



REVIEW ARTICLE

TABLET GRANULATION: CURRENT SCENARIO AND RECENT ADVANCES

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Abstract



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Granulation is a size enlargement process, in fine or coarse particles converted into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity, prevent segregation of the blend components, improve content uniformity, and eliminate excessive amounts of fine particles. Size of granules has a size range of 0.2 to 4.0 mm, depending on their subsequent use. Size of the granules depends on the quantity and feeding rate of granulating liquid. The selection of process to prepare granules requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, to name a few. At current scenario available technologies includes, spray drying, roller compaction, high shear mixing, and fluid bed granulation etc. The objective of present work is to focus on the commonly used and novel granulation technologies like such as pneumatic dry granulation, steam granulation, moisture-activated dry granulation, thermal adhesion granulation, freeze granulation, and foamed binder or foam granulation.

Keywords: Active pharmaceutical ingredients, content uniformity, granulation, moisture activated dry granulation technology.

INTRODUCTION

Granulation Technology is the art and science for process and production of granules in which primary powder particles are made to adhere to form larger, multiparticle entities called granules¹. Granules are used in production of tablets or capsules, when granules are prepared as an intermediate product and having size range between 0.2 and 0.5 mm, but larger granules are used as a dosage form in their own right².

Granulation process commences after dry mixing of the necessary powder ingredients along with drug to achieve uniform distribution of each ingredient throughout the powder mixture. Agglomerated granules are formed by solid bridges, sintering, chemical reaction, crystallization and deposition of colloidal particles³. After granulation the granules either packed, or they may be mixed with other excipients before tablet compaction or capsule filling⁴. The effectiveness of granulation depends on particle size of the drug and excipients, type of binder, volume of binder, wet massing time (less or more), amount of shear applied, drying rate (hydrate formation and polymorphism)⁵.

Reasons for granulation

1. To avoid segregation of the constituents.
2. To improve the flow properties of the mixture.

3. To improve the compaction of the powder⁶.
4. The granulation of toxic materials avoid hazard of toxic dust that may arise when handling powders⁷.
5. To avoid formation of cake in hygroscopic substances.
6. Granules occupy less volume per unit weight so more convenient for storage or shipment⁸.
7. To improve appearance of the product.
8. To improve compression properties of the mixture⁹.

Ideal characteristics of granules

1. It should have spherical shape for improved flow
2. It should have narrow particle size distribution for content uniformity and volumetric dispensing, sufficient fines to fill void spaces between granules for better compaction and compression characteristics¹⁰.
3. It should have adequate moisture and hardness to prevent breaking and dust formation during process¹¹.

Methods of granulation

- A. Dry granulation B. Direct compression
 C. Wet granulation

A. Dry granulation

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The primary powder particles are aggregated under high pressure. There are two main processes-

i) **Slugging**- Either a large tablet known as a 'slug' is produced in a heavy-duty tableting press¹².

ii) **Roller compaction**- the powder is squeezed between two rollers to produce a sheet of material.

In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction¹³. Steps involved in dry granulation process are-

1. Milling of drugs and excipients
2. Mixing of milled powders
3. Compression into large, hard tablets to make slug
4. Screening of slugs¹⁴.
5. Mixing with lubricant and disintegrating agent
6. Tablet compression

Advantages

1. It uses less equipments and space.
2. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation¹⁵.
3. Slugging can be advantages for moisture and heat sensitive materials and improved disintegration since powder particles are not bonded together by a binder.

Limitations-

1. It requires a specialized heavy-duty tablet press to form slug.
2. It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
3. The process tends to create more dust than wet granulation.

B. Direct compression

This method is used when ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed²⁶. However this is not very common because many tablets have active pharmaceutical ingredients which will not allow for direct compression due to their concentration or the excipients used in formulation are not contributory to direct compression²⁷.

Direct compression involves following steps:

1. Milling of drug and excipients
2. Mixing of drug and excipients
3. Tablet compression

Advantages-

1. It is more economic since the direct compression requires few unit operations.
2. More suitable for moisture and heat sensitive drugs.
3. The tablets prepared by direct compression exhibits comparatively faster dissolution.
4. Less wear and tear of punches.

Disadvantages

1. Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression.
2. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
3. In some cases, require greater sophistication in blending and compression equipments. Direct compression equipments are expensive²⁸.

C. Wet Granulation

Wet granulation process involves wet massing of the powder blend with a granulating liquid, wet sizing and drying. The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic²⁹. Typical liquids include water, ethanol and isopropanol, either alone or in combination.

