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SOLID DISPERSIONS AND SUPERSATURABLE DRUG DELIVERY SYSTEM: A BRIEF REVIEW

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Abstract:

The most common characteristic which pharmaceutical scientists encounter in context to new drug candidates in pharmaceutical development pipelines is their poor aqueous solubility. Aqueous solubility is an important attribute which is considered during drug discovery, formulation development and subsequent stages. Solid dispersion technology and supersaturable formulations have been demonstrated as effective approach to improve solubility and oral absorption of poorly water soluble compounds. Solid state manipulation techniques, particularly amorphization are preferred ways of enhancing solubility and optimizing delivery of poorly soluble drugs. However, they presents challenges in context to their stability. Therefore, polymeric carriers have been recognized as drug precipitation inhibitors and have been used to inhibit or, delay such precipitation. In this manner, maintenance of drug in supersaturated concentration is achieved for an extended period of time, leading to significant improvement in bioavailability and effective therapeutic outcome of the poorly water soluble drugs. This technology has wide perspective in the development of poorly soluble new chemical entities aiming at converting drug into suitable system of high energy and thus stabilizing the formed metastable system through crystal growth inhibition utilizing various suitable polymeric crystallization inhibitors.

This review is an attempt to address the diverse issues pertaining to amorphous drug delivery systems. It also discusses about the stability aspects, properties and stabilization mechanisms of amorphous forms, different types of precipitation inhibitors and working hypotheses for stabilizing the amorphous form of drugs.

Keywords: *Amorphous, bioavailability, dissolution, drug precipitation, solid dispersions.*

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INTRODUCTION:

The fundamental aspect behind pharmacokinetic profile of any drug after oral administration comprises of a cascade of absorption, distribution, metabolism and excretion (ADME). Overall, bioavailability is defined as the limit of therapeutically active drug approaching the systemic circulation and thus, available at the site of action. Thus, absorption step is accounting for one of the important step which govern the bioavailability of an orally administered molecule. Bioavailability of a drug can be well determined by Fick´s law of diffusion applied to gastrointestinal membrane which is the simplest model for oral absorption.

$$J_{mem} = P_{mem}.C_{int}$$

Where, J_{mem} is flux of drug across homogenous intestinal membrane, P_{mem} is the effective permeability, which is defined as the rate with which the dissolve drug will cross the intestinal membrane to reach portal blood circulation and C_{int} is the drug concentration in the luminal fluid. According to this mathematical equation, the flux of the drug across the membrane is a function of drug permeability and solubility (Amidon et al., 1995).

It is understood that solubility behaviour of a drug along with the permeability factor is a key determinant of oral bioavailability. Compound having poor solubility, results in inadequate absorption across the gastrointestinal membrane and ultimately limit the systemic exposure required to induce therapeutic outcome. Thus, solubility of drug in gastrointestinal milieu is the major factor governing absorption alluding that higher the solubility, higher is the rate of absorption.

Solubility and permeability interactions and their impact on intestinal drug absorption are most prominently described by the biopharmaceutical classification system (BCS) (Flynn et al., 1974). The bioavailability from conventional formulations of poorly soluble drug candidates may be unacceptable and represents focus for formulation improvement. According to BCS, drugs belonging to BCS class II having good absorption property exhibit limited oral availability on account of their poor solubility. When drug-solubility is less than 1 µg/mL in water, which we often encounter for contemporary drug candidates, the bioavailability from conventional formulations may be unacceptable (Lipinski et al., 1997 and Liu, 1997). The number of active pharmaceutical substances having high therapeutic potential but limited water solubility is constantly increasing, making it difficult to formulate these compounds as oral dosage forms. As a result of which the pharmaceutical world is encountering many high hydrophobic and poor water-soluble new chemical entities (Lipinski et al., 1997 and Fahr, 2007). It has been estimated that approximately 40% of currently marketed drugs and 75% of drugs under development as poorly soluble molecules and thus they present challenges in context to their bioavailability. It is also recognized that the failure incurred in pre-clinical and clinical development is attributed to the poor oral bioavailability (Di et al., 2009). The insoluble drugs show dissolution process as the rate-controlling step and thus result in erratic and incomplete absorption from the gastrointestinal tract leading to therapeutic failure.

Oral drug delivery has long been recognized as the simplest and easiest way for drug administration on account of their better patient compliance, stability, accurate dosage and easy production. Therefore, new molecular entities under development are intended to be developed as solid dosage form to elicit effective and reproducible plasma drug concentration after oral administration (Anguiano-Igea et al; 1995, Serajuddin, 1999 and Craig, 2002). However, due to the advent of new techniques in the design of new molecular entities like high throughput screening, combinatorial chemistry and the like, pharmaceutical world is witnessing new molecular entities with very poor solubility and bioavailability and thus affecting drug's inherent efficiency and expected therapeutic outcome. Many molecules also exhibit smaller absorption window where they get absorbed only in the upper small intestine and reduced significantly after the ileum (Van den Mooter, 2006, and Tanaka, 2005). The major current challenge that the formulation scientists are encountering is the growing number of insoluble molecules and on account of which research efforts are more focussing in exploring technology based platforms to improve solubility and bioavailability of these molecules.

