CHAPTER II

LITERATURE REVIEW

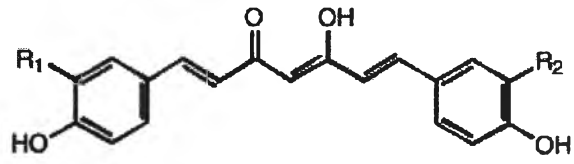
1. Curcuminoids

1.1. *Curcuma longa* (Turmeric)

Turmeric (*Curcuma longa* Linn.) commonly known in Thai as Khamin or Khamin Chan, belongs to the genus *Curcuma* that consists of hundreds of species of plants that possess rhizomes and underground root like stems. Turmeric is of special importance to humans with the discovery that its rhizome powder, when added to various food preparations, preserves their freshness and imparts a characteristic flavour. Turmeric, which belongs to a group of aromatic spices, had been originally used as a food additive in curries to improve the storage condition, palatability and preservation of food. Turmeric is grown in warm, rainy regions of the world such as Thailand, China, India, Indonesia, Jamaica and Peru (Jayaprakasha et al., 2005).

1.2. Curcuminoid: Isolation, Chemistry, and Technological Aspects

The colouring principle of turmeric was isolated in the 19th century and was named curcumin. Curcuminoids refer to a group of phenolic compounds present in turmeric, which are chemically related to its principal ingredient curcumin. Three curcuminoids were isolated from turmeric viz., curcumin, desmethoxycurcumin and bisdesmethoxycurcumin (Figure 1). All three impart the hallmark yellow pigmentation to the *C. longa* plant and particularly to its rhizomes. Although the chemical structure of curcumin was determined in the 1970's and 1980's, recently the potential uses of curcuminoids in medicine have been studied extensively.



CUR I $R_1 = OCH_3; R_2 = OCH_3$
CUR II $R_1 = OCH_3; R_2 = H$
CUR III $R_1 = H; R_2 = H$

Figure 1. Structures of curcumin (CUR I), desmethoxycurcumin (CUR II) and bisdesmethoxycurcumin (CUR III) (Pfeiffer et al., 2003).

Considering the various biological activities of curcuminoids, attempts were made by several researchers in the past to isolate curcuminoids from turmeric rhizomes by solvent extraction using organic solvents and many other methods as indicated below.

Janaki and Bose (1967) reported the isolation of curcuminoids in higher yield (1.1%) involved prior extraction of rhizomes with hexane to remove much of the volatile and fatty components and then extracting with benzene. The concentrate readily crystallised on cooling and was further purified by crystallization from ethanol to yield orange–yellow needles.

Sastry (1970) reported the isolation of curcumin and related demethoxy compounds from turmeric by extraction with organic solvents.

Krishnamurthy *et al.*, (1976) reported the hot and cold percolation extraction methods with good yields with a high recovery of curcumin.

Tonnesen *et al.*, (1989) reported the isolation of curcumin by insoluble lead salt.

Recently, Baumann et al. (2000) have claimed efficient extraction of curcuminoids using supercritical CO_2 modified by 10% ethanol. Although supercritical fluid extraction is known to be a clean technology giving acceptable yields and purity, its major disadvantage lies in its high operating pressures. The scale up problems could also be severe when the extraction is to be done at large scales.

Dandekar and Gaikar (2003) reported the hydrotropy based extraction method for selective extraction of curcuminoids from *C. longa*. Sodium cumene sulfonate was reported to be an efficient hydrotrope for the extraction of curcuminoids.

Numerous methods are available for isolating curcuminoids from *C. longa.* Isolation of pure curcumin from plant material is time consuming and pure curcumin sold on the market is therefore, a purified extract containing a mixture of the three curcuminoids i.e. curcumin (75–81%), demethoxycurcumin (15–19%) and bisdemethoxycurcumin (2.2–6.6%). Except by the chromatographic routes, all other methods generally provide several curcuminoids, with curcumin as the dominant constituent (Jayaprakasha et al., 2005).

1.3. Analysis of Curcuminoids

The curcuminoids isolated from *C. longa* exhibit strong absorption between 420–430 nm in organic solvents. The official methods for assaying curcumin or *Curcuma* products as food colour additives are based upon direct spectrophotometric absorption measurements (British Standard Methods of Test For Spices and Condiments, 1983 and WHO, 1976). The evaluation of the total amount of curcuminoids in a sample by use of direct absorption measurements is only valid if the calculations are based on reference values obtained from pure standards. It should however, be noted that the presence of other compounds absorbing in the region of 420–430 nm influence the results strongly (Jayaprakasha et al., 2005).

Sunipon et al. (2003) reported the qualitative and quantitative method for the determination of curcumin, desmethoxycurcumin, and bisdesmethoxycurcumin by using high performance liquid chromatography (HPLC), which were also validated and proved to be the stability-indicating assay (SIA).

