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Review Article

PREPARATION AND ASSESSMENT OF AMORPHOUS SOLID DISPERSIONS USING VARIOUS METHODOLOGIES

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ABSTRACT

Amorphous products and particularly amorphous solid dispersions are currently one of the most upcoming and widely used areas in the pharmaceutical field. This approach offers huge potential and advantageous features regarding the overall improvement of drug bioavailability. Presently, different manufacturing processes are being developed to produce amorphous solid dispersions with suitable robustness and reproducibility, ranging from solvent evaporation to melting processes. In the present paper, laboratorial and industrial scale processes were reviewed, and guidelines for a rationale selection of manufacturing processes were suggested. This would ensure an adequate development (laboratorial scale) and production according to the good manufacturing practices (GMP) (industrial scale) of amorphous solid dispersions, with further suggestions on the process validations and drug development pipeline.

Keywords: Solid dispersion, BCS Classification, Poor-water solubility, Bioavailability

INTRODUCTION:

The majority of drugs molecules developed by the pharmaceutical industry during the last decades of the 20th century were classified according to the biopharmaceutical classification system (BCS) as class I drugs i.e. most of the drugs presented high permeability and high solubility. If a molecule failed to meet these criteria, it would most probably be superfluous from the industry development pipeline due to concerns about low bioavailability and/or troublesome formulation process[1].

In the 1990s, with the advancement of Computer Science and its application to the pharmaceutical field, a new paradigm was raised in the Pharmaceutical Industry regarding drug candidate selection, which introduced target-modulation candidate selection[1]. This new tool provided the Pharmaceutical Industry with the ability to produce more potent and target specific drugs. However, these more potent drugs are generally poor water solubility, and consequently, fit BCS classes II or IV[2]. This change in drug candidate properties brought new challenges since most of the new molecules resulted in poor *in vivo* dissolution and consequently poor and/or highly variable bioavailability. Moreover, most of them present small absorption windows, generally located in the upper small intestine. In addition, and emphasizing the current challenges faced by the Pharmaceutical Industry, numerous of these drugs present poor permeability or are substrates of efflux transporters[3].

This challenges forced the Pharmaceutical Industry to search approaches to improve dug solubility, exploring chemical, physical or formulation approaches[2]. Chemical approaches comprise molecular modification of drug structure, such as the inclusion of polar groups, resulting in the formation of new chemical entities that may present different potency and pharmacokinetics[4]. Other examples of chemical approaches include the formation of salts and co-crystals, but their application is very restricted. Salts are only feasible for weak acid or basic drugs and co-crystals generally do not satisfactorily enhance *in vivo* drug solubility. Additionally, both salts and co-crystals tend to precipitate *in vivo[5]* ; [6]. The basic principle behind all physical

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approaches is that increasing the contact surface area enhances solubility[7]. This is accomplished by particle size reduction, resulting in crystals in the micro- or nano-size range. The feasibility and simplicity of this approach is adequate in some cases. However, tends to be inadequate for drugs presenting water solubility below 50 µg/mL. Formulation approaches consist in the production of liquid systems based on lipid vehicles and/or surfactants, or solid formulations that generally resembles in using carrier(s)[7]. From the later, amorphous solid dispersions depict one of the most interesting approaches, since drug presents a reduced particle size, improved wettability, high porosity and enhanced solubility[2]. A wide range of manufacturing processes to obtain amorphous products are currently available and will be further explored in this review, as well as, a rational approach for the selection of the manufacturing process.

Manufacturing of amorphous products

Two major distinct processes are used to manufacture amorphous materials: solvent evaporation and melting. Both of these methods have shown useful at the laboratorial and industrial scales (production accordingly to the good manufacturing practices—GMP). Some mechanical processes, such as ball milling or grinding, are also able to induce someamorphization [8]. However, degree and robustness of amorphisation are very low.

Solvent evaporation processes consist in solubilizing both drug substance and carrier(s) in common solvents or solvent mixture followed by solvent removal. Non-covalent molecular interactions between drug and carrier(s) during solvent removal are responsible for the formation of an amorphous product [9].

As for melting processes, these generally comprise solubilizing a drug in a molten of amorphous polymer(s). The molten product is further solidified by cooling resulting in formation of an amorphous solid dispersion[2].

