A REVIEW: OVERALL INSIGHTS OF NOVEL MOISTURE ACTIVATED DRY GRANULATION TECHNOLOGY

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ABSTRACT

Granulation is the most important step in tablet formulation when dealing with substances which are sensitive to moisture. The essential move depends on the success of the formulation. The present study focuses on the use of adapted granulation technology (GT), involving the use of least moisture while creating stable granules; the moisture activated dry granulation technique (MADG).).The technology overcomes problem of degradation of substances by water since it employs use of negligible amount of water (as moisture). The current article deals with in depth basic information about granule growth mechanisms during granulation and effectiveness over wet conventional wet granulation. Moisture Activated Dry Granulation (MADG) was created in response to the difficulties of endpoint, drying, and milling encountered with wet granulation. It also overcomes the problem of showing undesirable bimodal distribution in relation to having either too many fines or too many (or both) coarse particles in the granulation process.

Key word: Granulation, Moisture activated dry granulation, Reasons of MADG , Process of MADG.

INTRODUCTION

oral solid dosage forms are most widely used by the pharmaceutical manufacturers, physicians and patients due to the convenience in manufacturing, administration and suitability for delivery of most of the active ingredients. Tablets are manufactured by different methods such as wet granulation, dry granulation and direct compression. Granulation is defined as the size enlargement process in which fine and smaller particles are aggregated to form

strong and stable particles called granules. Present article mainly focuses on advanced granulation techniques such as moisture activated dry granulation, thermal adhesion granulation, foam binder granulation.[1]

Granulation:

Granulation is characterized as any mechanism through which small particles are accumulated into larger, permanent masses[2]. Granulation is a method of particle design in which small particles are assembled to form mechanically strong agglomerates. Granulation is a method in which primary particles of powder are made to bind to form larger, multi-particle structures called granules.. Pharmaceutical granules usually vary in size from 0.2 to 4.0 mm, based on their actual application. Upon granulation, the granules are either compressed (when used as a treatment form) or combined with other excipients before compaction of the tablet or capsule filling.[3]

Reasons for Granulation

- Improve flow
- Densify materials
- Enhance content uniformity
- Improve compression characteristics
- Control the rate of drug release
- Facilitate metering or volume dispensing
- Remove dust generation and reduce employee exposure to drug product
- Enhance tablet appearance

Aspect of formulation using granulation

Granulation was achieved for improving flow and compression characteristics, improving material uniformity, minimizing segregation, encouraging metering or volumetric dispensing, controlling / manipulating release velocity, removing production of excessive amounts of fine particles thereby raising bulk density of the substance, decreasing dust generation thereby reducing employee exposure to the drug, Reducing the output of dust while decreasing the sensitivity of workers to the commodity and increasing yield and efficiency, decreasing down time.[4]

Types of granulation:

[a] Wet granulation

This is the most commonly employed method of agglomeration within the pharmaceutical industry. This method includes combining the material with the liquid granulating, the wet scale and the drying. [5-9]

Important steps involved in the wet granulation

a. Mixing of the drug(s) and excipients

b. Preparation of binder solution

c. Mixing of binder solution with powder mixture to form wet mass.

d. Drying of moist granules

e. Mixing of screened granules with disintegrant, glidant, and lubricant.

Advantages:

a. Permits mechanical handling of powders without loss of quality of blend.

b. The flow properties of powder are improved by increasing particle size and sphericity.

c. Increases and improves the uniformity of powder density.

d. Improves cohesion during and after compaction.

e. Air entrapment is reduced.

f. Reduces the level of dust and cross contamination.

g. Allows for the addition of a liquid phase to powders.

h. The hydrophobic surfaces are made hydrophilic.

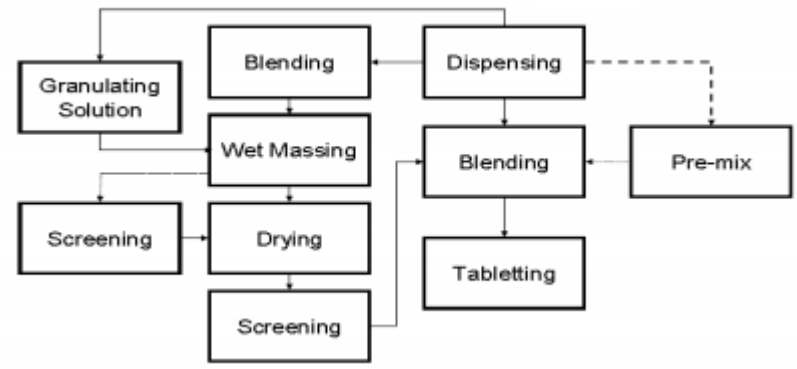

Figure 1: Flow chart for wet granulation process

Limitation of wet granulation

a. The main downside of wet granulation is their price. It's a expensive method because of the demands of labour, money, machinery, electricity and resources.

