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Updated Insight on Moisture Activated Dry Granulation: Approaches & Challenges

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ABSTRACT

Granulation becomes most critical step in formulation of tablet when it deals with moisture prone substances. The success of formulation depends on this important step. The present review focuses on use of modified granulation technology (GT), involving use of least moisture yet producing 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 along with the in-process variables that are influencing the granulation process and their respective determinations. Moisture Activated Dry Granulation (MADG) was developed in response to the difficulties experienced with wet granulation, in terms of endpoint, drying and milling. Moreover it also overcomes the problem of showing undesirable bimodal distribution associated with having either too many fines or too many coarse particles (or both) in the granulation process. Present handy note also focuses on existing and new pharmaceutical excipients that are well-suited for the MADG process, highlights the advantages and wide applicability of the MADG process in solid dosage form formulation development. An updated literature were collected from databases, studied and presented here for easy reference of scientists engaged in granule production, so that they can adopt appropriate and suitable MADG to have desired features. Present handy note will help researchers in designing a robust MADG for getting optimized granule.

INTRODUCTION

Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation process is defined as ‘‘any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified.’’ The term ‘‘granulated’’ material is derived from the Latin word ‘‘granulatum’’ meaning ‘grained’. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use [1]. In modern times, granulation technology has been widely used by a wide range of industries such as coal, mining and agrochemical. These industries employ agglomeration techniques to reduce dust, provide ease of handling and enhance the material’s ultimate utility [2].

Pharmaceutical granulation process is used for tablet and sometimes capsule dosage forms; however, in some applications the process is used to produce spherical granules for the modified release indications or to prepare granules as sprinkles to be used by pediatric patients. In some countries like Japan, having granulated product in a ‘‘sachet’’ is acceptable where a large dose of the drug product is not suitable for swallowing [3].

Changing regulatory compliances that was directed towards enhancement of product quality came up with process validation of each unit operation, increasing product output, decreasing product throughput time, reducing labour and energy cost; had revolutionized the GT, since its introduction, thereby resulting in development of novel granulation technologies [4].

Granulation Technology: A three phase system

Granulation is a particle design process that involves gathering of small particles into large masses in which the original particles can still be identified. Granulation was done for improving flow and compression characteristics, improving content uniformity, reducing segregation, facilitating metering or volumetric dispensing, controlling/manipulating release rate, eliminating generation of excessive amounts of fine particles thereby increasing bulk density of the product, decreasing dust generation thereby reducing employee exposure to the product, and resulting in improvement of yield and productivity, reduced down time, and so on [5].

GT is defined as the art and science for process and production of granules. It is the oldest and most conventional method for making granules and the components involved in this process forms a three phase system made of:

- **Dispersed solid**
- **Granulation liquid and**
- **Air** [6].

Prerequisites of an Ideal Granulation Technology

1. Must have potentiality to improve reproducibility in the product performance,
2. Must decrease variability in the process performance,
3. Must have potentiality to minimize post-approval process changes,
4. Must have potentiality to decrease cost and time, and
5. Should produce spherical granules with controlled size distribution, specific granule voidage (i.e., intragranular porosity), specific bulk density, good flowability and compact-ability, suitable structural stability and physical strength.[5]

Mechanisms of particle-particle interactions in Granulation technology

Mechanism of particle-particle interactions are to be studied appropriately that will provide an insight for the granule formation mechanism, an essential parameter for predicting not only energy requirement for the formation of granules but also its stability. Independent of the process employed, five discrete bonding mechanisms at the point of particle–particle interactions had been recognized that were enlisted as below:

1. **Solid bridges:** chemical reaction and/or sintering/heat hardening associated solid bridges were formed due to dissolution during granulation with subsequent solvent removal in the drying phase.
2. **Immobile liquids:** addition of speciality binder(s) solution in granulating solvent that softens, deforms, and adhere to particles, then hardens during drying.
3. **Mobile liquids:** liquid bridges, at higher fluid levels, which occupy void spaces thereby bonds particles.
4. **Intermolecular and long-range forces:** Vander Waals forces, electrostatic forces results in bonding of the particles.

5. **Mechanical interlocking:** Fracture and deformation due to pressure that results in shape related bonding or intertwining of long fibrous particles. [5]

Theoretical Aspects of conventional granulation technology

According to Iveson there are fundamentally only three stages of process, which determines the wet agglomeration behavior.

1. Wetting and nucleation

Wetting of the particles is necessary for nucleation, i.e. the formation of initial agglomerates.

As per Hapgood the nucleation rate is governed by following-

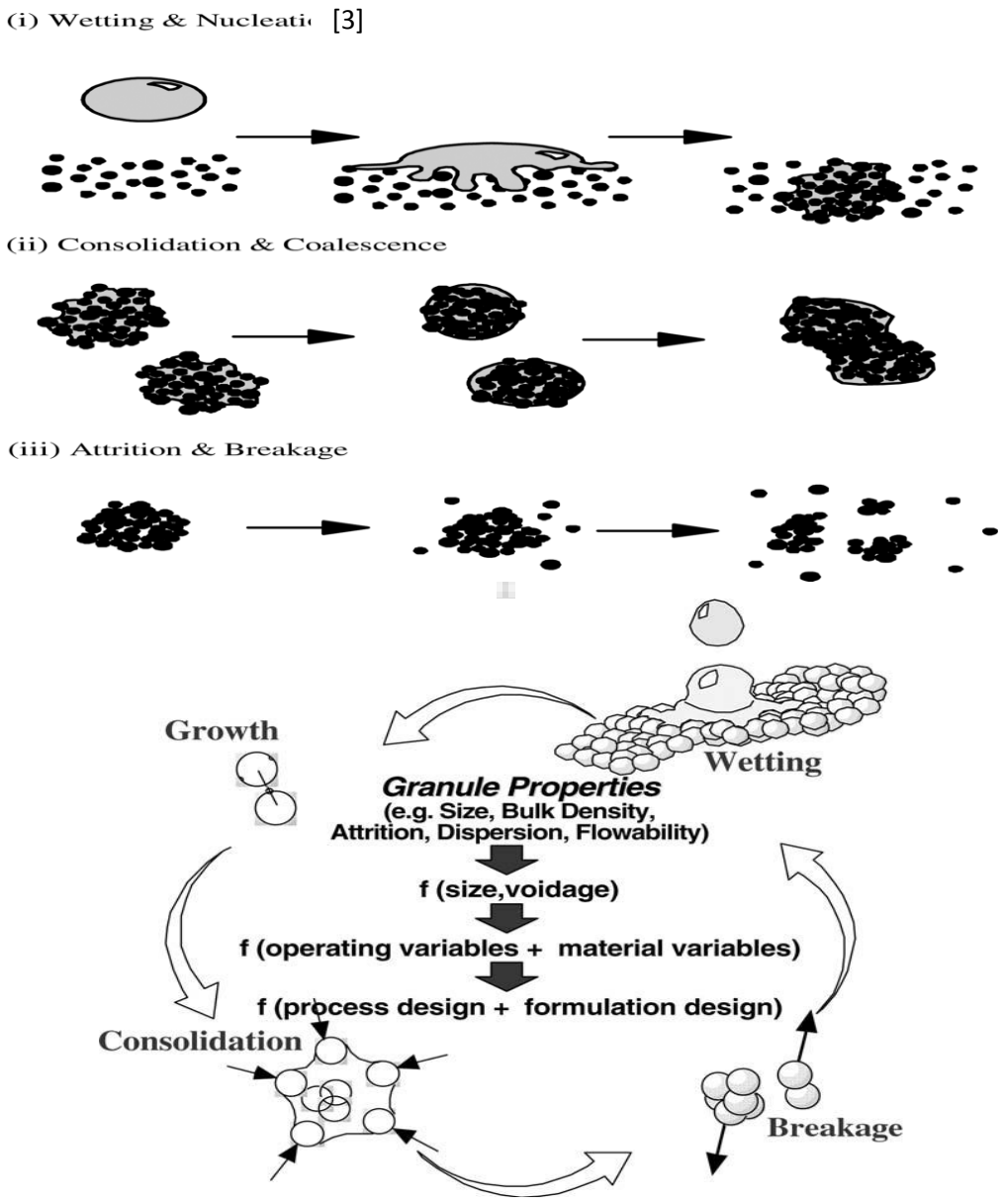
- Wetting thermodynamics
- Drop penetration kinetics and
- Binder dispersion (depends on the liquid delivery parameters and powder mixing).

2 Consolidation, growth and finally

- Droplet formation
- Droplet overlap and coalescence at the bed surface

3 Breakage and attrition

These phenomena often take place simultaneously in the granulation equipment, making the investigation of the effect of an individual phenomenon on the agglomerate properties difficult [6].



All over the world solid dosage form like tablet is prepared by either direct compression or granulation process (Dry or Wet). The choice of method for the manufacturing is dependent on a number of factors like the physical and chemical stability of the therapeutic agent during manufacturing process, the availability of the necessary processing equipment, the cost of the manufacturing process and the excipients are used to formulate the product [7].

Direct Compression

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by

wet or dry granulation procedure is required. Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression, thus offering advantage particularly in terms of speedy production, as it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability [8].

Advantages:

1. Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
2. The most important advantage of direct compression is that it is an economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipments is required, less process validation, reduced consumption of power.
3. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API.
4. Particle size uniformity.
5. Prime particle dissolution.
6. In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution [8].

Disadvantages:

Excipients Related

1. Problems in the uniform distribution of low dose drugs.
2. High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression for example, Aluminum Hydroxide, Magnesium Hydroxide.
3. The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability.
4. Many active ingredients are not compressible either in crystalline or amorphous forms [8].

Process Related

1. Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
2. In some cases require greater sophistication in blending and compression equipments.
3. Direct compression equipments are expensive [8].

B. Dry Granulation

Dry granulation involves granule formation without using liquid solution as the product may be sensitive to moisture and heat. It is the least desirable of all the methods of granulation. In this process dry powder particles may be brought together mechanically under low pressure by compression into slugs or by roller compression to obtained flakes [8]. The compacts so-formed are broken up gently to produce granules (agglomerates). Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules. At last powdered lubricants are added [7].

Advantages

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

i) For moisture sensitive material.

ii) For heat sensitive material.

iii) For improved disintegration since powder particles are not bonded together by a binder. [7]

Disadvantages

i) It requires a specialized heavy duty tablet press to form slug

ii) It does not permit uniform colour distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.

iii) The process tends to create more dust than wet granulation, increasing the potential contamination [7].