General advantages and disadvantages

Both solvent evaporation and melting processes have their own advantages and shortcomings that should be considered in order to select the most suitable manufacturing process. Significant, different manufacturing processes may originate products with different properties [10]. Therefore, an adequate selection of the manufacturing process is crucial for the success of the product.

In solvent evaporation processes the thermal decomposition of drugs and/or carriers is avoidable in most cases since organic solvent evaporation can be performed at low temperature. Additionally, the wide availability of organic solvents allows selecting a solvent or mixture of solvents able to solubilize both drug and carrier(s). However, organic solvents may be difficult to remove from the final product, which can be especially concerning when highly toxic solvents are required to be employed[11]. Moreover, it is also possible that slight alterations in the conditions used for solvent evaporation may lead to large changes in product performance.

Avoidance of organic solvent use is a major advantage of melting methods as it better assures product safety and compliance with quality control and environmental requirements. However, high temperatures can induce drug degradation; this is the major drawback of melting processes. Moreover, some drugs may decompose under melting, thus limiting application [12]. Melting processes also require drug solubility/miscibility, which can be very difficult to achieve for some molecules.

Laboratorial scale

Laboratorial processes by either melting or solvent-evaporation are expected to be fast, cheap and require low material resources, especially drug substance. Laboratorial processes can be divided in micro-scale and mini-scale. Micro-scale processes are intended to produce a few micrograms of product and can generally be used for preliminary screening. These processes have limited robustness and poor reproducibility. Mini-scale processes can already generate a few to several hundred grams of product and are characterized for being more robust and reproducible.

Solvent evaporation

Laboratorial solvent evaporation processes can be divided in four major groups depending on solvent removal conditions: (i) high temperature and normal pressure, (ii) high temperature and negative pressure, (iii) freeze-drying, or (iv) supercritical fluids (SCFs).

Solvent casting is a basic laboratorial process of preparing solid dispersions and consists in dissolving the drug and the polymeric carrier(s) in the same solvent(s). The solution is then spread into a petri dish and allowed to evaporate under normal pressure at room temperature, in a hot plateor in a low temperature oven followed by cooling in a desiccator which havesuccessfully been employed in the development of solid dispersions of paracetamol, dimenhydrinate and resveratrol respectively. Typically, the resulting films are pulverized and milled. As an alternative, miniaturization can be achieved by replacing petri dishes with low volume glass vials or by use of 96 well plate[13]. This type of approaches presents the possibility of producing very small amounts of product and was used for preliminary screening of itraconazole. However, it can only be used for solvents with very low boiling temperature such as ethanol chloroform or a mixture of ethanol and dichloromethane. Additionally, it may be difficult to ensure that the solvent is completely removed, which may affect data generated for solubility, permeability or bioavailability. An alternative involves the use of scalable laboratorial spray driers. The solution of drug and polymer(s) is sprayed into a hot air stream that induces fast solvent evaporation and, consequently, the production of small homogenous solid particles composed by drug and carrier(s) in an amorphous state[14].

One of the most practical laboratorial processes used to produce solids dispersion involves the use of a rotary evaporator which has recently used in the development of celecoxib[15], glibenclamide , itraconazole, nifedipine. This is used to remove the solvent(s) under vacuum, allowing a faster sample processing and/or the use of solvents with higher boiling point such as tetrahydrofuran, dimethyl formamide or dimethyl sulfoxide (DMSO) that could not be used in a solvent casting process. The final product is removed from the volumetric flask and can be further milled if desirable. An alternative approach involves solvent casting in a petri dish or vial followed by evaporation in a low pressure chamber or oven.

Freeze-drying or lyophilisation, recently employed in the development of celecoxib, diazepam, docetaxel, tadalafil, nifedipineand zoplicone, comprises freezing a solution/suspension of drug and carrier(s) followed by reducing the surrounding pressure to allow water and solvents in the sample to undergo solid–gas transition.

The use of supercritical fluids (SCFs) is also used to prepare solid dispersions. SCFs are gases that under certain pressure and temperature present simultaneously gaseous and liquid state properties. Liquid properties are advantageous for solubilisation, while gaseous features favour drug and carrier(s) diffusion and solvent removal[16]. Almost all gases present SCFs properties under adequate conditions. However, only few can be used in the pharmaceutical field due to their adequate critical temperature. More than 98% of all applications have been developed using carbon dioxide. Carbon dioxide presents low critical temperature (31.18 °C) and pressure (7.4 MPa), and is inexpensive, non-flammable, non-toxic, recyclable and environmentally friendly. Another example of SCF used in the pharmaceutical field is trifluoromethane[17] which was recently used in the development of simvastatin nanoparticles. SCFs major disadvantages are the difficulty to completely remove organic solvents (when used) and to scale-up, as well as the price of the equipment.

