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Solubility and dissolution of binary co-amorphous ritonavir-lopinavir solid dispersions

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Abstract

Title: Solubility and dissolution of binary co-amorphous ritonavir-lopinavir solid dispersions
Purpose: To study the effect of lopinavir (LPV) on the dissolution and solubility of amorphous ritonavir (RTV) solid dispersion in HPMCAS and PVP
Methods: Amorphous solid dispersions of LPV and RTV and co-amorphous mixtures at weight ratios of 3:7, 5:5 and 7:3 were prepared in HPMCAS-MF and PVP K29-32. The dispersions were all prepared at drug loadings of 20% by roto-vaporation followed by cryomilling. X-ray powder diffraction (XRPD) of the dispersions was done using a Rigaku smartlab to confirm the formation of an amorphous solid. Differential scanning calorimetry of the dispersions and physical mixtures of only the drugs was done to determine the glass transition temperature (T_g) and miscibility. Films of RTV, LPV and mixtures of the drugs at the three ratios in the absence of polymer were prepared in scintillation vials by roto-vapping using a vial adapter. Dissolution of the films at 25°C in 10ml of 100mM pH6.8 phosphate buffer was done while the dissolution of the dispersions with polymers was determined by adding 10mg of the dispersions in 40ml of dissolution media and filtering aliquots of the medium through 0.45µm glass syringe filters at different time points. The samples were analyzed using an Agilent HPLC using a 60:40 Acetonitrile:Water mobile phase and C-18 reverse phase column and a detection wavelength of 205nm.
Results: XRPD showed that the dispersions were amorphous. Only one T_g was obtained for all the dispersions with the T_g of the HPMCAS dispersions being lower than the PVP dispersions. For the mixtures of pure drugs without any polymer, only one T_g was observed at temperatures between that for the two pure drugs indicating good miscibility. The PVP dispersions resulted in clear solutions upon filtration while the HPMCAS dispersions formed tiny particulates during dissolution which passed through the syringe filter. Therefore the final concentration after the dissolution of the HPMCAS dispersions was done by ultracentrifuging followed by HPLC analysis of the supernatant. The results showed that the maximum concentration achieved for the drugs matched the amorphous solubility at that temperature. For the co-amorphous dispersions, the concentrations achieved for both drugs were significantly lower than that achieved when the drugs were present alone. For example, the concentration for the 3:7 mixture was 5.5 of RTV and 12 µg/ml of LPV while for the pure drugs the amorphous solubility was approximately 25 and 17 µg/ml respectively. Dissolution of the two pure drug dispersions added separately in the dissolution medium at the same time also resulted in a much lowered final drug concentration.
Conclusion: The data from the dissolution from the co-amorphous films and dispersions showed that the maximum concentration achievable for the drugs is lower than that obtained when the drugs are formulated alone as amorphous dispersions. Co-administering two separate amorphous formulations can also result in decreased free drug concentration in solution. This can have significant impact on the bioavailability of combination products or when drugs are administered at the same time.

Introduction

Low aqueous solubility of compounds makes it necessary to use formulation strategies that can improve delivery. One approach is the formulation of amorphous solid dispersions. The increase in free energy of the amorphous solid results in an improvement in transient solubility. This also results in an increased possibility for crystallization during processing and storage. This is circumvented by the addition of polymers which interact with the drugs to increase the glass transition temperature and decrease the molecular mobility.

Recently, there are products entering the market that contain more than one drug in the same formulation. However, little is known about the influence of one drug on the solubility and dissolution behavior of the other drug for such amorphous solid dispersion combination products. In this work we look at the effect of different ratios of two drugs in the same solid form in the presence and absence of polymers on the dissolution and final solubility achieved in aqueous buffered media. We also study the effect of polymer used in the preparation of the dispersion on the dissolution behavior.