1.4 Biological Activities

1.4.1 Antioxidant Activity

Pulla Reddy and Lokesh (1992) observed that curcumin is capable of scavenging oxygen free radicals such as superoxide anions and hydroxyl radicals, which are the initiators of lipid peroxidation. Sreejayan and Rao (1994) have reported that three curcuminoids were inhibitors of lipid peroxidation in rat brain homogenates and rat liver microsomes. All of these compounds were more active than tocopherol as reference and curcumin showed the better results. Curcumin is reported to be a powerful antioxidant to repair both oxidative and reductive damage caused to proteins by radiation (Kapoor & Priyadarsini, 2001). Recently, Gayathri, Kalpana, Jamuna, and Srinivasan (2004) reported that the loss (27–71%) of β-carotene in vegetables was observed during the two domestic methods of cooking commonly used, namely, pressure-cooking and open pan boiling. However, presence of antioxidant spice turmeric generally improved the retention of β-carotene.

1.4.2. Antiprotozoal Activity

Araujo et al., 1999 and Araujo et al., 1998 reported the anti-protozoal activity of curcumin and some semi-synthetic derivatives against tripanosomatids in promastigotes (extracellular) and amastigotes (intracellular) forms of *Leishmania amazonensis*.

1.4.3. Antimicrobial Activity

Curcuma oil was tested against cultures of *Staphylococcus albus*, *Staphylococcus aureus* and *Bacillus typhosus* and the results showed inhibition of the growth of *S. albus* and *S. aureus* at different concentrations (Chopra *et al.*, 1941). Bhavanishankar and Srinivasamurthy (1979) investigated the activity of turmeric fractions against some intestinal bacteria in vitro. Total inhibition of growth of *lactobacilli* in the presence of whole turmeric was reported (4.5–90 µl/100 ml). The

alcoholic extract was also effective (10–200 mg/ml), but the inhibition was not equal as the whole turmeric. Jayaprakasha, Negi, Anandha Ramakrishanan, & Sakariah (2001) reported the antifungal activity of turmeric oil, which was also isolated from mother liquor after isolation of curcumin.

1.4.4. Antivenom Activity

Ferreria *et al.*, (1992) reported the activity of turmeric and its constituents against snake venom. The fraction consisting of *ar*-turmerone, isolated from *C. longa* neutralized both the hemorrhagic activity and lethal effect of venom in mice.

1.4.5. Anti-tumour Activity

Huang *et al.*, (1988), studied the effect of curcumin, chlorogenic acid, caffeic acid and ferulic acid on tumour promotion in mouse skin by 12-O-tetradecanoylphorbol-13-acetate (TPA) and observed that all these compounds inhibit the epidermal ornithine decarboxylase (ODC) and epidermal DNA synthesis, curcumin being the most effective. Limtrakul, Lipigomgoson, Namwong, Apisariyakul, and Dum (1997) showed an inhibitory effect of curcumin on mouse skin carcinogenesis initiated by 7, 12-dimethylbenz (a) anthracene (DMBA) and promoted by TPA. Thus, curcumin administration decreased both the number of tumours per mouse and tumour volume. Furthermore, Ozaki *et al.*, (2000) studied the action of curcumin on rabbit osteoclast apoptosis and demonstrated that curcumin drastically inhibits bone resorption and stimulation of apoptosis in the cells. Since, cancer and bone inflammation are diseases that increase bone resorption, the authors suggest that curcumin may be useful in the therapy of these diseases.

In a recent review on cancer chemoprevention by dietary constituents, it was mentioned that curcumin have tumour-suppressing properties in rodent models of carcinogenesis, and interfere with cellular processes involved in tumour promotion and progression (Gescher, Sharma, & Steward, 2001). Curcumin is reported to prevent DNA damage even in individuals who may be genetically susceptible to toxic

effects of xenobiotic exposures and is also able to exert antimutagenic/anticarcinogenic properties at levels as low as 0.1–0.5% in the diet (Polasa, Naidu, Ravindranath, & Krishnaswamy, 2004).

1.4.6. Anti-inflammatory Activity

Arora, Basu, Kapoor, and Jain (1971) investigated the anti-inflammatory activity of different fractions of the rhizomes of turmeric in animals. It was reported that the extracts reduced the granuloma growth and no toxic effects were observed. Chandra and Gupta (1972) demonstrated the anti-inflammatory and anti-arthritic actions of volatile oil of *C. longa.* Mukhopadhayaya *et al.*, (1982) demonstrated the activity of curcumin and other semi-synthetic analogues (sodium curcuminate, diacetyl curcumin, triethyl curcumin and tetrahydro curcumin) in carrageenin-induced rat paw edema and cotton pellet granuloma models of inflammation in rats. Among the curcumin analogues, triethyl curcumin was the most potent anti-inflammatory in the chronic model of inflammation, when compared with the others, as well as with a reference drug. Tetrahydrocurcumin showed no activity. In the acute inflammation condition, all the substances were more effective. Ammon and Wahl (1991) reported that the *Curcuma* extracts showed a high anti-inflammatory effect after parenteral application in standard animal models. Curcumin was reported to suppress activation of nuclear factor-kappa B NF-KB by repression of degradation of the inhibitory unit IKBα, which hampers subsequent nuclear translocation of the functionally active subunit of NF-KB (Surh *et al.*, 2001).