Steps involved in the wet granulation

1. Mixing of the drugs and excipients
2. Preparation of binder solution
3. Mixing of binder solution with powder mixture to form wet mass.
4. Coarse screening of wet mass using a suitable sieve (6-12 screens)³⁰.

Advantages

1. It allows mechanical handling of powders without loss of quality of blend.
2. The flow properties of powder are improved by increasing particle size and sphericity¹³.
3. Increases and improves the uniformity of powder density.
4. Improves cohesion during and after compaction.
5. There is reduction of air entrapment.
6. Less dust and cross contamination.
7. The hydrophobic surfaces are made hydrophilic.

Limitations of wet granulation

1. It is an expensive process because of labor, time, equipment, energy and space requirements.
2. Loss of material during various stages of processing
3. Not suitable for moisture sensitive or thermo labile drugs³¹.
4. It involves multiple processing steps add complexity and make validation and control difficult
5. Incompatibility between formulation components is aggravated.

Advanced granulation techniques

1. Melt agglomeration/ thermoplastic granulation

This technique consists of the agglomeration of powder particles using binders that, which melts or softens at relatively low temperature (50–90°C). Solid fine particles are bound together into agglomerates by agitation, kneading, and layering in the presence of molten binding liquid³².

After cooling of the agglomerated powder and the consequent solidification of the molten or soften binder complete the formation of the granules.

It utilizes two methods one is spray on method that involves spraying of the molten binder onto the powder and by simple cooling of the product at room temperature followed by milling to obtain dried granules. Another one is in situ melt granulation method that employs a solid binder which is heated above its melting point by hot air, when it is processed in fluidized bed processor.

Advantages

1. No requirement of any solvent either aqueous or non-aqueous.
2. Less time consuming and economical process.
3. Uniform dispersion of fine particle.
4. Release profile of drugs can be controlled and modified.

5. Suitable for enhancing dissolution profile and bioavailability of poorly water soluble drugs by forming solid dispersion³³.

6. Improved product stability.

Disadvantages

1. Not suitable for thermo-labile materials.
2. There is need of high energy input.
3. During handling and storage of agglomerates melting or softening of binder may occur.

2. Foam granulation

This technique is analogous to spray agglomeration; it involves the addition of liquid/aqueous binder as foam instead of spraying or pouring liquid onto the powder particles. Adding the binder solution as foam rather than a spray eliminates the problems of inconsistent and unpredictable binder distribution that can affect tablet hardness and drug release³⁴.

A foam generator is used in the binder solution tank with high-shear granulator or fluid bed granulator to introduce the binder as foam rather than spraying or pouring in binder onto the moving powder particles³⁵.

Advantages

1. No need of spray nozzle.
2. Less water required
3. Economical process
4. Suitable for water sensitive formulations.

3. Freeze granulation technology

This technique enables preservation of the homogeneity from suspension to dry granules. By spraying a powder suspension into liquid nitrogen, the drops are instantly frozen into granules, and by freeze drying process, the granules are dried by sublimation of ice without any segregation effects. The result will be spherical, free flowing granules, with optimal homogeneity³⁶.

Advantages

1. Granule density can be controlled by the solids content of the suspension.
2. Cavities in the granules can be avoided.
3. High yield, less wastage of material.
3. Easy cleaning of equipments.
4. Organic solvents can be recycled.

4. Moisture activated dry granulation

This technique is a variation of conventional wet granulation technique. This technology is widely used in granulation of moisture sensitive active pharmaceutical ingredients³⁷. This process involves the utilization of very little granulating fluid, to activate granule formation and it also eliminates the drying steps by using moisture absorbing materials like microcrystalline cellulose, potato starch, a mixture of MCC and potato starch (50% w/w to remove excess of moisture present in the granulate. The moisture absorbents absorb the moisture from the agglomerates, resulting in moisture redistribution within the powder mixture, leading to relatively dry granule mixture.

This process is accomplished by two major steps agglomeration and moisture distribution. It involves the formation of wet mass by using granulating fluid and then utilizing the moisture absorbing materials to dry the granules.

Advantages

1. A simple, clean, lean process that utilizes very little granulating fluid.
2. Produce granules with more uniform particle size distribution (particle size range of 150–500 μm) and excellent flowability.
3. Economical and time efficient, as requires less energy and eliminates drying step³⁸.
4. Suitable for continuous processing.
5. Used for preparation of floating and sustained release products.
6. Applicable to more than 90% of the granulation need for pharmaceutical, food and Nutritional industry.

