CHAPTER II

LITERATURE REVIEW

1. Pellets

Pellets are defined as small, free-flowing, spherical or rounded agglomerates. Due to the numerous advantages that solid spherical products possess, incorporation of drugs in pellets has been a prevalent practice in the pharmaceutical industry. Pellets are not only attractive in appearance as a result of the various shades of color which can be imparted to them, but they also have a free flowing property that can alleviate handling problems (Ghebre-Sellassie et al., 1985). Furthermore, they are easily mixed when either a combination of ingredients or various drug release rates from a particular drug delivery system is desired (Ghebre-Sellassie et al., 1985). When they are formulated as multiple unit formulations in controlled-release preparations, pellets maximize drug absorption (Bechgaard and Nielsen, 1978), reduce variations in gastric emptying rate and over-all transit time (Bechgaard and Nielsen, 1978), eliminate local irritative or anesthetizing effect of an active substance and avoid dose-dumping (Reynold, 1970).

1.1 Pelletization technique

Several techniques can be used to manufacture pellets. In the pharmaceutical industry, pelletized products are usually prepared by extrusion/spheronization process (Ghebre-Sellassie and Knoch, 1995) and the process of coating of a seed material such as inert spheres or coarse crystals with a mixture of the drug substance and suitable excipients. Other methods, such as melt pelletization, might be also used (Schæfer et al., 1990; Thomsen et al., 1993; Maggi et al., 1996 and Zhou et al., 1997).

Melt pelletization is one of types of granulation. It is based on agglomeration by use of a binder material that is solid at room temperature and softens and melt at higher temperature, i.e. 50-90°C. When melted, the action of the binder liquid is similar to that of a wet-granulation process (Augsburger and Murali, 1997).

Melt pelletization or melt granulation is known as a process in which finely devided powder is agglomerated. Its process proceeds by agitation of mixture of particulate solid and a meltable binder in a mixer, and finally, solidification of the binder by cooling resulting in dry granules or pellets. The binder was melted by heat form heating jacket or friction of impeller. Many types of equipment such as fluidized-bed granulators, rotary processors and high shear mixers are used to prepare pellets bv melt pelletization. High shear mixers, which give a simple process, are preferable. Preferable size of products are in the range 0.5-2.0 mm. (Thomsen et al., 1993).

Schæfer (2001) and Schæfer and Mathiesen (1996b) reported that two different mechanisms of agglomerate formation would be active depending on the binder particle size of the viscosity of the molten binder as presented in Figure 1. In fluidized bed granulator, distribution of the molten binder on the surface of the solid particles would occur when the molten binder droplets were smaller than the solid particles or were of the same order of size. Subsequently, agglomerates would be formed by coalescence between the wetted particles. Immersion of the solid particles in the molten binder would occur when the molten binder droplet were larger than the solid particles. By melt agglomeration in high shear mixers, both mechanisms would be active simultaneously because the binder droplets become comminuted by the high shearing forces. Normally, one of the mechanism would be dominate. The distribution mechanism was promoted by a small particle size of the solid binder, by a low binder viscosity and by a high impeller speed. The immersion mechanism was promoted on the other hand by using the meltable binder as flakes, by a high binder viscosity and by low shearing forces during the process. In rotary processors, Vilhelmsen and Schaefer (2005) found that in a rotary processor, the binder particle/droplet size influenced the mechanisms of agglomerate formation and growth during melt agglomeration. If the size of PEG 3000 particles or droplets was markedly larger than the size of the solid particles, agglomerate formation and growth were expected primarily to occur by the immersion mechanism. If the size of the binder particles or droplets was smaller than or at the most only slightly larger than the size of the solid particles, the formation of nuclei was expected primarily to occur by distribution and coalescence in accordance with previous findings (Schæfer and Mathiesen, 1996b). Further agglomerate growth would occur by coalescence between nuclei and/or agglomerates.
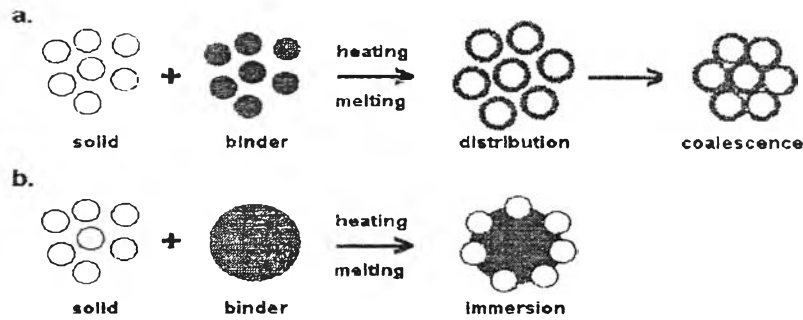
Figure 1 Agglomerate formation mechanisms in melt agglomeration (Schæfer, 2001).
(a) Distribution mechanism. (b) Immersion mechanism.

Augsburger and Vuppala (1997) explained the bonding mechanisms in wet massing that the cohesive forces that operate during the most agglomeration process are mainly due to the liquid bridges that develop between the solid particles, even though intermolecular attractive forces, Van der Waals forces, and electrostatic forces also play an initial role. Intermolecular attractive forces are short-range interactions. Van der Waals forces, in general, make the largest contribution to intermolecular attraction owing to a longer of effectiveness. Electrostatic forces are generated primarily through interparticle friction, which alters surface electron states. The overall contribution of electrostatic attractive forces is to keep particles in contact long enough for other mechanisms to govern the agglomeration process. In practice, more than one bonding mechanism may be acting simultaneously. With very fine powders, it is difficult to determine if bonding through long-range force or through adsorption predominates.

The mechanisms of bonding in the wet state depend on capillary and interfacial forces between the particles (Augsburger and Vuppala, 1997). Immobile, adsorbed surface liquid serves to reduce surface imperfections and increases particle-particle contact by decreasing the effective interparticle distance. Once sufficient liquid is added, the granulation shifts from an immobile surface liquid state to a mobile liquid film state. These four states are termed: pendular, funicular, capillary, and droplet or suspension state, which are depicted schematically in Figure 2. The mechanism of agglomeration can be considered as a gradual change from a triphasic stage (air-liquid-solid) in which most granules are in pendular and funicular states, to a biphasic (liquid-solid) particulate assembly, in which the granules will be in the capillary and droplet states.
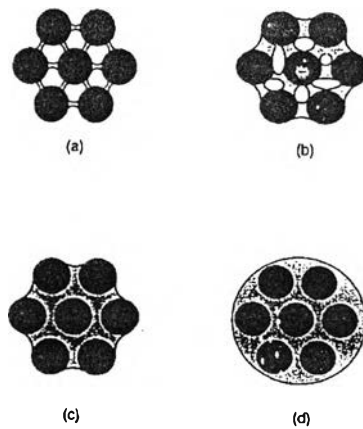
Figure 2 States of liquid content in an agglomerate during wet granulation (Augsburger and Vuppala, 1997): (a) pendular state, (b) funicular state, (c) capillary state, (d) droplet state