b. Loss of content at various manufacturing phases.

c. Stability may be a big problem for medications which are prone to moisture or thermo-labile.

d. Different production stages bring uncertainty, which hinder confirmation which control.

e. An intrinsic disadvantage of wet granulation is the aggravation of some incompatibility with components of the formulations.

[B] Dry granulation:

In dry granulation process the compression of the powder is without the use of heat and solvent. Of all granulation processes, it's the most attractive. The two basic steps are the compact forming of material by compression, and then the compact milling to extract the granules. [5-9]

Advantages

The main advantages of dry granulation

1. For moisture sensitive material
2. For heat sensitive material
3. Enhance disintegration owing to the fact that powder particles are not bound together by binder.

Disadvantages:

1. It requires a specialized heavy duty tablet press to form slug.
2. To form slug a customized heavy duty tablet press required.
3. This does not allow for a consistent distribution of color that can be achieved by wet granulation where the pigment can be integrated into the liquid binder.
4. The process appears to produce more dust than wet granulation and the potential for contamination increases.

Recent advancement in granulation

Novel Granulation Techniques [10]

(i) Moisture activated dry granulation

(ii) Thermal adhesion granulation

(iii) Pneumatic dry granulation

(iv) Melt / thermoplastic granulation

(v) Fluidized bed granulation

(vi) Extrusion-spheronization granulation

(vii) Spray drying granulation

(viii) Freeze granulation

(ix) Foam binder granulation

(x) Steam granulation

Needs of using novel granulation technology

Increasing regulatory enforcement aimed at increasing product quality resulted in process validation of each unit service, increased product production, decreased product efficiency, reduced labor and energy costs; had revolutionized the GT since its launch, contributing to the emergence of Novel granulation technologies.[4]

(i) Moisture activated dry granulation (MADG):

MADG technology is commonly utilized in the granulation of active pharmaceutical ingredients which are sensitive to moisture. This technique requires the use of very limited granulating fluid to enable the forming of granules and

also removes the drying measures by using moisture-absorbing materials such as microcrystalline cellulose (MCC) potato starch, a mixture of MCC and potato starch (50% w/w), silicon dioxide, Spress® B818 Pregelatinized Corn Starch NF, Maltrin® maltodextrins, to eliminate excess moisture in granulate.[10,11,12]

(ii) Thermal adhesion granulation:

It implies granulation of the mixture by introducing very little water or solvent. The binder is first moisturized by spraying water or ethanol in this process, and then this mixture is shifted to a pre-warm glass bottle and sealed. It is then adequately heated by an infrared lamp to increase the vessel's surface temperature to 90°C-105°C for water and 70°C-90°C for ethanol, and then mixed for 3-20 minutes under tumble rotating before the granules are formed.. Thermal adhesion granulation process is done by subjecting a mixture of excipients to heating under low moisture or low pharmaceutically suitable solvent content. Compared to traditional wet granulation technique this process requires less water or solvent.[13-18]

(iii) Pneumatic dry granulation:

Pneumatic dry granulation is a novel granulation technique in which traditional roller compaction process is implemented with corresponding milling and fractionation of milled materials to compressed materials at very low compaction power. A newly innovated fractioning tool is used to separate the granules and recycle the discarded fraction. Pneumatic dry granulation is suitable for automated or semi-automatic granulate processing.[13-18]

(iv) Melt agglomeration/thermoplastic granulation:

Melt agglomeration is the process used to produce controlled release reservoir systems composed of copolymer polyethylene vinyl acetate. For this process granulation is accomplished by the use of a meltable binder that is in solid condition at room temperature and melts as a binding liquid in the temperature range of 50°C-80°C. This employs two methods: spray on method: spray the molten binder onto the powder and merely cool the liquid at room temperature accompanied by friction to extract dried granules.Insitu melt granulation method: It employs a solid binder which is heated above its melting point by hot air, when it is processed in fluidized bed processor. During the melt agglomeration phase strong fine particles in the form of melted binding material are bound together into agglomerates through friction, kneading, and layering. The molten binding material cools down to receive dry agglomerates. There is a gradual changes in the size and shape of the agglomerates through the agglomeration cycle. Melt agglomeration is achieved by using equipments such as rotating drums or pans, fluid-bed granulators, low-shear mixers such as Z-blade, planetary mixers and high shear mixer granulators.[13-18]

(v) Fluidized bed granulation:

Fluidized bed processing is an air suspension procedure that sprays binder solution onto the fluidized powder bed to produce finer, free flowing and homogeneous granules. This fluidized bed processor includes air handling unit, air dispenser, spay nozzle, disengagement area, process filters, exhaust blower / fan, control panel, and solution delivery systems.[10,11]

(vi) Extrusion-spheronization granulation:

The main aim of extrusion spheronization is to produce uniformly sized granules or pellets with high drug load capacity. It is a multi-step process of wet mass extrusion followed by spheronization to produce uniform spherical particles with distribution of narrow sizes. Extrusion spheronization is mainly used for the oral controlled drug delivery system of multiparticulates. The granules are collected using speronizer by extruding the tacky mass by means of the extruder and eventual spheronisation. Liquid agglomeration technique includes extrusion of the powder mixture's liquid agglomerate (tacky mass) with an extruder. Hot melt agglomeration technique involves extrusion of thermoplastic content through an extruder powered by thermostatics. It is more labor intensive than other method of granulation, but it is useful when desiring uniform spherical shape, uniform size, excellent flow properties, high strength, low friability and smooth granulate surface.[10,11,15]

(vii) Spray drying granulation:

In this method dry granular product is obtained by feeding into the drying system an active agent solution along with excipients, where the feed is atomized and dried with a heated gas stream followed by the separation of granular product from the gas stream. Particulate agglomeration is achieved by spraying the binder solution onto the fluidized powder bed, followed by hot air drying. Dried granulation spray enhances the flow and distribution of drugs, colors, etc., and requires less lubricant than a wet massed product. Spray drying results in dense binder layer at the granular material layer, providing the strong tablets.[13-18]

(viii) Freeze granulation Technology:

It requires preservation of homogeneity from suspension to dry granules The drops (granules) are immediately frozen by spraying a powder suspension into liquid nitrogen. In a subsequent freeze-drying process the granules are dried by ice sublimation without any isolation consequences, as in the case of traditional air drying. The result is spherical, free flowing granules with outstanding homogeneity. FG provides optimized condition for the subsequent processing of the granules, for example easy crushing to homogeneous and dense powder compacts in a pressing operation. High degree of compact homogeneity will then support the following sintering with minimal risks for granule defects.[19]

(ix) Foam binder granulation:

This technology greatly enhances binder delivery in the formulation mix and provides a notable range of manufacturing benefits Compared to conventional spray processing, foamed binder technology can reduce processing times by reducing water requirements. This will improve reproducibility by making binder application more uniform. Additionally, it removes spray nozzles in granulation processing systems and their other variables. Foam processing also offers improved end-point determinations and shortened clean-up time for the equipment. Although the processing of foamed binder provides many advantages this technology does not require new equipment or drastic processing techniques adjustments.[14-19]

(x) Steam granulation:

It is an easy modification of traditional wet granulation method where steam is used instead of water as binder. Steam is injected with fluidized particles to be granulated into the bed.. Steam Granulation Steam granulation technology concept involves the injection of steam into the fluidized bed processor located in the hermetically airtight and thermo-stated condition through one or more jets. Wrapping and jacketing. jet of steam in a gas jet that prevents premature condensation of the steam jet into droplets thereby preventing lump formation of particles in the fluidized bed processor (due to powder aggregation at the water droplet formation site) Alternatively gas stripping method can use. Steam and gas jets may be pumped onto the bed of fluidized particles found in the fluidized bed device, transversally and/or axially. The steam and gas jets can be pumped coaxially through concentrated nozzles that will connect to the interior of the fluidized bed processor. Choking of the nozzle may be avoided by focusing or shielding or covering the nozzles downwards, thereby inhibiting the entry of fluidized particles into the nozzles that interfere with the proper functioning of the apparatus. This technique allows the creation of granulated substance without any lumps with near particle range. Binders most commonly used for hypromellose and pregelatinized starch.[10-11]