Disadvantages

1. Unsuitable for thermo-labile, moisture sensitive, high moisture absorbing substances.
2. Formulations with high drug loading are difficult to develop.

5. Extrusion-spheronization granulation

This technique involve in production of granules or pellets of uniform size with high drug loading capacity. It consists of multiple steps of wet mass extrusion followed by spheronization to produce uniform sized spherical particles with narrow size distribution. It is mainly used in multi particulates for oral controlled drug delivery system³⁹.

Steps involved in extrusion-spheronization process:

- a. Dry mixing of materials for homogeneous dispersion.
- b. Wet granulation of the mixture to form wet mass.
- c. Extrusion of wet mass to form rod shaped particles.
- d. Rounding off the rod shaped particles using spheronizer.
- e. Drying.

Advantages

- a. Suitable for higher levels of active ingredients without production of larger particles.
- b. Suitable for combination of two or more active agents within the same unit, in any ratio.
- c. It produces spherical particles with high bulk density, low hygroscopicity, narrow particle size distribution and smoother surface.

Disadvantages

1. Time consuming process having requirement of more labour.
2. Moisture sensitive and thermo-labile materials are not suitable candidates for it.

6. Fluidized bed granulation

It is an air suspension technique in which binder solution is sprayed on to the fluidized powder bed in order to get finer, free flowing and homogenous granules. This fluidized bed processor contains air handling unit, product container, air distributor, spray nozzle, disengagement area, process filters, exhaust blower/fan, control system, and solution delivery systems⁴⁰.

The particle formation in fluidized bed granulation is influenced by numerous parameters like moisture content in solids, liquid spray flow rate, airflow rates, and atomization pressure.

Granulation in fluidized state can be achieved either by batch process or continuous process. For granulation in batch process, the dry starting product is placed in the

product container, where it is mixed vigorously in the heated gas stream, held in the suspension and granulated by spraying with a suitable bonding material. The product is finally dried to the required end moisture content.

7. Spray drying granulation

This process is used to produce microcapsules, food ingredients, flavors and various biotechnological preparations. Dry granular product is obtained by feeding a solution of active agent along with excipients into the drying system, where the feed is atomized and dried with a heated gas stream followed by separation of granular product from the gas stream. This process differs from other methods in that it is a continuous process in which a dry granular product is made from a solution or a suspension rather than initially dried the primary powder particles⁴¹.

The spray drying process involves three fundamental steps,

1. Liquid feed's atomization into fine droplets
2. Mixing of sprays droplets with a heated gas stream, for liquid evaporation.
3. Separation of the dried powder from the gas stream.

Advantages

1. It is a rapid and continuous process
2. It reduces overall cost by eliminating labor intensive drying and granulation steps.
3. Less exposure to dust.
4. Heat sensitive product are suitable candidates.

8. Steam granulation

This process is simply a modification of conventional wet granulation method. In this technique, water steam is used as binder. Pure form of steam is transparent gas, and it provides a higher diffusion rate into the powder and a more favorable thermal balance during the drying step. 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. After condensation of the steam, water forms a hot thin film on the powder particles, requiring only a small amount of extra energy for its elimination, and evaporates more easily⁴².

Advantages

1. Results in more spherical granule formation
2. Higher diffusion rate
3. Environment friendly, safe for working operator.
4. Maintain sterility

Disadvantages

1. There is need of special equipment for steam generation and transportation.
2. Need of high energy inputs
3. Not suitable for thermo labile materials.

9. Thermal adhesion granulation

This technique was developed by Wei-Ming Pharmaceutical Company (Taipei, Taiwan). It involves granulation of the blend by addition of very less amount of water or solvents. This technique is quite simple and convenient with low moisture and binder contents in a closed system for preparing highly compressible materials or for modifying the poor characteristics of excipients⁴¹.

In this process the binder is first moisturized by spraying water or ethanol, and then this blend is transferred into a pre warmed glass bottle and sealed. It is then heated properly by an infrared lamp to raise surface temperature of the vessel to 90°C-105°C in case of water and 70°C-90°C in case of ethanol, and mixed under tumble rotation for 3-20 minutes until the granules are formed. Thermal adhesion granulation process is performed under low moisture content or low content of pharmaceutically acceptable solvent by subjecting a mixture of excipients to heating. This method utilizes less water or solvent when compared to conventional wet granulation technique³⁸.

