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A Review on Hot Melt Granulation

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ABSTRACT

Granulation transforms fine powders into larger, more manageable granules, ensuring a uniform mixture. This process, crucial for particle design, falls into two main categories: wet and dry granulation. The size of the resulting granules is controlled by the amount and rate of liquid added during wet granulation. Modern granulation techniques, such as foam binder, fluidized bed, hot melt, and spray drying, have expanded the process's capabilities. This review explores principles behind Hot Melt Granulation, key factors influencing the process such as Reasons for conducting granulation process, Techniques of granulation, methodology of hot melt granulation**,** commonly used binder during hot melt granulation (hydrophilic & lipophilic binders) its potential to enhance solubility, and recent advancements in its application. HMG including the need for precise thermal control and the compatibility of excipients with the active pharmaceutical ingredient, the review provides insights into the future of this technique for improving drug solubility.

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INTRODUCTIOpN

The process by which everything crystallizes into granules is called granulation. There are two methods of granulation techniques: Wet granulation and Dry granulation. Some of the most recent granulation

techniques include steam granulation, foam binder technology, hot melt granulation, pneumatic dry granulation, and freeze granulation. [shown in fig. no.1]

Hot Melt Granulation (HMG) is being used in an increasing number of pharmaceutical formulations for improvement of solubility and bioavailability of drugs which are not soluble in water.[1] This process involves heating and granulating a medication and excipient combination, usually in the form of molten binder. The process creates granules with better flow properties and smaller particles, which can significantly accelerate the drug's rate of degradation. A variety of excipients, such as fatty acids, waxes, and polyethylene glycols, are used to regulate drug release profiles and to optimize the melting points. Hot Melt Granulation has several advantages over traditional granulation methods, including easier processing and solvent elimination.

Hot Melt Granulation, often referred to as melt granulation, it is based on agglomeration of a binder material that is solid at room temperature and softens after heat & gets melts at higher temperature. Binders that dissolve in water are used for hot melt granulation. [2]

The various binders are used for melt granulation for pharmaceutical applications [shown in Table no.1, 2]. The binder used during hot melt granulation is one of the main determinants of granule quality by using hydrophilic binders immediate-release systems are formed as the granules disintegrate quickly or dissolves in aqueous media. [3,4]

as compared, a sustained-release dosage form is prepared with melt granulation using hydrophobic binders as the water insoluble binder retains its matrix structure in aqueous media. [5,6].

As the action of the melt binder is same to the action of liquid (water, organic solvent) added during wet granulation, so that most of the hot melt granulation methods are work using the same equipment as that of the wet granulation. [7,8]

ADVANTAGES

- Improved drug solubility and bioavailability
- Enhanced granule properties
- Exclude the solvents from being used in process.
- Stability enhancement.
- Compatibility with excipients.

- Waxes, fatty acids, polyethylene glycol (PEG), and others, providing flexibility in formulation design.
- Enhanced manufacturing process.
- It shows fast disintegration time.

DISADVANTAGES

- It is a thermal process so, it may result drug degradation and polymer instability.
- It requires high energy input.
- Limited polymer availability.
- Heat sensitive materials are poor candidates for hot met granulation technique.
- When handled or stored, a binder with a lower melting point may melt or soften.

Reasons for conducting granulation process:

- To enhance the flow properties.
- To prevent the problems of dust during compression.
- To produce uniform size particles.
- To improve drug compressibility.
- To regulate drug release by the formulation.

TECHNIQUES OF GRANULATION [13]

The various techniques are used for the granulation, the some of these are given in fig. no. 1

GENERAL METHODOLOGY OF HOT MELT GRANULATION: [9,10,11,12,16]

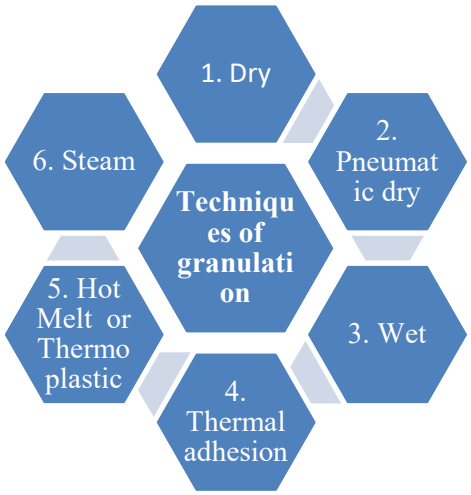

Fig 1; Techniques of granulation

The general steps involve in the methodology of hot melt granulation as given in the below fig. no. 2