2. Microencapsulation

Microencapsulation can be described as a process in which very thin coatings of polymeric materials are deposited around particles of solids or droplets of liquids, and the products from this process are called microcapsules or microspheres (Luzzi, 1970, 1976; Madan, 1978b; Deasy, 1984; Li et al., 1988; Bakan, 1986, 1994). The microcapsules developed for use in medicine consist of a solid or liquid core material

containing one or more drugs enclosed in coating as shown in figure 2. The core may also be referred to as the nucleus or fill and the coating as the wall or shell. Depending on the manufacturing process, various types of microcapsule structure can be obtained as illustrated. The most common type is the mononuclear spherical. Microcapsules usually have a particle size range between one and 2000 μm. Products smaller than 1μm are referred to as nanocapsules, because their dimensions are measured in nanometers. When no distinct coating and core regions are distinguishable, the analogous used are microparticles and nanoparticles. (Luzzi, 1976; Deasy, 1984)

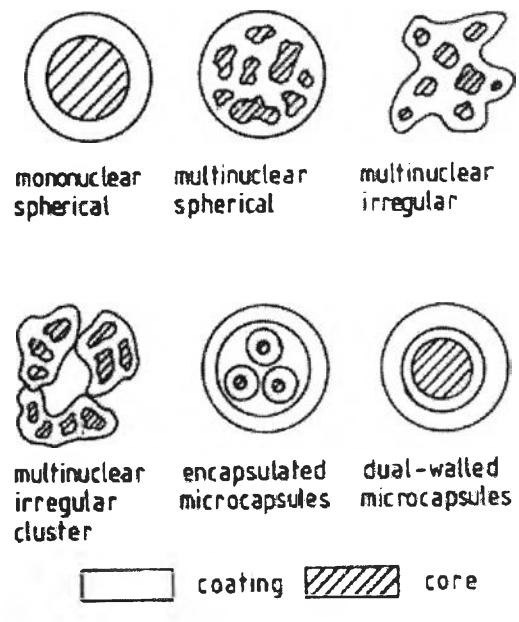


Figure 2. Some typical structures of microcapsules (Deasy, 1984).

2.1. History and Considerations of Microencapsulation

The first research leading to the development of microencapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and Kaas in 1931 and dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process for coating. In the late 1930s and 1940s, Green and co-workers of The National Cash Register Co., Dayton, Ohio, developed the gelatin coacervation process, which eventually lead to several patents for carbonless carbon paper. This

product used a gelatin microencapsulated oil phase usually containing a colorless dye precursor. The microcapsules were affixed to the undersurface of the top page and released the dye precursor upon rupture by pressure from the tip of the writing instrument. The liberated dye precursor then reacted with an acid clay coating on the top surface of the underlying page to form the copy image as illustrated in figure 3 (Deasy, 1984).

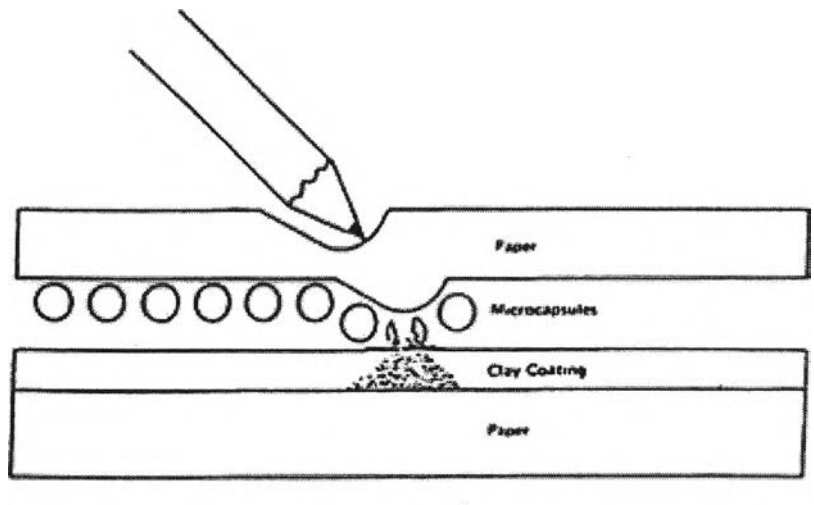


Figure 3. Pressure-activated release of encapsulated dye precursor to give a color reaction on paper coated with an acidic clay (Fanger, 1974).

2.2. Reasons for Microencapsulation

The technique of microencapsulation has gained popularity because of its potential applicability in a wide variety of situations. The microencapsulation processes have been used in many industries such as food, food additives, cosmetics, adhesives, household products, agricultural materials, and aerospace industry, and many others. In the pharmaceutical industry the microencapsulation processes have been used since the 1960's and there are many reason why drug and related chemicals have been microencapsulated (Deasy, 1984; Bakan and Doshi, 1991; Bakan, 1994).

a) Microencapsulation has been employed to provide protection to the core material against atmospheric effects. Bakan and Anderson (1976) reported that microencapsulated vitamin A palmitate had enhanced stability compared to the unencapsulated control. Klaui et al. (1970) described the enhancement of the stability of fat-soluble vitamins by microencapsulation. Likewise, microencapsulation has been used to evaluate the storage stability of lycopene microencapsules using gelatin and sucrose as wall materials. Lycopene microcapsules were prepared by a spray-drying method using a wall system consisting of gelatin and sucrose. Shu et al. (2004) reported that the retention percentage of lycopene in microencapsulated lycopene decreased slightly compared with the control. The reason may be due to the effective microencapsulation of lycopene in wall materials which can effectively avoid the damage from oxygen and light, etc., during storage (Shu et al., 2004).

