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RESEARCH ARTICLE

DEVELOPMENT AND IN VITRO CHARACTERIZATION OF EXTENDED RELEASE TABLETS OF LEVETIRACETAM

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ABSTRACT

Extended release formulation levetiracetam is approved by Food and Drug administration as an antiepileptic drug for adults with partial onset seizures. The main objective of present study was to develop and evaluate matrix tablets levetiracetam by various polymers (Eudragit RL100, Eudragit RS100 & ethyl cellulose) of different concentrations. The pre and post compression parameters were evaluated and results reveals that all parameters such as angle of repose, bulk density, compressibility index, hausner's ratios, weight variation, friability, hardness and drug content were within the acceptable limits. In vitro drug release performed in phosphate buffer pH 6.8 showed that the formulations prepared by using Eudragit RS100 extended its release until 12 hrs. Among all prepared formulations F6 elicits slow, gradual and drug release extended upto 12 hrs and drug release mechanism followed zero order kinetics.

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. 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. [1] A rational approach to dosage form design for any drug requires a complete understanding of its physiochemical and biopharmaceutical properties which can have a tremendous impact on its bioavailability and thereby on its efficacy and toxicity profile.[2] The USP/NF presently recognizes several types of modified-release dosage forms, extended-release dosage forms (e.g. sustained release dosage forms, controlled release dosage forms) and delayed release dosage forms (e.g. enteric coated tablets).[3]

Extended-release dosage forms are those that allow at least a two-fold reduction in frequent dosing compared to the drug presented in a conventional form (e.g., a solution or an immediate release dosage form).[4] A sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug." Ideally, a sustained release oral dosage form is designed to rapidly release some predetermined fraction of the total dose into the gastro intensive tract.[5,6] This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then released at a constant rate.[7] The rate of the drug absorption from the entire maintenance dose into the body should equal the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required.[8] Eudragit RS and RL polymers are copolymers of poly (ethylacrylate, methyl-methacrylate and chloro trimethylammonioethyl methacrylate), containing quaternary ammonium groups in the range of 4.5-6.8% and 8.8-12% respectively. Both are insoluble at physiological pH and capable of swelling, thus representing themselves as good materials for the dispersion of drugs.[9-12]

In the present study, we attempted to formulate an extended release tablets of levetiracetam, a new generation antiepileptic drug used for the treatment of complex partial seizures. The goal of controlled drug delivery systems is to improve the effectiveness of drug therapies. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience.[13] The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in

blood plasma. The Immediate release drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral sustained drug delivery has some potential advantage like sustained release rate & dose maintenance in plasma. The sustained release formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate.[14]

The aim of present work is to formulate extended-drug drug delivery system of Levetiracetam suitable for twice-a-day dosing.[15] In general, extended-drug -release drug delivery is attempted to maintain constant, effective drug level in the body with concomitant minimization of undesired side-effects. Levetiracetam rapidly and almost completely absorbed after oral administration (99%). The major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. No CYP450 metabolism detected. The short biological half life of drug also favours development of a extended-drug release formulation.[16,17]

MATERIALS

Levetiracetam (Nutra Specialties Pvt. Ltd.), Eudragit RL & RS100 was purchased from Evonoik, Ind, Ltd, ethyl cellulose, Magnesium stearate and talc were purchased from S.D. Fine-chem. Ltd., Mumbai, India.

METHODOLOGY

Preparation calibration curve

Levetiracetam (100mg) pure drug was dissolved in 100ml of 0.1 N HCl (stock solution). Different concentrations of 5,10,15,20,25,30,35 and 40µg/ml of Levetiracetam per ml of solution were prepared by serial dilution of stock solutions. The absorbance of the above dilutions was measured at nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose.

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 %.

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in **Table 1**. Levetiracetam and all other ingredients were individually passed through sieve no.≠60. All the ingredients were mixed direct compression method. Total weight of the tablet was considered as 900mg. Total F1 to F9 batches were prepared by varying the polymers and their concentration.

Table 1 Formulation composition prepared tablets

Formulation No.	Levetiracetam (mg)	Eudragit RL 100 (mg)	Eudragit RS 100(mg)	Ethyl cellulose (mg)	MCC pH102(mg)	Mag.Stearate (mg)	Talc (mg)
F1	500	60	-	-	322	9	9
F2	500	90	-	-	292	9	9
F3	500	180	-	-	202	9	9
F4	500	-	60	-	322	9	9
F5	500	-	90	-	292	9	9
F6	500	-	180	-	202	9	9
F7	500	-	-	60	322	9	9
F8	500	-	-	90	292	9	9
F9	500	-	-	180	202	9	9

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage.

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of levetiracetam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies

The USP apparatus –II (Paddle Method) and the medium (900ml of 0.1 HCl) was allowed to equilibrate to temp of 37°C $\pm$ 0.5°C. Tablet were placed in the vessel and the vessel was covered the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 298nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULTS AND DISCUSSION

The present study was aimed to developing extended release tablets of Levetiracetam using various polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

Analytical Method

Graphs of Levetiracetam were taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 298nm obeys Beers law at a concentration range of 5-40µg/ml as shown in Figure 1&2.

