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Comparison of granule properties produced using Twin Screw Extruder and High Shear Mixer: A step towards understanding the mechanism of twin screw wet granulation

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ABSTRACT

The wet granulation process plays an important role in the pharmaceutical industry. With the introduction of a Twin Screw Extruder (TSE), it allows the possibility of wet granulation to be run continuously in contrast to a conventional batch process using a High Shear Mixer (HSM). However, the mechanism of Twin Screw Extruder wet granulation is not well understood and the aim of this study is to investigate this process and compare it with the High Shear Mixer granulation process with regard to the granule properties.

Granules of pure microcrystalline cellulose (MCC) were produced using a Twin Screw Extruder and a High Shear Mixer with water as liquid binder under different process conditions and formulations. The properties (particle size distribution, shape, surface morphology, internal structure, internal porosity and strength) of the granules were then compared. It was found that the granules produced by the two methods have different physical properties. Granules produced by the HSM are spherical in shape and are made up of smaller granules through coalescence process. It is believed that the granules produced by HSM in the present study are over-granulated which leads to the production of strong dense granules. On the other hand, granules produced by TSE have irregular shapes with tiny pores spread uniformly throughout the granules. The granules produced by HSM are affected by process conditions and are stronger at higher impeller speed. However, granules made by TSE are consistent in strength and relatively independent of process conditions. Due to over-granulation in HSM process, the granules produced result in the production of weak tablets whilst granules made by TSE manage to produce stronger tablets.

Finally, by observing the structure of the granules, it is believed that the mechanism of HSM and TSE granulation is different. Although the granules made by HSM were over-granulated, it shows the existence of consolidation process that is apparently absent in TSE granulation. Nevertheless, more work will be needed to further understand the mechanism in continuous TSE wet granulation process.

1. Introduction

Granulation of powder materials is one of the most important unit operations in today's chemical industry. It is widely used in industries such as pharmaceutical formulation, food manufacture, agriculture product manufacture, and the plastics industry. The objective of granulation is generally to improve the product behaviour such as material handling, flow, dust reduction and resistance to segregation. In addition, it can improve material appearance and mechanical properties as well as control final product dissolution or disintegration rate. Wet granulation comprises, in general, a combination of mixing and consolidation processes. Most of the commercial wet granulation processes have been run in batch mode for the past few decades and there is limited application of continuous processing in pharmaceutical wet granulation. Since continuous processes bring significant advantages over batch processes, many techniques have been developed for continuous wet granulation for example fluid bed agglomeration, extrusion and instant agglomerators. Among these, extrusion is one of the most studied, and most promising continuous wet granulation technique for pharmaceutical applications [1].

The Twin Screw Extruder (TSE) is widely used in polymer and food processing. It is becoming popular in wet granulation operations as it allows for continuous processing. Research in other industries indicates that scale up is straight forward from laboratory tests, resulting in reduced development costs [1]. It can also minimize material loses and gives consistent final or intermediate products. The fact that the TSE is inherently self-wiping (the entire surface of the screw and barrel is continuously scraped by screws) helps prevent accumulation of material and is expected to lead to a more economic process (saving labour costs and time) and allow a 24 hour production line with automated control.

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TSE granulation was first applied in the pharmaceutical research by Gamlen et al. in 1986 [2] to produce paracetamol extrudates. The quality of extrudates was evaluated to investigate the influences of formulation and moisture content. Lindberg et al. then carried out similar research in 1987, exploring the use of TSE granulation for effervescent granulation formulation as well as investigating the suitability and advantages of the TSE as an instant granulator [2–5]. In 2002, Keleb et al. [6–8] reported that TSE granulation is more efficient than HSM, stating that the granules produced by TSE have improved properties. TSE melt granulation and the impacts of screw configuration on granule properties were studied by Van Melkebeke et al. [9,10]. It was concluded that TSE granulation is a robust process as the mixing efficiency remains good irrespective of modified configurations.

Conventionally, the mechanism of wet granulation consists of i) wetting and nucleation, ii) coalescence and consolidation and iii) breakage and attrition. Wetting is the step when liquid binder is introduced to the system and nucleation is the step when liquid binder droplets overlap with and imbibe into the powder bed forming granule nuclei. Coalescence and consolidation is the process where granules start to grow and become dense and is related to a series of important parameters for example the amount of liquid present and the kinetic energy of the system [11,12]. Breakage and attrition which is the least studied area is the step that determines the final granule size distribution. Granules will break and attrite when they experience high impact and/or shear forces induced when they collide with blades, vessel walls and neighbour granules. Granule breakage depends on the dynamic strength and when impact forces are larger than the granule strength, continuous breakage and immediate coalescence of the granules will take place.

