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Research paper

Theoretical and experimental investigation of drug-polymer interaction and miscibility and its impact on drug supersaturation in aqueous medium

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ABSTRACT

Amorphous solid dispersions (ASDs) have the potential to offer higher apparent solubility and bioavailability of BCS class II drugs. Knowledge of the solid state drug-polymer solubility/miscibility and their mutual interaction are fundamental requirements for the effective design and development of such systems. To this end, we have carried out a comprehensive investigation of various ASD systems of dipyridamole and cinnarizine in polyvinylpyrrolidone (PVP) and polyacrylic acid (PAA) at different drug loadings. Theoretical and experimental examinations (by implementing binary and ternary Flory-Huggins (F-H) theory) related to drug-polymer interaction/miscibility including solubility parameter approach, melting point depression method, phase diagram, drug-polymer interaction in the presence of moisture and the effect of drug loading on interaction parameter were performed. The information obtained from this study was used to predict the stability of ASDs at different drug loadings and under different thermal and moisture conditions. Thermal and moisture sorption analysis not only provided the composition-dependent interaction parameter but also predicted the composition dependent miscibility. DPM-PVP, DPM-PAA and CNZ-PAA systems have shown molecular level mixing over the complete range of drug loading. For CNZ-PVP, the presence of a single T_g at lower drug loadings (10, 20 and 35% w/w) indicates the formation of solid solution. However, drug recrystallization was observed for samples with higher drug weight fractions (50 and 65% w/w). Finally, the role of polymer in maintaining drug supersaturation has also been explored. It has been found that drug-polymer combinations capable of hydrogen-bonding in the solution state (DPM-PVP, DPM-PAA and CNZ-PAA) are more effective in preventing drug crystallization compared to the drug-polymer systems without such interaction (CNZ-PVP). The DPM-PAA system outperformed all other ASDs in various stability conditions (dry-state, in the presence of moisture and in solution state), which was attributed to the drug's low crystallization tendency, the strong DPM-PAA interaction, the robustness of this interaction against moisture or water and the ability of PAA in maintaining DPM supersaturation.

1. Introduction

Active pharmaceutical ingredients (APIs) may exist either in a crystalline form or in the amorphous state [1]. The former consists of an orderly arrangement of molecules whereas the latter lacks molecular periodicity. The random molecular arrangement gives the amorphous APIs a higher free energy compared to their crystalline counterparts which contributes to their higher apparent aqueous solubility [2]. However, the higher free energy also makes the amorphous systems inherently unstable which may lead to crystallization during storage and/or upon exposure to humidity or in aqueous solution. We have shown in previous research paper the amorphous form of the drug may be unstable and have a tendency to revert back to its crystalline form. Furthermore, we have also shown the effect of drug crystallization on the stability of ASD based products [3]. The devitrification of amorphous drugs may lead to subsequent decline in dissolution due to crystallization. Such limitations often necessitate the incorporation of polymeric excipients as a stabilizer for the amorphous API producing solid dispersions [4].

The solubility and miscibility of a drug within a polymeric carrier system has a significant effect on the stability of the amorphous solid dispersion (ASD) formulation [4]. Several factors are involved in stabilizing an amorphous drug within a polymeric carrier such as a reduction in chemical potential and molecular mobility, an increase in the activation energy for crystallization,

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an increase in T_g, strong drug-polymer interactions or a combination of these factors [5]. To achieve the maximum crystallization inhibition, regardless of the specific mechanism, intimate mixing of the drug in the polymeric matrix at the molecular level is highly desirable; poor mixing may lead to drug crystallization as observed with sucrose-PVP or indomethacin-PVP physical mixtures [6,7]. A better understanding of the phase behaviour of ASD systems helps to avoid supersaturation driven phase separation or crystallization of the API at drug-loadings beyond the solubility/miscibility limit of a specific polymer [1,3,8,9]. Therefore, it is of interest to assess drug-polymer miscibility and their mutual interaction in order to rationally select the optimal formulation for the desired storage conditions and dissolution performance.