Each of the four states represents a progressive increase in the moisture content, with a corresponding change in capillary forces until the droplet state is reached. In the droplet state, only surface tension holds the drop together and there are no longer any internal interfacial forces. At low moisture contents water forms discrete lens-shaped rings at the point of contact of the particles; this is known as the pendular state as shown in Figure 2(a). Here, particles are held together by surface tension at the solid-liquid-air interface and the hydrostatic suction pressure of the liquid bridge, so they are topically nonspherical, dry surface, soft and low density. As the moisture content increases, the rings coalesce to form a continuous network of liquid interspersed with air. This state is called the funicular state as shown in Figure 2(b). Characteristics of funicular is more nearly spherical, dry surface, firm and denser than pendular. With a further increase in water content the capillary state as shown in Figure 2(c) is reached when all the pore spaces in the granule are completely filled with liquid, and concave menisci develop at the surface of the agglomerate, so they are tend to spherical, surface normally wet, dense and plastic. The droplet state as shown in Figure 2(d) occurs when the liquid completely surrounds the granule, resulting in an external phase consisting of liquid, with an internal solid phase. The strength of the droplet is dependent on the surface tension of the liquid phase. Characteristics of droplet is maximal density and consistency.

Melt granulation is advantageous compared with an ordinary wet granulation process (Holm, 1997): (1) the amount of liquid binder can be controlled precisely, resulting in highly reproducible granule properties; (2) the liquid addition and drying phase are eliminated; (3) melt granulation is suited for water-sensitive materials, it is an alternative to the use of organic solvents, which is desirable for both environments and economic reasons (Hamdani et al., 2002); (4) the production labor and equipment costs are reduced; (5) by selecting a melting binder which is insoluble in water, melt granulation might be a way of producing sustained release granulation (Hamdani et al., 2003; Zhou et al., 1998; Vergote et al., 2001); (6) it is possible to prepare 1-4 kg batches of pellets with a high load of hygroscopic drug by melt pelletization in a high shear mixer (Thies and Kleinebudde, 1999); Finally, (7) solid dispersions can be prepared by dissolution a drug in the molten binder (Schæfer et al., 1990; Seo et al., 2003).

Melt granulation has not only advantages, it has disadvantages too. Because of melt pelletization requies high temperature, the process may be the risk of chemical degradation of themolabile substances, i.e. loss of water of crystallization (Holm, 1997). Pellets produced by melt pelletization have a wide size distribution compared with those obtained by extrusion (Hamdani et al., 2002). Moreover, the melt pelletization in high shear mixers can be affected by the physico-chemical and thermal characteristics of the starting materials, i.e. particle size and shape, binder viscosity, melting range, and by the different process variables, such as mixer load, impeller speed, chopper speed and moving time (Thomsen et al., 1993). Furthermore, the process is sensitive to changes in the process and formulation variables (Schæfer et al., 1992a; Schæfer et al., 1993).

The ability to form pellets by melt technique is dependent on formulation and process variables (Thomsen et al., 1993; Schæfer et al., 1993). In addition, type of equipment may also affect the product quality (e.g. Thomsen et al., 1993; Schæfer et al., 1993; Mills et al., 2000; Vilhelmsen and Schæfer, 2005). Using this technique, two types of melt pelletization processes were reported; a binder is added as a molten form or as a solid powder which was melted by heat form heating jacket or friction of impeller.

1.2 Effect of formulation variables

Formulation variables such as the concentration of the binder (Schæfer et al.,1990; Schæfer et al.,1992a), the viscosity of the binder (Schæfer and Mathiesen, 1996a; Schæfer and Mathiesen, 1996b) and the particle size of the binder (Schæfer and Mathiesen, 1996a), fillers (e.g. Schæfer et al., 1990; 1992a ; Schæfer and Mathiesen, 1996c; Schæfer, 1996; Vonk et al., 1997; Rameker et al., 1998) and drugs (e.g. Thomsen, 1994; Vergote et al., 2001) have been found to affect the quality of the final product.

1.2.1 Effect of binders

The meltable binders used in melt pelletization are varied. These materials include PEGs (Schæfer et al.,1992a; Thomsen et al., 1993; Heng et al., 1999), glycerides (Evrard et al., 1990; Thomsen et al.,1993; Thies and Kleinebudde, 1999; Hamdani et al., 2002; Franceschinis et al., 2005), mixture of glyceride and PEG esters of fatty acids (Eliasen et al., 1998 ; Seo et al., 2003), and wax such as stearic acid (Thomsen et al.,1993; Voinovich et al., 2000; Grassi et al.,2003), carnauba wax (Thomsen et al.,1993), bees wax (Thomsen et al.,1993) and microcrystalline wax (Thomsen et al.,1993; Zhou et al.,1996; Zhou et al.,1998; Vergote et al.,2001).

Normally, the material chosen to be a binder should have melting point in the range of 45°C - 100° C, because lower melting points may cause stability problems during storage and higher melting point may cause the process difficulty and risk of chemical degradation of themolabile substance (Thomsen et al., 1994).

Using a high shear mixer, the binder in the formulation often contributes some effects on the processability, product quality and drug release. Evidence showed that polyethylene glycols (PEGs) were particularly suitable as binders for melt pelletization because the deposition of moist mass onto the bowl of the mixer was much less with the PEGs than with the other meltable binders (Schæfer et al., 1990). The type, size and concentration of the PEGs might influence the mean granule size and size distribution of the agglomerates, probably because of differences in the viscosity of the molten PEGs. A lower viscosity, 222 mPa.s for PEG 3000 at 70°C, of the molten binder

might be favourable (Schæfer et al., 1992a). A higher binder viscosity, 4,660 mPa.s for PEG 10000 and 26,500 mPa.s for PEG 20000 at 70°C, resulted in a lower initial agglomerate growth and in a higher subsequent growth rate. A lower binder viscosity gave more spherical pellets (Schæfer and Mathiesen, 1996a). However, the optimum binder viscosity for the production of spherical agglomerates would depend on the agglomerate strength as well as the impeller speed.

Schæfer and Mathiesen (1996b) found that when the powdered binder was added in a high shear mixer, at high binder viscosities, 4,660 mPa.s for PEG 10000 and 26,500 mPa.s for PEG 20000 at 70°C, the binder particle size was reflected in the initial granule size. When low binder viscosities, 222 mPa.s for PEG 3000 and 938 mPa.s for PEG 6000 at 70°C, were used, the binder particle size had only a slight effect on the agglomerate formation, and the dominate mechanism was the distribution of the molten binder on the surface of the solid particles. The subsequent agglomerate growth by coalescence is dependent on the binder particle size too. Three grade of PEGs were used, flake, powder and fine powder. When highly viscous PEG 20000 was used, at 15 min massing had to be interrupted owing to the formation of large balls caused by an uncontrollable agglomerate growth. PEG 20000 flakes having particle size of 1,780μm caused a larger initial size than the powder. PEG 10000 powders having particle size of 294 μm and PEG 20000 powders having particle size of 263 μm gave a slightly lower agglomerate growth rate than the flakes. The fine powders of PEG 8000 having particle size of 64 μm were seen to gave rise to a lower agglomerate growth rate than the corresponding PEG 8000 flakes having particle size of 1,280 μm and PEG 8000 powders having particle size of 258 μm. The binder particle size was found to have no significant effect on the sphericity. They found that at the low binder viscosity, the pellets became more spherical. The surface plasticity of the agglomerates became lower at a high viscosity, and this resulted in agglomerates of an irregular shape. However, the deformability of the agglomerates depended on shearing forces too. So optimum binder viscosity for the production of spherical agglomerates will depend on the agglomerate strength as well as the impeller speed (Schæfer and Mathiesen, 1996a).

