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BENI-SUEF UNIVERSITY JOURNAL OF BASIC AND APPLIED SCIENCES 5 (2016) 126–133

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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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ARTICLE INFO

Article history:
Received 23 June 2015
Received in revised form 12 April 2016
Accepted 22 April 2016
Available online 3 June 2016

Keywords:
Levetiracetam
Taste masking
Ion-exchange resins
Solid-state characteristics
Suspension

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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http://dx.doi.org/10.1016/j.bjbas.2016.04.004

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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.

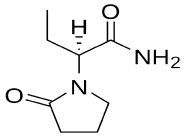

Fig. 1 – Chemical structure of Levetiracetam.

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

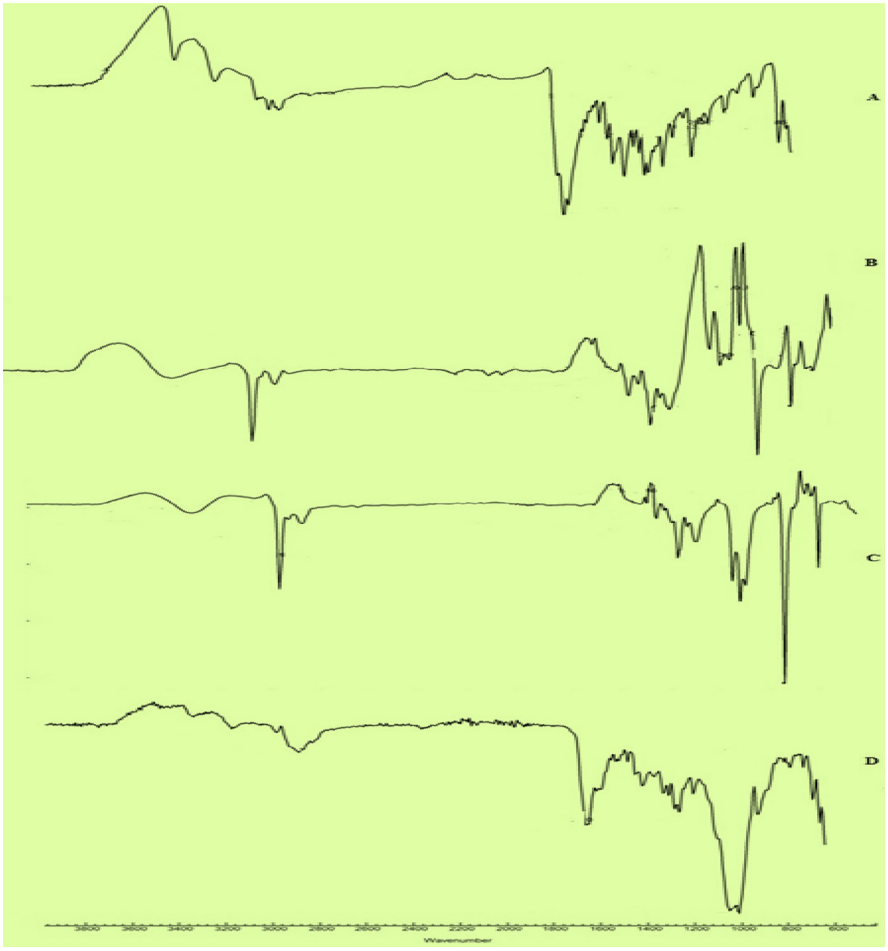

Fig. 2 – FT-IR spectra of Levetiracetam (A), Levetiracetam–Amberlite IRP69 complex (B), Levetiracetam–Duolite AP 143 complex (C), and Levetiracetam–Xanthan gum physical mixture (D).

prepared using two different resins such as Amberlite IRP69 and Duolite AP143. Drug:resin ratios of 1:1, 1:2, 1:3 were weighed and added to deionized water (50 ml) in a glass beaker and the suspension was stirred on a magnetic stirrer for 30 min and allowed to stir for another 5 hour at 37 ± 0.5 °C. The complexes were harvested by vacuum filtration and washed free of any unbound drug and ions with deionized water and then dried to constant weight. To determine the actual loading capacity, the supernatant was analyzed spectrophotometrically (Shimadzu UV-1700) at 210 nm. The amount of drug loaded into complexes was calculated as the difference between the initial and the remaining amount of drug in the supernatant.