Another process named as aerosol solvent extraction system (ASES), both organic solvent and SCF are sprayed at the same time by different nozzles into the chamber[18]. Itraconazole solid dispersions have been produced by ASES using HPMC as carrier. Obtained amorphous nanoparticles (100–500 nm) showed enhanced solubility and bioavailability . Solid dispersions of atenolol have also been produced using ASES[19]. Alternatively, the SCF can be added into the organic solvent, being gaseous antisolvent (GAS) technique one example of this approach.

Recently, solid dispersions of fenofibrate and Gelucire® 50/13 have been manufactured by particles from gas saturated solutions (PGSS)[20]. In this process, the SCF saturates the organic solution that is then sprayed to form particles. In another study, PGSS was employed to produce solid dispersions of progesterone. Optimized conditions included high pressure and temperature, and longer processing, as well as a lower drug:carrier ratio.

Melting

Melting processes comprise heating a formulated sample followed by its cooling. The techniques employed to heat and cool are important variables of melting processes. Laboratorial melting processes can be extremely simple. For example, a solid dispersion can be obtained by combining the formulation ingredients in a differential scanning calorimetry (DSC) pan and heating the sample until melting of all components, followed by natural or forced cooling[20]. Generally, less than 10 mg of product are obtained in this case.

Moving up in scale, when both components present a low melting point, or when the drug substance has high solubility in the carrier(s), a melt- quenching method can be used. Briefly, a water bath or a hot platecan be used to melt both components. Then the homogenous molten mass can be rapidly solidified by (i) placing it in a freezer, (ii) using an ice bath, (iii) placing it over a stainless steel surface as thin layer spreading followed by a cool air draft, (iv) spreading it on plates placed over dry ice, (v) immersing in liquid nitrogen or grinding the material in liquid nitrogen (cryo-grinding), or (vi) pouring it into petri dishes placed at room temperature inside a desiccator. After solidification, the mixture needs to be pulverized in order to facilitate handling and release of drug. These techniques can be used to produce up to several grams that then can be used to further physicochemical and technological characterization.

Hot melt extrusion (HME) has been explored as a scale-up procedure to produce solid dispersions by melting process. It consists in the extrusion at high rotation speed of the drug and carrier(s), previously mixed, at melting temperature for a small period. The resulting product is then collected after cooling at room temperature and milled into a powder or granule form[21, 22]. A significant advance of HME has been the introduction of twin-screw melt extrusion as illustrated in Fig. 1[21] ; [23]. It consists in the use of a special twin screw extruder and the presence of two independent hoppers in which the temperature can vary over a broad range[24]. Currently several laboratory-scale equipment are available from different manufactures, such as Thermo Fisher Scientific, Brabender Technologies, Coperion GmbH or Leistritz Advanced Technologies Corp., which use this technology and can be used to produce from few grams of product to several Kilograms.Advantages and description of hot melt extrusion will be further detailed below when industrial scale processes are discussed. Variations in preparation methods affect final product properties.

Industrial scale

Industrial and, consequently, good manufacturing practices (GMP) compliant processes to manufacture solid dispersions are scarce. Mostly because the majority of the simple and easy laboratorial processes and equipment are difficult to scale up and accomplish GMP requirements, such as contact materials, reproducibility (automatization), and hygiene in addition to the most evident, such as the impossibility to perform installation/operational and performance qualification of these equipment. Furthermore, processes need to be robust and reproducible, which again is hard to ensure for processes such as solvent cast evaporation or water bath melting process. At industrial scales, the production outputs vary from 1 kg batch size to several hundred kilograms.

Solvent evaporation

From an industrial point of view, the manufacture of solid dispersions by solvent evaporation is usually limited to a few specific cases. The types of solvent, drying conditions and therefore the rate of evaporation vary extremely among different processes. Overall, spray-drying and frezee-drying are the most representative of the solvent evaporation methods used in the industry for manufacturing solid dispersions.

