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Improved Physicochemical Characteristics of Amorphous Drug Solid Dispersions

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ABSTRACT

In order to improve the solubility, stability and the dissolution rate of carbamazepine, amorphous carbamazepine, solid dispersion (SD) of carbamazepine with Polyacrylic acid (PAA) and co-precipitate with PAA and hydroxypropylmethyl cellulose (HPMC) in different ratios were prepared by the spray drying technique. Saturation solubility and dissolution studies were performed to differentiate performance after processing. Differential scanning calorimetry revealed the amorphous form of carbamazepine. The dissolution profile of the solid dispersion and co-precipitate improved compared to carbamazepine and amorphous carbamazepine. Amorphous carbamazepine was not stable on storage whereas the solid dispersion and co-precipitate powders were stable. The present study demonstrates the synergistic effect of combining two types of stabilizers, PAA and HPMC, on the solubility, dissolution and stability of amorphous drug as compared to their effect when used alone.

Keywords: carbamazepine, amorphous, solid dispersion, co-precipitate, PAA, HPMC

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INTRODUCTION

Throughout the past decade, in the development and commercialization of new pharmaceutical products, the formulation and delivery of Active Pharmaceutical Ingredients (APIs) have played a crucial role. To improve bioavailability, stability and convenience to the patient, is the major objective of formulation chemistry [1]. Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action [2]. The bioavailability of an orally administered drug depends on its solubility in aqueous media over the pH range of 1.0–7.5 and the rate of mass transfer across biological membranes [3]. Carbamazepine (CBZ) is a widely prescribed antiepileptic drug having poor water solubility (~170 mg/L at 25-C) [4]. Because of having poor water solubility, its absorption is dissolution rate limited, which often results in irregular and delayed absorption [5].

The critical requirement for a poorly water-soluble drug for absorption to be possible from the gastrointestinal (GI) tract is, achieving a solution of drug in the GI fluid. Horter and Dressman [6] defined a poorly water-soluble drug as the one whose dissolution in the GI fluid under ordinary conditions takes a longer time than its transition through the absorption sites in the GI tract. To increase dissolution rates of drugs, salt formation, particle size reduction etc., have commonly been used but achieving desired bioavailability enhancement may not always be possible due to some practical limitations with these techniques [7]. Solid dispersion systems have shown promising results in increasing bioavailability of poorly water-soluble drugs in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles [8-10].

Usually, solid dispersions (SDs) are prepared with water soluble low melting point synthetic polymers such as polyvinylpyrrolidone (PVP), mannitol, or polyethylene glycols (PEGs) [11]. These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/polymer) ratio [12]. In certain similar experiments it has been observed that, PVP and PEG get dissolved first in dissolution media (owing to their high water solubility) leaving the drug back in undissolved state. In such case, though the drug is in controlled crystallization state or amorphous state, the polymers are unable to provide wetting ability to the drug particles. In such cases, there may be the possibility of rapid reversion of amorphous drug to the more stable crystalline state in presence of small amount of plasticizers such as water [13].

In the present study, solid dispersion (SD) of carbamazepine with Polyacrylic acid (PAA) and co-precipitate with PAA and hydroxypropylmethyl cellulose (HPMC) in different ratios were prepared by the spray drying technique for solubility, stability and the dissolution rate of carbamazepine.

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MATERIALS AND METHODS

Materials

Carbamazepine was received as gift from SellwellPharma (India). PAA was purchased from Paarichem Resources (Mumbai, India), HPMC was purchased from Signet (Mumbai, India), other materials and solvents used were analytical reagent grade.

Methods

Preparation of solid dispersion, co-precipitate and physical mixture CBZ alone or in combination with PAA (1:0.5, 1:1 and 1:1.5, parts by mass) was dissolved in a sufficient amount of methanol to obtain a clear solution and spray-dried to obtain amorphous carbamazepine (ACBZ) or solid dispersion of carbamazepine with PAA (SD-CP), respectively. To the clear solution of CBZ and PAA (1:1 parts by mass) in methanol, HPMC (2 parts by mass) was added slowly under stirring to obtain uniform dispersion and spray-dried to obtain spray-dried co-precipitate (SD-CPT) of CBZ with PAA and HPMC. Spray drying was done using a laboratory scale spray drier (Jay Instruments & Systems Pvt. Ltd., India) under the following conditions: inlet temperature 100 °C, outlet temperature 90 °C, feed rate 4–6 mL min–1, atomization air pressure 98.07 kPa and aspiration pressure –1.96 kPa.

All the samples were kept in vacuum dryer for 24 hours to remove residual solvent and stored in a dessicator until further study. Physical mixture of carbamazepine with PAA and HPMC (PM-CPH) in the ratio 1:1:2 was prepared by mixing them gently. All the samples were analyzed for crystallinity immediately after preparation by DSC.

Solubility Determination

For the determination of solubility of CBZ, ACBZ, SD-CP and SD-CPT, excess material was placed in contact with 7 mL of solvent in sealed glass tubes. The tubes were shaken on a vortex mixer and were maintained at 25^0C for 24 hours. The saturated solution was centrifuged and the supernatant was filtered through 0.45-µm Whatman filter paper (Whatman Ltd, Middlesex, UK) diluted suitably with water and analyzed by UV spectrophotometer at 285 nm (model UV-1601, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan).

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) thermograms of solid dispersions were measured using differential scanning calorimeter (DSC 60, Shimadzu) previously calibrated using indium. The samples ~2 to 3 mgs were accurately weighed into solid aluminum pans with seals and crimped. Reference pan was an empty sealed aluminum pan. The measurements were obtained at a heating rate of 10^0C/min with purging of dry nitrogen at a constant rate of 20 mL/min.

