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The impact of drug-loading factors on the solid-state form of ritonavir-mesoporous silica systems

Tanweer Al-Dagamin*, Joseph O'Shea, Abina Crean

SSPC, the SFI Research Centre for Pharmaceuticals, School of Pharmacy, University College Cork, Ireland.

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*Corresponding author.
Tel.: +353 21 4901667
E-mail:
120225049@umail.ucc.ie

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SUMMARY

Among the formulation techniques used to enhance the solubility and dissolution rate of poorly, aqueous-soluble drugs, mesoporous silica drug delivery systems have shown promise. A range of processes are employed to load drugs onto silica and solvent-based approaches are widely employed. This study aims to understand the influence of drug concentration in solvent and drug-silica ratio on drug solid-state form and amorphization within silica. Ritonavir which belongs to BCS Class II was used as a model drug. Ritonavir was loaded into Syloid®244 FP using a solvent evaporation method. Ritonavir loading percentage was calculated based on the assumption that the entire specific surface area of silica is exposed and available for drug adsorption. Ethanol solutions with 3 different ritonavir concentrations; 70%, 32% and 20% saturated solubility at 25°C were employed. Ritonavir was loaded into silica at 1:1, 1:2 and 1:3 ritonavir:silica ratios. All systems included ritonavir loaded beyond monolayer surface coverage. Ritonavir- Syloid®244 FP formulations were characterised using DSC, PXRD, FT-IR, and TGA. The results showed that all ritonavir-Syloid®244 FP systems prepared contained ritonavir in a non-crystalline state.

INTRODUCTION

Following oral administration, drugs with good oral bioavailability can easily reach the systemic circulation and elicit t therapeutic action. However, this can be challenging in the case of drugs that have low aqueous solubility and/or permeability.

Mesoporous silica drug delivery system has shown a promising role in improving the solubility and dissolution rate of poorly water-soluble drugs[1]. There are many factors that influence drug loading and release from mesoporous silica; drug loading techniques, type of silica, drug, and type of solvent (for solvent-based techniques)[2].

In this study, two main factors were investigated: the loading concentration of the drug, relative to drug saturated solubility in the solvent employed, and drug to silica ratio.

MATERIALS AND METHODS

Ritonavir solutions were prepared by dissolving ritonavir in 96% ethanol to achieve 3 solutions with 20% (29 mg/ml), 32% (47 mg/ml) and 70% (101 mg/ml) saturated solubility of ritonavir in ethanol at 25°C. Syloid®244 FP was pre-heated at 120°C overnight to remove physiosorbed water. Ritonavir solution was then added to pre-treated Syloid®244 FP at different ritonavir: Syloid®244 FP ratios; 1:1, 1:2 and 1:3. The ritonavir-Syloid®244 FP systems were placed in an oven at 60°C under vacuum to load drug into Syloid®244 FP pores and evaporate solvent. Ritonavir-Syloid®244 FP physical mixtures were prepared as experimental controls.

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RESULTS AND DISCUSSION

DSC was used to characterise the thermal properties of ritonavir-Syloid®244 FP systems. Figure 1. represents the DSC results of all ritonavir-Syloid®244 FP systems prepared. Complete disappearance of the melting peak was observed for ritonavir loaded Syloid®244 FP formulations at all studied systems. Furthermore, a presence of small endothermic peak was observed at 47°C may be related to either a nanocrystal ritonavir form inside the silica pores or a ritonavir glass transition event.

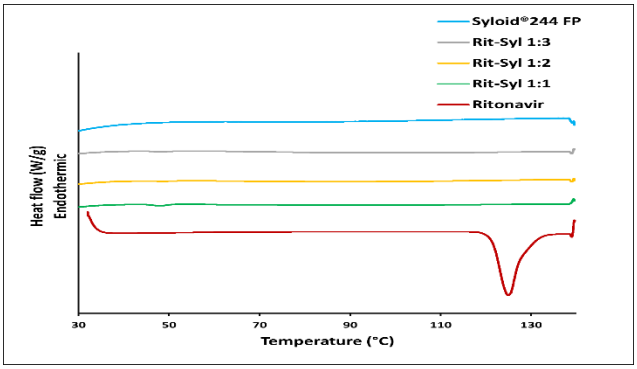

Fig. 1. *DSC results of Ritonavir-Syloid®244 FP using ritonavir solution at 32% saturated solubility at 25°C in ethanol.*

Powder X-ray diffractograms Figure 2. show the loss in the crystal lattice after drug loading.

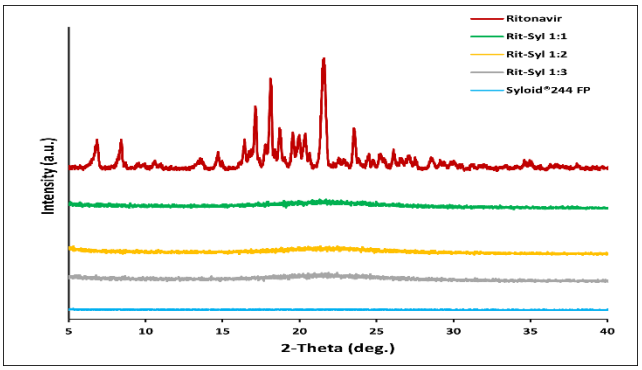

Fig. 2. *PXRD diffractograms of Ritonavir-Syloid®244 FP using ritonavir solution at 32% saturated solubility at 25°C in ethanol.*

Crystalline ritonavir peaks observed for the physical mixtures (data not shown) were completely absent for all ritonavir- loaded Syloid®244 FP formulations.

FT-IR results of Ritonavir-Syloid®244 FP formulations was used to examine any intermolecular interaction between Ritonavir and Syloid®244 FP. Peaks related to the ritonavir crystalline structure were lost for all Ritonavir-Syloid®244 FP formulations, indicating the creation of a non-crystalline ritonavir form. However, distinctive clear drug peaks were observed in case of Ritonavir- Syloid®244 FP physical mixtures (data not shown).

CONCLUSIONS

In all ritonavir-Syloid®244 FP formulations prepared using ritonavir solution at 20%, 30% and 70% saturated solubility contained ritonavir loaded in a non-crystalline state. Future studies will determine the impact of these drug-loading parameters on ritonavir dissolution.

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