Two main dry granulation processes:

1 Slugging process

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not much important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling [8].

Factors which determine how well a material may slug

i) Compressibility or cohesiveness of the matter
ii) Compression ratio of powder
iii) Density of the powder
iv) Machine type
v) Punch and die size
vi) Slug thickness
vii) Speed of compression
viii) Pressure used to produce slug [8]

2 Roller compaction

The compaction of powder by means of pressure roll can also be accomplished by a machine called chilosonator. Unlike tablet machine, the chilosonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules [8].

C. Wet Granulation

WG technique is receiving great significance and widely used by pharmaceutical industry, because direct compression method is not the most suitable technique for many active substances that are in high dosages or in fine powder form, also the moisture content of drugs, excipients combined with the drugs to manufacture a final dosage form (i.e. compressed tablets), and/or

processing manipulations involving moisture may have a significant impact on wide range of chemical and physical properties of the finished product [4].

WG involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. The wet mass is dried & then sized to obtained granules. The added liquid binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during subsequent drying which leads to the formation of agglomerates [9]. As Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems [7]. There are few drawbacks associated with the wet granulation technique is that the process is expensive because of labor, space, time, special equipment and energy requirement, multiple processing steps involved in the process add complexity which makes validation and control difficult, loss of material during various stages of processing and not suitable for moisture sensitive and thermolabile drugs. An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated [8].

I. Hydrate formation

For example, theophylline anhydrous during high shear wet granulation transfers to theophylline monohydrate. The midpoint conversion occurs in three minutes after the binder solution is added. For online monitoring of the transformation from one form to another, Raman spectroscopy is most widely used [9].

II. Polymorphic transformation

The drying phase of wet granulation plays a vital role for conversion of one form to another. For example, glycine which exist in three polymorphs that is a, β, g . g is the most stable form and a is the metastable form. The stable Glycine polymorph (g) converts to metastable form (a) when wet granulated with microcrystalline cellulose [9].

All of the Traditional or conventional granulation processes are excellent ways to produce quality granules for tableting or capsule filling, but they require significant production time and energy, so efforts have been made to simplify processes, reduce processing time, increase efficiency, and improve drug content uniformity [7].

Ullah et al. in 1987 described a modified wet granulation process that was named as moisture activated dry granulation (MADG), where granules are formed by moisture and heat is not used for drying of granules. During this process, the generation of moist agglomerates is followed by the stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute the moisture, which results in a uniform, free-flowing and compactable granulation. In MADG process, the whole process is considerably shorter than a typical wet granulation [8].

C. Advanced Granulation Techniques

Over a period of time, due to technological advancements and in an urge to improve commercial output various newer granulation technologies have been evolved such as:

1. Steam Granulation
2. Melt/Thermoplastic Granulation
3. Moisture Activated Dry Granulation (MADG)
4. Moist Granulation Technique (MGT)
5. Thermal Adhesion Granulation Process (TAGP)
6. Foam Granulation

All are having their own applicability's and advantages and are showing superiority over each other. [8]

Moisture Activated Dry Granulation: A standard granulation approach:

Background of the Moisture Activated dry Granulation Process

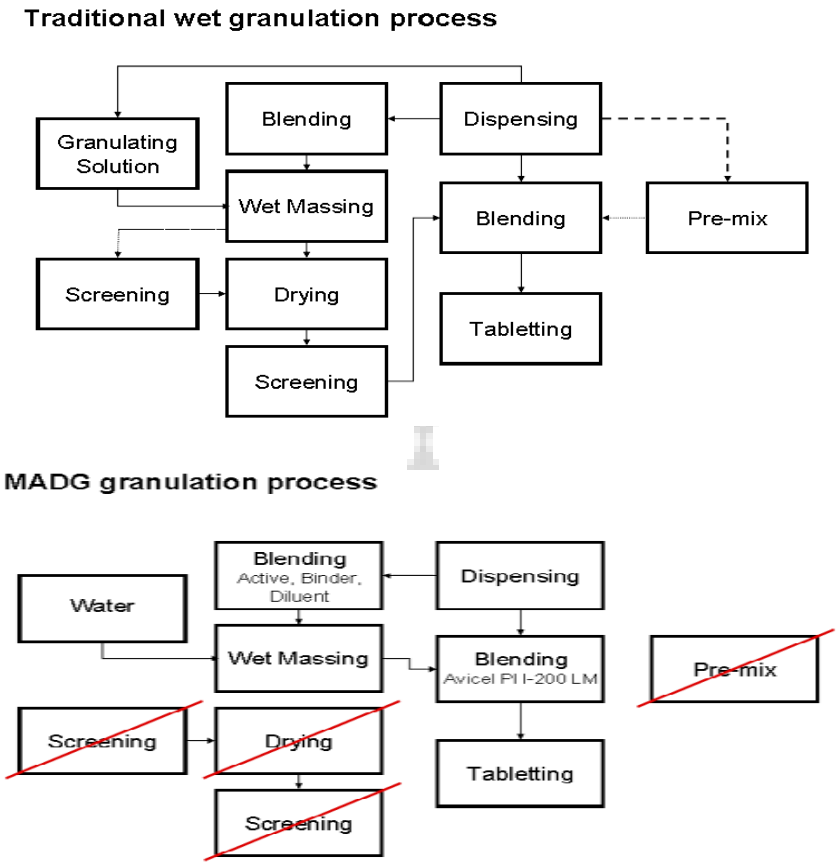
The present article relates to a moisture-activated granulation process for manufacturing pharmaceutical compositions, in particular solid dosage forms of active substances which are prone to chemical degradation and/or physical phase transitions upon contact with heat and water or aqueous liquids such as those used during conventional wet granulation processes [10].

Numerous active substances are sensitive to the heat and presence of relatively high amount of moisture. Moisture may stem from the excipients used in the formulation or from the manufacturing process, e.g. aqueous granulation, this can pose significant problems in the manufacturing of pharmaceutical formulations and dosage forms containing such active substances. So the presence of moisture or requirement of heat as processing parameter is particularly undesirable if the active substance is prone to chemical degradation and/or physical phase transitions into an undesired crystalline and/or amorphous form (polymorphism) when being in contact with water or water-containing solutions. Examples for such active substances are aliskiren, in particular aliskiren hemifumarate, ACE inhibitors selected from lisinopril, ramipril, enalapril, theophylline, valsartan, orlistat, desloratadine, solifenacin and its salts such as the maleate, malonate, hydrogen sulphate, succinate and citrate, donepezil and its salts, benzimidazole proton pump inhibitors selected from omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole and their salts such as sodium and magnesium salts, inhibitors of HGMCo reductase selected from rosuvastatin, atorvastatin and its salts, in particular atorvastatin Ca, fluvastatin and its salts, platelet aggregation inhibitors selected from clopidogrel, in particular clopidogrel salts with HCl and H_2SO_4, and prasugrel. Said active substances are in particular known to form chemical degradation products when moisture is present in the pharmaceutical formulation containing them. Another example is tadalafil, a phosphodiesterase type 5 (PDE5) inhibitor [10].

Other active substances such as theophylline, pantoprazole, aliskiren and others are in particularly known to undergo physical transformation into undesired crystalline and/or amorphous forms in the course of manufacturing processes including steps wherein the active substance is contacted with moisture and subjected to subsequent drying. One specific example for a manufacturing process where this problem may occur is wet granulation, in particular wet granulation using water or aqueous liquids such as aqueous solutions common in the manufacturing of solid dosage forms such as tablets and capsules [10].

Moisture Activated Dry Granulation (MADG) was developed in response to the difficulties experienced with wet granulation, in terms of endpoint, drying and milling. Wet granulation process endpoint is very sensitive to granulation time and shear. The wet granules need to be dried to a narrow range of moisture contents, which is difficult. The dried granules need to be

milled, but the milled granules often have either too many fines or too many coarse particles (or both) - an undesirable bimodal distribution [6].



Although the process is most widely used in the pharmaceutical industry, the conventional wet granulation process has following merits and demerits [12]

Merits	Demerits
• It improves flow property and compression characteristics and increases density of granules. • Better distribution of color and soluble drugs if added in the binding solution. • It reduces dust hazards. • Prevents segregation of powders. • Makes hydrophobic surfaces more hydrophilic.	• Process is expensive because of labor, space, time, special equipment and energy requirement. • Multiple processing steps involved in the process add complexity. • Loss of material during various stages of processing. • Moisture sensitive and thermolabile drugs are poor candidates. • Any incompatibility between the formulation components is aggravated during the processing.

Criteria behind the Granule formation in MADG process

The granule formation mechanism in MADG is the same as in conventional wet granulation. In both cases, it is a process of powder particle size enlargement, often in the presence of water and binders, through wet massing and kneading. The main differences between the two are the amount of granulating liquid used and the level of agglomeration achieved. In conventional wet granulation, substantially more water is utilized to create larger and wetter granules. This is then followed by heat drying to remove the excess water and milling to reduce the granule size [13].
In MADG, only a small amount of water is used to create agglomeration, followed by moisture distribution and absorption. Neither heat drying nor milling is required. Because the amount of water used in MADG is small (usually only 1–4% of the entire formulation), it is important that the water is delivered accurately and distributed uniformly during the agglomeration stage this makes the selection of a spray system that provides accurate delivery and a well-defined spray pattern very important [13].

In terms of equipment, a high-shear granulator is more suitable for the MADG process, and an ideal machine should have efficient impellers/blades and choppers to allow good mass movement and proper mixing. It should also allow water to be sprayed only on the powder bed and not on the blades, choppers or granulator wall. Also, the blades and bowl configuration should be such that it does not allow "wet pockets" or "dead spots" to remain after the moisture distribution or absorption stage, which would then necessitate additional sizing and shifting of the granulation. [13]

MADG is a simple, economical, clean, and robust process that creates granulation with very good physical properties and finished products with satisfactory quality attributes. It is applicable to many of the pharmaceutical industry's granulation needs for solid dosage form development and can be described as a 'one-pot' granulation process also helps to minimize endpoint sensitivity [13]. Additionally, because of the necessary excipients required for MADG are already commonly used by the pharma industry so there is no conceivable regulatory concern. 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 [14].