Schæfer et al. (1990) found that when lactose and PEG 3000 15–20% w/w was used to prepared pellet in high shear mixer, granule size and size distribution

were makedly influenced by binder concentration and massing time. When the PEG 3000 concentration was increased, large agglomerates were achieved. It was shown that pellets of a narrow size distribution could be produced by the use of a high impeller speed, 1400 rpm. In 2004 – 2005, PEGs were mostly used as a meltable binders in the rotary processor. Vilhelmsen et al. (2004) found that when using a rotary processor, increasing the binder concentration, the agglomerate size increased in accordance with previous findings (Mills et al., 2000) where using silicone fluids having viscosity about 100 mPa.s were used as a binder.

PEG 3000 could be used as a binder for improving the dissolution rate. Melt granulated agglomerats containing solid dispersions of diazepam, a poorly water-soluble model drug, was examined (Seo et al., 2003). The mixture of molten PEG and diazepam was added by a pump-on procedure or by a melt-in procedure of solid binder particles. A higher dissolution rate was obtained with a lower drug concentration, 15% m/m of the amount of binder, i.e. a liquid to solid mass ratio by weight of 0.15.

PEG 1500 and PEG 6000 were used as meltable binders to form agglomerates in a high shear mixer with a low impeller speed, 400 rpm (Seo and Schæfer, 2001). It was found that a higher content of binder, 28 m/m of the amount of lactose, i.e. a liquid to solid mass ratio by weight of 0.28, could be incorporated. In this experiment, PEG 1500 and 6000 were added as solid beads with particle size of 276 and 475 μm, respectively; it was advantageous in that it enabled a low and controllable growth with a high binder content to be obtained. However, the binder beads might cause a breakage of the initial agglomerates, and this made it difficult to maintain the spherical shape of the beads.

PEGs were not only used in a high shear mixer, but also they are used in hot-melt extrusion and spheronization process (Young et al., 2002). Controlled-release theophylline containing spherical pellets were successfully produced with PEG 8000. Theophylline pellets could be used for immediate release or controlled-release applications depending on the properties of the matrix polymer, while conventional pellets must be coated to prevent rapid drug release. Theophylline pellets did not require film coating to control drug release, but they could be film coated to further modify drug release in the gastrointestinal tract.

PEG-based pellets used in prolonged release formulation had to be coated due to the PEG water solubility (Thomsem et al., 1993). If a hydrophobic binder could be use instead, it might be possible to obtain pellets possessing prolonged release properties directly. Glyceride groups as a lipophilic binder were interested. Thomsen et al. (1994) found that glyceryl monostearate (GMS) appeared to be the most suitable substance. It was observed that the presence of GMS in a binder combination enabled the pelletization process to proceed in a controlled, regular and harmonic way, while the presence of more hydrophobic substances in the binder mixture ensured constitutive prolonging of the release. Pellets prepared with combination of GMS and microcrystalline wax demonstrated the slowest release (Thomsen et al., 1994).

GMS was used as a binder for hygroscopic drug such as a sodium valproate (Thies and Kleinebudde, 1999). Pellets contain only GMS and sodium valpoate were produced. It was found that the binder concentration was the most important influencing the mean granule size and size distribution.

Mono and di-glycerides (Cithrol GMO®) were used by mixing with polysorbate as a binder for prepare nimesulide self-emulsifying pellets in high shear mixer (Franceschinis et al., 2005). They could improve drug solubility of nimesulide as poorly water-soluble model drug.

A mixture of Compritol® 888 and Precirol® ATO5 as melting binders were evaluated (Hamdani et al., 2002). The mean size, size distribution and morphology of pellets were highly dependent on the process parameter during the pelletization step, mainly product temperature, mixing time, impeller speed and chopper speed. Low mean particle size and high size distribution values were obtained at the lowest impeller speed, 400 and 600 rpm, and mixing time, 6 min. The smaller particle size values were observed because of an insufficient energy input and/or a improper movement of the powder mass at the lowest. On the other hand, at the highest impeller speed, 1000 rpm, an excessive powder agglomeration caused by an overwetting phenomenon was observed.

Compritol® 888, Cutina® HR and Precirol® ATO5 were used as meltable binders for investigating about influence of melting and rheological properties of

fatty binders on the melt granulation process in a high shear mixer (Evrard et al., 1990). They found that agglomeration rate of granule was high when melting range was narrow.

Compritol ® 888 was not only used as a binder. It is also used as a coating material for controlled release preparation. Faham et al. (2000) prepared theophylline pellets by using Compritol® 888 as a coating material by hot-melt technique in fluidized bed. When the percentage of coating material was increased drug release could be prolonged.

However, preparation of pellets in a high shear mixer by using Compritol® 888 and Precirol® ATO5 must be carefully controlled. Hamdani et al. (2003) found that the lipophilic binder might present a relatively complex behaviour depending on the sample treatment, i.e. untreated, freshy solidified, aged sample. Both untreated and freshy solidification Precirol® ATO5 and Compritol® 888 samples presented partically amorphous layered structure which slowly crystalline in time. The rate of crystallization was found to be more rapid for Precirol® ATO5, and highly dependent on the storage temperature.

Seo et al. (2003) prepared diazepam pellets by using PEG 3000 and Gelucire 50/13, 22.0% m/m of the amount of lactose, i.e. a liquid to solid mass ratio by weight of 0.22, as a meltable binder. Gelucire 50/13 gave a lower amount of agglomerates with the size greater than 4 mm and a narrower size distribution. This could be explained by a lower binder viscosity, being 70 mPa.s for Gelucire 50/13 and 306 mPas for PEG 3000 at 60°C, which caused a better distribution of the binder. They found that PEG 3000 and Gelucire 50/13 could improve the dissolution rate. The faster dissolution rate obtained with Gelucire 50/13 compared to PEG 3000 and agglomerates with Gelucire 50/13 were more spherical and regular than agglomerates with PEG 3000.

In 1998, Eliasen et al. prepared pellets containing lactose by using Gelucire 50/13 or stearate 600 WL or PEG 3000 as meltable binders. They found that to obtain the same size of agglomerates of pellets, the amount of Gelucire 50/13 used was more than the amounts of stearate 600 WL and PEG 3000. The low viscosity of Gelucire

50/13 produced wide sized, more porosity and more spherical agglomerates when using low impeller speed, 800 rpm.

