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Alternative matrix formers for nanosuspension solidification: Dissolution performance and X-ray microanalysis as an evaluation tool for powder dispersion

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ABSTRACT

Four alternative matrix formers [Avicel®PH101, Fujicalin® ($CaHPO_4$), Aerosil®200 (SiO_2) and Inutec®SP1] were evaluated for their capability in preserving rapid dissolution after spray-drying of nanosuspensions. Model drug compounds selected were cinnarizine (CIN), itraconazole (ITR) and phenylbutazone (PHB) as they showed a decrease in dissolution rate upon spray-drying in the absence of additional matrix formers, yielding release values after 5 min of dissolution ($release_{5\,min}$) of 57.7 ± 1.0% (CIN), 56.3 ± 3.8% (ITR) and 67.4 ± 1.3% (PHB). Compared to the situation without matrix former inclusion, the performance of Avicel®PH101 was good for CIN ($release_{5\,min}$ = 90.9 ± 7.7%), intermediate for PHB ($release_{5\,min}$ = 81.0 ± 6.4%) and poor for ITR ($release_{5\,min}$ = 42.1 ± 4.2%). For Fujicalin®, intermediate (PHB: $release_{5\,min}$ = 87.7 ± 3.0%) or poor (CIN: $release_{5\,min}$ = 66.1 ± 3.4%; ITR: $release_{5\,min}$ = 55.9 ± 5.2%) performance was seen. Results for Aerosil®200 were good for all compounds (CIN: $release_{5\,min}$ = 91.5 ± 2.5%; ITR: $release_{5\,min}$ = 83.8 ± 3.4%; PHB: $release_{5\,min}$ = 95.5 ± 2.4%), indicating that the large specific surface area was in this case translated into good matrix forming capabilities. Finally, the best results were obtained for Inutec®SP1 (CIN: $release_{5\,min}$ = 88.7 ± 1.2%; ITR: $release_{5\,min}$ = 93.4 ± 2.4%; PHB: $release_{5\,min}$ = 101.3 ± 4.9%). Except for Avicel®PH101, Cl-maps from X-ray microanalysis of the itraconazole powders supported the hypothesis that better dispersion of drug in the powders results in faster dissolution.

1. Introduction

Formulation of drugs as nanocrystals has rapidly gained interest during the last decade as witnessed by the appearance of literature on the subject and marketed products relying on this approach (Kesisoglou et al., 2007a). Currently, all marketed products are produced by so-called top-down techniques, by which the nanoparticles are obtained through size reduction into the submicron-range. Technically, size reduction is achieved either by milling or homogenization techniques (Date and Patravale, 2004), both conducted in the suspended state. The suspending liquid is usually water, to which a stabilizer is added to prevent nanoparticle agglomeration (Müller et al., 2006).

There is however a general preference for solid oral dosage forms, from a marketing (patient convenience) and physical

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stability perspective (Müller et al., 2006). This preference is illustrated by the fact that currently four out of the five marketed drug nanocrystal products are solids. Therefore, drying of nanosuspensions should be considered as an almost essential step in the production of a final nanoparticulate dosage form intended for oral delivery. Drying can be achieved by unit operations like pelletization, granulation, spray-drying or freeze-drying (Müller et al., 2006). Although freeze-drying sometimes is a valuable drying process, methods relying on water evaporation are generally preferred for non-thermosensitive compounds, since these processes are more attractive from an economical point of view.

Upon drying of nanosuspensions, agglomeration is a phenomenon that has been reported to be able to profoundly impact the properties of products intended for a diversity of applications (Wang et al., 2005). For drug nanocrystals, the increased dissolution rate originating from the increased specific surface area is generally recognized as its key attribute (Kesisoglou et al., 2007b). Therefore, evaluation of the impact of agglomeration on the dissolution performance upon redispersion of the dried product is essential. Recently, we evaluated the dissolution performance of nine model drug compounds after freeze-drying and spray-drying. This study confirmed that desagglomeration upon redispersion can indeed become a rate-limiting step in the overall dissolution process. Furthermore, the results showed that the decrease in dissolution rate was correlated with the surface hydrophobicity of the nanoparticles. Whereas for compounds with less hydrophobic surfaces the drying effect on dissolution was negligible, drying was devastating for the dissolution of more hydrophobic compounds (Van Eerdenbrugh et al., 2008a).