Advantages

1. Utilizes less amount of water or solvent.
2. Granules with good flow properties and binding capacity were obtained even with substances having poor tableting properties.
3. Minimizes the dust generation during powder processing.

10. Pneumatic dry granulation

This method involves production of granules from powder particles by initially applying mild compaction force by roller compactor to produce a compacted mass comprising a mixture of fine particles and granules. To separate the granules and to recycle the rejected fraction, a newly innovated fractionating device is employed. Granules pass through the fractioning chamber to be compressed into tablets. Pneumatic dry granulation is suitable for automatic or semi-automatic production of granules⁴³.

Advantages

- a. High drug loading is possible.
- b. Faster development (within weeks).
- c. Suitable for thermo-labile and moisture sensitive drugs.
- d. Improved stability with increased shelf-life.
- e. Compatible with other technologies like coating, sustained release.
- f. Produce soft and porous granules with improved flow property and compressibility.
- g. Taste masking can be achieved.
- h. Sterile products and toxic materials can be handled.
- i. Reduces cost of final product by minimizing waste through recycling and production cost.

Table 1: Characterization methods for granules.

Parameters	Method
Particle morphology	Optical microscopy
Granule flow ability and density	Density apparatus, mechanical and Hopper method
Particle size distribution	Sieve analysis, laser light scattering
Granule porosity	Mercury intrusion methods
Thermal analysis	DTA, TGA, DSC
Nature Identification	Powder X-ray diffraction Near-Infrared spectroscopy (NIR)
Surface area	Gas adsorption

CONCLUSIONS

Granulation is one of the most important unit operations in the production of pharmaceutical dosage forms. It is used to prevent segregation of formulation components in a powder blend, bulk volume of granulation, improve blend flow, content uniformity, compressibility, and other properties. In pharmaceutical industry, tablets are manufactured by either of the three methods viz. direct compression, wet granulation, dry granulation. Each technique has its own advantage and disadvantages. Selection of correct granulation method depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Selection of appropriate technology for carrying out the granulation process is the key to achieve a targeted granulation and final product parameters. So, depth knowledge of the processing techniques and their merits and demerits is required to adopt during development stage of product. This review discussed the recent developments in granulation technology; it may be beneficial for many researchers to work at development of granules for various dosage forms like tablets and capsules.

AUTHOR'S CONTRIBUTION

Verma BK: writing, review, and editing. **Pandey S:** writing, review and editing. **Arya P:** formal analysis, writing, review, and editing. All the authors approved the finished version of the manuscript.

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CONFLICT OF INTEREST

No conflict of interest associated with this work.