In the course of the formulation development of poorly soluble molecules, different technologies have been approached to improve the bioavailability through oral route. In this context, a number of formulation strategies have been framed to improve the bioavailability of class II drugs either by increasing the dissolution rate or, by maintaining the drug in solution in the gastrointestinal tract (Liu, 1997 and Lipinski, 2000). The drug solubility and bioavailability improvement has been possible by chemical and physical approaches.

There are various techniques being explored to increase the drug solubility and are broadly classified into chemical and physical approaches. Chemical approaches aim at improving drug solubility by prodrug and salt formation. These approaches improve bioavailability without changing the active target and can suitably be achieved by either salt or, prodrug formation. However, salt formation is applicable only to ionic drugs, which excludes the use of this strategy for neutral drug molecules. The chemical modification of a parent molecule to form soluble prodrug requires the drug molecule to possess functional group(s) capable of derivatization by reacting with a promoiety. However, the alteration of chemical structure can affect many other properties, including toxicological profile. It is also sometimes evident that salt formation does not achieve better bioavailability because of its *in-vivo* conversion into acidic or basic forms. For example, salts of acidic drugs undergo disprotonation to neutral species during dissolution in the stomach due to the low pH. This phase conversion from a salt to the thermodynamically stable neutral phase generally corresponds to a reduction in drug solubility. From the regulatory perspective, the approval of prodrugs and salts is a tedious task, disfavoring their general applicability. Stability issues and obligation by the sponsor companies to perform clinical trials on the salt forms are some of the other reasons on account of which this approach lack interest in the formulation development of poorly soluble molecule. Due to these disadvantages of chemical approaches, there exist other technologies which encompass approaches like complexation (inclusion complexes); use of cosolvents, emulsions and microemulsions; use of surface active agents and solid-state manipulation to circumvent such solubility issues.

In context to the physical approaches for improving the solubility of poorly soluble molecules, particle size reduction techniques are also well recognized technique. However, particle size reduction limit particle size around 2-5 mm which frequently is not enough to improve considerably the drug solubility or, drug release in the small intestine and consequently, to improve the bioavailability. Moreover, solid powders with such a low particle size have poor mechanical properties, such as poor flow, high adhesion and are extremely difficult to handle. Surfactants improve solubility by promoting wetting and causing micellar solubilization. However, their possible interaction with drugs, the effect of pH on their performance and their capacity to alter physiological processes are causes of concern. The use of complexing agents, including formation of inclusion complexes with cyclodextrins, is plagued by problems of its concentration dependent toxicity and reversibility of complex, which prevents their widespread use. Cosolvents, emulsions and micro-emulsions, although useful for formulation of liquid products, cannot be used in solid dosage forms (Liu, 1997, Kaushal et al; 2004).

In addition to the abovementioned technologies, solid dispersion has been demonstrated as an effective approach to improve solubility and oral absorption of poorly water-soluble drugs (Serajuddin, 1999 and Leuner, 2000). Stabilized amorphous forms have been the targets in the formulation development of solid dispersions of different molecules. The solubility, dissolution rate and thus bioavailability of the poorly water-soluble drugs can be enhanced by the formation of such stabilized amorphous forms. Currently, formulation as solid polymer dispersions is the preferred method to enhance drug dissolution and to stabilize the amorphous form of a drug. The term solid dispersion signifies a range of pharmaceutical products with one or more drugs homogeneously dispersed within a matrix of carrier(s), prepared by melting (fusion) or, solvent evaporation method. In principle, the conversion of crystalline drug into their amorphous counterparts is one of the most promising tools, compared e.g. to simple micronization (Kesisoglou, et al), salt formation (Serajuddin, 2007) and mechanical activation or, milling (Huttenrauch, 1985) which are having many practical limitations. The enhancement in the drug solubility in the solid dispersion is achieved using drug in its amorphous state which is highest energy form of a solid material with no long range molecular order. The amorphous state solid dispersion have greater molecular motion and enhanced thermodynamic properties compared to the crystalline state which lead to higher apparent solubility and dissolution rate (Hancock and Zografi, 1997). The amorphous nature of drug and characteristic feature of disorderness is demonstrated by excess enthalpy, specific volume, entropy and free energy. The excess free energy in the solid amorphous state reduces the energy required for fluidization of the drug molecule to participate in the solubilization process. Typically, solid dispersions are the strategy of development where, amorphous drug is embedded in a polymer matrix or, the drug is molecularly dispersed in the polymer matrix. Basing upon this dispersion pattern, the solid dispersions can be classified as

