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A review on amorphous solid dispersions for improving physical stability and dissolution: Role of polymers

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Abstract

Amorphous solid dispersion (ASD) has been a successful strategy to improve solubility and dissolution rate of poorly soluble drugs. ASD improve the solubility and dissolution of drugs by existing as separate molecules in a polymer matrix. The stability of amorphous solid dispersions is dependent on thermodynamic, kinetic and environment factors. Thermodynamic factors include drug-polymer miscibility and solubility. Kinetic factors include glass transition temperatures, molecular mobility, drug-polymer interactions. Environment factors indirectly affect the stability of ASD by influencing the thermodynamic and kinetic factors. The focus of this review is to discuss the role of polymer in influencing the thermodynamic and kinetic stability of ASD.

Keywords: Amorphous solid dispersion; Dissolution; Polymer matrix; Role of polymer; Bioavailability; Physical Stability

1. Introduction

Oral solid dosage forms are prevalent form of administration of drugs due to non-invasiveness, ease of administration, lack of microbial concern, etc [1-5]. However, API with limited solubility are not suitable for oral administration due to bioavailability concerns. Bioavailability can be improved by buccal drug delivery, microneedles, parenteral administration, controlled drug delivery, nanoparticulate drug delivery, complexation, Liquisolid technique[51] etc. [6-16]. Around 40% of the marketed drugs and 90% of the API in clinical development face solubility challenges. Solubility enhancement can improve the bioavailability which are limited by solubility but not by drug absorption. Solubility enhancement can be achieved by several methods like micronization, nanonization, amorphous solid dispersions, pH modification, salt formation, etc. Often, some of the polymorphic forms exhibit higher solubility based on their thermodynamic energies. Use of such polymorphic forms to enhance solubility may be constrained response by patent litigations[17-21]. Solubility enhancement technique is selected based on the nature of API and other parameters. Amorphous solid dispersions (ASDs) are preferred as solubility enhancement technique for APIs which cannot be enhanced through particle size reduction. Hot melt extrusion, spray drying, wet granulation, KinetiSol, fluid bed coating technologies are generally used in industry to produce ASDs. In addition of ASDs. Hot melt extrusion is capable of preparing a wide variety of dosage forms like controlled drug release, films, semi-solids, nanoparticles etc [22-29].

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ASDs are prepared by dispersing drug as separated molecules in a polymeric matrix. The polymeric matrix typically consists of one or more hydrophilic polymers capable of maintaining the dispersed molecules throughout the shelf life. Crystalline drugs need to break the lattice energy to dissolve and be available for absorption through gastro-intestinal tract. The dispersed molecules avoid the need to overcome the lattice energy during dissolution thereby enhancing the solubility, dissolution and bioavailability [30-31].

The amorphous drugs have higher free energy compared to the crystalline form of the drug, hence tend to recrystallize during storage and dissolution. Amorphous-amorphous phase separation and crystalline conversion are solid-state physical instabilities associated with ASDs. Such instabilities are observed during storage and dissolution rather than immediately after preparation of ASDs. Selection of polymer plays a crucial role in enhancing the solubility and stability of the ASDs. Factors like glass transition temperature (Tg), drug-polymer miscibility, drug-polymer interaction, molecular weight, viscosity of polymers influence dissolution and stability of the ASDs. This review focuses on techniques to predict physical stability of the ASD and case studies which explain the role of polymer in enhancing the stability and dissolution of the drug [32-35].

2. Techniques to predict physical stability of ASD

Physical stability of ASDs can be classified as thermodynamic, kinetic and environment factors. Thermodynamic factors are related to spontaneity of occurrence of physical instability like phase separation. Kinetic stability is related to rate of drug precipitation and environment factors affect the physical stability by influencing the thermodynamic and kinetic stability of ASDs [36-37].

2.1. Drug-Polymer Miscibility

The miscibility of drug and polymer can be calculated through the following methods which help in predicting the thermodynamic stability.