Eron Jr., et. al., The Lancet, Aug 2006, 476-482

Methods

Drugs used: Ritonavir (RTV), lopinavir (LPV)

Preparation of dispersion: 20% w/w of pure RTV and LPV and their mixtures in the ratios of 7:3, 5:7 and 3:7 w/w with a total drug content of 20 wt. % in the ASD were prepared in PVP and HPMCAS by first dissolving the drugs and polymer in methanol and then subjecting them to rotary evaporation The resultant material was then cryomilled to obtain a powder. Films were prepared by spin coating the drug solutions on scintillation vial walls.

Physical characterization: X-ray powder diffraction (XRPD) was done using a Rikagu smartlab at angles between 5-40° at a scan speed of 20°/min. Thermal analysis of the samples was done using a differential scanning calorimeter (DSC) (TA Instruments) at 10°C/min heating rate.

Fluorescence probe: Pyrene was used a probe to determine crystallization by using an excitation wavelength of 332nm and an emission range of 350-450nm and monitoring the change in the I_3/I_1 ratio as a function of time.

Ultracentrifugation: After dissolution of the dispersions, the dissolution medium was ultracentrifuged at 40,000rpm for 20 minutes using a Beckman-Coulter ultracentrifuge and the supernatant analyzed by HPLC.

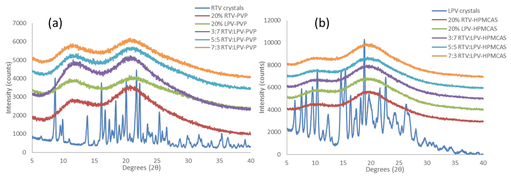
HPLC: Chromatographic analysis was done using an Agilent Infinity system using a Zorbax C-18 analytical column with a mobile phase of Acetonitrile:Water (60:40) and a detection wavelength of 205nm.

Particle analysis: The particles in the media after dissolution were analyzed with the Nanoparticle tracking analyzer (NTA, Malvern) using scattering of light by the particles.

Results and Discussion

Characterization of dispersions:

The 20% drug loading dispersions were completely amorphous as seen by the x-ray diffraction halo.

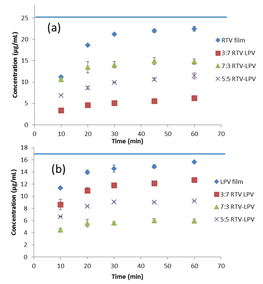


Thermal analysis of the dispersions showed that PVP dispersions had highest T_g followed by the HPMCAS dispersions. The two drugs by themselves exhibited only one T_g at all the three ratios indicating miscibility of the drugs.

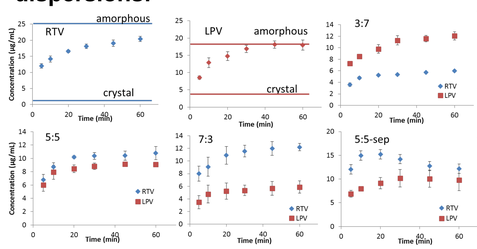
Sample	T_g Drugs (°C)	T_g PVP dispersion (°C)	T_g HPMCAS dispersion (°C)
RTV	46 (1.5)	125.5 (0.7)	73 (1.3)
LPV	77 (2.8)	140 (3)	91 (1.4)
3:7 RTV:LPV	66 (1.5)	135 (1.6)	87 (0)
5:5 RTV:LPV	60.5 (0.7)	133 (1.5)	84 (1.5)
7:3 RTV:LPV	54 (1.5)	128 (0.8)	80 (2)

Dissolution of drug films:

These data provide reference values for the dissolution behavior and maximum achievable solution concentration of the amorphous drug alone and in combination with a second drug. Using films also makes it is possible to control the exact ratio of the drugs in the amorphous phase and also provides a large surface area for dissolution. All solutions are supersaturated with respect to the crystal forms whereby the highest concentration is achieved for the pure drug film, and the presence of increasing amounts of the second compound reduces the plateau concentration achieved.



