Wet and hot melt granulation for producing granules engineering essay

Abstract: Continuous granulation processes has always been one of the topics of interest in the pharmaceutical industry. Research for new approaches and reforms of technology is constantly ongoing. Wet granulation extrusion technology has been the conventionally exploited method used in the pharmaceutical industry. However recently there has been an innovative form of granulation which has surfaced for the purpose of pharmaceutical industry namely hot-melt extrusion. With much interest in this, a great deal of study and research has been invested in the hot-melt extrusion technique, and is now recently being applied in an array of pharmaceutical manufacturing operations. This study in detail constructs a comparative review between wet and melt granulation technology currently used in the pharmaceutical industry. It will proceed with reviews of the processes and equipments used in creating granules, an in depth analysis of granule quality and a final supposition will conclude this research project.

The purpose of undergoing the comparison between wet granulation and melt granulation is to identify which method of granulation is better qualified and if hot-melt granulation can supersede the current commonly used wet granulation.

Key words: Hot-melt granulation; Wet Granulation; Mixer torque rheometer; Twin screw extruder;

Within the past decade much research has been performed to establish a technology for the continuous processing of pharmaceuticals, pro1

Introduction

The application of extrusion technique in terms of granulation for industry has been recorded to be used back in the 1930's (Rauwendaal Ch. 1986). Initial examination of the use of twin-screw extruder for wet granulation was done by Gamlen and Eardley (Gamlen MJ, Eardley C. 1986). From here on there has been numerous research done on the process variables and optimisation of the material formulation. A milestone was reached when hot-melt extrusion technology found its place in an array of the pharmaceutical manufacturing operations. Repka et al (Repka MA et al 2007.) and Van Melkebeke et al (Van Melkebeke B et al 2006) had successfully shown that granulation in an extruder can be done using a molten binder replacing the aqueous system seen in wet granulation.

1. 1 Granulation Rationale

Granulation is a ' process in which primary powders particles are made to adhere or agglomerate together to form larger multi-particle entities called granules' (Pharmaceutics Aulton 2007). It is a process of size enlargement. Granulation is used in pharmaceutical industry primarily for the manufacturing different dosage forms such as: capsules, tablets, pellets, suppositories, transdermal systems, implants and ophthalmic inserts, whereby ' granules are made as an intermediate product.' (Pharmaceutics Aulton 2007)

The granulation process is often necessary for various primary reasons:

Prevent segregation of constituents of a powder mix

Improve flow properties of the mix

Improve the compaction characteristic of the mix

There are two main types of granulation methods that are employed in modern pharmaceutical industry: wet granulation and dry granulation. Wet granulation methods utilize a liquid in the process whilst dry granulation methods do not use liquids in the process.

For different drug formulations a different number of excipients are required to be added with the active ingredient(s). Common types of excipients are diluents, disintegrating agents and adhesives which are usually added before the granulation process. Dry granulation involves aggregating primary powder particles at high pressure without the use of liquid solution due to materials being sensitive to moisture and heat. An intermediate product is produced undergoes a subsequent screening stage involving a milling technique to break agglomerates of granules to produce a mixed sized variety of granules separated by a sieve to remove fine material.

1. 2 Wet Granulation

Continuous wet granulation is the standard method currently used in the pharmaceutical industry. The basic principle of wet granulation involves adding a solution containing a dissolved binding agent (granulating fluid) to the powder comprising of the remaining drug ingredients. It then proceeds with mass mixing using different techniques depending on type of machinery used. The mixing allows and binder allows the powder to mix uniformly and to be distributed evenly in the granular product. The wet mass is then forced through a die of an extruder to produce granules of desired design which are

then dried to remove the solvent from the initial granulating fluid. Individual particles adhere upon drying to form granules.

Examples of typical granulating fluids used alone or in combinations are: Water, Ethanol and Isopropanol. It is vital to understand that the amount of granulating fluid added will have significant effects on the granule properties, too little will cause granules to become friable, and too much would cause the over-wetting and results in no granule formation. Thus to gain the optimal quantity of granulating fluid the rheology or viscosity of the wet mass would be closely monitored to determine the level of liquid saturation, knowing this would allow the optimal quantity of granulating fluid to be added.

Granulators are the machinery used to form granules. Although there are many forms of machines currently used they all work on one of three principles either (1) shear, (2) high speed or (3) fluidised bed technology. Each granulator therefore differ in form exteriorly but same interiorly.

Shear granulator (fig 1)

High speed granulator (fig 2)

Fluidised bed granulator (fig 3)

Fig 1. Shear granulator

Fig 2. High speed granulator

Fig 3. Fluidised bed granulator

1. 3 Melt Granulation

Hot-melt extrusion has been widely applied to the industrial processing of plastics, rubber and foods. Now over half of all plastic products produced are manufactured by this process, examples of these include plastic bags, pipes and polystyrene tiles (Kruder GA 1985).

Hot-melt granulation is an agglomeration technique where granules are obtained by either softening or melting binders that are heated to near or above their melting point (Barbara Van Melkebeke et al, 2006).

