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Melt Granulation: A Versatile Technique in Pharmaceutical Processing

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ABSTRACT

Melt granulation has gathered increasing interest in the pharmaceutical industry for the concept of utilizing a molten liquid as a binder. Melt granulation process is currently applied in the pharmaceuticals for the manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets. This technique has been used for improving bioavailability of poorly water soluble drugs. The review article gives updates about the latest developments in technology behind use of melt granulation process. Article deals with in depth basic information about granule growth mechanisms during melt granulation. The article also provides an insight to Equipments and factors influencing the melt granulation process & its applications to improve the dosage form characteristics which are utilized for industrial production.

Keywords: Melt granulation, Bioavailability, Binder.

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INTRODUCTION

In pharmaceutical industry, Melt Granulation (MG) Technique has been widely used for the preparation of both immediate and controlled release formulations such as granules, pellets and tablets. By selecting the suitable binder, MG can be used either to prepare modified or immediate release dosage forms and also to improve bioavailability of poorly water soluble drugs[1,2,3,4]. Melt agglomeration also known as "Thermoplastic Granulation". MG can be used either to prepare immediate release or modified dosage forms and also to improve bioavailability of poorly water soluble drugs by using suitable binder. In this process, pharmaceutical powders can be efficiently agglomerated by adding a molten binder at relatively low temperature (50–80 ◦C). Molten binder can be added to the powders either in the form of a solid that melts during the process or form of a molten liquid (spray on procedure)[5]. The role of the molten substance acts like a liquid binding and the dry granules are obtained as the molten binder solidifies by cooling. By using this process, preparation of sustained released dosage forms by using lipophilic binders, such as glycerol monostearate[6], and a combination of starch derivative[1] which is hydrophobic material and stearic acid[7] or a combination of hydroxypropyl methyl cellulose and hydrophobic polymers[8,9,10]. By utilizing water-soluble binders such as PEG[11,12], It also can be used to prepare fast release formulations. Commonly, PEG has been widely used in melt granulation because of its low-melting point , its favorable solution properties, low toxicity, rapid solidification rate and low cost. Gelucire® is another generally used binder. It is a mixture of glycerides and fatty acid esters of PEGs. It has been shown to further increase the dissolution rate of poorly water-soluble drugs, attributed to the surface active and self-emulsifying properties of this excipients[13,14].

Now-a-days, application of melt granulation has increased due to the numerous advantages of this technique over wet granulation. The melt granulation does not require the use of aqueous or organic solvents. In the absence of organic fluids to avoid risk originating from residuals solvents in the final dosage form and the absence of problems associated with environmental requirement of solvent capture and recycle and other advantage for moisture sensitive drugs is the absence of water, results in the elimination of the wetting and drying phases[5,15] . The whole manufacturing process less consuming in terms of time and energy as compared to wet granulation. A additional significant advantage of melt granulation is that by an suitable selection of meltable binders, this technique can be used either to prepare enhanced release or controlled release granules. Examples of hydrophobic binders such as fatty acids, waxes, glyceride and fatty alcohols can be utilized for

prolonged-release formulations[5], while hydrophilic binders used to prepare improved-release dosage forms include polyethylene glycols and poloxamers.

Advantages

1. When the binder is added in solid form, the liquid addition step is avoided, simplifying the equipment, the process and the cleaning.
2. Water sensitive drugs are good candidates.
3. Controlling and modifying the release of drugs.
4. When the binder used is insoluble in water, melt agglomeration may present a simple way to form sustained release formulations.
5. As no liquid is added, the drying phase – often the most time-consuming step in a conventional process – is eliminated.
6. Time and cost effective.
7. Regulatory compliance

Disadvantages

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

HOW DOES MELT GRANULATION WORKS[5]

The solid fine particles stick together into agglomerates by agitation, Kneading, layering in company of molten binder liquid. This process is called melt agglomeration. Melt pelletization and melt granulation are common examples of melt agglomeration. Gradual change in shape and size of the of agglomerates happens during agglomeration process. Also, failed pelletization process is also classified as granulation. while studying the effect of meltable materials on the formation and growth processes of melt agglomerates , it is necessary to thoroughly understand the process of melt agglomeration. The working of melt agglomeration and wet agglomeration are identical. Both are dependent on the elementary mechanism i.e., distribution and immersion. When a distributed of molten binding liquid on the surfaces of primary particles will occur and agglomerates are formed by coalescence between the wetted nuclei, it is known as agglomeration by distribution mode. On the other hand, when the nuclei are formed by immersion of the primary particles onto the surface of droplet of molten binding liquid, it is called as agglomeration by immersion mode(figure 1). Densification prior to coalescence between the nuclei has to effect the distribution of molten binding liquid to surfaces of nuclei. When the molten binding liquid droplets are smaller than the solid particles or of a similar size, the distribution will be a dominant mode. But it also depends on the relative size between the solid particles and the molten binding liquid droplets,

