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Improvement of the Dissolution Rate of Poorly Soluble Drugs by Solid Crystal Suspensions

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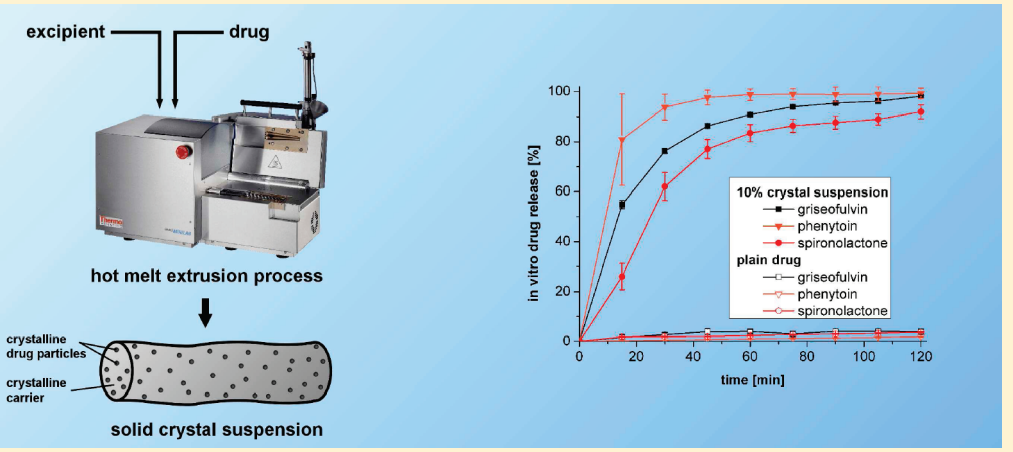
ABSTRACT:



We present a novel extrusion based approach where the dissolution rate of poorly soluble drugs (griseofulvin, phenytoin and spironolactone) is significantly accelerated. The drug and highly soluble mannitol are coprocessed in a hot melt extrusion operation. The obtained product is an intimate mixture of the crystalline drug and crystalline excipient, with up to 50% (w/w) drug load. The in vitro drug release from the obtained solid crystalline suspensions is over 2 orders of magnitude faster than that of the pure drug. Since the resulting product is crystalline, the accelerated dissolution rate does not bear the physical stability concerns inherent to amorphous formulations. This approach is useful in situations where the drug is not a good glass former or in cases where it is difficult to stabilize the amorphous drug. Being thermodynamically stable, the dissolution profile and the solid state properties of the product are maintained after storage at 40 °C, 75% RH for at least 90 days.

KEYWORDS: dissolution rate, extrusion, mannitol, solid dispersion, solid crystal suspension, solubility, stability, amorphous

INTRODUCTION

Over recent years, drug discovery has seen an increase in the number of drug candidates obtained by combinational chemistry and high throughput screening. While the approach is effective in optimizing for drug potency, a significant portion of these drugs have very low solubilities and, consequently, exhibit low bioavailability.[1] This situation has, in turn, led to increased effort aimed at improving bioavailability of poorly soluble drugs. The pharmaceutical repertoire includes a number of approaches for the solubilization of drugs. Typical solubilization techniques include salt formation, cosolvents, surfactants, complexation and hydrotropic agents.[2] These approaches increase solubility by altering a solvating environment, making it better suited for maintaining hydrophobic solutes in aqueous solution. However, even though the vast majority of drugs are hydrophobic, the low aqueous solubility of many drugs is not solely the result of their hydrophobicity. The thermodynamic stability of the crystal structure of the solid solute is an equally important factor in limiting drug solubility.[3] A good portion of poorly soluble drugs and drug candidates are inherently insoluble in the sense that their strong crystalline structure (roughly assessed by a high melting point)[4] makes them poorly soluble in water as well as in many pharmaceutical organic vehicles. Consequently, there has been a great level of interest in the production of solid dispersions of poorly soluble drugs.[5−9] The term solid dispersion is a rather loose term covering different types of formulations, including things like eutectic mixtures as well as drug−polymer dispersions. The commonality is that such preparations are aimed at improving (accelerating) drug release.[8] There are a number of commercial products that fall in the category of solid dispersions. They have been developed to enhance the bioavailability of some poorly soluble drugs such as everolimus (Certican, Novartis),[10] griseofulvin (Gris-PEG, Novartis),[9] itraconazole (Sporanox, Janssen),[11] nabilone (Cesamet, Lilly),[9] lopinavir/ritonavir (Kaletra, Soliqs)[12] and tacrolimus (Prograf, Astellas).[13] These

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Table 1. Overview of Solid Dispersions

name	phases	drug	carrier
glass solution	1	molecularly dispersed	amorphous
solid solution	1	molecularly dispersed	crystalline
glass suspension	2	amorphous	amorphous
		crystalline	amorphous
eutectic mixture	2	crystalline	crystalline
amorphous precipitations	2	amorphous	crystalline

systems are broadly categorized as solid dispersions and are differentiated by their physicochemical constitution.[7,8,14] A summary of the different types of solid dispersions is shown in Table 1.