Stearic acid was a binder of interest. Theophylline sustained-release pellets was prepared by using stearic acid as a binder and anhydrous lactose as a filler (Voinovich et al., 2000). They found that the drug release rate decreased with the 2000 µm fraction, exhibiting a substantially zero-order release. Grassi et al. (2003) prepared paracetamol sustained-release pellets by using stearic acid as a binder and anhydrous lactose as a filler. They found that the 2000 µm size fraction exhibited the slowest in vitro drug release. Comparison between the appearance of the pellets with different size fractions indicated that the 2000 µm size fraction mainly consisted of spherical particles having a satisfactory regular surface, while the smaller the pellet size, the lesser the roundness and surface smoothness. They also found that pellets having dimensions smaller than 630 µm were in fact quite irregularly shape, caused by the short massing time, 8 min, chosen to avoid the uncontrolled ball growth phenomenon.

Microcrystalline wax (Lunacera®) is a hydrophobic substance used to prepared matrix pellets for sustain-release in a high shear mixer (Zhou et al., 1996; Zhou et al., 1997; Vergote et al., 2001). With varied wax concentrations between 25 and 45 % w/w, when the wax concentration was increased the drug release rate was decreased (Zhou at el., 1996). Microcrystalline wax could be also mixed with GMS and prepared slowest release rate of paracetamol pellets (Thomsen et al., 1993). Microcrystalline wax was used in melt extrusion for prepared mini-tablets (Brabander et al., 2000). The matrix mini-tablets based on a combination of 23% w/w microcrystalline wax, 17% w/w starch and 60% w/w ibuprofen offered a flexible system able to sustain the drug release even at high drug loading.

1.2.2 Effect of fillers

Fillers used in melt granulation are varied. In general, lactose is used as a water soluble filler (e.g. Schæfer et al.,1992a; 1992b; 1992c; Schæfer and Matheisen,1996a) and dibasic calcium phosphate is used as a water insoluble filler (Thomsen et al., 1993). Other fillers appearing to be useful in melt granulation include

starch derivative such as waxy maltodextrin (Zhou et al., 1998), drum-dried corn starch (Zhou et al.,1996; Zhou et al., 1998), manitol (Schæfer,1996) those of which are swellable.

Four qualities of lactose, 200, 350 or 450 mesh lactose and anhydrous lactose, were used to prepare pellets in a high shear mixer with PEG 3000 (Schæfer et al., 1992c). The anhydrous lactose gave rise to smaller pellets than the hydrous lactose. It was to be expected that the higher binder concentration had to be used for pelletization when the particle size of the hydrous lactose decreased, but it was not that. The three qualities of hydrous lactose were compared at binder concentrations, which resulted in nearly the same final size of pellets. With 200, 350 and 450 mesh lactose, higher binder concentration, i.e. 18.5%, 21% and 23% w/w, respectively and higher impeller speed, 700 rpm resulted in a larger granule size. The 200 mesh lactose was the most sensitive to variations in binder concentration, which could only be varied within the range of 18.5 – 19.5 % w/w of formulation if pellets were to be produced. A concentration of 20% w/w of formulation gave rise to overwetting, causing a large amount of lumps in the product. They explained that the cohesion forces between the particles became so strong that agglomeration required a lower amount of binder. When hydrous lactose and anhydrous lactose were compared, difference in surface properties between hydrous and anhydrous lactose might also contribute to the different binder requirement. They found that the comparisons become complicated because different binder concentrations had to be used for pelletization of different qualities. The binder concentration, therefore, could not be kept constant.

Zhou et al. (1996) prepared pellets by using pregelatinized starch or hydrolysed starch as a filler, microcrystalline wax as a binder and ibuprofen as a model drug. They found that pellets containing drum-dried corn starch failed to form matrix pellets. The pellets released over 80% of the drug within the first hour of the dissolution test. The slowest drug release was obtained for formulations containing waxy maltodextrin, releasing 95% of the incorporated ibuprofen after 48 hour in vitro by using phosphate buffer pH 7.2 as a medium. These results showed that the wax/starch system offered a flexible matrix system, allowing to produce pellets with the desired release profile depending on the wax type and concentration, the starch concentration and the swelling rate of the starches.

Manitol was used as a filler in melt pelletization (Schæfer, 1996). The results showed that manitol was unsuitable for melt pelletization without an admixture of lactose, because the plate-like and needle-like shape of the manitol particles resulted in irregular agglomerates, a wide granule size distribution, and a formation of a large amount of loose lumps in the product.

1.2.3 Effect of drugs

There have been reported that many drugs could be formulated to be pellets by melt technique. They are such as ibuprofen (Zhou et al., 1996; Zhou et al., 1997), diazepam (Seo et al., 2003), theophylline (Voinovich et al., 2000), ketoprofen (Vergote et al., 2001), paracetamol (Thomsen et al., 1993) and hygroscopic drug such as sodium valproate (Thies and Kleinebudde, 1999).

Particle size of drugs had effect to agglomerates of pellets. Three grades of 8, 21, 60 μm theophylline were used to prepare pellets (Thomsen, 1994). For pellets made from 8 and 21 μm theophylline, the release rate increased as the drug content increased. He found that it was not possible using 100 μm theophylline to manufacture pellets of an acceptable quality with a drug content larger than approximately 50% by weight. These results suggested that manufactures using melt pelletization should avoid starting materials containing considerable amount of crystals larger than 60 μm. Sensitivity of the manufacturing process to variation in starting materials can be decreased by decreasing the drug content.

Vergote et al.(2001) prepared nanocrystalline ketoprofen pellets containing 15% w/w ketoprofen, 35%w/w microcrystalline waxes and 50%w/w starch derivative. They found that pellets contained nanocrystalline ketoprofen and sodium laurylsulphate made the dissolution rate of ketoprofen independent of pH. Lowering the pH of the dissolution medium decreased the solubility of ketoprofen, i.e. being 11 g/l at pH 7.5 and 400 mg/l at pH 4.6, and drug release mechanism was a non-Fickian diffusion.

When using 60% w/w of drug, 25% w/w of microcrystalline waxes (Lunacera M / P® - ratio 7 : 3) and 15% w/w of maltodextrin as a filler to prepare pellets

in a high shear mixer (PP1 processor, granulation bowl), the ibuprofen pellets size between 0.7-1.4 mm were failed, but theophylline pellets were successfully manufactured. So the properties of the drug could influence the formation and the growth of the particles (Zhou et al., 1997). When Gral 10, Vactron 75, LFS granulator and PP1 processor (Pelletization bowl) were used, they could prepared ibuprofen and theophylline pellets. The release mechanism of the ibuprofen pellets was characterized as a Fickian diffusion, whereas a non-Fickian release mechanism was observed in case of the theophylline pellets.

