WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 10, 249-263. Review Article ISSN 2277– 7105

HOT MELT EXTRUSION TECHNIQUE FOR SOLID ORAL DOSAGE FORM - A REVIEW

Gitanjali Shivaji Bhatjire* and Kishor Sahebrao Salunkhe

Department of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner 422605, India.

Article Received on
10 July 2017,

Revised on 31 July 2017,
Accepted on 21 August 2017

DOI: 10.20959/wjpr201710-9327

***Corresponding Author**
Gitanjali Shivaji Bhatjire
Department of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner 422605, India.

ABSTRACT

Interest in hot melt extrusion technique for pharmaceutical application is growing rapidly as HME offers several advantages over traditional pharmaceutical techniques. Hot, melt extruded dosage forms are complex mixture of active medicaments, functional excipients, and other processing aids. Melt extrusion or agglomeration is a process in which agglomeration or size enlargement of fine particles which bound together to form agglomerates or granules. Granulation may be defined as a size enlargement process which converts small particles into physically stronger and larger agglomerates. Granulation is performed for improving flow, compression characteristics and content uniformity, eliminating generation of fine particles thereby increasing bulk density and productivity of the product. Hot melt extrusion is advance granulation technique achieved by the addition of meltable binder which is in solid state at room temperature but melts in the temperature range of 50-80^0 c. Melted binder then acts like a binding liquid, granules are obtained by cooling it to room temperature. This method is an appropriate alternative to wet granulation for water sensitive materials and it is efficiently applied to enhance the stability of moisture sensitive drug and to improve the poor physical properties such as floe properties. Tablets are solid oral dosage forms containing medicinal substances with or without suitable diluents, manufactured by compression or molding. This review majorly focuses on the hot melt extrusion-an innovative granulation technique and its critical process parameters, evaluation methods for granules and tablets, some of the marketed products available which are prepared by HME technique.

KEYWORDS: Hot melt extrusion, meltable binder, critical process parameters, and granulation.

1. INTRODUCTION[1,2,17,12,6,5,7,9]

1.1. Granulation

It is the most significant operation in the production of pharmaceutical solid oral dosage forms. Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle aggregate called granules. Pharmaceutical granules usually made in the size range of from 0.2 to 0.4 mm, depending on their subsequent application. After granulation process, the granules will either be packed or they may be mixed with other excipients prior to tablet compression or capsule filling.

Essential properties of granules: granules should have

- Spherical shapes
- Smaller size, particle size distribution with sufficient fines to fill void spaces between granules.
- Optimum moisture content (1-2%)
- Good flow
- Good compressibility

1.2. Hot melt extrusion

1.2.1. Definition: Hot melt extrusion is the process of embedding drug in a polymeric carrier. It is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions. This is a recognized manufacturing process that has been used in the plastics and food industries since the 1930s. Melt extrusion process based on polymers with high glass transitions temperatures such as polyvinylpyrollidones to pharmaceutical is raised in 1980s. Several research groups have demonstrated that the HME process is a viable technique for the preparation of pharmaceutical drug delivery systems, including granules, pellets, sustained release tablets and implants. In melt extrusion method, the drug/carrier mix is typically processed with a twin-screw extruder. The drug/ carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. HME offers many benefits over traditional processing techniques as given in following table. HME can be simply defined as the process of forming a new material called extrudate by forcing it through an orifice or die under controlled conditions. Such as temperature, mixing, feed rate and pressure. ME differs from simple extrusion in that polymer, drug and excipient blends are mixed thoroughly in the

molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder. Melt granulation is an appropriate alternative to other wet granulation techniques which are used for water sensitive materials.

Table 1: Benefits of HME over traditional processing.[12]

Sr. No.	Traditional process of aqueous & organic solvent extrusion	Hot melt extrusion
1	Require solvent & drying step	An anhydrous process and no solvent is required
2	May be a concern for moisture sensitive drugs	Suitable for moisture sensitive drugs
3	Aqueous extrusion mostly involves the use of microcrystalline cellulose (MCC) which yields no disintegrating pellets and lowering of drug load may be required to increase the API release	No such limitation
4	Large amount of water is required for granulation and hence long drying times	No such limitation
5	Organic solvent extrusion is suitable for moisture sensitive drugs, but the non-volatile organic solvents and oils result in sticky products and the large amount of volatile solvents required for granulation	No such limitation
6	Multi-step, non-continuous process: at least for spheronization	A fast-continuous manufacturing process without the requirement of drying and a short thermal exposure of active allows processing of heat sensitive drugs

