Impact of Various Polymeric Matrices on the Dissolution of Itraconazole from Surfactant-Sugar-Free Nanocomposite Microparticles

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Purpose

Bioavailability of a poorly water-soluble drug can be improved by preparing its aqueous nanosuspension in the presence of various stabilizers via wet milling and subsequently drying the suspension into nanocomposite microparticles or shortly nanocomposites. Unfortunately, drug nanoparticles aggregate during milling and drying, causing incomplete recovery and relatively slow dissolution from the nanocomposites. While various stabilizers/dispersants can be used to mitigate the extent of nanoparticle aggregation, excessive use of surfactants and sugars/sugar alcohols may be undesirable due to toxicity, relatively low drug loading, etc. In addition, due to differences in wetting and dissolution behavior, different types of polymeric stabilizers or different molecular weights of the same polymeric stabilizer can affect the drug release from the nanocomposites. The aim of this study is to (i) investigate the feasibility of preparing high drug-loaded, surfactant-sugar-free nanocomposites and (ii) explore the impact of various polymeric stabilizers on the wet-milled drug particle size and dissolution performance.

Methods

Precursor aqueous nanosuspensions of 10% (w/v) itraconazole (ITZ, a model poorly water-soluble BCS Class II drug) were prepared in the presence of various polymers via wet stirred media milling and spray dried to form the nanocomposites. Hydroxypropyl cellulose (HPC) with three different molecular weights (UL, SSL, and SL grades in ascending order of molecular weight), hydroxypropyl methyl cellulose (HPMC E3 grade), and polyvinyl pyrrolidone (K30 grade) were used at 4.5% (w/v) as nanoparticle stabilizers and matrix formers/dispersants because these polymers have been widely used in drug nanoparticle formulations in industry/academic research. In a positive control experiment, we also wet-milled ITZ in an aqueous solution of 2.5% HPC SL–0.2% sodium dodecyl sulfate (SDS). SDS is an anionic surfactant and its combination with cellulosic polymers is known to have synergistic stabilization–dissolution enhancement effects [1,2]. We characterized the suspension particle size (laser diffraction)–viscosity (cylinder-in-cylinder viscometer) and determined the drug assay–dissolution profiles for the nanocomposites via UV spectroscopy. As-received ITZ powder was used as a negative control in the dissolution tests. Moreover, the morphology and solid-state of ITZ were assessed by SEM and XRD/DSC, respectively, for selected samples to elucidate any potential changes during the milling–drying.

Results

Wet media milling of ITZ led to different particle sizes depending on the stabilizing polymer used because ITZ nanoparticles tended to aggregate severely. SEM imaging proved the formation of primary ITZ nanoparticles of 50–250 nm size range, whereas laser diffraction revealed aggregate sizes. Except PVP K30 and HPC UL, the polymers reduced the extent of aggregation significantly and enabled preparation of drug nanosuspensions with median size below 300 nm. For HPC, the median ITZ particle size decreased with an increase in polymer molecular weight, suggesting better stabilization imparted by the higher molecular weight grades (SSL and SL). The highly aggregated suspensions with PVP K30 and HPC UL exhibited much stronger shear thinning (pseudoplasticity) than the suspensions with HPC SL and HPMC E3. The spray-drying of the wet-milled suspensions led to the formation of high drug-loaded (54–66%), surfactant-free nanocomposites. XRD diffractograms and DSC thermograms overall suggest that spray-dried samples had mostly crystalline form of ITZ, i.e., only a small fraction of amorphous ITZ was present. Such nanocomposites enabled a significant improvement of the dissolution rate of ITZ owing to high surface area of the ITZ nanoparticles, the presence of relatively hydrophilic, polymeric matrix formers besides the presence of a small fraction of amorphous ITZ.Among all nanocomposite formulations, only the one with HPC SL exhibited fast, immediate ITZ release; it also exhibited faster ITZ dissolution than HPMC E3 and PVP K30 formulations. Formulations with HPC SSL and HPC UL exhibited slower drug release than those with HPMC E3 and PVP K30. While the 2.5% HPC SL–0.2% SDS formulation, the positive control, indeed led to slightly smaller nanoparticles in the wet-milled suspension due to presence of SDS; its sprayed dried powder showed a similar dissolution profile to that of 4.5% HPC SL formulation.

Conclusion

Our findings overall demonstrate that high drug-loaded, surfactant-free nanocomposites exhibiting immediate release of poorly water-soluble drugs are feasible upon wet-media milling of drug–HPC and spray-drying of the respective precursor suspension.

References

[1] M. Li, N. Lopez, E. Bilgili, “A Study of the Impact of Polymer–Surfactant in Drug Nanoparticle Coated Pharmatose Composites on Dissolution Performance,” Adv. Powder Technol., Vol. 27, 2016, pp. 1625-1636

[2] E. Bilgili, M. Li, A. Afolabi, “Is the Combination of Cellulosic Polymers and Anionic Surfactants a Good Strategy for Ensuring Physical Stability of BCS Class II Drug Nanosuspensions?” Pharm. Dev. Technol., Vol. 21, 2016, pp. 499-510.