CHAPTER I

GENERAL BACKGROUND

Introduction

The continued development of sustained release technology over the past decades has provided countless ways of producing long acting dosage forms. A number of technical advancements that have been recently made in developing new techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action and/or targeting the delivery of drug to a tissue. These advancements could provide one or more of the following benefits: (i) controlled administration of a therapeutic dose at a desirable delivery rate; (ii) maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment; (iii) maximization of efficacy-dose relationship; (iv) reduction of adverse side effects; (v) minimization of the needs for frequent dose intake and (vi) enhancement of patient compliance (Chien Y.W., 1990; Theeuwes F.et al.,1991).

The term oral sustained release is commonly used to describe orally administered drug products that are capable of controlling the release of the drug. The matrix system, consisting of drug and polymer being mixed homogeneously, is the most frequently used and easily obtained system to formulate the sustained release oral preparations in the form of capsules or tablets (Theeuwes F.et al.,1991).

Chitosan, a natural, non-toxic, biodegradable, high molecular weight polymer is now modified both chemically and physically to produce materials with a wide variety of potentially useful properties. In Thailand, there have been a number of references using chitosan as pharmaceutical excipient in formulation as tablet disintegrant (Ritthidej G.C.et al.,1994), film-coating polymer (Paechamud T.,1994), beads (Puttipipatkhachorn and Anantakul, 1997), controlled release solid dispersions carrier (Dangprasirt and Ritthidej, 1995 & 1997), and controlled release microparticulates and

matrix tablet from spray drying process (Pearnchob N., 1996; Kulvanich P.et al.,1997; Patomchaiviwat V.,1993).

Spray drying technique may prove to be more useful for the preparation of microcapsules because the coated particles can be produced directly from droplets in a single process (Bodmeier and Chen, 1988; Wan, Heng and Chia, 1991; Broadhead J.et al., 1992 & 1994). Matrix microcapsules, a matrix of wall material contains many small, fine core particles, are usually prepared by spray drying because it can be used simply to separate previously prepared microcapsules from the vehicle (Voellmy et al., 1977). This technique has been employed for the manufacture of drug matrix that are subsequently processed into various solid dosage forms.

Several researchers (Kornblum S.S., 1969; Takenaka H.et al., 1980; Takeuchi H.et al., 1989; Palmieri G.F. et al., 1994; Kulvanich P.et al., 1997) determined the suitability of a spray drying technique in the manufacture of a drug matrix that would possess sustained action when compressed into tablets. The results showed that free flowability of directly compressible co-spray dried powder, uniformity of drug and polymer, distribution in the matrix and ease of reproducibility are the major factors comprising the utility of spray drying.

Extrusion-spheronization as a pelletization technique is gaining popularity and increasing acceptance in the pharmaceutical industry nowadays. Preparation of pellets as a drug delivery system by using this techniques not only offer therapeutic advantages such as maximum in drug absorption, less irritation of the gastro-intestinal tract and a lower risk of side effects due to dose dumping but also technological advantages, for example, better flow properties, less friable dosage form, narrow particle size distribution speed of production ease of coating and uniform packing (Gamlen M.J., 1985; Chien Y.W., 1990; Vervaet C.et al.,1995). Several reports (Tapia, et al., 1993; Gaskonda S.R. et al., 1994) have been published dealing with sustained release matrix pellets using extrusion-spheronization technique.

In the present study diclofenac sodium was chosen as a model drug for development of controlled release preparation. Due to short biological half life and associated adverse effects, it is considered as an ideal candidate for controlled drug delivery (Reynolds et al., 1988; Schubiger B.I. et al., 1980). Although there are a number of reports on the case of chitosan as excipient in producing controlled release diclofenac sodium formulations, the 24 hours controlled release preparation has not been reported and developed by spray drying and extrusion-spheronization techniques (Lin and Kao, 1991; Tapia C.et al.,1993; Pearnchob N, 1996; Sabnis S.et al.,1997).

In addition, the use of hydrophilic plasticizers, propylene glycol and glycerin, in chitosan solution for spray drying process were studied. The compatibility, plasticizing properties and suitable amount and type of platicizers in the manufacture of controlled release powders were investigated. The physicochemical properties were also evaluated. The drug release characteristics of controlled release products prepared by spray drying and extrusion-spheronization process and a commercial product (Voltaren® SR) were comparatively studied.

Objectives of the Study

1. To study the properties of chitosan as a controlled release polymer for diclofenac sodium microspheres using spray drying and extrusion-spheronization techniques.
2. To evaluate the effects of viscosity grade and amount of chitosan in the formulations on physicochemical properties and drug release characteristics of microspheres.
3. To evaluate the effects of type and amount of plasticizer in the formulations on physicochemical properties and drug release characteristics of microspheres.
4. To study and compare the physicochemical properties and drug release characteristics of different formulations: spray dried powders, matrix pellets and matrix tablets containing spray dried powders.

Literature Review

1. Spray Drying Technique

Spray drying is a process describing the transformation of liquid feed into a dried particulate form by spraying the feed into a hot drying gaseous medium (Masters K.,1985). The process has been commonly used in the pharmaceutical industries include drying heat-sensitive materials such as protein drugs with minimal loss of activity (Broadhead J.et al.,1994; Maa Y.et al.,1998), improving the solubility of poorly water-soluble substances (Takeuchi H.et al.,1987; Matsuda Y.et al.,1992), and improving flow properties in the preparation of free-flowing granules for tablet production (Kawashiwa Y.et al.,1972, Kornblum S.S.,1969).

Recently this technique has received considerable interest as a microencapsulation process to obtain a controlled delivery system. (Takeuchi H.,1989; Wan L.et al.,1992; Palmieri G.F.et al.,1994). The method may offer, in comparison with the usual coating techniques, the advantage of realizing the microencapsulation process in one step. Either a solution, suspension or paste can be fed in the spray drying process. The resulting dried products conform to powders, granules or agglomerates, the form of which depends upon the physical and chemical properties of the feed and the dryer design and operation (Masters K.,1979).

1.1 The Spray Drying Operations

The spray drying process encompasses the following four stages (Broadhead J. et al.,1992) :

I Atomization of the feed into a spray

II Spray-air contact

III Drying of the Spray

IV Separation of the dry product from the drying gas.

Atomization system 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 sent into the drying chamber by spinning disc or wheel which creates a spray of droplets. Pressure atomization occurs when the feed is fed to the nozzle under pressure which caused the fluid to be dispersed into droplets as it leaves the nozzle. The two-fluid nozzles separate the feed fluid and atomizing air into two lines that finally mix and the air causes the feed to break up into a spray.

Spray drying 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. 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. On the other hand, counter-current drying is a superior process in terms of heat utilization and economics, but subjects the driest powders to the hottest air stream.

The final step involves the separation of the product from the air stream using cyclone separator 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. In this manner, the drying gas would usually be air. In addition, the closed cycle spray dryers are available which enable organic solvents to be used as the feed medium. The closed cycle may be required if the material being dried is extremely susceptible to oxidation or has explosive tendencies (Takeuchi et al.,1989). Nevertheless, this system will get rid of the unacceptable solvents that create serious pollution problems using a high efficiency

condenser to secure maximum recovery of the solvent, make the closed cycle dryer more expensive than the open system (Nielsen F.,1982).

A modified and less costly version of the closed cycle system is applicable for drying aqueous feeds when the dry product must only be in contact with aid of reduced oxygen content in the recirculated air. In comparison with the conventional open drying system the closed system concept offers a radical reduction in air pollution from this machine.

1.2 Advantages and Disadvantages of Spray drying

Advantages (Masters K.,1979; Nielsen F.,1982)

1. Continuous in operation.
2. Adaptable to full atomization.
3. Dried product specifications are met through dryer design and operational flexibility.
   (i) Required product form (particles as spheres, fines, agglomerates)
   (ii) Required product properties (dusty or dustless, degree of flowablilty, wettability)
4. Applicable to both heat sensitive and heat resistant materials.
5. Economic in operation. Dried product specifications are related to the properties of :
   (a) Particle size distribution
   (b) Appearance
   (c) Moisture content
   (d) Friability
   (e) Color, aroma, taste
   (f) Activity
   (g) Sterility.
6. Many kinds of feed stocks (solution, slurry, thixotropic paste or melted form) can be handled, if pumpable.
7. Corrosion and abrasion can be reduced or prevented because the material dose not contact the equipment surface until it is dry.

8. Low maintenance costs because there are few moving parts.
9. Low labor costs because only one operator is required, even on large installation. The evaporation usually done under slight vacuum, thus it is easy to keep clean.
10. Same operation for both small and large dryers.
11. Spray drying is an airborne process, hence there is very low material holdup in the equipment.
12. Designs are available to handle
    (I) organic solvent explosion and fire risks
    (II) explosive mixtures in air from powders
    (III) odor products
    (IV) toxic products
    (V) products requiring aseptic and hygienic drying condition.

Disadvantages (Broadhead et al.,1992)

1. High cost both in equipment and operation.
2. Poor thermal efficiency unless extremely high drying temperature is used and causing heat degradation.
3. High cost of the end product 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.

