GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Considerations in the formulation of amorphous solid dispersions by hot melt extrusion

Siddharatha Dhoppalapudi *

Analytical Research and development, Hikma Pharmaceuticals, Columbus, OH, 43228, USA.

GSC Biological and Pharmaceutical Sciences, 2022, 21(02), 012–021

Publication history: Received on 29 September 2022; revised on 01 November 2022; accepted on 04 November 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.21.2.0421

Abstract

Hot melt extrusion is one of the most popular techniques for the manufacturing of amorphous solid dispersions (ASDs). Over few decades, it has transitioned from lab scale to commercial scale with various products in the market. The current review aims at summarizing various considerations in the formulation development of ASDs using HME. Various types of ASDs from Type I to Type IV are discussed along with the solid state of drug and polymeric carrier in each type. Also, various polymeric carriers used in ASDs are outlined along with information about their glass transition temperature, melting point, hygroscopicity and regulatory status. There are various mechanisms by which the polymeric carriers stabilize the amorphous form of drug in ASDs. These mechanisms are classified as crystallization inhibition, anti-plasticization, intermolecular interactions, and reduction of molecular mobility. These four mechanisms are discussed along with case studies. Finally, various considerations in the formulation of ASDs like, rationale selection of polymers, process design and optimization and stability testing with respect to formulation of ASDs using hot melt extrusion are discussed. In conclusion, the current state of formulating ASDs using HME are discussed and the need for restructuring the formulation approach is mentioned.

Keywords: Hot Melt Extrusion; 3D Printing; Amorphous Solid Dispersions; Flory-Huggins Theory

1. Introduction

Around one third of the current active pharmaceutical ingredients suffer from poor aqueous solubility, which in turn effect their oral bioavailability (1, 2). Various solubility enhancement techniques have been developed over few decades to increase the solubility of poorly water-soluble APIs. These techniques include but not limited to milling (3), solid dispersions, complexation, and pH adjustment, liquisolid technology (4-8), hydrotropy (9), cocrystals (10) , salt formation etc. An ideal technique depends on various factors like physicochemical properties of the drug molecule, desired pharmacokinetic profile, intended dosage form and commercial viability (11, 12). Out of all the solubility enhancement techniques, solid dispersions are widely explored with numerous commercially approved formulations (13, 14). Their popularity can be attributed to the ease of manufacturing and commercialization (15). The concept of solid dispersions was first proposed by Sekiguchi and Obi in the year 1961 (16). They defined solid dispersions as biphasic systems where the drug particles are dispersed in polymeric matrix. Since the drug particles are size reduced in the polymeric matrix, their solubility will be high due to increased surface area (17-19). Over the decades, the concept of solid dispersions was widely explored to understand the basic principles governing the increase in solubility and stability. The most widely accepted definition of solid dispersions was, “formulations of poorly-soluble compounds which might lead to particle size reduction, improved wetting, reduced agglomeration, changes in the physical state of the drug and possibly dispersion on a molecular level, according to the physical state of the solid dispersions that depends on the physicochemical properties of carrier and the drug, the drug-carrier interaction and the method of preparation” (20). Based on the definition, solid dispersions can be divided into Type I to Type VI depending on the

* Corresponding author: Siddharatha Dhoppalapudi
Analytical Research and development, Hikma Pharmaceuticals, Columbus, OH, 43228, USA.

solid state of the drug and the polymeric matrix (Table 1) (16, 21). The selection of the type of solid dispersion depends on the properties of the API, especially the amorphous solubility when compared to the crystalline form (22, 23). The most desired types of solid dispersions are amorphous solid dispersions in which the drug is in amorphous form and dispersed in either crystalline or amorphous polymeric matrix.

Table 1 Various types of amorphous solid dispersions

Type	Description	Characterization using DSC
Type I	Eutectic mixtures of drug and polymer in specific ratio	A single melting point which is lower than the melting point of drug and polymer.
Type II	Amorphous precipitates of drug in crystalline polymeric matrix.	A single glass transition point of drug and a sharp endothermic peak of polymer
Type III	Monophasic or biphasic systems where the amorphous drug is molecularly dispersed in crystalline polymeric matrix.	A single glass transition point of drug and a sharp endothermic peak of polymer
Type IV	Biphasic system in which crystalline drug is dispersed in the amorphous polymer phase.	A sharp endothermic peak of drug and glass transition peak of the polymer.
Type V	Amorphous drug precipitates dispersed in amorphous polymeric matrix.	Two glass transition peaks of drug and polymer
Type VI	Monophasic system of amorphous drug molecularly dispersed in amorphous polymeric matrix	Single glass transition peak for the homogeneous system.