b) A liquid such as eprazinone may be converted to a pseudo-solid by the microencapsultion as an aid of handling and storage (Si-nang et al., 1973).

c) Toxic chemicals such as insecticides may be microencapsulated to reduce hazard to operators (Raun and Jackson, 1966).

d) Microencapsulation was employed to reduce the hygroscopic properties of many core materials such as sodium chloride.

e) National Cash Register (1966) reported that the flow properties of vitamins thiamine hydrochloride, riboflavin, and niacin with iron phosphate could be improved by microencapsulation prior to compression into teblets. The choice of suitable coating material should improve the compaction and subsequent disintegration of encapsulated drugs from tablets.

f) The process has been used to reduce the volatility of several substances such as methyl salicylate and peppermint oil (Bakan and Anderson, 1976).

g) Incompatibilities between drugs such as aspirin and chlorpheniramine maleate can be prevented by microencapsulation (Bakan and Anderson, 1976).

h) Microencapsulation has been used to disguise the unpleasant taste of a number of drugs, however, taste masking has been a subsidiary consideration to the provision of other properties. Microencapsulation and sugar or film coating conventional tablets are usually much cheaper ways of masking an unpleasant taste

associated with drugs. Carbon tetrachloride and a number of other substances have been microencapsulated to reduce their odor and volatility.

i) Many drugs have been microencapsulated to reduce gastric and other gastrointestinal (GI) tract irritation, including ferrous sulfate and potassium chloride (Elwood and Williams, 1970; Arnold et al., 1980). Likewise, sustained-release aspirin preparations have been reported to cause significantly less gastric bleeding than conventional aspirin preparations (Frankle et al., 1968).

j) Also the local irritation and release properties of a number of topically applied products can be altered by microencapsulation (Sudekum, 1976).

2.3. Core and Coating Properties

2.3.1 Core Properties

A core material, which is defined as the specific material to be coated, plays a significant role in microencapsulation. It dictates the process as well as the polymer used as a coating material. It should be insoluble and nonreactive with the coating material and the manufacturing vehicle. Water soluble and insoluble solids, water immiscible liquids, solutions, dispersions of solids in liquids can be microencapsulated. The solid core can be a mixture of active constituents, stabilizers, diluents, excipients, and release rate retardants or accelerators (Bakan, 1986, 1994).

Liquid core may be composes of polar or non-polar substances that comprise the active ingredient or that act as vehicles for dissolved or suspended drugs. The solvent properties of such liquids will critically influence the rate of drug release and the selection of coating materials, which obviously should not be significantly affected by the vehicle over the shelf life of the product. For drugs of low water solubility with know bioavailability problems associated with low rate of dissolution, decrease in particle size of suspended drugs may be important in enhancing in vivo absorption. There is, of course, a general tendency for smaller microcapsules to have faster release rates because of their increased surface area per unit volume or weight of core material.

Solid cores are used more frequently than liquid ones. However, very small core particles tend to give rise to some aggregation problems during production because of the relative importance of their surface attractive forces. Large particles can also cause problems because of their rapid sedimentation. The shape of these cores is also very important. It is much easier to deposit uniform coatings on regular spherical particles of narrow size range that are devoid of sharp edges. Accordingly, choice of particular polymorphs of drugs, reduction of irregularly shaped crystalline materials by grinding, or the use of spray-dried forms may aid the ease of deposition of uniform coatings onto their surfaces (Deasy, 1984).

2.3.2. Coating Properties

Depending on the microencapsulation procedure employed, coating for microcapsules may contain several different additives such as film formers, plasticizers, and fillers, and may be applied from various solvent systems (Deasy, 1984). The microcapsule coating can be chosen from a wide variety of natural and synthetic polymers (Bakan, 1986, 1994).

2.3.2.1 Film Formers

By far the most important material governing the properties of the coating is the film former. One or more of these materials, which are usually high-molecular-weight polymers, may be used alone or in combination with others additives to form the coating. Table 1 lists some of the more commonly used film formers employed for microencapsulation and related uses. Obviously, an enormous variety of polymers are employed, often in various grades.

Table 1. Some commonly used film formers for microencapsulation and related use (Deasy, 1984).