whereas when the molten binding liquid droplets are larger than solid particles, immersion mode dominates. Low molten binding liquid promotes the distribution mode while it is helpful for molten binding liquid of high viscosity that can resist breakup by dispersive forces in case of immersion.

MODES OF MELT AGGLOMERATION:

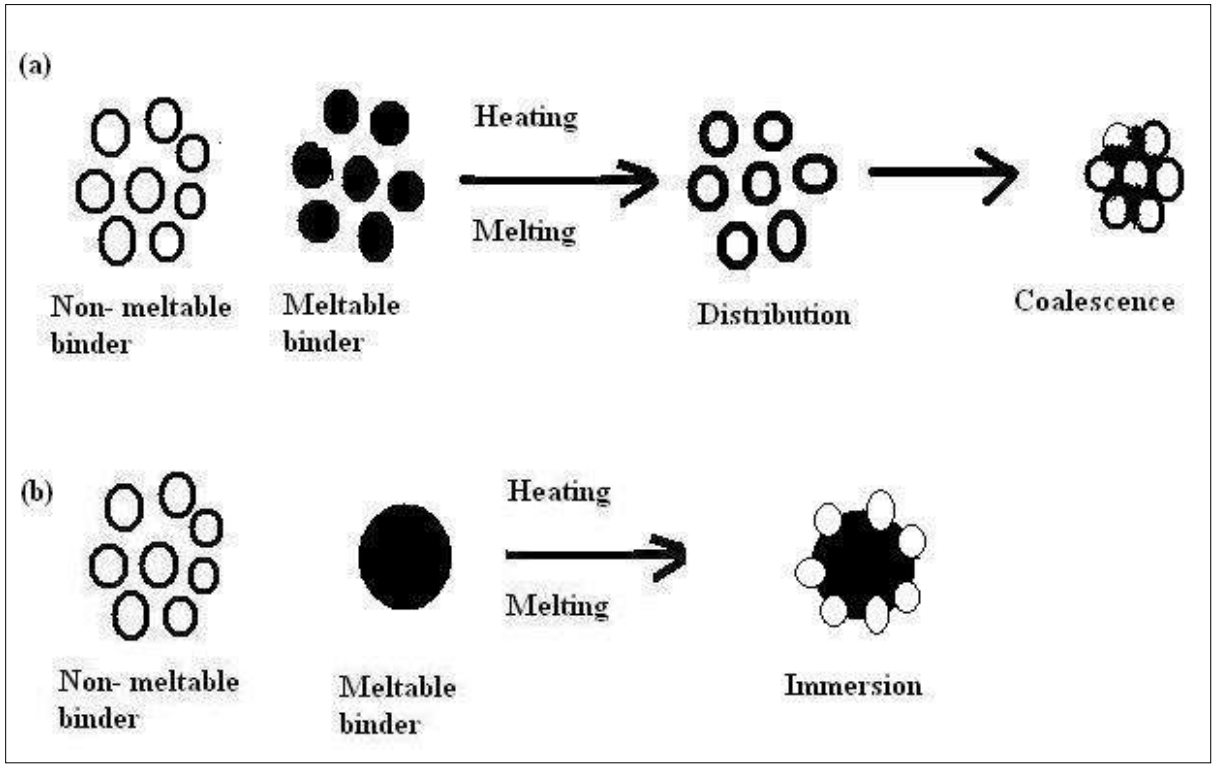

Figure 1: Modes of melt agglomeration: (a) Distribution and (b) Immersion

Equipment

The apparatus of choice for melt granulation are the high shear mixers and fluid bed granulators. In Early 1990s, studies on melt granulation in high shear mixers carried out. A series of papers published in that extensively investigated the effect of process and formulation variables on melt agglomeration and the mechanisms involved in the growth of the agglomerates. After that, others researchers have examined the melt granulation process in high-shear mixer demonstrating that this process can be beneficially employed both to enhance the dissolution rate of poorly water soluble drugs and to control the release of short half-life drugs.