Hot melt extrusion has been established as a robust means of producing amorphous solid dispersions with improved dissolution rate.[15,16] Such molecular dispersions, obtained through the obliteration of the crystal lattice of the drug, are often supersaturated dispersions.[17] Solubilization approaches based on altering the properties of the solid form of poorly soluble drugs are not limited to solid dispersions. Crystal engineering and pharmaceutical cocrystals, in particular, have been the subject of increasing interest in recent times.[18−21] It should also be pointed out that (hot melt) extrusion is a quite versatile unit operation, applicable beyond solid dispersions. It has been shown that hot melt extrusion can be used for the production of pharmaceutical cocrystals.[22] In this report, the versatility of hot melt extrusion for producing crystalline dispersions of poorly soluble drugs is further explored. We report on a type of intimate mixture of a crystalline carrier with a crystalline drug resulting in a stable formulation with considerably fast dissolution rate, relative to that of the plain drug. In the plastics industries, extrusion is commonly used to disperse color pigments or filler particles in polymer melts. Therefore, the use of the extrusion process to disperse drug particles in a molten matrix substance seems a viable pharmaceutical application of this unit operation. An interesting side effect is the granulation of the powdered substances subjected to this technology. This has additional advantages for the obtained product such as the prevention of segregation.

Amorphous solid dispersions offer a means of achieving increased solubility and accelerated dissolution rate for poorly soluble drugs. Such high energy formulations also present challenges since they are, by nature, thermodynamically unstable. Consequently, their successful development depends in good measure on the understanding of the specific interactions responsible for their stabilization.[9,14,23,24] The aim of this report is to present a complementary platform for producing solid, physically stable dispersions exhibiting high dissolution rates. The approach consists of dispersing crystalline drug particles in a highly water-soluble, crystalline. For purposes of the present discussion, the type of formulation obtained by this approach is termed "solid crystal suspension." The approach presented here differs from traditional solid dispersions in the sense that a thermodynamically stable system is generated whereby the end product consists of a crystalline API suspended in a crystalline carrier matrix. We should point out that this type of crystalline dispersion is not a eutectic mixture.

Hot-melt extrusion is an efficient, reliable process that offers some of the advantages of a continuous manufacturing process.[25] The basic process used here consists of carrying out the extrusion above the melting point of the matrix carrier but below the melting point of drug. By preventing the melting of the API, polymorphic changes often associated with crystallization from the melt can be prevented. The approach presented here does not involve either liquefaction or vitrification of the drug, as is the case in other processing approaches.[21,23,26]

Table 2. Process Parameters Extrusion Process

step	time [min]	temperature [°C]	screw speed [rpm]
feeding	3	165	360
mixing	15	158	200
extrusion	1	165	200

The following substance properties were established as criteria for excipients to serve as carrier matrix forming agents in the hot melt extrusion process:

- highly water-soluble
- low toxicity
- solid at room temperature
- melting without decomposition
- rapid recrystallization from the melt

As discussed later, there is more than one excipient candidate. Nevertheless, mannitol was selected, based on its particularly rapid crystallization behavior.[27] We use griseofulvin as model drug for the approach presented here. Two additional drugs, phenytoin and spironolactone, were selected to test the applicability of the approach to other APIs. All drugs used were chosen based on their aqueous solubilities[28] and their suitability for UV based assays.[29]

MATERIALS AND METHODS

Griseofulvin and spironolactone were obtained from Hawkins (Minneapolis, MN, USA), and phenytoin was obtained from Spectrum (Gardena, CA, USA). Mannitol (Pearlitol 50 C, Roquette, Lestrem, France) was used as the excipient. All substances were US Pharmacopeia (USP) grade and were used as received. The drugs used in this study are known to formulation scientists for their low solubilities and slow dissolution rates; they are hence supplied in micronized form. As model compounds, they represent a stringent test for the solid crystal suspension methodology presented.

Extrusion. The powdered API and mannitol were premixed and transferred into the ram feeder of a small-scale, corotating twin screw extruder (Haake MiniLab, Thermo Electron, Newington, NH, USA). Approximately 7 g powder batches were mixed and extruded through a 1 mm diameter die.[30,31] The outflow extrudates were cooled on aluminum foil to 25 °C and then stored for further characterization at 25 °C, 60% relative humidity (RH) for 24 h, as well as at 40 °C, 75% RH for 28 and 90 days.[32] The extrusion conditions were adjusted based on a series of preliminary experiments. Table 2 shows the process conditions used for this study.

The extrusion process consisted of three main steps, which were carried out sequentially, rather than simultaneously because of the small scale of the extruder. The feeding step was performed at the melting temperature of mannitol (165 °C) with the screw speed set to 360 rpm. The feeding procedure was completed in 3 min. During the subsequent mixing phase, the screw speed was reduced to 200 rpm, which was found to be adequate in several preliminary tests. The barrel temperature was also reduced in

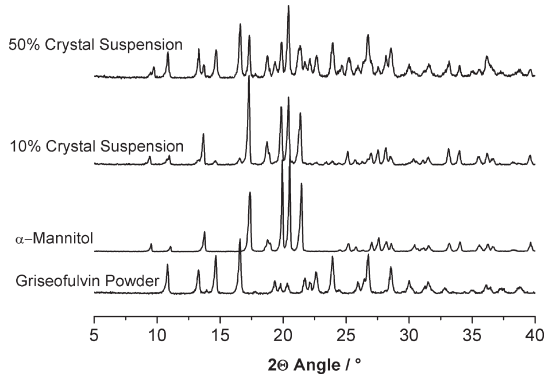

Figure 1. X-ray diffraction patterns of griseofulvin, mannitol and the solid crystalline suspensions containing 10% and 50% (w/w) drug load.