1.3 The Properties of Spray Dried Powder

Spray dried powders are 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. By modifying the spray drying process, it is possible to alter and control the following properties of spray dried powder; appearance, particle size and size distribution, bulk density, particle density, porosity, moisture content, flowability, stability, dispersability, friability and retention of activity aroma and flavor (Newton J.M.,1966).

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 K.,1979). Particle size is usually increased as the feed concentration or viscosity increases (Masters K.,1979; Corsby and Marshall,1958). The rotation speed of the atomizer is the main factor affecting the drug content of the products. With increasing rotating speed, the drug content increases. The excipient is separated easily from the spray drying droplet than the drug because of the different density, which results in increasing the drug content in the product. (Kawashima Y.et al., 1983). Wan, Heng and Chia (1991) concluded that the air-to-liquid ratio affects the product particle size. As the mean particle volume of the spray dried product decreases, the rate of dissolution increases.

Masters (1979) described that at low feed rates, the droplet size is of high homogeneity. At higher feed rates, the atomizing air cannot penetrate the thick liquid jets. Atomizing is incomplete and wide droplet-size distribution in the spray results. According to Seager (1977), increasing feed rates will lead to a reduction in the outlet temperature and increase in equilibrium solvent content or moisture level.

The efficiency of the spray dryer is occurred, when a suitable feed type is used. The different types of spray dried products obtainable from a solution-feed and suspension-feed observed from the SEM are depicted in Figures 1(a)-(f). Different formulation conditions affect the predominance of the type of product formed (Wan, Heng and Chia,1992).

From the solution feed, some spray dried drugs were coated with a thin polymer film (Fig.1(c)). The predominant product has drug protrusions on the surface of the polymer (Fig.1(d)). These particles were obtained by the initial formation of a polymer solid crust, followed by the diffusion of water within the crust of the surface, carrying dissolved drug. On evaporation, rod-like drug crystals were deposited on the surface of the microcapsules. With a suspension feed, the undissolved drug remained a large crystals. Some of these drugs crystals appeared not to be coated after spray

drying (Fig.1(e)), whereas the majority of the drug crystals were enveloped by polymer film (Fig.1(f)). The dried products are microencapsulated drug crystals with fairly smooth surfaces compared to the solution-feed spray dried product which has a higher degree of roughness due to drug deposition. The suspension-feed products show better flow properties and slower drug dissolution than solution-feed product. Two factors affected this slow release are the coating around the drug crystals and the larger size of the microcapsules.

Figure 1 Possible types of products obtained by spray drying a solution-feed (a)-(d) and a suspension feed (a)-(f).

The feed concentration or viscosity at the processing temperature influenced by the solid content of the feed. The yield can be increased by using a high total solid content (Broadhead J. et al.,1994). Particle size is usually increased as the feed concentration or viscosity increases. If the feed rate increases, particle size will again increase (Masters K.,1979).

The effect of temperature on particle appears to be highly dependent on the material being dried (Crosby and Marshall,1958). A tendency for the particle size to increase and agglomerate with increasing inlet temperature is observed by Broahead J.et al (1994). A high inlet temperature gives rise to products which are larger and have lower moisture content. Both factors contribute to an improved flowability while the large particles result in slower dissolution (Wan et al.,1991). The effect of temperature on drug content is presented by Kawashima (1983). With decreasing inlet temperature, the drug content increases. The effect of temperature on decreasing the drug content is more significant than that of atomizing rotation speed.

An increased inlet temperature often causes a reduction in bulk density, as evaporation rates are faster, a product dries to a more porous or fragmented structure. It also showed great effect in reducing the particle size (Masters K.,1979). In contrast, Newton (1996) reported an increase in particle size is shown from the increase in drying air temperature.

The outlet temperature of the spray dryer is the single most important parameter that determined the water drying rate and moisture content of the product (Maa Y.et al.,1998; Masters K.,1979). At the given inlet temperature, a decreased feed rate will cause the outlet temperature to rise resulting in a lower moisture content of the final product.

1.4 The Application of Spray Drying for Controlled Release System

A renewed interest in the use of spray drying to coat drugs with polymer to produce controlled release product is widespread. The main advantage over other coating methods is the coated particle can be prepared directly from the droplet in a single process. Moreover spray dried product have improved flow properties, thus increasing the ease of incorporation into a dosage form.

Spray dried 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 (Broadhead J.,1992).

Takenaka et al. (1980) prepared enteric coated microcapsules of sulfamethoxazole efficiently by spray drying using cellulose acetate phthalate (CAP) as polymer with and without additives. The products including the additives were tableted easily due to their good flowabilities whereas, products from the nonadditive formulations could not be tableted. The additives also improved the surface texture of the spray dried products as compared to particles of non-additive formulations, which tented to have flaky surfaces. The crystals from formulations containing CAP were converted from Form I to From II and amorphous from during spray drying (Takenaka et al.,1981). CAP was presumed to interact with the drug, since the degree of amorphism increased with an increase in the concentration of CAP in the formulation.

Coated theophylline particles using an aqueous solution of various polymers, hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC), and sodium carboxymethylcellulose (NaCMC), were prepared by spray drying process (Wan, Heng and Chia,1992). The results showed that drug release from the coated products was dependent on the hydrophillicity of the polymer. NaCMC, which is more hydrophillic,

gelled faster and retarded the drug release more efficiently. HPMC and MC produced flake-like drug particles embedded in the polymer that showed faster release rate than NaCMC. These two polymers produced products with similar dissolution profiles and flow properties. The long needle-like theophylline with scattered HPMCAS particles were affected unsuccessful controlled release because HPMCAS did not hydrate on wetting.

Palmieri, Wehrle and Stamm (1994) evaluated the possibility to obtain microcapsules or microspheres for controlled release by spray drying. Theophylline and sodium sulfamethazine were coated with an hydroalcoholic solution or suspended (pseudolatex) of Eudragit RS in water, in different weight ratios. The obtained solution or suspension was spray dried. No microencapsulation occurred by spray drying a drug and polymer solution; the spray-dried particles were simple minimatrixes, that was a fine drug dispersion in the polymer network. Even if these microparticles were not to reduce the rate of drug release, the tablets, derived from their compression, were very effective as controlled release system and offered a real advantage compared with the matrix tablets obtained by direct compression of the polymer powder (Eudragit RS PO) or by compression of the solid dispersion powders realized by evaporation under vacuum. So, spray drying is a useful step in the formulation of controlled release matrix tablets.

Spray drying process has been reported to provide a free-flowing powder with decreased dissolution rate of drug when compressed into matrix tablets that are subsequently processed into solid dosage form (Kornblum S.S., 1969; Takeuchi H.et al.,1989; Kulvanich and Leesawat,1996). The mixture solution of the drug and polymeric materials was spray dried to attain co-spray dried powder which could be directly compressed into the matrices. This technique provides a number of advantages: producing directly compressible co-spray dried powder with free flowing property and yielding uniform distribution of polymer and drug content hence very reproducible drug release profiles for consecutive batch are obtained.

Takeuchi (1989) produced controlled release theophylline tablets containing various grades of Eudragit. 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. In each tablet, the controlled drug release was attributed to continuous and well-dispersed polymer matrix formed by spray drying and subsequent compressing process.

Controlled release theophylline spray dried matrices containing cellulose derivatives such as: ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate were also prepared by Kulvanich and Leesawat (1991). The types and amounts of matrix additives affected the physical properties of co-spray dried powders obtained from this study.

The suspension feed of the drug and polymers was also spray dried and compressed into matrix tablets (Dangprasirt and Ritthidej,1997; Lin and Kao,1991). The suspension feed showed the difference in appearance, flowability and release profiles of the microcapsules from those of solution feed (Wan L.et al.,1992). These differences still presented in these two experiments.

Controlled release diclofenac sodium solid dispersion having an optimum dissolution profile for sustained release compressed tablets were produced from ethylcellulose (EC) and chitosan (Dangprasirt and Rhitthidej, 1995 and 1997). Combined carriers of EC-chitosan exhibited more dissolution retarding effect than single carrier of EC or chitosan. The optimized diclofenac sodium controlled release solid dispersion were compressed to produced matrix tablets. The optimum levels of compression force and amount of the diluent, disintegrant and lubricant were studied.

Lin and Kao (1991) prepared sodium diclofenac coated microcapsule by spray drying technique with Eudragit L30D as enteric-coating material. The spray dried powder, mixed with Neocel and Flo-starch, or the mixture of them was

directly compressed into tablets. The spray dried powder, the mixed powder before tabletting, and the tablet all exhibited enteric coated release properties. The weight ratio of Neocel to Flo-starch played an important role in controlling the release of sodium diclofenac from enteric coated tablets.

The plasticizer showed the great effect on the release profiles of the spray dried formulation (Palmieri G.et al.,1994). Because of high hydrophobic property of dibutyl phthalate, the formulations exhibited the different release depended on the presence and absence of plasticizer. The tablet formulations of Eudragit RS microparticles (from the hydrophilic solution) without plasticizer and Eudragit RS 30D microparticles (from the aqueous suspension) with dibutyl phthalate were very effective in delayed drug release rate.