The MADG process offers many advantages-

- It creates relatively small granules of narrow particle-size distribution with good flowability. The MADG-based granulations also tend to have good compactibility and weight control during tablet compression [14].
- The potential for segregation is eliminated for two main reasons. First, the agglomeration stage constitutes 70–90% of the entire formulation in most cases. Second, the excipients added in the moisture-absorption stage often have a particle size similar to that of the agglomerates [14].
- The MADG process is also amenable to scale-up with few or no risks. For example, a large-scale batch typically results in a uniform water distribution, which is desirable and beneficial [14].
- 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, also offers energy savings and no additional requirements for drying, extra material transfer, milling, and separate blending exist, which makes it an easier candidate than conventional wet or dry granulation processes with which to implement the FDA's Quality by Design concepts [14].
- These advantages make the MADG process a good candidate for the application of the US Food and Drug Administration's quality by design (QbD) philosophy. Because the process does not need granulation drying or milling steps, it is a green process that has a great potential to be developed into a continuous process [14].
- The MADG process has been employed successfully at Bristol-Myers Squibb (New York) to develop tablet formulations for at least 20 new investigational drug compounds. In addition, several existing wet-granulation and roller-compaction tablet formulations have been converted to the MADG process successfully with or without formula changes. The finished products made with the MADG process have had similar or better product quality attributes than those of the original formulations. In short, MADG has the best attributes of dry blending and wet granulation [14].
- The main drawbacks of the MADG process for solid dosage-form development arise from the use of drug compounds that are water labile and when a large amount of water (i.e., more than 5–10%) is needed for special reasons (e.g., phase transformation) during the granulation process. Product instability results from the use of water-labile drug compounds, and the

excessive use of water defeats the fundamental purpose of the MADG process. For these reasons, the authors do not recommend the MADG process if these two situations exist.[14]

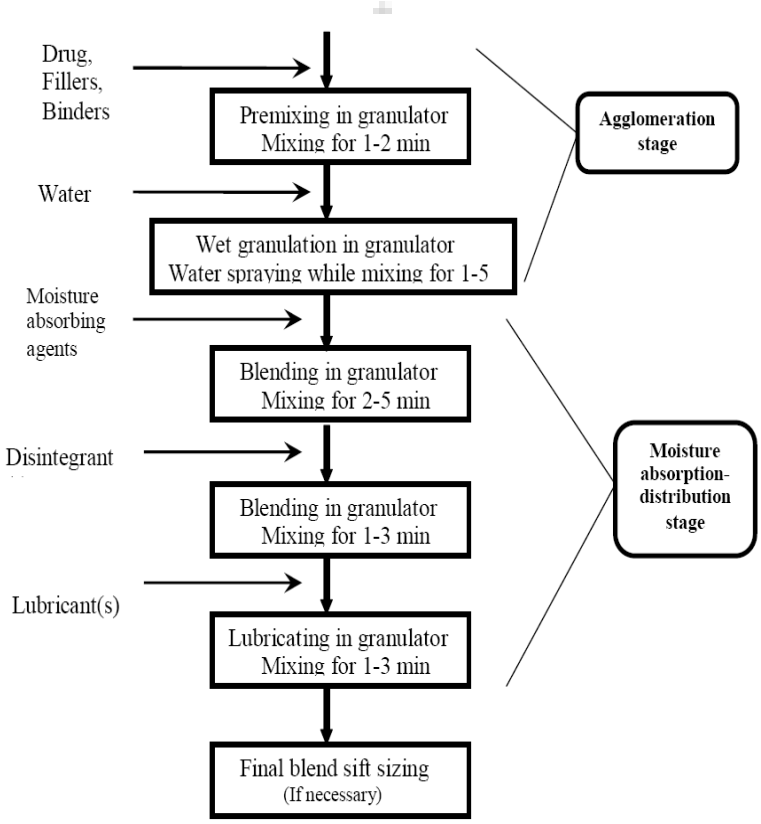
The Principle of MADG process

The Moisture Activated Dry Granulation involves two major stages:

1. Agglomeration

2. Moisture distribution And Absorption Stage [20]

Success depends on the selection and order in which the formulation ingredients added, as well as how the process is carried out. Figure shows a flow diagram of the MADG process [15].



Moisture- Activated Dry Granulation – Formulation Development:

In accordance with the present invention, the term "dry" means that the water content of the excipients which are mixed with the one or more active ingredient is less than 2 wt-%, preferably less than 1.5 wt-%, based on the total weight of the excipients mixed with the active ingredient and determined by the loss on drying method according to Ph. Eur. Chapter 2.2.32 (determined

on 1.000 g by drying in an oven at 105^0C for 3 hours). So, the active substance will also be used in the starting mixture as a dry component [10]. Furthermore, in the description of the moisture-activated granulation process for the manufacturing of the pharmaceutical dosage forms, focus is made to intragranular excipients. This term means those excipients which are used during the preparation of the granulate. Excipients which are added during the further processing of the granulate into dosage forms such as tablets may be referred to as extragranular excipients. Preferably, the ratio of the total amount of water to the total amount of all the solid ingredients including the active substance(s) and all intragranular excipients is less than 20:100, in particular less than 10:100, based on weight. In particular, the granulation liquid consists of water, purified in accordance with pharmaceutical requirements. In case excipients such as binders, buffering/alkalizing agents, surfactants or antioxidants are dissolved or dispersed in the water of the granulation liquid, they are taken into account in the calculation of the above ratios as solid, dry excipients. The excipients and the active ingredient(s) which are mixed in primary steps are present in the form of finely divided solid particles, e.g. as powders. Usually, the particles have an average particle size in the range of micrometers, e.g. 0.1 and up to 500 μm, preferably 0.5 to 450 μm. Average particle size is preferably determined by laser diffraction using equipment such as Malvern instruments. Preferably, the dry components are mixed in the form of powders [10].

1 Agglomeration

In this stage, all or part of the drug is mixed with filler(s) and an agglomerating binder to obtain a uniform mixture. During mixing, a small amount of water (1–4%) is sprayed onto the powder blend; water droplets hydrate the dry binder and create tacky nuclei or tacky wet mass. The binder functions as the drug and excipients move in the circular motion caused by the mixer impellers or blades.

Dry powder particles adhere to the wet nuclei or wet tacky mass to create moist agglomerates. The resulting agglomerates are small and spherical because the amount of water used in the MADG process is much lower than that in conventional wet granulation. The agglomerates therefore cannot grow into large, wet lumps. The particle size of the agglomerates generally is in the range of 150–500 μm. It is possible, based on the drug loading technique, to add only part of the drug to the formulation during the agglomeration stage. The remaining drug can be added after the moist agglomerates have been formed. The added drug particles adhere to the wet

agglomerates and become incorporated into them. The process does not create large granules, which would need milling, and because very little water is used in the process, the endpoint is not sensitive to blending [15].

2. Moisture-Distribution and Absorption Stage

In this stage, moisture absorbents such as microcrystalline cellulose or silicon dioxide are added as mixing continues. When these agents come in contact with the moist agglomerates, they pick up moisture from the agglomerates and redistribute moisture within the mixture. The entire mixture thus becomes relatively dry. Although some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact, and some, usually the larger particles, may break up. This process results in a granulation with uniform particle size distribution. To achieve adequate lubrication this step completes the MADG granulation process. Excluding material loading, the actual processing time for the MADG process is only 10–20 min. Even for a commercial-scale batch, the processing time is essentially the same as it would be for a laboratory- or pilot-scale batch. Beginning with the premixing of the process continues with the addition of a disintegrant to the mixture, followed by blending for a few minutes. Then, during mixing, lubricant is added and blended for sufficient time to drug and excipients, the final granulation could be ready for tablet compression, encapsulation [15].

Advantages:

- Applicable to more than 90% of the granulation needs for pharmaceutical, food and nutritional industry
- Short processing time.
- It utilizes very little granulating fluid, so decreases in drying time also produces granules with excellent flowability.
- Very few variables, resulting in less need for expensive PAT technology.
- Applicable to number of formulation, including low and high drug load formulation, polymer matrix type controlled release formulations, soluble and insoluble type drug formulation.
- Single production equipment (high shear granulator) hence Suitable for continuous processing.
- It uses very little energy, therefore it is green process.
- Reproducible and scalable.

- No equipment change.
- Lower tablet capping.
- No over and under granulation [15].

Disadvantages:

- Moisture sensitive and high moisture absorbing APIs are poor candidates.
- Formulations with high drug loading are difficult to develop.
- Could be other issues with the API, with high-drug load formulations being particularly difficult to develop [15].

MADG Formulation development:

The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for humans and other mammals, each containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with suitable pharmaceutical excipients [17].

For the formulation of proposed pharmaceutical dosage form, three main components which should be consider are-

a. Properties and limitation of API

b. Properties and limitation of excipients

c. Advantage and limitation of method(s) used

In term of development of dosage form, all three considerations are of equally important [18,19].

Assessment of API Wettability

Drug solubility, particle-size distribution, and desired drug loading in the formulation are the primary factors to be considered for an MADG-based development. In general, a great amount of agglomerating binder and water are needed to create the agglomerates when a high drug load is desired for a drug with low solubility and small particle size. The converse is also true. Less agglomerating binder and water is required if the drug is water-soluble, the particle size is not small (e.g., >10 μm), and the drug loading is low (e.g., <25%). Self-granulating drugs sometimes do not require any binder and need less water to granulate. Drug attributes such as Wettability

and agglomeration characteristics should be determined experimentally if they are not already known [15].

Scientists can add water to the drug in a vial or in a small beaker using a syringe and stir the mixture with a small spatula. Generally, the drug is a suitable candidate for an MADG process if it can be wetted with 1–2% of water. If, on the other hand, the drug does not easily wet with 1 to 2% water, the formulation likely needs more binding material and water. Therefore, the higher the percentage of water needed to wet the drug, the more water or binder is needed for the agglomeration stage. As previously mentioned, it is difficult to develop an MADG process if a high amount of water or binder is required for the formulation. [15]

Characterization of MADG process excipients

To facilitate the development of novel drug delivery systems, the demand of new excipients has been increased**.** Excipients is selected and used because it contributes one or more functional attributes to the product characteristics. The quality of medicines depends not only on the active principles and production processes, but also on the performance of the excipients. In earlier days, excipients (s) were considered inactive ingredients, but they may have tremendous effect on performance of active pharmaceutical ingredients in dosage form. The magnitude of this effect will depend upon physicochemical properties of drugs as well as quantity and quality of excipients used [18,19].