Moisture activated dry granuation

Moisture Activated Dry Granulation (MADG) was created in response to the difficulties of endpoint, drying, and milling encountered with wet granulation. Endpoint of the wet granulation process is very sensitive to time of granulation and shear. Dry the wet granules to a limited range of moisture content which is difficult. It is important to mille the dried granules, but the milled granules also have either too many fines or too many coarse particles (or both)-an unnecessary bimodal distribution[4,20]. This technique is a variation of conventional technique for wet granulation. To activate a binder and start agglomeration it takes very little water. This method includes two phases, wet powder particle agglomeration, and absorption or distribution of the moisture. Agglomeration is promoted by adding a small amount of water to the mixture of drug, binder and other excipients, typically less than 5 percent (preferably 1-4 percent)[21]. Agglomeration occurs when the granulating fluid (water) activates the binder. After the agglomeration is completed, content that absorbs moisture, such as microcrystalline cellulose, silicon dioxide, etc., is introduced to promote the absorption of excess moisture. The moisture absorbents remove the moisture from the agglomerates, contributing to the redistribution of moisture within the powder mixture, resulting in a relatively dry granule mix. Some of the agglomerates remain intact in size without change during this moisture redistribution process, while some larger agglomerates can break, leading to a more uniform distribution of particle size. It does not involve an expensive drying .[22]

The method does not result in the creation of larger lumps, as the volume of water used is very small compared with the normal wet granulation. The particle size of the agglomerates is primarily in the range of 150-500 microns. Often known as the "moist granulation technique" this approach tends to confusion in the use of appropriate terminology. Some authors assume that dry granulation requires the use of a roller compaction or a slugging step to obtain granules, followed by milling. However, any of those steps was not used in this technique. Furthermore, because this technique utilizes a limited amount of water, it would be inappropriate to use the word "dry granulation." The

authors therefore conclude that a suitable word for this technique should be "moist granulation." In any case, the technique is the same and this study uses the "Moisture-Activated Dry Granulation (MADG)" terminology coined in 1987 by the inventors of that technique. The application of MADG to types of dosage for immediate release and controlled release demonstrated the advantages of wet granulation, such as increased particle size, improved flow and compressibility. Additional benefits of this technique include broad applicability, time efficiency and less energy consumption, and the application of few process variables with continuous process suitability. However, because of the stability and processing problems associated with these types of drugs, this technique may not be used for the preparation of granules that involve high drug load and for moisture-sensitive drugs and hygroscopic drugs. A high-shear mixer coupled with a sprayer would be a suitable MADG-process equipment. To allow good mass movement and proper mixing of the granulation material, an ideal machine should be fitted with effective impellers, blades, and choppers.[21-23]

Comparison of MADG with Conventional wet granulation

The process for the formation of granules in MADG is similar to traditional wet granulation. In both cases, by means of wet massing and kneading, this is a method of powder particle size enlargement, often in the presence of water and binders. The key differences between the two are the amount of granulating material used and the agglomeration level achieved. Considerably more water is used in traditional wet granulation to produce larger and wetter granules. It is accompanied by heat-drying to eliminate the excess water and milling to reduce the granule size.[4]

In MADG, only a small amount of water is used to produce agglomeration, followed by distribution and absorption of moisture. Neither drying heat nor friction is required. As the quantity of water used in MADG is low (usually just 1–4 percent of the entire formulation), it is crucial that the water is delivered accurately and distributed uniformly during the agglomeration step, making it very crucial to choose a spray system that delivers accurate application and a well-defined spray pattern. A high-shear granulator is more suitable for the MADG method in terms of equipment and an ideal system should have effective impellers / blades and choppers to allow for good mass movement and proper mixing.[23]

This should also require spraying of water only on the powder bed, not on the blades, choppers or granulator walls. The blades and bowl design should also be such that "wet pockets" or "dead spots" are not permitted to persist after the moisture distribution or absorption stage which would then require additional sizing and shifting of the granulation. MADG is a process that is quick, economical, clean and stable, creating granulation with very good physical properties and finished products with satisfactory quality attributes. It applies to many of the granulation needs of the pharmaceutical industry for the production of solid dosage form and can also be defined as a 'one-pot' granulation process which helps minimize sensitivity to endpoints[20,24].