Microencapsulated theophylline particles were prepared by an aqueous spray drying process using hydroxypropylmethylcellulose (HPMC). The effect of different plasticizers, triethylacetate, polyethylene glycol, propylene glycol, glycerin and citric acid, was investigated. The presence of the plasticizer also influenced crystallization of drug. The formation of a solid drug dispersion was observed with the addition of citric acid or glycerin. Changes in the pH of liquid feed caused by the plasticizer had an effect on the product dissolution profile, but this was not a major factor. Formation of pores due to leaching of plasticizers during dissolution enhanced drug release. Flow property measurements indicated that the plasticizers also affected the cohesiveness of the products. Compared to the microcapsules formed without any plasticizers, propylene glycol, glycerin and citric acid appeared to be beneficial to the microcapsule wall formation, with microcapsules containing citric acid having the slowest drug release (Wan, Heng, Chai, 1992b).

Further studies examined the effect of a plasticizer, citric acid, with NaCMC and HPMC (Wan, Heng, Chia, 1993). With varying plasticizer concentrations, changes in interaction between plasticizer and polymer, and in size of crystallized drug crystals, were observed with HPMC film. The plasticizer content also

affected the film of NaCMC by bringing about a change in the form and arrangement of the drug. With HPMC, as plasticizer content was increased there was a corresponding increase in mean size of the spray dried products. In terms of drug release and formation of spherical particles, a plasticizer concentration of 30%w/w was recommended for both HPMC and NaCMC.

2. Pelletization Technique

Extrusion-spheronization as a pelletization technique was developed in the early 1960s, and since then has been extensively researched and discussed. The technology is unique in that it is not only suitable for manufacture of pellets with a high drug loading, but it can also be used to produce extended-release pellets in the same step in certain situations, and hence obviate the need for subsequent film coating.

2.1 Equipment Used During an Extrusion-Spheronization Cycle

The extrusion-spheronization process is a multistep procedure, involving dry mixing, wet granulation, extrusion, spheronization, drying and (if necessary) screening. Many types of equipment are utilized in each process as the following:

2.1.1 Granulation

The first step of an extrusion-spheronization cycle consists of the preparation of the plastic mass. Different types of granulators are used to perform the mixing of the powder blend and the granulation liquid. The most commonly used granulator is a planetary mixer, although the use of high shear or sigma blade mixers has also been reported (Vervaet C.et al.,1995). During the granulation step the evaporation of the fluid phase should be restricted to a minimum. This could especially be a problem with the high shear mixers as they introduce a large amount of energy into heat and influence the extrusion behavior of the wet mass. Cooling of the granulation bowl might avoid this problem.

2.1.2 Extrusion

The second step of the process is the shaping of the wet mass into long rods during extrusion. The extrusion process can be performed using four main classes of extruders: screw, sieve and basket, roll and ram extruders.

Screw-fed extruders have screws that rotate along the horizontal axis and hence transport the material horizontally; they may be axial or radial screw extruders (Fig. 2a). Sieve and basket or gravity-fed extruders include the rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counterrotating cylinders (Fig. 2b). Two types of roll extruders can be distinguished: an extruder equipped with two contrarotating wheels of which one or both are perforated. Using this type, the mass is fed between the two wheels and the extrudate is collected inside the extrusion wheels (Fig. 2c). The second type has a perforated cylinder which rotates around one or more rollers, discharging the material to the outside of the cylinder. Ram extruders is the oldest type of extruders, a piston displaces and forces the material through the screen situated at the end of the barrel (Fig. 2d).

2.1.3 Spheronization

During the third phase, the static cylinders are dumped onto the spinning plate of the spheronizer or marumerizer, called the friction plate, where the extruders is broken up into smaller cylinders with a length equal to their diameter. The static cylinder can be jacketed for temperature control. The friction plate, a rotating disk with a characteristically grooved surface, is the most important component of the equipment. A standard friction plate with a cross-hatch pattern, where the grooves intersect at a 90° angle is the most popular type. Another type of friction plate is radial geometry where a radial pattern is used (Fig. 3).

According to Rowe (1985), those plastic cylinders are rounded due to frictional forces. In the spheronization process different stages can be distinguishes depending on the shape of the particles, i.e. starting from a cylinder over a cylinder with round edges, dumb-bells and elliptical particles to eventually perfect spheres (Fig. 4a). Baert and Remon (1993) suggested that another pellet-forming mechanism might exist (Fig. 4b). In this mechanism, a twisting of the cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have a round and a flat side. Due to the rotational and the frictional forces involved in the spheronization process the edges of the flat side fold together like a flower forming the cavity observed in certain pellets.

2.1.4 Drying

The final step is the drying of the pellets. The pellets can be dried at room temperature or at elevated temperature in a fluidized bed, a hot air oven or a microwave oven. Comparing a formulation dried in a microwave and ordinary oven, the pellets dried with microwave differed from those dried in the oven as their surface was rougher and those pellets were more porous and of lesser hardness (Bataille B.et al.,1993).

The cGMP requirements for equipment serving in pharmaceutical industry are all the parts of the machines that contact with the product must be of high quality stainless steel and the construction must be such that the machine can be easily cleaned. In addition, it must be controlled all critical parameters that affect the properties of the pellets.

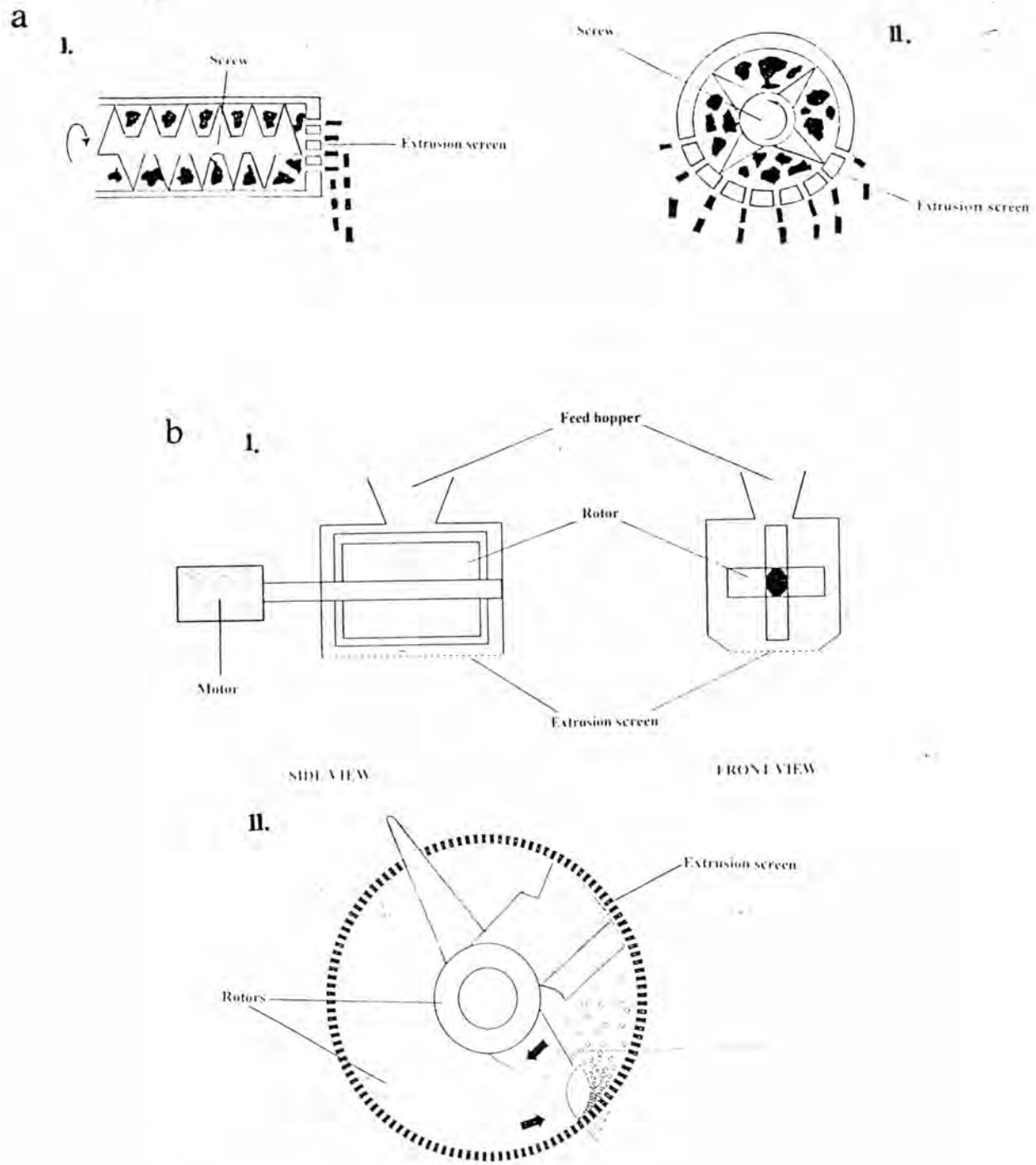
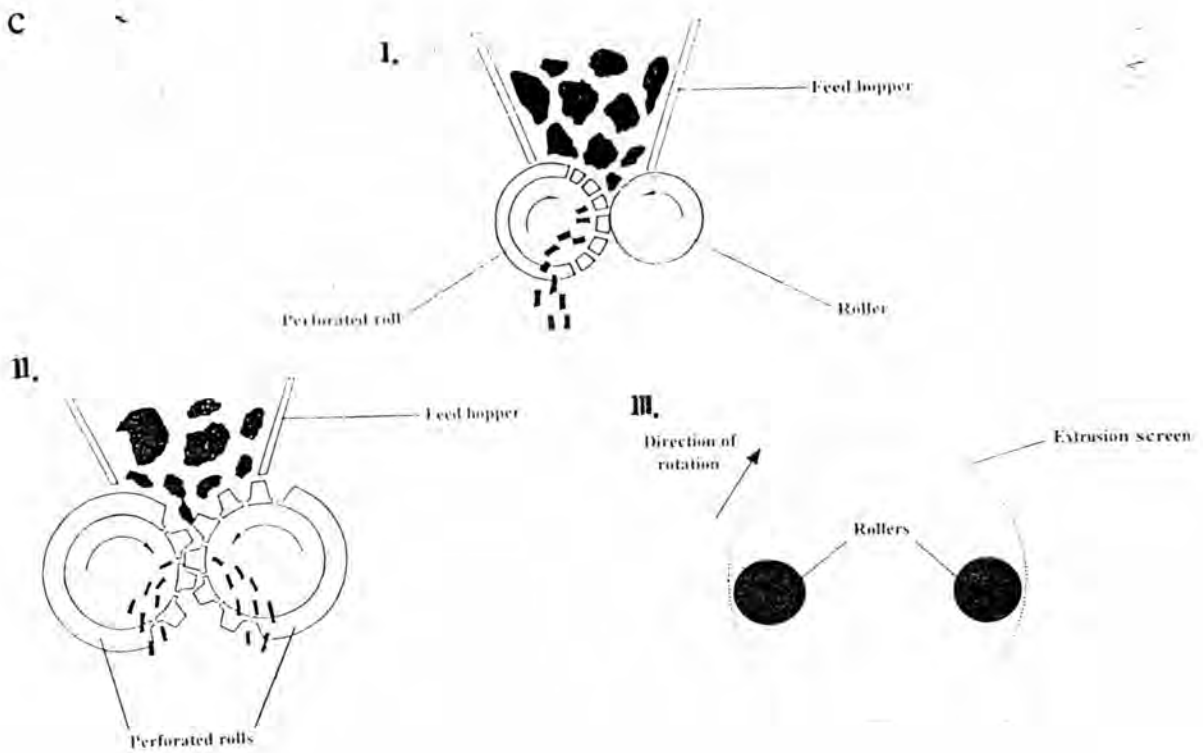