It is critical to select suitable excipients for a successful MADG process. Unlike the conventional wet granulation process, which often employs microcrystalline cellulose or starch as fillers. It uses nonabsorbent, easy-to-wet fillers such as lactose monohydrate and mannitol. The main reason for this selection is that microcrystalline cellulose and starch-based excipients absorb and retain a considerable amount of moisture during agglomeration. Because of this characteristic, more than the desired amount of water must be used during processing to form proper wet agglomerates. To ensure proper agglomeration, filler particles must not be too coarse or too fine. In general, coarse particles do not agglomerate easily, and fine particles require more moisture for agglomeration. In rare cases, the drug itself could be soluble and become tacky upon moistening. Such drugs are classified as self-granulating. For these types of drugs, it is beneficial to include moisture absorbents during the agglomeration stage if a high drug-load formulation is

desired in the MADG. Microcrystalline cellulose or starch products can help to avoid over wetting and over granulation of the product even when little moisture is used [15].

In the MADG process, the ratio of the total amount of water to the total amount of all the solid ingredients including the active substance (s) and all intragranular excipients is less than 30:100, preferably less than 20:100, in particular less than 10:100, based on weight. In particular, the amount and contacting time of the mixture of the active ingredient (s) and excipients are selected such that a measurable chemical degradation and/or undesired physical phase transition does not occur, although a granulation liquid is used which is known for the respective active substance to have in principle the potential of causing such undesired changes. The concentration of dissolved or dispersed solid components in the granulation liquid, if present, is less than 25 weight %, preferably less than 15 weight % [10].

1 Agglomerating binders for the MADG process

The binders used in the agglomeration stage should be easily wettable and become tacky with the addition of a small amount of water. Previous studies indicate that low-viscosity polyvinylpyrrolidones (PVPs) such as PVP K-12 are ideal for this purpose. If PVP is not an acceptable choice because of formulation concerns such as chemical compatibility, binders such as hydroxypropyl cellulose (HPC), crosspovidone, maltodextrins, sodium carboxymethylcellulose (Na CMC), or hydroxypropyl methylcellulose (HPMC) can be used instead. The binders can be used singly or in multiple combinations to achieve the desired effects or address specific concerns. If binders are available in various viscosity grades, it is desirable to use the ones with low viscosity because they tend not to retard tablet or capsule dissolution. However, binders with very low viscosity may not provide enough tackiness for agglomeration.

In general, high-viscosity binders are often required in small amounts. The amount of binder needed does not depend on the viscosity alone; other factors such as binder mass must be considered. For example, if 5% of PVP K-12 is sufficient for one formulation, 2% of PVP K-30 may not be the correct proportion for the same formulation. Experiments have shown that about 3% or more of PVP K-30 would be required for proper agglomeration. This difference results from the fact that, in addition to binder viscosity and tackiness, the mass of the binder also plays an important role in covering and coating the blend particles that are to be agglomerated. The binders with small particle size and great surface area would be advantageous as well.

Generally, binders such as HPC, Na CMC, and HPMC require more water and longer hydration time compared with PVP or maltodextrin. On the other hand, binders such as Starch 1500 would not be suitable for the MADG process because this binder has a significant percentage of unhydrolyzed starch components that could absorb considerable amounts of water. As a result, the amount of water needed to effect agglomeration when using Starch 1500 would not be practical for the development of a typical MADG formulation. Completely hydrolyzed starch is not recommended because it does not have sufficient tackiness to cause agglomeration. In all cases, the binder chosen should have fine particles and sufficient tackiness upon moistening to cause adequate agglomeration.

Binders selected from povidones with a K value of from 7 to 100, copovidone, Povidone K25 or K30 polyvinyl alcohol, block copolymer of ethylene oxide and vinyl alcohol sold under trade name Kollicoat IR, microcrystalline cellulose, water soluble types of cellulose ethers such as hydroxypropylcellulose, hydroxylpropylmethylcellulose, starch, pregelatinised starch, microcrystalline cellulose are preferred [15].

2 Moisture absorbents for the MADG process

About 70–95% of any MADG formulation is agglomerated, and the remaining portion of excipients is added. In general, the non agglomerated portion consists of moisture absorbents, disintegrates, and lubricants. It is desirable that non agglomerated excipients be closer in particle-size distribution to the agglomerated portion of the formulation to minimize the potential for segregation. Microcrystalline cellulose, which doubles as a filler and moisture absorbent, is available in the approximate particle size of 200 μm. Low moisture grades are also available [20].

FMC Biopolymer has introduced two new excipients products to the Pharma market: Avicel HFE-102 and Avicel PH-200 LM, which are based on already existing excipients but have been generated 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 FMC Biopolymer's Avicel PH-200 which had a moisture level of five percent. The new product has a moisture level of not more than 1.5 percent and can absorb approximately 3 to 4 times as much water from the granule. This

advantage, along with enabling the use of MADG, meant the use of Avicel PH-200 LM could eliminate the extra steps of milling, drying and screening, thereby reducing manufacturing costs and energy used. The process also produced a larger particle size for optimal flow. This increases efficiencies to the manufacturing process. It takes aspects of wet granulation but eliminates the drawbacks of it. Also be useful for the use of active pharmaceutical ingredients (APIs) which were sensitive to moisture [17,18,19].

Avicel HFE-102 is a new, proprietary co-spray dried MCC/mannitol high functionality binding excipient for direct compression. The co-spray drying added extra benefits to the excipient as it changed its properties combining the high compressibility of MCC and the low lubricant sensitivity of Mannitol. The outcome was a harder, less friable and faster disintegrating tablets. 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. The amount of Aeroperl 300 typically needed for the MADG formulation is small, which is advantageous from the standpoint of preventing tablet-ejection problems [20,21,22].

The disintegrant crospovidone is available in coarse particle size grade from either ISP (Wayne, NJ) or BASF (Ludwigshafen, Germany). This material is not only a superdisintegrant, but is also compactable and acts as moisture absorbent. Overall, excipients such as Avicel PH 200 LM, Aeroperl 300, and the coarse grade of crospovidone for the non agglomerated portion of the MADG process can significantly improve the quality of the formulation and facilitate the process. If the recommended excipients are not available, regular microcrystalline cellulose (e.g., Avicel PH101, PH102, and PH200), regular silicone dioxide, and crospovidone can be used as substitutes [15].

Spress B818 Pregelatinized Starch NF: New Excipient for Moisture Activated Dry Granulation Process It is the newest addition to the Spress family of pregelatinized starches. As with all of the Spress products, Spress B818 has excellent flow properties and good binding, but what makes this starch unique is its lower degree of pregelatinization. This lower degree of pregelatinization allows the starch to retain the properties of a pregelatinized starch such as good flow and

excellent binding characteristics, but also has the benefits of the quick disintegration times seen with a regular non-pregelatinized corn starch. The use of Spress B818 Pregelatinized Corn Starch NF in capsules virtually eliminates gel-blocking (often seen with pregelatinized starches), which can slow down capsule core disintegration and dissolution. A study comparing disintegration times of Spress B818 Pregelatinized Corn Starch NF and regular Corn Starch NF demonstrates that there is no difference seen in disintegration times between the two starches [23].

Along with Spress B818, prosolv SMCC is also finding wide application in MADG Technique. ProSolv SMCC is silicified microcrystalline cellulose composed of 98% microcrystalline cellulose and 2% colloidal silicon dioxide. It combines the excellent compactibility of microcrystalline cellulose with superior flow properties. The following sections describe the details of the excipients used in the preparation of stable formulation such as in particular a tablet dosage forms.

3 Diluents

Diluents can be selected from soluble saccharides such as mannitol, xylitol, powdered cellulose, microcrystalline cellulose, starch and its derivatives, alkaline earth metal phosphates such as calcium hydrogen phosphate in hydrated or anhydrous form. In order to achieve good processibility during compression, the particle size of the diluents is important. In case of diluents used intragranularly, the average particle size determined by laser diffraction method such as by Malvern instrument can be in the range from 10 to 150 µm, preferably 25 to 120 µm. The average particle size of diluents used in the extragranular phase can be in the range from 50 to 400 µm preferably 75 to 350 µm. Co-processed diluents having improved compressibility and flowability such as silicified microcrystalline cellulose alone or co-processed with additional excipients such as disintegrants and lubricants (e.g. different Prosolv types obtainable from Penwest), a combination of microcrystalline cellulose and lactose such as MicrocelLac obtainable from BASF) can be used [10].

4 Surfactants

Surfactants can in general be selected from nonionic or ionic surfactants having an HLB value of more than 8, preferably of more than 10. Nonionic surfactants can in particular be selected from polyoxyethylated glycol monoethers, cetomacrogol, sorbitan esters (Spans), polysorbates

(Tweens), polyoxyethylene polyoxypropylene copolymers such as poloxameres and sugar esters with fatty acids with 10 to 22 C atoms. Ionic surfactants can in particular be selected from the group of anionic surfactants such as organic sulphonates (RSO3-), sulphates (ROSO3-) e.g. sodium lauryl sulphate CH3(CH_2)SONa, potassium laurate. Cationic surfactants include organic quaternary ammonium halides, cetrimides, as well as benzalkonium chloride and ampholytic surfactants selected from sulfobetaines or betains [10].

5 Lubricants

Lubricants for use in the present invention are in general selected from metal stearates comprising magnesium, calcium, sodium, aluminium or zinc stearate, talc, hydrogenated castor oil, sodium stearyl fumarate, partial fatty esters of glycerol such as glycerol monostearate, fatty acids such as stearic acid. Preferably, talc or magnesium stearate are used [10].

6 Disintegrants

Disintegrants are in general selected from the group consisting of crospovidone e.g. Kollidon Cl of type A or B, Polyplasdone XL average particle size in the range 100-130 µm or Polyplasdone XL-10 average particle size in the range 30-50 µm , starch, pregelatinised starch, sodium starch glycollate, microcrystalline cellulose, carboxymethylcellulose sodium (CMC-Na) , also called croscarmellose sodium, or calcium (CMC-Ca), cross- linked CMC-Na, polacrilin potassium, low-substituted hydroxypropylcellulose or mixtures thereof. A particularly preferred disintegrant is crospovidone [10].