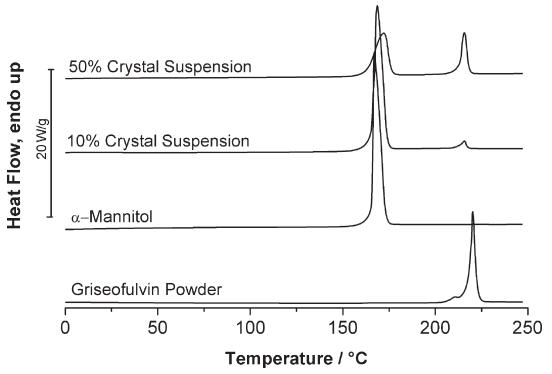

Figure 2. DSC thermograms of mannitol, griseofulvin, and the solid crystalline suspensions containing 10% and 50% (w/w) drug load.

order to increase the frictional forces on the extrudate, effected by the accompanying increase in viscosity. The torque on the extrusion screws increased after an equilibration period of an additional 1 min. The material was then mixed for 15 min in order to produce a homogeneous mixture. Subsequently, the barrel temperature was increased to 165 °C with an equilibration time of 7 min to eliminate any potential clogging of the die. The mannitol crystallizes quickly upon extrusion through the die. Therefore, brittle extrudates with a cylindrical shape were obtained.

Dissolution. The dissolution tests were performed using a paddle apparatus (VK7030, Varian, Cary, NC, USA) in accordance with the USP at 50 rpm using sink conditions. Six replicates from each batch were tested in water at 37 °C as the dissolution medium. For the dissolution test, the extrudates were cut into small pieces of approximately 2 mg. The drug release was quantified with a UV-photometer (DU 640, Beckman, Fullerton, CA, USA) using different wavelengths (griseofulvin 296 nm, phenytoin 220 nm and ppironolactone 243 nm) during 120 min using a cuvette with a 50 mm path length. Additionally, compacts formed from a (nonextruded) physical mixture containing 10% griseofulvin and 90% mannitol served as comparator for the dissolution test. The griseofulvin powder was first passed through a 100 μm sieve to remove powder agglomerates. The physical mixture was prepared by blending 1 g of griseofulvin and 9 g mannitol in a 60 mL stainless steel bin using a Turbula (T2C, Bachofen, Basel, Switzerland) blender for 5 min. The powder mixture was compressed (2 kN) to biplane tablets of about 20 mg and 5 mm diameter.

Differential Scanning Calorimetry (DSC). Thermograms were obtained using a differential scanning calorimeter (Q10, TA Instruments, New Castle, DE, USA). Accurately weighed samples of approximately 2 mg were hermetically sealed in aluminum pans (40 μL) and heated from −25 to 250 °C at 10 K/min. Dry nitrogen with a flow rate of 50 mL/min was used to purge the sample compartment of the oven. The physical mixture of drug and excipient was prepared with a mortar and pestle and subjected to DSC in the same way. Each batch was analyzed in duplicate.

X-ray Diffraction (XRD). The crystalline character of the samples was assessed by X-ray diffraction (LabX XRD-6000, Shimadzu, Columbia, MD, USA). A Cu Kα radiation point source (λ = 1.5406 Å) was operated at 40 kV and 30 mA. The samples were powdered manually using mortar and pestle, placed in aluminum holders and measured in the reflection mode from 10° to 40° 2θ. The scanning rate was 5°/min using a sampling step of 0.02°. Each formulation was analyzed in duplicate.

Particle Size. Particle size distribution measurements were carried out using a Lasentec probe (Mettler-Toledo, Giessen, Germany). Approximately 5 mg of powdered particles was measured with the probe for 3 min while stirring at 50 rpm using a paddle apparatus (900 mL, USP apparatus II). A total of 12 replicate particle size measurements were performed for each batch.

RESULTS AND DISCUSSION

Figure 1 shows the XRD patterns of griseofulvin, mannitol and the crystalline suspensions containing 10% and 50% (w/w) griseofulvin. The diffractograms show the crystalline nature of the extruded formulations, which consist of a combination of the patterns of the drug and the excipient. During the extrusion process, β-mannitol melted with subsequent crystallization to the α-modification. However, the metastable α-mannitol is kinetically very stable and remains as such for indefinite periods without spontaneous transformation into the stable β-mannitol.[33]