Other equipment such as coating pan, drum granulator or extruder are not as popular as high-shear mixer. As it provides intense shear forces from the high-speed rotation of the impeller . A more homogenous distribution of molten binding liquid is facilitated by the impeller mixing action which results in formation of agglomerates with narrower size distribution and uniform drug content . Also, the frictional heat generated from the high shearing forces of the impeller, can melt

the binder without external heat supply. A continuous agglomeration and rounding effect of the high-speed impeller rotation produces highly spherical pellets in a high-shear mixer.

High mechanical agitation by an impeller and chopper completes melt agglomeration process. Shearing and compaction forces exerted by the impeller achieves mixing, densification, and agglomeration of wetted materials. The impeller rotates on the vertical shaft at a rotational speed corresponding to a radial blade tip speed of approximately 5-15 m/s. The chopper rotates at a similar tip speed which, because of its small diameter, corresponds to a very high rotation speed in revolutions per minute (rpm) (i.e.1500-4000 rpm). A more homogenous liquid distribution can be achieved by cutting, lumps into smaller fragments and helping the bowl or spray onto the powder which is also the primary function of chopper.

Advantages

- Gravity loaded
- Unit formula maintained mixing, massing and granulation are all performed within a few minutes in the same piece of equipment.
- Forms desired wet granule rapidly
- Less wetting and more rapid drying
- Homogeneously dry mixes quickly: color distribution is excellent; can eliminate premixes of addition by geometric progression
- Improved coefficient of weight variation
- Improved content uniformity
- Self-discharging
- Sanitary construction
- Mixing bowl may be jacketed
- Relatively easy to clean
- Option to dry granulation with mixer
- Adequate safety devices
- Conforms to good manufacturing practices(GMP)

Disadvantages

- Relatively high cost
- High noise level
- Adding material directly is not convenient
- Temperature rise from head of friction

- Non movable
- Must be raised to working height
- Foreign spare part

High shear mixer were used in various melt granulation formulations such as sustained release hydrophilic matrices and carbamazepine fast-release tablets by melt granulation were prepared by Rotolab® (Zanchetta, Italy) equipped with an electrically heated jacket (maximum temperature 100 ◦C).

FLUIDIZED BED GRANULATOR

In recent years, the interest on melt granulation of pharmaceutical powders in fluidised (or fluid) bed increased thereafter, considerable amount of work has been performed by Shaefer's group at the Danish University of Copenhagen .

These studies have helped in finding a significant potential of fluidized hot melt granulation (FHMG) that prepares granules with excellent flow properties and suitable for compression into tablets[16,17,18,19].

Inspite, having differences between fluidized beds and high-shear mixers, particularly the lower shear forces in fluidized beds, identical mechanisms of the agglomerate growth have been used. Early studies FHMG helped in finding that the prevalence of one or the other mechanism is primarily controlled by the ratio between the size of solid particles and molten binder droplets[18]. Larger molten binder droplets promotes nucleation by immersion and subsequent layering. When solid particles are smaller than molten binder droplets nucleation by distribution and further growth by coalescence happens. FHMG is better than melt granulation in high shear mixers. Example: Better control of the product temperature, which simplifies the whole process and allows the cooling phase to be performed easily and quickly in the same piece of equipment. Agglomerates produce in high shear mixers are generally more spherical because of high shear forces. On the other hand, It is capable to produce the agglomerates with high binder content with the use of low shear forces in fluid bed processor than high-shear mixer and rotary processor[20].

The rotary processors are suggested as an alternative equipment for melt pelletization[20], also conventional fluid bed processors may not be suitable for pelletization. Highly spherical pellets can be obtained in fluid bed granulator when dominant mechanism of agglomeration is immersion and layering as suggested by recent studies. Despite some differences in particle size distribution and morphology of the granules. FHMG can be considered an alternative to melt granulation in high-shear mixers[21]. Investigation of the suitability of conventional fluid bed granulator as an

alternative equipment for melt pelletization was carried out by using two different binders, poly ethylene glycol 2000 as hydrophilic meltable binder and glyceryl palmitostearate as hydrophobic.

FACTORS AFFECTING MELT GRANULATION[5]

The growth processes and formation of melt agglomerates are governed by formulation, processing, and equipment variables to a greater extent than those of conventional wet agglomerates as a result of the involvement of high impeller speeds and high shearing forces for agglomeration and viscous molten binding liquid.