7 Granulation aids

Granulation aids, which are used to prevent stickiness of the composition during granulation and subsequent compression, can be selected from substances having surface area of at least 0.25 m^2/g, preferably 0.5 m^2/g, more preferably 1 m^2/g and even more preferably of more than 50 m^2/g. Granulation aids can be hydrophilic such as colloidal anhydrous silica sold under trade name Aerosil 200, bentonite, talc, zeolite, porous silicone dioxide sold under trade name Sylysia 350 or magnesium aluminometasilicate sold under trade name Neusilin, and types such as UFL2 and US2. Hydrophobic excipients used as granulation aids can be selected from, but are not limited to, fatty acids having 10 to 24 carbon atom such as stearic acid, metal salts of fatty acid having 10 to 24 carbon atom such as magnesium, calcium, sodium, aluminium or zinc salts of

stearic and/or palmitic acid, hydrogenated castor or vegetable oil and hydrophobic colloidal anhydrous silica sold under trade name Aerosil R972. Most preferably, hydrophobic or hydrophilic colloidal silica sold under trade name Aerosil R972 or Aerosil 200D are used [10].

8 Antioxidants and buffering/alkalizing agents

Specifically, the buffering/alkalizing agents can in general be selected from substances such as sodium or potassium hydroxide, ammonia solution, mono or dibasic alkali and alkaline earth metal phosphates such as disodium hydrogen phosphate in anhydrous or hydrated state, calcium hydrogen phosphate in anhydrous or hydrated state, alkali and alkaline earth metal hydrogen carbonates, earth alkali carbonates and hydroxy carbonates such as magnesium carbonate; heavy alkaline earth oxides such as magnesium oxide, alkali and alkaline earth metal salts of polycarboxylic acids such as citric acid or mixtures thereof. The buffering/alkalizing agents can be added partly or fully either in dissolved form in the granulation liquid or in a solid form such as in powder form to the dry components of the granulate.

Antioxidants can be selected from butylhydroxyanizole (BHA), butylhydroxytoluene (BHT), ascorbic acid, ascorbic acid metal salts, α-tocopherol and its salts, pharmaceutically acceptable substances having kinone moiety in the molecule such as gallic acid, caffeic acid, quercetin, rutin or combination thereof, and the like [10].

Formulation assessment:

Assessment of the formulation itself is the next task to be completed once the wettability of the drug has been established. For most drugs, a preliminary formulation development evaluation can be initiated with a small batch. For non-wettable drugs or high drug-loading formulations, additional agglomerating binder (e.g., PVP) and more water during the agglomeration stage might be required. In addition, for drugs that are more difficult to granulate, mannitol (e.g., Perlitol 160 C, Roquette, France) or the wettable fillers can be used in place of lactose monohydrate to achieve the desired granulation. Conversely, small amounts of binder and water are needed if the drug is easily wettable and self-granulating [15].

The ratio of Aeroperl 300 or other silicon-dioxide-type excipients to water should be kept to at least 1:1 by weight in the formulation. If PVP is not desirable in a given formulation, other agglomerating binders can be used, as described above.

Final formulation and optimization:

Using the knowledge gained from the formulation-screening experiments described above, a large batch can be manufactured with a high-shear granulator. The preliminary studies enable adjustments to be made to improve formulation characteristics such as granulation and tableting, which can be further optimized as needed. Upon the successful completion of optimization exercises, the accelerated stability of the formulation can be evaluated. The scale-up & design-space studies can be conducted as needed [15].

Additional considerations for the MADG process:

Moisture in the MADG formulation

The amount of water used in the MADG process is part of the formula composition. This amount is a fixed value in the formula and is determined during formulation development. For example, if 2.0% (w/w) water is used, the rest of the ingredients should make up the 98.0% (w/w) of the formula. Because the MADG process does not include a heat-drying step, the water added would not be intentionally removed from the formulation. Because moisture is added but not removed in the MADG process, what happens to the moisture and how it affects product quality might be causes for concern.

To answer these questions, an MADG formulation that uses 1.5% water, 20% Avicel PH 200 LM, 1.5% Aeroperl 300, and other ingredients for a total weight of 100 g can be considered. First, 1.5 g of water is used in the agglomeration stage. During the moisture-absorbing and -distribution stage, 20.0 g of Avicel PH200 LM (with an inherent moisture level of 1.5%) can take 0.7 g of moisture, while 1.5 g of Aeroperl 300 can absorb 2.25 g of moisture from the wet agglomerates. As a result, the final granulation reaches its equilibrium moisture level, and neither Avicel PH200 LM nor Aeroperl 300 appears damp or lumpy. Such a MADG formulation would not have much more free water than that produced by a typical conventional granulation process. Even if only regular Avicel PH200 (with a moisture content of ~5%) is used without Aeroperl 300 in the same formulation, the amount of the remaining moisture (0.8 g) would be well

distributed in the other formulation excipients, thus resulting in a free-flowing final granulation Silicone dioxide in an MADG formulation sometimes may be preferred to minimize the risk of granulation caking during storage, to avoid flowability problems, and to reduce the chance of moisture-induced chemical instability. In general, unless the drug in the MADG formulation is moisture-sensitive, additional stability risks of the finished product would not be expected.

Required equipment for MADG

MADG only requires two pieces of equipment:

1. An appropriate granulator
2. An airless spray system

1 Granulator

The granulator can be a planetary or high-shear granulator, but the blades should be at the bottom (either top or bottom driven) and not exposed. This is necessary because the amount of water used is very small and added on top of the powder bed by a fine spray. If the blades were exposed, the water could hit the blades and cause loss of water, possibly creating wet lumps and non-uniform granulation. The granulator should not have dead spots or spots where material could stick. A chopper in the granulator is also useful.

2 Water delivery system/airless spray system

The preferred mechanism to deliver water spray consistently would be an airless spray system, which enables the water to be directed onto the powder bed in a high-shear granulator. Any airless spray nozzle with a gear pump or pressure vessel, where the spray pattern can be reproduced and the exact amount of water delivered, would be adequate. Spray nozzles with an orifice of 0.1 mm or 0.15 mm can be attached to a syringe to deliver a low (5–10 mL) volume of water for small experiments.

This process also requires an airless spray system that accurately delivers the desired amount of water in small (50–200 μm) droplets. The system should not have drips; peristaltic pumps, in particular, are not suitable. The gear pump or pressure vessel must also provide the right type of spray. At the developmental stage, however, an appropriate spray tip attached to a syringe is sufficient.

3 Granulation sizing and milling

An optimized MADG formulation and process should not produce large lumps in the granulation that require sizing or milling. Therefore, once lubricant is blended in with the granulation, the result may be the final blend that can be directly used for tablet compression, encapsulation, or powder filling. At times, small amounts of lumps in the granulation may stem from material buildup on the blades, choppers, walls, or the bottom of the granulator during agglomeration. In such situations, it may be necessary to pass the granulation through a screen such as 10 mesh or any other suitable size. Often, sizing or sifting is needed only if the formulation or process contains imperfections [15].

Increasing uptake

One of the main issues with MADG is the capability to accurately deliver a very small amount of water in spray form (i.e. 0.2 mL). It is not always possible to start new formulation development on a large scale, but often if a process cannot be tried out on the small scale, then there is a good chance that it will never be further developed. Presently, there is no system available that can accurately deliver such a small amount of spray. Recently, however, nozzle manufacturer Orthos/Schlick (SC, USA) has developed a special spray kit for MADG applications. If development scientists have access to this, or any other technology that can accurately spray small amounts of water, they have much better chances of success at the small scale and, therefore, are more likely to follow through to large scale applications.

The MADG process can still be improved upon and, with time, this will happen. Improvements may come from multifunctional excipients, which can make the MADG process simpler and more economical; for instance, excipients could be developed that is both a moisture absorbent and a disintegrant, or a moisture absorbent, a disintegrant and a dry binder. The development of specialized granulators for MADG, as well as continuous processors and feeders, will also be beneficial. Increased uptake could also be encouraged by educating more companies about the merits of MADG. Many schools and other organizations offer courses on granulation and it would be good if these included hands-on training of MADG processes.

Companies considering the use of MADG should not be too apprehensive. In essence, MADG is not a new process, but a creative form of wet granulation without the usual drawbacks, such as endpoint sensitivity, the need to dry and mill, and the waste of product, time and energy. Anyone interested in the process should first read MADG related articles to get a good grasp of the process and try out a placebo or any other simple formulation. To speed up the learning process, companies can also invite experts to give presentations or advice.

In essence, MADG is just a creative form of wet granulation, granules are created with water with the help of granulating material, but no more water is added than necessary. Additionally, because the necessary excipients are already commonly used by the pharma industry there is no conceivable regulatory concern.

Some examples:

Sr. no.	Ingredient	API	Name of company	Reference
1	Agglomerating binders PVP K 12	Citalopram Hydrobromide 10,20,40 mg Kelnor 1/35 ethinyl estradiol 35 mcg / ethynodiol 1 mg Robitussin long acting Coughgels-dextromethorphan hydrobromide 15 mg Tinidazole 250,500 mg	Amneal Pharmaceuticals Teva Pharmaceuticals USA Richmond Division of Wyeth RoxanLaboratories, I	1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] Folttman H, Quadir A. Excipent Update. Polyvinylpyrrolidone (PVP) - one of the mosy widely used excipients in pharmaceuricals: an overview. Drug Delivery Technology. Vol 8;6:22-7. Accessed April 9, 2012. http://www.pharma-ingredients.basf.com/Documents/ENP/Review%20Articles/DDT-June2008.
2	Microcrystalline cellulose	Acetaminophen and Hydrocodone Bitartrate 500 mg/5 mg, 325mg/10mg Acetaminophen and Oxycodone Hydrochloride	Mallinckrodt Pharmaceuticals Mallinckrodt Pharmaceuticals Watson Pharmaceuticals Actavis	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] FDA's SCOGS database;

		325 mg / 5 mg 325mg/10mg Alprazolam 1 mg,0.5mg Cyclobenzaprine Hydrochloride 10 mg Endocet 325 mg / 10 mg Hydromorphone Hydrochloride 4 mg Oxycodone Hydrochloride 30 mg Promethazine Hydrochloride 25 mg Tramadol Hydrochloride 50 mg Abilify 5 mg Amitriptyline Hydrochloride 50mg, 25 mg,10mg	 Mylan Pharmaceuticals Inc Breckenridge Pharmaceutical, Inc. Qualitest Pharmaceuticals Inc. Endo Pharmaceuticals Inc. Mallinckrodt Pharmaceuticals Actavis Mallinckrodt Pharmaceuticals Sandoz Pharmaceuticals Inc. Amneal Pharmaceuticals Teva Pharmaceuticals USA Zydus Pharmaceuticals Bristol-Myers Squibb Mylan Pharmaceuticals Inc. Sandoz Pharmaceuticals Inc. Teva Pharmaceuticals USA Lilly, Eli and Company Actavis pharmaceuticals Sandoz Pharmaceuticals Inc. Aurobindo Pharma Purdue Pharma LP Zydus Pharmaceuticals	Microcrystalline cellulose, Report No. 25, 1979.; ID Code: 9004-57-3; Accessed July 28, 2011. [3] Food and Agricultural Organization of the United Nations. Corporate Document Repository. Compendium of Food Additive Specifications, Addendum 5. Microcrystalline cellulose. http://www.fao.org/docrep/W6355E/w6355e0l.htm Accessed July 28, 2011 [4] US Dept of Agriculture, Agricultural Marketing Service. Cellulose processing. Executive Summary. Accessed 7/28/2011.