Figure 2 Schematic views of four types of extruders:

(a) Screw extruder; (I) axial type, (II) radial type

(b) Sieve extruder (I) and basket extruder (II)



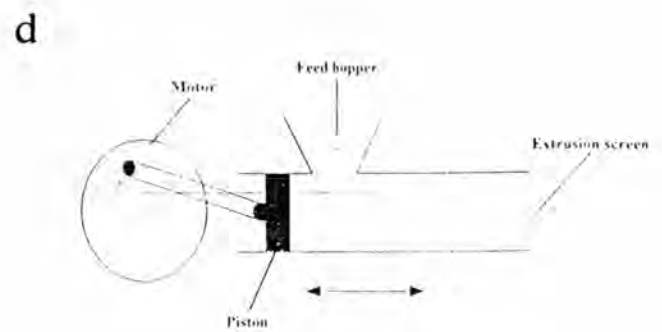


Figure 2 (cont.) Schematic views of four types of extruders:

(a) Screw extruder; (I) axial type, (II) radial type

(b) Sieve extruder (I) and basket extruder (II)

(c) Roll extruder; (I) with one perforated roll, (II) two perforated roll and (III) with the extruder with the extrusion screen rotating around rollers

(d) Ram extruder.

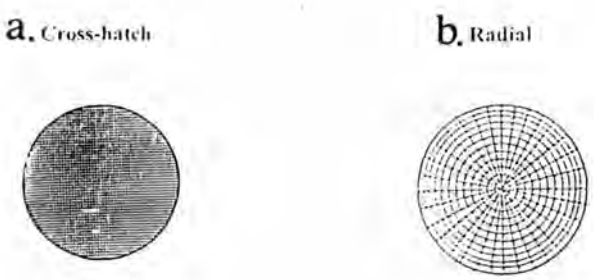


Figure 3 Geometry of the spheronization plate; (a) cross-hatch and (b) radial type.

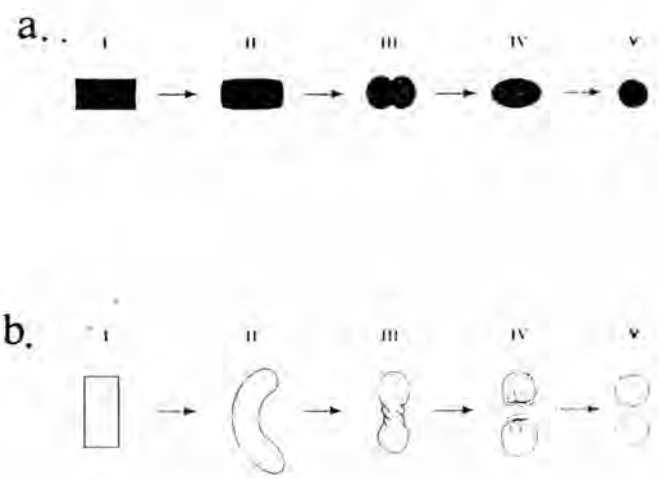


Figure 4 Pellet-forming mechanism according to:

(a) Rowe: I. cylinder, II. cylinder with rounded edges, III. dumb-bell, IV. ellipse, V. sphere. and (b) Baert: I. cylinder, II. rope, III. dumb-bell, IV. sphere with a cavity outside, V. sphere.

2.2 Parameter Influencing the Final Pellet Quality

2.2.1 The moisture content of the granulated mass

The moisture content is necessary to give the powder mass its plasticity so that it can be extruded and shaped afterwards. The moisture content can range between a lower and upper limit and still produce pellets of an acceptable quality. If moisture content is less than lower limit, a lot of dust will be formed resulting a large yield of fines. Exceeding the upper limit, it leads to an overwetted mass and agglomeration of the individual pellets that affect the hardness and dissolution release of the pellets. The rheological characteristics of the wet mass are important for achieving good properties for extrusion process (Vervaet C.et al.,1995).

Generally, the liquid content of the wet powder mixture is about 20 - 30% (w/w). Solvents, such as ethanol or mixtures of water and ethanol, may be used as granulating liquids when pure water is not suitable, for instance, for stability or solubility reasons.

2.2.2 The physical properties of the starting material

Excipients plays a critical role in imparting strength and integrity to pellets following drying and governing final pellet formation (Ghebre-Sellassie,1989). Microcrystalline cellulose, the most important and widely investigated excipient, is used as a filler and a spheronization aid, regulating the water content and distribution in the granulation. Lactose is another excipient that has been studied extensively and used occasionally to evaluate the mechanism and process of pelletization by extrusion-spheronization.

There is not only the obvious difference in pellet quality from different compositions but also a difference when different types of the same product are used. Avicel® type and concentration affect the pellets size, sphericity as

well as release rate of an including drug (Hileman G.A.et al.,1993). The effects of various viscosity grades of chitosan show the different results on bead formation and on release profiles. Incorporation of higher viscosity grades of chitosan yield beads with rough surfaces and slower release characteristics (Goskonda and Upadrashta,1993). Nevertheless, the particle size of the starting material has a profound influence on the extrusion characteristics of the wet mass and on the size and the roundness of the resulting pellets (Vervaet C.et al.,1995).

The drug substance itself plays an important role in the pelletization process, particularly at the high drug loading. Physical properties such as particle size and polymorphism, and chemical properties such as pKa and solubility determine the amount of active ingredient which can be incorporated in the formulation and influence the quality of the final pellet with respect to shape and surface smoothness. These properties must be carefully characterized during the development program.

2.2.3 The spheronization speed

The spheronization speed affected the particle size of the pellets (Woodruff and Nuessle, 1972; Hileman G.A.et al.,1993; Vervaet C.et al.,1995). An increase of the yield of the smaller fractions was seen, probably due to a great degree of fragmentation during the initial stages of the spheronization process. In contrast, a decreasing amount of fines and increasing spheronization speed correlating with an increased mean diameter were also observed. The hardness, roundness, porosity, bulk and tapped densities, friability, flow rate and surface structure of the pellets were also influenced by a change in the spheronization speed (Woodruff and Nussle,1972). According to Rowe (1985), the spheronization speed should be optimized to obtain the desired densification. He stated that a low spheronization speed would not provide sufficient densification to obtain perfect spheres, as opposed to a spheronization process at higher speed which could lead to agglomeration of the individual pellets.

