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Stable and Fast-Dissolving Amorphous Drug Composites Preparation via Impregnation of Neusilin® UFL2

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ABSTRACT

A promising approach to increase the aqueous solubility, hence the bioavailability, of poorly water-soluble drugs is to convert them into their amorphous state through impregnation into mesoporous silica. Unfortunately, mesoporous silica is not yet available in bulk quantities due to high manufacturing costs. In this work, feasibility of using a commercially available cost-effective mesoporous fine grade Neusilin® UFL2 to prepare amorphous drug composites of 2 model poorly soluble drugs, fenofibrate and itraconazole, is established. In contrast to fluidized-bed spray-impregnation, only mixing and drying steps are required. Complimentary assessment using X-ray powder diffraction, differential scanning calorimetry, and Raman spectroscopy confirmed drug within the composites to be amorphous at as high as 30% drug loading both after formation and after 3 months of storage at 40°C and 75% relative humidity. Amorphous drug recrystallization was completely suppressed due to the confinement effect due to the Neusilin®. The amorphous drug composites resulted in higher apparent solubility and faster dissolution rate of the model drugs as compared to their crystalline counterpart, confirmed by United States Pharmacopeia II dissolution and ultraviolet surface dissolution imaging. Overall, stable, high drug-loaded fast-dissolving amorphous drug composites preparation using Neusilin® UFL2 is demonstrated as a promising approach to enhance solubility of poorly soluble drugs.

Introduction

A high percentage of promising drug candidates in the development pipeline (~66%) exhibit low aqueous solubility in their crystalline form,[1] resulting in limited drug absorption in the gastrointestinal tract. This results in low *in vivo* bioavailability, which severely limits their therapeutic efficacy. As a result, a high number of therapeutically promising, poorly soluble drugs or active pharmaceutical ingredients (APIs) never reach the patient due to the lack of suitable formulation methods.[2] To circumvent this problem, a number of different strategies have been developed, including crystalline salt formulations,[1] making nano/micro API particles via grinding or antisolvent crystallization,[3-5] use of solubilizers, forming co-ground mixtures, pro-drugs,[6] lipid-based formulations,[7,8] and stabilization of APIs in their amorphous state.[9]

APIs in their amorphous form are highly promising because of enhanced thermodynamic properties (i.e., energy, entropy and free energy) and high internal energy.[10] During administration, amorphous forms can lead to highly supersaturated solution in the presence of crystallization inhibitors, leading to an apparent solubility that is much higher than the saturation solubility of their crystalline counterparts. The high supersaturation level would lead to a higher drug concentration gradient, which in turn would drive drug absorption across the gastrointestinal lumen, resulting in greater therapeutic activity than the corresponding crystalline counterpart.[11] Unfortunately, the amorphous state holds the risk of reverting back to energetically more favorable crystalline state during processing or storage. Typically, the physical stability of amorphous APIs is improved by combining them with polymers (such as polyethylene glycol, cellulosic polymers [hydroxyl propyl methyl cellulose, and polyvinylpyrrolidone]) to form amorphous solid dispersions.[12] However, stabilization by this approach requires careful investigation of several issues. Those include, optimization of polymer content and formulation that usually reduces effective drug content,[13] proper selection of manufacturing process,[14] and the need to examine chemical stability of the ingredients and final products to assure shelf-life, which may further necessitate adjusting both the formulation and process.[15,16]

A technology that is gaining interest as a means to stabilize amorphous drugs is adsorption inside or onto mesoporous materials. In the past decade, mesoporous materials (silica, carbon,

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Table 1
Physicochemical Properties of the Drugs Used

Drug	Chemical Formula	Type	Application	Molecular Weight (g/mol)	Aqueous Solubility (mg/L)	Log *p*	Melting Point (T_m) (°C)	Glass Transition Temperature (T_g) (°C)
Fenofibrate (FNB)	$C_{20}H_{21}ClO_4$	Nonionizable	Lipid lowering agent	360.83	0.8	4.75	79-81	−21.3
Itraconazole (ITZ)	$C_{35}H_{38}Cl_2N_8O_4$	Weak base	Antifungal	705.63	0.1	7.13	166.8	59

oxides, and so forth) having pore diameters between 2 and 50 nm according to the International Union of Pure and Applied Chemistry guidelines,[17] have attracted great attention of pharmaceutical researchers. They are able to effectively suppress the crystallization of amorphous substances via geometrical constraints.[2,18,19] Mesoporous materials allow homogeneous and reproducible drug loading and release due to their high surface areas, large mesopore volumes, narrow mesopore size distributions (5-8 nm), and ordered unidirectional mesopore networks.[20] Among mesoporous materials, mesoporous silica-based materials have many unique properties, such as their nontoxic nature, tunable pore size, as well as chemically inert and easily modifiable surface properties.[21,22] However, the preparation of mesoporous materials is multistep, high-cost and time-consuming in general.[23] The mesoporous silica industry struggles with high manufacturing costs due to expensive silica sources and surfactants used in the fabrication, as well as environmental concerns related to the often toxic surfactants needed as pore-forming templates in their synthesis.[24] Thus, mesoporous silica is not yet available in bulk quantities and the price for the mesoporous silica MCM-41 is very high, for example, Sigma-Aldrich sells it €20,000 per kg.[2]