3	Hydroxy propyl cellulose	Budeprion XL 150 mg Cialis 20 mg Gabapentin 600 mg HydrOXYzine Pamoate 25 mg, 50mg Mirtazapine 15 mg OxyContin 80 mg, 10mg Promethazine Hydrochloride 25 mg Sertraline Hydrochloride 50,100 mg Simvastatin 20 mg	Aurobindo Pharma Lupin Pharmaceuticals,Inc Camber Pharmaceuticals InvaGen Pharmaceuticals, Inc. Aurobindo Pharma	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] Innovate Us. What is Hypromellose? http://www.innovateus.net/health/what-hypromellose. Accessed 08/19/2011
4	Maltodextrines	Celecoxib Indomethacine Budesonide Efaverenz Griseofulvin Ibuprofen Glicazide	Roquette pharma.	[1]CFR-code of federal regulations title 21 of USFDA. Reg. no. 9050-36-6. [2] A book by Dionysios Douroumis, Alfred Fahr 2012. [3] Formulation and characterization of solid dispersion of Efaverenz by BADA pragati kumar etal. [4]KLEPTOSE-New taste masking solution. [5] Ibuprofen-Maltodextrin interaction by Claudia Garnero etal. [6] Formulation and evaluation of Glicazide loaded maltodextrin based pronisomes by Dr.B.P.Rao etal. [7]Development and optimization of

		Glipizide Norfloxacin Cumin oleoresin microencapsule.		pronisome for oral delivery by D.Akhilesh etal. [8] Development and evaluation of Norfloxacin loaded maltodextrin based pronisomes by D. Akhilesh etal. [9]A book by Valdir cechinel filho 2012.
5	crospovidones	Acetaminophen and Codeine Phosphate 300 mg / 30mg Acetaminophen and Hydrocodone Bitartrate 325mg/10mg, 500mg/5mg Acetaminophen & Hydrocodone Bitartrate 500 mg / 7.5mg ,500mg/10mg 325mg/5mg 325mg/7.5mg Acetaminophen and Oxycodone Hydrochloride 325mg/10mg 325 mg / 5 mg , Alprazolam 0.5mg, 2 mg Buprenorphine Hydrochloride (Sublingual) 8 mg Cyclobenzaprine Hydrochloride 10 mg Endocet 325 mg / 10 mg Meloxicam 15 mg	Mallinckrodt Pharmaceuticals Watson Laboratories, Inc. Mallinckrodt Pharmaceuticals Watson Laboratories, Inc. Vintage Pharmaceuticals Inc. Mallinckrodt Pharmaceuticals Qualitest Pharmaceuticals Inc. Mallinckrodt Pharmaceuticals Amneal Pharmaceuticals Dava Pharmaceuticals Inc. Roxane Laboratories,Inc. Teva Pharmaceuticals Endo Pharmaceuticals Inc Lupin pharmaceuticals,Inc	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] Ganesan S., Felo J., Saldana M. Embolized Crospovidone (poly[N-vinyl-2-pyrrolidone]) in the Lungs of Intravenous Drug Users. Mod Pathol 2003;16(4):286–92

6	Sodium carboxy methyl cellulose	Combunox 400 mg / 5 mg Flucytosine 500 mg Nalfon fenoprofen calcium 200 mg Pletal 100 mg ,50mg Ziprasidone Hydrochloride 80mg,60 mg, 20mg	Forest pharmaceuticals,Inc. Sigma pharm Lab.LLC Pedinol phamaceutical,Inc Otsuka American pharmaceutical,Inc. Sandoz,Inc.	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] FDA's SCOGS database; corn starch, Report No. 977050-51-3, 1979.; ID Code: 72; http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=72 Accessed October 17, 2011
7	Hydroxyl propyl methyl cellulose	Factive 320 mg Flumadine 100 mg Flurbiprofen 100 mg 50mg Isosorbide Dinitrate Extended Release 40 mg Metformin Hydrochloride 1000 mg Metoprolol Tartrate 50 mg Oxandrin 2.5 mg , 10mg Oxycodone Hydrochloride Extended Release 80mg,40 mg , 20mg,10mg Ranitidine Hydrochloride 300 mg Soma compound with Codeine 325	Oscient Pharmaceuticals Forest Pharmaceuticals, Inc. Caraco Pharmaceutical Laboratories Inwood Laboratories Inc. Actavis U.S. (Purepac Pharmaceutical Company) Caraco Pharmaceutical Laboratories Savient Pharmaceuticals Endo Pharmaceuticals Inc. Genpharm Inc.	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] Folttman H, Quadir A. Excipent Update. Polyvinylpyrrolidone (PVP) - one of the mosy widely used excipients in pharmaceuricals: an overview. Drug Delivery Technology. Vol 8;6:22-7. Accessed April 9, 2012. http://www.pharma-ingredients.basf.com/Documents/ENP/Review%20Articles/DDT-June-2008.pdf

		mg / 200 mg /16 mg TROVAN 200mg,100mg Zolpidem Tartrate 10 mg, 5mg	MedPointe Healthcare Inc. Pfizer U.S. Pharmaceuticals Group InvaGen Pharmaceuticals Inc.	
8	Povidone k 25	Boniva 150 mg Lamotrigine (Chewable, Dispersible) 25 mg Meloxicam 15 mg ,7.5mg Midol Extended Relief naproxen sodium 220 mg Ocella drospirenone 3 mg / ethinyl estradiol 0.03 mg Pantoprazole Sodium Delayed Release 40 mg, 20mg Protonix 40 mg ,20mg Quetiapine Fumarate 400mg,300mg, Yasmin inert Yaz drospirenone 3 mg / ethinyl estradiol 0.02 mg	Roche Laboratories Glenmark Generics Inc. Aurobindo Pharma Bayer HealthCare LLC - Consumer Care Teva Pharmaceuticals USA ESI Lederle Generics Wyeth Pharmaceuticals Wyeth-Ayerst Laboratories Teva Pharmaceuticals USA Inc. Berlex Laboratories Berlex Laboratories	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] Innovate Us. What is Hypromellose? http://www.innovateus.net/health/what-hypromellose. Accessed 08/19/2011
9	Povidone k 30	Acetaminophen and Hydrocodone Bitartrate 325 mg	Aurolife Pharma LLC Alvogen, Inc.	1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online).

		/ 10 mg , 325mg/7.5mg Acetaminophen PM 500 mg / 25 mg Alprazolam 2 mg, 1mg ,0.5mg Baclofen 10 mg Carisoprodol 350 mg Ciprofloxacin Hydrochloride 500 mg Clarithromycin 500 mg Lamotrigine 100 mg,25mg Lithium Carbonate 300 mg Meloxicam 15 mg Mirtazapine 15 mg Naproxen Sodium 550 mg Omeprazole Delayed Release 20 mg Venlafaxine Hydrochloride Extended-Release 75 mg	New World Imports, Inc Sun Pharmaceuticals Northstar Rx LLC Caraco Pharmaceutical Laboratories,Ltd. Aurobindo Pharma Aurobindo Pharma Teva Pharmaceuticals USA Teva Pharmaceuticals USA Roxane Laboratories, Inc. Carlsbad Technology, Inc. Teva Pharmaceuticals USA Teva Pharmaceuticals USA Apotex Corp. Teva Pharmaceuticals USA	Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] Folttman H, Quadir A. Excipent Update. Polyvinylpyrrolidone (PVP) - one of the mosy widely used excipients in pharmaceuricals: an overview. Drug Delivery Technology. Vol 8;6:22-7. Accessed April 9, 2012. http://www.pharma-ingredients.basf.com/Documents/ENP/Review%20Articles/DDT-June-2008.pdf
10	Pregelatinized starch	Acetaminophen & Hydrocodone Bitartrate 500 mg / 5 mg Acyclovir 400 mg Atropine Sulfate	Ranbaxy Pharmaceuticals Inc. Ranbaxy Pharmaceuticals Inc. Sandoz Pharmaceuticals Inc	1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/56104

		&Diphenoxylate Hydrochloride 0.025 mg /2.5 mg Baclofen 10 mg Bextra 20 mg, 10mg Furosemide 80mg 40 mg,20mg Hydrochlorothiazide 25 mg Lortab 2.5/500 500 mg / 2.5 mg Lovastatin 40 mg Meperidine Hydrochloride 100 mg Methadone HCl Diskets 40 mg Mirtazapine 15 mg Talacen 650 mg / 25 mg Topiramate 25 mg Tramadol Hydrochloride 50 mg VISKEN 10 MG	Caraco Pharmaceutical Laboratories G.D. Searle LLC Roxane Laboratories, Inc. Actavis UCB Pharma, Inc. Actavis Mallinckrodt Pharmaceuticals Cebert Pharmaceuticals Inc Caraco Pharmaceutical Laboratories Sanofi-Aventis Ranbaxy Pharmaceuticals Inc. Akyma Pharmaceuticals Watson Pharmaceuticals Novartis Pharmaceuticals	7. Accessed 08/19/2011 [2] David A Bender. Starch, Pregelatinized. A Dictionary of Food and Nutrition. 2005. Retrieved March 19, 2012 from Encyclopedia.com: http://www.encyclopedia.com/doc/1O39-starchpregelatinized.html [3] FDA's SCOGS database; Wheat Starch; SCOGS-Report Number: 115; http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=365 Accessed March 19, 2012.
11	Polyvinyl alcohol	Acetaminophen and Tramadol Hydrochloride 325 mg / 37.5 mg Bupropion Hydrochloride Extended-Release (XL) 150	Amneal Pharmaceutical Actavis Cobalt Laboratories Inc Amneal	Phenylephrine/Polyvinyl alcohol drops. Drugs.com Accessed March 31, 2012. http://www.drugs.com/cdi/phenylephrine-polyvinyl-alcohol-drops.html

		mg Ciprofloxacin Hydrochloride 500 mg Citalopram Hydrobromide 20 mg ,40mg Cyclobenzaprine Hydrochloride 10 mg ,5mg Hydroxyzine Hydrochloride 25 mg Morphine Sulfate Extended Release 30 mg,60mg Nucynta tapentadol 50mg 75mg,100mg Opana ER 40mg,30mg, 20mg,10mg. Pristiq 50 mg Tramadol Hydrochloride 50 mg	Pharmaceuticals Breckenridge Pharmaceutical, Inc. Amneal pharmaceutical,Inc. Breckenridge Pharmaceutical, Inc KVK Tech Inc. Mylan Pharmaceuticals Inc. Ortho-McNeil-Janssen Pharmaceuticals, Inc. Endo Pharmaceuticals Inc. Wyeth Northstar Rx LLC	
12	Starch	Atarax 50mg,25 mg,10mg Benazepril Hydrochloride 5mg, 10 mg, 20mg, 40mg Dantrium 100mg,50 mg, 25mg, Dexamethasone 1 mg,1.5mg LIORESAL	Pfizer U.S. Pharmaceuticals Group Ethex Corporation P&G Pharm Procter & Gamble Pharmaceuticals Inc. Roxane Laboratories, Inc. Novartis Pharmaceuticals P&G Pharm AstraZeneca	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] David A Bender. Starch, Pregelatinized. A Dictionary of Food and Nutrition. 2005. Retrieved March 19, 2012 from Encyclopedia.com: http://www.encyclopedia.com/doc/1O39-starchpregelatinized.html