In addition, the pharmaceutical industry is still widely used because of the requisite excipients needed for MADG so there is no conceivable regulatory risk. The MADG process makes it possible to do only that which is necessary to produce solid dosage forms with desirable quality attributes. In a sense, it is a minimalist process. [20,24]

Wet Granulation	Moisture activated dry granulation
Dispensing and Shifting	Dispensing and Shifting
Dry mixing	Dry mixing
Granulation	Granulation
Pre-drying	-
Shifting	-
Drying	-
Pre-mixing (unlubrication)	Pre-mixing (unlubrication)
Lubrication	Lubrication
Compression	Compression

Table 1: Comparison between step of MADG with Conventional Wet granulation.

Merites of MADG

1. It produces relatively small particle-size narrow granules with a good flowability. In tablet compression, the MADG-based granulations also appear to have improved compactibility and weight control.[4,25]
2. It eliminates the potential for segregation for two main reasons. First, in most cases, the agglomeration stage represents 70–90 per cent of the entire formulation. Second, in the moisture-absorption stage, the excipients also have a particle size close to that of the agglomerates.[4,25]
3. The MADG method is also suitable for scale-up with little to no risk. A large batch, for example, usually results in a uniform distribution of water which is desirable and beneficial.[4,25]
4. The minimalist aspect of the process is manifest in the fact that the process involves few pieces of equipment and manufacturing steps. The net processing time of the MADG process is short, it also provides energy savings and there are no additional requirements for drying, extra material transfer, Milling and separate blending, making it easier to apply than conventional wet or dry granulation processes to implement the FDA's Quality by Design Concepts.[4,25]
5. These advantages make the MADG process a good candidate for the implementation of the Quality by Design (QbD) concept of the US Food and Drug Administration. Since the process does not involve granulation drying or milling steps, it is a green process that has great potential for continuous process developement.[4,25]
6. The finished products produced with the MADG process have characteristics of product quality close to or better than those of the initial formulations. In short, MADG has the best Dry Mixing and Wet Granulation attributes.[4,25]

Demerits:

1. Moisture sensitive and high moisture absorbing APIs are poor candidates.[26]
2. Formulations with high drug loading are difficult to develop.[26]
3. Could be other issues with the API, with high-drug load formulations being particularly difficult to develop.[26]

Steps of MADG

The Principle of MADG process The Moisture Activated Dry Granulation involves two major stages:

1. Agglomeration
2. Moisture distribution And Absorption Stage

1. Agglomeration

At this stage, to get an uniform mixture, all or part of the drug is blended with filler(s) and an agglomerating binder. A small amount of water (1–4 per cent) is sprayed onto the powder mixture during mixing; water droplets hydrate the dry binder and produce tacky nuclei or tacky wet mass. The binder acts as the drug and excipients move in circular motion induced by the impellers or blades of the mixers. To produce moist agglomerates, dry powder particles adhere to the wet nuclei, or wet tacky mass. The resulting agglomerates are small and spherical, as in traditional wet granulation the volume of water used in the MADG process is much smaller than that. Therefore, the agglomerates can not develop into big, sticky lumps. The agglomerate particle size is typically in the range of 150–500 μm. At the agglomeration stage, it is possible to add only part of the drug to the formulation, based on the technique of drug loading. After the moist agglomerates have been established the can drug can be added. The added product particles bind to and become trapped in the wet agglomerates. The method does not create large granules that would need milling, and since very little water is used in the method, the endpoint is not susceptible to blending.[27]