Hot-met granulation has been applied into the manufacturing of pharmaceutics for various purposes (Rina Chokshi, Hossein Zia, 2004):

Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion of solid solution

Controlling or modifying the rate of the drug release

Masking the bitter taste of an active drug

Hydrophobic binders such as microcrystalline waxes, paraffin and glycerol are used for producing formulations that require sustained release, whereas hydrophilic binders such as polyethylene glycol (PEG) are used for immediate release formulations (Barbara Van Melkebeke et al, 2006). Scharfer et al demonstrated the effects of the process and formulation variable with PEG (Schaefer, 1996) and Zhou et al showed a process using high shear mixer using microcrystalline waxes as the binders (Xhou et al, 1006, 1007)

Like wet granulation there are various ways of performing hot-melt granulation, of them the most commonly performed is via high shear mixers.

In high shear mixers temperatures used to melt of soften the binder is reached by external heating or by heat generation from friction. Another variation has been recently been applied: fluidised bed granulators (Abberger et al. 2002; Seo et al., 2002): Initially applied only in wet granulation it has now been used for melt agglomeration, having the advantage of better temperature control. However twin-screw extrusion introduced by Gamlen and Eardley (1986) and used by Lindberg et al (1987, 1988) for continuous granulation of paracetamol was quickly further developed and applied into the pharmaceutical industry. For the purpose of this study the twin-screw extrusion method will be used.

2 Materials and Equipment

2. 1 Materials

a-Lactose monohydrate 200mesh (DMV, Veghel, The Netherlands) was used as a model for excipients and acted as a filler for both PEG and PVP.

The aqueous binder prepared for the wet granulation experiments used 2%, 4% and 6% w/w polyvinyl pyrrolidone K30 (PVP) dissolved in distilled water. Distilled water served as the granulation fluid.

Polyethylene glycol (PEG) 2000, 4000 and 6000 (Fluka chemicals, Germany) flakes was used as the meltable binder in the hot-melt granulation experiments made to 10%, 15% and 20% PVP concentration respectively, made up to 40g batches with lactose monohydrate.

Magnesium stearate (BUFA, Uitgeest, The Netherlands) was used as lubricant during tabletting.

2. 2 Equipment

Throughout the experiment the Precisa 125 Swiss weight balance was used to measure powders, granules and appliances.

Specifically for wet granulation this study used the Caleva Mixer Torque Rheometer (MTR) (Caleva Ltd, Dorset, England), a “ Wet Mass” Rheometer and highly efficient GLP compatible high sheer mixing tool for small quantities. It provides a way to quantitatively measure the consistency (or pseudo-viscosity) of a wet mass in terms of the torque produced when shearing the granulation within a mixing bowl.

A Twin-screw extruder was used for the hot-melt granulation process

To transform granules to tablet a single tablet press (manual press) by Caleva process solutions Ltd was applied for all tablets forming throughout experiment. Tablet properties were measure using a diametric thickness gauge (Mitutoyo, Japan) using a hardness tester (Copley Scheiniger 4H, UK) to test crushing strengths.

3 Methods

3. 1 Experimental protocol

Prior to wet granulation the PVP solution was prepared by weighing out 2g, 4g and 6g of PVP powder using a weight balance. Each PVP measured out was made up to 100ml’s with distilled water and mixed until dissolved, forming 2%, 4% and 6% w/w PVP binder solution namely batch 1, 2 and 3 respectively.

20g of a-Lactose monohydrate was weight out.

For each batch the MTR was left to operate on an empty bowl for approximately 60 seconds simultaneously logging torque data. 1ml of binder solution was added drop wise and left for another 60 seconds interval to record data; this step was repeated once more. 0. 5ml’s of binder solution was added drop wise and left to log detail, this step was repeated once more. A total of 3 ml’s of binder solution was added to the lactose for each batch.

The wet granules were removed from the rheometer bowl and placed into an oven for drying. After a minimum of 45 minutes the granules were removed from the oven as individual dry granules.

Contrary to wet granulation, melt granulation was a much simpler and less time consuming experiment.

Prior to feeding into the extruder three 40g batches were made with concentrations of 10% (4g), 15% (6g) and 20% (8g) PEG. Note the PEG flakes were reduces to smaller granules using a pestle and mortar before making up to the total weight of 40g with lactose.

The twin screw extruder was set to standard temperatures throughout granulating all three batches shown in table 1. The screw geometry and a speed of 50 RPM were consistent for all three experimental batches.

Heating Zones

Z1

Z2

Z3

Z4

Z5

Z6

Z7

Z8

Z9

Die

Temperature

25

40

70

80

80

80

80

80

70

x

Table temperature profile zones

Formed granules from both wet and melt granulation were subjected to various tests: bulk and tapped density determination, particle size, angle of repose, and tablet tensile strength.

300mg tablets were prepared from all batches using a Caleva single tablet press (Caleva process solutions Ltd). It is equipped with a flat faced double punch of 9mm at a compression force of 10 kN per tablet. Magnesium stearate was used to lubricate the punch and die for ease of motion and reduction of friction.

Granule Characterisation

Bulk and tapped density (granule flowability)

These calculations are used for the purpose of measuring the flow properties of powders.