2.2.4 The spheronization time

A wide variety was witnessed when assessing the importance of this parameter on formulations containing mixtures of microcrystalline cellulose: an increased diameter, a narrower particle size distribution, a change in the bulk and tapped densities and a change in the yield of a certain size range were observed with extended spheronization time. Baert et al. (1993) also found an increase of the sphericity of the pellets when a formulation containing only Avicel® PH101 was processed. In contrast, they found that no influence on the granulometry, the hardness and the friability when formulations containing only Avicel® PH101 were spheronized for different periods of time.

2.2.5 Spheronizer load

The importance of the spheronizer load was determined by means of an experimental design. The yield of pellets of a specific range decreased with increased spheronization speed at a low spheronizer load and increased with extended spheronization time at higher spheronizer load. The influence of spheronizer load on particle size distribution was the mean diameter increased with increasing spheronizer load. In addition, the size of the pellets decreased and their bulk and tapped densities increased with an increasing spheronizer load (Vervaet C.,1995).

3. Plasticizer

The plastcizer is defined as a substantially nonvolatile, high boiling and nonseparating substance that changes certain physical and mechanical properties of the polymer to be plasticized. Polymeric films employ plasticizers to impart flexibility, improve flow, and reduce brittleness. These changes are caused by a decrease in the cumulative intermolecular forces along the polymer chains (reduction in cohesion), which generally decreases tensile strength, lowers the softening temperature, and decreases the glass transition temperature (Banker G.S.,1966).

3.1 Important Terms in Plasticization

The important terms for plasticization process are minimum film-forming temperature (MFT) and glass transition temperature (Tg). MFT is used for the temperature in degree celcius above which a continuous film is formed under distinct conditions. This term is correlated to the Tg, which is defined as the temperature at which the viscosity of a melted thermoplastic polymer increases considerably while the temperature is continuously decreasing. In molecular terms this is the temperature at which the flexibility of polymer chains changes. This results in distinct variations in material properties as the temperature decreases or increases (Lehmann K.O.R.,1989).

A plasticizer has to be added in order to reduce the MFT below the coating temperature and allow coalescence of the colloidal polymer particles in a homogeneous film (Lehmann K.O.R.,1989; Steuernagel,1989). The added plasticizers are generally classified as water soluble or water insoluble. A potential disadvantage of water soluble plasticizers is their leaching from the coating after contact with dissolution or physiological fluids (Bodmeirer and Paeratakul,1992). The release kinetics will vary because of this change in film composition, the system are therefore difficult to be controlled accurately. While, lipophilic plasticizers remain in the coating, assuring more constant conditions during the entire release process (Siepmann J.et al.,1998).

The Tg is reached at which the material becomes glassy. At the point the decrease in volume continues, but the amount of change is smaller. The decrease must represent the decrease in space between the atoms and molecules. Because an increase of hole free volume permits increased motion of polymer molecules, plasticization is a way to increase free volume (Sear and Darby, 1982).

The plasticizer and polymer are generally thought to be held together by intermolecular secondary valence forces forming a complex or molecular aggregate. The lowering of the glass transition temperature below room temperature by plasticization changes a hard, brittle, glass-like material at room temperature to a soft, flexible and tough material (Banker G.S., 1966).

3.2 Plasticizer Effects in Formulations

The effect of plasticization on polymeric material behavior has been a focus of research for many years. The basic requirements of any plasticizer in a polymer system are compatibility and permanence. To be compatible, the plasticizer should be miscible with the polymer, which indicate similar molecular forces in the two-component system. It has been theorized that the most effective plasticizers will generally resemble most closely in structure of the polymer they plasticized (Steuernagel C.R.,1989).

Entwistle and Rowe (1979) found a correlation between the intrinsic viscosity of the polymer/plasticizer solutions and the tensile strength, elongation at the rupture and work done in stressing to failure of cast films. The mechanical properties being at a minimum when the intrinsic viscosity was at a maximum. This correlation held only within a homologous series of plasticizers and none was found for plasticizers of different structures. A relationship was found between the lowering of a calculated glass transition temperature of hydroxypropylmethylcellulose in the presence of propylene glycol, polyethylene glycol 200 and glycerin and the intrinsic viscosity of the corresponding solutions. The higher the viscosity the greater the lowering of the transition temperature.

The mass transport of water insoluble plasticizers in an aqueous colloidal polymer dispersion was studied by Siepmann, Paeratakul and Bodmeier (1998). There are two important mass transfer processes: dissolution of the plasticizer droplets and diffusion of the plasticizer within the polymer particles. Dissolution and diffusion are taken into account simultaneously, which was used to determine the diffusion coefficients and dissolution rate constants of various plasticizers.

Secondary plasticizers was mentioned in the formation of transdermal drug delivery in order to improve the flexibility and adhesiveness of Eudragit E-100 film (Lin, Lee and Lin, 1991). Plasticizer/polymer compatibility was evaluated by

measuring transparency, surface topography and solubility. Secondary plasticizers with a low molecular weight and solubility parameter similar to that of polymer and primary plasticizer were compatible. Further, a low molecular weight or high concentration of the secondary plasticizers might lead to greater plasticizing action, reduce tensile strength and increase film elongation, independent on the hydrophillicity of the plasticizer. The results indicate that PEG 200, propylene glycol, diethyl phthalate and oleic acid can serve as a secondary plasticizer of Eudragit E-100 film.

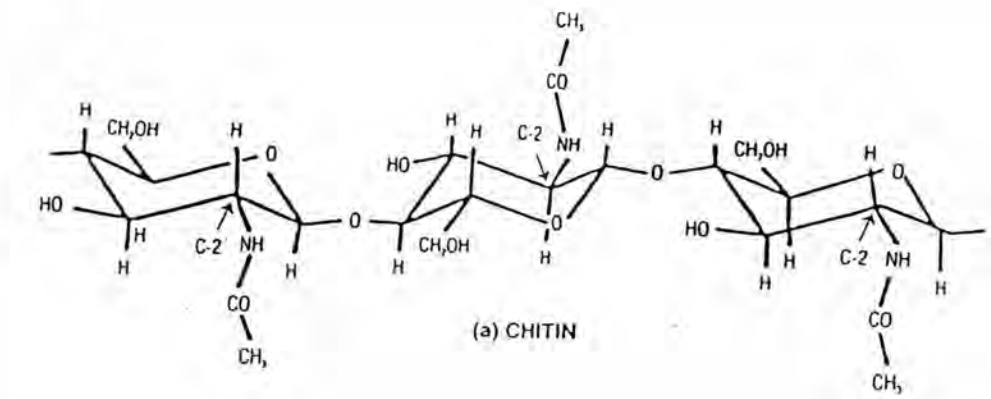
4. Chitosan

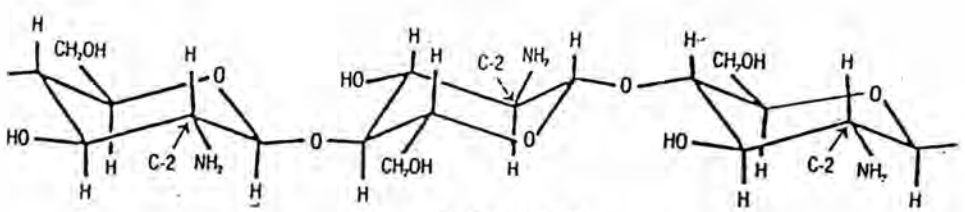
Chitosan, one of the most plentiful natural polymer, is a hydrophilic cationic polyelectrolyte prepared by N-acetylation of chitin. Chitin and chitosan are manufactured commercially in the large scale from the outer shell of crustaceans (mainly decapods). Approximately 15 - 20 and 15 - 30% chitin on dry weight basis from crab and shrimp shells, respectively are the main source of chitin by most chemical industries (Paul A.S.,1989).

Chitin is a highly hydrophilic material that is insoluble in water and most ordinary solvents. Its properties restrict its use to applications that do not require solubilizations of the polymer. So preparation by deacetylation of chitin in strong alkali was invented by Hoppe Seyler in Germany (Lower E.S.,1984)

4.1 Structure (Filar and Wirick,1987)

Similar to cellulose , chitin and chitosan are long linear chained molecules of (1-4) linked glycans. The repeating unit in chitin is 2-acetamido-2-deoxy-D-glucose (N-acetylglucosamine), while an inhomogenous mixture with the deacetylated from (glucosamine) is the structure of chitosan. Structures of cellulose, chitin and chitosan can be found in Figure 5 (Sandford, P.A.,1989).





