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Optimization of Drug-Polymer Mixing Ratio in Albendazole-Polyvinylpyrrolidone Solid Dispersion by Moisture Absorption Studies

R. Kalaiselvan[1*], G.P. Mohanta[2], K. Kannan[2], P.K. Manna[2] and R. Manavalan[2]

[1]Novel Drug Delivery Department, Ranbaxy Research Labs, R&D-I, Sector-18, Gurgaon, Haryana, India.
[2]Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamil Nadu-608 002, India.

Abstract

The main aim of the study was to investigate the moisture absorption behavior and the molecular mobility of albendazole-polyvinylpyrrolidone solid dispersions. Moisture gain magnitude of the dispersions was found to be significantly less compared to the amorphous physical mixture upon equilibration with 75% RH. Such decrease in moisture absorption magnitude was found to be high at 35-50% polymer content. The extent of plasticization of absorbed water was observed to be minimum at 50% polymer content. Therefore, the drug-polymer weight ratio was optimized to be 1:1 for obtaining the physically stable dispersion. Morphology of the solid dispersion of 1:1 drug-polymer mixing ratio was investigated using scanning electron microscopy. The tablets (equivalent to 400 mg of albendazole) formulated using this solid dispersion complied with the pharmacopoeial dissolution requirement.

Key words: Albendazole, solid dispersion, moisture absorption, plasticization, crystallization

*Corresponding author: e-mail: kalaipharmacy@yahoo.com

Introduction

The solubility and dissolution related bioavailability of poorly water-soluble pharmaceuticals could be improved by preparing amorphous solids. However, crystal growth or conversion from amorphous (metastable) to the crystalline state during storage inevitably results in decreased dissolution rate (Mooter *et al.*, 1999). Polyvinylpyrrolidone (PVP) has been found to have incredible inhibitory effects on the crystallization of amorphous system due to its antiplasticizing effect in which the glass transition temperature (T_g) of the system is increased and hence the mobility of drug molecules is reduced (Sekikawa *et al.*, 1978; Ziller and Ruprecht, 1988; Ma *et al.*, 1996). However, antiplasticization effect of PVP is reduced due to its hygroscopic nature upon exposure of solid dispersion to humid environments (Taylor and Zografi, 1997; Matsumoto and Zografi, 1999; Shamblin and Zografi, 1999).

In the present study, the moisture absorption behavior of albendazole (ABZ)-PVP solid dispersions (SDs) and the plasticizing effect of absorbed water in the SDs were investigated. Effects of Tg on the isothermal and nonisothermal crystallization of ABZ-PVP SDs have been reported recently (Kalaiselvan *et al.*, 2006).

Materials and Methods

ABZ (Juggat Pharma, Bangalore, India) and PVP K-17 (BASF India Ltd., Chennai, India) were gift samples. Commercial albendazole tablets CT-1 (Zentel tablets, Glaxo SmithKline, Mumbai, India) and CT-2 (Cidazole tablets, Juggat Pharma, Bangalore, India) equivalent to 400 mg of ABZ were purchased from a local pharmacy store. All other materials used were of either pharmaceutical or analytical grade.

Preparation of amorphous albendazole: Amorphous ABZ was obtained as reported previously (Kalaiselvan *et al.*, 2006). Crystalline ABZ (5 g) contained in a stainless-steel beaker was heated in an oven under a stream of nitrogen gas and held at 210°C for 5 min. It was then cooled by immersion into liquid nitrogen. The quench-cooled drug was removed from the beaker and ground gently with a mortar and pestle,

passed through 60 mesh sieve and stored at 0°C over phosphorous pentoxide prior to use in experiments.

Preparation of amorphous solid dispersions and physical mixtures: Solid dispersions were prepared by solvent casting method as reported previously (Kalaiselvan *et al.*, 2006). Drug-polymer mixtures (5-100 % w/w of polymer) were dissolved in methanol and cast on Teflon sheets. The solvent was allowed to evaporate in a partially open desiccator at room temperature for 3 days. The samples were then placed under vacuum for 2 days and the resulting films were gently ground into powder form with a mortar and pestle for 1 min. The powder obtained was dried under vacuum at room temperature for 24 h and at 40°C for 12 h. The samples were passed through a 60 mesh sieve and stored at 0°C over phosphorous pentoxide prior to use until used. The drug content of solid dispersions was determined spectrophotometrically (UV-1601PC, Shimadzu, Japan) by dissolving the sample in methanol followed by sufficient dilution with hydrochloric acid medium (pH 2) to measure the absorbance at 291 nm.