The reason for high apparent solubility of the amorphous form is due to their high enthalpy, entropy and Gibbs free energy compared to crystalline counterpart. When ASDs are subjected to dissolution, the amorphous drug undergoes rapid solubilization, resulting in supersaturated solution. This is followed by decrease in solubility due to devitrification. This phenomenon of rapid increase in solubility followed by crashing down is called spring and parachute effect. From pharmacokinetic point of view, the spring phase (rapid solubilization) followed by sustained parachute phase is required for higher bioavailability (24). One of the major challenges in formulating ASDs is rapid crashing out of supersaturated solution, that hampers the bioavailability of the drugs (25, 26). Therefore, selection of ideal polymeric matrix is essential for successful formulation of ASDs. The following section discusses about various polymeric carriers used for ASDs.

2. Various Polymeric Carriers for ASDs

In general, polymers are widely classified according to their origin as natural, semisynthetic, or synthetic polymers. They can be homopolymers where a single repetitive monomer is present or a copolymer which has two monomeric units crosslinked together (27). Since the introduction of ASDs, various polymer manufacturers have focused their attention on ideal polymeric materials suitable for ASDs. Currently, there are various amorphous, semicrystalline, and crystalline polymers that are suitable for ASDs (28). The complex three-dimensional structure of the polymer will help prevent recrystallization of the amorphous drug and improve their physical stability. The choice of ideal polymeric carrier for formulation development of ASDs depend on the physicochemical properties of drug like molecular weight, melting point, pH solubility profile etc (25, 29). The list of various polymers used for development of ASDs are given in Table 2.

Table 2 List of polymeric carriers used in the formulation of ASDs

Chemical name	Molecular weight	Glass transition temperature, Tg (°C)	Melting temperature Tm, (°C)	Hygroscopicity	Regulatory status
Methylcellulose	10,000-220,000	70	290-305	Slightly hygroscopic	GRAS Listed
Hydroxypropylmethylcellulose	10,000-1,500,000	170-180	190-220	Hygroscopic but stable	GRAS Listed
Hypromellose acetate succinate	55,000-90,000	113	286	Hygroscopic, undergo hydrolysis	GRAS Listed
HPC (L-HPC)	50,000-125,000	NA	130-260	Hygroscopic but stable	GRAS Listed
Hypromellose phthalate (HPMCP)	80,000-130,000	133-137	150	Hygroscopic	US FDA IIG
Carbomer (Carbopol 940)	7×10^5 to 4×10^9	100-105	~260	Very hygroscopic	GRAS Listed
Polyethylene glycol 4000	3,000-4,800	NA	50-58	Non-hygroscopic	US FDA IIG
Polyethylene glycol 8000	7,000-9,000	NA	60-63	Non-hygroscopic	US FDA IIG
Polyethylene glycol 20,000	19,000 – 21,000	NA	60-63	Non-hygroscopic	US FDA IIG
Poloxamer 407	9,840-14,600	NA	52-57	Hygroscopic above 80% RH	US FDA IIG
Povidone K17 (PVP K17)	10000	130	NA	Hygroscopic	GRAS listed
Povidone K25	30000	178	NA	Hygroscopic	GRAS listed
Povidone K30	50000	160	NA	Hygroscopic	GRAS listed
Crospovidone	>10,000	100	NA	Hygroscopic	GRAS/SA status
Copovidone	45,000-70,000	106	140	Low degree of hygroscopicity	GRAS/SA status
Polyvinyl acetate phthalate	47,000-60,700	42.5	116	Non-hygroscopic	US FDA IIG
Kollicoat® IR	~45,000	180	208	Low hygroscopicity	NA
Chitosan hydrochloride	10,000-1,000,000	45	203	Hygroscopic	NA
Soluplus®	90,000-140,000	70	NA	Non-hygroscopic	Drug Master File filed in USA

3. Various Mechanism for Stabilization of ASDs:

Various factors like molecular mobility, thermodynamic properties, environmental stress, and method of preparation effect the physical and chemical stability of ASDs. The choice of the polymeric carriers will affect these factors and stabilize the ASDs by four main mechanisms like crystallization inhibition; anti-plasticization; intermolecular interactions and reduction of molecular mobility (Figure 1).