1.3. Process

In hot melt extrusion, a blend of polymer and excipients in powder form is transferred by a rotating screw through the heated barrel in the extruder. The molten mass is continuously pumped through the die at the end of the extruder and rapidly solidifying when existing the machine. The screw itself is divided into three parts; feeding, melting and metering zone. The extrusion barrel with an extruder can be divided into following zones:

1. **Feeding zone:** The objective of this zone is to convey material from hopper to barrel.
2. **Melting zone:** The purpose of this zone is to heat / melt the material and reduce its viscosity.
3. **Mixing zone:** In this zone, the material moves in a helical path by means of transverse flow, drag flow, pressure flow and leakage.
4. **Metering zone:** It helps to reduce the pulsating flow of molten mass so that consistent product comes out.

5. **Venting zone:** Remove any of the volatile materials and gases generated during processing.
6. **Shaping zone:** The shape of the extrudate is determined by the shape of the die.

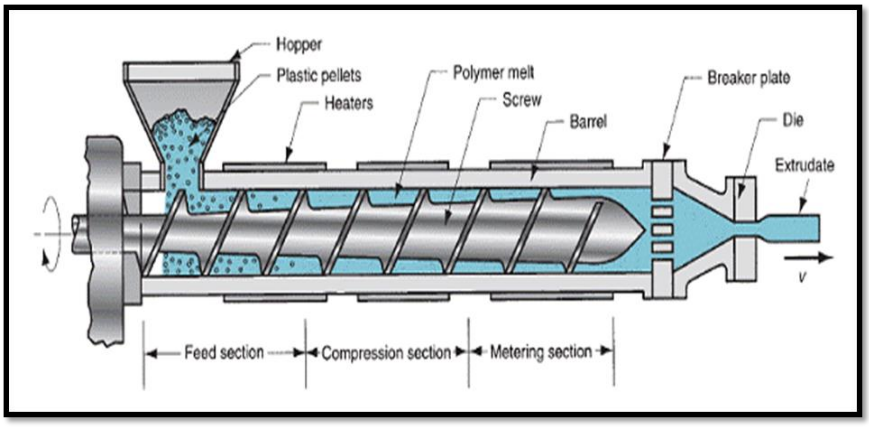

Fig. 1: Heating barrel with different sections in Hot melt extruder.

HME technology offers several distinct advantages over manufacturing techniques that have beem typically used to produce orally administerd solid dosage forms. The technique does not involve a granulation fluid and thus avoids problems associate with instability. At the most fundamnetal level, a single screw extruder consist of one rotating screw positoned inside a stationary barrel, whereas more advanced machines involve twin screw systems using either a co rotating or counter rotating screw configuration.

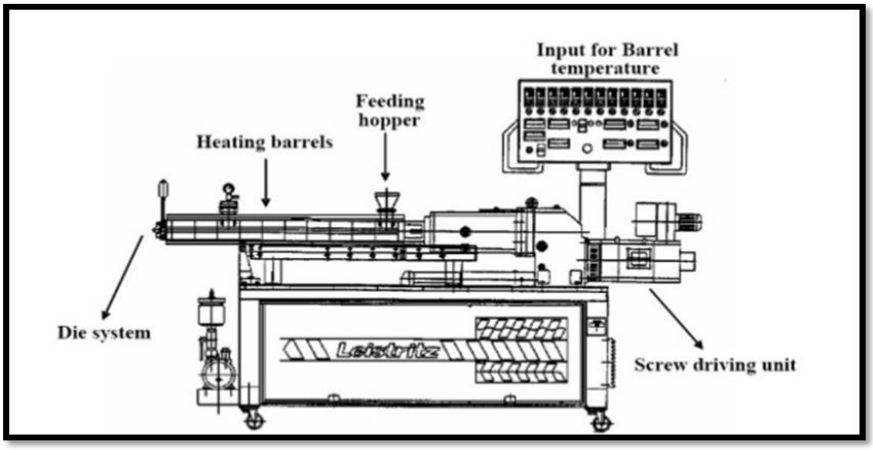

Fig. 2: Twin screw co rotating leistritz extruder.

Hot melt extrusion provides a continuous manuafcturing process for moisture sensitive thermo stable drugs. Extruder are of different types and twin screw extruder is the most widely used.[20]

2. Critical Process Parameters[18]

As the extruder has several zones the barrel of the zone can be heated to a desired temperature depending upon the temperature profile required for extrusion process.