eutectic mixtures, solid solutions (continuous and discontinuous solid solutions, substitutional crystalline, interstitial crystalline and amorphous solid solutions) and the like (Leuner, 2000). Irrespective of the system, the drug is contained by the system in its high energy state which enable the drug to get solubilized and on account of which solubility and bioavailability increases (Brouwers, 2009). The maximum solubility advantage is expected from solid dispersions in which the drug is present as a single phase in the amorphous state. The underlying factors behind increase in solubility are: a) overcoming of crystal lattice energy in the amorphous state reducing thermodynamic barrier for the dissolution, the energy required to break up the crystalline structure of the drug before it can dissolve; b) particle size reduction and c) modifying the hydrophobic surface of the drug with an effect in the diffusion layer surrounding the dissolving particle. On complete dissolution of the particle, drug is present as supersaturated solution or, is precipitated as fine colloidal particles or, oily globules. However, the supersaturated solution is being prevented precipitation by the polymers/carrier system present. Sometimes if the drug precipitates, then it precipitate as metastable polymorph with high solubility compared to that of the stable form (Kaushal et al; 2004).

The carrier agent varies from polymers, surfactants, processing aids and plasticizer. Typically, solid dispersion contain polymers, surfactants and the like which act as plasticizers and crystallization inhibitors during production. Furthermore, they serve as wetting agents, precipitation inhibitors or, solubilizing agents in the aqueous dispersions of solid dispersion (Brouwers, 2009). Solid dispersions aim at generating high and possibly supersaturated intraluminal concentrations of poorly water soluble drugs by increasing their apparent solubility and/or dissolution rate. Supersaturation in the gastrointestinal tract is the focused formulation strategy to enhance the intestinal absorption of the poorly water soluble drug to generate supersaturation relative to poorly soluble neutral phase and polymers were added to the system in order to maintain the compound in the supersaturated state.

Supersaturable formulations: spring and parachute theory

Solid dispersions in the form of supersaturable formulations have been reported as one of the approach to improve solubility and bioavailability of poorly water-soluble drugs. However, when such formulations are exposed to gastrointestinal fluids the drug concentration surpasses the equilibrium solubility and hence, get precipitate out before getting absorbed. This precipitation results in lowering of bioavailability and encumbering therapeutic outcome. The precipitation behaviour has been addressed by many researchers and utility of polymers has also been explored to inhibit such precipitation. Generally, supersaturation occurs in the gastro intestinal tract due to the gastric emptying of weak bases or, loss of solubilisation capacity of a formulation upon its dilution in the gastrointestinal tract. The fundamental aspects of generation and up keeping of a supersaturated state in gastrointestinal fluid is commonly described by the "spring and parachute" theory (Guzman et al; 2007).

Supersaturation has been identified as a strategy to improve intestinal absorption of poorly water soluble drugs. The two critical steps considered in this regard are generation ('spring') and maintenance of the metastable supersaturated state ('parachute'). The theory explains that in the development of supersaturable formulations the optimal concentration of "spring" and "parachute" identification is an important factor. The high energy form of the drug in a thermodynamically unstable system usually denoted by "a spring" (Brouwers, 2009 and Teja et al; 2013). However, a drug has to be maintained at a high concentration for prolonged period of time from the supersaturated state by using precipitation inhibitors ("parachutes") for temporary inhibition of drug precipitation (Warren et al; 2010). Under the "spring" category, two different types of supersaturated solutions are available i.e. highly concentrated solution and high-energy and/or rapidly dissolving solid forms due to the changed morphology, particle size and/or wettability (Brouwers, 2009 and Teja et al; 2013). The spring category encompasses co-crystals, nanoparticles, solid solution/dispersion, amorphous forms and lipid formulations. However, parachute category includes different precipitation inhibitors like polymers (polyvinylpyrrolidone, polyvinylalcohol, polyethylene glycols, cellulose derivative etc.), surfactants (pluronics, d-α-tocopheryl polyethylene glycol 1000 succinate and sodium dodecyl sulfate) and cyclodextrins (hydroxypropy β cyclodextrin, sulfo butyl ether β cyclodextrin). Thus, the inclusion of such precipitation inhibitors prevent the crystal growth and thus result in improved bioavailability.

Precipitation inhibition: mechanisms and examples

Precipitation process is associated with two important stages which includes nucleation and subsequent crystal growth. The nucleation stage is related with gathering of the solute molecules into two or, three dimensional clusters within the solution. Crystal growth is the subsequent stage characterized by the growth of these small clusters if they are larger than the critical size (Warren et al; 2010 and Burda et al; 2005). Consequently, the molecules arrange themselves in orderly manner and form ordered crystal structure.

In order to get optimum and effective therapeutic outcome it is desirable to get increased concentrations from the supersaturated state which can be maintained for a period sufficient for absorption. This require temporary inhibition of precipitation by interfering nucleation and/or crystal growth that is, the 'parachutes' or, precipitation inhibitors.