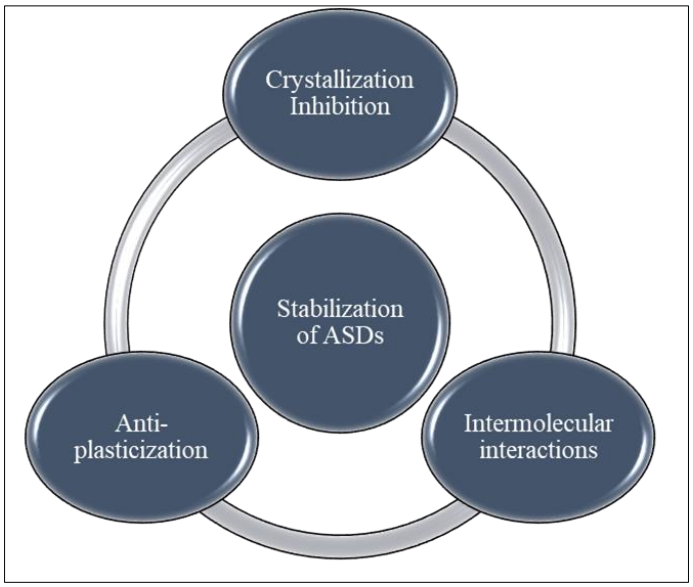

Figure 1 Various mechanisms of stabilization of amorphous drugs in ASDs

3.1. Crystallization Inhibition

The crystallization of an amorphous drug is a 2-step process that occur simultaneously. The first step is nucleation and occurs at a lower temperature, and the second step is the crystal growth that requires higher temperatures (30). Thus, nucleation may not start until a certain degree of supersaturation is reached to overcome the energy barrier. The supersaturated concentrations where no nucleation occurs is known as the 6 metastable zone. An ideal polymeric excipient increases the degree of supersaturation, thus expands the metastable region. Polymeric excipients that increase aqueous solubility can retard the nucleation rate by decreasing the free drug concentration available for nuclei/ seed formation. Since polymeric carriers have sufficiently high configurational entropy due to their large, complex, and flexible structures, they significantly reduce the chance of drug recrystallization as it lowers the total Gibbs free energy of the amorphous drug.

3.2. Anti-plasticization

Anti-plasticization is described as a phenomenon which leads to an increase in glass transition temperature, Tg of the material. This results in an increase in the free energy required by the amorphous drug to convert into the crystalline form. When two materials having different Tg are mixed, the final Tg of the mixture will be somewhere between the Tg of both the materials. Mixing a low Tg amorphous drug with a high Tg polymer at the molecular level leads to the formation of ASDs with a Tg intermediate of these two components. In other words, the polymer undergoes plasticization whereas the Tg of the drug increases, and it undergoes anti plasticization. Sathigari et al. have studied the stabilization of amorphous efavirenz in Plasdone S-630 carrier (24). They have reported that the stability of the amorphous efavirenz in the solid dispersion is due to the anti-plasticizing effect of the polymer which increased the viscosity of the system and decreased the diffusion of drug molecules (31).

3.3. Intermolecular Interaction

The drug molecules may interact with polymers by several weak forces such as hydrogen bonding, van der Waals forces, electrostatic, ionic, or hydrophobic interactions. These intermolecular bonds restrict the molecular mobility of the drug molecules in the polymer matrix and increases the physical stability of the drug-polymer system. Meng et al. highlighted the importance of drug-polymer interactions in the stability of amorphous curcumin as a model drug (32). They examined the ability of different polymers, such as PVP K90, Eudragit EPO®, HPMC, and PEG 8000, to interact with the model drug through stable bond formation. It was concluded that a certain degree of interaction between a drug and a polymer is important for successful formulation of ASDs. Maniruzzaman et al. have reported that the drug polymer ratio and miscibility define the magnitude of the intermolecular interactions (33).

3.4. Reduction of Molecular Mobility

The molecular mobility of amorphous materials determines their physical stability. Polymeric carriers have the capacity to restrict the molecular mobility of the amorphous API which can be determined using certain analytical

techniques like differential scanning calorimeter (DSC), solid-state nuclear magnetic resonance (ssNMR), and dielectric spectroscopy. Knapik *et al.* have shown that the physical stability and water solubility of the amorphous ezetimibe was improved over 6 times when mixed within a ASD using Soluplus® as carrier (34). DSC and dielectric spectroscopy analysis of amorphous ezetimibe have led to the conclusion that the high molecular mobility, reflected in structural relaxation, is mainly responsible for its high 8 crystallization tendency. This indicates that formation of ASDs in the Soluplus® matrix acts as physical barrier to the molecular motions of glass ezetimibe leading to improved stability. In another study, Kothari *et al*. reported that the relaxation time of the drug increases with an increase in polymer concentration (35).

4. Preparation of ASDs using Hot Melt Extrusion

The pharmaceutical industry is shifting from the traditional spray drying process towards hot-melt extrusion for the preparation of solid dispersions. This is to reduce the use of solvents and to achieve the goal of continuous manufacturing. Hot-melt extrusion (HME) has been revealed as a viable technology for variety of applications in the pharmaceutical industry. The enhancement of solubility and bioavailability through the manufacturing of ASDs is the primary use of HME, as indicated by the multiple papers and patents. Current, interest in the formulation of ASDs using HME is growing rapidly with several papers published in the scientific literature during the past two decade (36). Although there is a huge potential for formulating poorly soluble drugs into ASDs, only a few commercial formulations are available in the market.