Agglomerating binders for the MADG process

Upon the application of a small amount of water, the binders used in the agglomeration stage would be quickly wettable and become tacky. Previous studies indicate that polyvinylpyrrolidones (PVPs), such as PVP K-12, with low viscosity are suitable for this purpose. Binders such as hydroxypropyl cellulose (HPC), crosspovidone, maltodextrins, sodium carboxymethylcellulose (Na CMC), or hydroxypropyl methylcellulose (HPMC) can be used instead if PVP is not an acceptable choice because of formulation issues such as chemical compatibility. The binders may be used individually or in various combinations to produce the desired results or fix specific problems. When binders are available in various grades of viscosity, it is preferable to use those with low viscosity as they appear not to retard dissolution of the tablet or capsule. However, binders with very low viscosity do not have adequate tackiness for agglomeration. In general, binders with high viscosity are often needed in small amounts. The amount of binder required does not depend solely on the viscosity; consideration must be given to other factors such as binder mass. For example, if 5 percent of PVP K-12 is appropriate for one formulation, 2 percent of PVP K-30 for the same formulation may not be the correct proportion. Experiments have shown that for proper agglomeration, around 3 per cent or more of PVP K-30 will be needed. Such difference results from the fact that, besides the binder viscosity and tackiness, the binder mass also plays an significant role in the covering and coating of the agglomerated blend particles. It will also be beneficial for the binders with small particle size and large surface area. Binders like HPC, Na CMC, and HPMC typically allow more water and longer hydration time compared to PVP or maltodextrin. On the other hand, binders such as Starch 1500 will not be ideal for the MADG process, as this binder has a large percentage of unhydrolyzed starch components which could absorb considerable amounts of water. Binders like HPC, Na CMC, and HPMC typically allow more water and longer hydration time compared to PVP or

maltodextrin. On the other hand, binders such as Starch 1500 will not be ideal for the MADG process, as this binder has a large percentage of unhydrolyzed starch components which could absorb considerable amounts of water. In all cases, the binder chosen should have fine particles and sufficient tackiness to cause adequate agglomeration upon moistening. Copovidone, povidone K25 or K30 polyvinyl alcohol, block copolymer of ethylene oxide and vinyl alcohol marketed under the trade name Kollicoat IR, microcrystalline cellulose, water-soluble cellulose ethers such as hydroxypropylcellulose, hydroxylpropylmethylcellulose, starch, pregelatinised starch, microcrystalline cellulose are preferred.[26]

2. Moisture-Distribution and Absorption Stage

At this stage, as mixing continues, absorbents of moisture, such as microcrystalline cellulose or silicon dioxide are added. Once these agents come into contact with the wet agglomerates, the agglomerates absorb moisture and redistribute moisture within the mixture. Therefore the whole blend is relatively dry. Although some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact, and some can break up, typically the larger particles. This process results in a granulation with an uniform distribution of particle size. This stage completes the MADG granulation process to get sufficient lubrication. Except loading of material, the actual processing time for the MADG process is only 10–20 min. The processing time is exactly the same as it would be for a laboratory- or pilot-scale batch, even for a commercial batch. Beginning with the premixing of the process continues with the Starting with the method premixing, adding a disintegrant to the mixture continues, followed by blending for a couple of minutes. Then, during the mixing process, lubricant is applied and combined to drugs and excipients for sufficient time, the final granulation the be ready for tablet compression, encapsulation.[27]

Moisture absorbents for the MADG process

Approximately 70–95 per cent of any formulation of MADG is agglomerated and the remaining portion of excipients is added. The non-agglomerated portion is usually consisting of moisture absorbents, disintegrates, and lubricants. It is preferable for non-agglomerated excipients to be similar to the agglomerated portion of the formulation in particle-size distribution to reduce the potential for segregation. Microcrystalline cellulose is available at an average particle size of 200 μm, acting as a filler and moisture absorbent. Low moisture grade are also available. Two new excipients have been introduced to the pharmaceutical market by FMC Biopolymer: Avicel HFE-102 and Avicel PH-200 LM, based on existing excipients but developed to produce a different entity with improved benefits. Avicel PH-200 LM, based on microcrystalline cellulose (MCC), has been formulated to reduce the amount of water added to the granulation process. Avicel PH-200 LM is a step up from Avicel PH-200 of FMC Biopolymer which had a 5 percent moisture level. The new product has a level of moisture not beyond 1.5 percent and can contain around 3 to 4 times as much water from the granule. This benefit, along with enabling the use of MADG, meant that the use of Avicel PH-200 LM could reduce the additional steps of milling, drying and screening, thereby minimizing the costs of production and the resources used. As well, the process provided a larger particle size for optimum flow. That increases manufacturing process efficiencies. It takes aspects of wet granulation but removes its drawbacks. Can be useful for the use of moisture sensitive active pharmaceutical ingredients (APIs). Avicel HFE-102 is a new, proprietary dried co-spray MCC / mannitol high functionality excipient binding for direct