Compounds which are weakly basic in nature get ionize in the acidic environment; when they are exposed to the higher pH intestinal milieu on gastric emptying, the equilibrium solubility get reduced and thus precipitation occurs. The generation of a supersaturated state and subsequent inhibition of precipitation have been interesting. Therefore, precipitation inhibition is required to get optimum therapeutic utility from the formulation system and it depends purely upon the properties of drug and the medium (Van Speybroeck et al; 2010). The supersaturating systems characteristically provide only momentary increase in solubility and thus inclusion of precipitation inhibitors may interfere in nucleation and/or crystal growth stages, ultimately prolonging the supersaturation.

Polymeric precipitation inhibitors work by different mechanisms towards precipitation inhibition and they maximally alter the bulk solution properties of the drug depending upon the properties of drug and polymers. Solubility and modulation of bulk solution properties like surface tension impact precipitation. Researchers have reported that decreasing surface tension moves crystallization from diffusion control to surface nucleation control and increasing solubility reduces supersaturation and the possibility of nucleation. The effective decrease in the diffusion of drug molecules to the crystal nuclei by changing the adsorption layer at the crystal-solution interface can also contribute towards the precipitation inhibition (Machefer et al; 2008, Pellett et al; 1997 and Gao et al; 2009).

The concealing up and smoothening of rough surfaces and disrupting the growth of steps across the crystal surface can also be optionally accounting for the precipitation inhibition (Gao et al; 2009). Precipitation inhibitors uphold supersaturated state of the drug *in-vivo* in the gastrointestinal fluid for an extended period to achieve optimum absorption. Mechanistically, the precipitation behaviour of drug from a supersaturated system can suitably be addressed by various means like: thermodynamic inhibition and kinetic inhibition. Thermodynamic inhibition targets in increasing drug solubility and reducing degree of supersaturation and crystal growth. Surfactants, co-solvents, cyclodextrins and various solubilizing agents are accounting for the thermodynamic inhibition. On the other hand, different polymers come under the category of kinetic inhibitor as they interfere with nucleation and crystal growth by interaction with compounds. They may also change the properties of the medium so as to prevent the crystal growth. Most importantly, inhibition of crystal growth by blocking access of the solute molecules to the crystal terrace has been explored by various researchers for precipitation inhibition (Machefer et al; 2008, Pellett et al; 1997, Gao et al; 2009, Chauhan et al; 2013, Loftsson et al; 1996 and Usui et al; 1997).

In context to the kinetic inhibition, suitable polymers at judicious concentration help in enhancing wettability and surface area but also result in supersaturated drug concentrations and inhibit precipitation. The different mechanisms and attributes responsible for the inhibition aims at the different aspects like hydrogen bonding, hydrophobic interactions, polymer rigidity, polymer molecular weight and steric hindrance and solution viscosity. The inhibition effect basically depends upon the properties of the inhibitor, the drug and the medium.

As discussed, the inhibition can be conceded either in the first step or, in the subsequent stage of drug crystallization. In context to the first stage, the nucleation can be suppressed or delayed by the impact of polymer additives like hydroxyl propyl methyl cellulose, methyl cellulose, polyvinylpyrrolidone (PVP) and polyethylene glycols (PEG). It was observed that spontaneous nucleation occurred without polymers whilst presence of polymers suppressed the drug

nucleation. It was also suggested that the inhibition effect of polymer is concentration dependent (Raghavan et al; 2001).

It is understood that the increase in the nucleation activation energy due to hydrogen bonds between drug molecules and polymers leads to delay in the nucleation and thus inhibit the crystallization. It is alluded that drugs rich in hydrogen-bond donors (e.g., hydroxyl, amide groups, etc.), polymers with hydrogen-bond acceptors such as polyvinyl pyrolidones can inhibit drug precipitation through polymer-drug hydrogen bonds. The same interaction is also contemplated for polymers rich in hydrogen-bond donors such as cellulose derivatives are more suitable for drugs with hydrogen-bond acceptors (carbonyl, amide, nitro acceptor group, etc.) (Trasi and Taylor, 2012). Moreover, hydrogen bonding between polymers and drugs also act in the second stage of drug crystallization and inhibit crystal growth (Balani et al; 2010)