For the latter group of compounds, addition of matrix formers prior to the drying step is necessary if one wants to preserve the dissolution potential of the nanosized products. Typical matrix formers reported in literature are sugars (e.g. sucrose, saccharose, lactose), sugar alcohols (e.g. mannitol, sorbitol) and water-soluble polymers (e.g. PVP, polyvinylalcohol, long chained PEG) (Müller et al., 2006; Kesisoglou et al., 2007a). Although these matrix formers are valuable, cases exist where their ability to preserve high dissolution rates is poor. For example, in the case of freeze-drying of a loviride nanocrystal formulation, we found that sucrose proved to be successful in the conversion of a semisolid product with poor dissolution into a fast-dissolving solid product (Van Eerdenbrugh et al., 2007). However, freeze-drying of an itraconazole–sucrose system, led to the opposite effect. Although sucrose acted cryoprotective, increasing amounts in the formulation resulted in more pronounced agglomeration during the last phase of the drying process. As a result, dissolution dropped upon adding higher amounts of sucrose (Van Eerdenbrugh et al., 2008b). In the same study, microcrystalline cellulose (Avicel®PH101) proved to be a more efficient alternative as a matrix former during freeze-drying. These results advocate the evaluation of alternative matrix formers for nanosuspension drying purposes. Furthermore, evaluation of the potential of a matrix former should ideally be done using several model drug compounds, in order to establish a rational formulation base.

In this study, four alternative matrix formers were evaluated for nanosuspension spray-drying purposes. Potential matrix formers chosen were Avicel®PH101, Fujicalin® ($CaHPO_4$), Aerosil®200 (SiO_2) and Inutec®SP1. Avicel®PH101 (microcrystalline cellulose) is a cheap water-insoluble excipient commonly applied as a binder/diluent in oral tablet and capsule technology (Weller, 2003) and was selected as its potential as a matrix former for freeze-drying of nanosuspension has previously been demonstrated with itraconazole (Van Eerdenbrugh et al., 2008b). Fujicalin® ($CaHPO_4$) is a rather recent, free-flowing spherically granulated anhydrous dicalcium phosphate ($CaHPO_4$) for direct compression (Schlack et al., 2001). The product is prepared by reacting phosphoric acid with an alkaline calcium compound using restricted crystal growth synthesis (Tamaki et al., 1996), followed by spray-drying granulation. The final product consists of highly porous spherical agglomerates of typically submicron-sized primary particles (Takado and Murakami, 1996). Given the nature of its composition, the specific surface area of the product has been reported to be about 100 times larger ($27.01 \pm 0.03\ m^2/g$) than for an alternative directly compressible dicalcium phosphate dihydrate ($0.30 \pm 0.03\ m^2/g$) (Schlack et al., 2001). This characteristic makes the product interesting for the evaluation of its matrix-forming capabilities upon nanosuspension drying, since a higher specific surface area might be translated in good matrix forming capabilities. Aerosil®200 (colloidal silicon dioxide, SiO_2, fumed silica, aerosil) is a water-insoluble product consisting of primary particles of about 15 nm, resulting in a very high specific area ($200 \pm 25\ m^2/g$, as determined by the BET method) (Morefield and Seyer, 2003), which was again the reason why this excipient was evaluated for its matrix-forming potential. Finally, Inutec®SP1 is a polymer that has been used for the formulation of solid dispersions (Van den Mooter et al., 2006) and as a stabilizer for bottom-up nanoparticle production (Panagiotou et al., 2007). The product is a hydrophobically modified inulin (polyfructose) that has surface active properties (Stevens et al., 2001a,b). The model drugs evaluated were three compounds for which a decrease in dissolution rate of a nanosuspension has been reported upon drying in the absence of matrix formers [cinnarizine (CIN), itraconazole (ITR) and phenylbutazone (PHB)] (Van Eerdenbrugh et al., 2008a). Nanosuspensions were stabilized with D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) applied in 25 wt% (relative to the drug weight), as nanosuspension production was previously found to be successful with this stabilizing system.

The study consists of three parts. First, the effect spray-drying has on the matrix formers is shortly discussed. Second, drug-matrix former combinations are prepared by spray-drying. Dissolution of the powders is performed and analyzed in terms of the drug compound and matrix former. In the final part, X-ray microanalysis is introduced as a tool to evaluate dispersion of itraconazole in the different powders, thus enabling to make the link between the drug dispersion and the observed dissolution results.

2. Materials and methods

2.1. Materials

D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS, Eastman Chemical Company, Kingsport, TN, USA),