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Review Article

To Study and Evaluate the Various Aspects in Manufacturing Amorphous Spray Dried Dispersion.

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ABSTRACT

Spray-dried dispersions have become ansignificant formulation technology for the pharmaceutical product development of poorly water-soluble compounds. Even though this technology is now widely used in the industry, especially in the early-phase development, the lack of mechanistic understanding still causes difficulty in selecting excipients and predicting stability of SDD-based drug products. In this review, the authors aim to discuss various principles of polymer science pertaining to the development of SDDs, in terms of selecting polymers and solvents, optimizing drug loading, as well as evaluating physical stability on storage and supersaturation maintenance after dissolution. Spray drying of polymer-API solutions, low critical solution temperature was discussed for setting the inlet temperature for drying. The impact of polymers on the supersaturation creation and maintenance of APIs in dissolution media was also discussed. Moreover, the nature of SDDs, with reference to solid solution and the notion of solid solubility, was examined in the context of pharmaceutical application. Finally, the importance of robust analytical techniques to characterize the SDD-based drug products was highlighted, considering their complexity.

Keywords: Solid dispersion, spray drying, polymer, solvent, stability

INTRODUCTION

Most of the new chemical entities being discovered nowadays are poorly water-soluble, it is a common practice in the pharmaceutical industry to develop amorphous dispersions (ASD), either by spray drying or an extrusion process, to increase the dissolution and, in turn, the bioavailability of these compounds [1]. Particularly for the early phases of clinical development, it is often necessary to combine spray drying technology with polymers such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS) to prepare spray-dried dispersions (SDD)[2]. This is obvious by the fact that formulations containing ADs have been commonly used in first-in-human (FIH) trials and about a dozen of pharmaceutical products with amorphous dispersions have been marketed, most of the drugs used the manufacturing processes involving solvent evaporation [3]. Although only four of commercially marked drugs are manufactured based on spray drying technology, in the early pharmaceutical development process, spray drying is widely used to prepare ASD to enhance bioavailability. While ASD can be generated by both spray drying and hot melt extrusion (HME), in this review, we will concentrate on the issues associated with SDD.

The use of ASD technology to formulate poorly water soluble compounds can be historically dated back to the time when the dispersion of β-carotene with polyvinylpyrrolidone (PVP) was prepared in 1965 by Tachibana and Nakamura, where β-carotene and PVP were dissolved in methanol followed by drying. However, the systematic investigation of the amorphous systems in relation to their pharmaceutical usage was not initiated until the 1990s when George Zografi and his associates, from the University of Wisconsin at Madison, started to examine these systems at molecular level[4].

It is a common practice to combine spray drying technology with polymers such as HPMCAS to achieve practical shelf life and biorelevant dissolution[2]. Since polymeric excipients typically account for about 50–75% (w/w) of the composition of the formulation, their properties considerably influence the physical properties of SDDs and the performance of SDD-based dosage forms, including properties such as interaction with water, physical stability, dissolution, and even compressibility. As HPMCAS becomes the polymer of choice for

preparing drug-polymer dispersions due to its capability of maintaining supersaturation of active pharmaceutical ingredients (APIs), thus improving their physical stability, it is increasingly being used for supporting toxicological investigations and early clinical studies [5]. Though the SDD approach is promising, there are still many tasks to develop oral solid dosage forms with SDDs including selecting appropriate polymers and solvents, optimizing spray drying processes, and preserving the physical stability of dispersions, along with maintaining supersaturation after dissolution. In this review, we will discuss some of these challenges related to the development of SDD-based drug products.

Solid Dispersions and Solid Solutions

Even though solid solution systems are commonly found in alloy systems, it is very rare for organic molecules to form solid solutions due to constrains in terms of matching the same/similar size and shape [6]. Because polymers are much larger than drugs (small molecule-API), dispersions such as SDDs are intrinsically heterogeneous even though they are occasionally misnamed as solid solutions. The microstructure of polymer chains in solution ranges from a few nanometers to over 10 nm, which depends on both the properties of polymers (chemical structure and size of molecules and degree of polymerization) and solvents used. The size of a polymer expands in a good solvent and shrinks in a poor solvent[7].

