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Original Research Paper

Role of excipients in the crystallization of Albendazole

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ABSTRACT

Cocrystallization of drugs in presence of excipients can become an effective tool to improve physicochemical and mechanical properties of drugs which may ultimately affect its bioavailability and manufacturability. Aim of present investigation was to understand the influence Benzoic acid (BA) on recrystallization behavior of Albendazole (ABZ) using slow (conventional) evaporation technique. Benzoic acid treated crystals showed a unique melting behavior, improved solubility (12.53 folds) and dissolution rate (8.6 folds) with higher drug content (72.17%). Control batch crystals showed a possibility of a new crystalline form with much improved properties. SEM photographs revealed bigger and plate-shaped BA treated crystals with aspect ratio near to unity which improved flow and packability of crystals. Heckel parameters suggested greater plastic deformation and high tensile strength with negligible elastic recovery compared with pure drug. FT-IR studies assumed a formation of hydrogen bond between drug and excipient. Treated crystals were stable even after six months of accelerated stability study. Use of directly compressible excipients could be minimized in the tablet formulation in case of treated crystals. Pharmacokinetic study showed improved (3.42 times) in vivo performance in rats. In this study, improvement in physicomechanical and pharmacokinetic parameters of Albendazole by its cocrystallization could be highlighted.

1. Introduction

Pharmaceutical solids can exist in many crystalline forms. These crystalline solids have direct impact on the bioavailability due to their unique physicochemical properties. Hardly 1% of active pharmaceutical ingredients (APIs) are getting entry into the marketplace due to their poor biopharmaceutical properties [1]. Improvement in solubility and dissolution are the most challenging tasks for any pharmaceutical industries [2]. Various techniques have been applied for improving aqueous solubility and dissolution of drugs. These includes micronization, salt formation, emulsification [3], cosolvency, complexation with β-cyclodextrin [4], jet milling, high-pressure homogenization, co-precipitation, cocrystallization [5] and use of polymer-drug vehicles for delivery of poorly water soluble drugs [6]. Though various techniques have been reported so far to improve oral bioavailability, success is again dependent on the specific physicochemical properties of molecules under study [2]. Apart from poor aqueous solubility and dissolution, majority of APIs have poor flow property, packability and compressibility [7]. Tableting of such APIs need high quantity of directly compressible excipients [8]. It may increase the final weight of tablet [9]. The only choice for those kinds of APIs is a tedious, laborious, time-consuming and uneconomic wet granulation process [10]. Direct compression is a more possible alternative for manufacturing of tablets in the pharmaceutical industry [11].

Direct compression, despite being a simple technique, is influenced by powder characteristics such as particle shape, size, flowability, compressibility, packability, compatibility, plastic behavior and dilution potential.

Improvement of either physicochemical or mechanical properties alone cannot generate a robust product. In nut-shell, a technique which can simultaneously improve both the properties can become of a great interest to pharmaceutical industry.

Recrystallization of poor functionality API in presence of polymers and excipients have been reported improving both the properties. Polymers and excipients (excipients as whole) may

Abbreviations: ABZ, Albendazole; BA, Benzoic acid; DSC, differential scanning calorimetry; HPLC, high performance liquid chromatography; ICH, international conference on harmonization; pXRD, powder X-ray diffraction; rpm, revolution per minute; FT-IR, Fourier transform infrared spectroscopy; ppm, parts per million.

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adsorb or form a net like structure over the growing faces. They may also interact with the faces having more number of hydrogen bond forming groups to inhibit the growth of that particular faces [12]. Barot et al. and Raval et al. improved properties of poorly compressible Metformin HCl by its recrystallization in presence of PVP K-30 and lactose anhydrous, respectively [13,14]. Maghsoodi et al. improved mechanical properties of naproxen as agglomerated forms [15]. Nokhodchi et al. studied influence of PEG 4000, PVP K30 and Tween 80 on recrystallization behavior of carbamazepine [16]. Various other APIs like Hydrocortisone acetate [12], paracetamol [17,18] Nifedipine [19] have also been studied for their physicochemical property improvement. Few works have also been conducted to study influence of excipients on simultaneous improvement of both physicochemical and mechanical properties with its influence on bioavailability of API in suitable animal model.

Albendazole (ABZ), a member of the benzimidazole family of compounds and is a broad spectrum anthelmintic drug (Fig. 1). Based on powder rheology, it is classified as a powder with poor flow property and compressibility [20–22]. Besides, Albendazole has low aqueous solubility (log *P* is 13.94) and high permeability (BCS Class II), which limits its oral absorption [23–25]. Molecular weight of ABZ is 265.33 gm/mol and is weakly basic in nature. Hence, solubility of drug is higher at lower pH rather than at neutral pH. Moreover, the drug has two p*K*a values of 2.68 and 11.83, respectively. At acidic pH 1.2, the solubility of ABZ is reported 900 μg/ml, whereas at pH above 5, solubility reported was even less than 1 μg/ml. Due to this, ABZ cannot be absorbed completely if not solubilized in the GI tract. Hence, USP has mentioned phosphate buffer pH 1.2 as an official dissolution profile for ABZ tablets [26,27].