In view of these challenges, this study aimed to investigate the strength of drug-polymer interaction and solubility/miscibility of two poorly water soluble APIs, dipyridamole (DPM) and cinnarizine (CNZ), in two different polymeric carriers, polyvinylpyrrolidone (PVP) and polyacrylic acid (PAA), using a multi-methodological approach. Flory-Huggins (F-H) binary interaction theory has been used to estimate drug-polymer interactions and assessed for its usefulness in the successful development of ASD-based formulations of DPM and CNZ. We have also calculated ternary F-H interaction parameters (drug-polymer-water) using dynamic vapour sorption (DVS) analysis to understand the effect of moisture on amorphous DPM and CNZ within PVP and PAA solid dispersions. Finally, the ability of different types of polymers to prolong drug supersaturation in aqueous media has also been assessed by using the *supersaturation parameter*. The main objective of this study was to investigate the usefulness of F-H theory as a preformulation tool for evaluating different polymers in order to gain an insight into the drug-polymer interaction and miscibility. Another important aspect of this work is to correlate this information with the maintenance of *in-vitro* drug supersaturation. Subsequently, this methodology can be used as a road map to guide the selection of an appropriate drug loading for the chosen polymer and to optimize the processing conditions to maintain long term stability and prediction of *in-vitro* dissolution performance of the ASD products [10].

2. Materials and methods

2.1. Materials

Dipyridamole (DPM), cinnarizine (CNZ), polyvinyl pyrrolidone (PVP) K30 and polyacrylic acid (PAA) were purchased from Sigma Aldrich, Ireland. The chemical structure of model drugs and polymers is shown in Fig. 1. All reagents were of analytical grade and used without further purification.

2.2. Preparation of physical mixtures

Physical mixtures were prepared by manually mixing (using mortar and pestle) model drugs and polymers at 100%, 95%, 90%, 85% and 80% (w/w) drug concentrations. Sample preparation was carried out in triplicate at each concentration. During preparation of the physical mixture, the amorphous to crystalline drug ratio may have changed. It must be noted that grinding may increase the amorphous content of the drug which may reduce its chemical potential [11]. Thus, care was taken to attain optimum mixing with minimum amorphization of drugs. Similarly, interaction between drug and polymer may also reduce the chemical potential and decreases the melting point of the drug in the mixture.

2.3. Preparation of solid dispersions

Amorphous solid dispersions (at 10, 20, 35, 50 and 65% w/w drug loading) were prepared in two steps. First, the drug and polymer were dissolved in a common solvent (methanol) and the solvent was removed using rotary evaporation under reduced pressure. The mixture was then dried in a vacuum oven for 24 h at 40 °C. However, there are two main challenges of using this method. The first challenge is to mix the drug and the polymer in one solution which can be difficult if they have significant polarity differences. This was not found to be a problem with the drug, polymer and solvent used in this work. The second challenge is the phase separation which may occur during removal of the solvent [5]. To overcome this, the dried mixture was ground in mortar and pestle, heated to the melting temperature of the drug, held isothermally for 5 min, and then cooled −60 °C in a DSC pan. This additional step was performed to ensure complete mixing of drug and polymer at a molecular level. It is important to mention here that different preparative techniques may generate solid dispersions with different physico-chemical properties for the same drug-polymer combination [4,12,13]. However, the effect of manufacturing techniques on amorphous solid dispersion properties is beyond the scope of this work.

2.4. Differential scanning calorimetry

Thermal analysis was performed using a TA Instruments Q2000 differential scanning calorimeter equipped with an electrical

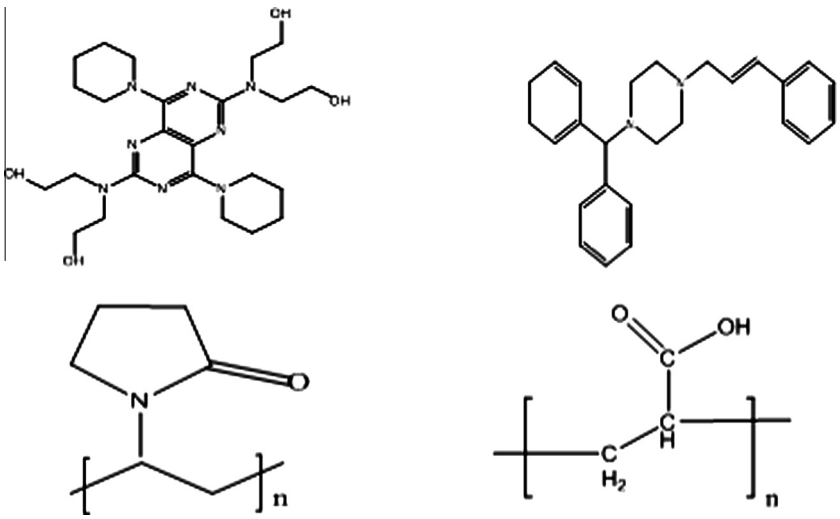

Fig. 1. Chemical structure of DPM, CNZ, PAA and PVP K30 (clockwise from top).