DFE pharma

Introduction to tableting by wet granulation

The pursuit of excipient excellence

1 Introduction

Most pharmaceutical tablets are processed by wet granulation, and yet it is the most complex means of tablet processing. The popularity of wet granulation is because it can be applied to all drugs, and for many formulators it is the method of choice for drugs with a high dose and a very low dose.
In this introduction we look at some of the main formulation factors that affect the properties of tablets made by wet granulation, and also touch on some process related factors concerning end point determination and scale-up. The process related factors are the source of a great number of studies and a comprehensive review is beyond the scope of this introduction, although it is possible to give general guidance concerning process related factors. The potential for various measureable factors to be used as end point detection has been extensively reviewed [(1)] elsewhere.

2 Why choose wet granulation

Most product formulators see wet granulation as a universally applicable means of tablet processing. All of the required functionality of a compression mix – good flow, good compactability, uniform distribution of drug and controllable drug release – can be built in using wet granulation without relying on the intrinsic properties of the drug or the excipients. Additionally using wet granulation it is possible to get stabilising agents such as pH modifiers into close contact with the drug and so potentially maximise tablet stability.
For high dose drugs, poor flow and compaction of the active mean that wet granulation may be the only feasible means of producing tablets, and for low dose drugs the granulation process is seen as being capable of “locking” drug into granules and thereby minimising the potential for segregation and poor content uniformity.
There are therefore a number of advantages inherent to wet granulation, but there also a number of disadvantages. Water used in granulation processes can bring about unwanted changes in drugs or in excipients; the benefits of content uniformity of low dose drugs are not necessarily realised; and the complexity of the process compared to, say, direct compression greatly increases the number of quality critical factors that need to studied and controlled in a QbD development programme. Thus despite the broad applicability of wet granulation it may be simpler and ultimately more production efficient to first look at direct compression or dry granulation.

3 Types of wet granulation

Wet granulation can be divided into three main processes of low shear, high shear, and fluid bed granulation. Additionally there is a drive towards continuous wet granulation for improvement in manufacturing efficiency. Each process has its own pros and cons which may be useful for different formulations, but in practise a formulator may not have the choice of which process to use for a particular product, the selection being determined by equipment availability and company preference.
Figure 1 shows the typical process for low and high shear granulation with examples of the different types of equipment used.