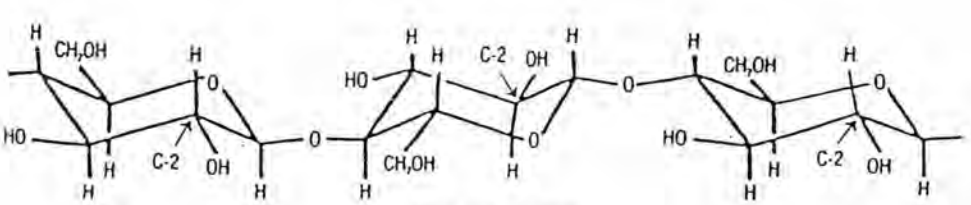


Figure 5 Structures of cellulose, chitin and chitosan.

4.2 Manufacturing Process (Paul A.S.,1989)

The production of chitosan is shown in Figure 5. The shells of crab and shrimp are ground into small size, then proteins are removed from ground shell by treating with NaOH. Minerals such as carbonate and calcium phosphate are extracted with HCl. After rinsing, the chitin is dried and used to produce chitosan by treating with strong NaOH to hydrolyze the N-acetyl linkage, then rinsed, pH adjusted and dewatered.

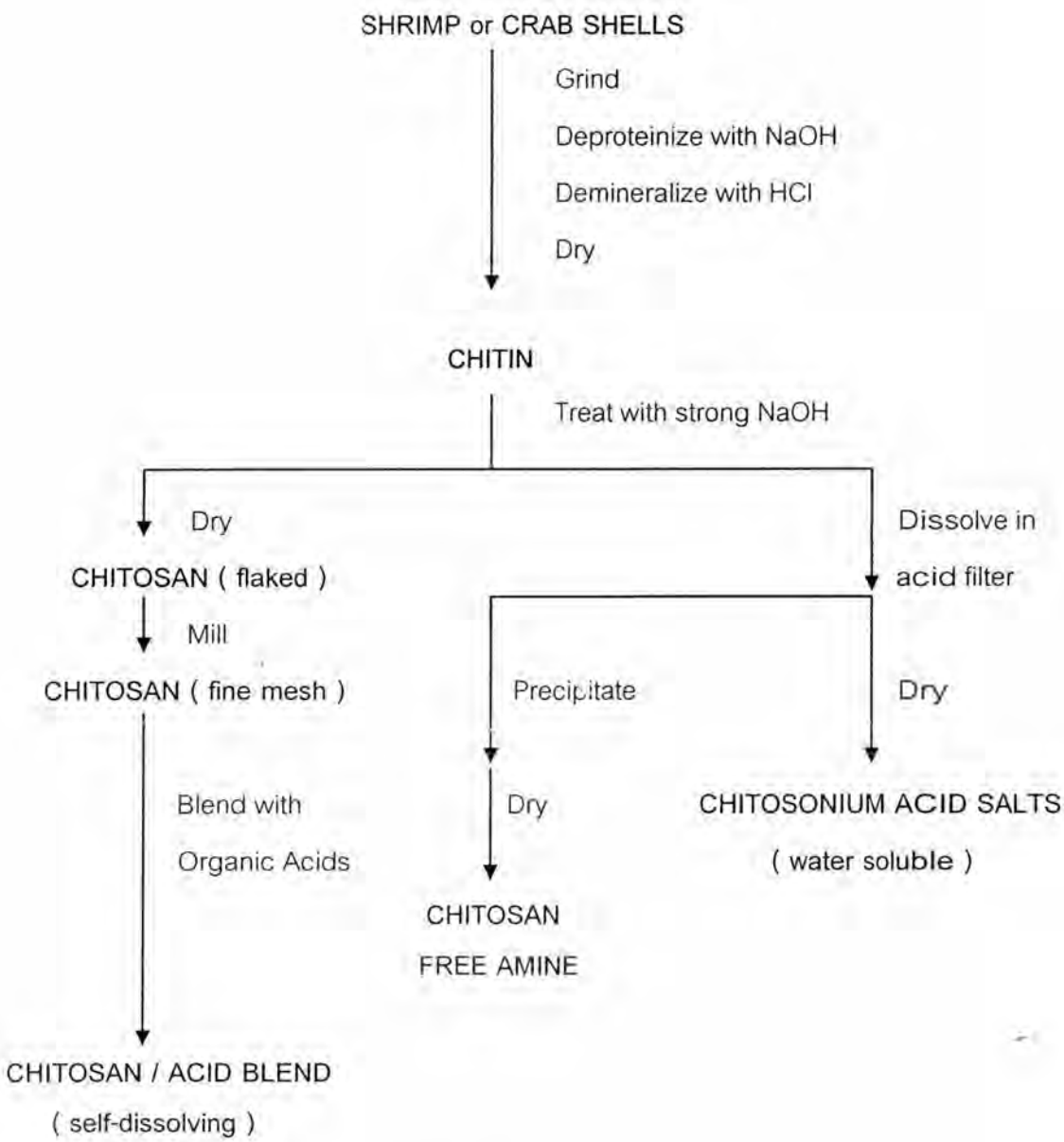


Figure 6 Chitosan manufacturing process.

This coarse mesh product is reduced by milling to give a fine mesh powder. Chitosan powder can be dry blended with an organic acid to give a chitosan acid blend that is self-dissolving.

One scheme to prepare chitosan of improved purity is to dissolve it in an acid (e.g. acetic acid) and to filter it to remove extraneous materials. The clarified product can then be reisolated to give an ultrapure product, as a water chitosonium acid salt or precipitated, washed and dried to give an ultrapure product in the free amine form. In some literature, spray drying method was used after the filtering process to make a specified size of chitosan.

4.3 Physicochemical Properties (Skaugrud, O.,1989)

Chitosan is a white , odorless and biodegradable substance. The molecular weight of chitosan will, for commercial products, depend on the processing condition, and more grade within the range 10,000 - 1,000,000 dalton will be available. The mole fraction of deacetylated units (glucosamine), defined as the degree of deacetylation will usually range from 70% to 90%.

The most important factor of chitosan derivatives are degree of deacetylation and depolymerization because of their significantly different physicochemical properties, especially water solubility.

Since chitosan is a cationic polymer (pKa = 6.3), its solubility depends on the presence of the free amine groups capable of being protonated by the acid medium. Therefore, the level of deacetylation would be supposed its solubility in acid solution. (Robert,1994).

Acetic acid is commonly used as a reference for solubilizing chitosan. It is insoluble in sulfuric acid and phosphoric acid, while soluble in other mineral acids like hydrochloric, nitric and perchloric acid that limited with concentration

ratio/acid. Compatibility of chitosan with acetone, ethanol and methanol depends on the concentration of the organic solvent. At the concentrations as high as 50%, chitosan still function as a viscosifier without precipitation (Muzzarelli,1977)

The apparent viscosity of a solution of chitosan is not only depended on the molecular weight (i.e. the degree of polymerization) of the polymer, but also depended on the salt concentration in the solution. Turning to its rheological properties, due to the high molecular weight and the linear unbranched structure of the molecule, chitosan is an excellent viscosifier in an acid environment. It behaves as a pseudoplastic material showing decrease viscosity at increased shear. The addition of salts will reduce the repelling effect of each positively charged deacetylated unit on neighboring glucosamine units. This will result in an extended conformation of the polymer molecules in solution. At higher concentrations of electrolytes a salting-out effect will occur, precipitating the chitosan from the solution (Muzzarelli,1977).

Filar and Wirich (1987) defined the molecular weight ranges of chitosan in terms of solution viscosity. These viscosity types were selected as representatives of readily by produced on a commercial scale from shrimp shell. The viscosity ranges are shown in Table 1.

Table 1 The viscosity of chitosan solution measured from different grade of chitosan.

Grade	Polymer Concentration	Medium	Viscosity (cps)
High	1%	1% acetic acid	> 1,000
Medium	1%	1% acetic acid	> 100 - 250
Low	2%	2% acetic acid	25 - 70

4.4 Commercial Products (Sandford, P.A.,1989)

The type of chitosan used commercially is determined by physical forms (flake, powder, solution), its purity (ultrapure, standard, industrial) and its molecular from (high to low viscosity, percent deacetylation, free amine and acid salt), and ultimately the cost. The commercial products of chitosan are presented in Table 2

Table 2 Commercial products of chitosan

Product Name	Unique Characteristics	Application Area
PROTOSAN™	- Ultrapure quality - Powder - Water soluble - Chitosan-acid salt	- In vivo biomedical uses - Any application requiring very high purity
SEA CURE-PLUS™	- High quality - Powder - Water soluble - Chitosan-acid salt	- Pharmaceutical / medical - Cosmetic / personal care
SEA CURE™	- High quality - Flake / powder - Free amine form - Low, medium, high viscosity grade	- Enzyme / cell immobilization - Pharmaceutical / medical - Membranes - Cosmetics / personal care
PRO FLOC™	- Flake / powder - Free amine form - Self dissolve blends available - Low, medium, high viscosity grade	- Agriculture uses - Industrial uses - Metal recovery - Waste treatment - Detoxification

4.5 Application of Chitosan in Pharmaceutical Preparations

The studies of potential application of chitosan for pharmaceutical preparations are mentioned as the following:

4.5.1 Application of chitosan in conventional tablets

Sawayanagi, Numbu and Nagai (1982) studied the fluidity and compressibility of combined powders of lactose or potato starch or mannitol with chitin and chitosan as well as the disintegration and lubricating properties of the tablets made from these powders. The results showed that the fluidity of combined powder with chitin and chitosan was greater than that of crystalline cellulose. The hardest tablet was obtained with chitosan. Moreover tablets containing less than 70% of chitin and chitosan passed the disintegration test of JP X. So, chitin and chitosan may be suitable for use as diluents with friction-lowering properties in direct compression process.