Batches from both wet and melt granulation underwent tapping three times to determine an average.

The bulk volume (V0) of the total granule for every batch (30g wet granules, 40g melt granules) was measured using a 100ml measuring cylinder and subjected to 200 taps using a tapping machine (.....) and the tapped volume was recorded (V200), the cylinder was emptied and the repeated two

more times for each batch. Bulk and tapped densities were calculated using the following equation:

Mass(g)/Volume(V0) and Mass(g)/tapped volume(V200) respectively

From the bulk and tapped densities the Hausner ratio was calculated using:

Hausner ratio = Tapped density(VD200)/Initial bulk density(VD0)

Integrating the Hausner ratio, the Carr compressibility Index (C%) was calculated using:

C% = ((Tapped density – initial bulk density)/tapped density)x100

The compressibility of granules determined from the Carr index (C%) was evaluated by the Heckel equation in triplicate using:

Heckel equation = Ln(1/1-pr)kP+A pr= relative density, K= slope of linear portion of plot, A= constant

The Heckle plot is constructed by plotting the natural log of the inverse of the compact against respective compression pressures. The regression analysis was performed on the linear portion of the curve and the slope values converted to mean yield pressure using the relationship (Py= 1/slope(k)).

Particle size

Angle of repose (flowability)

Tablet tensile strength (Tablet hardness)

These measurements tested granule compressibility and compactibility, which required granules to be in tablet form. Three 300mg granules tablets were made in a single tablet press for each batch. Each tablet was subjected to three measurements: (1) weight, (2) tablet thickness using a diametric thickness gauge (Mitutoyo, Japan), (3) hardness (crushing strength) using a hardness tester (Copley Scheiniger 4H, UK). The average weight, thickness and crushing strength were taken for each batch for both wet and melt granulation.

4 Results and Discussion

4. 1 Bulk and tapped density (granule flowability)

The average bulk volume tapped volume was calculated to determine the bulk density and tapped density respectively (Full results found in appendix). These densities were used to calculate the Hausner and Carr compressibility index for wet and melt granulation as show below:

Batch 1

Batch 2

Batch 3

Hausner ratio: wet granulation

1. 260

1. 297l

1. 250

Hausner ratio: melt granulation

1. 294

1. 206

Table Results: Calculated; Hausner ratio

Batch 1

Batch 2

Batch 3

Carr compressibility index: wet granulation

20. 690

22. 933

20. 067

Carr compressibility index: melt granulation

22. 742

17. 073

Table Results: Calculated; Carr compressibility index:

4. 2 Particle size

4. 3 Angle of repose

4. 4 Tablet tensile strength (Tablet hardness)

Average weight, tablet and pressure were determined from three sample tests of each batch, (Full results found in appendix). Calculated average values are as shown below.

Average tablet Weight: Batch 1

Average tablet Weight: Batch 2

Average tablet Weight: Batch 3

Wet granulation

0. 300

0. 299

0. 289

Melt granulation

0. 290

0. 300

0. 299

Table Calculated Average tablet weights

Average tablet

Thickness: Batch 1

Average tablet Thickness: Batch 2

Average tablet Thickness: Batch 3

Wet granulation

0. 300

0. 299

0. 289

Melt granulation

0. 290

0. 300

0. 299

Table Calculated average tablet thickness

Average Pressure:

Batch 1

Average Pressure: Batch 2

Average Pressure:

Batch 3

Wet granulation

3. 33

03. 53

3. 7

Melt granulation

11. 6

15. 07

16. 13

Table calculated average pressure

4. 4. 1

Melt extrusion now being applied to the pharmaueticial manufaturuing of medicine have been found to achieve enhancement in dissolution rates for poorly water soluble drugs

Twin-screw extrusion

was introduced by Gamlen and Eardley (1986) using a Baker

Perkins MP50 extruder to produce paracetamol extrudates

Hydrophobic

binders such as microcrystalline waxes, paraffin and glycerol

monostearate are used for sustained release formulations, while

hydrophilic binders such as polyethylene glycols are well suited

for immediate release formulations (Barbara Van Melkebeke et al, 2006)

Due to rapid densification and agglomeration that are caused by the shearing and compressing action of the impeller in a high-shear single pot system, mixing, granulation and wet massing can be done relatively quickly and efficiently. The dangers lie in a possibility of overgranulation due to excessive wetting and producing low porosity granules thus affecting the mechanical properties of the tablets.

As the liquid bridges between the particles are formed, granules are subjected to coalescence alongside with some breakage of the bonds.

Additional Factors in Wet Granulation

Melt garnua: However, milling was required to remove oversized agglomerates. Keleb et al. (2004) recently demonstrated that modifying the extrusion screw profile resulted in a granulation process yielding no oversized granules, eliminating the need of (wet or dry) milling

Extrusion is a process used to create objects of a fixed cross-sectional profile. A material is pushed or drawn through a die of the desired cross-section. The two main advantages of this process over other manufacturing processes are its ability to create very complex cross-sections and work materials that are brittle, because the material only encounters compressive and shear stresses. It also forms finished parts with an excellent surface finish.[1]