This inhibition effectiveness is dependent upon the nature of the drug and the polymer. It has been reported that at the same viscosity grade; amongst various hydroxyl propyl methyl cellulose (HPMC) types (E and K series), E series have improved inhibition effect than K series on account of higher degree of methyl substitution (more hydrophobic) in HPMCE series (~29%) than that of HPMC-K series (~22%) (Bi et al; 2011). C. Vora et al investigated the influence of different molecular weight grades of HPMC (HPMC E5, HPMC E15 and HPMC E50) and polyvinylpyrrolidone (PVP K30 and PVP K90) on dipyridamole precipitation behaviour upon acid to neutral pH transition and concluded that the order of the polymers for inhibiting precipitation and maintaining supersaturation after pH transition was HPMC E 50 > HPMC E 15 > HPMC E5 >PVP K90 > PVP K30. It is also anticipated that the viscosity of the solution increases with increase in molecular weight of the polymer which is due to increased chain entanglements. This entanglement result in greater steric hindrance to nucleation and crystal growth of dipyridamole. The increase in viscosity of solution hinders the drug diffusion into the bulk of the solution and thus more of the drug will remain in intimate contact with the stabilizing polymer (Vora et al; 2015). Miller et al, investigated amorphous itraconazole solid dispersion systems with different polymeric carriers with respect to the ability to produce or, maintain supersaturation following an acidic to neutral pH transition. This has shown an insight about the polymeric stabilizers affecting dissolution characteristics of itraconazole from amorphous solid dispersions. It was reported that irrespective of molecular weight, Methocel® was found to produce greater drug release than Kollidon® which was attributed to stronger intermolecular interactions between itraconazole and Methocel®. Additionally, it was also predicted that with an increment in the local viscosity, there is a retard in the diffusion of solubilized drug molecules into bulk solution. This resulted in stabilization of itraconazole molecules in thermodynamically unfavorable aqueous environment (Miller et al; 2008).

It is generally assumed that any drug which is weakly acidic or, weakly basic in nature with p*K*a above the physiological range, shows that solubility behavior within the gastrointestinal tract will be similar to the behaviour of neutral compounds. Stabilization and site-targeting components for such systems may also be included based on the precipitation kinetics and regional absorption behaviour of the moiety. Weak bases exhibiting low p*K*a values (≤ 5) present a unique situation because such compounds will exhibit a substantial decrease in equilibrium solubility during intestinal transit. In the framework of anatomical construction of the gastrointestinal tract, it is designed to facilitate absorption of most nutrients at the upper small intestine due to enormous surface area relative to other regions as a result of villi and microvilli. Greater dissolution rate and magnitude of supersaturation as a result of the greater solubility in these conditions also result in oversaturation, resulting in higher crystallization driving force during transit. Rasenack et al. concluded that HPMC, methyl hydroxyethyl cellulose and polyvinyl alcohol inhibited crystal growth of a drug substance, ECU-01, effectively by forming a protective layer around the newly formed crystals (Rasenack et al; 2003). Several researchers also proposed that with the increase in the hydrophobicity of the excipient, the size of the nascent microcrystal particle size decreases. Some researchers also suggested poor effectiveness of hydrophilic polymers to inhibit crystal growth and few also confirmed that the polyethylene glycols being hydrophilic, did not adsorb to crystal surfaces and therefore had no crystallization prevention capability. Additionally, an increase of a given polymer's hydrophobicity seemed to increase polymer's adsorption on crystal surfaces, leading to an enhanced inhibition effect on drug precipitation (Douroumis and Fahr, 2007 and Zimmermann et al; 2009). In accordance with this, some researchers

also suggested that due to more favourable interaction of hydrophilic polymers with the solvent molecules due to which there is weak adsorption of polymers to the drug crystal surfaces resulting in a compromised inhibition effect.

As discussed, the attributes like rigidity of the polymers determine the adsorption capability of polymers on drug crystal surfaces. The rigid structures enable them to crystal surfaces more easily than flexible polymers as they form loops and afford only limited contact with the crystallizing surface (Ilevbare et al; 2012). In addition to the rigidity of the polymers, molecular weight of polymers and their steric hindrance effect play a critical role in determining the effect of inhibition on drug crystallization.

The higher molecular weight polymers are reported to have better impact are usually more efficient in maintaining the supersaturated state than lower molecular weight polymers (Plaizier-Vercammen, 1983 and Garekani et al; 2000). The higher number of functional groups on the polymer chains contribute towards the enhanced interaction of polymers with crystal surface and thus better coverage by polymers in delaying or, inhibiting crystal growth (Zimmermann et al; 2009, Kumavat et al; 2013, and Lechuga-Ballesteros, 1995). However, some researchers have studied and concluded that increased molecular weight does not always exhibit the strong inhibition effect. The inhibition performance of polyvinylpyrrolidone (PVP) polymers with different molecular weights (PVP K10, K25, K40 and K360) were investigated in context to model drug, salbutamol sulfate and reported that higher molecular weight PVP can provide higher concentration of the repeated vinyl pyrrolidone segments interacting with the crystal growth in the order K40 > K25 > K10) and a greater adsorbing tendency as the inhibition of crystal growth is controlled by the adsorption of the polymer onto the crystal surface. However, the inhibition effect of PVP K360 (highest molecule weight, 360,000 Da) was not as effective as PVP K10 (10,000 Da). The study found that the rate of PVP K360 diffusion to the crystal surface was the rate-determining step for polymer/crystal interactions and that PVP K360 had limited access to the crystal surface due to steric hindrance from its larger molecular structure (Xie et al; 2010).

