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WHITE PAPER: Amorphous Solid Dispersions-One approach to improving Bioavailability



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Amorphous Solid Dispersions-One approach to improving Bioavailability

Though amorphous solid dispersions can add complexity to a drug development project, the difference they make can be the difference between bioavailable drug and failed project.

During product development, the formulator's first task is to understand the properties of the API they are working with. This includes not just an understanding of the basic physicochemical properties, but the biopharmaceutical properties of the candidate as well. For BCS II drug candidates, a common product development approach is to utilize manufacturing processes that generate amorphous solid dispersions with a high degree of prolonged supersaturation. The

A promising drug development project can be slowed or halted if the candidate compound has poor aqueous solubility and dissolution characteristics.

choice of excipients for these formulations is critical not just to achieve drug delivery goals (bioavailability), but the excipients selected also

need to be compatible with the selected manufacturing process. The excipients used and the specific formulation compositions selected also directly impact the stability of the disordered system and impact the packaging selection and dictate the environmental controls/handling requirements of the final product. Many small molecules cannot be crystallized in forms that are stable and suitable for formulation. Crystalline solids can be inadvertently rendered partially amorphous by processing (e.g. milling and drying) leading to instabilities. In addition, many crystalline APIs lack sufficient aqueous solubility to provide adequate oral bioavailability whereas the amorphous form can enhance dissolution characteristics. It is important to have adequate rate and extent of the oral absorption of solid API for bioavailability during various stages of the drug development process. For example, exposure is needed during early safety assessment, animal PK studies, First in Human (FIH) studies and for the final commercial product. While amorphous characteristics can complicate matters, they don't have mean that a promising project is halted. The utilization of disordered systems (amorphous solid dispersions) to optimize the delivery of poorly soluble (BCS II) drugs has become more commonplace due to an increase in "challenging" API properties. Drug candidates with properties similar to "brick dust" or "grease balls" are driving this need. To this end, our scientific understanding of disordered systems as well as the tools available to formulators has been increasing steadily over the past 20+ years. The number of new drug candidates with these issues has

grown steadily over the past decades due in part to the use of high throughput and combinatorial screening tools during the discovery and selection phase. Currently there are a few drugs on the market with amorphous active pharmaceutical ingredients (APIs) including: Accolate® (zafirlukast), Ceftin® (cefuroxime axetil) Accupril® (quinapril hydrochloride) and Viracept® (nelfinavir mesylate). One of the development risks associated with amorphous products is their long term chemical stability is less than those of crystalline materials. Amorphous materials are typically less physically stable and tend to crystallize over time and under stress. Examples of stress are temperature and relative humidity, both of which can present storage issues for drugs over time. Crystalline drugs are typically more stable, but the strong interactions in the crystal lattice can lead to poor aqueous dissolution and poor oral bioavailability. Dissolution of solid crystalline material is a complex process. The crystal lattice of the solid needs to be disrupted to allow individual molecules to be solvated or hydrated. Thus, solvent/water hydrogen bonds must be broken to accommodate the solute molecules. This process can be represented by lattice energy, solvation energy, and cavitation energy. Solubility issues can be related to high lattice energy, poor solvation or a combination. There are methods to overcome aqueous dissolution limitations of crystals including chemical change (salt forms, ionizable prodrugs), formulation and processing (increasing specific surface area by particle size reduction or adding solubilizers), physical form selection (using more water-soluble higher energy polymorphic crystalline forms and co-crystals) and using amorphous solid forms. Amorphous materials lack the long range ordering of molecules typical for crystalline solids which gives rise to greater free energy and molecular mobility. Amorphous materials display a glass transition (T_g). A glass has



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For over 45 years, George Zografi has carried out basic research to study the hydration of crystalline and amorphous solids as well as interfacial phenomena of surfactants and polymers as they relate to pharmaceutical systems. His pioneering studies in understanding the amorphous solid state, water-solid interactions, solid state stability, and wetting of solids have helped in the design and development of stable and functioning pharmaceutical dosage forms. His leadership in teaching and applying basic science to both preformulation and formulation activities has had profound effects on the drug development process as well as the field of pharmaceuticals. His unique blend of scientific depth and rigor sprinkled with his human warmth and sensitivity have stimulated and promoted the research efforts of two generations of pharmaceutical scientists.

the molecular conformation of a highly viscous liquid with the appearance of a solid due to very slow molecular motions and relaxation processes. These glassy materials represent the most energetic solid state of a material and it can be expected that these materials will offer useful solubilities and dissolution rates.

