Interplay of Amorphous-Amorphous Phase Separation and Liquid-Liquid Phase Separation in Governing the Dissolution Performance of Ritonavir Amorphous Solid Dispersions
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Purpose
Amorphous solid dispersions (ASDs) are growing in importance as a solubility enhancement strategy for poorly water-soluble compounds. Since the amorphous drug in the ASD has a higher free energy as compared to its crystalline counterpart, a variety of phase transformations can occur when the ASD comes in contact with water. Two of these phase transitions, namely amorphous-amorphous phase separation (AAPS) in the dissolving matrix, and liquid-liquid phase separation (LLPS) in the aqueous phase are the focus of this study. Both AAPS and LLPS are governed by the thermodynamics of mixing and/or demixing in presence of water.

AAPS occurs when drug-rich and drug-lean phases are formed in ASD matrix in the presence of water. AAPS can negatively impact the performance of the ASD as the crystallization inhibitory and wetting effect of the polymer is lost due to phase separation. The second phenomenon, LLPS, occurs when the concentration of the drug in the dissolution medium exceeds the amorphous solubility. The drug in excess of the amorphous solubility forms drug-rich nanodroplets that exist in metastable equilibrium with the drug in the solution phase. From a biological perspective, the drug-rich nanodroplets can serve as drug reservoir and can replenish drug that is absorbed from the intestine into the blood stream. Thus LLPS can be beneficial whereas AAPS might lead to decrease in the dissolution performance of the drug from the ASD. The purpose of this research was to examine the interplay of AAPS versus LLPS during dissolution of ritonavir (RTV) ASDs and to study the impact of polymer type and loading on the dissolution performance.

Methods
Amorphous solubility determination: A methanolic stock solution of RTV (5mg/mL) was added to pH 6.8 phosphate buffer, stirred at 300 rpm. Addition of drug stock solution was performed using a syringe pump infusing the drug solution at a controlled rate. A dip probe ultraviolet (UV) spectrometer was used to measure the changes in the extinction at a non-absorbing wavelength i.e. 350 nm. A plot of extinction versus concentration of RTV gives the amorphous solubility, as indicated by the inflection in the plot.

Preparation of RTV ASDs: ASD consisting of RTV- Polyvinylpyrrolidone (PVP), RTV- Polyvinylpyrrolidone vinyl acetate (PVPVA) and RTV- hydroxypropyl methylcellulose acetate succinate (HPMCAS) were prepared by dissolving the drug and polymer in methanol and solvent removal via rotary evaporation. The obtained ASDs were dried and milled.

Hydration studies and fluorescence spectroscopy: A trace amount of an environment sensitive fluorescent probe, pyrene, (0.1% w/v) was added to the methanolic solution of drug and polymer. The solution was then spin coated to obtain thin ASD films. The ASD films were kept at 97% RH for hydration and fluorescence emission of pyrene in ASD films was monitored with time.

Monitoring drug and polymer dissolution: Polymers were quantified colorimetrically. PVP and PVPVA were quantified using potassium iodide and citric acid at 500 nm whereas, phenol and sulfuric acid were used to quantify HPMCAS at 490 nm. The amount of drug dissolving in pH 6.8 phosphate buffer was monitored by measuring the absorption at 240 nm using a dip probe UV spectrometer. Drug dissolution was also studied after exposure of ASDs to 97% RH to study the impact of AAPS on dissolution.

Results
The inflection point on the extinction as a function of concentration plot gave the amorphous solubility as 27 μg/mL.

Hydration studies: By monitoring pyrene emission in the ASD films, it was observed that RTV-PVP and RTV-PVPVA ASDs underwent AAPS after exposure to 97% RH whereas, RTV-HPMCAS ASDs did not phase separate.

Dissolution behavior: Dissolution behavior of RTV-PVP ASDs determined before and after exposure to 97% RH revealed that the fresh ASD resulted in LLPS upon dissolution whereas, ASDs after exposure did not. Fresh RTV-PVPVA ASDs did not result in LLPS even at low drug loadings, however, their dissolution was further impaired upon exposure to moisture. RTV-HPMCAS ASDs on the other hand showed similar dissolution profiles before and after exposure to moisture and all of them resulted in LLPS. When the dissolution of polymer was studied, it was observed that all the three polymers present in the ASDs quickly dissolve and reach the maximum plateau concentration in around 10 minutes.

Conclusion
RTV-HPMCAS ASDs are resistant to phase separation in the presence of water and therefore lead to LLPS upon dissolution. RTV- PVP and RTV-PVPVA dispersions on the other hand undergo AAPS in the presence of water and therefore have a poor dissolution performance.

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