2.1. Barrel temperature: extrusion temperature profile of various zones is dependent upon glass transition or melting temperature of polymer used and degradation temperature of the drug.

2.2. Feed rate and screw speed: The constant feeding rate and screw speed throughout the process is important as the combination of these two factors establishes the level of fill in the extruder. Due to constant feed rate and screw speed, there will be a constant amount of material in the extruder and thus the shear stress and residence time applied to material remains constant.

2.3. Melt viscosity: Melt viscosity is dependent upon the barrel temperature and molecular weight of the polymer used.

2.4. Melt pressure: Melt pressure and melt temperature are the most important parameters as these are the best indicator of extruder function. Process problems become obvious from their value. However, it cannot be controlled directly as it is affected in a complex manner by changing other process parameters such as screw rotation speed and temperature profile.

2.5. Melt temperature: Melt temperature is a actual temperature at which blend start melting. It is function of melt pressure, barrel temperature and viscous heat dissipation.

2.6. Die temperature: Die temperature indirectly determines the viscosity and pressure that are necessary to overcome the resistance of the die leading to output.

2.7. Die design: The design of the die decides the shape of the extrudes.

3. Components of the Formulation[24]

Hot melt extruded dosage forms are complex mixtures of active drug and excipients. The excipients may be broadly classified as matrix carriers, release modifying agents, bulking agents and various additives. The excipients can impart specific properties to melt extruded pharmaceutical in manner like those in traditional dosage form. Components of the formulation are,

1. Drug/API
2. Meltable Binder
3. Plasticizer
4. Thermal Lubricant
5. Glidant

Table 2: Components of the hot melt formulation.

Sr.No.	Ingredient	Amount
1	Drug	20-40%
2	Meltable Binder	10-30%
3	Plasticizer/ Surfactant	5-30%
4	Glidant	0.25-3%
5	Thermal Lubricant	0.5-2%

3.1. Active pharmaceutical ingredient

HME is a relatively new technique to the pharmaceutical industry. The process is anhydrous, thus avoiding any potential drug degradation from hydrolysis. In addition, poorly compactable materials can be incorporated into tablets produced by cutting an extruded rod, thus eliminating any potential tableting problem seen in traditional compressed dosage forms. The properties of the active drug substance always limit the formulation and processing choices available in the dosage forms development e.g. incompatible ingredient and processing temperature. Depending on the properties of the drug substance and the other material, the drug may be presented as solid dispersion, a solid solution, or a combination in the final dosage form. In hot melt extrusion, the active compound is embedded in a carrier formulation comprised of one or more meltable substances and other functional excipients. The meltable substances may be polymeric material or low melting point waxes. Active ingredients selected must be stable at the processing temperature and be capable of mixing in Molten state. It should be compatible with the polymer and other excipients used in the process.

3.2. Carriers[8,4,10]

The selection of polymer for hot melt extrusion process mainly depends on drug polymer miscibility, polymer stability and function of final dosage form. A variety of carrier systems have been studied or used in hot melt extrusion dosage forms. In hot melt extrude dosage form, the active drug is embedded in the carrier which must be able to deform easily and remains stable during processing. The molten carriers functioned as thermal binder and drug

release retardants. Typical carrier materials include vinyl polymer, polyethylene oxide, and acrylates, polyethylene glycol, and cellulose derivatives.

3.3. Binders as a carrier for melt extrusion[14,17]

- Usually, meltable binder at a concentration of 10-30% w/w, with respect to the fine solid excipients is used.
- The meltable binder should have the melting point in the range of 50-100^0 c.
- Hydrophilic meltable binders are employed to produce immediate release formulations, while hydrophobic meltable binders are preferred for prolonged release formulations.
- The melting point of other fine solid excipients should be at least 200^{0}c higher than that of maximum processing temperature.
- These polymers are mainly used as binder in tablet formulations or as matrices to increase the bioavailability of poorly water soluble drugs by improving their dissolution rate. Copovidone is a copolymer consisting of the monomers vinylpyrrolidone and vinyl acetate (VA), which has a molecular weight of around 55000 Da and Tg of 101^{0}c.

The most important newer technology for the application of Copovidone (Kollidon VA64) as binder and matrix former is the melt extrusion. In this technology, they also can be combined with surfactants. A drug containing Kollidon VA 64 and the anti HIV protease inhibitors, lopinavir and ritonavir was the first co formulated pharmaceutical compound to be successfully tableted using a proprietary melt extrusion process. The melt extrusion appears to have overcome the poor solubility and negligible oral bioavailability of previous formulations of lopinavir/ritonavir.