Zhou et al.(1998) prepared pellets containting 60% w/w of ibuprofen, 25% w/w of microcrystalline waxes (Lunacera M / P® - ratio 7 : 3) and 15% w/w of maltodextrin as a filler in a high-shear mixer (Gral 10) and tested them in vivo studies. They found that the sustained as well as immediate release pellets could be prepared. The bioavailability of pellet formulations based on the combination of microcrystalline waxes and starch derivatives could be adjusted by means of varying the type and the content of both the waxes and the starch derivatives.

1.3 Effect of process variables

Process variables were the most important for preparing pellets. Method of binder addition, equipment and process parameter such as speed of impeller (Theis and Kleinebudde, 1999) and chopper (Schæfer et al., 1992a), temperature of product (Thomsen et al., 1993; Schæfer and Methiesen, 1996c), mixing time (Schæfer et al., 1993; Schæfer et al., 1992a; Thomsen et al., 1993) and product load level (Schæfer et al., 1993) had influence on the granule quality.

1.3.1 Method of binder addition

In general, binders could be added in the process as a powdered form or molten form. Seo et al. (2003) prepared pellets using PEG 3000 as a binder by using a high shear mixer. It was found that adding the PEG 3000 by the melt-in, i.e. powdered form, procedure was seen to result a lower amount of agglomerates with the size greater

than 4 mm compared to the pump-on, i.e. molten form, procedure, probably due to a better distribution of the binder.

Velhelsem and Schaefer (2005) prepared pellets by using PEG 3000 as a binder in a rotary processor. They found that the binder addition procedure and the binder particle/droplet size influenced the mechanisms of agglomerate formation and growth during melt agglomeration. If the size of the binder particles or droplets was markedly larger than the size of the solid particles, agglomerate formation and growth were expected primarily to occur by the immersion mechanism. If the size of the binder particles or droplets was smaller than or at the most only slightly larger than the size of the solid particles, the formation of nuclei was expected primarily to occur by distribution and coalescence. Further agglomerate growth would occur by coalescence between nuclei and/or agglomerates.

1.3.2 Equipment

High shear mixers, single-step granulator, have been used to prepare pellets by melt technique. Pellmix PL1/8, Niro A/S, Denmark which a laboratory scale high shear mixer was used for the many experimental (e.g. Schæfer et al., 1993; Schæfer and Mathiesen, 1996c; Eliasen et al., 1999). The Pellmix PL1/8 (Figure 3) is equipped with an electrically heated jacket, which can be heated to a maximum temperature of about 120°C. The inner wall of the bowl is coated with polytetrafluoroethylene (PTFE) in order to reduce adhesion of material to the bowl. The volume of the bowl is about 8 litre. The impeller is a two-bladed impeller of stainless steel with changeable impeller blades.The impeller speed is continuously adjustable within the range of 0 to 1500 rpm. The mixer is not equipped with a chopper. The Pellmix 10, Niro A/S Denmark, 50 litre high shear mixer (Figure 4) is equipped with a removable chopper, but the effect of the chopper has been found to be inappreciable (Schæfer et al., 1992a). The temperature of the product and of the heating jacket are measured with thermoresistance probes which is in the side wall of the bowl at 53 mm from the bottom.
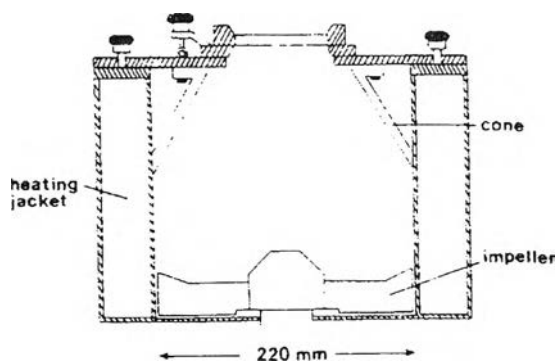
**Figure 3** Outline of Pelmix PL 1/8 high shear mixer (Schæfer et al., 1993)
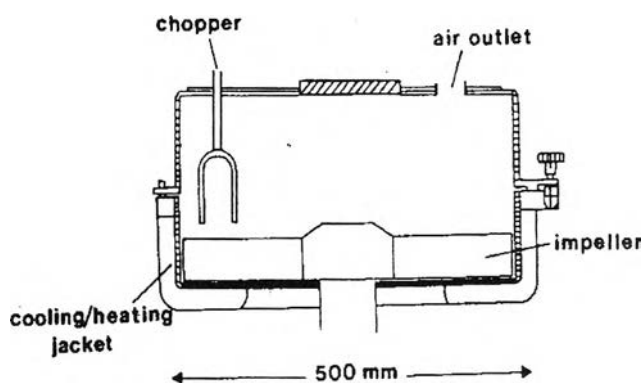
Figure 4 Outline of Pelmix 10 high shear mixer (Schæfer et al., 1992a)

Four types of high shear mixers (Gral 10, Vactron 75, LFS granulator and PP1 processor) were investigated by Zhou et al. (1997). Impeller speed of Gral 10, Vactron 75, LFS granulator and PP1 processor was 430-600, 150-440, 300-2000 and 300-1500 rpm, respectively. Chopper speed of Gral 10, Vactron 75 and LFS granulator was 1500-3000, 1500-3000 and 1200-4500 rpm, respectively. PP1 had 2 types, pelletizer bowl and granulation bowl, in case of PP1 pelletizer bowl as shown in Figure 5, where no chopper was available, the mass was dispersed using a high impeller speed. Chopper speed of PP1 granulation bowl was 1500-3000 rpm. The PTEF lining of PP1 pelletizer bowl was efficient in preventing the mass from adhering to the wall in comparison to the metal surfaces. Impeller geometry of Gral 10, Vactron 75 and LFS granulator was curved but PP1 granulation bowl was plain. The preparation of 60 %w/w ibuprofen pellets size between 0.7-1.4 mm failed in the PP1 granulation bowl as the growth of the particles stopped at a size range between 0.5-0.7 mm. This might be due to the impeller design equipment with short and plain blades causing an insufficient mass movement and a too low energy input. In this study, the binder was added as a molten phase. At a too high

mass temperature a part of the wax remained in a liquid state and induced a quick but uncontrollable pellet growth. When the effect of processing parameters on the porosity and the drug release from the pellets was investigated, the results showed that the final porosity of the ibuprofen and the theophylline pellets was nearly independent of the mixing time and the equipment choice. When the PP1 pelletization bowl was used, porosity decreased when mixing time and impeller speed were increased.
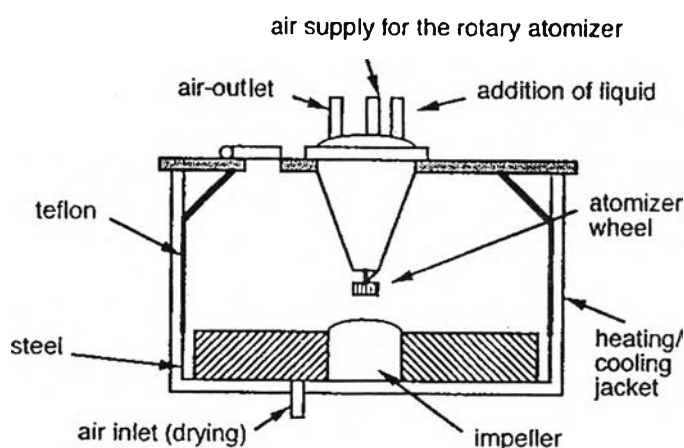
Figure 5 Schematic view of a high shear mixer, Pellet processor PP1 (Holm, 1997)

Fluidized-bed coater/granulator that is composed of a rotation apparatus, liquid spray and powder feed units, a control panel and a source of heated fluidizing air was used to prepare pellets (Ghebre-Sellassie et al., 1985). The process technique is simple, reproducible and involves a minimum number of steps. This equipment is called that a rotating drum granulation (Mills et al., 2000) and rotary processor (Vilhelmsen et al., 2004; Vilhelmsen and Schæfer, 2005) which are shown in Figure 6.

