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Impact of solid state miscibility on quantitative nano-precipitation of budesonide and PVP-VA.

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SUMMARY

Three approaches: calculation of Hansen solubility parameters, analysis of melting point depression and analysis of glass transition temperature (Tg) in comparison to theoretical approach proposed by Gordon-Taylor, were applied to assess miscibility of amorphous phase of budesonide (BUD) with selected polymers (PVP-VA E 735, 635 and 535). Budesonide nanoparticles were prepared by sonocation technique. The combined effect of four significant formulation variables namely, polymer and surfactant concentrations, time and amplitude of sonication on particle size, polydispersity, drug loading and entrapment efficiency of drug was investigated by a 2^4 factorial design. The calculated values of miscibility parameter (χ) based on melting point depression method were negative for each BUD/PVP-VA pair and ranged from: -2.01 to -1.95 mol.g^{-1} indicating good miscibility. The analysis of Tgs for each BUD/ PVP-VA pair in various w/w ratios indicated that experimental Tg values deviated positively from theoretically calculated Tgs based on Gordon-Taylor model indicating intermolecular interactions between drug molecule and polymer. Moreover, differential scanning calorimetry did not indicate any additional Tgs which would suggest amorphous phases separation in any of tested materials. Results indicated, that the content of vinyl acetate (VA) in PVP-VA polymers impacts entrapment efficiency and particle size of the nanoparticles.

INTRODUCTION

Budesonide (BUD) is a poorly soluble drug belonging to class II of the Biopharmaceutics Classification System. Nanosizing and amorphisation are common approaches applied to improve the apparent solubility of drugs. Amorphisation produces a physically unstable form of a drug requiring stabilisation to prevent its crystallisation. Preparation of a solid dispersion of a drug with a suitable polymer at a specific ratio is known to prevent or slow down the kinetics of a drug's crystallisation. The stability of an amorphous drug polymer mix in a composite is challenging to achieve and control during nanoprecipitation.

It was hypothesised that the use of a polymer, with the best miscibility with the amorphous phase of a drug, would result in the highest content of drug in amorphous, composite nanoparticles produced by sonoprecipitation.

MATERIALS AND METHODS

Budesonide (Kemprotec™, UK), Tween 20 (Sigma-Aldrich), polyvinylpyrrolidone (PVP)/vinyl acetate (VA) PVP/VA™ copolymers: E-535 (PVP/VA 535, weight ratio: 50/50), E-635 (PVP/VA 635, weight ratio: 60/40) and E-735 (PVP/VA 735, weight ratio: 70/30) were kindly donated by Ashland, USA). Solvents: acetone, acetonitrile, methanol and ethanol (HPLC grade) were purchased from Fisher Scientific (Loughborough, UK).

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Hansen solubility parameters were calculated to assess drug–polymer miscibility and solid state intermolecular interactions, the melting point (MP) depression of crystalline budesonide dissolved in PVP/VA polymers (535, 635 and 735) was analysed based on the Flory-Huggins approach (Marsac et al., 2006). Tgs of amorphous solid dispersions, as confirmed using pXRD, were measured using DSC. FT-IR studies were applied to investigate possible interactions between the BUD and the PVP and PVP(VA) copolymers. Factorial design was used to assess the impact of the sonoprecipitation process parameters on the BUD/polymer ratio and the particle size of the resulting nanoparticles was measured by dynamic light scattering (DLS).

RESULTS AND DISCUSSION

The smallest difference in total Hansen solubility parameters, indicating the greatest miscibility, was calculated for BUD and PVP/VA 535. All solid dispersions, produced by ball milling, of crystalline BUD (MP: 529.4 K°, ΔH 65.72 J/g) with selected polymers resulted in a depression of its MP ranging from 529.4 to 511.70 K°. Calculated negative miscibility parameter39s (χ) suggested drug/polymer miscibility for each pair. The miscibility of the polymer containing the lowest fraction of VA (PVP VA 735) was the best (X: - 2.012 mol.g^{-1}). All amorphous solid dispersions, produced by quench cooling in DSC, were homogenous as indicated by "single" Tgs for all ratios of drug/polymer blends suggesting miscibility. Positive deviations of measured Tgs from those predicted, by using the Gordon-Taylor (GT) approach to determine theoretical Tg values, indicated the likelihood of the occurrence of propulsive interactions between drug and all polymers, (Marsac et al., 2006). Positive deviations from the GT equation decreased with an increasing vinyl acetate (VA) polymer fraction. FTIR analysis did not indicate strong intermolecular interactions between BUD and polymers. Factorial design indicated that: polymer and surfactant (Tween 20) concentration ranging from 7.5 to 10 mg/ml and 0.2, 0.35 v/v% respectively as well as amplitude and time of sonication varying respectively from 75 to 100% and from 1 to 5 mins have a statistically significant ($p<0.05$) impact on the particle size and polymer content. Nanoparticles varied in size from 641 nm to 357 nm (Table 1) depending on the polymer used and surfactant concentration (Fig. 1). Drug loading ranged from 99% to 97% for the three polymers.

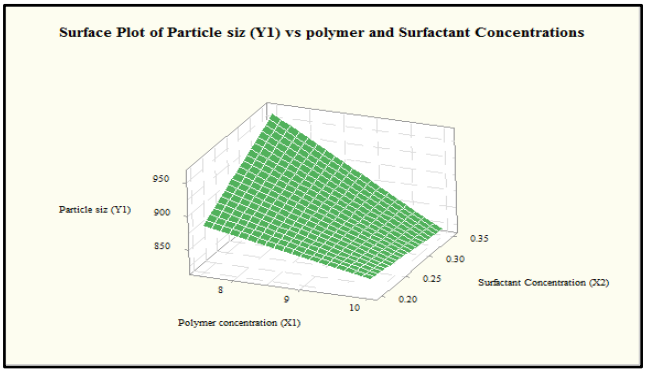

Fig. 1. *Surface plot of particle size vs. polymer and surfactant concentrations for BUD with PVP/VA E735.*

Table 1. *Influence of PVP/VA copolymer composition on nanoparticles production.*

Polymers	Particle size	PDI	Drug loading (%)	Entrapment efficiency %
PVP/VA E735	641.03 ± 5.9	0.2 ± 0.004	99.02 ±0.16	81.2±0.5
PVP/VA E635	560.4± 11	0.2 ± 0.04	98.8±0.2	80.72±0.05
PVP/VA E535	357.3 ± 18.5	0.5 ± 0.00	97.4±0.2	77.13±0.46

CONCLUSIONS

Calculation of Hansen solubility parameters, analysis of melting point depression, and measurement of glass transition temperatures confirmed the miscibility of BUD with all polymers. The influence of PVP and PVP/VA copolymer composition on budesonide was investigated. It has been confirmed that there is an apparent correlation between the VA content and particle size and entrapment efficiency of BUD and PVP/VA E 735, 635 and 535.

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