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Formulation of cyclodextrin inclusion complex-based orally disintegrating tablet of eslicarbazepine acetate for improved oral bioavailability

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ABSTRACT

The present investigation was aimed towards developing a beta-cyclodextrin (β-CD) solid dispersion (SD) based orally disintegrating tablet (ODT) of eslicarbazepine acetate (ESL), for improving the dissolution and providing fast onset of anti-epileptic action. Optimum ratio of ESL and β-CD was determined by Job's plot. Thereafter, solid dispersions were prepared by solvent evaporation method and evaluated for yield, assay, Differential scanning calorimetry (DSC), Fourier transform infra red spectroscopy (FTIR), X-ray diffraction (XRD), and *in vitro* dissolution. Optimized SD was compressed into ODT by direct compression using super disintegrants and evaluated for wetting time, drug content, *in vitro* drug release and *in vivo* studies. The results of DSC, FTIR and XRD analysis supported the formation of inclusion complex. An improved dissolution with 99.95 ± 2.80% drug release in 60 min was observed in comparison to 24.85 ± 2.96% release from a plain drug suspension. Tablets with crosspovidone as a super disintegrant showed the least disintegration time of 24.66 ± 1.52 s and higher *in vitro* drug release against marketed tablets. *In vivo* studies indicated that the formulated tablets had 2 times higher bioavailability than marketed tablets. Thus, the developed β-CD–ESL SD-ODT could provide faster onset of action and higher bioavailability, which would be beneficial in case of epileptic seizures.

1. Introduction

Many patients, particularly children and the elderly population, find it inconvenient to ingest conventional solid dosage forms such as tablets and capsules due to an impaired ability to swallow. Oral therapy in such situations leads to poor patient compliance and potentially prolonged duration of treatment. This issue can be addressed through the development of orally disintegrating dosage forms such as tablets that disperse or dissolve in the saliva and be swallowed without water. Besides improving the acceptability and compliance, orally disintegrating tablets (ODT) have the potential to increase the bioavailability through enhancement of the dissolution rate [1,2]. Additionally, development of new dosage forms like ODTs help pharmaceutical companies to extend the life cycle of their products [3].

Eslicarbazepine acetate (ESL) is a third generation novel anti-epileptic drug. It is a class II compound as per the Biopharmaceutical Classification System (BCS), exhibiting dissolution rate-limited absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37 °C) due to erratic or incomplete absorption from the gastrointestinal tract (GIT).

The dissolution rate of such class II drugs, can be improved by methods like the use of surfactants [4], complexation with cyclodextrins [5] and solid dispersions with water soluble agents such as Poloxamer, polyethylene glycol and polyvinylpyrrolidone [6,7].

Solid dispersion (SD) is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the fusion, solvent or the melting solvent method. Dispersions obtained through the fusion process are often called melts and those obtained by the solvent method are frequently referred to as coprecipitates or coevaporates [8]. Preparation of solid dispersion by solvent method mainly involves the use of cyclodextrins (CD). CDs are cyclic oligosaccharides with six to eight dextrose molecules joined through one to four carbons of dextrose [4]. Cyclodextrins can form host guest inclusion complexes by weak intermolecular interactions with a wide variety of guests including organic molecules, inorganic ions, and coordination compounds. This phenomenon was shown by researchers as one of the techniques of alleviating the issue of solubility of water insoluble drugs [8–10]. There are a number of US FDA (U.S. Food and Drug Administration) approved products of water insoluble drugs which utilize cyclodextrin inclusion technology. In addition to improving the solubility and taste masking of drugs [11], CD also improve their physical and chemical stability [12], absorption [13] and bioavailability [10].

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Orodispersible tablets (ODT) are dosage forms for oral administration which, when placed in the mouth, rapidly disintegrate or dissolve and can be swallowed in the form of a liquid. ODTs have several advantages over conventional tablets like ease of administration for pediatrics, geriatrics, mentally ill, and uncooperative patients; quick disintegration and dissolution of the dosage form; overcome unacceptable taste of the drugs, when suitably taste masked; can be designed to leave minimal or no residue in the mouth after administration and provide a pleasant mouth feel [14].

There are many successful formulations which have incorporated the techniques of SD of poorly soluble drugs in the form of ODT. Kou et al. developed a solid dispersion of carbamazepine by complexation with hydroxypropyl-β-cyclodextrin with 95 times increase in the solubility of Carbamazepine. The SD when formulated as an ODT showed 1.5-fold increased bioavailability ($P < 0.05$) as compared to commercial tablets [15]. Similarly, Rao et al. prepared SD of Nimodipine which were compressed into fast dissolving tablets and demonstrated enhanced dissolution (99.63% drug release within 9 min) [16]. Wang et al. prepared perphenazine hydroxypropyl–β-cyclodextrin (HP-β-CD) inclusion complex based ODTs to improve its solubility and dissolution [17].

Thus, development of an ODT might be beneficial for an anti epileptic like ESL to provide fast onset of action. Hence, an attempt was made in the present investigation to improve the dissolution of ESL through the formulation of solid dispersions using β-cyclodextrin and to convert the optimized SD into fast disintegrating tablet formulations.