For PVP (K29/32), its degree of polymerization is about 400 (MW = 40,000). In comparison, the size of a drug molecule, such as indomethacin, is usually less than a nanometer—very small relative to a polymer. Hence, SDDs are inherently heterogeneous where drug molecules are dispersed either among chains of polymers of much larger size and various structures or along polymer chains, depending on solvent conditions.

Dynamically, drug-polymer dispersions also exhibit significant heterogeneity in terms of relaxation—thus molecular mobility. Since drugs (small molecules) tend to have higher mobility compared to polymeric molecules, representing faster rotation and transport coefficient, the heterogeneity in relaxation can drive phase separation [8]. When the mobility of drug molecules reaches certain threshold, they will move around a polymer matrix to phase separate, which increases the proclivity for crystallization.

Solid solubility has been used in the pharmaceutical industry to show the maximum concentration of APIs in amorphous dispersions at equilibrium[8]. However, given that drug-polymer systems are heterogeneous, the concept of solid solution of APIs in polymers is not adequate to describe SDD systems. Therefore, SDDs need to be treated as dispersions in which drugs are dynamically stabilized by polymers. For the majority of miscible SDDs in which no separate distinct Tg is detected by differential scanning calorimetry (DSC), they are made miscible by selecting appropriate polymers, processing solvents, and spray drying conditions [9]. Particularly, for high drug loading SDDs (25% and above, w/w), they are mostly miscible (not phase separated) at the time of manufacturing, with an anticipation that these SDDs remain stable through product shelf life. In summary, SDDs are amorphous systems where drug molecules are mostly kinetically stabilized, possibly by reducing molecular mobility. Further, analytically it is very hard to confirm that SDDs are actually solid solution or to meaningfully measure solid solubility, and so it is confusing to use these terms loosely in the development.

Development challenges

Spray Drying

Polymer Selection

Polymer selection for forming stable drug-polymer amorphous dispersions is commonly discussed in the literature. Many interesting methods have been taken including in silico solubility calculation, F-H interaction parameter calculation, phase diagram prediction, and crystallization inhibition[10]. To enhance the bioavailability of APIs and to maintain their physical stability against crystallization, certain properties of polymers are preferred such as having high enough Tg to maintain the physical stability of APIs even when being exposed to humidity. Alternatively, the polymers with a right balance between hygroscopicity and hydrophobicity, in which the final Tg values of the resultant SDDs are not significantly impacted by moisture, are preferable. Furthermore, the selected polymers should exhibit good dissolution in aqueous media while maintaining supersaturation through strong API-polymer

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interactions. Because of these constrains, only a few of polymers that are used to prepare SDDs are included in the drug products made to market.

Drug Loading

High doses are required to explore the therapeutic window for clinical candidates to support toxicological and early clinical studies,.Nevertheless, one of concerns for SDDs is that the dosage form with SDD is limited for increasing drug loading [10]. This is because the presence of large amount of polymers, typically around 75% (w/w) in SDDs, leaves a little room for increasing drug loading in the final dosage forms. Typically, SDDs of 25% drug loading are commonly used for pressing tablets which typically transforms to a drug loading of approximately 15% or less in tablets. However, the maximum drug loading for SDDs can differ depending the physical properties of compounds[11]. The question is how to establish the maximum drug loading in SDDs. Essentially, there are a few parameters to consider when evaluating the impact of drug loading on SDDs given that SDDs are dispersions consisted of a drug molecule and a polymer. Drugs are small molecules with low glass transition temperatures. An increase of drug content in SDDs will often decrease the final Tg values of SDDs and therefore increase the molecular mobility of APIs, which potentially impacts both product stability and manufacturability [12]. Further, the miscibility between the API and the polymer may be reduced with an increase of drug loading, leading to phase separation. Additionally, depending on the interactions between water and a polymer, higher drug loading can result in instability issue as water may preferably interact with the polymer. This may cause API phase separated from the polymer and crystallized out. Overall, to optimize the drug loading in SDD dosage forms, multiple factors are needed to be considered including the physical properties of API and polymer as well as the mechanical properties of SDD prepared[13].