Therefore, the α-mannitol was considered acceptable for stability purposes, and no efforts were made to obtain the stable β-mannitol form. The DSC thermograms of griseofulvin, mannitol and crystalline formulations containing 10% and 50% drug are shown in Figure 2. The melting temperature of mannitol in the final extrudates was very slightly lower than the melting temperature of pure α-mannitol. This is expected since the presence of a molten liquid often depresses, to some extent, the melting point of the higher melting component. There were no glass transitions observed for either the extrudates or the physical mixtures (data not shown), presumably due to the strong crystallization tendency of mannitol.[34] The extrudates appear as physical mixtures of α-mannitol and the drug. The DSC results in Figure 2 provide additional information showing that the two components in the formulation exist as separate crystalline phases. The negligible melting point depression indicates that molten mannitol is in fact a poor solvent for the drug. Figure 3 shows the melting temperatures of mannitol and griseofulvin obtained when mixing the two components in different proportions. The melting point depression of griseofulvin is, again, very small, practically negligible, showing that molten mannitol makes a poor solvating environment for griseofulvin. Based on the thermograms, amorphous solid

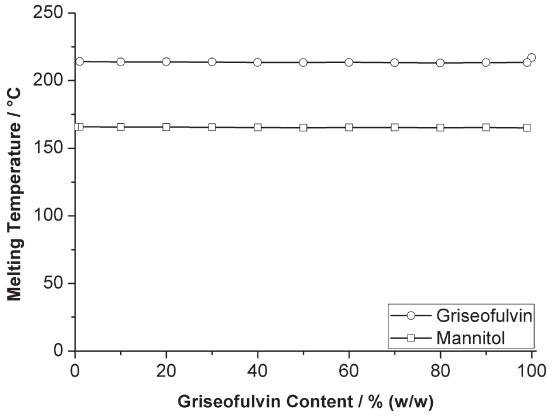

Figure 3. Melting point of griseofulvin and mannitol obtained from physical mixtures containing different proportions of the two compounds. The mixture is not eutectic, and the minimal depression of the melting temperatures indicates immiscibility of the two compounds in the liquid state.

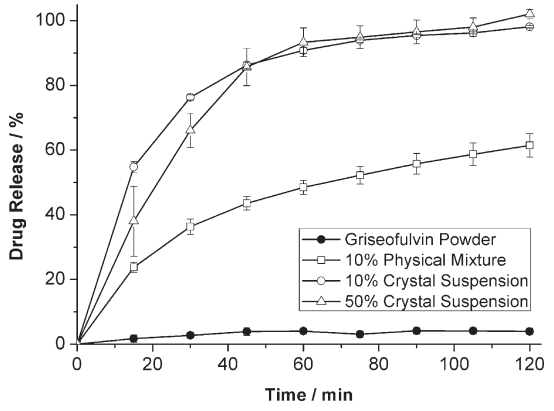

Figure 4. Dissolution rate of the crystalline suspensions of griseofulvin in mannitol containing 10% and 50% drug load. The dissolution rate of the plain drug and of a (10:90) physical mixture of griseofulvin and mannitol are also shown for comparison.

dispersions, cocrystals and eutectic mixtures can be excluded as underlying reasons for the observed effect on drug release.

The USP dissolution method for griseofulvin uses a high concentration of surfactant (sodium lauryl sulfate) in the dissolution medium. In this study, water free from any additives was used as the dissolution medium. At high concentrations, surfactants work as solubilizing agents, thus accelerating the dissolution rate. They also have the effect of narrowing differences in dissolution among different formulations. By not adding any wetting or dissolution aids to the medium, any medium-induced, confounding effects on dissolution are eliminated, hence the choice of deionized water as the dissolution medium. The drug release profiles from the extrudates of griseofulvin are shown in Figure 4. The dissolution rate from the extrudates is considerably faster, by over 2 orders of magnitude, than that of the pure drug. The dissolution rate of the 10% physical mixture of griseofulvin and mannitol is also shown in Figure 4. The presence of mannitol produces a significant increase in the dissolution rate. However, dissolution from the physical mixture is not nearly as fast as that from the extruded formulations. The accelerated dissolution rate

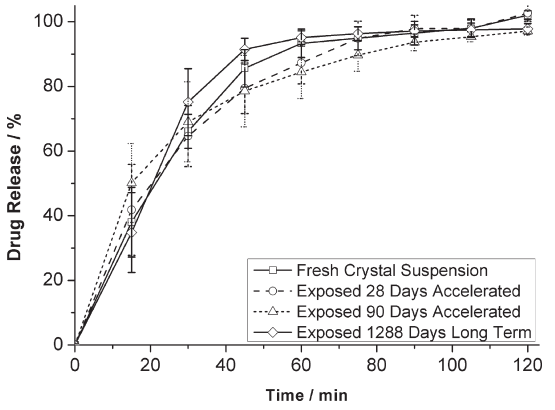

Figure 5. Dissolution rate of the 50% crystalline suspension of griseofulvin in mannitol after 28 and 90 days of storage at 40 °C/75% RH (accelerated stability conditions) as well as storage at 25 °C/60% RH (long-term) for 1288 days. The dissolution rate profile of the fresh, unexposed suspension is also plotted.

of griseofulvin observed from the physical mixture suggests that even though molten mannitol is a poor solvent for griseofulvin, it is nevertheless effective in facilitating wetting of the drug particles. The dissolution results show that the crystalline suspension method produces formulations with similar accelerated dissolution rates at drug loads of 10% and 50% (w/w). The relative increase in the dissolution rate obtained with the crystalline suspension approach is of similar order of magnitude as that achieved with approaches based on solubility enhancement such as solid amorphous dispersions.[35,36]