3.4. Thermal lubricant[12]

Thermal lubricant is defined as materials which are added into the formulation to improve its processability. Thermal lubricants decrease the melt viscosity of the molten materials and reduce the friction of molten material in the extruder during processing. Unlike plasticizers thermal lubricants have just little effect on the solid state properties. Thermal lubricant is also affecting the final product properties. Glycerol monostearate, wax material, are two examples of the thermal lubricant.

3.5. Glidant[13]

Helps in free flowing of granules from hopper to die cavity. Minimize friction between particles. Examples Colloidal Silicon dioxide (aerosol), cornstarch, talc etc. silica derivative colloidal silica such as Cab-O- sil, Syloid.

3.6. Plasticizer[3,12]

Plasticizer is used to reduce the glass transition temperature and thus melt viscosity of a polymer leading to facilitate the hot melt extrusion process. Plasticizers are low molecular weight compounds capable of softening polymers to make them more flexible and lower the processing temperature of the HME, which can reduce the degradation of thermolabile APIs. Conventional plasticizer such as triacetin or polyethylene glycol is used in concentration range of 5-30% weight of the extrudate that lowers the processing temperature. The application of HME in bioavailability enhancement can be best understood from the case of protease inhibitors Kaletra (Lopinavir plus Ritonavir) as prescribed in United States patent application by Rosenberg et.al. The invention claims a dosage form comprising a solid dispersion of the drug and a water-soluble polymer such as Copovidone having a Tg of at least 50^0 and a surfactant such as sorbitan monolaurate having a hydrophilic–lipophilic balance (HLB) value of from 4-10.

3.7. Equipment[8]

Hot melt equipment consists of an extruder, auxiliary equipment for the extruder, downstream processing equipment and other monitoring tools used for performance and product quality evaluation. The extruder is typically composed of feeding hopper, barrels, single or twin screws, and the die and screw driving unit. The auxiliary equipment for the extruder mainly consists of a heating/cooling device for the barrels, a conveyer belt to cool down the product and a solvent delivery pump. Generally, the extruder consists of one or two rotating screws inside a stationary cylindrical barrel. The barrel is often manufactured in sections, which are bolted or clamped together. An end plate die, connected to the end of the barrel, determines the shape of the extruded product.

4. Precompression Study[15,16,23]

Tablet formulation comprising different drug loading are prepare using HMG method. All the ingredients mixed as per specified ratio. HME process can be perform using single screw hot melt extruder equipped with a 100 mm long and 20 mm diameter screw using the following parameters: processing temperature 110±20 ^{0}c (much below the melting temperature of drug),

screw speed:50 rpm. The obtained product was then cooled to ambient temperature and subject to milling and sieving through a screen of # 40. The powdered extrude then subjected to tablet compression. The products obtained from all above operations are evaluated for their physicochemical properties.

4.1. Bulk density-BD[16]

It is performed by filling 100 ml glass cylinder to its capacity with the granules and then weighing it. The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in gram per ml although the international unit is kilograms per cubic meter because the measurements are made using cylinders. It may be expresses in grams per cubic centimeter. It is calculated by following formula;

Bulk density = weight of powder / bulk volume of powder

4.2. Angle of repose[25]

Angle of repose of the test materials can be assessed by the fixed funnel method. Powders are classified as "light" or "heavy". Light powders have high bulk volume. Fines (upto15%) increases angle of repose. Rough and irregular surface increases angle of repose. Lower the angle of repose better is the flow property. Angle of repose is commonly used to measure flow of powders, and is the maximum angle between the plane of powder and horizontal surface. The value of less than 30^0 usually indicates free flowing material. It is determined by the static funnel method and calculated using the formula;

Angle of repose ($\tan\theta = h/r$)

Table 3: The relationship between angle of repose and flowability.

Sr. No	Flow property	Angle of repose
1	Excellent	25-30
2	Good	31-35
3	Passable	41-45
4	Poor	46-55
5	Very poor	56-65

4.3. Compressibility index-CI

Compressibility index and hausner ratio are closely related: both are based on the comparison of "as poured" and tapped bulk density. Both the US and European pharmacopoeia already

have separate monographs that defines methods for determining bulk density and tapped density. Compressibility index is defined as the percentage change in volume induced by tapping a sample of fixed mass. Hausner ratio is simply the unsettled volume divided by the tapped volume. It is calculated by the formula;

Compressibility index = Tapped Density-Bulk density/Tapped density×100

Hausner ratio = Tapped density/Bulk density

Table 4: The relationship between Compressibility Index/Hausner ratio and flowability.