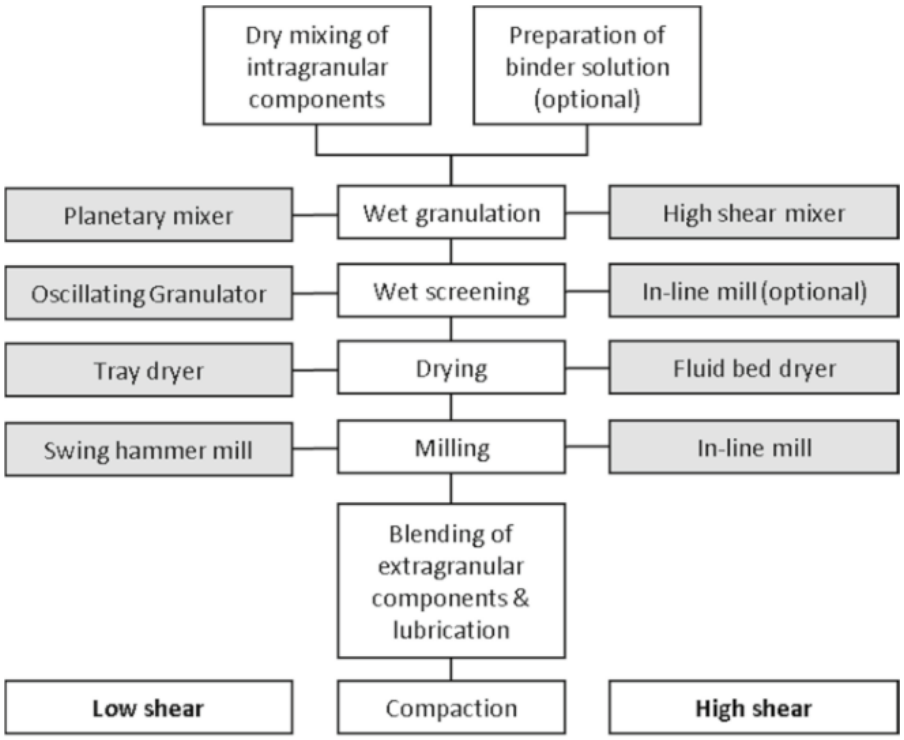

Figure 1: *Schematic of wet granulation by low shear and high shear processing*

3.1 Low Shear Granulation

This is the traditional means of granulation employing low speed planetary or trough mixers in which the drug and intragranular excipients are granulated with a binder solution, the resulting wet mass is screened to form discrete granules which are typically dried in a tray drier. The dried granules are rescreened or milled to the required size, blended with extragranular excipients, lubricated and compressed. The main disadvantages of this process are the open nature of the equipment and the manual transfer of the materials being processed, the long drying times, potential for migration of soluble components during tray drying [(2)] and the general lack of instrumentation for in-process control.

3.2 High shear granulation

High shear mixer granulators are characterised by their use of two mixing blades. An impeller that rotates in the base of the mixer and a high speed “chopper” that continually breaks up the wet mass as granulation proceeds. This combination provides for very effective mixing of components and usage of small amounts of water compared to low shear granulation. The entire process of mixing and granulation can be completed in a few minutes and the systems can be fitted with a variety of devices to monitor and determine the end point of granulation.
A high shear mixer granulator is a closed vessel, and the granules produced are generally able to be transferred to a fluid bed drier in a closed system thus minimising the extent of handling necessary.
A key advantage of high shear granulation is its wide applicability to almost any formulation.
However, the intensity of the mixing process can rapidly lead to overgranulation with adverse effects on granule tabletability [(3)]. In general any process factor that increases the extent of granulation (increasing water, massing time or impeller speed) tends to increase granule density and reduce tabletability [(4)]. It may be possible to counteract the effect of overgranulation to some extent by milling the dried granules [(5)]. Our general advice, based on published studies and work in our own laboratories, is to make a light granulation but one that is consistent with good flow. Such a granulation is achieved by carefully controlling the relative proportions of diluents, the amount of granulating water and the duration of wet massing.

Thus with high shear granulation it is important to control the end point of the granulation process to achieve consistency of granule properties such as size and density. Typically end point determination is

achieved by monitoring the power consumption of the impeller motor, although many other methods have been investigated [1].

A disadvantage shared by both low and high shear granulation is that water is intimately mixed with the formulation components. The water may be in contact with these components for a significant time, and thus water activated changes to drug and excipients can occur. Reported water activated transitions of actives usually involve formation of hydrates. Examples include amlodipine besylate [6], caffeine, carbamazepine, sulfaguanidine [7], theophylline [8] and baclofen [9]. In some cases the transition can be minimised by the inclusion of polymeric excipients such as hypromellose [7, 8], in other cases these polymers had no effect on drug transformation. There appears to be generally applicable formulation approach therefore to preventing such transitions.
Water induced transitions have also been observed for excipients such anhydrous β-lactose to α-lactose monohydrate [10] and δ-mannitol to β-mannitol [11]. However it is possible to granulate anhydrous β-lactose without the reported transition by employing fluidised bed granulation, and this technique may reduce such transitions for sensitive actives.

3.3 Fluidised bed granulation

Drug and excipients are loaded into a fluid bed processor, fluidised with air, and granulating fluid is sprayed into the bed, usually from above, with a continuous stream of warm drying air. This is often a three stage process of

- Blending, in which the drug and excipients are blended with a low volume of fluidising air to achieve homogeneity and to warm the dry powders. Care needs to be taken in this stage that fine drug particles are not removed from the bed by entrainment in high velocity air. Effective fluidisation depends in part on the particle size of the powders to be fluidised, and in practise an easily fluidised powder will have a mean particle size of 30 to 120μm [12] and many diluents such as milled lactose and microcrystalline cellulose lie in this range.
- Granulation, in which water or a binder solution is sprayed onto the fluidised bed. Granule growth during this phase depends on a number of factors such as granulating fluid viscosity and droplet size and spray rate. In general increasing any of these factors tends to increase granule growth rate.
- Drying, in which the spraying is stopped and the powder bed is gently fluidised until the granulation is dry. The end point is usually determined by the bed temperature. During this phase there may be some granule attrition.

