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TABLET MANUFACTURING BY GRANULATION METHOD AND COMMON PROBLEMS IN TABLET MANUFACTURING

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ABSTRACT

In the direct compression method of tablet production, dry ingredients are thoroughly mixed and then compressed into tablets. This eliminates the drying steps associated with the wet granulation method. It also reduces the higher costs involved in wet granulation including increased equipment, labor, time, process validation and energy-expenditure. The tableting mixture prepared by three techniques Wet granulation, Dry granulation or direct compression.

KEYWORDS: Direct Compression, Wet Granulation, Dry Granulation, Stability.

INTRODUCTION

As a result, direct compression is both efficient and economical, well suited to the production of high quality tablets, which exhibit hardness, low friability and excellent dissolution rates. As an added benefit, direct compression can improve the physical and chemical stability of tablets as compared to wet granulation (Bolhius and Lerk, 1973).

Direct compression demands the use of excipients with strictly defined properties. Kerry has designed a range of excipients specifically to meet the requirements of the direct compaction process.

The tableting mixture prepared by three techniques Wet granulation, Dry granulation or direct compression. But the invention of direct compression had increased the production of tablets enormously all over the world due to its advantages over the other two techniques.

Drugs with minute doses(potent drugs) as well as drugs with large doses are not suitable for direct compression due to segregation problems and large tablet size respectively.

In general direct compression method involves the direct compaction of tableting mixture without the step of granulation, provided the tableting mixture should have enough flow properties and should form a robust tablet. For suppose, if the tableting mixture is not having good flow properties, we can either use direct compression vehicles(DCV) for improving the flow and compatibility of tableting mixture or by subjecting the mixture for granulation process(wet or dry granulation).

1. Methods for tablet preparation[1]

2.1 Granulation Method

a. Wet granulation

b. Dry granulation.

2.2. Direct compression method.

3. Steps involved in preparation methods[2-3]

Wet granulation	Dry granulation	Direct compression
Blending	Blending	Blending
Wet massing and screening	Slugging/roller compaction	__
Drying	__	__
Dry screening	Screening	__
Blending(with lubricant)	Blending(with lubricant)	Blending(with lubricant)
Compaction	Compaction	Compaction

TABLE NO.1

This method involves simple blending of active pharmaceutical ingredient (API) with other ingredients and direct compaction of their mixture.

2. Advantages of Direct compression[2]

a. Cost Effectiveness

The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets.

b. Stability

Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients. Changes in Dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.

c. Faster Dissolution

Disintegration or dissolution is the rate limiting step in absorption in case of tablets with poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution.

d. Less wears & tears of punches

The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less.

e. Other advantages

As ingredients are processed for a shorter period of time, the chance for contamination is low. Due to fewer unit operations, the validation and documentation requirements are reduced and will become easier. Due to the absence of water in granulation, chance of microbial growth is minimal in case of tablets prepared by direct compression.

3. Limitations of Direct compression[3-4]

a. Segregation

Direct compression is more prone to segregation due to the difference in density of the API and excipients. The dry state of the materials during mixing may induce static charges and lead to segregation. This may lead to the problems like weight variation and content no uniformity.

b. Cost

Directly compressible excipients are the speciality products produced by spray drying, fluid bed drying, roller drying or co-crystallization. Hence, he products are relatively costly than the respective raw materials.

c. Low dilution potential

Most of the directly compressible materials can accommodate only 30-40% of the poorly compressible active ingredients like acetaminophen that means the weight of the final tablet to deliver the 500 mg of acetaminophen would be more than 1300mg.The large tablets may create difficulty in swallowing.

d. Lubricant sensitivity

Lubricants have more adverse effect on the filler, which exhibit almost no fracture or shear on compression (e.g. starch 1500).The softening effects as well as the hydrophobic effect of alkaline stearate can be controlled by optimising the length of blending time to as little as2-5 min.

e. Variation in functionality

There is a lack of awareness in some situations that the Excipient behave differently, depending upon the manufacturer so much so that substitution from one source to that of another is not possible. Hence, there is a need for greater quality control in purchasing ofraw materialsto assures batch uniformity.

4. Formulation[5]

General formula for direct compression includes the following ingredients-

6.1Binder-Filler (DC-vehicles)

These DC vehicles (either binders or fillers) play an important role as that of API in this method. In general, the terms binder and filler are always confusingly used in direct compression. But, the major difference between these two is their Dilution capacities. (Dilution capacity is the maximum proportion of the API that can be compacted into an acceptable compact by the binder or filler.)