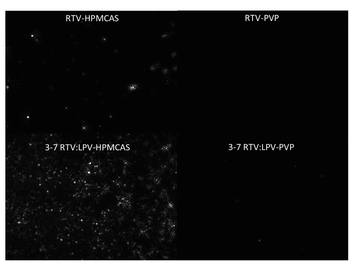
Dissolution of powdered dispersions:



When present in combination, the concentration of both drugs is significantly below that for the pure drug dispersions. Even when the two drugs are added separately at the same time, the final concentration matches that observed when the drugs are formulated together in the same solid.

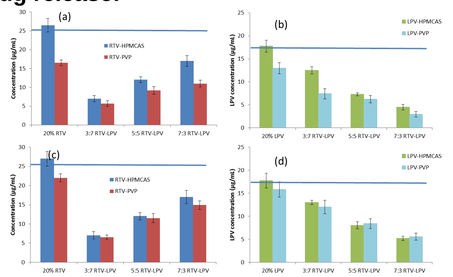
Formation of droplets

When PVP was used as the stabilizer, the filtrate of the dissolution media after the dispersion was dissolved appeared clear. The HPMCAS dispersion resulted in significantly faster dissolution resulting in the formation of nanoparticles which passed through a 0.7µm glass filter and were clearly visible from the scattered light obtained from the NTA. The particle size in the pure drug only dispersion was 500nm while in the presence of both drugs it was around 160nm.



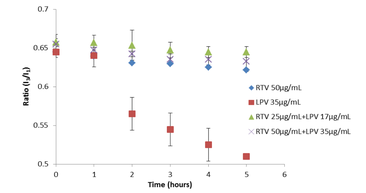
Impact of polymer on drug release:

Maximum concentration of the drugs was achieved within 20 min for HPMCAS and 2 hours for PVP. The final concentration of the drugs was same irrespective of the polymer type. Final concentration depends on the relative amount of drug in the dispersion.



Stability of drug rich phase against crystallization:

The drug-rich phase was prepared by anti-solvent addition. Analysis of the I_3/I_1 ratio of the pyrene emission peak showed that the solution containing the LPV drug-rich phase crystallized between 1-2 hours. When RTV was added to this solution no crystallization occurred indicating that the presence of RTV stabilized the system against crystallization.



Sample	Average RTV (µg/mL)	Average LPV (µg/mL)
50ug/mL RTV-5h	25.4 (0.2)	
35ug/mL LPV-5h		4.3 (0.4)
25ug/mL RTV+17ug/mL LPV-5h	14.2 (0.5)	7.4(0.1)
50ug/mL RTV+ 35ug/mL LPV-5h	15.5 (0.9)	7.0(0.0)
25ug/mL RTV+17ug/mL LPV-0h	15.2(1)	7.4(0.1)
50ug/mL RTV+ 35ug/mL LPV-0h	15.8(0.9)	7.5(0.3)

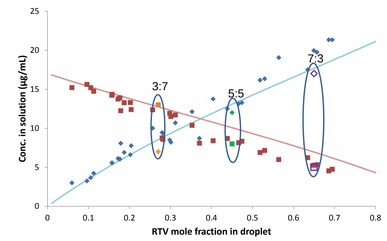
Phase behavior

The concentration of the drugs in solution obtained after complete dissolution of the drugs from the dispersion and films matched those obtained from anti solvent addition of the two drugs.

The final concentration in solution can be calculated from the simple equation given below,

$$C_{max} = S_a \, x_d$$

X_d is the mole fraction of the drug in the dispersion and S_a is the amorphous solubility of the pure drug. This equation is valid provided the two drugs are completely miscible in the solid state and form an ideal mixture.



Conclusions

Administering two amorphous drugs in combination in the same dosage form can result in a lowering of amorphous solubility of each component, and hence the maximum achievable supersaturation. This is due to a decrease in the chemical potential of each drug when they are miscible in the amorphous state as in the case of ritonavir and lopinavir. A decrease in the maximum achievable solution concentration can also occur when two amorphous formulations are administered separately but at the same time. One potential advantage of using combinations of amorphous drugs is that the lowered chemical potential decreases the maximum achievable supersaturation and hence the driving force for crystallization.

Acknowledgments

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