The crystalline character of the formulations obtained by the approach presented here makes them, at least in principle, free from concerns regarding their physical stability like those associated with high energy (amorphous) formulations. There are two aspects of physical stability inherent to amorphous formulations. One of them is the potential for crystallization of the drug. Solid dispersions often are kinetically stabilized, supersaturated mixtures, where the degree of supersaturation varies according to the preparation method.[14,37] Another aspect pertaining to the physical stability of amorphous formulations has to do with the inherent (and unavoidable) relaxation (aging) process of all glasses.[38] The structural relaxation of glasses is a stabilization process where the amorphous solid gradually loses enthalpy, entropy and free energy over time.[39] Such a change necessarily affects the solubility and dissolution rate of the glassy material as a function of time. The solid suspensions prepared in this study are crystalline to start so that they would be expected to retain their dissolution properties. The long-term stability of the crystalline suspension was investigated by long-term exposure to accelerated stability conditions (40 °C/75% RH) and assessing changes in the drug release performance of the formulation. Figure 5 shows the dissolution profiles of the griseofulvin−mannitol crystalline suspension containing 50% drug load after exposure to accelerated stability conditions for periods of 28 and 90 days. Differences in dissolution profiles between the fresh and stored extrudates are statistically non significant ($\alpha = 0.05$) for the accelerated test conditions as well as for long-term room temperature test conditions (data not shown). The formulations produced can be considered physically stable.

In order to investigate if results similar to those obtained with griseofulvin are also obtainable with other drugs, phenytoin and

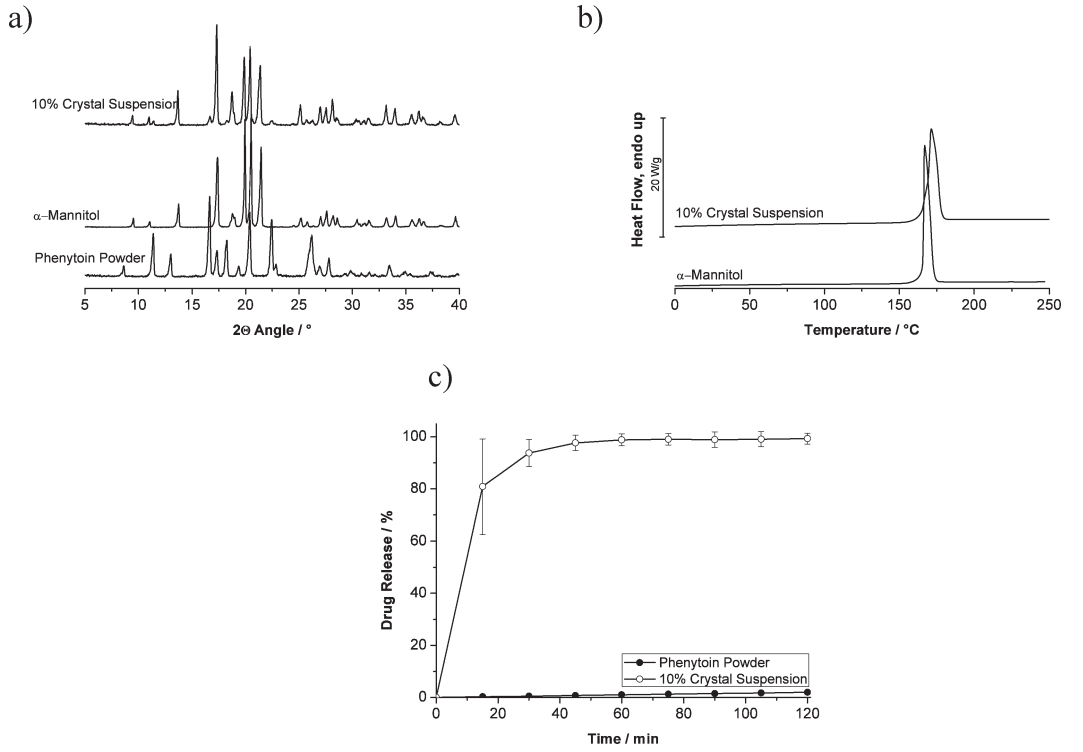

Figure 6. Properties of a 10% crystalline suspension of phenytoin in mannitol. (a) X-ray diffraction patterns of the suspension and mannitol. (b) DSC thermograms of the suspension and mannitol. (c) Dissolution rate profile. The dissolution profile of the plain drug is also plotted.