Acacia		
Acrylaic polymers and copolymers		
	e.g.,	polyacrylamide
		polyacryldextran
		polyalkyl cyanoacrylate
		polymethyl methacrylate
Agar and agarose		
Albumin		
Alginates		
	e.g.,	calcium alginate
		sodium alginate
Aluminium monostearate		
Carboxyvinyl polymer		
Cellulose derivatives		
	e.g.,	cellulose acetate
		cellulose acetate butyrate
		cellulose acetate phthalate
		cellulose nitrate
		ethylcellulose
		hydroxypropylcellulose
		hydroxypropylmethylcellulose
		hydroxypropylmethylcellulose phthalate
		methylcellulose
		sodium carboxymethylcellulose
Cetyl alcohol		
Dextran		
Gelatin		
Hydrogenated beef tallow		

Table 1. (Continued)

Hydrogenated castor oil

12-Hydroxystearyl alcohol

Gluten

Glyceryl mono- or dipalmitate

Glyceryl mono-, di-, or tristaerate

Myristyl alcohol

Polyamide

e.g., nylon 6-10

poly(adipyl L-lysine)

polyterephthalamide

poly(terephthaloyl L-lysine)

Poly (ε-caprolactone)

Polydimethylsiloxane

Polyester

Polyethylene glycol

Poly(ethylene-vinyl acetate)

Polyglycolic acid, polylactic acid, and copolymers

Polyglutamic acid

Polylysine

Poly(methyl vinyl ether/maleic anhydride)

Polystyrene

Polyvinyl acetate phthalate

Polyvinyl alcohol

Polyvinylpyrrolidone

Shellac

Starch

Stearic acid

Stearyl alcohol

Table 1. (Continued)

Waxes		
	e.g.,	beewax
		carnauba wax
		Japanese synthetic wax
		paraffin wax
		spermaceti

When a film former is applied to a core, two sets of forces are involved. These are the cohesional forces between the polymer molecules that comprise the film former and the adhesional forces between the coating and the core. High levels of cohesive force occur in high-molecular- weight polymers as a result of diffusion of individual macromolecules or segments thereof under favorable conditions such as elevated temperature (semisolid state) or suitable solvent (gelation). This results in the coalescence of individually applied layers to form a relatively homogeneous coating devoid of lamination. Increasing cohesiveness tends to increase film density and rigidity while reducing porosity and permeability, which properties and others may be modified by appropriate choice of film former, its grade, and the presence of other additives.

Polymer structure and chemistry have a major influence on the degree of cohesion attained in a film coating. The typical polymer molecule is a macromolecule formed from a sequence of repeating monomer units. Its size plays a very important role in determining the properties of the polymer, so it is important to assign a molecular weight to the material.

Often, rather use molecular weight data, apparent viscosities of polymer solutions are cited. For example, ethylcellulose is available in a range of grades such as 50 and 100 cP, where the apparent viscosity of a 5% w/w solution 80:20 toluene:ethanol at 25°C is measured in centipoise units under specified test conditions.

Other rheological properties are sometimes used to characterize particular polymer. The melt index (MI) is defined as the number of grams of molten polymer that will flow through a standard orifice at a standard temperature and pressure.

Polymers tend to have two types of structures within the material, a crystalline region (A) and an amorphous region (B) as shown in figure 4. Crystallization occurs when linear polymer molecules orientate themselves in whole or in part to form an ordered compact configuration known as a crystallite that lies scattered throughout the amorphous zone of the polymer material. Highly crystalline polymers have a high cohesive strength and are characterized by compactness, toughness, rigidity, surface hardness, and brittleness, and by lack of permeability and flexibility. The molecular necessary for crystallization is favored by the bonding of interactant groups such as –OH and –COOH regularly distributed along the backbone of these molecules. It is also favored by the stereo-configuration of neighboring chain segments, which is denoted by the tacticity of the polymer. Isotactic polymers contain molecules that are at least partially orientated in space in the same manner for each molecule of the polymer, which facilitates interlocking of two or more polymer segments to give rise to crystallinity. A polymer has rarely 100% crystalline because of the molecular weight distribution of its constituent molecules and their lack of perfectly ordered chemical and steric interaction. Atactic polymers tend to have no steric order and are therefore more amorphous-like. The formation of amorphous polymers is thusfavored in polymers that contain bulky side chains, irregular substitutions, or that have an irregular repeating sequence of dissimilar monomer units, which frequently occurs in copolymers. Elastomers ("rubbers") such as silicone rubber are typically amorphous polymers whose relatively weak interchain cohesive forces give them their property of elasticity, flexibility, and permeability. Particular film formers used for microencapsulation can vary enormously in the relative amounts of crystalline and amorphous regions they contain, which obviously influence the fine structure of these materials.

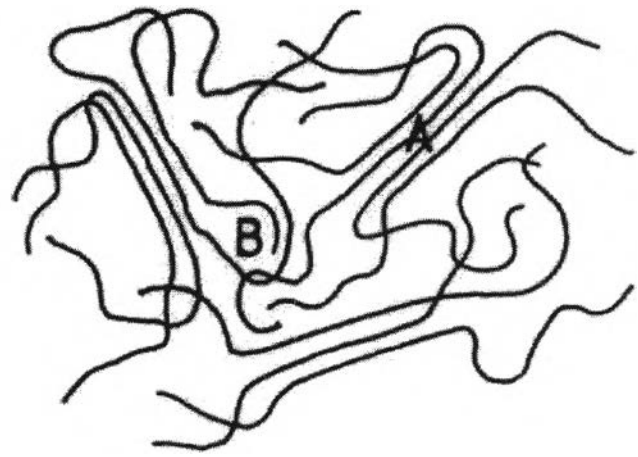


Figure 4. Plane structure of a typical film former showing ordered (crystalline A) and disordered (amorphous B) alignment of linear polymeric molecules (Deasy, 1984).