Solubility Parameter: The solubility parameter is square root of cohesive energy needed to separate unit volume of molecules from condensed phase to infinite distance. Group contribution theory is usually used to calculate the solubility parameters for compounds of complex structure and high molecular weight. The solubility parameters are calculated by different methods like Fedors method or Hansen solubility parameter. In case of Fedors method, the solubility parameter of the individual groups of the molecule are summed together to calculate the solubility parameter of the complete compound. In case of Hansen solubility parameter method, the solubility parameter is calculated by through dispersion force, hydrogen bonding and polar force. A difference in the solubility parameter value of less than 7.0 $MPa^{0.5}$ between the drug and polymer indicates that they are miscible and a value more than 7.0 $MPa^{0.5}$ indicates that they are immiscible [38-39].

Glass transition temperature: Modulated DSC is also a technique used to predict the drug-polymer miscibility for preparation of ASDs. A single glass transition temperature in between the amorphous drug and polymer indicates that the ASD is a miscible homogenous system [40].

Molecular Modelling: Molecular modelling is also used to predict the miscibility of drug and polymer. It involves utilizing quantum mechanical calculations to predict the interactions between drug and polymer. The feasibility of hydrogen bonding between drug and polymer is calculated from the binding energies when a drug molecule is placed in the vicinity of the polymer molecule. The possibility of hydrogen bond formation between drug and polymer increases if the binding energies are comparable to that of a normal hydrogen bond [36].

2.2. Drug Solubility in Polymer

Drug solubility in polymer can be predicted through following approaches.

Melting Point Depression: Drug and polymer physical mixture at different ratios will be heated at low heating rate on DSC. Free energy change of the crystalline drug should be equivalent to the chemical potential change of crystalline drug in liquid and in the amorphous polymer phase. The decreased chemical potential will result in melting point depression of crystalline drug. The melting point depression is used in calculation of thermodynamic solubility of drug in polymer.

Drug dissolution in polymer: Drug solubility can also be predicted using hot state microscopy. Physical mixtures of drug and polymer at different ratios are heated gradually on hot stage. The ratio at which drug completely dissolved in the polymer without any birefringence is considered as drug solubility in polymer.

Enthalpy approach: In this approach, the drug solubility is predicted by DSC. The drug concentration and enthalpy are plotted and the solubility is calculated by X-intercept from the regression equation.

Gordon-Taylor equation: Glass transition temperature of ASDs increases when polymers of high glass transition temperature are used.

Molecular mobility: Molecular mobility is defined as inverse of the relaxation time. Relaxation time is the time needed for structural relaxation in the form of enthalpy and configurational entropy when they are stores below the glass transition temperature. Recrystallization rate of amorphous materials is related to the molecular mobility [41].

3. Case Studies

3.1. Binary Amorphous Solid Dispersions

In a study performed by Zhao Et al, the performance and mechanism of various polymers in stabilizing ASDs was investigated. Nimodipine was used as a model drug to study the effects of polymers on the dissolution and stabilization of ASDs. Three polymers, polyvinylpyrrolidone (PVP), vinylpyrrolidone-vinyl acetate copolymer (PVP VA), and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus), were used to prepare ASDs. ASDs were prepared at four different drug loading with each of the polymers using a solvent evaporation method. Solid state characterizations were studied to understand the mechanism underlying in stabilization of ASDs. The crystallization behavior was also studied by using polarized light microscopy. Liquid-liquid phase separation was studied using transmittance electron microscopy (TEM). Based on the results, ASDs prepared with PVP was able to improve dissolution and was stable compared to ASDs prepared with PVP VA and Soluplus [42].

Andrea Et al., studied the drug polymer interaction between acetaminophen and hydroxypropylmethylcellulose acetyl succinate in ASD using multidimensional multinuclear solid-state NMR spectroscopy. Different ASDs were prepared at three different drug loads (10%, 20% and 40%w/w) using spray drying technique. The ASDs were characterized using PXRD, standard and Modulated DSC measurements, Solid-State NMR experiments. The studies were performed by storing the ASDs over a year at room temperature. XRD studies indicate that the 20% drug loaded ASDs showed crystalline peaks after four weeks whereas 40% drug loaded ASDs showed crystalline peaks after a week. DSC studies indicate that negative deviations were observed with glass transition temperatures of drug loads from predicted glass transition temperatures. The largest deviation was observed with 40%w/w drug load among all drug loads. The chemical shift in ^{1}D ^{1}H, ^{13}C, and ^{15}N CP MAS NMR spectra between crystalline and amorphous acetaminophen indicates presence of hydrogen bonding between drug and polymer [43].