Vilhelmsen et al. (2004) found that the agglomerate size was also increased when increasing the shearing force by using a friction plate with a different surface structure. The friction plate with the smooth surface structure was found least suitable for melt pelletization because of insufficient shearing force. The crosshatched and the longitudinal friction plates were both found suitable for melt pelletization.
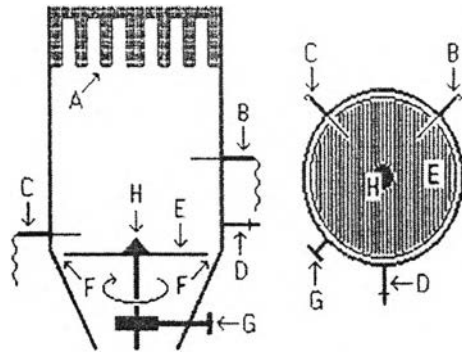
Figure 6 Schematic drawing of the rotary processor : (A) exhaust air filter, (B) upper product temperature sensor, (C) lower product temperature sensor, (D) sample thief, (E) friction plate, (F) air gap, (G) friction plate elevator, and (H) cone. (Vilhelmsen et al., 2004)

Compared to high shear mixers, the effects of the binder particle or droplet size was more pronounced in a rotary processor due to the lower shearing forces. A rotary processor resembles conventional fluid bed granulators in the mechanisms of agglomerate formation and growth. However, a rotary processor differs from fluid bed granulators since agglomerate growth by coalescence can occur at prolonged massing. This is due to fluid bed granulators, which give rise to a densification of the agglomerates during massing time (Vilhelmsen et al., 2004).

Coffee grinder could also make pellets. Ramaker et al. (1998) prepared pellets containing microcrystalline cellulose and lactose in the coffee grinder. The impeller speed of coffee grinder was 4.9×10^3 rpm. They found that an increased impeller speed resulted in a decrease of the mean pellet size. This result was in contrast with previous works (Schæfer and Mathiesen, 1996a; Zhou et al., 1997). It could be explained by the higher destructive forces of impeller. This causes two effects: first, the number of collisions is increased, and second the chance of successful collisions for coalescence is decreased, because of the low contract-time between the pellets. Break-up of pellets becomes more important compared to growth of pellets. In other words, the equilibrium between growth and break-up shifts towards a higher break-up, which leads to a lower mean pellet size.

1.3.3 Process parameters

Process parameters could influence pellet quality. The mixing speed, the product temperature, the mixing time and the product load level were also found to be critical parameters for melt pelletization process when formulation of pellets based on PEGs (Schæfer et al., 1992a; Schæfer et al., 1993; Schaefer and Mathiesen, 1996c), a mixture of microcrystalline wax and GMS (Thomsen et al., 1993) and microcrystalline wax (Zhou et al., 1997).

The mixing speed of impeller had effect of qualities of pellets. Schæfer et al. (1992b) prepared pellets containing lactose and PEG 3000. They found that at an impeller speed of 500 rpm which had the lower power input than 700 rpm, a longer mixing time was necessary. The lower power input at 500 rpm gave rise to pellets with a surface which was less smooth than the pellets produced at 700 rpm. Schæfer et al. (1993) found that high impeller speed, 1200 rpm, resulted in a larger granule and narrow size distribution as previously found (Schæfer et al., 1992a) because the granules became more densified at a higher power input. In 1996, Schaefer prepared pellets containing binary mixtures of lactose/manitol as a filler and PEG 3000 as a binder. He used impeller speed about 400, 600, 800 and 1000 rpm. The results showed that an impeller speed of 800 rpm was preferred for the final experiments. A larger amount of lumps in the product was obtained when a speed of 1000 rpm was used. Speeds of 400 rpm and 600 rpm resulted in a smaller mean granule size and a wide size distribution. Vojnovic et al. (1995) found that impeller speed could increase the yield of product.

The effect of the chopper on the mean granule size was found to be inappreciable compared with the effects of the other process variables (Schæfer et al., 1992a). The chopper had no significant effect either on the granule size distribution (S_g) or on the intragranular porosity. However, the temperature was found to be lower when the chopper was used because the chopper reduced the friction between the particles, and consequently the heat of friction, by dispersing them. The chopper was unnecessary for producing lactose pellets, but might be necessary for producing pellets with other materials having different physical properties.

Most of the previous studies on the agglomerate growth mechanisms involved in melt agglomeration in high shear mixers have been carried out with PEGs as meltable binders (Schæfer et al.,1992b; Schæfer and Mathiesen., 1996a; Schæfer and Mathiesen., 1996a) which had high viscosities, i.e. 80 – 26500 mPa.s. When PEGs used as binders, the lower viscosity, i.e. 182 mPa.s for PEG 6000 at 120°C, would give rise to a higher deformability of the agglomerates and thus promoted agglomerate growth by coalescence. The pellets were normally found to become smoother at a high product temperature, 120°C, because of a combined effect of a low viscosity, 182 mPa.s of PEG 6000, and a high liquid saturation. On the other hand, most of hydrophobic binders which had viscosities below 50 mPa.s, a low impeller speed, 500 rpm, and low jacket temperature, 56°C, were found to gave rise to smoother and more spherical agglomerates (Thomsen et al., 1993). They explained that the binder contacted and partly solidified during cooling and thereby lowered the potential for growth by coalescence, so pellets produced at low temperature, 56°C, was smooth and homogeneous and more spherical than pellets produced at high temperature, 86°C. Eliasen et al. (1999) prepared pellets containing lactose and stearic acid as a binder which had viscosity 10 mPa.s. In accordance to Thomesen et al. (1993) experiments, a lower impeller speed, 200 rpm and low jacket temperature, 35°C, were found to give rise to smoother and more spherical agglomerates.