REFERENCES

- Chokshi R, Zia H. Hot melt extrusion technique: a review. *Iranian J Pharm Res* 2004; 3(3): 16.
- Breitenbach J. Melt extrusion: from process to drug delivery technology. *Eur J Pharm Biopharm* 2002; 54: 107-117. [https://doi.org/10.1016/S0939-6411\(02\)00061-9](https://doi.org/10.1016/S0939-6411(02)00061-9)
- Ansel H, Allen L, Jr. Popovich N. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Eighth Edition, 227-259.
- Heng WS, Wong TW. Melt processes for oral solid dosage forms. *Pharm Tech* 2003; 1-6.
- Paul J, Shesky R, Colin K. New foam binder technology from Dow improves granulation process. *Pharmaceutical Canada* 2006; 19-22.
- Wade JB, Martin GP, Long DF. Controlling granule size through breakage in a novel reverse-phase wet granulation process; the effect of impeller speed and binder liquid viscosity. *Int J Pharm* 2014. <https://doi.org/10.1016/j.ijpharm.2014.11.067>
- Rodriguez L, Cavallari C, Passerini N, Albertini B, Gonzalez- Rodriguez M, Fini A. Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques. *Int J Pharm* 2002; 242: 285-9. [https://doi.org/10.1016/S0378-5173\(02\)00189-8](https://doi.org/10.1016/S0378-5173(02)00189-8)
- Vialpando M, Albertini B, Passerini N, Vander Heyden Y, Rombaut P, Martens JA, *et al.* Agglomeration of mesoporous silica by melts and steam granulation. part II: screening of steam granulation process variables using a factorial design. *J Pharm Sci* 2013; 102: 3978-86. <https://doi.org/10.1002/jps.23699>
- Gazikalovic E, Obrenovic D, Nidzovic Z, Colic O. Manufacture of tetracaine hydrochloride tablets using direct compression and moist granulation. *Vojnosanit Pregl* 2002; 59: 621-4. PMID: 12557620
- Takasaki H, Yonemochi E, Messerschmid R, Ito M, Wada K, Terada K. Importance of excipients wet ability on tablet characteristics prepared by moisture activated dry granulation (MADG). *Int J Pharm* 2013; 456: 58-64. <https://doi.org/10.1016/j.ijpharm.2013.08.027>
- Ullah I, Wang J, Chang S-Y, Guo H, Kiang S, Jain NB. Moisture-activated dry granulation part II: the effects of formulation ingredients and manufacturing-process variables on granulation quality attributes. *Pharm Tech* 2009; 33: 42-51.
- Sharma C, Rana AC, Bala R, Seth N. An overview of industrial process validation of tablets. *J Drug Deliv Therap* 2013, 3(3), 175-183. [https://doi.org/10.13040/IJPSR.0975-8232.3\(9\).3007-22](https://doi.org/10.13040/IJPSR.0975-8232.3(9).3007-22)
- Thompson MR, Weatherley S, Pukadyil RN, Sheskey PJ. Foam granulation: new developments in pharmaceutical solid oral dosage forms using twin screw extrusion machinery. *Drug Dev Ind Pharm* 2012; 38: 771-84. <https://doi.org/10.3109/03639045.2011.633265>
- Ismat U, Jennifer W, Shih YC, Hang G, San K, Nemichand BJ. Moisture-activated dry granulation part II: the effects of formulation ingredients and manufacturing-process variables on granulation quality attributes. *Pharm Tech* 2009; 33(12), 42-51.
- Shoung Y, Hungting Y. United State Patent Application: Process for the preparation of direct tableting formulation and aids 2003; 23(1), 19-24.
- Rundgren K, Lyckfeldt O, Sjöstedt M. Improving Powders with Freeze Granulation. *Ceramic Ind* 2003: 40-44. <https://doi.org/10.1517/bi.2015.04>
- Paul J, Shesky R, Colin K. New foam binder technology from Dow improves granulation process. *Pharmaceutical Canada* 2006; 19-22.
- Shanmugam S. Granulation techniques and technologies: recent progresses. *Bioimpacts* 2015; 5(1): 55-63. <https://doi.org/10.1517/bi.2015.04>
- Wade JB, Martin GP, Long DF. Feasibility assessment for a novel reverse-phase wet granulation process: The effect of liquid saturation and binder liquid viscosity. *Int J Pharm* 2014; 475:450-61. <https://doi.org/10.1016/j.ijpharm.2014.09.012>
- Vialpando M, Albertini B, Passerini N, Bergers D, Rombaut P, Martens JA. *et al.* Agglomeration of mesoporous silica by melt and steam granulation Part I: a comparison between disordered and ordered mesoporous silica. *J Pharm Sci* 2013; 102:3966-77. <https://doi.org/10.1002/jps.23700>
- Hong-Liang L, Hsiu-O HO, *et al.* Process and formulation characterizations of the thermal adhesion granulation (TAG) process for improving granular properties. *Int J Pharm* 2008; 357(1-2); 206-212. <https://doi.org/10.1016/j.ijpharm.2008.02.002>
- Sau LL, O'Connor TF, *et al.* Modernizing pharmaceutical manufacturing: from batch to continuous production. *J Pharm Innov* 2015; 10: 191-199. <https://doi.org/10.1002/jps.24311>

