CHAPTER I

INTRODUCTION

Pelletization is a size enlargement process which aims at producing uniformly sized spheres in the size range of 0.5 – 2.0 mm (Schæfer et al., 1992a; Thomsen et al., 1993). Pelletization products or pellets can be prepared in the various colour. Their free flowing property can reduce handling problem (Ghebre-sellassie et al., 1985). When pellets prepared as controlled-release preparations, they can increase 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). Pellets filled in capsule or compacted to tablet have been a prevalent practice in the pharmaceutical industry. Pellets are usually prepared by extrusion/spheronization or by coating a seed material such as inert spheres or coarse crystals with a mixture of the drug substance and suitable excipients (Ghebre-Sellassie I., 1989). Other methods, for example melt pelletization, might be used.

Melt pelletization or melt agglomeration is a type of wet granulation that requires the addition of a molten binder or a solid binder which melts during the process. The binder is liquified by the heat developed by the agitation or by a heating jacket (Thomsen et al., 1993). A suitable binder for melt agglomeration should be solid at room temperature, and the melting range of the binder should at least be 20-30°C above room temperature (Schaefer, 2001). Example of binders applied for melt agglomeration are polyethylene glycols (PEGs), glycerides, fatty acid and wax (Schæfer and Mathiesen, 1996a; Thomsen et al., 1993; Voinovich et al., 2000; Brabander et al., 2000). The use of a meltable binder seems to be suitable to produce pellets of water-sensitive materials, such as hygroscopic drugs (Thies and Kleinebudde, 1999) and/or freely soluble drugs (Zhou et al., 1997). Melt agglomeration has the advantage over wet pelletization in that the use of water is avoided, and the drying phase is eliminated. The end product from a melt agglomeration process might be either irregular granules of a wide size distribution or spherical granules of narrow size distribution.

A previous study (Schæfer et al., 1990) showed that polyethylene glycols (PEGs) are 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 others meltable binder examined. The type of PEGs might influence the size and size distribution of the agglomerates, probably because of difference in the viscosity of the molten PEGs (Schæfer and Mathiesen, 1996a). When the PEG concentration was increased, larger agglomerates were achieved (Schæfer et al., 1990). In order to produce rounded agglomerate with a narrow size distribution, i.e. pellets, the process variables have to be chosen carefully. It has been shown that a high impeller speed and prolonged massing time (Schæfer et al., 1990) gave rise to narrow size distribution.

Glycerides, e.g. glyceryl monostearate (GMS), glyceryl behenate (Compritol® 888), glyceryl palmito-stearate (Precirol® ATO5) and mixtures of glyceride and fatty acid esters of polyethylene glycol (Gelucires), are a family of excipients which have generated considerable interest for the preparation of oral dosage forms. The nature and the proportion of these components determine the hydrophobic characteristic, so they can be used to prepare sustained – release dosage forms (Thomsen et al., 1993; Hamdani et al., 2003).

The mean size, size distribution and morphology of pellets were highly dependent on the process parameters, e.g. product temperature, impeller speed and mixing time during the pelletization step. Product temperature has effect on pellets because a high temperature would decrease the viscosity of the molten binder and increase the volume of the binder liquid owing to thermal expansion (Schæfer and Mathiesen, 1996c). When PEGs which had viscosities in range 80 – 26,500 mPa.s were 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, i.e. 500 rpm, and low jacket temperature, i.e. 56°C, were found to gave rise to smoother and more spherical agglomerates (Thomsen et al., 1993). Hamdani et al (2003) found that low mean particle

size and high size distribution value were obtained at the lowest impeller speed, i.e. 400 rpm and 600 rpm, and mixing time, i.e. 6 min. The smaller particle size values were observed because of an insufficient energy input and/or improper movement of the powder mass at the lowest. A mixing time had effect to quality of pellet too. An increased mixing time gave rise to a significant larger mean granule size, narrow size distribution (Schæfer et al., 1993; Thomsen et al., 1993) and agglomerates which were rounder and smoother (Schæfer et al., 1992b).

Melt agglomeration has primarily been carried out in a high shear mixer. High shear mixers are capable of producing granules as well as pellets. A higher shearing force and a longer mixing time have been found to promote the formation of pellets (Schaefer et al., 1992a; Seo and Schæfer, 2001). Heating jackets can be applied to control the product temperature. It is difficult, however, to keep the temperature constant because the shearing forces raise the product temperature due to the heat of friction (Hamdani et al., 2002).

High shear mixing offers advantages as well as disadvantages compared to extrusion/spheronization. High shear mixing was found to be a quick way to produce spherical, smooth pellets. It is a one-step single-pot production process. A disadvantage is the wide size distribution of those pellets compared to extruded ones (Thomsen et al., 1993).

Fluid bed granulators have also been used for melt agglomeration (Seo et al., 2002). Because of the low shearing forces in fluid beds, it is difficult to obtain spheronization of the agglomerates. The fluid bed granulator has an advantage compared to the high shear mixer in a better control of the product temperature. However, the fluid bed granulator lacks a simple way to determine the end point of the agglomeration process (Vilhelsem et al., 2004). A rotary processor is a fluid bed granulator equipped with a rotating friction plate, which increases the shearing forces. The friction plate with the crosshatched and the longitudinal friction plates were both found suitable for melt pelletization (Vilhelsem et al., 2004).

Compared to high shear mixers, the rotary processor has shown to be an alternative in the choice of equipment for melt pelletization. The agglomerates produced by the rotary processor were of a similar size and size distribution and with a similar reproducibility as those produced by a high shear mixer. The high shear mixer, however, is able to produce agglomerates, which are more spherical than those from the rotary processor due to higher shearing forces. On the other hand, the rotary processor produces more spherical agglomerates than a conventional fluid bed granulators (Vilhelsem et al., 2004).

However, high shear mixers have disadvantage about the control of product temperature. Schæfer et al.(1992a) found that longer mixing time is inexpedient since it may result in an extremely high product temperature. The temperature increase during the process is a problem, since it might lead to decomposition of the materials. Low shear force in a planetary mixer may avoid the rise in product temperature or give better control of product temperature by heating jacket. The heat is only developed by a heating jacket and could be kept constant during pelletization.

Nothing has been published so far on preparation of pellets in planetary mixers which has low impeller speed, i.e.100 - 200 rpm, although pellets prepared with high impeller speed, i.e. 3000 rpm (Vonk et al., 1997), or low impeller speed, i.e. 200 rpm (Eliasen et al., 1999), in high shear mixers were mostly investigated.

In the study, a jacketed – planetary mixer was used to prepare diclofenac sodium pellets by melt technique. The effect of process variables, impeller speed, product temperature and mixing time on the formation of pellets with varying binders was investigated.

The release profile of pellets was also studied to signify whether the variables could modify the drug release as previously reported by many researchers (Zhou et al., 1996; 1997; Vergote et al.,2001).

Objectives of the study

1. To investigate the effect of process and formulation variables on formation and physical properties of diclofenac sodium pellets prepared by melt technique in a planetary mixer.
2. To study diclofenac sodium released from pellets prepared by melt technique.