Jacket temperature had effect to adhesion of product to the wall of the mixing bowl and amount of lumps (Schæfer et al., 1993). They prepared pellets containing lactose and PEG 3000 with melting point of 60-63°C as a melting binder in a concentration 23%m/m, i.e. a liquid to solid mass ratio by weight of 0.23. Jacket temperature of 65°C and 80°C resulted in a marked adhesion of product to the wall of the mixer bowl, and a jacket temperature of 40°C resulted in a large amount of lumps in the product. At a jacket temperature of 50°C no lump was seen during the start of the process, and practically no adhesion of material to wall occurred. Thomsen et al. (1993) used GMS and microcrystalline wax as a binder for preparing pellets in high shear mixer. They found that low jacket temperature of high shear mixer, 56°C resulted in increased tendency of moist mass to solidify on the walls of the bowl. The amount of aggregates larger than 2 mm was significantly higher at the low product load level, 600 g. However, the optimum values for the process variables depended upon the melting behavior of the

applied binder. Zhou et al. (1997) suggested that during production, the product temperature had to be controlled within a narrow range because the process of the pellets growth was sensitive to the product temperature. At a too high mass temperature, a part of the wax remained in a liquid state and induced a quick but uncontrollable pellet growth.

A mixing time had effect to quality of pellets too. An increased mixing time gave rise to a significant larger mean granule size, narrower size distribution and higher product temperature (Schæfer et al., 1993). The effects were in accordance with previous results (Schæfer et al., 1990; 1992a). An increased mixing time gave rise to agglomerates which were rounder and smoother (Schæfer et al., 1992b). Previous experiments (Schæfer et al., 1990; 1992a; 1992(b)) showed a decrease in intragranular porosity be cause of densification at prolonged mixing, 12 min, but the porosity is higher at long mixing time, 17 min and the high jacket temperature, 120°C, (Schæfer and Mathiesen, 1996c). Zhou et al. (1997) found that an increasing mixing time and an increasing mixing speed induced a larger pellet size and a lower porosity. For the ibuprofen pellets, the lower porosity correlated well with a decrease in release rate.

The effect of mixer load on the mean granule size was found. Schæfer et al. (1993) prepared lactose pellets and used PEG 3000 as a melting binder in a high shear mixer, Pellmix PL 1/8. They found that a decrease in mixer load resulted in a larger mean granule size and the narrow size distribution. It was generally observed that the pellets produced at a mixer load of 1000 g were more rounded and smoother that the pellets produced at the lower mixer loads, i.e. 600 and 800 g.

2. Materials

2.1 Lactose

Lactose, milk sugar, is a natural disaccharide consisting of galactose and glucose. It occurs as white to off-white crystalline sweet-tasting. The molecular weight of lactose monohydrate is 360.31. The solubility of lactose at 20°C is 0.22 mg/ml in water, practically insoluble in chloroform, ethanol. Lactose is widely used in pharmaceutical formulation as a filler or diluent in oral tablets and capsules formulation. In this study, lactose was incorporated as received as a filler to make the formulation up to the 100% level.

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown-colored products as shown in Figure 7. This reaction occurs more readily with the amorphous material than with crystalline lactose. Lactose may also develop a yellow-brown color, in the absence of amines, with browning again occurring most rapidly in the spray-dried material, possibly owing to the formation of 5-hydroxy-methyl-2-furfural. Lactose is incompatible with amino acids, aminophylline, amphetamines and lisinopril (Rowe et al., 2003).
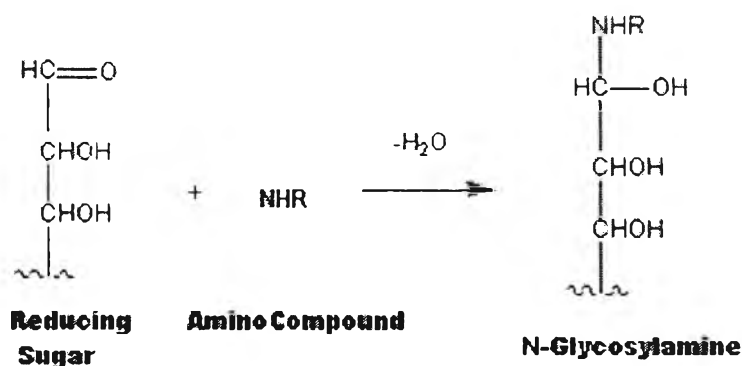
Figure 7 Maillard reaction of reducing sugar and amino compound

(http://www.landfood.ubc.ca/courses/fnh/410/colour/382.htm[2006, April 1])

2.2 Dibasic calcium phosphate ($CaHPO_4 . 2H_2O$)

Dibasic calcium phosphate dehydrate (dbcp) is a white, odorless, tasteless powder or crystalline solid. It occurs as monoclinic crystals. The molecular weight of dbcp is 172.09. It is practically insoluble in water, ethanol and ether. It is nonhygroscopic and stable at room temperature and humidity, it can lose water of crystallization below 100°C. Dibasic calcium phosphate is widely used in oral pharmaceutical products. The surface of dbcp is alkaline and consequently it should not used with drugs that are sensitive to alkaline.

2.3 Glyceryl monostearate

Glyceryl monostearate (GMS) is waxy to touch and has a slight fatty odor and taste. It is white to cream colored, wax like solid in the form of beads, flake or powder. Its HLB value is 3.8. The molecular weight of GMS is 358.6. Glyceryl monostearate is soluble in hot 95% ethanol, ether, chloroform, hot acetone, mineral oil and fixed oils, practically insoluble in water, but readily dispersible in hot water with the aid of anionic or cationic agent. Melting range of GMS is 55°C -60°C (Rowe et al., 2003). GMS is used as a non-ionic emulsifier, stabilizer, emollient and plasticizer in a variety of food, pharmaceutical and cosmetic preparations. It acts as an effective stabilizer, i.e. as a mutual solvent for polar and non-polar compounds, which may from W/O or O/W emulsions. It is also used as a lubricant and to sustained release of active ingredients in tablet formulations.

$$CH_2\text{-}OOCC_{17}H_{35}$$
$$|$$
$$CHOH$$
$$|$$
$$CH_2OH$$
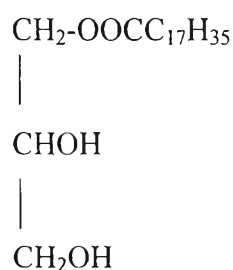
Figure 8 The structural formula of glyceryl monostearate (Rowe et al., 2003)

2.4 Precirol® ATO 5 (Glyceryl palmito-stearate)

Glyceryl palmito-stearate is mixture of mono-, di- and triglycerides of fatty acids, mainly palmitostearic acid (C16-C18 fatty acid). It occurs as a fine white to off white powder with faint odour. Its HLB value is 2. Glyceryl palmito-stearate is freely soluble in chloroform and dichloromethane, practically insoluble in 95% ethanol, mineral oil and water. Melting range of glyceryl palmito-stearate is 53°C -57°C (Rowe et al., 2003). Glyceryl palmito-stearate is used as a lubricant and lipophilic matrix for sustained release tablet and capsule. Sustained release tablet formulations that contain glyceryl palmito-stearate as the base may be prepared either by granulation or by a hot melt technique. Glyceryl palmito-stearate may also be used to form microsphere, which may be used in capsule or compressed to form tablets.

