



International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com



ADVANCED GRANULATION TECHNIQUES FOR PHARMACEUTICAL FORMULATIONS - OVERVIEW

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ABSTRACT

The Present study was focus on different techniques adopted while formulating solid dosage forms like tablets, Capsules and Granules etc. The ideal characteristics of granules include uniformity, good flow and compatibility. Nowadays the agglomeration process used in pharmaceutical industry for granulation. Based on the characteristics, suitable excipients were selected for the formulation of dosage forms. Physiological properties like bulk density, tapped density, hausners ratio and compressibility index have to evaluated and optimized for good pharmaceutical formulations. Apart from Physiological properties we have to consider evaluation parameters of finished products such as disintegration time and *In-vitro* release studies. Here we are mainly focusing on different types of granulation technique.

KEYWORDS

Granulation, Spray drying, Steam Granulation, Moisture Activated Dry Granulation and Moist Granulation Technique.

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INTRODUCTION

Active pharmaceutical compounds (drugs) are used for the treatment of a disease or for prophylactic purpose. An Active Pharmaceutical ingredient may exist in solid, liquid or semisolid form. They are rarely prescribed to the patients as such i.e. without adding excipients, since the desired effect may not be obtained. Earlier, it was thought that excipients are inert in nature but, in recent time it is well known that excipients can greatly modify the intended effect of a drug. The API and excipients are suitably processed in pharmaceutical industry to convert them into dosage forms such as tablet, capsule, suspension, solution,

etc. The selection of excipients and processing of drug excipients mixture is as important as API itself.

Granulation method

Granulation may be defined as a size enlargement process which converts small particles into physically stronger and larger agglomerates. Granulation method can be broadly classified into three types¹:

- Wet granulation
- Dry granulation
- Granulation incorporating bound moisture

Ideal characteristics of granules

The ideal characteristics of granules include uniformity, good flow, and compatibility. These are usually accomplished through creation of increased density, spherical shape, narrow particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), and incorporation of binder, if necessary.

The effectiveness of granulation depends on the following properties²

- Particle size of the drug and excipients
- Type of binder (strong or weak)
- Volume of binder (less or more)
- Wet massing time (less or more)
- Amount of shear applied to distribute drug, to the binder and moisture.
- Drying rate (Hydrate formation and polymorphism)

Wet granulation

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying³.

A. Steps involved in the wet granulation

- Mixing of the drugs and excipients
- Preparation of binder solution
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve (6-12 screens)
- Drying of moist granules.

- Screening of dry granules through a suitable sieve (14-20 screens)
- Mixing of screened granules with disintegrant, glidant, and lubricant.

B. Special wet granulation techniques

- High shear mixture granulation
- Fluid bed granulation
- Extrusion-spheronization
- Spray drying

Dry granulation

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed and the resulting tablet or slug are milled to yield the granules. The other method is to precompress the powder with pressure rolls using a machine such as Chilsonator⁴.

A. Steps involved in the dry granulation

- Milling of drugs and excipients
- Mixing of milled powders
- Compression into large, hard tablets to make slug
- Screening of slugs
- Mixing with lubricant and disintegrating agent

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 as⁵-

- Steam Granulation
- Melt/Thermoplastic Granulation
- Moisture Activated Dry Granulation (MADG)
- Moist Granulation Technique (MGT)
- Thermal Adhesion Granulation Process (TAGP)
- Foam Granulation

Steam Granulation

Pure steam is a transparent gas. At standard temperature and pressure, pure steam (unmixed with air, but in equilibrium with liquid water) occupies

about 1,600 times the volume of an equal mass of liquid water

This process is simply a modification of conventional wet granulation method. Here steam is used as a binder instead of water. Process offers several advantages and disadvantages over other conventional granulation methods such as-

Advantages

- Uniformly distributed in the powder particles
- Higher diffusion rate
- Results in more spherical granule formation
- Thermally aids in drying process
- Higher dissolution rate of granules because of larger surface area generated
- Time efficient
- Environment friendly
- No health hazards to operator
- Regulatory compliance
- Maintain sterility

Disadvantages

- Requires special equipment for steam generation and transportation
- Requires high energy inputs.
- Thermolabile materials are poor candidates
- More safety measure required
- Not suitable for all the binders.

Melt Granulation

Melt Granulation process has been widely used in the pharmaceutical industry for the preparation of both immediate and controlled release formulations such as pellets, granules, and tablets. This process has also been widely accepted for the enhancement of dissolution profile and bioavailability of poorly water soluble drugs by forming solid dispersion⁶.