Sr. No	Compressibility index	Flow characteristics	Hausner ratio
1	<10	Excellent	1.00-1.11
2	11-15	Good	1.26-1.34
3	32-37	Very poor	1.19-1.25
4	21-25	Passable	1.46-1.59
5	26-31	Poor	1.12-1.18

4.4. Tapped density- TD[16]

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and volume or mass readings are taken until little further volume or mass change is observed. It is calculated by following formula;

Tapped density = Weight of powder/Tapped volume

4.5. Particle size distribution study-PSD[27]

Knowledge and control of the size, and the size range, of particles is of a profound importance in pharmacy. Thus, the size, and hence the surface area, of a particle can be related in a significant way to the physical, chemical and pharmacological properties of a drug. Clinically, the particle size of a drug can affect its release from dosage forms that are administered orally. In the area of tablets and capsules manufacture, control of the particle size is essential in:

- Achieving the necessary flow properties, and
- Proper mixing of granules and powders.

Sieve method: This method is the simplest and the most widely used method of determining particle size distribution.

1. Weigh accurately 100g of the supplied powder, then place on the top sieve of the stack of sieves, cover and shake (mechanically) for 15 minutes.
2. Weigh the remaining powder on each sieve.
3. Tabulate your results.
4. Plot the required curves for particle size distribution.

5. Compressed Tablet Evaluation[19,26]

5.1. General Appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

5.2. Size and shape

It can be dimensionally described and controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by another device. Tablet thickness should be controlled within a ±5% variation of standard value.

5.3. Hardness and friability

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. Tablet hardness can be defined as force required for breaking a tablet in a diametric compression. In this test the tablet is placed between two anvils, force is applied to anvils, and the crushing strength that just causes the tablet to break is recorded. Generally used hardness testers are:

- Monsanto tester
- Strong-cob tester
- Pfizer tester
- Erweka tester

5.4. Friability

Friability of tablet can be determined in laboratory by Roche friability. This consists of plastic chamber that revolves at 25 RPM, dropping the tablets through a distance of six inches in the friability, which is then operating for 100 revolutions. The tablets are reweighed and friability percentage was calculated using the following equation,

$$\%\text{Friability} = \frac{\text{Tablet wt. before friability - Tablet wt. after friability}}{\text{Tablet wt. before friability}}$$

5.5. Weight variation test

Take 20 tablets and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table 5: Weight variation limit for tablet.

Sr. No.	Average weight of tablets(mg)	Maximum percentage difference allowed
1	130 or Less	± 10.0
2	130-324	± 7.50
3	More than 324	± 5.0

5.6. Content uniformity

Randomly select 30 tablets. 10 of these assayed individually. The tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10^{th} tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

5.7. Disintegration test

The USP device to test disintegration uses 6 glass tubes that are 3” long; open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1litre beaker of water, simulated gastric fluid or simulated intestinal fluid at 37± 20 such that the tablet remains 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. According to the test the tablet must disintegrate and all particles must pass through the 10-mesh screen in the time specified. If any residue remains, it must have a soft mass.

- Disintegration time: uncoated tablet: 5-30 minutes
- Coated tablet 1-2 hrs

6. Marketed Formulations by Hot Melt Extrusion[18,21]

Several companies have been recognized to specialize in the use of HME as a drug delivery technology, Kaletra (Ritonavir/Lopinavir). Kaletra is mainly used for the treatment of human immunodeficiency virus (HIV) infections. The formulated, melt-extruded product was shown to have a significant enhancement in the bioavailability of active substances.

Table 6: Marketed formulations of Hot melt extrusion technique.

Sr No	Generic Name	Brand Name	Compositions
1	Ritonavir/Lopinavir	Kaletra	Copovidone, colloidal silicon dioxide, sorbitan monolaurate
2	Itraconazole	Sporanox	Sugar, HPMC, gelatin, PEG
4	Rosuvastatin	Crestor	Hypromellose, Crospovidone, lactose, MCC
5	Ibuprofen	Solufen	NA
6	Griseofulvin	Gris-PEG	Colloidal silicon dioxide, mg. stearate, methyl cellulose, povidone
7	Tacrolimus	Prograf	Lactose, HPMC, Croscarmellose sodium

CONCLUSION

Hot melt extrusion, a process used to disperse or dissolve a drug in a molten polymer, has become increasingly important in pharmaceutical due to the possibility of dissolving poorly soluble drugs in a solid solution. It is very important method for solubility enhancement and major advantage over conventional techniques for manufacturing of sustained release matrices. It is the process that involves different steps like mixing, melting, homogenizing and shaping can be carried out on single machine. The resultant product yields matrices with excellent homogeneity. Optimization of process parameters and selection of polymer are the critical factors during HME process. These factors are considered because HME process takes place at higher temperatures.