As mentioned above, the role of solution viscosity in the precipitation inhibition can't be ignored. Crystal growth depend upon the viscosity of the medium and increase in the viscosity of the solution results in inhibition of crystal growth. Some studies reported about slowing down of drug precipitation by minimizing diffusion rate with the increase in solution viscosity whilst other studies found that viscosity has minimal impact in behaviour of drug precipitation (Guzman et al; 2007, Gao et al; 2009, Usui et al; 1997 and DiNunzio et al; 2010).

Warren et al; have reported that in spite of the criticality and complexity of precipitation from super saturated solutions, the factors responsible are increasing degree of supersaturation, presence of impurities, lower temperature, lower solution viscosity and decrease in interfacial tension (Warren et al; 2010). Apart from the abovementioned contributing factors towards precipitation inhibition, temperature and dielectric constant also play a determinant role in the drug polymer interaction and thus contributing towards precipitation inhibition. Increase in temperature causes decrease in binding of drug and polymer which is attributed to weakening of intermolecular interactions and drug solubilisation improvement. Decrease in dielectric constant increases drug solubility and thus decreases degree of intermolecular interaction (Plaizier-Vercammen, 1983 and Zhao, 2012). The polymeric inhibitors work very effectively in preventing the precipitation irrespective of the mechanism and stage of their action.

Amorphous formulations

Compounds in crystalline form have the advantages of high purity and physical or, chemical stability. However, these crystalline molecules have major drawback of the strong lattice energy which is limiting the dissolution property of these molecules. On the other hand, the disordered structure of the amorphous system possess higher free energy (thermodynamic driving force) leading to higher apparent water solubility, dissolution rate and oral absorption (Mooter, 2012 and Zhang et al; 2012). Drugs in amorphous state, bear higher solubility than crystalline forms, resulting improved oral absorption of poorly water-soluble drugs. Nevertheless, due to the physical and chemical instabilities of pure amorphous drugs are rarely used in formulation development. But, by kinetically stabilizing the amorphous molecules utilizing various means, different amorphous solid dispersions products have been studied by various researchers.

The application of amorphous pharmaceutical production techniques has been gaining increased industrial acceptance and witnessed commercial

success with several products in market to some extent (Table 1). The commercial success is attribute to effectively designing and optimization of both magnitude and duration of supersaturation.

Table 1. Examples of FDA approved medicinal products that use solid dispersion technologies (Brough and Williams, 2013).

S. No.	Product name	API	Polymer*	Solid dispersion preparation method**	Year of approval***
1	Sporonax	Itraconazole	HPMC	Spray drying on sugar beads	1992
2	Prograf	Tacrolimos	HPMC	Spray drying	1994
3	Kaletra	Lopinavir/Ritonavir	PVP/VA	Melt extrusion	2005
4	Intelence	Etravirine	HPMC	Spray drying	2008
5	Zotress	Everolimus	HPMC	Spray drying	2010
6	Norvir	Ritonavir	PVP/VA	Melt extrusion	2010
7	Onmel	Itraconazole	HPMC	Melt extrusion	2010
8	Incivek	Teleprevir	HPMC AS	Spray drying	2011
9	Zelbroaf	Vemurafenib	HPMC AS	Co-precipitatiom	2011
10	Kalydeco	Ivacaftor	HPMC AS	Spray-drying	2012

*Best guess based on the inactive ingredients list, patents and other literature information; **From Brough and Williams; ***Information based on the drug product labels from the FDA website.

In the development of amorphous solid dispersions, the suitability of a drug to form amorphous phase is a major concern. Solubility improvement of a poorly soluble molecule can be achieved by two different mechanisms: modification of equilibrium solubility and/or temporary establishment of elevated metastable solubility. In context to the first mechanism, different solubilizing excipients that modify the thermodynamic properties are utilized to enhance the equilibrium solubility. However, the later aims at achieving greater metastable solubility through change in the material properties (DiNunzio et al; 2010).

The increase in dissolution rate for solid dispersions can be attributed to a number of factors which include reduction in particle size, absence of aggregation or, agglomeration of fine crystallites of the drug, possible solubilization effect of the polymer, excellent wettability and dispersibility of the drug from solid dispersion and partial conversion of the drug into amorphous form. There are different emerging alternative methods to prepare amorphous drug polymer dispersions which include converting crystalline material to a thermodynamically stable non-crystalline form either by quench cooling, solvent evaporation or, by solvent and pH controlled precipitation of drug in polymer matrix (Kaushal et al; 2004 and Hancock and Zografi, 1997). In context to fusion or quench cooling, the melt usually crystallizes at the melting point which subsequently leads to contraction of the system due to decrease in the specific volume of the system. However, faster cooling (quench cooling) causes direct corresponding changes in structure and thermodynamic properties in the supercooled liquid material. Solvent evaporation by spray drying or, rotary evaporation techniques results in formation of drug polymer complex in subdivided state. Solvent and pH controlled precipitation form crystalline nanostructured particles with rapid dissolution rates. However, these nanoparticles upon storage may act as seeds for further nucleation and crystal growth accounting for the stability issue of amorphous dispersion. Therefore, this aims at fabricating polymer stabilized coprecipitated drug polymer complex. However, different methods of preparation result in dispersions with different thermal, structural and physical properties attributing for different molecular mobility (Graeser et al; 2009). The process parameters variation within a single technology also play a great role in determination of stability of amorphous dispersion. Different underlying principles and physical factors govern the stability of the amorphous form during formation and on storage. For better understanding, some computational models are also available to predict the properties of drug polymer interaction in