The spray drying process is relatively easy to scale up from a laboratorial spray dryer to an industrial one (Fig. 1)[25]. Industrial spray dryers have a nominal drying gas rate ranging from 50 to 5000 kg/h which may result in a water evaporation capacity up to 400 kg/h. Product properties and performance depend on process parameters and formulation aspects. Appropriateprocess parameters include inlet temperature, feed rate humidity and flow rate of drying gas and atomization conditions. The type and size of the spray nozzles highly contributes to the amorphous solid dispersions particles, in particularly to the

particle size, but also texture and smoothness. Additionally, the solid content may also affect the solution viscosity and consequently the drying process and the final product. Formulation variables such as composition (drug, carrier, solvent) and solid content in the feed, solvent type, viscosity and surface tension of the drying solution are significant for product properties.

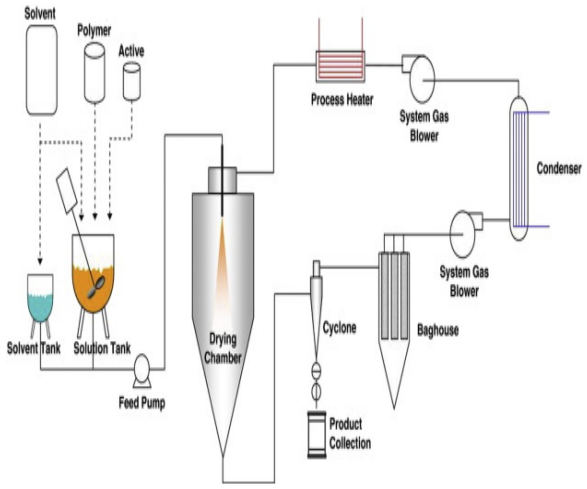

Figure 1: Schematic representation of a spray drying process.

Melting

Only two types of melting processes are available at an industrial scale. These are melt agglomeration and melt extrusion.

Melt agglomeration process use standard granulation equipment, like high shear mixersor fluid bed driers. However, instead of a granulation liquid, a melted mass of drug and carrier(s) is added to the remaining excipients of the formulation[26]. This molten material acts as a granulation liquid, ensuring an adequate homogeneity and adsorption of the drug and carrier(s) on the remaining excipients that can then be further processed. This process allows a production from few kg to around 500 kg batch size. Carriers used in melt-agglomeration can be liquids, namely polyethylene glycol (PEG) 300 and caprylocaproyl macrogol-8 glycerides (Labrasol®), or solids presenting low melting/glass transition temperature, such as PEG 3000, PEG 6000, poloxamer 188 or stearoyl polyoxyl-32 glycerides (Gelucire® 50/13).

The avoidance of organic solvents and drying procedures are advantages of melt-agglomeration. Additionally, it can be helpful for water sensitive drugs. The use of high temperatures, however, prevents its application to thermolabile drugs. The limited availability of suitable carriers for this process can also be seen as a limitation[26].

Hot melt extrusion (HME), and particularly the twin-screw melt extrusion is one of the most employed industrial solid dispersion manufacturing process. In fact, the development and application of twin-screw melt extrusion should be considered one of the major driving forces for the wide dissemination of the solid dispersion concept (Fig. 2 and Fig. 3).Twin-screw presents several advantages over single screw versions and represent the current state of the art for melting processes. The use of two screws contributes to a reduced residence time of the drug in the extruder, allowing for continuous mass flow with enhanced mixing. Moreover, twin-screw extruders avoid drug and excipients thermal stress and feature self-cleaning of the screws[27]. The application of twin-screw technology to drugs susceptible to oxidation and hydrolysis is also possible by eliminating oxygen and moisture from the mixture[27]. It further presents easier material feeding and less tendency to over-heat. The success is such that currently, almost all products developed by HME are in fact by HME using twin-screw extruders.

Figure 2: Hot melt twin screw extruder (Image courtesy of Thermo Fisher Scientific Inc.)

HME allows continuous processing, solvent-free and is easily scaled-up, since the same principle and design can be transferred to different scales. The major difference between laboratorial and industrial equipment is the diameter of the screws. Screws, from laboratorial extruders can vary from 11 to 16 mm in diameter, while values for the

industrial ones range from 16 to 50 m[27]. The possibility of having continuous processing is highly advantageous in the pharmaceutical field because it allows huge versatility in manufacturing capability even with small extruders. This process allows the industrial/GMP production of batch sizes ranging from few kg to tons.

