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Physicochemical characterisation of spray dried ternary solid dispersions of simvastatin.

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SUMMARY

Simvastatin (SMV) is a poorly soluble drug classified as belonging to Class II of the Biopharmaceutics Classification System. A common approach to improve the apparent solubility of drugs is the production of amorphous solid dispersions (ASD) by means of spray drying (SD) or hot-melt extrusion. Spray drying of low-glass transition temperature (Tg) ASDs is challenging due to the risk of material being exposed to SD outlet temperatures close to its Tg which may result in melting of ASD and subsequent crystallisation of amorphous drug. It was hypothesised that addition of an easily-crystallising material to ASD will improve its SD processability. In addition, it was hypothesised that ternary solid dispersions (TSD) composed of an amorphous composite of drug and the polymer (PVP K17, 55 and 150) and crystalline, soluble nanoparticles (NaCl) will improve dissolution of TSD tablets. The dissolution of SMV from TSDs was faster compared with that of binary solid dispersions in the case of SMV-TSDs produced with PVP K55 and 150. The tabletability assessment showed an improvement in compression leading to an increase in tensile strength and decrease in the porosities of SD tablets.

INTRODUCTION

Transformation of the solid state of a drug from crystalline into the amorphous form is commonly used to improve its apparent solubility. In order to improve the physical stability of amorphous drugs they are mixed with amorphous polymers usually with a higher glass transition temperature (Tg) than that of the drug itself to form amorphous solid dispersions (ASD). Upon contact with dissolution media, water wets the surface of the ASD microparticulates causing simultaneous: surface erosion and/or gelling, dissolution, as well as penetration of water into the microparticulate matrix. ASDs may be prepared by: milling, spray drying (SD), freeze drying or hot melt extrusion (among other methods). Spray drying of relatively low-Tg ASDs is challenging due to the risk of material being exposed to process outlet temperatures close to its Tg, which may result in melting of the ASD and subsequent crystallisation of the amorphous drug.

It was hypothesised that addition of easily-crystallising material to ASD will improve their SD processability. Inclusion of ASDs in tablet formulations may be associated with slower disintegration and dissolution, which subsequently could decrease an apparent solubility enhancement effect. In addition, it was hypothesised that ternary solid dispersions (TSD) composed of an amorphous composite of a drug and a polymer (PVP K17, 55 or 150) and crystalline, soluble nanoparticles (NaCl) could improve the dissolution of a drug from the TSD tablets.

MATERIALS AND METHODS

Simvastatin (SMV) was purchased from Kemprotec, UK. Polyvinyl pyrrolidone PVP K17, K55 and K150,

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ethanol (≥99.8%), acetonitrile, NaCl (≥ 99.5%), magnesium stearate, hydrochloric acid (35%), sodium lauryl sulphate (SLS), monobasic sodium phosphate, sodium hydroxide, trifluoroacetic acid were purchased from Sigma-Aldrich, UK.

All samples were spray dried with a Labultima LU-228 spray dryer (Labultima, India). The spray dryer was set in the open mode. Air was used as the drying and atomizing gas. Applied process conditions were: feed pump flow rate 3 ml/min, aspirator flow rate: 110Nm^3/hr, inlet temperature: 100 ℃, outlet temperature: ranging from 58 to 54.3 °C, total concentration of solids in SD feed was 5% w/v and the solvent system was ethanol: water (7:3 v/v). SD materials were characterised by DSC, TGA, PXRD, SEM, DLS, laser diffraction, HPLC and FTIR. Intrinsic dissolution rates (IDR) of SD materials were analysed as described before (Healy et al., 2002). ASDs were compressed using a rotary tablet press (Mini Press II, Karnavati Engineering, India) using a 12-mm convex-faced punch. Distance between the upper and the lower punches varied from 5, 6 to 7 mm. The tablets produced were characterised for disintegration time, hardness, tensile strength, porosity as well as dissolution studies.

RESULTS AND DISCUSSION

Spray drying of EtOH/water solutions containing NaCl, SMV and PVP rendered ternary solid dispersions composed of SMV/PVP ASDs (DSC, PXRD) and nanocrystalline NaCl (PXRD), drug load 5%w/w and ratio of PVP:NaCl used were 30:70, 50:50, 70:30, and 100:0. Microparticles of all SD materials were round with smooth surfaces (Fig. 1.)

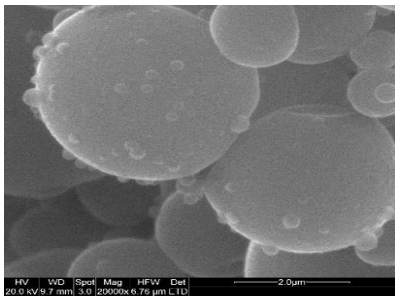

***Fig.1**. Scanning electron micrograph of spray dried ternary amorphous solid dispersion with nanocrystalline NaCl.*

The smallest particle size of NaCl nanocrystals was obtained for samples of SD with the highest tested concentration of polymers (70%) (Fig. 2). IDRs of SMV in spray dried materials were dependant on the content and size of NaCl nanocrystals.

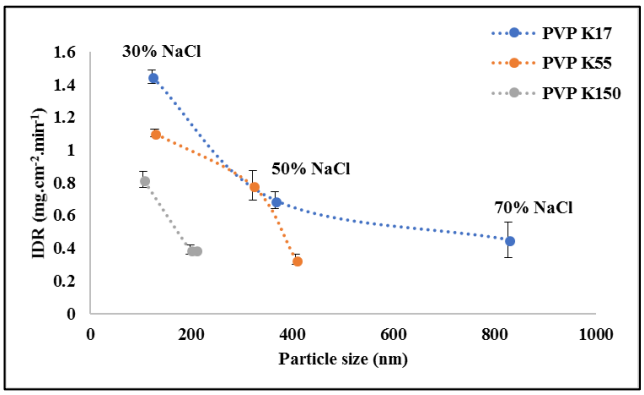

***Fig. 2**. Effect of sodium chloride particle size on IDR.*

Intrinsic dissolution studies indicated a significant ($p<0.05$) increase in dissolution of SMV in ternary SDs when dispersed in PVP K55 (30% and 50% NaCl) and K150 (all NaCl ratios) compared with corresponding binary SDs not containing salt. The tensile strength of compressed tablets varied from 0.2 to 3.2 MPa with porosity varying from 11.9 to 48.1%. The porosity of compressed tablets was dependant on the NaCl crystal size and salt content while tensile strength remained unaffected. SMV was faster dissolving from TSD tablets than from binary SD with PVP K150 (all ratios) and 70% PVP K55.

CONCLUSIONS

Addition of NaCl to amorphous solid dispersions of simvastatin and PVP improved its processability by spray drying, producing ternary solid dispersions containing nanocrystals of salt which, especially in the case of more viscous polymers (PVP K150), facilitated faster dissolution of simvastatin.

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