Present work shows recrystallization of Albendazole (ABZ) in presence of excipient to improve its physicochemical, mechanical as well as pharmacokinetic properties which were major key issues in processing and developing its solid oral dosage form. Various excipients tried for cocrystallization were Cinnamic acid, Benzoic acid, L-Malic acid, Maleic acid, Lauric acid and Myristic acid. Solid-state investigation of prepared crystalline samples is performed to check for generation of new crystal phase of ABZ during cocrystallization. Selection of carboxylic acid moieties as crystallizing excipient is done because of its amenability to form hydrogen bond with API.

2. Materials and methods

2.1. Materials

Albendazole IP (ABZ) was gifted by Nectar Pharmaceutical Pvt. Ltd., Mumbai, India. Benzoic acid (BA), Polyvinylpyrrolidone K30 (PVP K30), Maleic acid, L-Malic acid, Cinnamic acid, Lauric acid and Myristic acid were purchased from Sisco Research Lab., Mumbai, India. Sodium Hydroxide (NaOH) was procured from Rankem, New Delhi, India. Ammonium acetate HPLC grade was procured from Merck Pvt. Ltd., Mumbai, India. Magnesium stearate and microcrystalline cellulose PH 101 grade (MCC) were purchased from Molychem, Mumbai, India. Crospovidone was procured from Chemdyes, Ahmedabad, India. D-Mannitol was procured from Loba chemie, Mumbai, India. Talc was procured from Suvidhinath Lab., Baroda, India. All other solvents and chemicals used were of analytical and HPLC grade (Merck Pvt. Ltd., Mumbai, India).

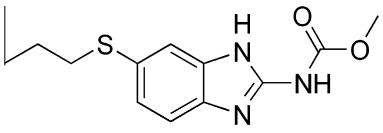

Fig. 1. Chemical structure of Albendazole.

2.2. Recrystallization of ABZ by solvent evaporation

Albendazole was recrystallized from acidified methanol (ratio of methanol to HCl is 99:1 ml) in presence of Benzoic acid at room temperature. Various molar ratios of drug (2.65 g ≅ 0.01 mol) and BA (1.22 g ≅ 0.01 mol) (1:1, 1:2, 1:3, 2:1, 2:3, 3:1 and 3:2) were prepared by dissolving both in acidified methanol. Stirring was continued even during evaporation [4]. True crystals were separated by filtration before complete evaporation of the solution to get product free from any impurity and dried at room temperature for removal of the surface moisture. The end point of collection (filtration) of crystals was determined when the least quantity of solvent remained which allowed the crystals floating. Solvent residue was further removed by vacuum oven (Nova Instruments, Ahmedabad) at 30 °C for 48 h. The obtained crystals (treated crystals) were gently triturated in a mortar with pestle and passed through a sieve 60 ASTM before characterization. A batch of control crystals was also formulated using same conditions in absence of any excipient. A batch of BA treated crystals was also kept for stability study in stability chamber (Remi Laboratory Instruments, Mumbai, India).

2.3. Saturation solubility study

Saturation solubility study was performed in distilled water, acidic buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. Excess quantity of pure ABZ, crystals from control batch and BA treated crystals were added separately into specific gravity bottles containing 10 mL solvent. Bottles were placed in a cryostatic constant temperature reciprocating shaker bath (Tempo Instruments and Equipments Pvt. Ltd., Mumbai, India) at temperature 37 ± 1 °C with constant shaking at 120 RPM for 48 h to allow saturation. Solutions were centrifuged (Remi Laboratory Instruments, Mumbai, India) and supernatant was filtered through Whatman filter paper No. 41. Filtrate was analyzed spectrophotometrically (UV-1800, Shimadzu, Japan) at 308 nm.

2.4. Percentage yield and drug loading efficiency

Percentage yield of treated crystals was calculated as given in Eq. (1). Drug loading efficiency (Eq. (2)) of treated crystals was determined by dissolving specified quantity of crystals in acidified methanol, diluted the content with 0.1 N HCl (pH 1.2) and mixed well. Resulting solution was filtered through Whatman filter paper No. 41 and filtrate was analyzed spectrophotometrically at 308 nm (USP XXX).

$$\%\ Yield = \frac{total\ weight\ of\ crystals}{Total\ weight\ of\ drug\ and\ excipient} \times 100 \quad (1)$$

$$\%\ Drug\ loading\ efficiency = \frac{Drug\ entrapped\ as\ crystals}{Theoretical\ drug\ content} \times 100 \quad (2)$$

2.5. Melting point determination

The melting point of pure drug, control batch and treated crystals was determined by closed capillary method using a digital melting point apparatus (Veego®, Model: VMP-DS) [28].