compression. The co-spray drying added extra benefits to the excipient as it altered its properties combining high MCC compressibility and low Mannitol lubricant sensitivity. The effect was a disintegrating tablets that were harder, less friable and fast disintegrate. Aeroperl 300, a moisture absorbent in the form of a non-lumpy, free flowing granulated silica consisting of ~30µm spherical particles is also available from Evonik Industries (Essen, Germany). It has excellent moisture-absorbing capacity, and its surface area is much lower than that of the colloidal silica used as a glidant for granulation. Generally, the amount of Aeroperl 300 needed for the MADG formulation is small, which is helpful from the point of view of preventing problems with tablet ejection. The disintegrant crospovidone is available in coarse particle size grade from either ISP (Wayne, NJ) or BASF (Ludwigshafen, Germany). Not only is this material a superdisintegrant, but it is also compact, and serves as an absorbent moisture. Overall, excipients such as Avicel PH 200 LM, Aeroperl 300, and the crospovidone coarse grade for the non-agglomerated portion of the MADG process will significantly increase formulation consistency and facilitate the process. If the required excipients are not available, regular micro-crystalline cellulose (e.g. avicel PH101, PH102, and PH200), standard silicone dioxide, and crospovidone can be used as alternatives.[24]

Spress B818 Pregelatinized Starch NF: New Excipient for Activated Moisture Dry Granulation Process This is the newest addition to the pregelatinized starch family Spress. As with all Spress products, Spress B818 has excellent flow properties and strong binding, but its lower degree of pregelatinisation is what makes this starch unique. The lower degree of pregelatinization helps the starch to maintain the properties of a pregelatinized starch such as good flow and excellent binding characteristics, but also has the advantages of the fast disintegration times seen with a typical non-pregelatinized corn starch. Using Spress B818 Pregelatinized Corn Starch NF in capsules completely prevents blocking of the gel (often seen with pregelatinized starches), which may slow down the disintegration and dissolution of the core capsule. A study comparing the disintegration times of Spress B818 Pregelatinized Corn Starch NF and regular Corn Starch NF shows that the disintegration times between the two starches do not indicate any difference. Prosolv SMCC, along with Spress B818, is also finding broad application in MADG Technique. ProSolv SMCC consists of 98 percent microcrystalline cellulose and 2 percent colloidal silicon dioxide. This blends superior flow properties with the excellent compactibility of microcrystalline cellulose.

Required equipment for MADG

MADG only requires two pieces of equipment:

1. An appropriate granulator
2. Water delivery system
3. Airless spray system
4. Granulation sizing and milling

1. Granulator

The granulator may be a planetary or high-shear granulator, but it should not be exposed to the blades at the bottom (either top or bottom driven). This is important because the amount of water used is very limited and is applied by a fine spray on top of the powder surface. If the blades were exposed the water could reach the blades and cause water

loss, causing likely wet lumps and uniform granulation. There should be no dead spots or places where material may stick to the granulator. A chopper is also useful in the granulator.[4]

2. Water delivery system

The preferred technique for consistantly distributing water spray would be an airless spray system, allowing the water to be guided onto the powder bed in a high-shear granulator. Any airless spray nozzle with a gear pump or pressure vessel where it is possible to reproduce the spray pattern and the exact volume of water delivered will be sufficient. In small experiments, spray nozzles with a 0.1 mm or 0.15 mm orifice may be connected to a syringe to deliver a low (5–10 mL) volume of water.[4]

3. Airless spray system

This process also demands an airless spray system which delivers the required amount of water precisely in small droplets (50–200 μm). The system shouldn't have drips; in particular, peristaltic pumps are not suitable. Also, the gear pump or pressure vessel must have the right type spray. But a suitable spray tip attached to a syringe is appropriate at the developmental stage.[4]

4. Granulation sizing and milling

An optimized formulation and process of MADG should not produce large lumps which require sizing or milling in the granulation. Hence, once the lubricant is mixed in with the granulation, the product can be the final blend that can be used directly for tablet compression, encapsulation, or powder filling. Sometimes small amounts of lumps in the granulation may arise during agglomeration from material buildup on the blades, choppers, walls, or the granulator bottom. In such situations, the granulation may need to be passed through a screen, such as 10 mesh or any other appropriate size. Sizing or sifting is often needed only if there are imperfections in the formulation or process.[26]