		10mg,20mg Macrodantin 25 mg,50mg Nolvadex 10 mg Norgesic Forte 770 mg / 60 mg / 50 mg Soma compound with Codeine 325 mg / 200 mg /16 mg Tambocor 150 mg)	Pharmaceuticals 3M Pharmaceuticals MedPointe Healthcare Inc. 3M Pharmaceuticals	[3] FDA's SCOGS database; Wheat Starch; SCOGS-Report Number: 115; http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=365 Accessed March 19, 2012.
2 1	**Adsorbent** Avicel-HFE102	meloxicam-beta-cyclodextrin Esomeprazole methanesulfonate		1 Development and e valuation of fast-dissolving tablets by Aiman A. Obaidat etal 2 Recent advances in granulation technology by Himanshu.K.Solanki 3A patent WO20120117074A1 on Oral p'ceutical formulations of esomeprazole by Tiziano Alighieri**.** 4 A patent US20120122993on Pharmaceutical composition by Kamalakar Talasila.
2	Avicel PH 200	Active drug substance Active drug substance Aliskiren hemifumarate Suitable active drug substance Ezetimibe	Metric.inc FMC pharma NCBI	1 A case study of using common low moisture fillers by Anshul Gupta etal. 2 MADG by Dr.Gerard Thone. 3 A patent EP 2393489B1 on MADG by Mitja stukelj. 4Advance granulation technique overview by Tejaswini etal. 5Evaluation of several MCC obtained from agricultural by product by John Rojas etal. 6 A patent WO2010037728A2 on novel Ezetimibe formulation by Rade injac.
3	Aeroperl 300	Suitable Active drug substance	Evonik industries	Aeroperl 300- A versatile carrier for liquid or low solubility API's.

		Valproic acid Artemether Suitable active drug substance Valsartan Fenofibrate Simvastatin		2 Formulation and development of stable solid oral dosage form by Naveen khetarpal etal. 3Development and evaluation of Artemether by Ritesh fule etal. 4 A patent EP1601347A1 on use of silica/ silica derivative as sorption material by Helle eliasen. 5.Design and evaluation of dispersion granule by shrivastava A.R.etal 6.A patent US8481078B2 on solid dosage form comprising a fibrate by per holm etal. 7 Highly purified Fenugreek gum based silica lipid drug delivery system by Sav A.R. etal.
4	Silicon dioxide	Acetaminophen and Hydrocodone Bitartrate 500 mg / 5 mg Acetaminophen and Oxycodone Hydrochloride 325 mg / 5 mg Alprazolam 2mg, 1 mg, 0.5mg Cyclobenzaprine Hydrochloride 10 mg Endocet 325 mg / 10 mg Meloxicam 15 mg	Mallinckrodt Pharmaceuticals Mallinckrodt Pharmaceuticals Actavis Dava Pharmaceuticals Inc. Mylan Pharmaceuticals Inc. Breckenridge Pharmaceutical, Inc. Endo Pharmaceuticals Inc. Lupin Pharmaceuticals, Inc Mallinckrodt Pharmaceuticals Qualitest Pharmaceuticals Inc.	[1] Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online). Advanstar. 10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011 [2] FDA's SCOGS database; Silicon dioxides, Report No. 61, 1979.; ID Code: 14808-60-7; http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=276; accessed August 12, 2011

		Methadone Hydrochloride 10 mg Methocarbamol 750 mg Morphine Sulfate SR 30 mg ,SR15 mg Oxycodone Hydrochloride 30 mg,15mg Roxicet 325 mg / 5 mg Tramadol Hydrochloride 50 mg Xanax 2 mg	Mallinckrodt Pharmaceuticals Actavis Roxane Laboratories, Inc. Teva Pharmaceuticals USA Pfizer U.S. Pharmaceuticals Group	
4	Spress B 818		Aesica pharmaceutical.	1.Build a Better Capsule with Spress B818 Pregelatinized Corn Starch NF by Grain processing corporation GCP. 2.Moisture activated dry granulation – Aesica 2013 3. Analysis of polymer by GPC-USFDA. 4. A technical note on granulation technology: a way to optimise granule by Mahammed Athar A. Saikh
5	Prosolv SMCC		AURORA Pharmaceutical. JRS Pharma.USA. S. Zaveri pharmakem private limited	1.Prosolv SMCC-Aurora 2. Formulation optimization of roller compacted spray dried dispersion for capsule filling by JRS pharma USA. 3. Tableting functionality evaluation of Prosolv Easytab in comparison to physical mixtures of its individual components by Aljaberi etal. 4.Prosolv SMCC-Active pharmaceutical ingredients by S. Zaveri pharmakem private limited.

DISCUSSION AND CONCLUSION

The old phrase "Time is Money" has never been more accurate than in today's world. With the current economy, companies are looking at every opportunity to cut costs, including manufacturing costs. There is great value in production processes that can be shortened, but still produce a high-quality, effective end product. In the manufacturing of tablets, direct compression is always the first option investigated. However, if direct compression does not produce a quality tablet, the formulator must use granulation. Granulation processes take time and add additional cost to the formula. A new trend in granulation, which saves both time and money, is Moisture Activated Dry Granulation. Since minimal moisture is needed in this specialty granulation process, no drying time is required, shortening the processing time greatly. The granulation can be "dried" using a new specialty starch from GPC. From the present article, it can be concluded that MADG is very controllable process can effectively yields granules with desired quality attributes and was found to be a simple, clean, lean, and robust for particle-size enlargement. The result from the evaluations was found that created granules with good physical properties and finished products with acceptable properties. The process is applicable for accomplishing most of the granulation need for solid dosage forms development as practiced in the pharmaceutical industry. It is also an economical, energy-saving, green, and efficient manufacturing process. By adopting this technique tablets can be prepared in short manufacturing time and with few critical formulation and process variables over conventional wet granulation process moreover it also evaluates the amount of water added during various stages of granulation which greatly affects the final product characteristics. A systematic approach should be followed for selected granulation process, this can be achieved by Better understanding of flow patterns, step by step following of procedure, excipients with their mixing behavior and impact velocities in different types of granulation equipment is needed. MADG process can be successfully used to get diversified product including control release and immediate release granules of several drugs, including heat and moisture sensitive formulations. Application of MADG technique by pharmaceutical and other industries will be a function of inherent conservatism and statutory limitation, a major challenge to overcome. Processing parameters, excipients, desired FQ, processing equipment should be judiciously selected to get granules with desired characteristics and robustness. The above article aims to provide comprehensive information in this regard, which will be useful for the researchers and scientists involved at the product development stage.