The successful development of a solid dispersion by HME depends on composition and process parameters. Adequate selection of carriers and plasticizers is crucial. Apart from screw design, which is the most important variable, other parameters such as feed rate, temperature and rotation speed are crucial for defining the final product properties. In a recent study, it was shown that the degassing process also enhanced the cross-sectional uniformity of the extruded material. The design of the equipment is highly versatile which allows the adaptation of processes to the desired results and to very different starting materials.

The reason for this versatility is the modular design comprising the screws and barrels. Barrels can be flanged together or linked by internal tie rods. Screws are the most important part of the extruder. Their design distinguishes between processes that the extruder can or cannot fulfil and, therefore, define the quality and quantity of the extruded material. The kneading paddle elements of the screws play an important role in changing the crystallinity and dissolution properties of solid dispersions. Nakamichi *et al*.[23] showed that the physicochemical properties of the extruded material were significantly influenced by the operating conditions of the machine, namely by the revolution rate of screws and the amount of water added to the feed materials. The screw speed and feeding rate are related to shear stress, shear rate and mean residence time, which can affect the dissolution rate and stability of the final products. Certain minimum temperatures are required in HME in order to reduce the torque needed to rotate the screw(s) and allow an efficient process[28].

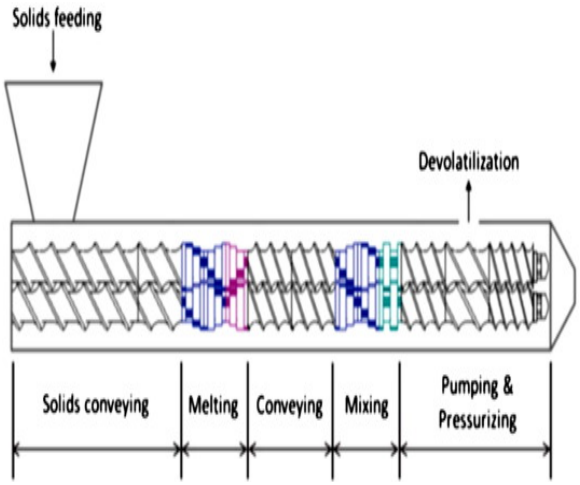

Figure 3: Schematic representation of a twin-screw extruder and elementary steps. Reprinted from[29]

Conclusions

Amorphous products, namely amorphous solid dispersions, are one of the most sought after areas in the pharmaceutical field and, in particular, in the pharmaceutical industry. There is a current need to develop production processes at the laboratorial scale and scale these up to the industrial level in a reliable manner. This review briefly discussed the current state of the art of manufacturing processes used at laboratorial scale for development was presented. There is a wide range of different manufacturing processes, allowing the suitable of a suitable solution for all types of drugs. Industrial manufacturing processes were also described, with focus on scalability of laboratorial methods previously used during development. Two decision trees for selecting available laboratorial and industrial scale manufacturing processes are also proposed. These tools could be used as guidance for an adequate development and industrialization of amorphous solid dispersions.

Conflict of Interest

The author declares that there is no conflict of interest

References

1. Borhani, D.W. and D.E. Shaw. The future of molecular dynamics simulations in drug discovery. Journal of computer-aided molecular design. 2012;26:15-26.

