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Full Length Article

Physiochemical characterization of taste masking levetiracetam ion exchange resinates in the solid state and formulation of stable liquid suspension for pediatric use

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ABSTRACT

In the present work, an attempt has been made to mask the bitter taste of Levetiracetam using various ion-exchange resins such as Amberlite IRP69 and Duolite AP143. The physicochemical characteristics of the drug–resin complex in the solid state were studied. FT-IR studies revealed that there is no interaction between drug and resin. The DSC and XRD studies proved that the drug is in amorphous nature. Using the same concentration of resins, Xanthan gum as suspending agent in a liquid dosage form for pediatric use was formulated. Evaluation parameters such as drug content, sedimentation volume, re-dispersibility and viscosity of the prepared suspension were found to be satisfactory. The higher Zeta potential value indicates the stability of the suspension. Suspension prepared with Duolite AP 143 efficiently masks the bitter taste of Levetiracetam compared to Amberlite IRP69. From the *in vitro* drug release, a formulation with 1:2 ratios of resin has shown the maximum release at the end of 90 minutes. The sustained effect is due to one of the properties of the resin. The release profile follows zero order kinetics. The results obtained in this work show that drug–resin complexes effectively masked the bitter taste of Levetiracetam while liquid formulation provides an easier way to administer and to overcome problems with noncompliance of pediatrics.

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1. Introduction

Levetiracetam [(S)-2-(2-Oxopyrrolidin-1-yl) butanamide] is a second-generation antiepileptic agent useful in the treatment of partial onset and myoclonic seizures (Fig. 1). Levetiracetam has been classified as a class-I substance according to the Biopharmaceutics Classification System (BCS) by the Food and Drug Administration (FDA), meaning that it is highly soluble and highly permeable. Levetiracetam has a short plasma half-life in adults, which is 7 ± 1 hour with a bitter taste and faint odor (Sharma et al., 2012). A major problem in the development of an oral dosage form of levetiracetam is its intensely bitter taste, leading to poor patient compliance (Nabin et al., 2014). To overcome the above problem, an attempt has been made to develop a bitterness-covered Levetiracetam suspension for pediatric use. Without changing its safety and efficacy, a drug's taste has to be masked and techniques are being adapted to meet this need, especially for the pediatric and juvenile patients (Khar and Sohi, 2004). These are as follows: taste masking with flavors, taste masking by granulation, microencapsulation, ion exchange resins, solid dispersion method, and bitterness inhibitor. Among the techniques mentioned above, taste masking by ion exchange resins was selected.

The use of ion-exchange materials that manifest specific functions such as drug release only in ionic environment, taste masked and mucoadhesive properties presents a robust alternative drug delivery system for achieving sustained-release. Ion exchange materials are water-insoluble polymers containing exchange groups in repeating positions on the polymer chain. The drug is not let out from complexes in an ion-free aqueous medium during storage, but after oral use it is released gradually through displacement of ions of the same charge being present in gastrointestinal fluids. As contrasted to the other drug delivery systems based on physical principle, the elution of drugs from complexes depends only on the ion strength of the gastrointestinal fluids and not on complex physiological factors (e.g., pH and enzymes) (Yuan et al., 2014).

Taste masking by drug–resin complexation is achieved when an ionizable drug reacts with a suitable ion exchange resin to form a drug–resinate complex (Nanda and Garg, 2002). Ion exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups (most common polymeric network is a copolymer of styrene and divinylbenzene). The drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromatography column or by prolonged contact of the resin with the drug solution (Atyabi et al., 1996). Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that the dissociation of the drug–resin complex does not occur under the salivary pH conditions (Cuna et al., 2000). This suitably masks the unpleasant taste and odor of drugs. Drug release from the resin depends on the properties of the resin and the ionic environment within the GIT (Gao et al., 2003). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecules out of the resins (Agarwal et al., 2000). In this work, we attempt to develop a taste masked dosage form of Levetiracetam by employing ion exchange resins and formulated into suspension. Oral suspension is preferred by many patients because of the ease of swallowing and the flexibility in the administration. It is particularly advantageous for children, the elderly and infants; in the meantime, the unpleasant taste of the bitter medicinal agents can be overcome by administrating as undissolved particles. The complex, by virtue of its insoluble nature of the salivary condition, exhibits no virtual taste due to which even extremely loses their taste when converted into a drug resinate. The main aim of this study was to develop and characterize Levetiracetam ion-exchange resin complex and to prepare a liquid dosage form using natural polymer like Xanthan gum as a suspending agent.

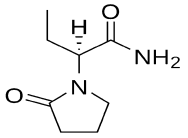

Fig. 1 – Chemical structure of Levetiracetam.

2. Materials and methods

2.1. Materials

Levetiracetam was obtained as a gift sample from Molecules Drugs and Research Laboratory, Chennai, India. Amberlite IRP 69 and Duolite AP 143 were obtained as a gift sample from Dow Chemical Company, France. Sucrose, sorbitol, glycerine, Xanthan gum, sodium saccharin, methyl paraben, propyl paraben and pineapple flavor were purchased from S.D. Fine Chemicals (Mumbai, India). All other chemicals and solvents were of analytical grade.

2.2. Drug characterization

The melting point of Levetiracetam was measured by the capillary method. Its solubility was determined in various solvents. The UV spectrum of Levetiracetam was recorded in the range of 200–400 nm in the solution of 0.1 N HCl (pH 1.2); the wavelength of maximum absorption (λ_{max}) in this range was found and then a calibration curve was prepared at that wavelength.

2.3. Purification of ion exchange resin

The resins were purified using the method reported by Irwin and co-workers (Irwin et al., 1987). The resins (5 g) were washed successively with deionized water, methanol (50 ml), benzene (50 ml) and several times with distilled water to eliminate organic and color impurities. Wet resins were activated by 5 ml 0.1 M HCl and washed several times with deionized water. All resins were dried overnight in hot air oven at 50 °C and kept in an amber glass vial.

2.4. Preparation of drug–resin complex

Drug–resin complex was prepared by batch process (Omar and James, 1989). In total, six drug–resin complexes were

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