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Physicochemical considerations in the preparation of amorphous ritonavir-poly(ethylene glycol) 8000 solid dispersions.

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A systematic study of the properties of ritonavir and the influence of polyethylene glycol 8000 (PEG) on ritonavir revealed that amorphous ritonavir dispersions in PEG would have an improved dissolution profile and could exhibit long-term stability. Ritonavir, a human immunodeficiency virus (HIV) protease inhibitor, is highly lipophilic [distribution coefficient (log D)= 4.3, 25 degrees C, pH 6.8], **poorly water soluble (400 microg/mL in 0.1 N HCl, 1 microg/mL at pH 6.8, 37 degrees C)**, and exhibits an exceedingly slow dissolution rate (0.03 mg/cm(2)-min in 0.1 N HCl at 37 degrees C). These properties indicated that a solid dispersion containing ritonavir might be useful for overcoming problems associated with slow dissolution. In addition, ritonavir is a good glass former [glass-transition temperature (T(g))/melting point (T(m)) > 0.7]. Amorphous ritonavir has an apparent solubility of 4 mg/mL in 0.1 N HCl at 37 degrees C and shows reasonable stability at 25 degrees C. Amorphous ritonavir, therefore, has properties desirable for preparing a solid dispersion containing this phase. Since PEG, a commonly used polymer, improved the aqueous solubility of crystalline ritonavir, it was expected to have a positive influence on the dissolution rate of ritonavir. Moreover, PEG was found to have negligible plasticizing effect on amorphous ritonavir, which was beneficial for the stability of the dispersion. Finally, solid dispersions of amorphous ritonavir in PEG were prepared, and these dispersions had improved in vitro dissolution rate and were physically stable for > 1.5 years at 25 degrees C when protected from moisture. The performance of this solid dispersion has been attributed to the physicochemical properties of amorphous ritonavir.

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Calculations: 1 microgram (µg) = 0.001 milligrams (mg)