2.5 Compritol® 888 (Glyceryl behenate)

Glyceryl behenate is a mixture of glycerides of fatty acids, mainly behenic acid (C22 fatty acid). It occurs as a fine white to off white powder or hard waxy mass with faint odour. It is soluble in chloroform, methylene chloride when heated and insoluble in ethanol, N-hexane, water, and minerals oils. Melting range of glyceryl behenate is 65°C - 77°C (Rowe et al., 2003). Glyceryl behenate is used as a lubricant (1-3%), binding agent by direct tabletting, lipophilic matrix for sustained release tablets or capsule (use level>10%).

2.6 Gelucire 50/02

Gelucire 50/02 is saturated polyglycolysed glycerides: specific mixture of mono, di and triglycerides and polyethylene glycol mono and di-esters. It occurs as a hard waxy mass with faint odour. Its HLB value is 2. It is be freely soluble in chloroform, methylene chloride, insoluble in ethanol, and dispersible in water and mineral oil. Gelucire 50/02 is used as excipient for hard gelatin capsules, a regulator for sustained formulation with (1) protective action against oxidation and hydrolysis, (2) handling of low density product or toxic or low dose active drug, (3) formulation of solid dosage form with liquid active.

2.7 Tristearin® (Glyceryl tristearate)

Glyceryl tristearate is the primary fat in beef. It is a triglyceride, a molecule of glycerine has reacted with three molecules of the fatty acid stearic acid. It is a saturated fat. This means that every carbon has as many hydrogen atoms as it can hold (it is saturated with hydrogen), and there are no double bonds between any two carbons. It occurs as a white greasy solid.
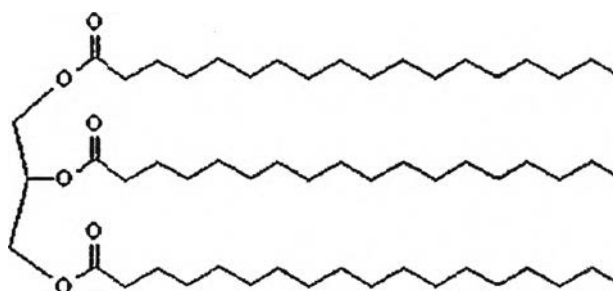

Figure 9 The structural formula of glyceryl tristearate

(http://sci-toys.com/ingredients/tristearin.html[2006, April 1])

2.8 Diclofenac sodium

Diclofenac sodium is a synthetic, non-steroidal anti-inflamatory and analgesic compound. It is widely used for relief of pain and inflammation. It is a white to off white crystalline, odorless and slightly hygroscopic powder. The molecular weight of diclofenac sodium is 318.13. The normal melting point of diclofenac sodium is 283°C - 285°C (Adeyeye and Li, 1990). The pKa of diclofenac sodium in water is 4 and the partition coefficient in n-octanol/aqueous pH is 13.4. The solubility of diclofenac sodium at 25°C is more than 9 mg/ml in pH 5.2 deionized water, more than 24 mg/ml in methanol, less than 1 mg in acetronitrile, cyclohexine and pH 1.1 hydrochloric acid and 6 mg/ml in pH 7.2 phosphate buffer. Impurities of diclofenac sodium as shown in Figure 10.

(a)   (b)   (c)
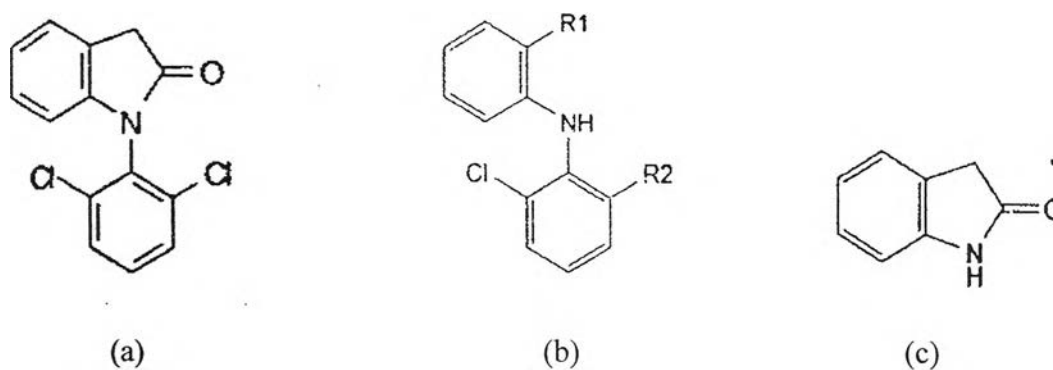
Figure 10 Impurities of diclofenac sodium (British Pharmacopoeia, 2002)

(a) 1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indolin-2-one

(diclofenac related compound A)

(b) R1 = CHO, R2 = Cl: 2-[(2,6-dichlorophenyl)amino]benzaldehyde

R1 = CH$_2$OH, R2 = Cl: 2-[(2,6-dichlorophenyl)amino]phenyl]methanol

R1 = CH$_2$-CO$_2$H, R2 = Br: 2-[2-[(2-bromo-6-chlorophenyl)amino]

phenyl]acetic acid

(c) 1,3-dihydro-2H-indol-2-one

The data presented that diclofenac sodium decomposed and/or undergoes a cyclization reaction before reaching its melting point as shown in Figure 11 depending on the environmental atmospheric condition under which the thermal process is carried out (Tudja et al., 2001). Apparently the decomposition process is a complex one and the extent of decomposition or conversion to 1-(2,6-dichlorophenyl)-indolin-2-one largely depend on the rate of heating of the substance.

Diclofenac sodium   1-(2,6-dichlorophenyl)-indolin-2-one
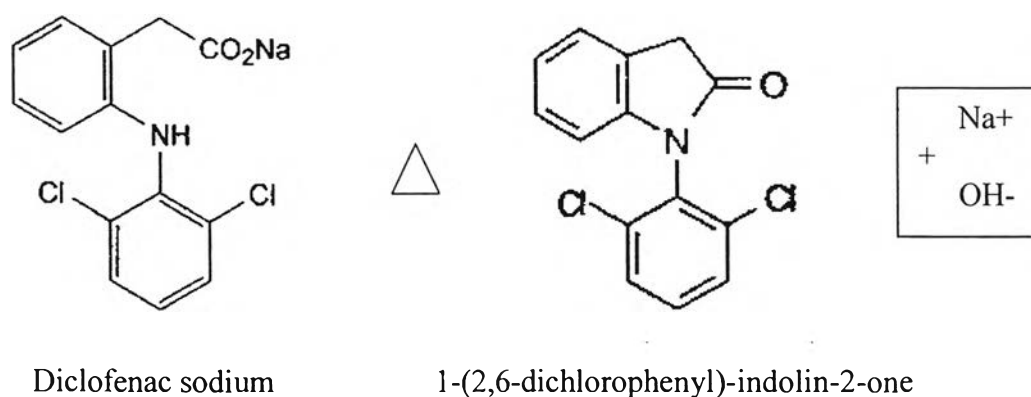
Figure 11 Schematic presentation of solid state cyclization of diclofenac sodium due to thermal reaction (Tudja et al., 2001)