amorphous materials and thus alludes the stability aspects of the dispersion.

In the design aspects of the amorphous dispersions, drug polymer interaction determine the performance of the formulations. The short-range order over a few molecular dimensions by hydrogen bonding in the amorphous solid dispersions; depend upon the carriers, method and the processing parameters for preparation for solid dispersions. The viscosity of the material also plays an important role in the prevention of the nucleation. The increase in the viscosity reduces the molecular motions and the random movement of molecules get slows down and thus have no time to rearrange themselves (Laitinena et al; 2013). These abovementioned characteristics also result in higher chemical reactivity and the tendency to spontaneously crystallize. The thermodynamically unstable amorphous forms tend to revert back to stable crystalline form over time. This phenomena is governed by nucleation and the subsequent crystal growth. In this context, there is recrystallization after the formation of the stable nuclei in the dispersion (Craig, 2002). As discussed earlier, the nucleation step of the crystal growth is characterized with clustering of solute molecules within the solution. Clusters on attending critical size, move for the next stage of crystallization i.e. crystal growth and resulting in the rearranging of molecules in periodic manner. The growth of the nuclei is also characterized with attachment of solute molecules to energetically favoured sites. In the process of heterogenous nucleation, presence of impurities decreases the energy barrier and result in the nuclei formation. The induction of the crystallization also depends on other environmental factors like temperature, pressure, presence of impurities and mechanical stress.

The crystallization behaviour of an amorphous material is governed by multiple factors like thermodynamic factors (configurational entropy, enthalpy or, Gibbs free energy) (Marsac et al; 2009), kinetic factors (molecular mobility, glass transition temperature, structural relaxation time) (Andronis et al; 1997, DiMartino et al; 2000 and Grzybowska et al; 2010), molecular factors (hydrogen bonding interactions) (Ambike et al; 2005), moisture content (Patterson et al; 2005 and Savolainen et al; 2007). Furthermore, compounds with low molecular mobilities, high glass transition temperature and high configurational entropy barriers generally show the highest stability (Zhou et al; 2008). It is presumed that rigidity of the molecule reduces the scope of possible conformations which lead to low configurational entropy as it is an indicator of crystallization from the amorphous state. Configurational entropy and high molecular mobility thus lead to crystallization from the amorphous state. Drug inside the amorphous dispersions tend to crystallize due to its configurational entropy and relatively high molecular mobility. The increased nucleation rate of drug in the polymer matrix may be attributed to the higher configurational enthalpy resulting in the driving force for crystallization (Marsac et al; 2009).

The rate of crystallization increases, when the temperature is somewhere between melting temperature (T_m) and glass transition temperature (T_g) (Craig, 2002). It is commonly accepted that storing the amorphous material below T_g (T_g-50 K rule) should lower the risk of recrystallization due to lower molecular mobility (Yu, 2001). The stability of the amorphous dispersions generally increases with the increase in the T_g, which alludes that the dispersions containing plasticizer decrease the T_g of the drug may also possess threat of crystallization tendency of the molecule (Zhou, 2008). Table 2 enumerate few examples of drug and polymer interactions published elsewhere which is accounting for precipitation inhibition. The intermolecular hydrogen bonding play an important role in determination of stability profile of the amorphous dispersion. The interaction pattern in the molecular level determines the physical stability (Marsac et al; 2009).

Table 2. Few examples of drug polymer interaction.