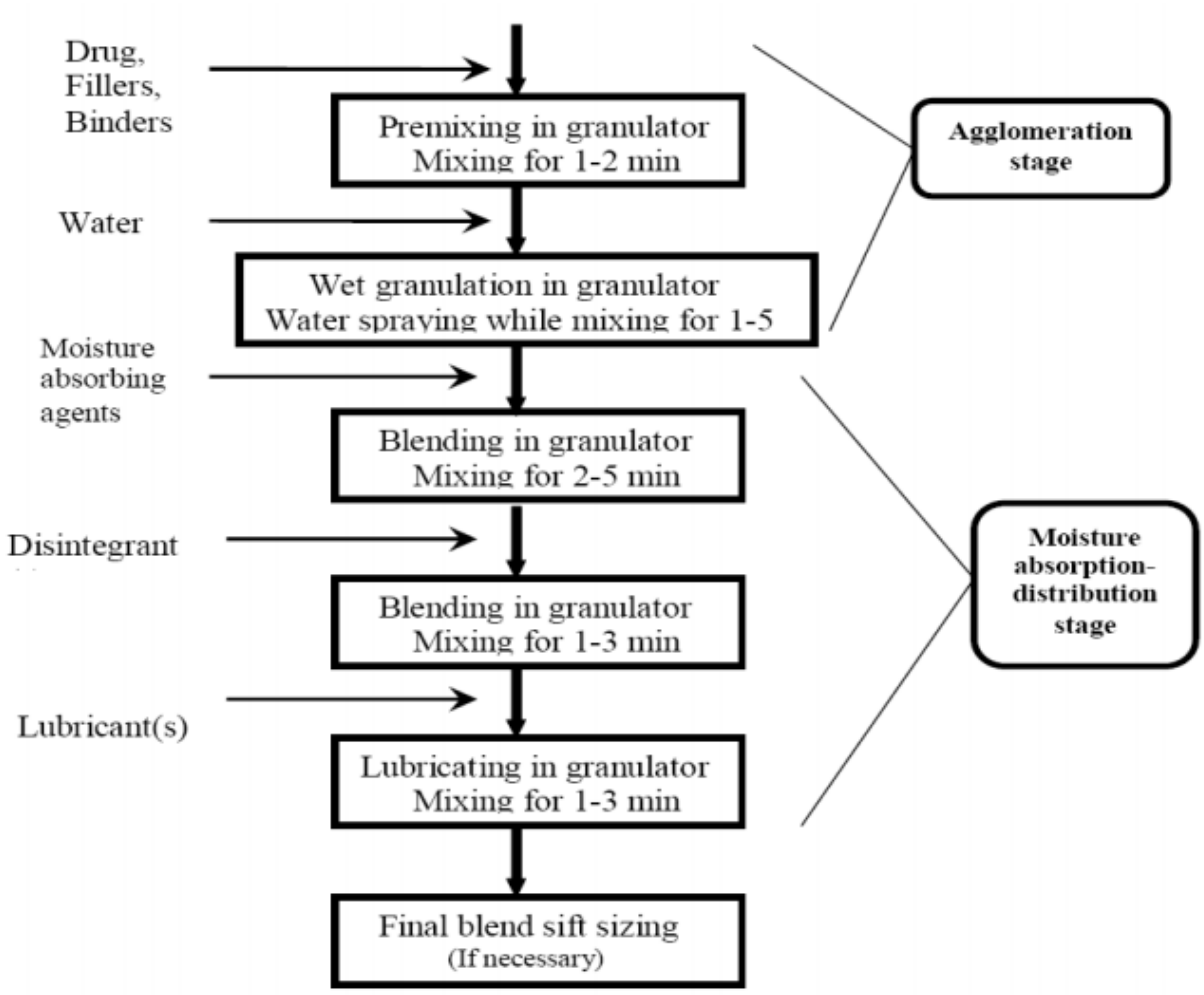

Figure 2: Process flow chart of MADG [19]

Disscussion and Conclusion:

It can be concluded from the present article that MADG is a very controllable process that can effectively yield granules with desired quality attributes and has been found to be quick, clean, lean, and robust for particle-size enlargement. It's also a cost-effective, energy-saving, renewable and efficient production process. Through following this technique tablets can be prepared in a short manufacturing period and with few essential formulations and process variables over traditional wet granulation process, it also determines the quantity of water applied during different granulation stages, which greatly affects the final product specifications. The MADG process can be used effectively to produce diversified product including the release of control and the immediate release of many drug granules, including formulations sensitive to heat and moisture. Application by pharmaceutical and other industries of the MADG technique would be a result of intrinsic conservatism and regulatory restriction, a major challenge to overcome.

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