However, with an increase in the number of some high-quality research in the field of ASDs, more and more scientific data is available to understand the drug-polymer interactions and the effect of the HME process on the performance of ASDs. This is evident as more and more HME-based drug products appear in the pipeline of many pharmaceutical companies. Lately, there have been new product submissions to the FDA and to the European Medicines Agency (EMA) (14). In HME-based drug products, a robust preformulation assessment is the key to a successful development. A step-by-step approach, starting with the thermodynamic evaluation of several systems, followed by a polymer screening test is useful to rapidly identify optimized HME formulations. The three main aspects of developing ASDs are:

- Rationale selection of polymer
- Process design and optimization
- Predictive stability testing

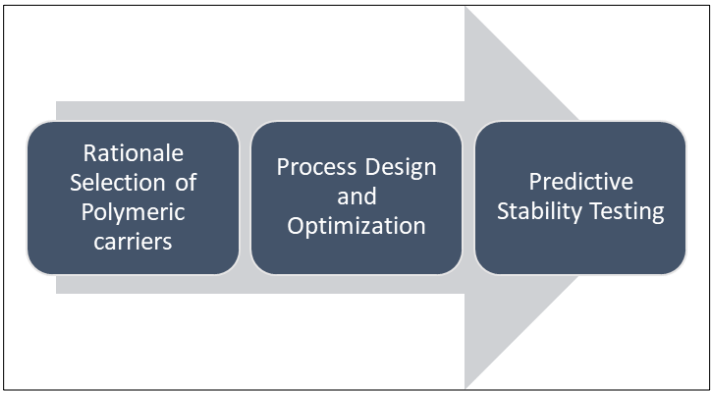

Figure 2 Three main considerations in the formulation of ASDs

4.1. Rationale Selection of Polymeric Carrier

The rationale for the selection of polymer has been largely its glass transition temperature (Tg), melt viscosity and dissolution rate. Polymers with high glass transition temperature Tg are generally used to prepare ASDs owing to their antiplasticizing effect that reduces the molecular mobility of amorphous drug. However, when there is no Tg differences between amorphous drug and the solid dispersion, then the drug-polymer interactions will determine the shelf life of ASDs. Increasing the molecular weight raises the Tg of polymers which favors antiplasticization of amorphous drugs (25, 27). Whereas, at high molecular weight, the rise in Tg becomes insignificant as other factors such as viscosity come into play during the dissolution process. Viscosity of polymers increases with molecular weight which has significant effect on the dissolution properties. Once the polymers are selected, they are further screened based on the miscibility with the drug which is determined by film-casting method. It involves mixing the drug and polymer in a common solvent and then applying the solution as a film. Once the solvent is evaporated, the film is then analyzed under hot-stage

microscopy to observe the presence of phase separation. However, this approach is applicable only in processes such as spray drying where a solvent is used. In the case of hot melt extrusion, the drug and polymer are directly in physical contact with each other without the presence of a solvent. Their molecular mobility is less and depends on the processing temperature. Therefore, results obtained from film-casting method are often overestimated compared to the actual results obtained from hot-melt extrusion. This shows that there is a need to develop a robust methodology with the use of minimum material to successfully formulate solid dispersions. Different methods such as solubility parameter approach, Flory-Huggins theory and melting enthalpy approach as preformulation tools for the rational selection of polymers have been reported in the literature.

4.1.1. Solubility Parameter Approach

Solubility parameters are the numerical values that represent the dispersive, polar and hydrogen bonding forces in a molecule. They are calculated based on the functional groups present in the chemical structure of a molecule and they contribution to various intermolecular forces. These intermolecular forces were calculated using various group contribution methods, viz. Hoftyzer and Van Krevelen, Hoy, Small, Dunkel, Hayes, and Di Benedetto. Generally, drug polymer systems with similar solubility parameter values are predicted to be more miscible. Drug-polymer mixtures with the solubility parameter difference, $\Delta\delta < 7.0$ MPa1/2 are found to be miscible whereas systems with $\Delta\delta > 10.0$ $MPa^{1/2}$ are likely to be immiscible (37). Estimation of drug-polymer miscibility based on the difference in the solubility parameter values is still one of the most applied approaches in the academia and pharmaceutical industry owing to its relative simplicity. Just et al. discussed about various attempts to improve group contribution parameters and to develop new values based on solids. Wlodarski et al. reported the use of the solubility parameters for the prediction of miscibility between itraconazole and two polymers, polyvinyl alcohol and copovidone (38). Pawar and co-workers used Hansen solubility parameters to predict the miscibility of efavirenz in polymers for the preparation of ASDs using HME (39). Although the solubility parameter can be useful for the fast screening of polymers, it often leads to the exclusion of good polymeric candidates. Therefore, additional experimental work is required to confirm the 14 interpretations obtained using solubility parameter approach. Recently, Turpin et al. experimentally determined the miscibility of various model drugs, and the results were compared with that of the results predicted using Hansen solubility parameters approach. The study showed that the predicted results from the solubility parameters did not match the experimental data. The authors attributed this to the negligence of not considering the intermolecular interactions in the solubility parameter approach. To address these drawbacks, more complex methods were introduced to predict the drug-polymer miscibility. One of these methods is the calculation of the Flory–Huggins interaction parameter, usually through the application of the melting point depression method.