The effect of Processing variables such as mixing speed, mixer load, mixing time, jacket temperature, and method of binder addition on melt agglomeration have been extensively investigated[16,17]. Typically, an increase in mixing speed or mixing time promotes agglomerate growth through squeezing the molten binding liquid from agglomerate core to surfaces by means of a densification process, thus increasing the degree of liquid saturation of agglomerates and their propensity to grow by binary coalescence following the collision between two or more plastically deformable surfaces. Under the continuous stirring action of impeller rotation, the deformable surfaces of these agglomerates can be rounded via intra-agglomerate rearrangement of particles leading to the formation of spherical pellets.

The influences of equipment variables on melt agglomerate growth are more marked with high-shear mixers than with low-shear mixers and fluid bed granulators. One main reason is that the intensity of shearing forces is greater in high-shear mixers. The high shearing forces promote a more even distribution of molten binding liquid making the size distribution of melt agglomerates becoming narrower. The level of shearing Forces generated in a high-shear mixer is dependent on the geometry of impeller blade, design of processing chamber, and relative dimension between the blade and chamber[16]. The construction of both impeller blade and processing chamber can have a significant impact on the flow pattern of processing material. The use of a truncated cone-shaped lid and an inner wall lining made of polytetrafluoroethylene reduced the adhesion of mass undergoing agglomeration onto the wall of the processing chamber. Variation in the curvature of impeller blade and the distance from its base to the floor of the chamber likewise brought about changes in the flow pattern of the wet mass[17] .The pattern of material flow is related to the mechanical force distribution and homogeneity of melt agglomeration.

In the case of formulation variables, the effects of size, size distribution, shape, density, and packing properties of fine solid particles have been reported .The use of solid particles of mean size smaller than 10μm is usually problematic in melt agglomeration because a very high level of liquid saturation is need to overcome the high agglomerate strength resulting from the

cohesiveness of small particles in order to provide sufficient agglomerate deformability for growth This in turn can lead to a potentially uncontrollable melt agglomerative process. Generally, solid particles with size ranges between 20 and 25 µm are preferably for the production of melt agglomerates. The effects of size, size distribution, shape, density, and packing property of fine solid particles on melt agglomeration are interdependent. size, size distribution, shape and density affect the packing geometry of solid particles, bound by molten binding liquid , within the agglomerates. The strength of particulate interlocking, state of liquid distribution, and saturation of agglomerates can be altered via the modification in these properties of fine solid particles.

The effects of binder volume, binder rheology, binder surface property, and binder particle size on melt agglomeration have largely been reported in relation to the influences of other formulation or processing variables. The growth of melt agglomerates is promoted predominantly by an increase in viscosity tack, and specific volume as well as a decrease in surface tension of the molten binding liquid.

Materials Used In the Melt Granulation Technique

Melt granulation (MG) is a rising technique based on the use of binders having low melting point (between 50 and 80◦C) and act as a molten binding liquid.

Criteria for selection of carriers

Since the carrier in the solid dispersion affects the dissolution rate of drug from the surface. So the selection of carrier has an ultimate influence on the dissolution characteristics of dispersed drug, therefore hydrophilic carrier results in a fast release of drug from dispersion and a poorly soluble or insoluble carrier leads to slower release of drug particles, and thereby hampers the drug solution, but can be used for sustained release of drug. Usually the carrier forms the bulk of solid dispersions. The carriers used for dispersion should possess following properties.

- Physiologically inert
- Soluble in fast release or insoluble for sustained release.
- Melting point typically within the range of 50-100^{0}C.
- Relatively low vapour pressure .
- Thermal stability up to its melting point
- Non-toxic, non- irritant
- Organic in nature

The commonly used carriers

Sugars

Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol, Mannitol, Lactose

Acids

Citric acid, Tartaric acid, Succinic acid

Surfactants

Polyoxyethylene stearate, Renex, Poloxamer, Texafor, Deoxycholic acid, tweens and spans Gelucire.

Polymeric materials

PVP, PEG, CMC, HPMC, Guar gum, Xanthan gum, Sodium Alginate, Methylcellulose, Pectin, Hydroxyethylcellulose, Hydroxypropylcellulose, Cyclodextrin, Galactomannan,

Miscellaneous

Pentaerythritol, Urea, Urethane, Hydroxyalkylxanthines

The carrier presence not only prevents aggregation/agglomeration of individual drug particles exhibiting a high solid liquid interfacial tension but it also creates a microenvironment in which the drug solubility is high.