Advantages of fluidised bed granulation are that it is a contained process, that a single piece of equipment may be used for granulation and drying, thus representing a capital saving over high shear granulation, and that fluid bed processed granules are typically low density and compressible [13].
Disadvantages are that some combinations of drugs and excipients are incapable of being mixed by fluidisation before granulation, and in these cases a premix has to be prepared. Finely milled or micronized drugs may be entrained in the fluidising airstream and lost from the powder to be granulated. Again a practical solution is to prepare a pre-blend and to start spray granulation immediately [12].

4 Excipients for wet granulation

Typically a wet granulated formulation will contain one or more diluents for bulk or to aid processing, a binder to facilitate granule growth and to aid compaction into hard tablets, a disintegrant and a lubricant. Additionally wetting agents, stabilising agents and colourants are used as required. Table 1 shows commonly used key excipients.

Table 1: *Commonly used excipients in wet granulation*

Function	Excipient	Typical Level (approximate)
Diluent	Microcrystalline cellulose	10% - 30%
	Lactose monohydrate	Up to 90%
	Dibasic calcium phosphate	Up to 90%
	Mannitol	Up to 90%
Binder	Pregelatinised starch	2% - 5%
	Povidone	1% - 3%
	Hydroxypropyl cellulose	1% - 3%
	Hypromellose	1% - 3%
Disintegrant	Partly pregelatinised starch	5% - 20%
	Sodium starch glycolate	2% - 6%
	Croscarmellose sodium	2% - 6%
	Crospovidone	2% - 6%
Lubricant	Magnesium stearate	0.5% - 1%
	Sodium stearyl fumarate	0.5% - 1%
	Talc / Stearic acid	3% - 5% / 1% - 2%
Glidant	Colloidal silicon dioxide	0.1% - 0.3%

4.1 Diluents

For low to medium dose drugs the diluents are likely to make up the majority of the tablet. But diluents do more than provide bulk and some properties of commonly used diluents are discussed below.

4.1.1 Microcrystalline cellulose

Microcrystalline cellulose (MCC) is very frequently used in wet granulation, and typically these are 101 grades with median diameter of about 50 µm. In low and high shear processes, MCC allows water to be distributed evenly through the granulation and lends robustness to the process. MCC is very highly compactable and its inclusion can add strength and robustness to a tablet. Additionally, formulations containing MCC are generally relatively easy to disintegrate (when used with a superdisintegrant) leading to the potential for rapid drug dissolution. However the compactability of MCC is influenced by granulation, and factors that tend to increase the extent of granulation such as increasing amount of water, longer massing time and higher mixer speed tend to reduce the compactability of MCC. When the amount of diluent is relatively high then MCC tends to be used in conjunction with another diluent.

4.1.2 Lactose

Lactose is a very frequently used in wet granulation, and it is preferable to use milled grades of α-lactose monohydrate for this purpose. It is known that finer grades of lactose possess improves compaction properties, and the most commonly used grade is “200 mesh” in which the majority of the particles will pass a 75µm sieve. It has been reported that, perhaps not surprisingly, that anhydrous β-lactose can be transformed into α-lactose monohydrate on wet granulation [(11)].

4.1.3 Mannitol

Mannitol is used in wet granulation in milled form. The most stable form for wet granulation is the β-form, and it has been reported that δ-mannitol undergoes moisture activated transition back to the β-form on wet granulation, with an increase in surface area and improvement in compactability [(12)].

4.1.4 Dibasic calcium phosphate

Dibasic calcium phosphate (DCP), again in milled form, is a wet granulation diluent. Anhydrous dibasic calcium phosphate appears to be more stable than the dihydrate, which is transformed partially or wholly to the anhydrous form on wet granulation [14].

4.2 Binders

Binder are usually natural or synthetic water soluble polymers that may be used as solutions, but in high or low shear granulation they may also be added to the dry powder mix and granulation effected using water only. Studies on various cellulosic binders showed that their use in solution increased the proportion of coarse granules compared to dry addition by both high shear [15] and fluid bed [16] granulation.

4.2.1 Starches

Starch is the most traditional binder, but in native form it has to be gelatinised (cooked) in hot water to form a paste. However nowadays pregelatinised starch is available and a fully pregelatinised form is preferred. Starches are typically used in relatively high concentrations of about 5% of the tablet weight, or higher for partly pregelatinised starch. Various botanical sources are found in pharmacopoeia, but maize and potato based starches are the most common.

4.2.2 Cellulose derivatives

Cellulose derivatives, most commonly hydroxypropyl cellulose and hypromellose are frequently used binders. They are available in a wide variety of viscosity grades and are typically used at levels of about 1% to 3% by weight.