Melt Granulation is also known as “Thermoplastic Granulation” as the granulation is achieved by adding a melt able binder which is in solid state at room temperature but preferably melts in the temperature range of 50oC – 80oC [20]. No further addition of liquid binder or water is required in the process as the binder in the melted state itself act as granulating liquid and dried granules can be easily obtained by simple cooling at room temperature. This process offers various advantages such as-

Advantages

- Time and cost effective, as it eliminates the liquid addition and drying steps.
- Water sensitive drugs are good candidates.
- Controlling and modifying the release of drugs.
- Regulatory compliance

Disadvantages

- Heat sensitive materials are poor candidates.
- Binders having melting point in the specific range can only be utilized in the process.

Moisture Activated Dry Granulation (MADG)

MADG is a process in which moisture is used to activate granule formation, without the need to apply heat to dry the granules. There are two main stages in MADG:

Agglomeration

Moisture distribution/ Absorption

During agglomeration, drug is blended with diluents and binder in the powder form, to obtain a uniform mixture. This blend constitutes approximately 50-80% of formula weight. While mixing, a small amount of water (1-4%) is sprayed as small droplets onto the powder blend, which moistens the binder and makes it tacky. The binder facilitates the binding of the drug and excipients as they move in a circular motion forced by the mixer blades. The process does not results in larger lumps formation as the amount of water used in this process is very small as compared to the other conventional wet granulation techniques. The particle size of the agglomerates generally falls in the range of 150–500 µm. In moisture distribution/absorption, moisture absorbents, such as microcrystalline cellulose or silicon dioxide, are added while mixing continues. When they come into contact, the moisture absorbents pick up moisture from the moist agglomerates, resulting in moisture redistribution within the mixture. When this happens, the entire mixture becomes relatively dry. While 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 granulation with more uniform particle size distribution.

Advantages

- Applicable to more than 90% of the granulation need for pharmaceutical, food and Nutritional industry.
- Time efficient
- Very few variables involved in the process.
- Suitable for continuous processing
- Less energy involved during processing.

Disadvantages

- Moisture sensitive and high moisture absorbing API is poor candidates.
- Formulations with high drug loading are difficult to develop.

Moist Granulation Technique (MGT)

MGT works on the same principle as Moisture Activated Dry Granulation (MADG) described earlier. It involves binder activation by adding a minimum amount of liquid. Then, excess of moisture present in the blend is removed by adding moisture absorbing material like Microcrystalline Cellulose (MCC) which eliminates the drying step. It is applicable for developing a controlled release formulation⁷.

Thermal Adhesion Granulation Process (TAGP)

TAGP involves granulation by adding very less amount of water or solvent as compared to the traditional wet granulation methods. In this process drug and excipient mixture heated at a temperature range from 30oC to about 130oC in a closed system under mixing by tumble rotation until the formation of granules take place. Drying step is not required in most instances due to low amount of moisture added in the process. Granules of required particles size can be obtained after cooling and screening. It provides granules with good flow properties and binding capacity to form tablets of low friability, adequate hardness and have a high uptake capacity for active substances whose tableting is poor.

Foam Granulation

Foam granulation technique involves addition of liquid binders as aqueous foam. The advantages of foamed binder addition conventional binder addition method includes-

1. No spray nozzle is used
2. Improve process robustness

3. Less water required for granulation
4. Time efficient drying
5. Cost effective
6. Uniform distribution of binder
7. No over wetting
8. Applicable for water sensitive formulation

Moisture activated dry granulation (MADG)

As the name implies, this is a process where moisture is used to activate the granule formulation, but the granules are not heat dried.

MADG is a simple, economical, clean, lean 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.

MADG is a very simple and innovative process where granules are created with water and a granulating binder, as in wet granulation, but are not heat dried or milled. This process helps to minimize endpoint sensitivity.

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.

In 1987, Ullah et al. published a paper about a simple and novel granulation process called moisture-activated dry granulation (MADG). In this granulation process, a small amount of water is used to activate the granule formation (i.e., perform agglomeration) without requiring hot air drying of the granules. After creating the moist agglomerates, this process uses stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute moisture, thus resulting in a uniform, free-flowing, and compatible granulation.

In 1990, Chen published a study comparing the MADG process with the conventional granulation processes for sematilide hydrochloride tablets. Although the active pharmaceutical ingredient (API) in the formulation was cohesive and fluffy, the granulation made with the MADG process was generally comparable with that made through the wet-granulation and roller-compaction processes. In addition, the authors found that MADG was not only a shorter process, but that the final granulation made with the MADG process showed superior flowability and better tablet-content uniformity⁸.

