things, shock, vibration, compression, temperature, etc.

2. Barrier protection - A barrier from oxygen, water vapor, dust, etc., is often required. Permeation is a critical factor in design. Some packages contain desiccants or Oxygen absorbers to help extend shelf life. Modified atmospheres or controlled atmospheres are also maintained in some food packages. Keeping the contents clean, fresh, and safe for the intended shelf life is a primary function.

3. Containment or agglomeration - Small items are typically grouped together in one package for reasons of efficiency. powders, and granular materials need containment.

4. Information transmission - Packages and labels communicate how to use, transport, recycle, or dispose of the package or product. Some types of information are required by governments.

5. Marketing - The packaging and labels can be used by marketers to encourage potential buyers to purchase the product. Package design has been an important and constantly evolving phenomenon for several decades. Marketing communications and graphic design are applied to the surface of the package and (in many cases) the point of sale display.

6. Security - Packaging can play an important role in reducing the security risks of shipment. Packages can be made with improved tamper resistance to deter tampering and also can have tamper-evident features to help indicate tampering. Packages can be engineered to help reduce the risks of package pilferage: Some package constructions are more resistant to pilferage and some have pilfer indicating seals. Packages may include authentication seals to help indicate that the package and contents are not counterfeit. Packages also can include anti-theft devices, such as dye-packs, RFID tags, or electronic article surveillance tags, that can be activated or detected by devices at exit points and require specialized tools to deactivate. Using packaging in this way is a means of retail loss prevention.

7. Convenience - Packages can have features which add convenience in distribution, handling, stacking, display, sale, opening, reclosing, use, and reuse.

8. Portion control - Single serving packaging has a precise amount of

contents to control usage. Bulk commodities (such as salt) can be divided into packages that are a more suitable size for individual households. It also aids the control of inventory: selling sealed one-liter-bottles of milk, rather than having people bring their own bottles to fill themselves.

2.3.2 Product quality or shelf life is determined by the following parameters:

(1) The product's physical, chemical and biological characteristics.

(2) Processing conditions.

(3) Package characteristics and effectiveness.

(4) The environment to which the product is exposed during distribution and storage.

The specific properties of the package required to adequately protect the product and, therefore, to maintain or extend product shelf life is a function of the product's susceptibility to environmental conditions (Kilcast *et al.,* 2000).