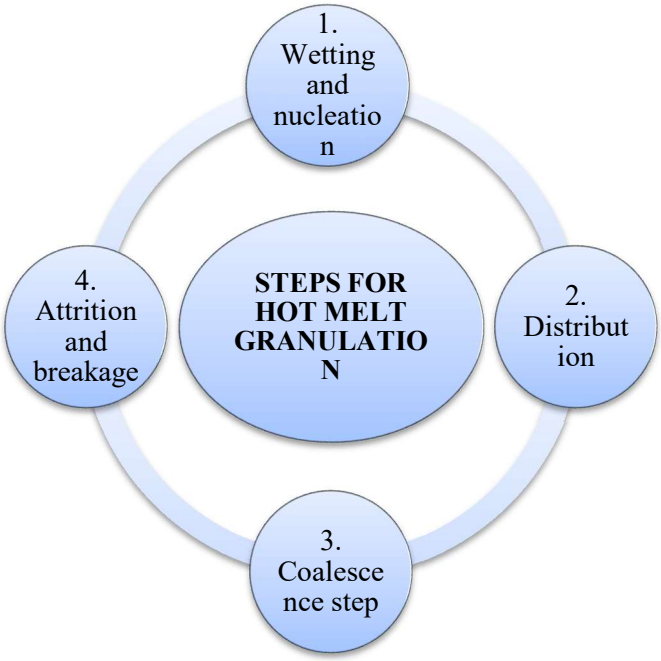

Fig 2; methodology of hot melt granulation

The most common method for hot melt granulation of powders has been high-shear mixers, and the substantial research has established the several factors influencing granule quality [9,10,11,12]. These studies identified the following critical variables: product temperature, atomization pressure, mixing time,

impeller speed, properties of solid non-melt able particle's, binder content, binder type, binder particle size, and binder rheology.

1. Wetting and nucleation step

- During the nucleation step the binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates. Two nucleation mechanisms are I. Immersion II. Distribution Immersion
- Wetting and nucleation step During the nucleation step the binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates.

2. Distribution step

- A melted binding liquid is distributed into the fine solid particles.
- The nuclei are formed by the collision between the wetted particles.
- Generally, small binder droplet size, low binder viscosity, and high shearing force this are the favourable parameters for nucleation by the distribution method.

3. Coalescence step

- It involves nuclei that has residual surface liquid to promote successful fusion of nuclei.
- The surface liquid imparts plasticity to the nuclei and is essential for enabling the deformation of nuclei surface for coalescence as well as promoting the rounding of granulation.

4. Attrition-breakage step

- The terms attrition-breakage describe the fragmentation of granules that is consolidated by tray cooling to room temperature without the requirement for tumble drying.
- Breakage is therefore understood to have a more crucial function in influencing the final qualities of hot melt granulation during the granulation.

Conditions of hot melt granulation [25,26]

- A meltable binders of hot melt granulation has a particular melting point within the range of 50–90 ºC.
- Hydrophilic meltable binders are used to prepare immediate-release dosage forms while the hydrophobic meltable binders are preferred for modified-release formulations.

- It needs to maintain a solid form under typical room conditions.

Commonly Used Binders During Melt Granulation

1)Hydrophilic meltable polymers

The hydrophilic meltable polymers are given in table 1

Table1; hydrophilic meltable polymer

Sr. no.	Hydrophilic meltable polymers	Melting point
1	Gelucire 50/30	46-51 ºC
2	Polyethylene Glycol 2000	58 ºC
3	Polyethylene Glycol 3000	64ºC
4	Polyethylene Glycol 4000	65ºC
5	Polyethylene Glycol 6000	70ºC
6	Polyethylene Glycol 8000	75ºC
7	Poloxomer 407	53ºC
8	Poloxomer 1800	52ºC
9	Poloxomer 188	52-57 ºC

2) Hydrophobic meltable polymers

The lipophobic meltable polymers are shown in table no. 2

Table2; lipophobic meltable polymers

Sr. no.	Hydrophobic meltable polymers	Melting point
1	Beeswax	64ºC
2	Carnauba wax	82ºC
3	Microcrystalline wax	60-90ºC
4	Paraffin wax	46-48ºC
5	cetyl alcohol	58ºC
6	Palmitic acid	62ºC

Examples of formulation prepared by Hot Melt Granulation

Sr. No.	Therapeutic molecules	Polymers	Result	Ref. no.
1	Carbamazepine	polyethylene glycol 4000	Fast-release tablets	2
2	Griseofulvin	PEG 3350 Gelucire 44/14	Enhancing the solubility of griseofulvin, a drug that dissolves poorly in water.	3
3	Ibuprofen	Poloxamer 188	Immediate release tablet.	4
4	Apixaben	PEG/ Gelucire	For enhancing solubility by formation of amorphous forms.	21
5	Fenofibrate	polyethylene glycol-6000 surfactant poloxomers-407	Enhancement of solubility and dissolution rate	22
6	Zolpidem tartrate	PEG 6000 PVP K30 HPMC K4M	Controlled release formulation	24
7	Curcuminoid	Gelucire® 50:13	Increase in solubility of curcumin	25
8	Cefpodoxime proxetil	poloxamer 1800	Eutectic forming by API incorporated into polymer by hot melt granulation technique.	26

CONCLUSION

In the hot melt granulation process, cooling is utilized to extract the water from the wet granulation process rather than drying. Heating and cooling may be done simultaneously in the same piece using the molten granulation technique. To further automate the process, power usage may be utilized to determine the granulation end point. Scaling up the melt granulation process has been successful, as seen by the production of repeatable product qualities. It has been demonstrated that the hot melt granulation process works well for both immediate-release and sustained-release dose forms respectively.

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