4.1.2. Melting Point Depression Method

The most widely used method for the estimation of drug solubility in a polymer is by using the melting enthalpy of the crystalline drug in a drug-polymer system measured by DSC. This method is based on a simple principle that the fraction of drug dissolved in the polymer does not contribute to the melting endotherm (40). Therefore, by measuring the melting enthalpy of a series of drug concentrations in drug-polymer mixtures and extrapolating the plot to zero enthalpy, the solubility of a given drug in selected polymers can be estimated from the x-intercept of the plotted line.

4.1.3. Flory-Huggins Theory

Flory-Huggins (F-H) theory is a well-known lattice-based theory which describes polymer-solvent miscibility based on the Gibbs free energy change associated with the mixing of a polymer in a solvent. Recently, this theory was applied for assessing drug-polymer miscibility using the melting point depression method to obtain F-H interaction parameter, χd-p. A negative value of χd-p indicates stronger drug-polymer interaction than individual drug-drug or polymer-polymer interaction which predicts drug-polymer miscibility, whereas a positive value indicates that homonuclear interactions are preferred over heteronuclear interactions which may lead to phase separation. This method is also used by the pharmaceutical industry and is probably the most popular approach, with research work published by many reputed pharmaceutical companies. Earlier, the assessment of acetaminophen and naproxen solubility in polymeric excipients, such as povidone and co-povidone, calculated with three models including F-H equation, was published by Lehmkemper and co-workers. The results were in line with the experimental solubility data (41). However, the F-H theory underestimated the effect of acetaminophen miscibility on stability.

4.1.4. Thermodynamic Phase Diagrams

Another common tool within the industry is the construction of phase diagrams which are usually based on the F-H theory. Phase diagrams depict the relationship between the free energy and drug loading. The use of phase diagrams has been described extensively in the literature. Still, phase diagrams are temperatures dependent, and an immiscible system can, therefore, become miscible if the temperature increases.

4.2. Process design and optimization

Once a suitable polymer is selected for the formulation of ASDs, the next challenge is to determine the optimum formulation and process parameters. When choosing a commercial ASDs manufacturing process, there are two leading choices: spray drying or hot melt extrusion (HME). Although solvent-based processes are more common because they are applicable to a wide range of compounds, HME offers several advantages for thermally stable systems. It is solvent-free, continuous, high-throughput, easily scalable and inexpensive. Avoidance of thermal degradation and an absence of residual crystallinity are two critical quality attributes of hot melt extruded ASDs. To avoid thermal degradation of drug and/or polymer, lower processing temperatures are desirable, although accompanied by a risk of residual crystalline content if the crystals do not fully melt or dissolve during the process. Various studies have reported the HME processing at temperatures below the drug's melting point utilizing melting point depression phenomenon. Studies providing strategies to mitigate the corresponding risk of crystallinity have thus far been limited to equipment setup like screw configuration and drug particle size reduction. Physical instability and dissolution performance are affected by many parameters, such as drug loading, polymer type, miscibility, Tg and the inherent crystallization tendency of the drug and may be accelerated by the presence of seed crystals. Therefore, it is considered critical to design the ASD manufacturing process to generate a fully amorphous system. Considering the FDA encouraging Quality by Design (QbD) practice for all the formulations, applying it in the case of ASDs seems challenging. This is due to various factors that affect the characteristics of ASDs. However, once the maximum drug loading was determined using preformulation studies, the process parameters can then be optimized using a suitable experimental design. Since fully amorphous systems are considered stable, it is significant to determine the maximum solubility of the drug in the polymeric carrier. The thermodynamic phase diagram has been conceptually proposed in the literature as a methodology for identifying the maximum solubility of the drug in the polymeric carrier as well as the processing temperature. A typical thermodynamic phase diagram consists of a solubility curve, a miscibility curve, and a glass transition curve. Most of the research in the field of HME is limited to a simple experimental design which fails to determine the interaction effect between the CMAs and the CQAs on the CMAs. Since HME is a complex process with various interaction effects, it is ideal to study the process using a design that better helps understand the effect of various CQAs and CPPs on the CMAs. However, it is challenging to perform enough experimental runs using HME, especially during initial phase of development due to limited availability of the drug. Therefore, material sparing techniques are necessary to speed up the formulation development process using HME. One such technique is DSC, a commonly used thermal analysis instrument. It is like HME in the case of heat conduction except the absence of mechanical stress. However, when the particle size of drug and polymer blend is reduced significantly, then the thermal events in the DSC and HME are comparable (42). Apart from that, DSC requires small quantity of material and the samples subjected to thermal analysis can be retrieved and analyzed. Phase diagrams coupled with DoE could provide useful information regarding formulation and process optimization.