2.5. *Characterization levetiracetam–resin complexes*

2.5.1. *FTIR spectroscopy*

Chemical interaction between the drug and resin was studied by FTIR spectroscopy (Raghunathan et al., 1981). The IR spectra of the samples were obtained using a Fourier transform infrared spectrometer (Model CARY 630, Agilent Technologies). Measurements were carried by KBr disk method, and the scanning range was 4000 to 400 cm^{-1}. The result is shown in Fig. 2.

2.5.2. *Differential scanning calorimetry (DSC)*

The molecular state of the drug in the resinate was evaluated by performing DSC analyses of pure drug and resinate. DSC curves of the samples were obtained with a differential scanning calorimeter (Model TAG 1000, Shimadzu). Each sample was placed in an aluminum pan and then crimped with an aluminum cover. The heating rate was 10 °C min^{-1}. All measurements were performed over 0–500 °C under a nitrogen purge at 50 ml min^{-1}. The results are shown in Fig. 3.

2.5.3. *X-ray powder diffraction (XRPD)*

X-ray diffraction studies of the samples were performed using an automated X-ray diffractometer (Rigaku, Smartlab) with a filter Cu K and SC70 radiation detector, voltage 40 kV, current 30 mA, and at a scanning rate of 10 mm/sec. The results are shown in Fig. 4.

2.6. *Drug content*

The resinate prepared by the batch process was evaluated for the drug content (Srikanth et al., 2010). The resinate equivalent to 100 mg of the drug was magnetically stirred with about 70 ml of buffer (pH 1.2) in 100 ml volumetric flask and then

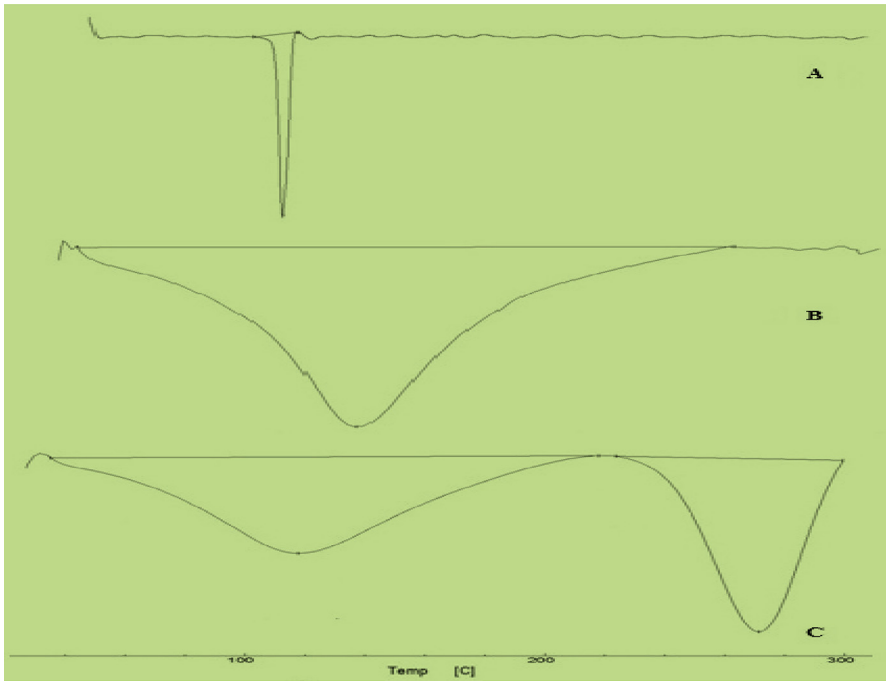

Fig. 3 – DSC thermogram of Levetiracetam (A), Levetiracetam–Amberlite IRP 69 complex (B), and Levetiracetam–Duolite AP 143 complex (C).