Solvent Selection

Selection of a right solvent is just as important as selecting a suitable polymer for SDD preparation[8]. In the pharmaceutical industry, solvents for spray drying are frequently selected based on the following criteria: the solubility of an API and a polymer in common solvents, drying efficiency of solvents, the acceptable level of residual solvents, desired shelf life stability, and their disposal. Because of these reasons, acetone, methanol, dimethylsulfoxide, dimethylacetamide, and N-methylpyrrolidone are commonly used. However, in this review, only the solvent properties affecting the behavior of polymers and APIs have been concentrated on, especially the solution characteristics of polymers in these solvents[14]. As shown in Fig. 1, the miscibility behavior of a ternary polymer solution is strongly influenced by solvent properties.

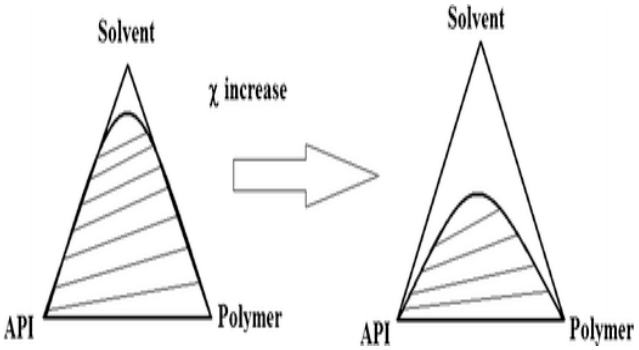

Fig. 1: Three-component phase diagram

Temperature-Induced Phase Separation

Temperature rise during spray drying can significantly impact SDD properties as a dryer is required to raise the temperature quickly from the ambient condition to the desired drying temperature which is above the boiling point of solvents [15]. This rapid increase in temperature can significantly change the phase behavior of polymer solutions as well as drying dynamics, thus impacting the physical characteristics of the final products. Basically, inlet temperatures are usually selected based on the boiling points of solvents to achieve the desired outlet temperatures: e.g., the inlet temperatures for acetone and methanol are 60 and 75°C, respectively, resulting in outlet temperatures of 40 and 58°C [16].

Process Development

To generate SDD dispersions with desired attributes such as controlled particle size, shape and size distribution the spray drying process needs to be controlled. For successful execution of a spray drying operation in large scale, optimization of operating parameters and the properties of polymer solutions is required. As a variety of spray dryers are used in the pharmaceutical industry, each with unique design, particularly nozzle and drying chamber design, optimization for processing parameter has to be

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based on the designs of equipments used. However, in this review, the focus is on the parameters related to solution properties. Commonly, droplet formation and droplet characteristics—droplet size and size distribution—are strongly influenced by both nozzle design and solution properties such as viscosity and surface tension. When pressure nozzles are employed in lab scale, they typically yield a particle size range of 100–1000 μm, which is a broad range for size distribution. To control particle size and size distribution, the formation of droplets and droplet size needs to be controlled, which is strongly influenced by the viscosity and surface tension of solutions[17].

While increasing solution temperature in general tends to reduce the viscosity and surface tension of a solution, viscosity rises considerably with increasing concentration, especially for polymer solutions. For spray drying, viscosity is the key process parameter controlling spray pattern. In addition, the surface tension of polymer solutions also influences the formation of droplets. The surface tension values of polymer solutions depend on the polymers and the solvents used. Additionally, polymers in a good solvent will tend to expand and yield higher viscosity values relative to those in a poor solvent. Solvents not only affect the viscosity of polymer solutions but also possibly impact the density of SDD particles after drying. The effect of solvent-induced expansion and contraction of polymers in solution on spray drying process and product attributes requires further investigation for SDDs.