4.2.3 Povidone

Povidone is available in a range of viscosities ranging from K12 to K90, and again is typically used at levels of 1% to 3%.

4.3 Disintegrants

A super-disintegrant that can effectively disintegrate a tablet when used at low concentrations (typically 2% to 6% by weight) is preferred. Croscarmellose sodium, sodium starch glycolate and crospovidone are the most commonly used superdisintegrants. Partly pregelatinised starch is additionally a disintegrant as well as a binder.
Disintegrants may be added to the intragranular phase or the extragranular phase, and different published studies have shown advantages to different forms of addition. Our recommendation when using Primojel® or Primellose® is to add at least 50% of the disintegrant to the intragranular phase [17]. This is especially important when the formulation contains high quantities of insoluble materials.

4.4 Lubricants

As with all tablet formulations, magnesium stearate is the commonest lubricant.
Sodium stearyl fumarate is an effective lubricant that is not hydrophobic.
Mixtures of talc and stearic acid can also be effective.

4.5 Glidants

Since one purpose of wet granulation is to prepare a free flowing compression mix, the need for a glidant should in principle be unnecessary. However in practise colloidal silica at 0.1% to 0.3% is sometimes used.

4.6 Others

Stabilisers can be brought into close intimate contact with the drug during wet granulation. For example, stabilisation of an unnamed drug sensitive to acid catalysed hydrolysis by sodium carbonate was found to be enhanced by wet granulation compared to dry processing [18].

5 Low Dose Drugs

Wet granulation is often the first choice for low dose drugs because it is considered that granulation fixes the drug in the granule and thus eliminates segregation concerns.
As with any formulation of a low dose drug, success starts with proper control over the drug particle size, and if this is not properly controlled then no tableting process will lead to good dose uniformity. A useful chart showing the required drug particle size that gives a 99% chance of passing USP uniformity requirements has been developed as guidance to an appropriate drug particle size specification [19].
The drug can now be blended with the dry powders (either in a high shear mixer or externally) and conventionally wet granulated or it may be suspended / dissolved in the granulating liquid. When the drug is added in the granulating liquid, then both low shear and high shear mixers have been found to give good content uniformity [20].
It is possible that the distribution of drug is not uniform between different granule size fractions, and this may lead to the possibility of poor content uniformity if there is size segregation of the granules during downstream processes, such as powder conveying and discharge from tablet machine hoppers.
In general it seems that the concentration of drug in granules tends to increase as the granule size increases, when the drug is finer than the excipients [21, 22]. Thus the larger granules tend to be super-potent and the fines tend to be sub-potent. One possible solution for micronized drugs is to granulate with micronised excipients. It has been shown that granulation of micronized salicylic acid or a hormone with micronised lactose improves the distribution of drug over granule sizes compared to granulation with unmicronised lactose [23].

6 Conclusion

Wet granulation is possibly the most frequently used means of producing a compression mix for tablets, and a process that is applicable to just about any drug, but the downside is that numerous formulation and process factors and their interaction results in complex development programmes even for apparently simple formulations. Nevertheless on a practical level there are some guidelines that seem to be generally applicable:

- Granulation tends to improve powder flow and worsen compactability, therefore concentrate on developing a light, granule with sufficient flow for tableting.
- Include at least 50% of the disintegrant in the intragranular portion of the formulation.
- Consider the potential for water to adversely affect the state of the drug or an excipient. If in doubt assess fluid bed granulation, dry granulation or direct compression.
- Stabilising agents may be more effective when used wet granulation than in dry processing.
- Minimise the potential for size segregation of granules in downstream operations to avoid potential tablet inhomogeneity.