X-ray diffraction analysis: Powder X-ray diffraction patterns were determined with an X-ray diffractometer (X'Pert MPD, Philips Electronics, Netherlands), employing CuK_α radiation source operating at 30 mA and 40 kV. Samples were scanned from 3 to 40° 2θ range at a scanning rate of 0.02°2θ s^{-1}.

Differential scanning calorimetry: Tg of the dry and moist samples was determined by differential scanning calorimetric (DSC) method (DSC 60 Shimadzu, Japan). Samples in hermetically sealed aluminum pans were scanned at a heating rate of 20°C min^{-1} under a dry nitrogen gas purge of 40 ml min^{-1}. TA 60 WS (version 1.4) software (Shimadzu, Kyoto, Japan) was used to detect and analyse thermogram events.

Moisture absorption studies: Water vapor absorption isotherm was measured gravimetrically after equilibration with 75% relative humidity (RH). Prior to the study, all samples were dried for 3h at 20-30°C below the dry sample T_g or 60°C, whichever was lower. They (0.2 to 2 g) were stored at 25°C above a saturated

solution of sodium chloride in a desiccator to provide a RH of 75%. Following 72 h of storage, constant sample weights and DSC study results revealed that an equilibrium water content had been reached without crystallization. Experiments were carried out in triplicate.

Scanning electron microscopy: The morphology of the pure drug, drug-polymer physical mixture (1:1 ratio) and the corresponding solid dispersion was studied using a scanning electron microscope (JSM-5610 LV Jeol, Japan). Samples were coated with platinum to provide a conductive layer for observing images at 15 kV and 800 times magnification.

Tabletting of solid dispersion and pharmacopoeial evaluation: ABZ-PVP (1:1) dispersion was formulated into tablet dosage form containing ABZ (400 mg), PVP (400 mg), microcrystalline cellulose (250 mg), lactose (250 mg) and magnesium stearate (15 mg). Solid dispersion and all other ingredients were mixed in a closed plastic container. The blend was then compressed on a mini rotary press (RSB4-1 GMP, Karnavati Eng. Ltd., Ahmedabad, India) with 19.5×10 mm capsule shaped punches to produce tablets of 6.8±0.15 mm thickness and 8-9 kg/cm^2 hardness for a tablet weight of 1300±30 mg. Friability of the tablets was tested using a Roche friabilator.

Both formulated and commercial tablets were tested for weight variation, drug content, and dissolution according to U.S. Pharmacopoeia XXIV. The dissolution method for ABZ tablet includes use of apparatus 2 at 50 rpm and 900 ml of 0.1N HCl as dissolution medium. Twelve replicates were used. Samples were filtered through a membrane filter (0.45 μm) and assayed spectrophotometrically at 291 nm.

Results and Discussion

Physical mixture and the solid dispersions were found to be X-ray amorphous (Fig. 1). The profiles of equilibrium moisture gain for the amorphous physical mixture (amorphous drug and polymer) and amorphous solid dispersions are shown in Fig.

2A. Pure amorphous drug and PVP showed 2.8% and 30.2% weight increase respectively.