Binders have high dilution capacity as these are more compactable where fillers have less dilution capacity due to their less compatibility nature. But, these values vary depending upon the compacting ability of the API used.

Table No.2.

API
DC-binder
DC- filler
Disintegrant
Lubricant
Others.

In general, dilution capacity values of binders and fillers are determined by using some reference materials which are difficult to compact. E.g.: ascorbic acid.

Based upon the solubility and disintegration properties of the Binders, these can be classified as-

1. Soluble Binders

These are always non-disintegrating. Some of the examples are Sugars, Ploy hydric alcohols etc.

2. Insoluble Binders

These insoluble binders are again of two types-

A).Disintegrating (MCC, starch etc.)

b).Non-disintegrating (DCP)

When we use soluble filler, there will be rapid release of API from the tablet, but the problem is that soluble erosion and release profile dominates the disintegration and release profile. (We observed faster release patterns in case of MCC tablets when compared with similar formula where lactose is used instead of MCC).

Factors influencing the selection of optimum DC-vehicle[2-4]

1. Properties of Powders. (Particle size, shape, density, solubility)
2. Properties of compacts. (Flow, compatibility)
3. Stability factors. (Temperature and moisture effects)
4. Others. (Cost, availability etc.)

6.2. Disintegrants

In general, we use less concentration of disintegrantsin DC method when compared with the wet granulation method which is nothing but super disintegrants. This can be explained by following reasons-

To minimize the softening and flow properties of the tablet mixture. The required uniform particle size of API upon disintegration can be achieved only if the disintegrants used is uniformly distributed in the tablet, which may be difficult when high loadings of API are used. Also when we use soluble fillers,erosion followed by dissolution occurs instead of

disintegration, which can be avoided if we use more concentration of disintegrants or super disintegrants.

Some of the examples of super disintegrants are sodium starch glycolate, crosspovidone, Croscarmellose etc. Though starch is not a super disintegrants, we use it in DC because it can also be used as DC filler.

6.3. Lubricants

We prefer hydrophilic lubricants over the hydrophobic ones in case of DC method. This is because, hydrophobic ones (magnesium stearate)may form a film around other ingredients used in the formula which may results in the decrease of tablet hardness. This problem can be overcome by following by–

a. Blending the tableting mixture (excluding lubricant) by high shear mixtures and then adding the lubricant to this main blend with low shear mixing.

b. By carefully controlling the particle size and surface area of the lubricant used.

c. Use of hydrophilic lubricants such as stearic acid, stearyl fumerate, hydrogenated vegetable oils etc.

Some works showed that ejection force, hardness, disintegration and dissolution times of MCC and lactose tablets were adversely effected depending upon the lubricant mix time. Also the type of blender used effects the crushing strength of the tablets. For example, crushing strength is much decreased for large industrial mixers compared with small laboratory blenders when same concentration of lubricant is used in both cases.

5. General requirements for Direct compression Vehicles[4-6]

In order to perform direct compression without any problems, we need to consider certain parameters which are to be maintained in optimum range and are as follows.

7.1. Compatibility

In general, a good conventional tablet must have enough hardness to withstand various stages of stress and must disintegrate and dissolve in almost 60 minutes. So for the tablet to have enough hardness, it should have enough compaction properties. If the API dose is low, then required computability can be achieved by using DC-filler.

But if the API loadings are high with poor compaction profile, then we must use a DC-binder to achieve a strong compact. (MCC is the best DC-binder but can’t be used in case of low

levels of insoluble API because the drug may get encased in the MCC aggregates formed upon disintegration and the dissolution may become slower. In this case we can use a soluble filler (Lactose) with a superdisintegrants.)

When we use more than one compactable agent(binders) then we can expect both additive(MCC and lactose) and antagonistic effects.(cellulose or starch with fast dissolving sugars like dextrose, sucrose and the result is poorer compatibility with long disintegration times).Also, as the crystal properties of tableting mixture increase, its compatibility decreases. So, pure crystals are generally inferior in terms of compatibility.

So, by increasing the amorphous nature either by spray drying or co-crystallization we can improve the compatibility.

Eg: Spray drying of lactose results in small alpha monohydrate crystals that are held together by amorphous glass. These agglomerates are superior to normal crystals in terms of flow and compactability.Also, spraydrying of acid hydrolyzate of cellulose (MCC), agglomeration of starch and partially hydrolysed starch, Co-crystallization of sucrose with modified dextrin's.