Jan Knapczyk (1991) studied again about chitosan in direct tabletting after long-term storage. When, chitosan from two different degree of deacetylation, 49% and 66%, were used, it did not affect mass flow; however, in the proportion of 50% of tablet mass, rapid tablet disintegration resulted. Following long-term storage, tablets produced from 66% deacetylation chitosan may be less resistant mechanically, nevertheless, the disintegration time remain unaffected.

Chitosan in paracetamol tablets showed faster disintegration, greater dissolution and slightly softer than those containing chitin (Ritthidej G.C.et al, 1994). An increase in chitosan amount presented the greater effect, whereas aging slightly altered these properties. Crystallinity, degree of acetylation, chain length and particle size were attributed to the efficiency of chitosan. Moisture sorption and water uptake were the major mechanisms of disintegration while dissolution related to the swelling capacity.

Chitosan was evaluated as a binder for chlorpheniramine maleate tablets in comparison with other cellulose binders (Upadrashta S.M.et al.,1992). Results showed that chitosan tablets exhibited best dissolution profiles.

4.5.2 Enhancement of dissolution of poorly soluble drugs

Sawayanagi et al. (1982, 1983) studied the dissolution and bioavailability of poorly soluble drugs from ground mixtures with chitosan. It was found that the dissolution rate of drugs from ground mixtures were significantly greater than that from physical mixtures or intact drug powders. The ground mixtures with chitosan showed the fastest dissolution and faster than those with chitin and crystalline cellulose. The decrease in degree of crystallinity of the ground mixtures indicated that chitosan is useful for an enhancement of dissolution properties of poorly soluble drugs.

Imai, et al. (1989) studied the dissolution behaviors of acid, basic and neutral drugs from kneaded mixtures with low-molecular (LM) chitosan in comparison with that of the drugs alone. LM chitosan made the surface drug of a powder hydrophilic by dispersion of drug into chitosan, and thereby enhances the dissolution rate of poorly water soluble drug. Moreover, it was expected that chitosan, a basic polysaccharide, interacted with acidic drugs rather than basic drugs. The enhanced dissolution rate of kneaded mixtures may be due to improvement of wettability and to changes of the crystallinity, microcrystal size and shape.

Further studies (Imai et al., 1991) found that the solubility of indomethacin enhanced with increasing concentrations of LM chitosan, especially chitosan which had the lowest molecular weight and least degree of deacetylation and this type of chitosan presented the fastest dissolution rates from kneaded mixtures.

4.5.3 Applications in controlled release preparations

The polymeric cationic character together with its potential reactive groups give chitosan unique properties for utilization in controlled release technologies (Karlsen J.,1991). A large number of studies published recently indicate the high efficiency of chitosan on production of various sustained release systems. Reports that have been published about these applications are mentioned below:

4.5.3.1 Drug Carriers

Chitosan sponges as sustained release drug carriers to be used in wound healing were prepared by freeze-drying partially N-acetylated chitosan gels and crosslinked chitosan solutions with glutaraldehyde (Oungbho and Muller, 1997). The water uptake ability of both chitosan sponges was more than 20 times of their weight. The drug release at pH 1.2 was faster than at pH 7.4. With increasing the drug content a slower drug release was found. The delayed release was due to the decreased chitosan solubility by either N-acetylation or crosslinking.

Sustained release of indomethacine and papaverine HCl dispersed in chitosan gel was also prepared by Miyazaki et al (1981). Drugs from dried gel were released at a constant rate (zero order).

4.5.3.2 Beads

Chitosan beads of sulphadiazine as a model drug were prepared by ionotropic gelation with tripolyphosphate ions by Wan et al (1994). The efficiency of drug loading, as well as bead size, opacity and sphericity, increased drug loading. Different drug release profiles depended on the drug loading in the beads and dissolution medium. In 0.1 M HCl, sulphadiazine beads showed a slower release rate and predominated by polymer erosion, whereas no apparent erosion was seen in simulated intestinal fluid.

4.5.3.3 Membranes

Sawayanagi, Nambu and Nagai (1982) investigated the permeation of several drugs through a chitosan membrane. The permeability decreased with increase in the molecular volume of the drugs. Greater permeability was observed for acidic drugs than basic drugs. Effect of pH on the permeation was considered to be attributable to the cationic state of the chitosan membranes. These results suggested that these permeation were controlled mainly by diffusion through pores and depended on the cationic state of the chitosan membranes.

Crosslinked chitosan membranes with different concentrations of glutaraldehyde and the effect of crosslinking on the permeability characteristics was studied by Thacharodi and Rao (1993). With increasing degree of crosslinking a definite decrease in the diffusion coefficient, equilibrium swelling, partition coefficient and permeability coefficient were observed. These data supported the involvement of both pore and partition mechanisms in the transport of a hydrophobic drug such as nifedipine through chitosan/crosslinked chitosan membranes. Altering membrane permeability by different degree of crosslinking the release of bioactive agents could be programmed.

4.5.3.4 Granules

The use of chitosan granules as a mean to achieve sustained release was studied by Hou et al (1985). Chitosan granules were gradually swelled and floated on the acid medium at pH 1.2. This floating properties can be applied to the formulation of sustained release preparations of various drugs. The release rate of the drugs from granules could also be controlled by varying the crosslinking procedure.

The potential of chitosan intragastric-floating granules of indomethacin was studied by the same group (Miyazaki S.et al.,1988). The drug-chitosan granules did not give a sharp peak of plasma concentration like that of conventional capsules, but produced slightly higher in sustained plateau level of

indomethacin. This may be due to the slow release from chitosan granules and the longer residence time in the stomach. So, indomethacin-chitosan granules may be useful as oral preparations with reduced side effects and with prolonged action.

4.5.3.5 Microspheres

Chitosan microspheres were prepared by a novel precipitation process using sodium sulfate as precipitant (Berthold A.et al.,1995). Sulfates leads to a poorly soluble chitosan derivative, whereby microspheres formulation become possible. The extent of precipitation was controlled by the concentration of sodium sulfate and turbidity measurements. The amount of sodium sulfate required for precipitation of the microsphers depended on the molecular weight of chitosan. The positive charge of chitosan seems to be very good advantageous for bioadhesion to the normally negative charged biological membranes.

4.5.3.6 Direct compressed matrix tablets.

The applicability of chitosan as a vehicle for sustained release preparation of water soluble drugs, propranolol HCl, was examined by Sawayanagi, Nambu and Nagai (1982). The greater the amount of chitosan used, the greater the retarding effect on drug release was observed. Zero-order controlled release was attributed to gel formation in the test medium. The gel forming properties of chitosan at low pH range may be useful for sustained release preparation because a constant release of the drug from the gel in the gastrointestinal fluid should be obtained and the gel might prevent irritation to the stomach.

The compressing aspirin agglomerated by massing with an acetic acid solution of chitosan as a prolonged release tablet was prepared by Kawashima Y.et al (1985). The parameters controlling drug release rate were chitosan content, the physical stage of chitosan used for granulation i.e. liquid solution or gel and pH of the

dissolution medium. The drug release became more prolonged with increasing chitosan content in the tablet or with decreasing pH of medium.

Kristmundsdottir T.et al (1995) studied the influence of excipients on drug release from chitosan matrix tablets using diltiazem HCl as model drug. Sustained release of direct compressed tablets was obtained in all case but the results indicated that both type and amount of excipient used influenced drug release rate. The results support the idea that chitosan can be suitable as a basis for sustained release matrix tablets, and that drug release rate can be influenced by the addition of excipient.

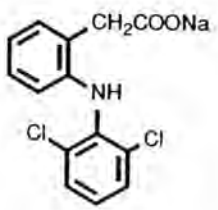
Theophylline tablets using chitosan as a sustained release base were evaluated (Nigalaye A.G.et al.,1990). It was found that when chitosan is used in a concentration of more than 50% of tablet weight, an insoluble non-erosion type matrix was formed, whereas at concentration less than 33%, fast releasing was seen. Chitosan 10% acted as a disintegrant and drug was dissolved very fast. Proper amount of citric acid and carbomer-943 could slow down the release rate of chitosan based theophylline tablets as a hydrocolloidal erosion type matrix .

The study of chitosan in compressed tablets of diclofenac sodium was mentioned on the inhibition of drug release in an acidic environment (Sabnis S.et al.,1997). Analyses of variance indicated that the degree of N-acetylation of chitosan significantly affected drug releases at pH 1.2 and pH 6.8. An increase in the pH of dissolution medium resulted in an increase in drug release. The ionic strength of the dissolution medium did not significantly affected drug release at any pH. Besides the poor aqueous solubility of diclofenac sodium, the two factors possibly affecting the drug release in the acidic environment were the formation of a rate-limiting chitosan gel barrier and ionic interaction of drug with ionized amino group of chitosan.