An important properties of the polymer is its glass transition temperature. Below this temperature there is a virtual cessation of the molecular motion, causing the polymer to become crystalline-like in its properties. Table 2 shows the glass transition temperature (T_g) of some polymers used as film formers.

Above the glass transition temperature, increase in temperature causes the surfaces of applied layers of film former to become more cohesive as a result of the greater rate of diffusion of polymer molecules or fractions thereof at the interface caused by increased thermal motion. Care must be taken not to cause the surface of partially coated core to become too cohesive or tacky, as this gives rise to aggregation problems that may cause coating damage when the cores are subsequently prized apart. Obviously, the longer the coating and core are held at elevated temperature, the more marked these effects will be.

The adhesion of film former to the core surface is also favored by chemical bonding at the interface and the flow of film former into irregularities on the surface of the core. Rowe (1980) reported that the adhesive force of various film coats were all found to be much less than the cohesive force within the film.

Table 2. Glass Transition Temperature (T_g) of some polymers used as film former (Deasy, 1984).

Polymer	T_g (°C)
Ethylcellulose	129
Hydroxypropylmethylcellulose	177
Nylon 6	47
Polyethylene	-110
Polymethyl acrylate	5
Polymethyl methacrylate	105
polyvinyl acetate	30
polyvinyl chloride	82
Silicone rubber	-123

2.3.2.2. Solvents

Film formers are usually applied to cores using a suitable organic or inorganic solvent system. The more crystalline a polymer is the greater will be its cohesive force and consequently it will be more difficult to dissolve in a solvent system. Dissolution may be aided in polar solvents by dissociation of functional group along linear polymer molecules, causing charge repulsion, leading to separation of neighboring molecules or uncoiling within molecules.

Increasing dissolution of a fixed overall concentration of a film former in a particular solvent system is normally accompanied by a progressive increase in apparent viscosity of the system as a result of the extended configuration of dispersed molecules, which increase the resistance to flow (Figure 5). However, it should be realized that whatever the solvent system used, it should not dissolve the core material, which is normally a low-molecular-weight drug.

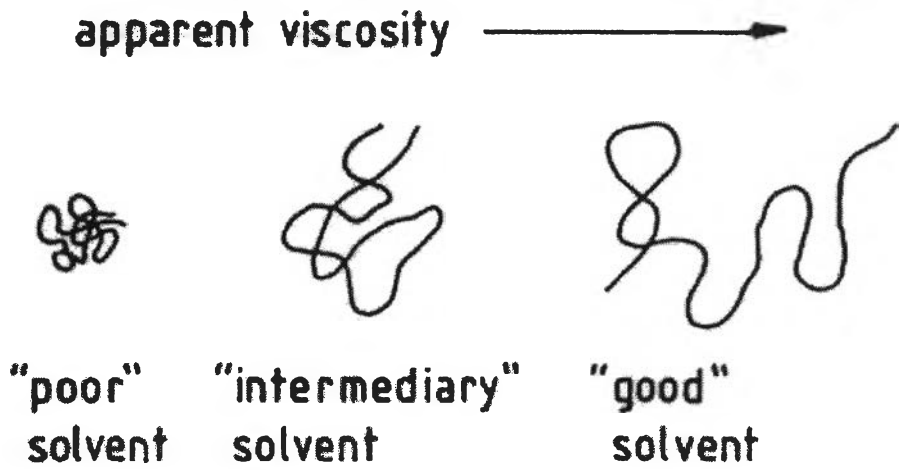


Figure 5. Uncoiling and extension of a linear polymer molecule with increasing efficiency of solvent used (Deasy, 1984).

2.3.2.3. Plasticizers

A plasticizer has been defined by Mellan (1961) as a substantially non-volatile, high boiling point, non-separating substance that when added to another changes certain physical and chemical properties of that material. Plasticizers are normally added to polymeric film formers in order to increase segmental mobility, impart flexibility, reduce brittleness, and increase resistance of the film coating to failure produced by mechanical stress.

Substances such as phthalate esters, fatty acid esters, and glycol derivatives are examples of common types of external plasticizers because they are added to film formers to influence their physicochemical properties.

The plasticizer achieves its effects by being interposed between the polymer chains to reduce cohesive force between polymer molecules as a result of a chemical association by secondary valence forces of both species. Effective plasticizers tend to have a chemical structure similar to the polymer they plasticize. Thus cellulose ethers retaining a high percentage of hydroxyl groups are best plasticized by hydroxyl-containing compounds such as polyhydric alcohols. Concentrations in the range 20 to 50% of plasticizer relative to film former are usually required for cellulosic polymers.

Polymers with lower cohesive force normally require 20% or less of plasticizer. Strongly crystalline polymers, unlike amorphous ones, are usually difficult to plasticize, as it is hard to disrupt their high intermolecular cohesive forces. Long cylindrical plasticizer molecules tend to be more effective than spherical molecules of the same molecular weight. Evidence of good plasticization may be observed from a decrease in the glass transition temperature of the polymer, as its chains are more mobile, which may alter a hard, brittle coating at room temperature to the one that is flexible yet tough.