Product Performance

Physical Stability

Moisture plays aimportant role in influencing the physical instability of SDDs. After sorbed moisture, binary SDDs are changed to a three-component system: water, an API, and a polymer. Depending on the polymer used and the humidity level being exposed, the water content of SDDs can vary from a few percents in the SDDs made with HPMCAS to over 10% in PVP SDDs. In terms of Gibbs free energy, the introduction of a small molecule (water) into a binary system (SDDs) should enhance mixing[18]. However, water often preferably interacts with polymers due to the formation of hydrogen bonding or hydration.

Chemical Instability

Drug molecules in SDDs also encounter chemical instability issue since molecules in an amorphous state are highly reactive due to their high energetic states. Furthermore, because hydrophilic polymers in SDDs absorb a fair amount of water, drug molecules in SDDs are subject to hydrolysis and other reactions initiated by water. The rate of degradation of drugs in SDDs is frequently increased because of high molecular mobility of API molecules in the amorphous state. Moreover, the impurities from polymers such as peroxides can also cause unintended degradation. Furthermore, the residual impurities from solvents used in spray drying (i.e., peroxides) can also react with APIs, which can result in chemical instability. Overall, amorphous nature, water sorption, and residual impurities from organic solvents are of major concerns for the chemical instability of APIs in SDDs.

Dissolution Rate Enhancement and Supersaturation Maintenance

Thermodynamically, the equilibrium solubility of an amorphous drug present in SDDs should be the same as that of the most stable crystalline form since molecules in an amorphous state will eventually revert to the most stable crystalline form due to their unstable nature[19]. However, SDDs could provide significantly higher dissolution rate and kinetic solubility (or degree of supersaturation) due to several factors including[1] the high energy or amorphous form of the drug,[20] the supersaturation maintenance by precipitation inhibitors, and [21]smaller particle size of SDDs[1, 22]. Recently, the generation and maintenance of supersaturation by SDDs has recently been described by a “spring and parachute” approach. In this model, the higher energy form of drug molecules creating supersaturation is compared with the “spring” analogy whereas the precipitation inhibitors (PIs) such as polymers are equated to the “parachutes” that maintain supersaturation by inhibiting drug precipitation[23]. If the supersaturation in the gastrointestinal (GI) tract is sustained throughout the absorption window—the time interval for complete GI absorption, it could enhance the oral bioavailability of a drug significantly. The bioavailability enhancement from SDDs depends on

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the degree of supersaturation and the extent of supersaturation maintenance[24].

With the aid of polymers, the amorphous form of the drug in SDDs can help in generating supersaturation once contacting dissolution media. However, the maintenance of supersaturation depends on the phase separation behavior of SDD interactions among drugs, polymers, and water as well as crystallization kinetics of the drug[25]. The conditions in the GI tract including pH, amount of bile surfactant, and permeation rate vary significantly based on the location in the GI tract. Due to the continuous change in the local GI microenvironment and a high patient-to-patient variability in the local GI conditions, the aqueous solubility of drugs in the GI tract can vary by several orders of magnitude during GI transit. This may result in either local supersaturation or rapid precipitation of solubilized/dissolved drug, leading to high variability in oral bioavailability of PWS compounds. Specifically for the SDDs, it is essential to understand how the drug and the polymer react to the introduction of water. Several studies have shown that in aqueous media, SDDs could form colloidal structures such as nano-aggregates depending on the interactions between the drug and the polymer[26-28]. These colloidal structures help create an environment in stabilizing the amorphous or high energy form of the drug during dissolution that results in generation of supersaturation[29]. Currently, there is a significant gap in the literature in terms of mechanistic understanding of the properties and behavior of these colloidal structures. This is predominantly due to the challenges of assessing the behavior of SDDs in vitro during dissolution such as formation of colloidal structures, phase conversions, and the effect of precipitation inhibitors.