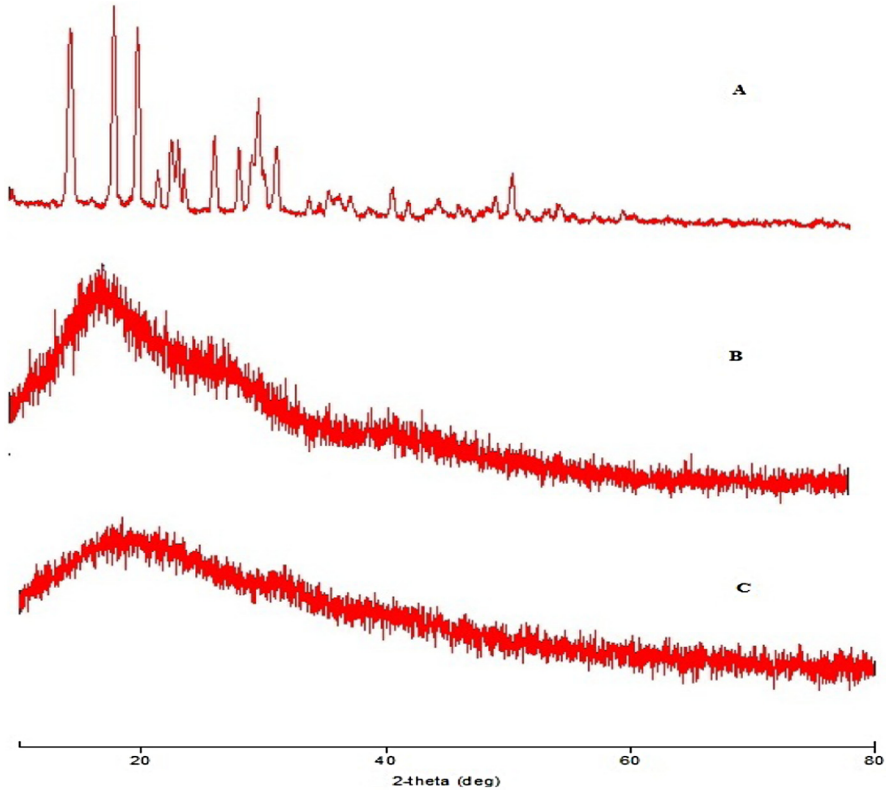

Fig. 4 – X-ray diffractograms of Levetiracetam (A), Levetiracetam–Amberlite IRP 69 complex (B), and Levetiracetam–Duolite AP 143 complex (C).

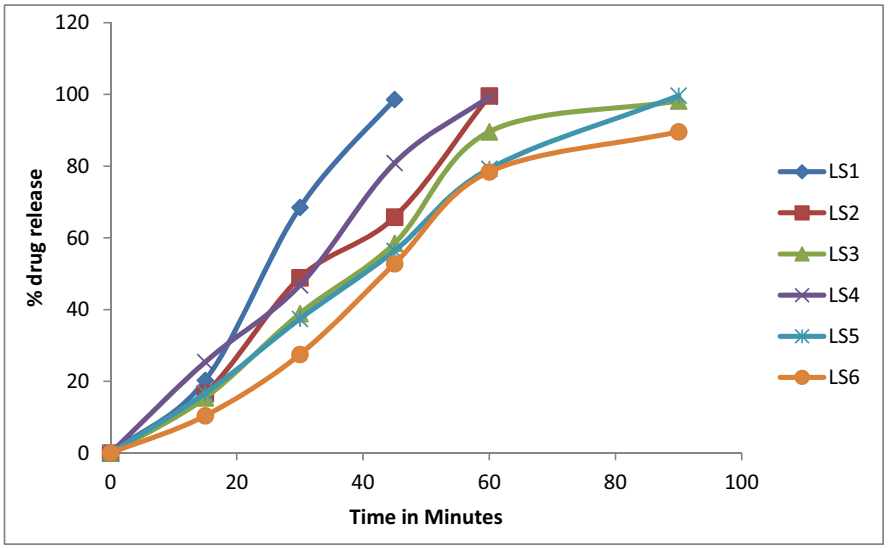

Fig. 5 – *In vitro* drug release profile of formulation (LS1–LS6).

diluted to volume with buffer. The solution was suitably diluted and analyzed spectrometrically at 210 nm using gastric simulated fluid (pH 1.2) as blank. The results are shown in Table 2.