ACKNOWLEDGMENT

I would like to thanks Amrutvahini College of pharmacy, sangamner, India for continuous support and encouragement throughout this Review work.

7. REFERENCES

1. Pharmacopoeial forum in- process revision, Sep.-Oct. 2009; 35(5): 1270.
2. Mahammed A, Saikh A, A technical note on granulation technology: a way to optimize granules, Int J Pharm Sci Res, 2013; 4(1): 55-67.
3. Patel PS, Raval JP, et.al. Review on the pharmaceutical applications of hot melt extruder, A J Pharm Cli Res, 2010; 3(2).

4. Sravya I, Tablets manufacturing methods and granulation techniques, Res Rev J Pharm Toxi Std, 2016; 4(3).
5. Shanmugam S, Granulation techniques and technologies: recent progresses, Bioimpact, 2015; 5(1): 55-63.
6. Reddy MS, Soujanya CH, Fazal MD, Enhancement of dissolution rate and solubility of losartan potassium by using solid dispersion method β-cyclodextrin as carrier, W J Pharm Res, 2015; 4(12): 1316.
7. Kolter K, Kael M, Geyczke A, Hot melt extrusion with BAFS pharm polymers, extrusion compendium, 2nd revised and enlarged edition, 2012; 19.
8. Jagtap PS, Jain SS, Dand N, Jadhav KR, Kadam VJ, hot melt extrusion technology, approach of solubility enhancement; a brief review, 2012; 4(1): 42-53.
9. Gavin P, Andrews P, Trans R, Advance in solid dosage form manufacturing technology, 2007; 365.
10. Naturwissenschaften DD, Roland B, Maincent P, Hot melt extrusion for the production of controlled drug delivery systems, 2011; 19-20.
11. Singhal S, Hot melt extrusion technique, webmed central review articles.
12. Solankhi HK, Patil KB, Gohel SN, Hot melt extrusion; an emerging technology in pharmaceuticals, W J pharm Sci, 4(4): 404-423.
13. Varma KV, Excipients used in the formulation of tablets, RRJ Chem, 2016; 5(2).
14. Volker B, Pharmaceutical technology of BAFS excipients, BAFS the chemical company, 3rd revised edition, 2008.
15. Vaingankar P, Amin P, accepted manuscript, continuous melt granulation to develop high drug loaded sustained release tablet of metformin HCL, A J Pharm Sci.
16. US pharmacopoeia, Bulk density and tapped density of powders, convention stage 6 harmonization official, 2012; 616.
17. Subhash PG, Srilatha KS, Bachupally AK, Punnuru M, emphasis on novel granulation technologies: an overview, Ind Ame J Pharm Res, 2011; 1(4): 305-316.
18. Ridhurakar D, Hot melt extrusion and its application for pharmacokinetic improvement of poorly water soluble drugs, PTB reports, 2016; 2-3.
19. Sahoo Pk, Pharmaceutical technology tablets, 2007; 25-26.
20. Madana S, Madan S, Hot melt extrusion and its applications, A J Pharm Sci, 2012; 7(2): 123-13.
21. Ali S, Kolter K, Challenges and opportunities in oral formulation development, Ame Pharm Rev, 2012.

22. http://shodhganga.inflibnet.ac.in/bitstream/10603/8541/18/18_chapter%206.pdf.
23. Copley M, Reviews current methods for powder flowability testing, manufacturing chemist, 2008; 31.
24. Crowley MM, Zhang F, Repka MA, Thumma Shridhar, Pharmaceutical application of Hot melt extrusion Part I, D Dev Ind Pharm, 2007; 33: 909-926.
25. Kale VV, Gadekar S, Ittadwar AM, Particle size enlargement: making and understanding of the behavior of powder system, Systematic Reviews in Pharmacy, 2011; 2(2).
26. http://www.srmuniv.ac.in/sites/default/files/files/TABLET.pdf.
27. Fac.ksu.edu.sa/sites/default//files/particle_size analysis.docx.