In 1994, Christensen employed the MADG process to successfully make pharmaceutical granulations with micro crystalline cellulose, potato starch, and both of these excipients.

MADG also offers energy savings, a short manufacturing time, and fewer critical formulation and process variables, which makes it an easier candidate than conventional wet or dry granulation processes with which to implement the FDA's Quality by Design concepts.

The MADG process

The Moisture Activated Dry Granulation involves two major stages

- Agglomeration
- Moisture distribution And Absorption Stage

Success depends on the selection and order in which the formulation ingredients are added, as well as how the process is carried out.

Figure showing a flow diagram of the MADG process.

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 stage⁹. 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.

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 into 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. 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 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 drug and excipients, the final granulation could be ready for tablet compression, encapsulation, or powder filling in about an hour.

Advantages

- Applicable to more than 90% of the granulation needs for pharmaceutical, food and nutritional industry
- Short processing time
- Very few variables, resulting in less need for expensive PAT technology
- Applicable to a number of formulations, including high and low drug load formulations, polymer matrix type controlled release formulations, and soluble and insoluble drug formulations
- Suitable for continuous processing
- It uses very little energy, so it is a green process.
- Reproducible and scalable.

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
- Less familiarity with the process and some apprehension towards adoption.

MADG Formulation Development

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 development¹⁰

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. 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 1–2% 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.

Excipients for the MADG Process

Fillers for the MADG Process During Agglomeration

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, MADG process 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 avoid overwetting and overgranulation of the product even when little moisture is used.

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), copovidone, 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.

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, disintegrants, 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. Avicel PH 200 LM (FMC, Philadelphia) is an excipient with low moisture content (< 1.5% by weight, as determined by loss on drying). Aeroperl 300, a moisture absorbent in the form of a non-lumpy, free-flowing granulated silica consisting of $\sim 30\text{-}\mu\text{m}$ spherical particles is also available from Evonik Industries (Essen, Germany). Granular Aeroperl 300 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. The disintegrant crospovidone is available in coarse particle-size grade from either ISP (Wayne, NJ) and BASF (Ludwigshafen, Germany). This material is not only a superdisintegrant, but is also compactible and acts as a moisture absorbent. Overall, excipients such as Avicel PH 200 LM, Aeroperl 300, and the coarse grade of crospovidone for the nonagglomerated 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.

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 nonwetable 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 other 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.

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 and design-space studies can be conducted as needed.

Mechanism of the MADG Process

The granule-formation mechanism in the MADG process is the same as that 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 these two granulation processes are the amount of granulating liquid used and the level of agglomeration achieved. In conventional wet granulation, substantially more water is used to create large and wet granules, and heat drying removes the excess water. This step is followed by milling to reduce the granule size.

In the MADG process, only a small amount of water is used to create agglomeration. Moisture distribution and absorption steps follow, and neither heat drying nor milling is needed.

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 concern¹¹.

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 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

Silicon 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: an appropriate granulator and an airless spray system.

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 nonuniform granulation. The granulator should not have dead spots or spots where material could stick. A chopper in the granulator is also useful.

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 experiments¹².

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.

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 meshes or any other suitable size. Often, sizing or sifting is needed only if the formulation or process contains imperfections.¹³

CONCLUSION

The Present study was focus on different techniques adopted while formulating solid dosage forms like tablets, Capsules and Granules etc. The ideal characteristics of granules include uniformity, good flow and compatibility. Nowadays the agglomeration process used in pharmaceutical industry for granulation. Based on the characteristics, suitable excipients were selected for the formulation of dosage forms. Physiological properties like bulk density, tapped density, hausners ratio and compressibility index have to evaluated and optimized for good pharmaceutical formulations. Apart from Physiological properties we have to consider evaluation parameters of finished products such as disintegration time and *In-vitro* release studies. Here we are mainly focusing on different types of granulation technique. Advanced Granulation techniques like Steam Granulation, Melt/Thermoplastic Granulation, Moisture Activated Dry Granulation (MADG), Moist Granulation Technique (MGT), Thermal Adhesion Granulation Process (TAGP), Foam Granulation selected depends on drug and excipient. In this review work describe detail about various methods.

ACKNOWLEDGEMENT

All authors are thankful to Krishna Teja Pharmacy College, Tirupathi, Andhra Pradesh for provides all the facilities and supports to do this work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Thejaswini P. et al., Advanced granulation techniques for pharmaceutical formulations - overview, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(6), 2013, 723-732.