4.3. Physical Stability of ASDs

The amorphous drug–polymer dispersion is commonly characterized in terms of physical properties such as glass transition temperature (Tg), heat capacity, and miscibility. Though it is widely regarded that an increase in Tg indicates the improvement of physical stability, there is no direct evidence disclosed to relate Tg to recrystallization activation energy, the critical parameter evaluating stability. Tg is not an intrinsic property and contingent to prior thermal history. Methods involving Tg measurement therefore are ambiguous. Some studies experimentally proved the surprising occurrence of nucleation below Tg indicating that Tg is not a reliable indicator of physical stability. Recrystallization kinetics is a mathematical model which has a potential to estimate the physical stability of ASDs (43). The model is based on the approximation of the nucleation and crystal growth contributions which are inherently essential to an accurate prediction of the physical stability of ASDs. This approach was first introduced by Avrami and is the commonly used model to estimate the crystallization kinetics for decades. However, the reliability and accuracy of this equation is compromised because of its critical oversimplifications, most notably that the nucleation rate is constant throughout the recrystallization process (19). Other models also have been developed based on solid state reaction kinetics, however, there has been little progress in their application to stability prediction of pharmaceutical solid dispersion. Most recently, a new kinetics model was developed by correcting the critical oversimplification on nucleation rate in the Avrami equation. However, further studies need to be done to validate the applicability of the kinetic model to determine the shelf life of ASDs.

5. Formulation Approach for ASDs

A systematization of a rational approach to design solid dispersions is crucial for a successful, fast, and low-cost development, which avoids promising formulations being prematurely eliminated from experimental studies. The most common approaches for screening excipients for HME formulations are based on solvent evaporation methods, DSC analysis, hot stage microscopy (HSM) and melt-based methods (29). Solvent evaporation methods are probably the

most common in the industry setting, because of their simplicity and low cost. Some studies have been published, describing ways of automating and miniaturizing the screening of excipients in a high-throughput manner. However, DSC studies, HSM or melt-based methods have the advantage of applying heat which can be beneficial when the manufacturing process under study is HME. One of the main advantages is including the assessment of physical stability at the early stages during product development (44). This approach is divided into four stages. During the first stage, an in-depth evaluation of physicochemical properties of the drug and potential polymers is performed. Then, in the second stage, excipients are assessed through solubility parameters, melting point depression and Flory-Huggins interaction parameter (45, 46). This preliminary evaluation can be complemented with experimental tests, such as DSC, where depression of the melting point evaluated and, eventually, the interaction parameter can be calculated (37). As an outcome, excipients with a high probability of miscibility and chemical interaction are taken to the third stage where the process optimization is done using the thermodynamic phase diagrams and a material sparing DSC method.

6. Conclusion

ASDs remain the most popular solubility enhancement techniques for poorly water-soluble drugs. When coupled with HME, there is a tremendous potential for continuous manufacturing of ASDs. Due to the amount of research already conducted in the field of HME, the science behind the formulation of ASDs is now well understood. There are various types of ASDs and the choice of ASDs depend on the drug and polymers and the required biopharmaceutical properties. One of the main challenges in the formulation of ASDs is the low amount of drug available during the development phase. Therefore, material sparing techniques are required for implementation of ASDs during the drug development phase.

Compliance with ethical standards

Acknowledgments

The corresponding author would like to thank Hikma Pharmaceuticals for provide required support.

Disclosure of Conflict of Interest

The author declare that they have no conflict of interest.

References

[1] Beloqui A, Solinís MÁ, Rodríguez-Gascón A, Almeida AJ, Préat V. Nanostructured lipid carriers: Promising drug delivery systems for future clinics. Nanomedicine: Nanotechnology, biology and medicine. 2016; 12(1):143-61.

[2] Mamidi HK, Srimathkandala MH, Sanka K, Ananthula MB, Bakshi V. Development and evaluation of nasal in situ gel formulations of alprazolam using in vitro and in vivo methods. International Journal of Pharmacy. 2015;5(1):278-88.

[3] Esfandiari NJTJoSF. Production of micro and nano particles of pharmaceutical by supercritical carbon dioxide. 2015; 100:129-41.

[4] Mamidi HK, Mishra SM, Rohera BD. Determination of maximum flowable liquid-loading potential of Neusilin® US2 and investigation of compressibility and compactibility of its liquisolid blends with PEG (400). Journal of Drug Delivery Science and Technology. 2019; 54:101285.