The other applications as mucoadhesive, stabilizer and bioadhesive carrier, nasal delivery system, peroral delivery, chitosan in peptides and liposomes are interesting and still on progress.

5. Diclofenac Sodium

Diclofenac sodium, a synthetic phenylacetic acid derivative, is a non-steroidal, anti-inflammatory, analgesic agent (Reynolds et.al., 1989; Adeyeye and Li, 1990). Its formula and molecular weight are presented below.



Empirical formula " $C_{14}H_{10}C_{12}NO_2Na$ " (MW. = 318.13)

Diclofenac sodium powder is odorless, white to off-white crystalline, slightly hygroscopic powder. The powder was melted, when heated at about 283 to 285°C. Dissociation constant (pKa) of diclofenac sodium in water is 4 and the partition coefficient in n-octanol / aqueous buffer pH is 13.4 (Adeyeye and Li, 1990; Herzfeldt and Kummel,1983). Its aqueous solubility is dependent on pH; solubility is poor at low pH vales but solubility is rapidly increase when pH rises above pKa.

The presence of cations (sodium or potassium ions) strongly affects the solubility of diclofenac sodium. The addition of sodium or potassium chloride to the dissolution decreased the solubility of diclofenac sodium and delayed the dissolution rate. Whereas, sodium salt has greater effect than potassium salt (Shue et al., 1992) The equilibrium solubility performed in various solvents at the room temperature (RT) are shown in Table 3 (Adeyeye and Li, 1990).

Table 3 The solubility of diclofenac sodium at room temperature

Solvent	Solubility (mg/ml)
Deionized water (pH 5.2)	> 9
Methanol	> 24
Acetone	6
Acetonitrile	< 1
Cyclohexane	< 1
Medium pH 1.1	< 1
Phosphate buffer pH 7.2	6

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

Diclofenac sodium has anti-inflammatory activity following with analgesic and anti-pyretic effects. As with other NSAIDs, its mode of action is not known: its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain and primary dysmenorrhea with regard to its analgesic effect, diclofenac is not a narcotic (Brogden R.N. et al., 1980; Reynold et al., 1989).

The drug is used in rheumatoid arthritis, degenerative joint disease, ankylosing spondilitis and allied conditions, and in the treatment of pain resulting from minor surgery, trauma and dysmenorrhoea.

Published data indicated that diclofenac 75 to 150 mg daily (25 to 50 mg 3 times a day) is used as a usual oral dose. It may be given by rectal suppository in a usual dose of 100 mg each evening. By intramuscular injection, a dose of 75 mg of diclofenac sodium may also be given once or twice daily in severe conditions. The recommended dose in children by mouth or rectally for juvenile chronic arthritis is 1 to 3 mg/kg body weight daily in divided dose.

Diclofenac sodium has been better tolerated than the prototype, aspirin (Brogden R.N. et al., 1990). Gastrointestinal side effects as peptic ulceration and gastrointestinal bleeding are the most frequently reported adverse effect of diclofenac and occur in about 10% of patients due to inhibition of cyclo-oxygenase, PGE_2 has a cytoprotective effect on the gastric mucosa by inhibiting gastric acid secretion and by helping to maintain the gastric mucosa barrier. The frequency of side effects appeared not to be closely related with either dosage or age. Other side effects included headache, dizziness, nervousness, skin rash, pruritis, tinnitus, edema, depression, drowsiness, insomnia and blurred vision and other ocular reactions are rare.

In order to diminish the gastrointestinal side effects, effective enteric coated products have been developed and commercialized (Lin and Kao,1991). The better product development allow a drug dosage form to pass through the acid environment of the stomach without irritation, to disintegrate in the upper small intestine and to release the drug.

Other salts of diclofenac were reported by PDR 50th ed.(1996) and Sheu M.et al. (1992). Diclofenac is also available in potassium salt with no difference to its sodium salt. Molecular weight of potassium salt is higher to 334.25. Diclofenac potassium is freely soluble in water while diclofenac sodium is sparingly soluble in water. The n-octanol / water partition coefficient and dissolution content of both diclofenac salts is equal. The suppression on the solubility of diclofenac sodium by an effect of Na^+ would be operative, resulting in a slower dissolution rate compared to that of KCl.

In addition, diethylammonium salt is used in the emulsion-gel commercial preparations. Because of its ability to absorb through the mammal skin, this preparations relieve the local treatment of traumatic inflammation, localized rheumatic disease and periarthropathy.

6. Propylene glycol (Wade A. and Weller P.J., 1994)

Propylene glycol is a glycol derivatives. Propylene glycol is widely used as a solvent, extractant and preservative in various pharmaceutical formulations. Its formula and molecular weight are shown below.

$CH_3CHOHCH_2OH$

Empirical formula " $C_3H_8O_2$ " (MW. = 76.09)

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling glycerine. Its auto-ignition temperature is 371°C, whereas boiling point is 188°C and melting point is about -59°C. Its density is slightly higher than that of water (1.038 g/cm^3 at 20°C). Its flash point is 99°C, when open cup method is used. Viscosity of propylene glycol is 58.1 mPa s (0.581 P) at 20°C.

Propylene glycol is miscible with acetone, chloroform, ethanol (95%), glycerin and water and soluble in 1 in 6 parts of ether. It is not miscible with light mineral oil or fixed oil, but will dissolve in some essential oils. It stables in a well-closed container, but at high temperatures, in the open, it tends to oxidize. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin and water. It is also hygroscopic and should be stored in an airtight container, protected from light, in a cool and dry place.

Propylene glycol is a very useful excipient in pharmaceutical formulations. It is a better solvent than glycerin and dissolves a wide variety of materials. It is also used as an antiseptic against molds and a carrier for emulsifiers in cosmetics and food. Concentrations of propylene glycol used in each application is listed in Table 4.

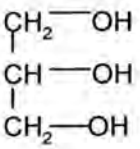
Table 4 Concentrations of propylene glycol used in each application.

Use	Dosage form	Concentration (%)
Humectant	Topicals	about 15
Preservative	Solution, semisolids	15 - 30
Solvent or cosolvent	Aerosol solutions	10 - 30
	Oral solutions	10 - 25
	Parenterals	10 - 60
	Topicals	5 - 80

Propylene glycol is generally regarded as a nontoxic material and its metabolism and excretion is less toxic than other glycols. In topical preparations, propylene glycol is more irritant than glycerin. Parenteral administration may cause pain and irritation when used in high concentration. The WHO has set an acceptable daily intake of propylene glycol at up to 25 mg/kg body-weight.

7. Glycerin (Wade A. and Weller P.J., 1994)

Glycerin is also a glycol derivatives. Like propylene glycol, glycerin is widely used in various pharmaceutical formulations. Its formula and molecular weight are shown below.



Empirical formula " $C_3H_8O_3$ " (MW. = 92.09)

Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose. Glycerin is miscible with ethanol (95%), methanol and water, while it is slightly soluble in acetone. It is also practically insoluble in benzene, chloroform and oils.

Typical properties of glycerin is different from those of propylene glycol. Its boiling point is 290°C followed with decomposition and its melting point is 17.8°C. Density of glycerin is dependent on the temperature. Its density at 15°C is 1.2656 g/cm^3, while the density is lower to 1.2636 g/cm^3 and 1.2620 g/cm^3 at 20°C and 25°C, respectively. Its flash point is 176°C, when open cup method is used.

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions, but decompose on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol and propylene glycol are chemically stable. Glycerin may crystallize if stored at low temperatures; the crystals do not melt until raised to 20°C. It should be stored in an airtight container, in a cool and dry place. The viscosity of aqueous glycerin solution at different concentrations is shown in Table 5.

Glycerin is used widely in pharmaceutical formulations including oral, otic, ophthalmic, topical and parenteral preparations and also used in cosmetics and food additive. Amount of propylene glycol used in each application is listed in Table 6.

Table 5 Viscosity of aqueous glycerin solution at different concentrations

Concentration of aqueous glycerin solution (% w/w)	Viscosity at 20°C (mPa s)
5	1.143
10	1.311
25	2.095
50	6.05
60	10.96
70	22.94
83	111.0

Table 6 Concentrations of glycerin used in each application.

Use	Concentration (%)
Antimicrobial preservative	> 20
Emollient / Humectant	up to 30
Ophthalmic formulations	0.5 -3.0
Plasticizer in tablet film coating	variable
Solvent for parenteral formulations	up to 50
Sweetening agent in alcoholic elixirs	up to 20

Glycerin occurs naturally in animal and vegetable fats and oils, so it is already absorbed and its metabolites are safe. It is generally regarded as a nontoxic and nonirritant materials. Adverse effects are mainly due to the dehydrating properties of glycerin. Glycerin may be used orally in dose of 1.0 - 1.5 g/kg body-weight to reduce intraocular pressure.