REFERENCES

1. B.J.ennis, J.D. Litster, 'perry's chemical engineering' handbook .chapter Particle size enlargement. Pg. no.20-56-20-89 ,Mc Graw hill,7th edition,1997.
2. D.E. Fonner, N.R. Anderson, G.S. Banker, Granulation and tablet characteristics- Pharmaceutical Dosage forms tablets, Vol 2 ,New York Marcel Dekker Inc 1982.
3. Dilip M, Granulation INC, Marcel T. Parikh, "Theory of Granulation", Handbook of Pharmaceutical New York. Drug development and industrial pharmacy; 1997:1-13.
4. Rathod H, Khinchi MP, Agrawal D and Gupta MK, "Recent advancement in tablet technology: A review", International Journal of Pharmaceutical Research and Development 2012; 4(04):021-030.
5. Mahammed Athar A. Saikh, "A technical note on granulation technology: a way to optimise granules" *IJPSR, 2013; Vol. 4(1): 55-67.*
6. Rajesh Agrawal and Yadav Naveen, " Pharmaceutical Processing – A Review on Wet Granulation Technology",International journal of frontier research *April-June 2011; 1(1): 65-83.*
7. A.Navelkishore singh, M. Sekar, V. Viswanath, Hussan reza, "formulation development and evaluavation of amoxicillin trihydrate and potassium clavulanate immediate release tablets",International journal of universal pharmacy and biosciences, Nov-Dec 2013;71-74.
8. Mayur V. Mahida, M. M. Gupta, "Immediate release tablet of antihypertensive drug olmesartan medoxomile", Journal of Drug Delivery & Therapeutics; 2013, 3(2);186-195.
9. Manufacturing method of tablet by mukesh gohel, www pharmainfo.net/tablet-ruling-dosage-form and Pharmaceutical Sciences, *Int J Pharm Pharm Sci, Vol 6, Issue 6, 2014 pg no. 312-317* -years/manufacturing-method-tablets.
10. A patent EP2393489A2 on moisture activated dry granulation by Mitja Stukelj, Vida Skrabanja, Andrej Ferlan, Franc Vreser, Simon Kukec.
11. Ismat Ullah," Moisture-activated dry granulation. Pharmaceutical Technology" Europe 2011, vol 23,issue 3.
12. Rajesh Agrawal and Yadav Naveen," Pharmaceutical Processing – A Review on Wet Granulation Technology",International journal of frontier research *April-June 2011; 1(1): 65-83.*
13. Ullah I and Wang J, "Moisture activated dry granulation: The 'one-pot' process", Pharmaceutical Technology, Europe 2010; 22(3) 44.
14. Ullah I, Wang J, Chang SY, Guo H, Kiang S and Jain NB, "Moisture-activated dry granulation part II: The effects of formulation ingredients and manufacturing-process variables on granulation quality attributes", Pharmaceutical Technology 2009; 33(12):42-51.
15. P.Thejaswini, B. Suguna, N. Sumalatha, K. Umasankar, P. Jayachandra Reddy, "advanced granulation techniques for pharmaceutical formulations overview", *International Journal of Research in Pharmaceutical and Nano Sciences. 2(6), 2013, 723 – 732*
16. B.Venkateswara reddy, K.Navaneetha, K.Venkata Ramana Reddy, "process development and optimization for moisture activated dry granulation method for losartan potassium tablets", International Journal of Pharmacy
17. Ismat U. Moisture-activated dry granulation. Pharm Tech Eur 2011;23(3):1–3.
18. R Christian Moreton. Excipients interaction. In: Ashok Katdare, Mahesh V. Chaubal (eds). Excipients Development for Pharmaceutical, Biotechnology, and Drug Delivery System, New York, Informa Health Care, 2006. Pg.no. 93-108.
19. Drug-excipient(s) interactions and compatibility study: A Review by Md. Zaki Ahmad, Vijay kumar, Atul kumar, Sohail Akhter
20. Armin H. Gerhardt, Moisture Effects on Solid Dosage Forms Formulation, Processing and Stability, Journal of GXP Compliance Winter, 2009; 13(1); 58-66.
21. www.colorcon.com/literature/marketing/mr/Extended%2520Release/METHOCEL/English/ads_invest_ mag_v1_01.2010.pdf Investigation of Moisture-Activated Granulation of Hydrophilic Polymer Blends in Verapamil HCl Extended Release Matrice.
22. Himanshu K. Solanki, Tarashankar Basuri, Jalaram H. Thakkar, Chirag A. Patel, "recent advances in granulation technology" Volume 5, Issue 3, November – December 2010; Article-008 pg.no.48-53
23. Engels S, Jensen B, Ullah I, Freers SO and Shipley C, "Optimization of binder level in moisture activated dry granulation (MADG) using absorbent starch to distribute moisture". AAPS Annual Meeting and Exposition Online Itinerary 11/15/2008 - 11/20/2008.

24. Dave RH. Overview of pharmaceutical excipients used in tablets and capsules. Drug Topics (online).Advanstar.10/24/2008 http://drugtopics.modernmedicine.com/drugtopics/Top+News/Overview-of-pharmaceutical-excipients-used-in-tabl/ArticleStandard/Article/detail/561047. Accessed 08/19/2011
25. Folttman H, Quadir A.,Excipent Update. Polyvinylpyrrolidone (PVP) - one of the most widely used excipients in pharmaceuticals: an overview. Drug Delivery Technology, Vol.8; 6:22-7. Accessed, 9April 2012. http://www.pharma-ingredients.basf.com/Documents/ENP/Review%20Articles/DDT June2008.
26. FDA's SCOGS database; Microcrystalline cellulose, Report No. 25, 1979; ID Code: 9004-57-3; Accessed July 28, 2011.
27. Food and Agricultural Organization of the United Nations. Corporate Document Repository. Compendium of Food Additive Specifications, Addendum 5. Microcrystalline cellulose. http://www.fao.org/docrep/W6355E/w6355e0l.htm Accessed July 28, 2011
28. US Dept of Agriculture, Agricultural Marketing Service. Cellulose processing. Executive Summary. Accessed 7/28/2011. Innovate Us. What is Hypromellose? http://www.innovateus.net/health/what-hypromellose. Accessed 08/19/2011.
29. CFR-code of federal regulations title 21 of USFDA. Reg. no. 9050-36-6.
30. A book by Dionysios Douroumis, Alfred Fahr 2012.
31. Bada Pragati kumar, Subbarao, K.V. Ramana Murthy, Ravi Kiran Sahu, "formulation, invitro-evaluation and solid state characterization of solid dispersion of efavirenz", Journal of Chemical and Pharmaceutical sciences, ISSN: 0974-2115 , JCPS vol.5,Issue 2,2012.pg. no.35-40.
32. KLEPTOSE-New taste masking solution of Gresiofulvin by Roquette pharma, in-Pharma technologies.com.
33. Claudia Garnero, Carolina Aloisio, Marcela Longhi, "Ibuprofen-Maltodextrin Interaction: Study of Enantiomeric Recognition and Complex Characterization", Pharmacology & Pharmacy, 2013, 4, 18-30 ,http://dx.doi.org/10.4236/pp.2013.41003 Published Online January 2013 (http://www.scirp.org/journal/pp).
34. SK. Gousia Parvin, Ch. Harika, N. Sriram and P. Prem kumar, " Recent trends of novel drug delivery in treatment of diabetis mellitus", International Journal of Pharmaceutical Archive-2(9), 2013, 224-232.
35. D.Akhilesh, G.Faishal, Dr. P.Prabhu and Dr. J.V. Kamath, "Development and optimization of proniosomes for oral delivery of glipizide", International Journal of Pharmacy and Pharmaceutical Sciences, ISSN 0975-1491 Vol 4, Issue 3, 2012.pg. no.307-314.
36. D. Akhilesh ,Gomes Hazel, Prabhu Prabhakara, Kamath Jagdish V, "Development and evaluation of Norfloxacin loaded maltodextrin based pronisomes", International research journal of pharmacy2012,3(6)176-179.
37. A book by Valdir cechinel filho 2012.
38. Ganesan S., Felo J., Saldana M. Embolized Crospovidone (poly[N-vinyl-2-pyrrolidone]) in the Lungs of Intravenous Drug Users. Mod Pathol 2003;16(4):286–92
39. FDA's SCOGS database; corn starch, Report No. 977050-51-3, 1979.; ID Code: 72; http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=72 Accessed October 17, 2011.
40. David A Bender. Starch, Pregelatinized. A Dictionary of Food and Nutrition. 2005. Retrieved March 19, 2012 from Encyclopedia.com. http://www.encyclopedia.com/doc/1O39-starchpregelatinized.html
41. Phenylephrine/Polyvinyl alcohol drops. Drugs.com Accessed March 31, 2012. http://www.drugs.com/cdi/phenylephrine-polyvinyl-alcohol-drops.html
42. Aiman Obaidat ,Rana Obaidat , "Development and evaluation of fast-dissolving tablets of meloxicam-β-cyclodextrin complex prepared by direct compression", Acta Pharmaceutica. Volume 61, Issue 1, Pages 83–91,March 2011.
43. Himanshu.K.Solanki, Tarashankar Basuri, Jalaram H.Thakkar, Chirag A. Patel, "Recent advances in granulation technology", Volume 5, Issue 3, November – December 2010; Article-008.
44. A patent WO20120117074A1 on Oral p'ceutical formulations of esomeprazole by Tiziano Alighieri.
45. A patent US20120122993on Pharmaceutical composition by Kamalakar Talasila .
46. A case study of using common low moisture fillers by Anshul Gupta,vol.224, July 2012, 281-286
47. MADG by Dr.Gerard Thone.
48. A patent EP 2393489B1 on MADG by Mitja stukelj.
49. P. Thejaswini, B. Suguna, N. Sumalatha, K. Umasankar, P. Jayachandra Reddy, "Advanced granulation techniques for pharmaceutical formulations overview" ,International Journal of Research in Pharmaceutical and Nano Sciences. 2(6), 2013, 723 - 732.

50. John Rojas, Alvin Lopez, Santiago Guisao, and Carlos Ortiz, "Evaluation of several microcrystalline celluloses obtained from agricultural by-products", Journal of Advanced Pharmaceutical Technology and Research. 2011 Jul-Sep; 2(3): 144–150.
51. A patent WO2010037728A2 on novel Ezetimibe formulation by Rade injac.
52. Aeroperl 300- A versatile carrier for liquid or low solubility API's by Evonic industries.
53. Naveen khetarpal, Ajay Kumar Sav Ramachal, Leena Rao, Purnima D. Amin "Formulation and development of stable solid oral dosage forms", International journal drug delivery, vol.4(2)2012.
54. Ritesh Amol Fule, Tarique S. Meer, Ajay R. Sav, Purnima D. Amin, "Dissolution Rate Enhancement and Physicochemical Characterization of Artemether and Lumefantrine Solid Dispersions", International journal drug delivery, vol.4(1)2012.
55. A patent EP1601347A1 on use of silica/ silica derivative as sorption material by Helle eliasen.
56. Santosh Kumar , Rishikesh Gupta, Dr. S. K. Prajapati , Nikhil Gupta, Snigdha Pattnaik and Ashu Agrawal, "proniosomes formulation and evaluation by slurry Method as an emerging provesicular drug carrier in NDDS", World journal of pharmacy and pharmaceutical sciences, Volume 3, Issue 9, 2014.pg.no.1486-1501.
57. A patent US8481078B2 on solid dosage form comprising a fibrate by per holm.
58. Ajay kumar Sav, Meer Tarique Ali, Ritesh Amol Fule, Purnima Dhanaraj Amin, "Formulation of highly purified fenugreek gum based silica lipid drug delivery system for simvastatin with enhanced dissolution rate and in vitro characterization, Journal of Pharmaceutical Investigation DOI: 10.1007/s40005-013-0081-4
59. Build a Better Capsule with Spress B818 Pregelatinized Corn Starch NF by Grain processing corporation GCP.
60. Moisture activated dry granulation – Aesica 2013
61. Analysis of polymer by GPC-USFDA.
62. Mahammed Athar A. Saikh, "A technical note on granulation technology: a way to optimise granule" ,*IJPSR, 2013; Vol. 4(1): 55-67,* ISSN: 0975-8232.
63. Prosolv SMCC-Aurora pharmaceuticals
64. Formulation optimization of roller compacted spray dried dispersion for capsule filling by JRS pharma USA.
65. Prosolv SMCC-Active pharmaceutical ingredients by S. Zaveri pharmakem private limited.
66. A .Aljaberi, A Ardakani, A Khdair, S A Abdel-Rahim, E Meqdadi, M Ayyash, G M Alobaidi, N AI Zaobi,"Tableting functionality evaluation of Prosolv Easytab in comparison to physical mixtures of its individual components, 01/2013; 23:499-504.