[5] Bheemidi VS, Tiruckovela M, Varanasi P. An imperative note on novel drug delivery systems. J Nanomed Nanotech. 2011; 2:100125.

[6] Mamidi HK, Mishra SM, Rohera BD. Application of modified SeDeM expert diagram system for selection of direct compression excipient for liquisolid formulation of Neusilin® US2. Journal of Drug Delivery Science and Technology. 2021;64:102506.

[7] Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. Nature reviews Drug discovery. 2014; 13(9):655-72.

[8] Mamidi HK. Establishment of Design Space for Direct Compression of PEG (400) Loaded Neusilin® US2 by Modified SeDeM Expert System: St. John's University; 2017.

[9] Kalepu S, Manthina M, Padavala V. Oral lipid-based drug delivery systems–an overview. Acta Pharmaceutica Sinica B. 2013;3(6):361-72.

[10] Narala S, Nyavanandi D, Alzahrani A, Bandari S, Zhang F, Repka MAJAP. Creation of Hydrochlorothiazide Pharmaceutical Cocrystals Via Hot-Melt Extrusion for Enhanced Solubility and Permeability. 2022;23(1):1-11.

[11] Mamidi HK. Nano sponge as versatile carrie. Research Journal of Pharmaceutical Sciences. 2019; 8(1):20-8.

[12] Patel P, Patel M. Enhanced oral bioavailability of nintedanib esylate with nanostructured lipid carriers by lymphatic targeting: In vitro, cell line and in vivo evaluation. European Journal of Pharmaceutical Sciences. 2021; 159:105715.

[13] Tambe S, Jain D, Meruva SK, Rongala G, Juluri A, Nihalani G, et al. Recent Advances in Amorphous Solid Dispersions: Preformulation, Formulation Strategies, Technological Advancements and Characterization. 2022; 14(10):2203.

[14] Chiou WL, Riegelman SJJops. Pharmaceutical applications of solid dispersion systems. 1971; 60(9):1281-302.

[15] Modi A, Tayade PJAp. Enhancement of dissolution profile by solid dispersion (kneading) technique. 2006; 7(3):E87-E92.

[16] Mamidi HK. Preformulation Studies for the Preparation of Amorphous Solid Dispersions: St. John's University (New York); 2021.

[17] Garg NK, Sharma G, Singh B, Nirbhavane P, Tyagi RK, Shukla R, et al. Quality by Design (QbD)-enabled development of aceclofenac loaded-nano structured lipid carriers (NLCs): An improved dermatokinetic profile for inflammatory disorder (s). International Journal of pharmaceutics. 2017; 517(1-2):413-31.

[18] Anderson BDJJops. Predicting solubility/miscibility in amorphous dispersions: it is time to move beyond regular solution theories. 2018; 107(1):24-33.

[19] Liu C, Xu C-Q, Yu J, Pui Y, Chen H, Wang S, et al. Impact of a single hydrogen substitution by fluorine on the molecular interaction and miscibility between sorafenib and polymers. 2018; 16(1):318-26.

[20] Mamidi HK, Rohera BD. Material-Sparing Approach using Differential Scanning Calorimeter and Response Surface Methodology for Process Optimization of Hot-Melt Extrusion. Journal of Pharmaceutical Sciences. 2021; 110(12):3838-50.

[21] Nyavanandi D, Mandati P, Narala S, Alzahrani A, Kolimi P, Pradhan A, et al. Feasibility of high melting point hydrochlorothiazide processing via cocrystal formation by hot melt extrusion paired fused filament fabrication as a 3D-printed cocrystal tablet. 2022:122283.

[22] Stocker MW, Healy AM, Ferguson SJMP. Spray Encapsulation as a Formulation Strategy for Drug-Based Room Temperature Ionic Liquids: Exploiting Drug–Polymer Immiscibility to Enable Processing for Solid Dosage Forms. 2020; 17(9):3412-24.

[23] Li S, Tian Y, Jones DS, Andrews GPJAP. Optimising drug solubilisation in amorphous polymer dispersions: rational selection of hot-melt extrusion processing parameters. 2016;17(1):200-13.

[24] Sathigari SK, Radhakrishnan VK, Davis VA, Parsons DL, Babu RJJJops. Amorphous-state characterization of efavirenz—polymer hot-melt extrusion systems for dissolution enhancement. 2012;101(9):3456-64.

[25] Nyavanandi D, Kallakunta VR, Sarabu S, Butreddy A, Narala S, Bandari S, et al. Impact of hydrophilic binders on stability of lipid-based sustained release matrices of quetiapine fumarate by the continuous twin screw melt granulation technique. 2021;32(7):2591-604.