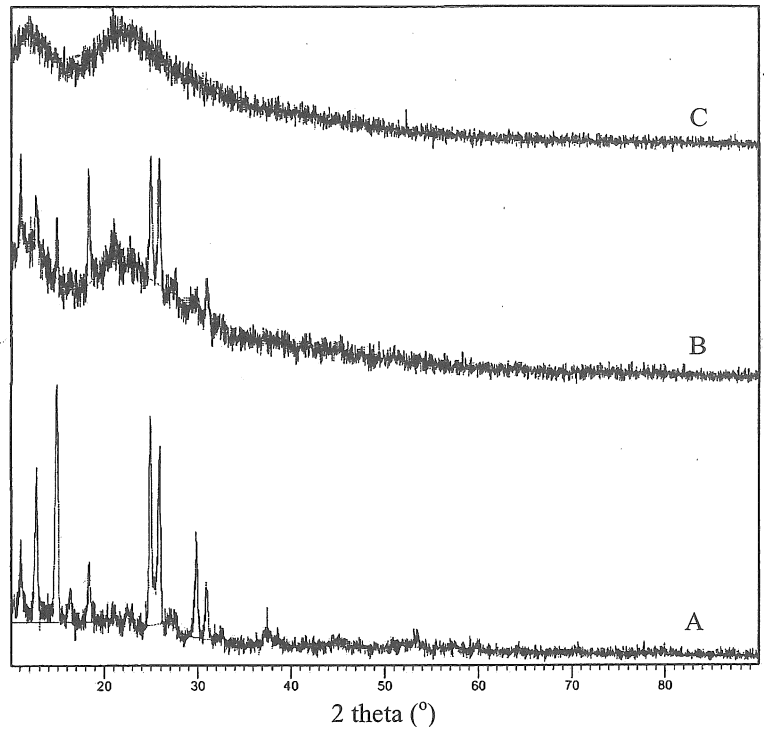

Fig. 1. Typical XRD pattern of ABZ-PVP system. Pure drug (A), physical mixture with 25% polymer (B) and the corresponding solid dispersion (C).

The magnitude of moisture gain into pure polymer was in agreement with the previously published work (Miyazaki *et al.* 2004). Moisture sorption of amorphous physical mixtures rose greatly with increase in polymer content. However, the moisture gain magnitude of the solid dispersions was significantly less than to the amorphous physical mixtures ($p<0.05$). The reduced moisture absorption in ABZ SDs might be due to drug-polymer interaction disfavoring drug / polymer-water interaction (Kalaiselvan *et al.*, 2006). The reduction in moisture absorption level in dispersions compared to the physical mixtures has also been reported for sugar-protein and indomethacin-PVP systems (Costantino *et al.*, 1998; Crowley and Zografi, 2002).

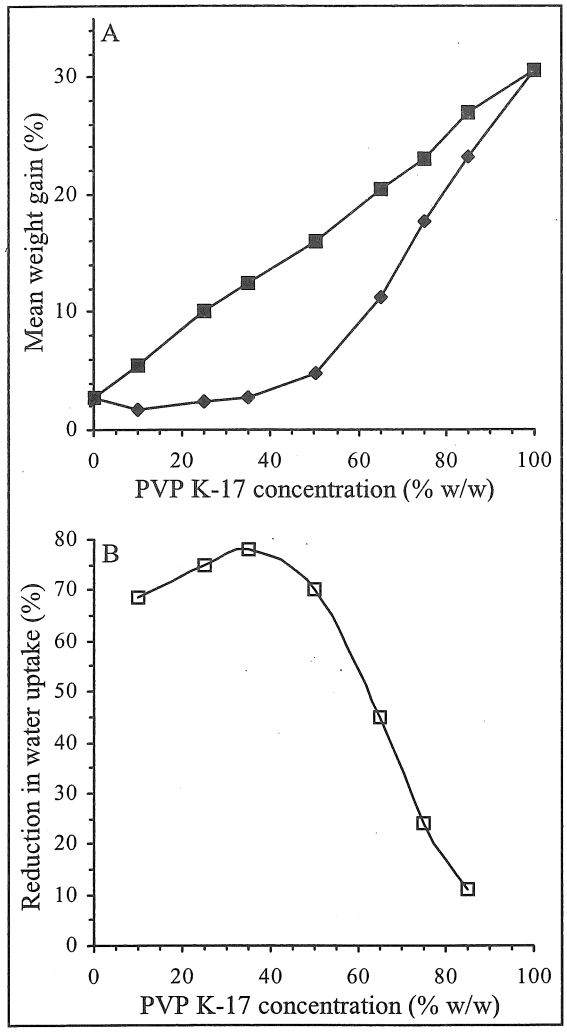

Fig. 2. Moisture gain behavior of solid dispersion. (A) Comparison with amorphous physical mixture [amorphous physical mixture (■), solid dispersion (◆)]. (B) Negative deviation in water gain of solid dispersion compared to the amorphous physical mixture.