2.6.1. *Taste evaluation of resinate*

Time intensity method was used to check the taste of the resinates (Sana et al., 2012). Six human volunteers were selected. The sample equivalent to a dose of 10 mg was kept in the tongue for 60 seconds, and the resinates and pure drug were evaluated for taste, and the volunteers were instructed not to swallow the drug. Bitterness levels were recorded at 2, 10 and 60 sec. Volunteers were advised to gargle their mouth thoroughly with distilled water.

2.6.2. *Formulation of suspension*

The syrup was prepared by heating between 60 and 80 °C under constant stirring and the stability of prepared syrup was improved by the addition of preservatives (Varaporn and Greepol, 2008). Xanthan gum mucilage was prepared by adding water and stirring well to allow it to swell completely. The drug–resin complex was added into the syrup solution and stirred for 30 min to allow proper dispersion complex. Then the Xanthan gum mucilage was added to above bulk syrup solution and stirred for 30 min. At the end, the flavoring agent was added and stirred for 5 min. A total of 6 formulations (LS1, LS2, LS3, LS4, LS5, LS6) were prepared using two different resins (1:1, 1:2, 1:3); all the formulations contain 70% sorbitol, 0.5% sucrose, 0.1% Xanthan gum, 0.01% methylparaben, 0.05% propylparaben, 0.2% sodium saccharin and pineapple flavor.

2.6.3. *Characterization of developed oral taste masked suspension of levetiracetam*

2.6.3.1. Evaluation parameters. All the developed batches of suspension were evaluated for organoleptic properties such as color, odor and taste. The pH of the suspension was determined by using the pH meter. The sedimentation ratio and redispersibility are also measured (Varaporn and Greepol, 2008).

2.6.3.2. In vitro dissolution study of oral taste masked suspension. The dissolution studies (Ogger and Noory, 1991) of the suspension were performed using USP-type II dissolution apparatus (ETC 116, Electro Lab). Suspension equivalent to 100 mg was transferred in each flask of dissolution apparatus containing 900 ml of buffer (pH 1.2) thermostatically maintained at 37 ± 0.5 °C at a rotation speed of 100 rpm. At appropriate intervals, 5 ml of the sample was withdrawn and filtered through 0.45 µm membrane filter, replaced with dissolution medium to keep a constant volume. The filtrate was analyzed by UV-Visible spectrophotometer at 210 nm. The release profile is shown in Fig. 5.

2.6.3.3. Zeta potential and viscosity. A number of factors contribute to disperse phase stability in the suspension and these may be thermodynamic or kinetic in origin. Examples of the former include steric and electrostatic stabilization, which induce stability through particle repulsion, while kinetic stability can be induced by increasing the viscosity of the suspending medium, thus slowing down particle aggregation and sedimentation (Larsson et al., 2012). Zeta potential is an important and useful indicator of the charge that can be used to predict and control the stability of colloidal suspensions. Zeta potential values (HORIBA Scientific SZ-100) and its stability behavior are shown in Table 1 and Fig. 6. The viscosity of the suspension was determined at ambient condition using DV III+, Brookfield Programmable Rheometer, values shown in Table 2.

Table 1 – Zeta potential values and its stability behavior.

Zeta potential [mV]	Stability behavior
From 0 to ±5	Rapid coagulation or flocculation
From ±10 to ±30	Incipient instability
From ±30 to ±40	Moderate stability
From ±40 to ±60	Good stability
More than ±61	Excellent stability