[26] Xi L, Song H, Wang Y, Gao H, Fu QJAP. Lacidipine amorphous solid dispersion based on hot melt extrusion: good miscibility, enhanced dissolution, and favorable stability. 2018;19(7):3076-84.

[27] Narala S, Nyavanandi D, Srinivasan P, Mandati P, Bandari S, Repka MAJJoDDS, et al. Pharmaceutical Co-crystals, Salts, and Co-amorphous Systems: A novel opportunity of hot-melt extrusion. 2021;61:102209.

[28] Bandari S, Nyavanandi D, Dumpa N, Repka MAJADDR. Coupling hot melt extrusion and fused deposition modeling: Critical properties for successful performance. 2021;172:52-63.

[29] Butreddy A, Nyavanandi D, Narala S, Austin F, Bandari SJCDD. Application of hot melt extrusion technology in the development of abuse-deterrent formulations: An overview. 2021;18(1):4-18.

[30] Bandari S, Nyavanandi D, Kallakunta VR, Janga KY, Sarabu S, Butreddy A, et al. Continuous twin screw granulation–An advanced alternative granulation technology for use in the pharmaceutical industry. 2020;580:119215.

[31] Alzahrani A, Nyavanandi D, Mandati P, Youssef AAA, Narala S, Bandari S, et al. A systematic and robust assessment of hot-melt extrusion-based amorphous solid dispersions: Theoretical prediction to practical implementation. 2022:121951.

[32] Meng F-B, Zhang Q, Li Y-C, Li J-J, Liu D-Y, Peng L-XJCp. Konjac glucomannan octenyl succinate as a novel encapsulation wall material to improve curcumin stability and bioavailability. 2020;238:116193.

[33] Maniruzzaman M, Morgan DJ, Mendham AP, Pang J, Snowden MJ, Douroumis DJIjop. Drug–polymer intermolecular interactions in hot-melt extruded solid dispersions. 2013;443(1-2):199-208.

[34] Knapik J, Wojnarowska Z, Grzybowska K, Jurkiewicz K, Stankiewicz A, Paluch MJMP. Stabilization of the amorphous ezetimibe drug by confining its dimension. 2016;13(4):1308-16.

[35] Kothari K, Ragoonanan V, Suryanarayanan RJMp. The role of drug–polymer hydrogen bonding interactions on the molecular mobility and physical stability of nifedipine solid dispersions. 2015;12(1):162-70.

[36] Rangaraj N, Sampathi S, Junnuthula V, Kolimi P, Mandati P, Narala S, et al. Fast-Fed Variability: Insights into Drug Delivery, Molecular Manifestations, and Regulatory Aspects. 2022;14(9):1807.

[37] Marsac PJ, Shamblin SL, Taylor LSJPr. Theoretical and practical approaches for prediction of drug–polymer miscibility and solubility. 2006;23(10):2417-26.

[38] Wlodarski K, Sawicki W, Kozyra A, Tajber LJEJoP, Biopharmaceutics. Physical stability of solid dispersions with respect to thermodynamic solubility of tadalafil in PVP-VA. 2015;96:237-46.

[39] Pawar J, Tayade A, Gangurde A, Moravkar K, Amin PJEJoPS. Solubility and dissolution enhancement of efavirenz hot melt extruded amorphous solid dispersions using combination of polymeric blends: a QbD approach. 2016;88:37-49.

[40] Pawar JN, Fule RA, Maniruzzaman M, Amin PDJMS, C E. Solid crystal suspension of Efavirenz using hot melt extrusion: Exploring the role of crystalline polyols in improving solubility and dissolution rate. 2017;78:1023-34.

[41] Lehmkemper K, Kyerematen SO, Heinzerling O, Degenhardt M, Sadowski GJMP. Impact of polymer type and relative humidity on the long-term physical stability of amorphous solid dispersions. 2017;14(12):4374-86.

[42] Vo AQ, Zhang J, Nyavanandi D, Bandari S, Repka MAJCp. Hot melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine. 2020;246:116519.

[43] Ivanisevic IJJops. Physical stability studies of miscible amorphous solid dispersions. 2010;99(9):4005-12.

[44] Alzahrani A, Narala S, Youssef AAA, Nyavanandi D, Bandari S, Mandati P, et al. Fabrication of a shell-core fixed-dose combination tablet using fused deposition modeling 3D printing. 2022;177:211-23.

[45] Mamidi HK, Rohera BD. Application of thermodynamic phase diagrams and Gibbs free energy of mixing for screening of polymers for their use in amorphous solid dispersion formulation of a non-glass-forming drug. Journal of Pharmaceutical Sciences. 2021;110(7):2703-17.

[46] Thakral S, Thakral NKJJops. Prediction of drug–polymer miscibility through the use of solubility parameter based Flory–Huggins interaction parameter and the experimental validation: PEG as model polymer. 2013;102(7):2254-63.