The aim of this study is to fundamentally understand the mechanism of wet granulation using a Twin Screw Extruder and compare it with conventional wet granulation. The High Shear Mixer was selected as the conventional method for this study. The influences of screw speed and liquid to solid ratio on granule properties are studied as a fundamental approach to understand the granulation process.

2. Materials and experimental method

2.1. Granulation process

In order to keep the system simple, the granule was produced using only Avicel PH 101 Microcrystalline Cellulose (FMC Biopolymer, Ireland) with mean particle size of 50 μm without any binder. Distilled water was used as the granulation liquid and was injected through the liquid injection point.

The granulation process was run using a laboratory intermeshing co-rotating Twin Screw Extruder (Haake, Thermo Scientific, Germany) with a diameter of 16 mm and length to diameter ratio of 25:1. In this initial study, the screws consist of conveying elements and two mixing zones each of five kneading elements oriented at 90° (see Fig. 1). 20 g/min of Avicel PH 101 Microcrystalline Cellulose (MCC) was fed continuously into the extruder barrel using a screw feeder (K-Tron T20) whilst distilled water was injected using a plunger metering pump (ProCam, Bran + Luebbe, SPX, Germany) at the desired rate. The temperature of the barrel was kept at 20 °C by circulating cool water through a jacket in the granulator.

For the batch process, granules were made by following the procedures reported in [13,14] using a built in house High Shear Mixer (University of Birmingham, UK) with a stainless steel bowl. The dimension of the bowl is 160 mm in diameter and 200 mm in height with a three bladed impeller (leading edges inclined at 13°) fitted at the bottom of the bowl and no side chopper. 200 g of MCC was first "stirred" at 100 rpm for 30 s and the required quantity of liquid binder was then added slowly within 30 s. The powder bed was then blended at desired speed for 30 min [15]. Granules were collected and allowed to dry overnight at room temperature before further analysis.

2.2. Tablet compaction

Tablets were made from granules produced by both TSE and HSM in order to investigate the influences of granule properties on the final products. The tablets were produced by compressing granules with a moving top piston in a confined cylindrical die. 700 mg of dry granules were manually fed into a 13 mm die (Specac, Kent, UK) and the powder bed was then compressed using a Universal Testing Machine (Zwick, Germany) to a maximum pressure between 50 MPa and 200 MPa. No lubricant was used when compressing the tablets and the load cell speed of the tester was set constant at 3 mm/s. A more detailed description can be found in [16–18].

2.3. Granule characterisations

2.3.1. Particle size distribution (PSD)

The granule size distribution was determined by sieving through 63, 90, 125, 180, 250, 355, 500, 710, 1000 and 1400 μm sieves series (ISO standard, every 3rd sieve of twentieth root of ten series). Approximately 100–200 g of the granules produced by the High Shear Mixer (HSM) and the TSE was sieved at 1 mm/"g" amplitude for 10 min (Retsch, AS 200, Germany). The weight of granules retained on each sieve was measured and particle size distribution curves were plotted. In this study we defined the fraction of granules smaller than 125 μm as fines, assumed to comprise un-granulated material.

2.3.2. Shape and morphology

The shape of the granule was measured in terms of aspect ratio and sphericity. Both aspect ratio and sphericity were determined using Sympatec Image Analysis (QICPIC) by dispersing the granules under gravity through high speed cameras. The aspect ratio and the sphericity were calculated simultaneously by the WINDOX software where aspect ratio is defined as the ratio of the maximal Feret

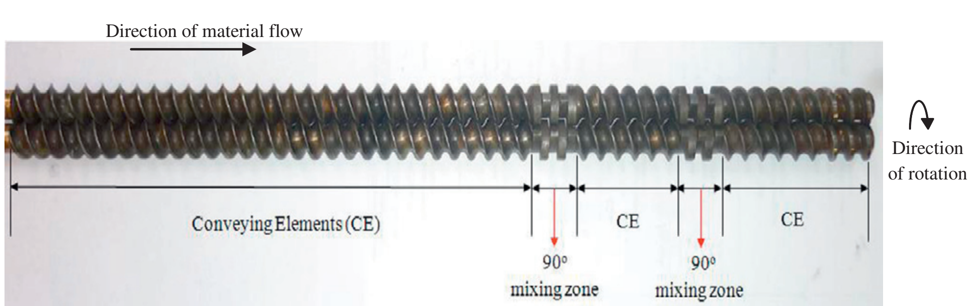

Fig. 1. Co-rotating twin screw with two 90° mixing zones.