2. Vasconcelos, T., B. Sarmento, and P. Costa. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today. 2007;12:1068-1075.
3. Giacomini, K.M., et al. Membrane transporters in drug development. Nature reviews Drug discovery. 2010;9:215-236.
4. Seo, J.H., et al. Improved oral absorption of cilostazol via sulfonate salt formation with mesylate and besylate. Drug design, development and therapy. 2015;9:3961.
5. Dimopoulou, M., et al. In-vitro evaluation of performance of solid immediate release dosage forms of weak bases in upper gastrointestinal lumen: experience with miconazole and clopidogrel salts. Journal of Pharmacy and Pharmacology. 2015;
6. Terebetski, J.L., et al. Combined use of crystalline sodium salt and polymeric precipitation inhibitors to improve pharmacokinetic profile of ibuprofen through supersaturation. AAPS PharmSciTech. 2014;15:1334-1344.
7. R Serrano, D., K. H Gallagher, and A. Marie Healy. Emerging nanonisation technologies: tailoring crystalline versus amorphous nanomaterials. Current topics in medicinal chemistry. 2015;15:2327-2340.
8. Lin, Y., R.P. Cogdill, and P.L. Wildfong. Informatic calibration of a materials properties database for predictive assessment of mechanically activated disordering potential for small molecule organic solids. Journal of pharmaceutical sciences. 2009;98:2696-2708.
9. Passerini, N., et al. Melt granulation of pharmaceutical powders: a comparison of high-shear mixer and fluidised bed processes. International journal of pharmaceutics. 2010;391:177-186.
10. Homayouni, A., et al. Preparation and characterization of celecoxib dispersions in soluplus®: comparison of spray drying and conventional methods. Iranian journal of pharmaceutical research: IJPR. 2015;14:35.
11. Dhirendra, K., et al. Solid dispersions: a review. Pakistan journal of pharmaceutical sciences. 2009;22:
12. Paudel, A., et al. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: formulation and process considerations. International journal of pharmaceutics. 2013;453:253-284.
13. Novozhilov, Y.V., et al. An improved kilogram-scale preparation of atorvastatin calcium. Chemistry Central Journal. 2015;9:7.
14. Chaudhari, S.P. and R.H. Dave. Investigating the Effect of Molecular Weight of Polyvinylpyrrolidone and Hydroxypropyl Methyl Cellulose as Potential Antiprecipitants on Supersaturated Drug Solutions and Formulations using Weakly Acidic Drug: Indomethacin. International Journal of Pharmaceutical Sciences and Research. 2016;7:3931-3948.
15. Xie, T. and L.S. Taylor. Dissolution performance of high drug loading celecoxib amorphous solid dispersions formulated with polymer combinations. Pharmaceutical research. 2016;33:739-750.
16. Pasquali, I., R. Bettini, and F. Giordano. Supercritical fluid technologies: an innovative approach for manipulating the solid-state of pharmaceuticals. Advanced Drug Delivery Reviews. 2008;60:399-410.
17. Fattahi, A., et al. Preparation and characterization of simvastatin nanoparticles using rapid expansion of supercritical solution (RESS) with trifluoromethane. The Journal of Supercritical Fluids. 2016;107:469-478.
18. Lee, S., et al. Preparation and characterization of solid dispersions of itraconazole by using aerosol solvent extraction system for improvement in drug solubility and bioavailability. Archives of pharmacal research. 2005;28:866-874.
19. Bhirud, Y.D. and H.M. Phalak. ADVANCES IN SOLID DISPERSION TECHNOLOGY AND ITS APPLICATIONS IN THE DEVELOPMENT OF SOLID DOSAGE FORMS. Journal of Drug Delivery and Therapeutics. 2016;6:40-47.
20. Pestieau, A., et al. Optimization of a PGSS (particles from gas saturated solutions) process for a fenofibrate lipid-based solid dispersion formulation. International journal of pharmaceutics. 2015;485:295-305.
21. Lee, J.-Y., et al. Soluplus®/TPGS-based solid dispersions prepared by hot-melt extrusion equipped with twin-screw systems for enhancing oral bioavailability of valsartan. Drug design, development and therapy. 2015;9:2745.

22. Stanković, M., H.W. Frijlink, and W.L. Hinrichs. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. Drug discovery today. 2015;20:812-823.
23. Nakamichi, K., et al. The role of the kneading paddle and the effects of screw revolution speed and water content on the preparation of solid dispersions using a twin-screw extruder. International journal of pharmaceutics. 2002;241:203-211.
24. Breitenbach, J. and J. Lewis. Two concepts, one technology: controlled release and solid dispersion with meltrex. Modified-release drug delivery technology. 2003;125:
25. Dobry, D.E., et al. A model-based methodology for spray-drying process development. Journal of pharmaceutical innovation. 2009;4:133-142.
26. Shanmugam, S. Granulation techniques and technologies: recent progresses. BioImpacts: BI. 2015;5:55.
27. Patil, H., R.V. Tiwari, and M.A. Repka. Hot-melt extrusion: from theory to application in pharmaceutical formulation. AAPS PharmSciTech. 2016;17:20-42.
28. Repka, M.A., et al. Melt extrusion: process to product. Expert opinion on drug delivery. 2012;9:105-125.
29. Brown, C., et al. *Hot-melt extrusion for solid dispersions: composition and design considerations*. in *Amorphous Solid Dispersions* 2014, Springer. p. 197-230.