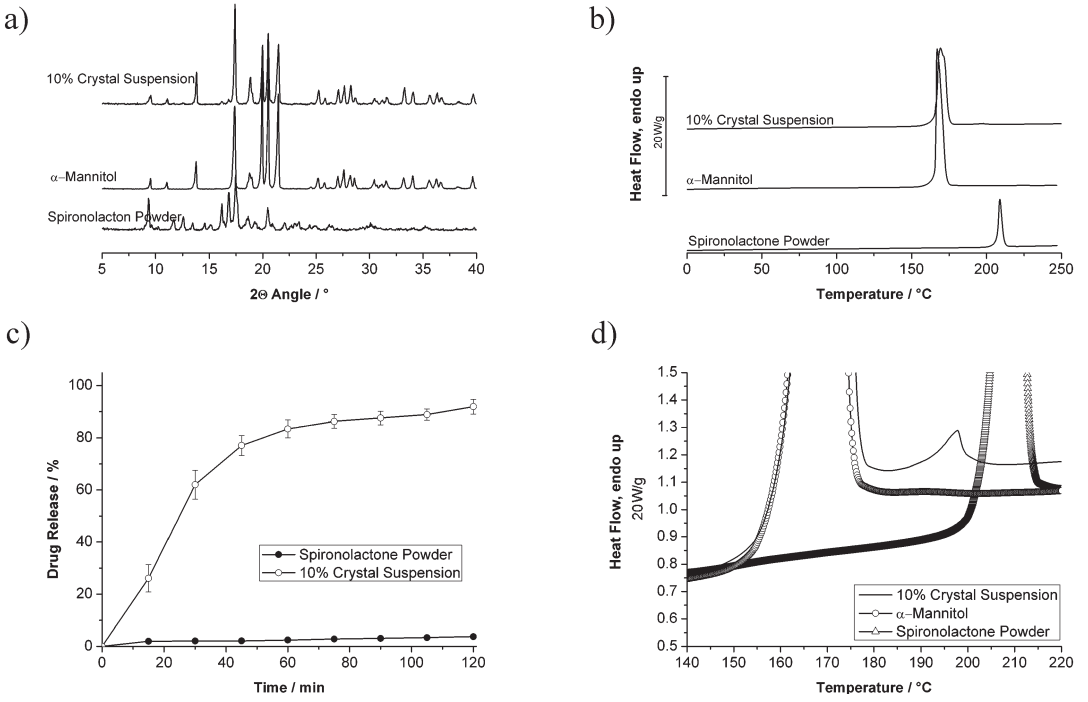

Figure 7. Properties of a 10% crystalline suspension of spironolactone in mannitol. (a) X-ray diffraction patterns of the two pure components and the suspension. (b) DSC thermograms of the suspension, spironolactone and mannitol. (c) Dissolution rate profile. The dissolution profile of the plain drug is also plotted. (d) Portion of the DSC thermogram shown in expanded scale.

spironolactone were included in this study as additional model compounds. These two drugs are also poorly soluble and slow dissolving in water. Crystalline suspensions containing 10% (w/w) of either drug in mannitol were prepared following the same procedure as that used for griseofulvin. The results from the XRD, DSC and dissolution for phenytoin and spironolactone are

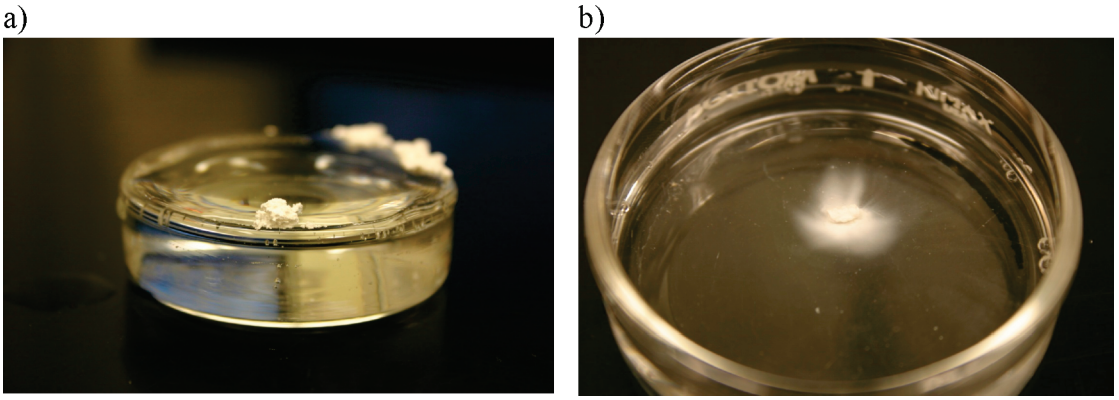

Figure 8. Wettability of (a) plain griseofulvin and (b) the crystalline suspension containing 50% griseofulvin in mannitol.

shown in Figures 6 and 7, respectively. In each case, the obtained suspension is crystalline and the dissolution rate is accelerated by a factor similar to that observed with griseofulvin. The model compounds used here are poorly soluble, and they are commercially supplied in micronized form. For this reason, the XRD profiles of pure phenytoin and spironolactone exhibit rather blunt peaks, some of which, even if not very conspicuous, can be seen in the XRD pattern of the crystalline suspension. All peaks in the diffraction pattern of the extrudate are consistent with either the diffraction pattern of α-mannitol or the diffraction pattern of drug in Figures 6a and 7a. This indicates that both the drug and mannitol are present in crystalline form in the final extrudate. The DSC in Figure 6b does not go up to the melting of the drug. The reason is that the melting temperature of phenytoin (295−298 °C) is very close to the boiling point of mannitol (290−295 °C).[40] The DSC in Figure 7b shows a small and depressed melting peak for spironolactone (see expanded scale in Figure 7d). These results suggest that molten mannitol is a somewhat better solvent for spironolactone than for griseofulvin. Even though crystalline suspensions of the three individual drugs each have some unique attributes, they also have a number of commonalities. With all three model drugs, crystalline formulations with accelerated dissolution rates were obtained. In addition, no differences in the solid state properties were found between the initial and the stored samples exposed to 40 °C and 75% RH for 90 days (data not shown).