(Figure 1)

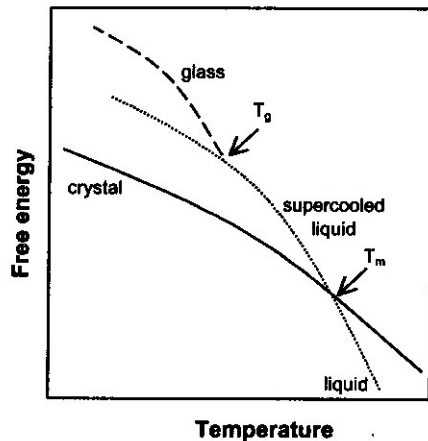


Figure 1: Hancock and Shamblin, *Thermochimica Acta*, 380 (2001) 95

These materials are inherently unstable, but combining the API with the proper excipients (that raise the T_g and thus decrease the molecular mobility or those that prevent nucleation and crystal growth) will stabilize the amorphous state during storage and prevent recrystallization during dissolution. The resulting amorphous solid dispersion can improve stability and dissolution. The amorphous drug is combined with a polymer that stabilizes the amorphous drug product resulting in better stability, higher apparent solubility and faster dissolution. An

amorphous solid dispersion is formed by mixing the API with the polymer as a “solid solution” (miscible) usually through hydrogen bonding. Some of the major polymers used pharmaceutically to prepare amorphous dispersions include Polyvinyl pyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC), HPMC Phthalate, and Polyethylene glycol(PEG). A stable dispersion is one with a T_g well above typical long term storage temperatures. Stability is also improved by storing the dispersions in a glassy state as free of absorbed water as is possible.

Why would one want to deal with all of the potential instability issues with amorphous compounds and amorphous dispersions? Traditional alternatives for improving bioavailability include salt formation, decreasing particle size, using lipids for drug delivery, and co-crystal generation. Salts are generally soluble if the counter ion can be hydrated. However, not all APIs have ionizable groups that can be used at biological pH values. In certain pH ranges the ionized forms of the salt may be metastable relative to the free forms. In addition, crystalline salt forms are generally more susceptible to hygroscopicity potentially leading to stability issues. Lipid drug delivery involves dissolving the API in a hydrophobic solvent that becomes available when encountering the GI environment in a supersaturated state. It offers the advantages of simple non-aqueous solutions useful for early stages of

drug development, the lipids can form nano-sized particles, the lipids can take advantage of fat digestive processes, and they can be pelletized for later dosage form development. However, specialized equipment is required, crystallization may occur from solid lipid matrices, there can be chemical instability issues, and they are not as convenient and economical as tableting or capsules. Another method is to create co-crystals which are molecular complexes containing the API and an additional non-toxic molecular species in the same crystal structure. Advantages of co-crystals for enhancing oral bioavailability include the intrinsic solid-state physical and chemical stability of crystals relative to their amorphous form, and they are viable systems for enhancing oral bioavailability when supersaturation of API occurs in dissolution media and is maintained over therapeutically relevant timescales. However, there is a questions as to whether or not co-crystals are new chemical entities (NCE) and patentable. Other potential disadvantages of co-crystals include a requirement of stoichiometric amounts of “co-formers” adding significantly to the required dose, the dissolution of co-crystals and potential polymorphic transitions with hydrate formation when exposed to high relative humidity.

The advantages of amorphous solid dispersions for enhanced oral bioavailability are: 1) Many crystalline drugs can be prepared in an amorphous form and be physically stabilized by an appropriate polymer and polymer composition; 2) Using formulation approaches, it is possible to maintain a sufficient amount of super saturation to enhance bioavailability in vivo, and 3) The currently used manufacturing methods (melt extrusion and spray drying) are adaptable from initially small samples for early studies to large-scale manufacturing. As described earlier amorphous systems are thermodynamically unstable and subject to crystallization, have physical and chemical properties that change significantly at critical temperatures (T_g) and higher relative humidity. The choice of polymer and amounts cannot be accurately determined a priori, but there are basic principles that can be applied to speed up the formulation selection process. When pursuing an amorphous dispersion, it is incumbent upon the development team to screen for and characterize various API-polymer combinations that provide miscibility, stability, and enhanced dissolution properties, while utilizing a suitable manufacturing process and packaging in order to produce a successful pharmaceutical product.

An excellent chance to learn about amorphous dispersions from experts will be April 24-26, 2017 in Madison, Wisconsin. “Understanding, Characterizing, and

Developing Amorphous Materials and Amorphous Solid Dispersions” features Professor George Zografi, a pioneer in this field, along with current industry experts. During this course, you will learn the various tools that can be used by formulators tackling a challenging BCS II drug candidate. The tools discussed will include those specific to the goal of developing amorphous solid dispersions and include: characterization of the drug candidate, selection of excipients (formulating with a “parachute”), identifying formulation compositions and understanding the challenges in early development. There are multiple examples in the literature that demonstrate how these concepts have been utilized and a few of these examples will also be discussed.