Plot of the percent reduction in water content versus PVP concentration indicates that maximum deviation occurred at 35% polymer concentration hypothesizing 1:1 stoichiometry of the drug-PVP monomer interaction (Fig. 2B). As the molecular weights of drug and PVP monomer are 265 and 111 respectively, the weight percent of polymer required for the interaction with the drug is 30%, which is closer to the optimum polymer level for the least moisture sorption. Increasing the polymer content beyond this level would therefore destabilize the amorphous system at 75% RH due to the fact that the free pyrrolidone carbonyl is capable of forming hydrogen

bond with water (Crowley and Zografi 2002). As shown in Fig. 2A, the magnitude of water vapor sorption of solid dispersions did not change appreciably in the concentration range of 10-35% w/w PVP, but underwent large increases as the PVP content increased from 50 to 85%.

The plasticizing effect of absorbed water on the solid dispersions and pure amorphous drug was studied by DSC analysis. The results are presented in Fig. 3. The moist dispersions with 35 and 50% polymer had the highest T_g (81-85°C), assuring more stability at ambient storage condition (Fig. 3A). Previous solid dispersion literatures show that crystallization rate constant of dry solid dispersion was greatly reduced by increasing the T_g of the system (69.1°C) (Kalaiselvan *et al.* 2006). A second order polynomial curve was obtained by plotting the ratio of T_g change to the weight change (dT_g/dw) versus polymer concentration ($r = 0.9822$; $Y = 0.0037X^2 - 0.3771X + 12.3$). The plasticizing effect of water was weaker in the moist dispersion with 50% PVP content as indicated by the least dT_g/dw, assuming better physical stability at this composition (Fig. 3B). The pronounced destabilizing action of water below and above this polymer concentration might be due to hydration of free drug and free PVP monomer respectively.

The morphology of ABZ-PVP system was investigated using a scanning electron microscope. ABZ-PVP (1:1) physical mixture showed drug crystals densely dispersed on the surface of every polymer particle. However, the crystals were not distinguishable on the surface of solid dispersions indicating a homogeneity (Fig. 4).

ABZ-PVP (1:1) dispersion was selected for tablet formulation because of its highest T_g value even after equilibration with 75% RH. All tablets (formulated as well as commercial) equivalent to 400 mg of ABZ were found to contain 98-101 % of the label claim. The percentage weight loss of the tablets in the friability test was <1%. Weight variation, drug content and content uniformity test results met the USP 2000 specifications. A novel wet-granulation method for the manufacture of mebendazole tablets exhibiting scale-independent dissolution was previously reported (Kalaiselvan *et al.*, 2004). In the present study, ABZ tablets were obtained by direct compression

method. This is to avoid granulating fluid decreasing the T_g of solid dispersion and consequent crystallization during drying.

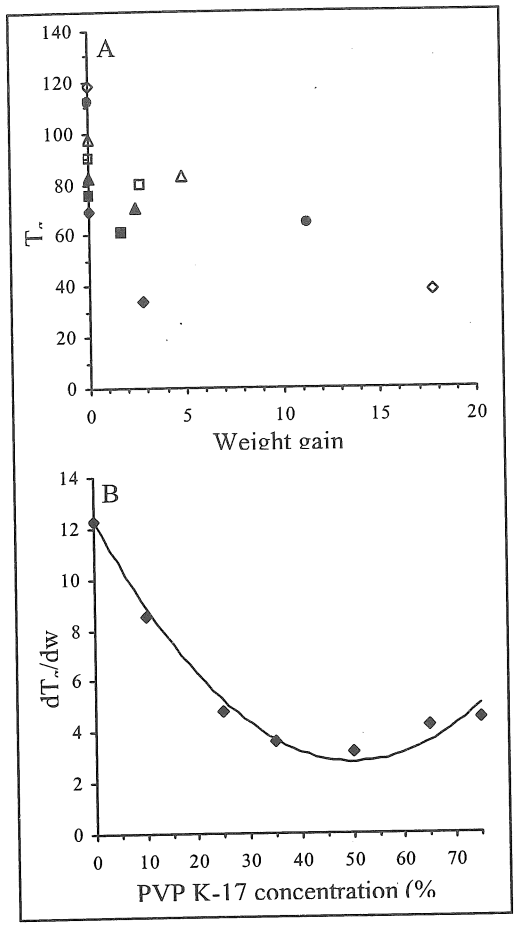

Fig. 3. Effect of absorbed moisture on the mobility of solid dispersion. (A) T_g of moist samples with polymer contents 0% (◆), 10% (■), 25% (▲), 35% (□), 50 (Δ), 65% (•) and 75% (□). (B) Ratio of T_g change to weight change (dT_g/dw) influenced by the polymer content.