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In vitro drug release

The dissolution study was performed using media, distilled water. Accurately weighed amount of solid dispersion, containing equivalent 100 mg of pure drug was placed in basket of USP XXIV dissolution apparatus (Type I, TDT-06P, Electrolab, India) with 900 mL deaerated dissolution medium. Deaeration of dissolution media was done by ultrasonication of dissolution medium for 15 minutes. The dissolution apparatus was run at 100 rpm at constant temperature 37-C ± 1-C. Samples (5 mL) were withdrawn at 0, 5, 10, 15, 20, 25, and 30 minutes, filtered through 0.45-µm Whatman filter paper, diluted suitably and analyzed spectrophotometrically at 285 nm (model UV-1601 UV-visible spectrophotometer, Shimadzu). An equal volume of fresh dissolution medium kept at the same temperature was added to maintain the sink conditions. The absorbance values were transformed to concentration by reference to a standard calibration curve. The dissolution test was performed in triplicate for each batch.

Storage-stability studies

The samples were stored in the desiccator over the saturated aqueous solution of ammonium chloride to provide 75% of relative humidity. The desiccator was kept in the thermostated cabinet at 40°C. After the end of storage time, the samples were physically observed in comparison with the initial sample.

RESULTS AND DISCUSSION

CBZ alone and in various ratios with PAA, as a stabilizer (1:0.5, 1:1 and 1:1.5, m/m), was spray-dried. The process was optimized on the basis of, saturation solubility, dissolution profile, and stability. Solubility of carbamazepine solid dispersion increased to 0.1903 mg/mL from its 0.0061 mg/mL aqueous solubility. This is a result of improved wettability of drug particles due to the presence of hydrophilic polymer PAA.

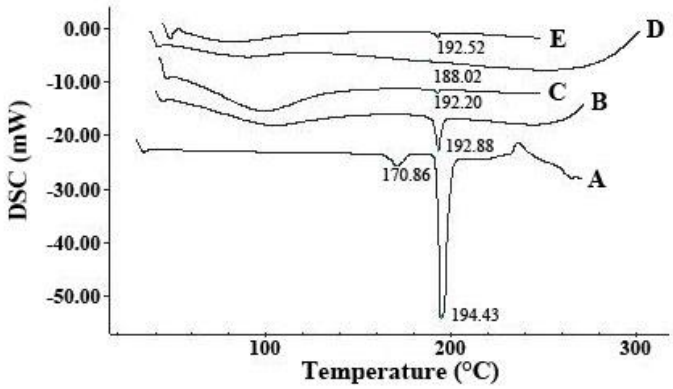

Figure 1: Differential scanning calorimetrythermogramsof (A) (CBZ), (B) ACBZ,(C) SD-CP, (D) SD-CPT, and (E) PM-CPH

DSC thermograms of samples at different time periods of CBZ, ACBZ, SD-CP, SD-CPT, PM-CPH are shown in Fig. 1. Pure CBZ showed a sharp melting endotherm at 194.43-C. A small endothermic peak at 170.86 was also observed, which can be attributed to the presence of a small amount of polymorphic form of carbamazepine.

Hydrophilic polymer drug solid dispersions increase drug dissolution because of the following possible reasons: first, usually in solid dispersions, the drug is partially dissolved in melted or dissolved polymer. After drying of these solid dispersions, the drug will not nucleate to form firm crystals resulting in formation of microcrystals. Drug microcrystals are embedded in the water-soluble matrix, where hydrophilic polymers present the ability of rapid wetting and thereby dissolution of drug [14]. Generally PEGs and PVP solid dispersions follow this principle. Second, for solid dispersions of SSG, higher dissolution rates observed when compared with other excipients may be owing to their easy and rapid dispersibility in the aqueous dissolution fluids [15]. Third, solid dispersions of hydrophilic swellable polymers such as CMC and HPMC become gelatinized in the dissolution medium. This gelatinized solid dispersion is constantly crushed by the attrition during stirring, and these finely gelatinized SDs diffuse to bulk solution through the diffusion layer [16]. Being water retentive, gelatinized dispersions also increase wetting of the drug, which attributes to increase in dissolution. However, the gelatinized dispersion formed should not be a barrier for the drug diffusion owing to its viscosity. In the present work, HPMC showed less drug dissolution compared with Na-CMC, which may be owing to the formation of highly viscous barrier layer at the interface of drug and dissolution medium.

Dissolution profiles of initial and stability samples of ACBZ and CBZ were performed in distilled water. Amorphous form showed an increase in the dissolution profile (42% in 60 min) compared to the crystalline form (20% in 60 min). Dissolution profiles for SD-CP (58% in 60 min) and SD-CPT (62% in 60 min) were even higher than that of ACBZ. The rate and extent of dissolution increased with increasing proportion of PAA. As compared to ACBZ, SD-CP and SD-CPT showed improved dissolution rate. Better dissolution of SD-CPT can be correlated with better wetting and dispersibility of the system due to the hydrophilic polymer, PAA, increased surface area due to adsorption of ACBZ on HPMC in the form of co-precipitate and prevention of water mediated recrystallization of CBZ in dissolution media due to the hydrogen bonding interaction with PAA.

Storage-stability studies showed that the samples were stable after physical observation.

CONCLUSION

The present study has clearly revealed that the preparation of the solid dispersion of CBZ with PAA and spray-dried co-precipitate with PAA and HPMC led to enhanced dissolution and stability compared to amorphous CBZ. Upon storage no physical changes were observed. The present study demonstrates the synergistic effect PAA and HPMC, on the solubility, dissolution, and stability of ACBZ compared to their effect when used alone.

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