Analytical and Regulatory Considerations

During drug development, SDDs can be used in various dosage forms, including suspensions, tablets, and capsules, to support different phases of clinical studies. Particularly, in phase 2 and 3 clinical studies, tablets or formulated capsules are generally preferred due to \ patient compliance. Various analytical tests against specifications are required for these dosage forms to ensure their quality consistency. These include characterizing the quality attributes of dosage forms to demonstrate the control of manufacturing process. To develop specifications, testing results reflecting the critical quality attributes of SDD dosage forms are gathered from both developmental batches and stability studies for assessment throughout the analytical development cycle. If either the formulation compositions of SDDs or spray drying conditions—solvent, solution concentration, drying temperature, flow rate, etc.—are altered, a new specification is deemed necessary. The final dosage forms comprised of SDD material, intended for clinical uses, are required to have release-tested against and passed regulatory specifications. However, there is no such requirement for SDD material alone although in some cases, SDDs have been treated as product intermediates and been monitored correspondingly. SDD dosage forms are typically subjected to the conditions of conventional stability studies, including temperature, humidity, and light exposure for assigning storage conditions and use-period extension process where experimental conditions as well as test method are based on scientific justification. Nevertheless, since SDDs are amorphous, their physical and chemical stability is generally inferior to their crystalline form. Hence, the degradants from oxidation, hydrolysis, and other types of reactions involving API need to be closely monitored and controlled, and even more critical, they should be qualified before using in patients. Moreover, prior to manufacturing stability batch, profiles of SDD materials are needed to be established during the product development. It is recommended that the stability batch be on station before the manufacture of the first clinical batch to facilitate the use-date and use-period extension process. In addition, the results from a stability study can also help in establishing the specification of the dosage form to be used in clinical studies. A typical specification for a product with a SDD includes dissolution, purity/impurity, and identity besides color and appearance. In addition, measurement for water content and other tests related to physical characteristics are also performed. Since spray drying involves using a large amount of volatile organic solvent (usually class 2 solvents) such as acetone, ethanol, methanol, tetrahydrofuran (THF), or dichloromethane, in which they are used to dissolve both APIs and polymers, the residual solvent content in the dosage forms of SDDs needs to be determined by gas chromatography (GC) with sufficient sensitivity and specificity. Regarding the control level of these

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solvents, the specification typically complies with the international conference on harmonization (ICH Q3C (R5)) guideline. Comparing with dosage forms of crystalline API, one of disadvantages of SDD dosage forms is their propensity to convert to crystalline forms during the spray drying process and storage, which can potentially impact their dissolution and bioavailability. Hence, it is important to monitor crystalline content in SDDs, which is commonly included in the stability studies and specifications. In terms of techniques, both polarized light microscopy and powder X-ray diffraction (pXRD) are used to assess the crystallinity of SDDs. While pXRD is more commonly used to quantify the crystalline content of SDDs, it is limited for its sensitivity when the crystalline content is low. In comparison, polarized light microscopy is more sensitive in measuring a trace amount of crystalline API in SDDs although it is less quantitative[30]. Moreover, thermal analysis, including thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC and modulated DSC), can provide important information related to the thermal stability of SDDs and phase transition from amorphous to crystalline phase: loss of water, solvent or decomposition, glass transition, melting temperature, energy flow associated with phase transitions, and crystallinity.

In addition to attributes listed in the specifications, there are many other parameters to be monitored during product development such as the particle size and size distribution of SDDs. Commonly used techniques for determining particle size and size distribution include light or scanning electron microscopy, as well as light scattering techniques. Considering SDDs as product intermediates to be incorporated into the final dosage forms, their particle size and size distribution are often measured prior to preparation of the final dosage forms. Typically, SDD particles are spherical, and their size is described by their geometric diameters, which can be measured with ultramicroscopic image analysis. Other common techniques such as light scattering are also used to characterize particle sizes by deriving their responses to probe in the analysis. Besides the SDD particle size, morphology and density can also be tuned through control of spraying drying process and particle size engineering to help achieve the desired drug product performance. Morphology is frequently characterized using transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) to qualitatively assess the crystalline states of drug active and phase separation. In terms of porosity, mercury porosity measurement is a quick analysis and often used to collect the information of pore size distribution and porosity of SDD materials. The density of SDD materials, as an important attribute, can be determined with a pycnometer.