Obviously, to be effective at a molecular level the plasticizer must dissolve in the solvent system used for the film former. This is normally facilitated by the fact that the polymer and plasticizer have common functional groups that prevent premature separation of either component as the solvent is evaporated off to deposit the film. Ideally the solubility parameter of the plasticizer should be close to that of the polymer.

Because of the loose association between the plasticizer and the film former, problems of permanence and uniformity of distribution of the former in the coating may arise. Migration of low-molecular-weight plasticizer during storage may profoundly affect the physical and mechanical properties of the film and may be associated with the leaching of undesirably high levels of plasticizer into the surrounding medium. Greater performance may be achieved by the use of the higher-molecular-weight, bulky compounds in an effective series of plasticizers that have low volatility during any heating process involved and that have a slow rate of diffusion from the coating.

The secondary of plasticizers is that they alter the permeability of the coating. Compounds of high water solubility will tend to make the coating more permeable to aqueous media, as they will rapidly dissolve out of the coating upon immersion into water. However, the effect can be more complex, as was observed by Okor and Anderson (1979), who showed that films composed of a mixture of acrylic copolymers became more permeable to urea as the content of the more hydrophilic plasticizers, glyceryl triacetate, decreased by leaching when used in combination with glyceryl tributyrate. This effect was ascribed to greater copolymer chain flexibility upon sorption of water produce by the permanence of the glyceryl tributyrate. On the

other hand, poorly water-soluble plasticizers will limit water permeation through the film and are often necessary for use with enteric and slow-release coatings to control diffusion of low-molecular weight drugs out of the core.

2.3.2.4. Surfactants

Various anionic, cationic, and nonionic surfactants are sometimes added to film coating formulations that are to be sprayed or poured onto the surface of cores in order to aid wetting and even spreading of the film coating solution. Plasticizers may permit the use of otherwise immiscible or insoluble additives by solubilizing them. They also influence the permeability of coatings.

2.4. Desolvation and Gelation of the Coating

As the solvent evaporates there is a tendency for the coating material to convert itself to a gel at a certain polymer concentration. This gelation of the film associating with increasing concentration of polymer gives rise to the formation of a network type of structure as individual molecules come into closer proximity. Gelation is also aided by decrease in temperature, which reduces further the mobility of polymer chains. With further loss of solvent the gel contracts more, finally forming a dry, viscoelastic film that unless adequately plasticized tends to be dimensionally constrained on the relatively immobile core substrate. This unwanted stress in the final film may be relieved by the formation of minute cracks in the coating. Accordingly, it is important to desolvate the coating slowly enough by proper choice of solvent and drying temperature so that polymer chains have adequate time to orientate themselves in order to dissipate as much stress as possible (Deasy, 1984).

2.5. Permeability to Oxygen, Carbon, Carbon Dioxide, and Water Vapor

Because of the importance of oxygen, carbon dioxide, and water vapor permeability from the atmosphere to the stability and shelf life of many core materials, these properties are often measured for free films. Table 3 shows the

permeability of various polymers to these three agents, from which it can be seen that there is a wide range between and within different polymers. Highly crystalline polymers tend to be less permeable, whereas elastomers are highly permeable. There often tends to be an inverse relationship between water vapor transmission and gas permeability. This is because water vapor permeability tends to be greater in more polar polymers, which usually have a more ordered and less porous structure that limits gas diffusion through them. Obviously, suitable choice of polymeric coating material can minimize the penetration of these agents into microcapsules and related dosage forms.

Table 3. Permeability of various polymers to oxygen, carbon dioxide, and water vapor at 30°C (Deasy, 1984).

Polymer	**$P(O_2)$**	**$P(CO_2)$**	**$P(H_2O)$**
Polyacrylonitrile	0.0002	0.0008	300
Polymethacrylonitrile	0.0012	0.0032	410
Polyethylene terephathalate	0.035	0.017	175
Nylon 6	0.038	0.016	275
Polyvinyl chloride	0.045	0.016	275
Polyethylene (density 0.964)	0.4	1.8	12
Cellulose acetate	0.08	2.4	6800
Butyl rubber	1.3	5.18	120
Polycarbonate	1.4	8	1400
Polypropylene	2.2	9.2	65
Polystyrene	2.63	10.5	1200
Polyethylene (density 0.922)	6.9	28	90
Natural rubber	23.3	153	2600
Polydimethyl siloxane	605	3240	40000

Units: CCS.(S.T.P.)/sq cm/cm/sec/cm Hg x 10^{10}

Nixon and Nouh (1978) investigated the effect of microcapsule size of the oxidative decomposition of benzaldehyde as raw material. A gelatin-acacia complex coacervation process of microencapsulation was used. Microcapsules with larger

diameter had higher oxidative rates, as they contained proportionally larger amount of core material and were less affected by termination reactions.

Banker (1966) reported that plasticizers increased the water permeability of acrylic films by increasing polymer chain segmentation and possibly by directly absorbing water.

Other additives for different films, such as surfactants, may also directly promote sorption of water. In soluble fillers, which tend to increase the glass transition temperature, lower water permeability.