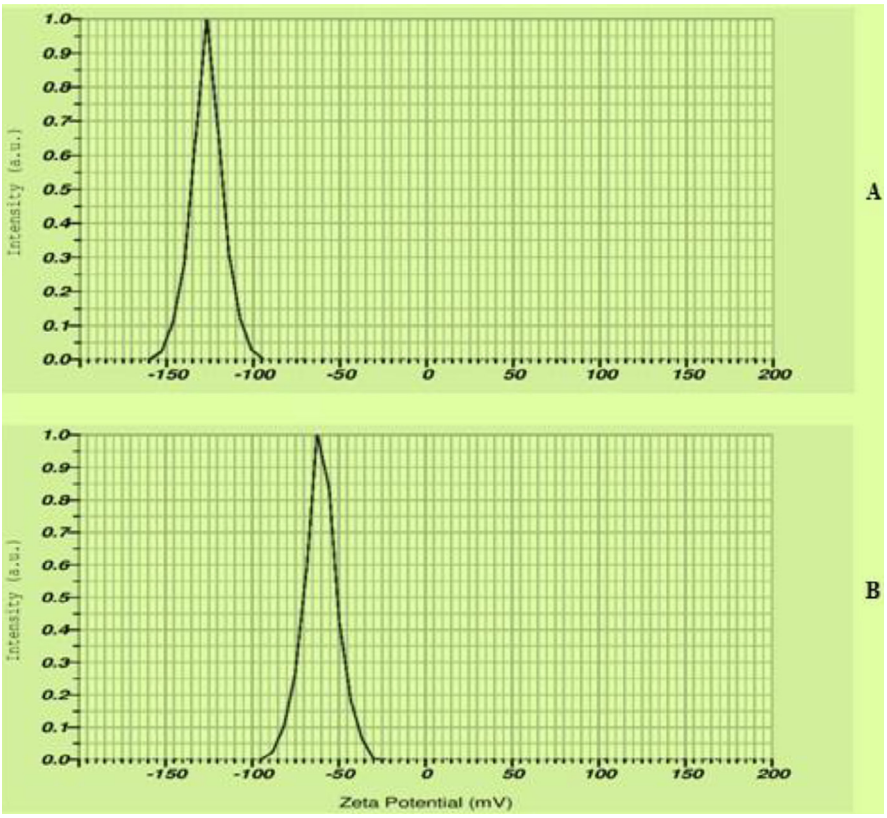

Fig. 6 – Zeta potential of Levetiracetam suspension containing Amberlite IRP 69 (A) and Duolite AP 143(B).

3. Results and discussion

The melting point of Levetiracetam was found to be 118–121 °C and freely soluble in water. UV analysis of Levetiracetam in 0.1 N HCl showed an absorption maximum at 210 nm. Selected excipients were checked for their compatibility with the drug and were analyzed by FT-IR spectra. The Levetiracetam FT-IR spectra have shown N—H stretching (3349 cm^{-1}), C—H stretching (2892 cm^{-1}), C—H bending (1426 cm^{-1}), amide C═O (1642 cm^{-1}), and C—N stretching (1083 cm^{-1}). The same peaks were found in the FT-IR spectra of resin complexes and drug–Xanthan gum physical mixture, ensuring that there is no change of drug form in the formulation, and thus concluding suitability of selected resins and excipients. The additional peaks were found in drug–resin complexes and there are no changes in the drug peak, concluding that complexes were formed and there are no changes in drug nature.

The thermogram of pure levetiracetam exhibited a sharp endothermic peak at 119 °C corresponding to its melting point. The Amberlite IRP69–levetiracetam complex exhibited a broad endothermic peak at 126 °C and Duolite AP143–levetiracetam complex exhibited a broad peak at 117.6 °C. The DSC thermogram of resin complex showed identical peaks corresponding to the pure drug, but not a sharp endothermic peak, indicating that the drug is uniformly dispersed and in an amorphous state.

The X-ray powder diffractogram pattern of levetiracetam revealed several diffraction peaks which are indicative of its crystalline character. The diffraction pattern of the Levetiracetam–Amberlite complex with a marked decrease in the intensity of the diffraction peaks can be attributed to the

Table 2 – Evaluation parameters of Levetiracetam suspension with different resins.

Parameters	LS1	LS2	LS3	LS4	LS5	LS6
Drug content (%)	98.41 ± 0.32	97.52 ± 0.47	96.21 ± 0.56	99.42 ± 0.78	98.52 ± 0.85	98.71 ± 0.39
pH	7.9	8.0	7.8	7.9	8.0	8.1
Sedimentation ratio	0.92	0.93	0.94	0.95	0.98	0.7
Viscosity (cps)	1146	1260	612	432	2070	1080
Taste	Slightly bitter taste	No bitterness	No bitterness	No bitterness	No bitterness	No bitterness

amorphous character of the ion exchange resins. However, in the case of Levetiracetam–Duolite complex system, it could be observed that the diffraction pattern completely diffuse, which revealed its amorphousness when compared to Amberlite complex.