S. No.	Drug	Polymer	Reference
1	Compound 1	Hydroxypropylmethyl cellulose acetate succinate (HPMCAS)	Curatolo, 2009
2	Compound 2		Curatolo, 2009
3	Compound 3		Curatolo, 2009
4	Compound 4		Curatolo, 2009
5	Compound 5		Curatolo, 2009
6	Compound 9		Curatolo, 2009
7	Griseofulvin		Curatolo, 2009
8	Felodipine		Konno, 2008; Alonzo, 2010
9	Itraconazole		Van Speybroeck, 2010
10	Nifedipine		Curatolo, 2009; Tanno et al; 2004
11	Phenytoin		Curatolo, 2009
12	Sildenafil citrate		Appel et al; 2006
13	Torceptrapib		Friesen et al; 2008
14	Ziprasidone		Appel et al; 2006
15	Albendazole	Hydroxypropylmethyl cellulose phthalate (HPMCP)	Kohri et al; 1999
16	Compound 5		Curatolo, 2009
17	Itraconazole		Miller, 2008; Overhoff et al; 2007; Kondo, 1987
18	Nifedipine		Kondo, 1987
19	Compound 4		Curatolo, 2009
20	Compound 5		Curatolo, 2009
21	EMD 57033		Vogt et al; 2008a; Vogt et al; 2008b
22	Felodipine		Konno, 2008; Alonzo, 2010
23	Felodipine		Konno et al; 2006
24	Celecoxib	Hydroxyproply cellulose (HPC)	Guzman et al; 2007
25	Compound 2		Curatolo, 2009
26	Itraconazole	Methyl cellulose (MC)	Miller et al; 2008, Overhoff et al; 2007, Kondo et al; 1987
27	Compound 4	Cellulose acetate phthalate (CAP)	Curatolo, 2009
28	Compound 5		Curatolo, 2009
29	Itraconazole	Polyvinylpyrrolidoneco polyvinyl acetate (PVPVA)	Janssens et al; 2008
30	Compound 4	Polyvinylpyrrolidone (PVP)	Curatolo, 2009
31	Repaglinide		Yin et al; 2012
32	Compound 5		Curatolo, 2009
33	EMD 57033		Vogt et al; 2008a;
34	Felodipine		Konno, 2008; Alonzo, 2010
35	Nifedipine		Tanno et al; 2004
36	Tacrolimus		Overhoff et al; 2007,
37	Compound 2	Polyvinyl acetate phthalate (PVAP)	Curatolo, 2009
38	Itraconazole		DiNunzio et al; 2008
39	Itraconazole	Polymethylacrylate (Eudragit, PMA)	Overhoff et al; 2007,
40	Nifedipine		Miller et al; 2008, Tanno et al; 2004
41	Tacrolimus	Polyvinyl alcohol (PVA)	Overhoff et al; 2007,
42	Celecoxib	Poly (ethylene oxide)– poly (propylene oxide)– poly (ethylene oxide) (PEO-PPO-PEO)	Guzman et al; 2007
43	Docetaxel		Chen et al; 2008
44	Felodipine	Polyethylene oxide (PEO), polyethylene glycol (PEG)	Teberekidis et al; 2007
45	Mefenamic acid		Liu et al; 2005
46	Rofecoxib		Ababio et al; 1998

The lowering of T_g due to increased molecular mobility and plasticization effect generally results from presence of moisture in storage conditions. This is an important factor accounting for the crystallization of the amorphous dispersion. The insight into thermodynamics and molecular level processes such as glass transition, molecular mobility and drug polymer interaction is important in the fabrication of efficient and stable amorphous systems. The molecular engineering of the amorphous drugs using polymers as carriers gives better control in stabilizing the solid dispersion products.

Nevertheless, the high internal energy and enhanced molecular mobility of the amorphous material represent tendency to nucleation and crystallization. This also attributes for their higher chemical reactivity and thus impurity generation. These problems encountered during manufacturing, storage or, dissolution (administration) sometimes limit the exploring of this technology with several disadvantages. This technology has witnessed much effort from different researchers in understanding various factors in recrystallization and finding methods for stabilization of these amorphous forms. An extensive amount of literature are also available on dissolution improvement and stability aspects of drug in a glassy polymer matrix. These dispersions are one of the preferred method to enhance drug dissolution and to stabilize the amorphous form of a drug.

Summary/ Conclusions and future perspectives

The configuration of supersaturated drug delivery system has been identified as emerging concept to address the issue of low oral absorption from poorly water soluble drugs. Prolonged supersaturation can be translated to extended dissolution and increased oral bioavailability. The high energy system of drug in the supersaturated system tend to precipitate out and thus affect therapeutic effectiveness. The stabilization of supersaturated system can be accomplished by the utilization of precipitation inhibitors which may act through different mechanisms. There are various studies available regarding supersaturated drug delivery system and precipitation inhibitors. Thorough and in depth understanding of physico-chemical nature of drug and polymers including the working mechanism of precipitation inhibitors is an important prerequisite in the formulation design of such supersaturated drug delivery system. The identification of suitable polymers that can inhibit crystallization and extend the dissolution profile of a supersaturated formulation *in vitro* has led to the identification of formulations that have also performed well *in vivo*. In a nutshell, the generation and stabilization of intraluminal supersaturation provide an efficient solution for the growing problem of solubility limited oral bioavailability. Hence, it is not surprising to see a rapidly increasing number of reports on supersaturating drug delivery systems in recent years. In the formulation development of solid dispersions, judicious selection of polymer is needed to stabilize and maintain supersaturation of any drug for extended period of time.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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