References

1. Wet Granulation: End-Point Determination and Scale-Up, Michael Levin, Ph. D. Metropolitan Computing Corporation, East Hanover, New Jersey, USA
2. Influence of drying temperature and granulation liquid viscosity on the inter- and intragranular drug migration in tray dried granules and compacts, F Kiekens, R Zelco and JP Remon, Pharm. Dev. Technol., 2000, 5 (1), 131 – 137
3. Massing in high shear wet granulation can simultaneously improve flow and deteriorate powder compaction, L Shi, Y Feng and CC Sun, Eur. J. Pharm. Sci., (2011), 43 (1-2), 50 - 56
4. Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer, SIF Badawy, MM Meening, MA Gorko and DL Gilbert, Int. J. Pharm., (2000), 198 (1) 51 – 61.
5. Role of granule size in over-granulation during high shear wet granulation, L Shi, Y Feng and CC Sun, J. Pharm. Sci., (2010), 99 (8), 3322 – 3325
6. Phase transformations of amlodipine besylate solid forms, V Koradia, AF Fontelonga de Lemos, M Alleso, H Lopez de Diego, M Ringkjobing-Elema, A Mullertz and J Rantanen, J. Pharm. Sci., (2011), 100 (7), 2896 – 2910.
7. Manipulating hydrate formation during high shear wet granulation using polymeric excipients, AD Gift, PE Luner, L Luedeman and LS Taylor, J. Pharm. Sci., (2009), 98 (12), 4670 – 4683.

8. Manipulating theophylline monohydrate formation during high shear wet granulation through improved understanding of the role of pharmaceutical excipients, H Wilkstrom, WJ Carroll, LS Taylor, Pharmaceutical Research, (2008), 25 (94), 923 – 935.
9. Solid state properties and relationship between anhydrate and monohydrate of of baclofen, S Mirza, I Myroshnyk, J Rantanen, J Aaltonen, P Harjula, E Kiljunen, J Heinamacki an J Ylirussi, J. Pharm. Sci., (2007), 96 (9), 2399 – 2408
10. Form conversion of anhydrous lactose during wet granulation and its effect on compactability, KR Shah, MA Hussein, M Hubert and SI Farag-Badawy, Int. J. Pharm, (2008), 357 (1-2), 228 - 234
11. Moisture induced polymorphic transition of Mannitol and its morphological transformation, T Yoshinari, R T Forbes, P York and Y Kawashima, Int. J. Pharm., (2002), 247(1-2), 69-77.
12. Development of low dose formulations using fluidised bed granulation, JJ Zhou and R Lipp in Formulation and Analytical development for Low Dose Oral Drug Products, J. Zheng, Wiley & Sons, (2009)
13. The relationship between bulk density and compactability of lactose granulations, K Zuurman, KA Riepma, GK Bolhuis, H Vromans, and CF Lerk, (1994), 102 (1-3), 1 – 9
14. Structural changes during the dehydration of dicalcium phosphate dihydrate, M Landin, RC Rowe and P York, Eur. J. Pharm. Sci., (1994), 2(3), 245 – 252
15. Effect of several cellulosic binders on particle size distribution of granules prepared by a high speed mixer, H Kokubo, S Nakamura and H Sunada, Chem. Pharm. Bull., (1993), 41 (12), 2151 – 2155
16. Effect of several cellulosic binders on particle size distribution of granules in fluidised bed granulation, H Kokubo, S Nakamura and H Sunada, Chem. Pharm. Bull., (1995), 43 (8), 1402 – 1406
17. DFE Pharma technical paper: Primojel® and Primellose® in wet granulation
18. Effect of processing and formulation variables on the stability of a salt of a weakly basic drug candidate, S.Badawi, R Vickery, K Shah, M Hussain, Pharm. Dev. Tech., (2004), 9 (3), 239 – 245.
19. Particle Size Limits to Meet USP Content Uniformity Criteria for Tablets and Capsules, BR Rohrs, GE Amidon, RH Meury, PJ Secreast, HM King and CJ Skoug, J. Pharm. Sci., (2006), 95 (5), 1049 - 1059
20. Comparison of low shear, high shear and fluid bed granulation during low dose tablet process development, DS Hausman, (2004), Drug Dev. Ind. Pharm., 30(3), 259 – 266)
21. Effect of particle size of drug and diluent on drug distribution in granule size fractions, H Egermann and W Reiss, Acta Pharm. Technol., (1988), 34, 5S.
22. Experimental and modelistic approach to explain granule inhomogeneity through preferential growth, K van den Dries and H Vromans, Eur. J. Pharm. Sci., (2003), 20, 409 - 417
23. Effects of high shear granulation on granulate homogeneity, H Vromans, HGM Poels-Janssen and H Egermann, Pharm. Dev. Technol., (1999), 4(3), 297 - 303

DFE pharma

Head Office
Klever Strasse 187
P.O. Box 20 21 20
47568 Goch, Germany
T. +49 2823 9288 770
F. +49 2823 9288 7799
pharma@dfepharma.com

www.dfepharma.com

DFE Pharma (#code/month year)