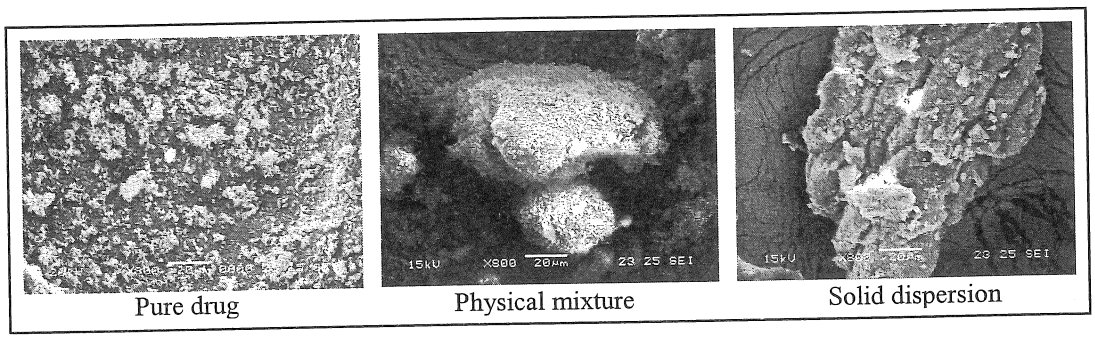

Fig. 4. Scanning electron micrograph of ABZ-PVP (1:1) system.

Fig. 5 shows the dissolution profile of the formulated tablet (FT) containing ABZ-PVP K17 (1:1) system in comparison with two commercial products (CT-1 and CT-2) in 0.1N HCl. The FT released 85-89 % of ABZ in 30 min, whereas the commercial tablets released only <35%. The FT complied with the dissolution test for ABZ tablets specified in USP XXIV (Q is not less than 80% in 30 min). Few commercial tablets with only 200 mg of ABZ have been so far reported to meet the test requirement (Hurtado de la Pena *et al.*, 2003).

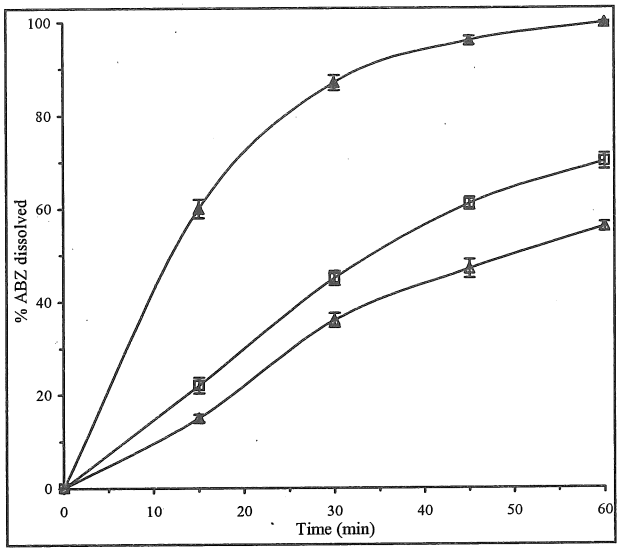

Fig. 5. Dissolution profiles of tablets containing ABZ-PVP (1:1) system (▲) in comparison with commercial tablets CT-1 (□) and CT-2 (Δ) in 0.1N HCl.

Conclusion

In the present study, the optimum drug-polymer ratio for ABZ-PVP SD equilibrated to 75% RH was found to be 1:1. The maximum moist Tg (85.4°C) was achieved at this mixing ratio indicating better physical stability of the system even after exposure to a higher humidity condition (75% RH). The tablets equivalent to 400 mg of ABZ formulated using this dispersion complied with the dissolution test requirements of albendazole tablets in the USP. Further studies such as bioavailability study and clinical evaluation against systemic helmintheases (eg. echinococcosis, trichenellosis) are to be carried out.

Acknowledgement

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