The organoleptic properties of the suspension such as color, odor and taste were found to be satisfactory. Brownian motion is usually significant to maintain the particles in a dispersed phase; however, for larger particles, the effect of gravity becomes significant if there is a sizeable difference in the density between dispersed and continuous phases. Sedimentation ratio is greater than unity; some degree of sedimentation can be expected while a ratio less than unity is likely to indicate a stable system. The sedimentation ratio of all the formulations (LS1–LS6) was found to be nearer to one, indicating good stability. Good redispersibility was observed in all the formulations. The prepared suspension (LS1–LS6) showed 96.21 ± 0.56 to 99.42 ± 0.78 % of drug content. The result shows that the drug–resin complex retains its drug loading capacity in the liquid dosage form. The results are shown in Table 2.

The dissolution study was conducted for 90 minutes to attain complete release from all the formulations. Formulations LS1, LS2 and LS3 were prepared by adding Levetiracetam–Amberlite IRP 69 complex in the ratio of 1:1, 1:2, 1: 3 respectively. Formulations LS4, LS5 and LS6 were prepared by adding Levetiracetam–Duolite AP 143 complex in the ratio of 1:1, 1:2, 1: 3 respectively. In all the formulations, the same concentration of suspending agent is maintained. To study the effect of various concentrations of resins in relation to drug release three different ratios of resins were selected. Formulations LS1, LS2 and LS3 showed drug release of 98.6%, 99.6% and 98.2% at the end of 45, 60 and 90 minutes respectively. Formulation LS3 showed sustained effect on drug release. Formulations LS4, LS5 and LS6 showed drug release of 99.4%, 99.7% and 89.6% at the end of 60, 90 and 90 minutes respectively. Formulation LS5, in the ratio of 1:2 drug–resin complex, showed complete release at the end of 90 minutes. From the drug release data, it was revealed that by increasing the concentration of resins drug release is in a controlled manner, i.e., one of the properties of resins. The *in vitro* release data obtained from formulation fitted with kinetic modeling follows zero order kinetics.

Being in liquid dosage form, stability parameters are to be considered. The formulation LS5 containing Duolite complex had a greater viscosity of 2070 centipoise when comparing to formulation LS3 containing Amberlite complex (Table 2). The formulations LS3 and LS5 were subjected to Zeta Potential measurement, because to prevent particles from becoming aggregated it is necessary to provide some barrier. The size of the potential barrier can be indicated by the magnitude of the zeta potential, which is the potential at the slipping plane between the particle and associated double layer with the surrounding solvent. If all the particles in suspension have a large negative or positive zeta potential, they tend to repel each other and there will be no tendency for the particles to come together. The general dividing line between stable and unstable suspensions is generally taken as +30 or –30mV, with particles having zeta potentials outside of these limits normally considered stable. The zeta potential values of formulations LS3 and LS5 were found to be –126.5 mV and –60.4 mV respectively.

The formulation LS5 containing Duolite AP143 is considered to be the best formulation because it has highly amorphous nature, masked the bitter taste efficiently, good stability behavior with greater viscosity and optimum zeta potential value.

4. Conclusion

The complexation with ion exchange resin is a simple and cost-effective technique for taste masking. Physiochemical characterizations of prepared complexes were studied. The efficient taste masking was obtained from drug–resin complex and formulated as an oral suspension for better patient compliance. The stability behavior of the suspension was studied. The results obtained in this work show that drug–resin complexes effectively masked the bitter taste of Levetiracetam while the stable liquid formulation provides an easier way to administer and to overcome problems with noncompliance of pediatrics.

Acknowledgment

The authors would like to thank the Management of Sree Vidyanikethan Educational Institutions, Tirupati, for providing a research facility and their support.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.bjbas.2016.04.004.

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