Figure 8 shows images of plain griseofulvin and of the 50% solid crystal suspension formulation placed in water. One significant difference between the two samples is that the extrudate formulation exhibits a very fast dispersion as opposed to the plain drug, which floats on the water surface for several minutes despite its density (1.4 g/mL).[41] In addition to being poorly soluble, a hydrophobic drug like griseofulvin is not easily wetted by water.[42] The extruded formulation, on the other hand, readily disperses in water. It has been proposed that polyols promote favored hydration of hydrophobic regions in proteins.[43] The same type of effect could result in the favored wetting of hydrophobic drug particles. The results obtained suggest that the accelerated dissolution rate of the "solid crystal suspensions" results from two main factors: favored wettability and reduced particle size. However, further studies to confirm this notion are needed and further research on the subject is warranted.

Regarding the particle size factor, the shear forces imparted by the extrusion process have the effect of further reducing the particle size of the already micronized (by the supplier) drug particles. In order to investigate this effect, mannitol was stripped from the extrudate formulation by placing it in griseofulvin-saturated water. The soluble mannitol in the extrudate quickly dissolved (within 1 min), leaving the drug particles suspended in the medium, thus allowing particle size measurement of the drug particles from the extrudate. Figure 9 shows the particle size distribution for the griseofulvin particles obtained from the formulations containing 10% and 50% drug load. The particle size distribution of the original (raw material) griseofulvin particles is also shown for comparison. The extrusion process reduced the particle size of the drug. It is noteworthy that the formulation with 50% drug load exhibits smaller particle size than the formulation with 10% drug content. The smaller particle size in the higher load formulation is attributed to lower shear forces in the 10% drug load formulation, resulting from a higher proportion of the liquid phase (90% molten mannitol) in the mixture during extrusion. Figure 4 shows that similar dissolution rates were obtained with formulations containing 10% and 50% drug. The combined results of Figures 4 and 9 suggest that, by controlling the shear forces of the extrusion process, it is possible to control the resulting particle size of the drug in the solid suspension and hence the dissolution rate. The formulations used in this study were produced using a research scale laboratory extruder, which does not have the degree of process control of

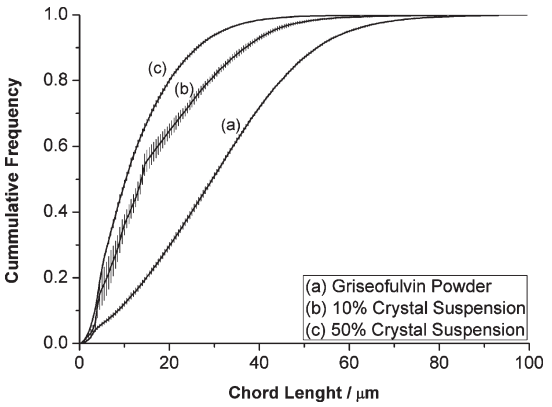

Figure 9. Particle size distribution of the crystalline suspensions of griseofulvin in mannitol: (a) original (raw material) griseofulvin powder, (b) 10% drug load, and (c) 50% drug load. Traces and vertical bars correspond to the mean and standard deviation of 12 observations, respectively.

larger units. However, one of the advantages of hot melt extrusion is its versatility, in the sense that through the different processing zones of pilot and larger scale equipment, controlling process parameters such as shear forces, temperature, residence time, etc.[44] is an integral part of the manufacturing process. From these considerations, control of shear forces and the resulting particle size and dissolution rate of the solid suspensions should be readily achievable in a production setting.

The properties of the solid suspension obtained indicate that the drug release attributes of these formulations are the result of the physical configuration of the extrudate more than from the interactions between the drug and the excipient. Griseofulvin serves as model for a poorly soluble drug that is hydrophobic but whose solubility is also strongly limited by its crystal lattice energy. We surmise that the combination of these two attributes of the drug determines whether a given API is a good candidate for formulation as a solid crystal suspension. The solubility of an organic nonelectrolyte or weak electrolyte such as the drugs of this study is given by[2]