To the best of our knowledge, no report mentioning the evaluation of the bioavailability of ESL tablets containing ESL–β-CD complex in the form of an ODT has been published.

2. Materials

Eslicarbazepine acetate was generously gifted by Lupin Laboratories Ltd. (Mumbai, India). Crosspovidone was obtained as a gift sample from Signet Chemical Corporation Pvt. Ltd. (Mumbai, India). β-cyclodextrin (β-CD) was purchased from Hi Media Laboratories Pvt. Ltd. (Mumbai, India). All other materials purchased were of pharmaceutical grade or reagent grade.

3. Methods

3.1. Complexation of ESL and β-CD

Standard solutions of ESL were prepared in the concentrations of 0.7×10^{-4} mol/l to 6.3×10^{-3} mol/l in methanol. These solutions were mixed with 1×10^{-3} mol/l solution of β-CD in methanol and kept for 30 min at room temperature. The solutions were filtered through 0.45 μm membrane filter (Millipore, India) and the UV absorption spectra were noted (UV spectrophotometer 1700, Shimadzu, Japan) in the range of 200 nm to 400 nm against blank solutions with the same concentration of cyclodextrin. The formation of a complex between ESL and β-CD was studied by observing the shift in the spectrum of drug as an indicator of complexation [18]. The shift in absorbance maxima (234.5 nm) of ESL was compared against plain drug solution in methanol.

The procedure was repeated in triplicate for each concentration of ESL.

3.1.1. Job's plot

A Job's plot is used to determine the stoichiometry of a binding event during complexation. In this method, the total molar concentration of complexing agent and ligand are held constant, but their mole fractions are varied. A measurable parameter that is proportional to complex formation (such as absorption signal) is plotted against the mole fractions of these two SD components [19]. Molecular inclusion complexes of the drug and β-CD were prepared in different molar ratios (R) by mixing solutions 3×10^{-4} mol/l each of ESL and β-CD in methanol to a fixed volume of 10 ml like 1: 9, 2: 8, 3: 7, 4: 6 and so on. The absorbance maxima were measured for all solutions (in triplicate) and the differences in absorbance of ESL in the presence and absence of β-CD were plotted against R.

After determining the optimum ratio for complexation between ESL and β-CD, solid dispersions of ESL and β-CD were formulated using three methods: kneading, solvent evaporation and co-precipitation.

3.1.2. Kneading method

Weighed quantity of β-CD was taken in a porcelain mortar. Thick slurry was prepared by adding distilled water. An appropriate quantity of drug was added to it under stirring and kneaded for about 40 min. During this process, sufficient quantity of water was added intermittently to maintain suitable dough like consistency. The final product was dried in a hot air oven (Modern Industrial Corporation, Mumbai, India) at 45 °C for 24 h. The dried mass was pulverized and sieved through sieve #60 [20].

3.1.3. Solvent evaporation method

ESL and β-CD were dissolved in the molar ratio of 1:1 in a minimum quantity of methanol (5 ml). The resultant solution was stirred and solvent was removed by evaporation in an open beaker on magnetic stirrer (Remi Instruments, India) at 40 °C for 1 h. The residue so obtained was further dried in a hot air oven (Modern Industrial Corporation, Mumbai, India) at 60 °C and stored overnight. The dried mass was sieved through sieve #60 [21].

3.1.4. Co-precipitation method

β-CD was weighed and dissolved in 5 ml of methanol. To this solution, weighed quantity of ESL was added under magnetic stirring. The solution was stirred for about 45 min and then heated up to 70 °C on a hot plate magnetic stirrer (Remi Instruments, India) for 30 min. The solution was then cooled to the point a precipitate was formed. The mixture was freeze-dried (Heto Drywinner, Germany) and passed through #60 sieve [22].

3.2. Evaluation of SDs

The quantitative yield was calculated for the prepared SD by using the Eq. (1):

$$\text{Quantitative yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100 \quad (1)$$

Assay of the SD was conducted by dissolving a weighed quantity of the product into acetonitrile, which selectively dissolved ESL. The dispersion was then filtered (Whatman paper no. 2) to remove undissolved cyclodextrin. The filtrate was analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 235.4 nm and quantity of ESL was determined against standard calibration curve in acetonitrile.

Based on the outcome of yield and assay calculation, the method for preparing the SD was selected.

The SD prepared by the selected method was then subjected to further physicochemical evaluations described below.

3.2.1. Differential scanning calorimetry

Differential Scanning Calorimetric (DSC) thermograms of ESL, β-CD, their physical mixture and solid dispersions were recorded (DSC-60, Shimadzu, Japan). Nitrogen gas flowed at 20 psi to create an inert atmosphere to prevent any oxidation reaction with the sample holder (made of aluminum). The equipment was calibrated for baseline and temperature with indium metal. The sample was hermetically sealed in an aluminum pan and scanned from 10 to 200 °C at a rate of 10 °C/min.