Various hydrophilic and hydrophobic binders used in the preparation of pharmaceutical formulation are as below in the table 1.

Table 1: **Hydrophilic and Hydrophobic Meltable Binders in the Melt Granulation Technique.**

Hydrophilic meltable binder	Typical Melting Range (^{0}C)	Hydrophobic meltable binder	Typical Melting Range (^{0}C)
Gelucire50/13	44-50	Bees wax	56-60
Poloxamer 188	50.9	Carnauba wax	75-83
PEG 2000	42-53	Cetyl Palmitate	47-50
PEG 3000	48-63	Glyceryl stearate	54-63
PEG 6000	49-63	Hydrogenated castor oil	62-86
PEG 8000	54-63	Microcrystalline wax	58-72
		Paraffin wax	47-65
		Stearic acid	46-69
		Stearic alcohol	56-60

Criteria for selection of drug

- Having poor water solubility
- Therapeutically significant
- Thermal stability up to its melting point
- Melting point should be not more than 250 C
- Relatively low vapour pressure

APPLICATIONS

Dissolution rate improvement and drug bioavailability enhancement

Dissolution rate of compounds which are poorly soluble are improved using the technique called melt granulation. It is a proven fact that enhancement in vitro dissolution rate of ibuprofen can be successfully done with the help of melt granulation using poloxamer188 as a melting binder[2]. Water insoluble model drug as Carbamazepine (CBZ) and lactose as hydrophilic filler are used in agglomeration process of both wet and melt nature[3]. Consideration of fast release rate formulation by melt granulation as feasible process is done. Employment of Polyethylene glycol (PEG) 4000 as a melting binder is considered for its low melting point, conducive solution property, fast solidification rate, low cost[22] and toxicity as a result a viable dissolution enhancer for Carbamazepine in solid dispersions and in-extrudates that are made using hot melt extrusion are done using melting binder also CBZ dissolution enhancer crospovidone as a disintegrant agent were taken into consideration[23,24]. The dissolution rate of griseofulvin can be enhanced using melt granulation has been proved thus it can be attributed that hydrophilic character of the system increases the dissolution rate because of the presence of water soluble carriers (PEG 3350, Gelucire 44/14). Praziquantel(PZQ) dissolution rate can also be enhanced by the preparation of granules in high shear mixer using melt granulation. This process also uses Polyethylene glycol 4000 and poloxamer188 as meltable binder and filler in the form of lactose monohydrate.

Drug release modification or controlling

It has been observed that release matrix tablet which were made using the technique of melt granulation were sustained while preparing diclofenac sodium .It can be considered as a fresh technique where you first add water-soluble drug in wax matrix using the process of melt granulation and thereafter this matrix is granulated using hydrophilic polymers. In the above process, It was assumed that when hydrophilic and hydrophobic polymers are used to make matrix tablets. It will give the expected slow release profile. Water soluble and short life diclofenac sodium is selected as a model drug. Final development of sustained release matrix tablets were done with the combination of various hydrophilic polymers like sodium alginate, sodium CMC , HPMC-K4M etc and hydrophobic polymer stearic acid.

Stability Enhancement of moisture sensitive drug

To develop commercially viable compositions using moisture-sensitive therapeutic compounds is very challenging. The reason being their incompatibility with excipients containing high intrinsic moisture also during long term accelerated stress stability conditions[25] , they have high propensity for moisture uptake. The degradation rate of active pharmaceutical ingredients are influenced by

the pharmaceutical excipients that are helpful for solid formulation in case of moisture sensitive drugs[26]. Moisture content is highly dependent on the physical and chemical properties of pharmaceutical solids. Some of these properties include compaction, powder flow , dissolution , stability upon storage etc.

Improvement of tabletting properties for poorly compatible high dose drug

Melt granulation process which uses a twin- screw extruder with the help of metformin Hcl as model drug and hydroxyl-propyl cellulose(HPC) as the polymeric excipients is developed to enhance tabletting properties of poorly compactible high- dose drug.

CONCULSION

The above said article provides a glimpse of melt granulation technologies that are prevalent in pharmaceutical industry. A careful and judicious choice of available technology to carry out the granulation process can be a main pillar in achieving final product parameters. Detailed Knowledge of processing techniques and their pros and cons plays a dominant role in developmental state of the product. This review article pinpoints towards substantial information that will be helpful for researchers and scientist involved in product developmental stage.

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