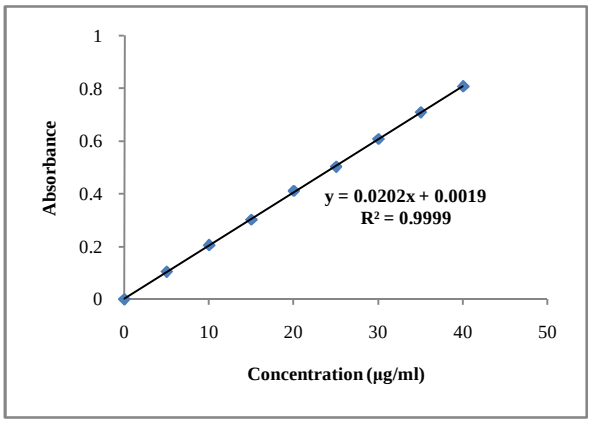

Figure 1 Standard graph of Levetiracetam in 0.1N HCl

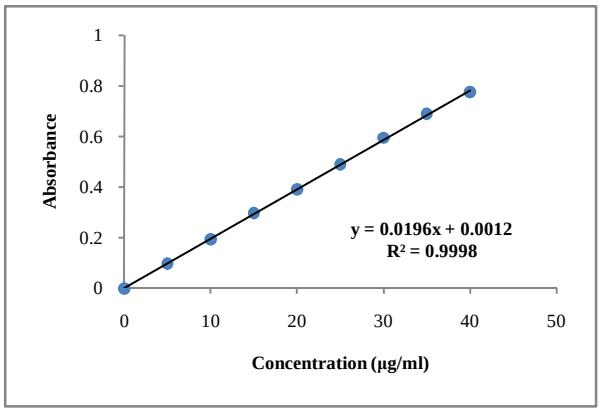

Figure 2 Standard graph of Levetiracetam p H 6.8 phosphate buffer

Tablet powder blend was subjected to various pre-formulation parameters and the data were shown in Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner's ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For the prepared tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 2 Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Table 3 Post compression parameters for prepared tablets

Formulation codes	Weight variation (mg)	Hardness(kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	912.5	4.5	0.50	6.8	99.76
F2	905.4	4.5	0.51	6.9	99.45
F3	898.6	4.4	0.51	4.9	99.34
F4	910.6	4.5	0.55	6.9	99.87
F5	909.4	4.4	0.56	6.7	99.14
F6	910.7	4.5	0.45	6.5	98.56
F7	902.3	4.1	0.51	6.4	98.42
F8	901.2	4.3	0.49	6.7	99.65
F9	898.3	4.5	0.55	6.6	99.12

In-Vitro Drug Release Studies

From the dissolution data it was evident that the formulations prepared with Eudragit RL 100 as polymer were unable to retard the drug release up to desired time period i.e., 12 hours as shown in Figure 3. Whereas the formulations prepared with Eudragit RS 100 retarded the drug release in the concentration of 180 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation as in Figure 4. The formulations prepared with ethyl cellulose showed more retardation even after 12 hours, however complete drug release was not found within 12 hrs as given in Figure 5. Hence they were not considered.

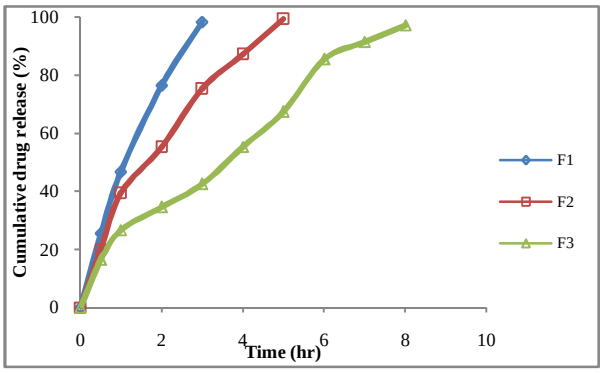

Figure 3 Dissolution profile of Levetiracetam (F1, F2, F3 formulations).

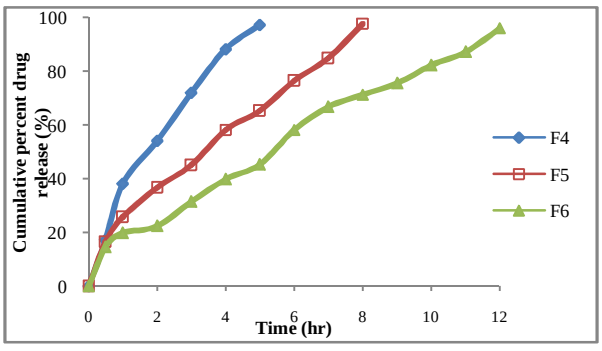

Figure 4 Dissolution profile of Levetiracetam (F4, F5, F6 formulations)

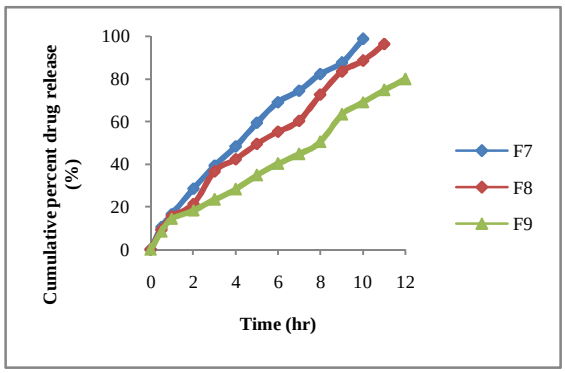

Figure 5 Dissolution profile of Levetiracetam (F7, F8, F9 formulations)

CONCLUSION

The aim of the present study was to develop an extended release formulation of Levetiracetam to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of polymethacrylate polymers and ethyl cellulose were employed as polymers. Levetiracetam dose was fixed as 500 mg. Total weight of the tablet was considered as 900 mg. Polymers were used in the concentration of 60, 90 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 96.10 % in 12 hours. It followed zero order release kinetics mechanism.

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