7.2. Flow properties[5]

"No flow, no tablets." It is required in each and every step of tablet preparation. Poor flow may result in difficulties for the compression mix to flow from hopper to the die cavity which may cause weight variation problems. Granulation step increases the flow in case of wet granulation method but in case of DC we must use DC grade excipients for better flow. Proper flow can be attained by using Glidiants at levels of 0.1-0.2%. Also if the flow exceeds the optimum range, it may results in segregation of tablet ingredients, this will leads to content uniformity problems.

6. Preparation of DC-vehicles[5-6]

As we have already discussed that DC excipients are speciality products prepared by modification of normal ingredients, these modification can be done in two ways.

a. Chemical modification

Ethyl cellulose, Methyl cellulose, HPMC, Na-CMC, Cyclodextrins etc.

b. Physical modification

Dextrates or compressible sugars, sorbitol, DCPetc.

c. Spray drying

MCC, Emdex, Spray dried Lactose etc.

d. Crystallization

Dipac etc.

e. Granulation

Tablet (granulated lactose) etc.

f. Co-processing

Cellactose: MCC, Lactose.

Ludipress: Lactose, PVP, Crosspovidone.

Starlac: Lactose, Maize starch.

Celocol: MCC, Calcium phosphate.

Prosolv: MCC, Colloidal Silica.

Di-Pac: Sucrose, modified dextrins.

Xylitab: Xylitol, Na CMC.

Pharmatose: Anhydrous lactose, lactitol.

Avicel CE 15: MCC, Guar Gum.

Advantose FS 95: Fructose, starch.

Barcoft CS 90: Calciumcarbonate, Starch.

Plasmon S-630: Vinyl acetate, vinylpyrrolidone.

CarbofarmaG10: Calcium Carbonate.

Carbofarma G11: Maltodextrins.

Some other examples for DCVs includes Avicel(pH-101, 102), Cab-O-Sil,Explotab, Emcocel, Ac-bi-Soletc.

7. Examples of drugs suitable for Direct compression

Aspirin, Caffeine, Acetaminophen, Propoxyphen,napsylate, Ascorbic acid, Sodiumascorbate, Thymine HCl, Pyridoxine HCl, Pyrillamine maleate, Sodium chloride, Calcium lactate, Doxylamine lactate, AmytriptyllineHCl,Quinidine HCl, Chlorpromazine.

Excipient choice: Standard tablets[8-9]

- **MCC**
  - Pharmacel® 102 : MCC that compacts more effectively and therefore the ideal choice for direct compression
- **Starch**

- SolaniAmylum: Purified potato starch
- Super Starch® 200: Party pregelatinised maize starch

- **Lactose**

- Lacto press® Spray Dried 250:
- Super Tab® 11SD:
- Lacto press® Spray Dried:
- Super Tab® 14SD:
- Lacto press® Granulated:
- Super Tab® 30GR:
- Super Tab® 24AN:
- Lacto press® Anhydrous 250:
- Super Tab® 21AN:
- Lacto press® Anhydrous:
- Lacto press® Anhydrous Crystals:
- Lacto press® Anhydrous Powder:
- Lacto press® Anhydrous Fine Powder:
- Lacto press® Anhydrous Micro fine:
- Super Tab® 22AN:

- **Superdisintegrants**

- Primojel®: Sodium starch glycolate
- Prime lose®: Croscarmellose sodium

8. Excipient choice: Orally disintegrating tablets[10-12]

- **MCC**

- Pharmacel® 101: MCC specifically developed as a key component for wet granulation and dry granulation formulations

- **Lactose**

- Lacto press® Granulated:
- Super Tab® 30GR:
- Super Tab® 24AN:

- **Superdisintegrants**

- Prime lose®: Croscarmellose sodium

9. CONCLUSION

As discussed earlier, the major challenge for tablet manufacturing comes from the powder flow properties and compressible characteristics of the materials to be compressed. This in turn poses a challenge in achieving greater productivity and better quality product especially on the new generation high-speed machines. The conventional method of wet granulation has inherent drawbacks in terms of achieving batch-to-batch reproducibility and higher productivity, especially in low particle size range. Compared to wet granulation, direct compression requires fewer processing steps, offers simplified validation and results in product with better stability. Hence, direct compression technique overrules the problems associated with wet granulation technique. But, there are also some problems associated with direct compression technique in case of drugs with poor flow, low compaction properties, segregation problems, high cost etc. and these can be over comed by the use of DCVs as a problem solver.

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