The effect of amorphous nature of the polymer on the stabilization of ASDs was studied by Daniel Et al. Posaconazole was selected as model drug. Four different polymer classes were selected for the study: amorphous homopolymers (Kollidon K30, K30), amorphous heteropolymers (Kollidon VA64, KVA), semi-crystalline homopolymers (Parteck MXP, PXP), and semi-crystalline heteropolymers (Kollicoat IR, KIR). ASDs were prepared by hot melt extrusion technique using twin screw extruder, RES-2P/12A Explorer, Zamak Mercator. The drug loading was maintained at 50:50 ratios in case of amorphous homopolymers and semi-crystalline polymers and was selected as 30:70 for the amorphous heteropolymers. The ASDs were characterized for melting point depression of the API, miscibility and homogeneity with POS, improvement of the amorphous API's physical stability, melt viscosity (and associated with it, drug loading), extrudability, API content in the extrudate, long term physical stability of the amorphous POS in the binary drug–polymer system (in the form of the extrudate), solubility, and dissolution rate of hot melt extrusion (HME) systems. The results indicated that physical stability of the ASDs improved with increased amorphous nature of the polymer used to prepare ASDs. The solubility enhancement was higher with homopolymers compared to copolymer excipients [44].

The impact of the polymers on the induction times of precipitation was studied by Grace Et al. Three drugs, celecoxib, efavirenz and ritonavir were selected as model drugs. Poly(vinyl pyrrolidone) K29/32, poly(acrylic acid) and cellulose acetate phthalate, poly(vinyl pyrrolidone vinyl acetate) K28, hydroxypropyl methyl cellulose 606 grade and hydroxypropyl methyl cellulose acetate succinate AS-MF grade, poly(allylamine) and poly(Nisopropylacrylamide), hydroxypropyl cellulose and carboxymethyl cellulose acetate butyrate. Solubility parameter, solubility studies, DSC, moisture sorption analysis, polarized light microscopy and induction times measurements were studied. Nucleation/induction times were quantitatively measured using time needed for induction of particulates from deseeded desupersaturation experiments. The results indicate that the induction times in the absence of polymers from unseeded desupersaturation experiments varied from approximately two minutes to two hours. Polymers were able to extend the induction time by 5-6 times. The effectiveness of the polymers was dependent on the hydrophobicity of

the polymer. Higher the hydrophobicity of the polymer, higher will be the polymer-solute interactions favoring avoiding precipitation [45].

In a study performed on ASDs, the effect of polymer on dissolution profile of felodipine was studied. ASDs were prepared using poly(vinylpyrrolidone) (PVP), hydroxypropyl methylcellulose (HPMC) or hydroxypropyl methylcellulose acetate succinate (HPMCAS) and the dissolution profiles were compared. The effect of polymer concentration on supersaturated solution of felodipine was also studied. The results indicate that HPMCAS was able to maintain highest level of supersaturation of felodipine with both dissolution and solution crystallization experiments. This is probably due to enhanced solution concentration during dissolution of ASDs [46].

Effect of polymer hygroscopicity was studied to study the stability of ASDs. ASDs were prepared with Felodipine, pimozide, indomethacin, and quinidine using PVP, polyvinylpyrrolidone-covinyl acetate (PVP VA), and hypromellose acetate succinate (HPMCAS). Effect of high relative humidity on the drug-polymer miscibility was studied using IR spectroscopy and DSC. The results indicate that moisture resulted in drug-polymer demixing with felodipine-PVP VA, quinidine-PVP, quinidine-PVP VA, pimozide-PVP VA, and pimozide-HPMCAS systems, but not with other HPMCAS dispersions and for indomethacin-PVP VA. It was inferred that balance between the thermodynamic factors in ternary water-drug-polymer system is essential to determine if solid dispersion systems are susceptible to moisture-induced amorphous phase separation. ASDs with strong drug-polymer interaction and a less hygroscopic polymer is less affected to moisture induces phase separation compared to hydrophobic drugs with low levels of moisture [47].