23. Hashemian; Armaou. Simulation, model-reduction, and state estimation of a two-component coagulation process". *AIChE J* 2016; 62: 1557–1567.
<https://doi.org/10.1002/aic.15146>
24. Osborne J, Althaus TL, Forny G. Neideiretter S, Palzer, Hounslow M, Salman AD. Bonding Mechanisms Involved in the Roller Compaction of an Amorphous Material". *Chemical Engineering Science*. 86 (5th International Granulation Workshop). 2013; 61–69.
<https://doi.org/10.1016/j.ces.2012.05.012>
25. Thompson MR, Weatherley S, Pukadyil RN, Sheskey PJ. Foam granulation: new developments in pharmaceutical solid oral dosage forms using twin screw extrusion machinery. *Drug Dev Ind Pharm* 2012; 38:771-84.
<https://doi.org/10.3109/03639045.2011.633265>
26. Rashid HA, Faisal KS, Bhyian MHU, Alam MJ, Hasan MM, Mixture design experiment on dissolution of pioglitazone Hcl solid dispersion as affected by hydrophilic polymers interaction. *Int J Biopharm* 2016; 7(1):17-23.
27. Chauhan V, Kumar K, Teotia D. Fast dissolving tablets: a promising approach for drug delivery. *Universal J Pharm Res*. 2017; 2(4): 58-64.
<https://doi.org/10.4103/2231-4040.90877>
28. Rodriguez L, Cavallari C, Passerini N, Albertini B, Gonzalez-Rodriguez M, Fini A. Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques. *Int J Pharm* 2002; 242:285-9.
[https://doi.org/10.1016/S0378-5173\(02\)00189-8](https://doi.org/10.1016/S0378-5173(02)00189-8)
29. Iveson SM, Litster JD, Hapgood K, Ennis BJ. Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review. *Powder Techn*. 2001; 117:3-39.
[https://doi.org/10.1016/S0032-5910\(01\)00313-8](https://doi.org/10.1016/S0032-5910(01)00313-8)
30. Agatonovic-Kustrin S, *et al.* Biorelevant dissolution studies of Pioglitazone HCL immediate release tablets and the determination of an *in vitro- in vivo* correlation. *J Bioequiv* 2015; 7:086-089.
<https://doi.org/10.4172/jbb.1000220>
31. Damodar R, *et al.* Formulation and evaluation of fast dissolving tablets of diclofenac sodium by novel hole technology. *J Mol Pharm Org Process Res* 2014; 2:116.
<https://doi.org/10.4172/2329-9053.1000116>
32. Kassem MA and El-Sayed GO. Adsorption of tartrazine on medical activated charcoal tablets under controlled conditions. *J Environ Anal Chem* 2014; 1:102.
<https://doi.org/10.4172/jreac.1000102>
33. Biswas D, Halquist M. Using biorelevant *in vitro* models testing to characterize release of non oral dosage forms as another tool for safety. *J Pharmacovigil* 2016; 4:e153.
<https://doi.org/10.4172/2329-6887.1000e153>
34. Ratnaparkhi MP. Formulation and development of taste masked orally disintegrating tablets of perindopril erbumine by direct compression method. *Pharmaceut Anal Acta* 2012; 3:162.
35. Vadlamudi MK, Dhanaraj S. Stability Indicating method for the determination of related substances in felodipine solid dosage form and in the drug substance by RP-HPLC. *J Bioequiv Availab* 2016; 8:153-166.
36. Kidokoro M, Sasaki K, Haramishi Y, Matahira N. Effect of crystallization behavior of polyethylene glycol 6000 on the properties of granule prepared by fluidized hot melt granulation (FHMg). *Chem Pharm Bull* 2003; 51(5): 487-493. <https://doi.org/10.1248/cpb.51.487>
37. Passerini N, Perissutti B, Monoghini M, Voinovich D, Albertini B, Cavallari C, Rodriguez L. Characterization of Carbamazepine-Gelucire 50/13 microparticles prepared by a spray congealing process using ultrasounds. *J Pharm Sci* 2002; 91(3): 699-707. <https://doi.org/10.1002/jps.10085>
38. Perissutti B, Rubessa F, Moneghini M, Voinovich D. Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique. *Int J Pharm* 2003; 256: 53-63.
[https://doi.org/10.1016/S0378-5173\(03\)00062-0](https://doi.org/10.1016/S0378-5173(03)00062-0)
39. Sandler N, Lammens RF. Pneumatic dry granulation: potential to improve roller compaction technology in drug manufacture. *Expert Opin Drug Deliv* 2011; 1: 8(2):225-36.
<https://doi.org/10.1517/17425247.2011.548382>
40. Kleinebudde P. Roll compaction/dry granulation: pharmaceutical applications. *European J Pharm Bio Pharm* 2004; 30, 58(2):317-26.
41. Remington J. Remington: The Science and Practice of Pharmacy; twenty first edition, Lippincott Williams and Wilkins.2006; 895-899.
42. Lachman L, Lieberman HA, Joseph LK the Theory and Practice of Industrial Pharmacy, 3rd Edition, 317-324.
43. Keary CM, Sheskey PJ. Preliminary report of the discovery of a new pharmaceutical granulation process using foamed aqueous binders. *Drug Dev Ind Pharm* 2004; 30:831-4. <https://doi.org/10.1081/DDC-200030504>