As an alternative to mesoporous silica, Neusilin® UFL2 (Fuji Chemical Industry Co., Ltd., Toyama, Japan) may be used as a mesoporous material for the stabilization of amorphous drugs and dissolution improvement of poorly soluble drugs. It is a fine synthetic amorphous powder of magnesium aluminometasilicate (represented by an empirical formula $Al_2O_3 \cdot MgO \cdot 1.7\ SiO_2 \cdot \times\ H_2O$) with median particle size of 2.94 μm, average pores size of 17 nm (high porosity), specific surface area of 300 m^2/gm, and pore volume of 1.37 cm^3/gm, and high adsorption capacity.[25-27] This large specific surface area and high adsorption capacity make Neusilin® a good core material for adsorption. Neusilin® is also less likely to promote reversion of the amorphous drug to the crystalline state during storage. This may be due to nano-confinement of drug and drug−Neusilin® complex formation that is attributed to acid−base reaction, ion−dipole interactions, hydrogen bonding, and so forth.[26-29] Neusilin® is extremely safe with no reports of adverse reactions and is an accepted ingredient by the U.S. Pharmacopoeia (USP)-National Formulary and Japanese Pharmaceutical Codex.[25]

The various applications of Neusilin® found in literature for making amorphous drug include: co-grinding with Neusilin®,[30] hot-melt extrusion,[28] melt adsorption using supercritical CO_2,[31] use in solid self-emulsifying drug delivery systems,[8] use as an adsorbent for development of solid from drug solutions,[32] and preparation of solid dispersion.[26,33] While these methods hold great promise, they also have inherent limitations that warrant further research. Co-grinding methods typically require several days of milling to complete amorphization.[34] For hot-melt extrusion methods, the overall stabilization mechanism depends on the polymer and excipients chosen for the amorphous complex. Thermal sensitivity of drug, drug-polymer hydrogen bonding, chemical reactions like hydrolysis and solvolysis, and so forth, limit the selection of polymers.[35] Hence, formulation components and their amounts must be carefully selected for maintaining physical stability of the amorphous complex and to enhance the dissolution properties.[28] Major limitations of the use of supercritical CO_2 include limited drug solubility in the supercritical CO_2 for most APIs and its relatively high capital cost for commercial scale implementation.[31,33] Direct incorporation of lipid loaded with drug into Neusilin® by mixing lipid with silica may lead to poor flow properties due to lump formation.[8] To reduce such issues, the lipid-based formulations were adsorbed onto solid carriers by multistep methods: first dissolving lipid in volatile organic solvents and then adding dry carrier powders to these solutions, which was followed by drying of the mixtures.[8] Although solid dispersions have the potential to enhance dissolution of poorly water-soluble drugs, some disadvantages such as difficulty in pulverization, poor compressibility, and poor flow limit their use in the pharmaceutical industry.[26]

In the present work, the main objective is to assess potential of the finest sized grade commercially available low-cost Neusilin® UFL2 for use in preparing stable high drug-loaded amorphous drug composites, and investigate their dissolution properties. A major reason for selecting finer size grades of Neusilin® is that may help address some of the potential shortcomings of using larger grades. Larger grades typically require fluid-bed processing and may require a grinding step to improve the content uniformity.[33] Use of finer size grades of Neusilin® may require only simple mixing followed by drying for solvent impregnation and may avoid content uniformity limitation. Three different weight percentages of drug loading were investigated: low (1.0%), medium (15%), and high (30% and above). A range of drug loading (low 1% to high 30% or more) was examined to demonstrate that the method can be also applied for low volume high potency drugs. Two poorly water-soluble Biopharmaceutics Classification System Class II APIs, Itraconazole (ITZ, an antifungal drug) and Fenofibrate (FNB, a cholesterol reducing drug), were selected as the model APIs. There are several studies[20,36,37] found in literature that considered FNB and ITZ as model compounds for improving their solubility and dissolution via amorphous conversion. The other major reason to choose these is that they have relatively low T_g values (FNB is −20°C, and ITZ is 58°C). Hence it is difficult to prepare and maintain their amorphous stability at room temperature. In this study, stability of the prepared composites after 3-month storage at 40°C and 75% relative humidity was evaluated. The composites were characterized by differential scanning calorimetry, X-ray powder diffraction (XRPD), and Raman spectroscopy, as complimenting techniques to assess amorphousness/crystallinity after formation as well as after 3 months storage. Each method has advantages and limitations. For example, the limit of detection and limit of quantification of the XRPD and differential scanning calorimetry (DSC) are >5%.[38] Raman spectroscopy has the advantage of being a nondestructive technique requiring small samples and no sample preparation. Consequently, using Raman spectroscopy, partially amorphous systems can be studied without any change of phase occurring either through processing or through measurement of the sample.[38] A detailed *in vitro* dissolution study was carried out using USP-II dissolution system, complimented by a novel ultraviolet (UV) surface dissolution imaging (SDI) to evaluate the dissolution improvement by amorphous drug composites compared with crystalline as-received drug.

Experimental Section

Materials

ITZ and FNB, white crystalline powders (see Table 1 for drug properties), were purchased from Jai Radhe Sales (Ahmadabad, India).