Influence of molecular weight and polydispersity index (PDI) on the dissolution of ASDs was studied using polyvinylpyrrolidone-co-vinyl-acetate 60:40 (PVP-VA64). Ketoconazole was used as a model drug. Placebo extrusions were run using PVP-VA64. The subsequent polymer was used to prepare ASDs using ketoconazole by spray drying. The molecular weight and polydispersity index was determined using absolute molar mass detection via muti-angle light scattering. The results indicated that slight changes in the molecular weight and PDI significantly impacted super saturation and precipitation of formulation [48].

In another study, impact of polymeric combinations on supersaturation kinetics and dissolution performance by Arun Et al. In this study, binary and tertiary ASDs were prepared using polymers hydroxypropylmethylcellulose acetate succinate (HPMCAS) LG, and HG, Eudragit® RSPO, Eudragit® FS100, Kollidon® VA64 and Plasdone™ K-29/32. Amorphous solubility, nucleation inductions time and particle size analysis was studied in a supersaturated solution in presence and absence of polymers. The ASDs with HPMCAS-HG and HPMCAS-HG + LG combinations had the highest nifedipine amorphous solubility and delay in nucleation induction time when compared with other combinations. Drug release studies under non-sink conditions indicated that in spite of binary nifedipine/HPMCAS-LG system had shown the greater supersaturation concentration of but could not maintain a supersaturation level. Supersaturation level with improved dissolution performance was achieved only by synergistic action of ternary nifedipine/HPMCAS-LG/HPMCAS-HG, and nifedipine/HPMCAS-LG/Eudragit®FS100 systems [49].

3.2. Tertiary Amorphous Solid Dispersions

Prasad Et al. studied synergistic effect of polymers on physical stability and dissolution of ASDs of indomethacin. In this study, Eudragit E100 and PVP K90 at a concentration of 2.5 – 40% w/w were selected as polymers. ASDs were prepared using solvent evaporation technique by dissolving drug and polymers in methanol and the solvents were evaporated using rotary evaporator at 60°C. The mechanism of enhanced dissolution and stability was studied by investigating the miscibility and intermolecular interactions between indomethacin and polymers. The prepared ASDs were studied using modulated DSC for melting point depression, powder XRD for determining crystalline and amorphous nature of drug in the ASDs, IR spectroscopy, stability and dissolution studies. The stability studies indicated that ternary ASDs were amorphous at both 40°C/33%RH and 40°C/75% RH up to 6 months compared to binary ASDs. The results also indicated that ternary ASDs were more stable and have higher dissolution compared to binary dispersions though the polymer concentration was low. Solubility parameters, melting point depression, molecular mobility were studied to understand improved stability of ternary ASDs. The difference in solubility parameters between both indomethacin and polymers was less than 3 $MPa^{1/2}$ indicating that they are miscible. In case of melting point depression, the depression in ternary physical mixtures with 10% of each polymer was comparable to the binary solid dispersion containing 20% individual polymers indicating synergism. FTIR studies indicated that in IND and PVP K90, hydrogen bond formation between hydroxyl group of IND and carbonyl group of PVP K90. In case of IND/Eudragit E100, dimethylamino group of Eudragit E100 interacts with hydroxyl group of IND. This confirms improved miscibility in ternary ASDs resulting in improved stability and dissolution compared to binary ASDs [50].

4. Conclusion

Nucleation inhibition and prolonged stability are important characteristics of ASDs to perform as intended to improve the solubility and bioavailability throughout shelf-life. It is important to study the polymer characteristics during the pre-formation if the polymer or polymers combination with drug will be able to maintain the supersaturation and physical stability as needed. The polymers should be selected based on the physicochemical characteristics of the API and processing conditions in order to create effective ASDs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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