To enhance a mechanistic understanding, a variety of other analytical techniques can be applied to measure the physical and chemical properties of SDD[31]. X-ray micro-tomography was used to characterize the SDD particles with varying degrees of wall collapse which cannot be accurately measured with a cryogenic SEM method[31]. Fourier transform infrared (FTIR) and FT Raman, both vibration spectroscopy techniques, are sensitive to molecular level interactions such as hydrogen bonding between API and its matrix. The in vitro dissolution test can be used to simulate the in vivo drug release profile, help in understanding the drug release mechanism, and therefore provide important information in guiding the development of the SDD and final dosage form.
Overall, many analytical tools have been used to characterize and monitor the stability of SDD materials. To successfully develop a solid dosage form with SDD materials, it requires an in-depth understanding of the physicochemical properties and its correlation with the product performance[32].

Conclusions

In this paper, challenges associated with developing SDD dosage forms for delivering poorly water soluble compounds are thoroughly assessed and summarized. In SDD strong interaction with waterare required. Moreover, to maintain supersaturation and enhance bioavailability after dissolution, a strong API-polymer interaction in an aqueous environment is preferred. Hence, a mechanistic understanding of supersaturation maintenance is needed. Additionally, a proper analytical assessment of the performance of SDD dosage forms will greatly expedite their development that challenges are not only associated with monitoring the dissolution of SDD alone or SDD dosage forms but also related to identification of physical/chemical attributes of SDDs and their dynamic implications. In conclusion, to increase the choice of selection for polymers, new polymers or

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modified polymers with the right balance of hydrophilicity and hydrophobicity need to be synthesized and approved for use. Without it, the industry will suffer the result of having a limited choice for polymer selection.

Conflict of interest

The author has no conflict of interest

References

1. Newman, A., G. Knipp, and G. Zografi. Assessing the performance of amorphous solid dispersions. Journal of Pharmaceutical Sciences. 2012;101(4):1355-1377.
2. Chauhan, H., C. Hui-Gu, and E. Atef. Correlating the behavior of polymers in solution as precipitation inhibitor to its amorphous stabilization ability in solid dispersions. Journal of Pharmaceutical Sciences. 2013;102(6):1924-1935.
3. Vaka, S.R.K., et al. Excipients for amorphous solid dispersions. Amorphous Solid Dispersions. 2014:123-161.
4. Tachibana, T. and A. Nakamura. A methode for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion ofB-carotene by polyvinylpyrrolidone. Kolloid-Zeitschrift und Zeitschrift für Polymere. 1965;203(2):130-133.
5. Ormes, J.D., et al. Design of experiments utilization to map the processing capabilities of a micro-spray dryer: particle design and throughput optimization in support of drug discovery. Pharmaceutical Development and Technology. 2013;18(1):121-129.
6. Hu, Y., et al. 3D cubic mesoporous silica microsphere as a carrier for poorly soluble drug carvedilol. Microporous and Mesoporous Materials. 2012;147(1):94-101.
7. Sperling, L.H. Introduction to physical polymer science. 2005.
8. Litvinov, V., et al. Solid state solubility of miconazole in poly [(ethylene glycol)-g-vinyl alcohol] using hot-melt extrusion. Molecular Pharmaceutics. 2012;9(10):2924-2932.
9. Utracki, L.A. and B. Favis. Polymer alloys and blends. 1989;4.
10. Li, J., et al. The effect of polymeric excipients on the physical properties and performance of amorphous dispersions: part I, free volume and glass transition. Pharmaceutical Research. 2015;32(2):500-515.
11. Tang, B., et al. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug discovery today. 2008;13(13):606-612.
12. Baumann, J., D. Dobry, and R. Ray. Amorphous Dispersion Formulation Development: Phase-Appropriate Integrated Approaches to Optimizing Performance, Manufacturability, Stability, and Dosage Form. Drug Dev. Deliv www. drug-dev. com/Main/Back-Issues/FORMULATION-DEVELOPMENT-Amorphous-Dispersion-Formu-605. aspx. 2013.
13. 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(10):3931-3948.
14. Delmas, G., D. Patterson, and S. Bhattacharyya. Heats of mixing of polymers with mixed-solvent media. The Journal of Physical Chemistry. 1964;68(6):1468-1474.
15. Rattes, A.L.R. and W.P. Oliveira. Spray drying conditions and encapsulating composition effects on formation and properties of sodium diclofenac microparticles. Powder Technology. 2007;171(1):7-14.
16. Woo, J.-S. and H.-C. Chang, *Non-crystalline cefuroxime axetil solid dispersant, process for preparing same and composition for oral administration thereof*, 2000, Google Patents.
17. Liu, H. Science and Engineering of Droplets:: Fundamentals and Applications. 1999.
18. Paudel, A. and G. Van den Mooter. Influence of solvent composition on the miscibility and physical stability of naproxen/PVP K 25 solid dispersions prepared by cosolvent spray-drying. Pharmaceutical Research. 2012;29(1):251-270.
19. Bhugra, C., et al. Prediction of the onset of crystallization of amorphous sucrose below the calorimetric glass transition temperature from correlations with mobility. Journal of Pharmaceutical Sciences. 2007;96(5):1258-1269.
20. Serajuddin, A.T.M. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent

© 2017 All Rights Reserved.

problems, and recent breakthroughs. Journal of Pharmaceutical Sciences. 1999;88(10):1058-1066.

21. Dixit, N.D. and S.K. Niranjan. A review: solid dispersion. World J Pharm Pharm Sci. 2014;3(9):238-57.

22. Leuner, C. and J. Dressman. Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics. 2000;50(1):47-60.

23. Guzmán, H.R., et al. Combined use of crystalline salt forms and precipitation inhibitors to improve oral absorption of celecoxib from solid oral formulations. Journal of Pharmaceutical Sciences. 2007;96(10):2686-2702.

24. Brouwers, J., M.E. Brewster, and P. Augustijns. Supersaturating drug delivery systems: The answer to solubility-limited oral bioavailability? Journal of Pharmaceutical Sciences. 2009;98(8):2549-2572.

25. Prasad, D., H. Chauhan, and E. Atef. Role of molecular interactions for synergistic precipitation inhibition of poorly soluble drug in supersaturated drug–polymer–polymer ternary solution. Molecular Pharmaceutics. 2016;13(3):756-765.

26. Purohit, H.S. and L.S. Taylor. Phase separation kinetics in amorphous solid dispersions upon exposure to water. Molecular Pharmaceutics. 2015;12(5):1623-1635.

27. Jackson, M.J., et al. Impact of polymers on the precipitation behavior of highly supersaturated aqueous danazol solutions. Molecular Pharmaceutics. 2014;11(9):3027-3038.

28. Ilevbare, G.A., et al. Influence of additives on the properties of nanodroplets formed in highly supersaturated aqueous solutions of ritonavir. Molecular Pharmaceutics. 2013;10(9):3392-3403.

29. Ilevbare, G.A. and L.S. Taylor. Liquid–liquid phase separation in highly supersaturated aqueous solutions of poorly water-soluble drugs: implications for solubility enhancing formulations. Crystal Growth & Design. 2013;13(4):1497-1509.

30. Vo, C.L.-N., C. Park, and B.-J. Lee. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2013;85(3):799-813.

31. Shekunov, B.Y., et al. Particle size analysis in pharmaceutics: principles, methods and applications. Pharmaceutical Research. 2007;24(2):203-227.

32. Gamble, J.F., et al. Application of imaging based tools for the characterisation of hollow spray dried amorphous dispersion particles. International Journal of Pharmaceutics. 2014;465 (1):210-217.

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