Increasing room humidity during drying has been reported by Gillard et al. (1980) to be responsible for an observed marked increase in the permeability of ethyl cellulose films.

It is important that coating films, apart from the core, should be stable to light during storage. Most films have adequate photo-stability but may be affected slightly in their physicochemical properties rather than their gross appearance. For example, it has been found that the rate of water vapor transmission decreased through gelatin film with increasing exposure time to ultraviolet irradiation, presumably due to greater polymer crosslinking (Matsuda et al.,1979).

2.6. Microencapsulation Processes

There are many processes available to make microcapsules. Processes which are most applicable to pharmaceuticals are given in table 4, which cites the process, the core materials which can be coated, and the approximate size range of microcapsules that can be manufactured.

Table 4. Microencapsulation processes and their application (Deasy, 1984).

Process	Core Material	Microcapsule Size (nm)*
Air suspension	Solids	35-5000
Coacervation-phase separation	Liquids and solids	1-5000
Multiorifice-centrifugal	Liquids and solids	1-5000
Pan coating	Solids	600-5000
Solvent evaporation	Liquids and solids	1-5000
Spray drying and congealing	Liquids and solids	5-600

*5000 nm is an arbitrary upper size as some processes may produce larger particles.

3. Spray-Drying

3.1. The Design and Operation of Spray-Dryers

Spray-drying, one of the techniques used for microencapsulation, converts a liquid into powder in one-step process (Nielson, 1982). It is capable of producing fine, dustless or agglomerated powders to precise specification. The spray-drying process encompasses the following four stages (Masters, 1979).

(i) Atomization of the feed into a spray

(ii) Spray-air contact

(iii) Drying of the spray

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

There are a variety of atomization systems available, which may be classified according to the nozzle design as rotary atomization, pressure atomization or two-fluid (pneumatic) atomization. In rotary atomization the feed fluid is introduced into the drying chamber by means of a spinning disc or wheel which creates a spray of droplets. Pressure atomization, 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-dryer (such as the Büchi 190 which is commonly used in pharmaceutical research).

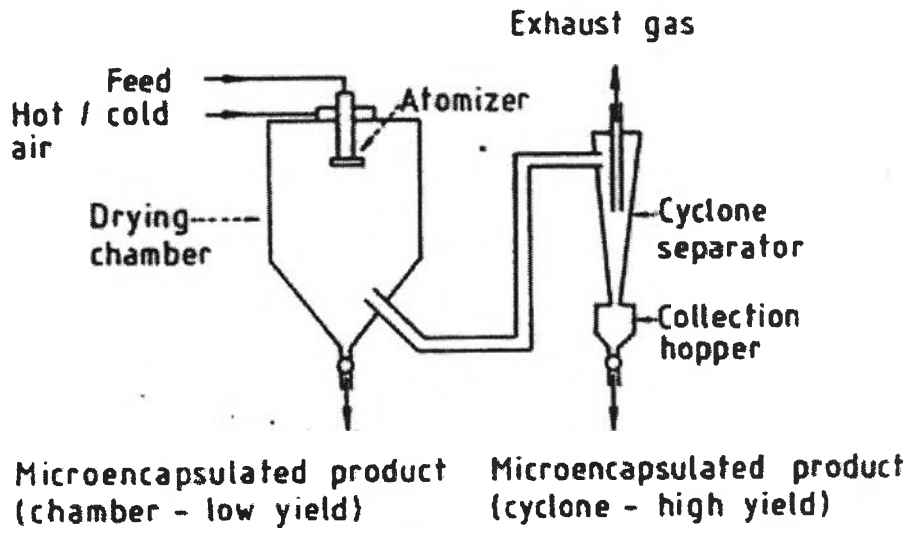


Figure 6. Schematic diagram of a co-current spray-dryer (Deasy, 1984).

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-dryers 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 a coolest air. Also, the high rates of moisture evaporation enable the temperature of the dry product to be considerably lower than that of the air leaving the drying chamber. Counter-current drying, on the other hand, is a superior process in terms of heat utilization and economics, but subjects the driest powders to the hottest air stream (Masters, 1979)

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-dryer 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 re-circulated. The organic solvent is also recovered. Other dryers are available which operate using air with 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.

3.2. The Properties of Spray-Dried Powders

Spray dried powders are usually approximately spherical with 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 et al., 1977). 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. Obviously, the design of the nozzle and drying chamber will affect particle properties, and the desired powder characteristics should be born 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, 1979). Particle size is usually increased as a feed concentration or viscosity increases (Masters, 1985). Masters reports that surface tension has a minimal effect on particle size, although some researches show 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. It was observed that for crystalline materials, such as sodium sulfate, temperature had very little effect where as 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 air increase. High drying air temperatures also seem to be associated with lower bulk densities. As a general rule, smaller particles will usually be more dense, and so the bulk density of the powder with a small particle size will be higher. Bulk density will also increase with a narrower particle size distribution. The outlet temperature of a spray dryer can be correlated with activity loss in the drying of heat sensitive materials. As would be expected, increase dryer outlet temperatures result in lower final product moisture content (Broadhead et al., 1992).