$$\log X = \frac{-\Delta S_m (T_m - T)}{2.303RT} - \log \gamma \qquad (1)$$

where X is the (mole fraction) solubility, T is the (absolute) temperature, R is the gas constant, ΔS_m and T_m are the entropy and temperature of melting, respectively, and γ is the activity coefficient. The first term on the right-hand side of eq 1 is the ideal solubility, which is a measure of the degree to which the stability of the crystal, i.e., the crystal lattice energy, limits the solubility. This term is an inherent property of the solid solute, so it contributes the exact same magnitude of the effect for every single solvent. The second term on the right-hand side of eq 1 is the activity coefficient, which is a property of the solute−solvent mixture and is a measure of the of the free energy barrier for their mixing, i.e., for the solvation of the solute by the solvent. For griseofulvin dissolved in water for example, the value of log γ is 2.54.[45] The extrusion process in these systems involves liquid (molten) mannitol and the solid drug. Liquid mannitol is a highly hydroxylated polar solvent, and as such, it is expected to present a poor (unfavorable) solvating environment for hydrophobic solutes. The precise value of log γ for griseofulvin dissolved in molten mannitol (at ~165 °C) is not known, but an estimate based on the UNIFAC model[46,47] gives a value of 2.1 for log γ of griseofulvin in mannitol at 165 °C. Molten mannitol is not much of a better solvent for griseofulvin than water. This condition explains the negligible effect on the melting points of griseofulvin and mannitol in the solid crystal suspension seen in Figures 2 and 3. Solubility parameters can also be used to assess the mixing compatibility between mannitol and a larger number of drugs. For example, using the software SPWin (version 2.1),[48] which calculates the three-dimensional solubility parameter using group contributions according to Fedors, van Krevelen and Hoftyzer,[49,50] the solubility parameters for phenytoin, spironolactone and mannitol are 25 $MPa^{1/2}$, 21.5 $MPa^{1/2}$ and 40.5 $MPa^{1/2}$, respectively. A difference in solubility parameters of 10 $MPa^{1/2}$ or greater is interpreted as an indication of immiscibility between components.[23] The difference in total solubility parameters between mannitol and either phenytoin and spironolactone is greater than 15 $MPa^{1/2}$. Therefore, liquid mannitol can also be considered as a poor solvent for these two drugs.

Based on the above considerations, the extrusion process of the approach presented here results in a suspension of the crystalline drug in the liquified excipient. In addition to the particle size reduction produced by the shear forces involved (Figure 9), the intense mixing and agitation of hot melt extrusion[51] results in a uniform distribution of fine particles. Upon the fast crystallization of mannitol, the uniformly distributed fine API particles get rapidly fixed in a spatially uniform crystalline suspension. It is important to point out that the fast crystallization properties of the excipient (mannitol) are critical to the approach presented here. This point becomes abundantly clear when considering that sorbitol for example, an isomer of mannitol, is unsuccessful in producing the type of crystalline suspensions with the physical and performance attributes exemplified in Figures 1−7. Sorbitol did not crystallize after extrusion, and an amorphous system was obtained (glass suspension). Mannitol and sorbitol are optical isomers; they differ only by the arrangement of the chiral centers in their respective molecular structures. However, the two isomers have substantially different melting and crystallization properties. Mannitol has a substantially higher melting point and a very strong tendency toward crystallization.[34] A comparison of the molecular structures of mannitol and sorbitol reveals that the chiral arrangement in mannitol makes its molecule more symmetrical. Molecular symmetry translates into a strong entropic effect, favoring crystal formation.[52] This is a likely factor in the crystallization properties of mannitol. We should also point out that the generation of crystal suspensions is not exclusive to mannitol. Preliminary investigations indicate that other fast crystallizing sugar alcohols like xylitol for example (mp 95 °C) successfully produce crystal suspensions at lower temperatures than mannitol (because of the lower melting point). Fast crystallization of the excipient, more than a high melting point, is a critical element for producing crystal suspensions.

The extrusion approach presented here is thought to result in a 2-fold effect in the type of formulation obtained. On the one hand, equipment used in hot melt extrusion is capable of generating mixtures under high (and controllable) shear forces. As a result, the API undergoes particle size reduction and the accompanying increase in surface area. On the other hand, the fine API particles become intimately mixed and completely surrounded by the highly hydrophilic carrier. As a result, wetting by the aqueous dissolution medium of the increased surface area of the API is highly favored. The result is a solid crystal suspension with fast dissolution rate. As a type of solid dispersion formulation, crystal suspensions are different from molecular level dispersions in various respects, especially with regard to the interaction between the drug and the excipient. In molecular drug−polymer solid dispersions, favorable interactions between drug and polymer are critical to the creation of a thermodynamically stable or a kinetically stabilized dispersion.[24] Solid crystal suspensions, on the other hand, are the opposite in the sense that their production relies on unfavorable mixing interactions between the drug and the liquid excipient. A suitable drug candidate for formulation as a solid crystal dispersion would be a poorly water-soluble compound, which, in addition to being hydrophobic and having a high crystal lattice energy, it is not necessarily a good glass former or it is difficult to stabilize in the amorphous state.

■ CONCLUSIONS

The preparation of crystalline mixtures by hot melt extrusion has the potential to be an effective way to increase the dissolution rate of poorly soluble drugs. The use of mannitol as a matrix forming agent with a low molecular weight showed a fast drug release for three poorly soluble drugs. The magnitude of

enhancement of the dissolution rate is comparable to that sought with other types of solid dispersions. The "solid crystal suspension" appears to be a general approach suitable for drugs that are difficult to stabilize in the amorphous form. The approach uses the robust, well-established extrusion process and mannitol as an excipient. It could be beneficial for class II drugs of the biopharmaceutics classification system where the bioavailability is limited by the dissolution rate. The product is a physical mixture of the crystalline drug and crystalline excipient that could be used for different oral dosage forms such as tablets and capsules.

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