Original Article

Formulation design of oral lamotrigine suspension for the treatment of epilepsy

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ABSTRACT

Aim: Lamotrigine is a broad-spectrum anticonvulsant drug widely used as mono- or adjunct therapy in adults and children. The aim of this study was to develop a liquid formulation of lamotrigine to fulfil the unmet needs of children and geriatric epileptic patients.

Materials and Methods: Suspension formulation was prepared using Carbopol 974P as a suspending agent. It was evaluated for its sedimentation and re-dispersibility, solubility, morphology, particle-size distribution, rheological properties, pH measurement, uniformity of dosage unit, *in vitro* drug release behaviour and results were compared with marketed formulation Lamictal tablets.

Results: The release profile of marketed product Lamictal tablets and developed lamotrigine oral suspension shows a complete release profile throughout physiological pH in all three media (0.1N hydrochloric acid, 4.5 pH acetate buffer and 6.8 pH phosphate buffer) and shows similar release as a marketed product. Microscopic observation clearly indicates the stability of the suspension (no aggregation of suspended particles) during the storage period of 12 months. The content uniformity of suspension was found well within the specified limits.

Conclusion: Lamotrigine oral suspension was developed successfully and found a suitable alternative for a commercially available tablet for the treatment of epilepsy in children and geriatric patients.

Keywords: Epilepsy, lamotrigine, re-dispersibility, sedimentation

INTRODUCTION

A seizure is the transient occurrence of a neurological disturbance due to abnormal excessive and synchronous brain activity. It may occur by some external factors which affect the brain. Epilepsy is defined by the occurrence of two uncontrolled seizures more than 24 h apart.[1] It is diagnosed by ictal and interictal electroencephalography and by brain imaging. In genetically pre-disposed individuals, genetic studies contribute to the diagnosis and management of epilepsy.[2] Blood tests, brain scans and electroencephalograms are used for diagnosis. Epilepsy could be able to treat with some antiepileptic drugs, but it cannot be able to cure completely, only helps to shorten or minimise its frequency.[3] The aetiology of epilepsy is known in 50% of patients and varies with the sociodemographic characteristics and the diagnostic workup. A genetic pre-disposition with environmental risk factors contributes to the heterogenicity of epilepsy.[4] The incidence rate of epilepsy was 61.44/100,000 person-years.[5] Target-driven therapeutic strategies have given way to the discovery of many new drugs against epilepsy and over the past 25 years, there have been more than 25 antiepileptics in the market to prevent the occurrence of seizures.[6] Amongst

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Submitted: 30-May-2022 **Revised:** 15-Aug-2022 **Accepted:** 17-Aug-2022 **Available Online:** 30-Aug-2022

Access this article online	
Website: www.cmrpjournal.org	Quick Response Code
DOI: 10.4103/cmrp.cmrp_45_22	

How to cite this article: Neerumalla S, Chhowala I, Patel M. Formulation design of oral lamotrigine suspension for the treatment of epilepsy. Curr Med Res Pract 2022;12:157-61.

them, lamotrigine could have the potential to treat epilepsy.[7] It works by blockage of voltage-gated sodium channels and inhibits sustained repetitive firing of neurons, resulting in a reduction of glutamate release.[8] Lamotrigine is available in the form of immediate-release (Tablets, chewable dispersible tablets, ODT) or extended-release tablets sold under the brand name of Lamictal.[9] Lamotrigine was first introduced into the market as Lamictal by GlaxoSmithKline, UK in 1991 and approved for use in the US market in 1994.[10]

Despite the fact that tablets are very easy to prepare and handle, oral liquids are always preferred for paediatric, geriatric and patients with dysphagia, due to its ease of administration and patient compliance, even at the time of epileptic seizure. In the present research work, oral liquid as homogeneous suspension of the lamotrigine was selected due to its various advantages over other conventional delivery due to their easy swallowability, flexible and accurate dosing and improved palatability, particularly in geriatric populations and children. In addition to this, the liquid formulation is advantageous with regard to content uniformity or dosage uniformity.[11,12] The utmost challenge of oral suspension formulation is that it is thermodynamically unstable, therefore, it is compulsory to include a suitable suspending agent or stabiliser or viscosity enhancer that can prevent the rate of settling and allow to re-disperse easily.[13]

The suspension containing lamotrigine was developed and evaluated for its physiochemical properties and microbiological assessment throughout its shelf life. The suspension was designed in such a way to establish the need of each excipient with a step-wise focus on parameters such as sedimentation and re-dispersibility.

MATERIALS AND METHODS

Lamotrigine was purchased from Aurobindo Pharma Ltd., (India). Methyl 4-hydroxybenzoate and propyl 4-hydroxybenzoate from Sigma-Aldrich. Carbopol 974P (Lubrizol); sodium saccharin, glycerol (Merck); Simethicone (RioCare); Flavours (H. E. Stringer) were used in this study. The rest of the materials and chemicals used during this study were of analytical grade.

Solubility studies of lamotrigine

As per the Biopharmaceutics Classification System of lamotrigine comes under Class II (low solubility/high permeability) drug substance, lamotrigine exhibits pH-dependent solubility. To identify the highest solubility of the drug substance, saturated solubility study was performed in different pH media covering the entire physiological range. The solubility of the drug was determined in water, acid buffer (pH 1.2 and 2.0), sodium acetate buffer (pH 4.5) and phosphate buffer (pH 6.8). An excess quantity of the drug was added to 10 ml of each solvent in sealed glass vials and the resulting suspensions were stirred on a magnetic stirrer for 24 h at room temperature. Samples were then filtered, appropriately diluted and analysed by high-performance liquid chromatography (HPLC) equipped with a pump and photodiode-array detection/ultraviolent detector (Agilent LC 1260) at 270 nm.

Design of suspension

First, dissolved methylparaben and propylparaben into 40% of the total volume of purified water with the aid of heating more than or equal to 90°C to get a clear, colourless solution. Add 30% of the total volume of purified water and keep aside to cool at room temperature. Simethicone PD30 was added to the above solution to prevent foaming. Carbomer 974P was added as a suspending agent into the above solution and mix it using Silverson mixer to get homogeneous dispersion. Separately add and disperse lamotrigine into glycerol and mix with the help of Silverson to get homogeneous dispersion. Add this dispersion in previously prepared dispersion to get off-white to white colour homogeneous dispersion. Saccharin sodium was added to it, resulting in dispersion of having off-white to white colour. The natural strawberry flavour was added to the above suspension. Make up to volume with purified water and mix it using Silverson mixer.

Evaluation of suspension

Morphological studies

The morphological characteristics (colour, consistency and homogeneity) of suspension at the 1st day to 12 months at room temperature were observed microscopically at ×100 magnification using Binocular Microscope (BA210, Motic 2.0, Hyderabad, India) presented in Figure 1a and b.

Determination of the Redispersibility

Allow a suitable quantity of the suspension being examined to settle, undisturbed, for 24 h. Shake the flask for 30 s and accurately take one dose (usually 5–10 mL) at a depth of 1 cm below the meniscus. Shake the flask again for 10 s and

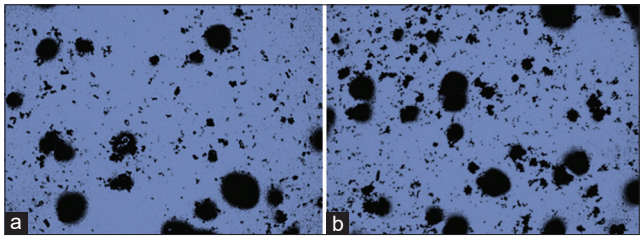

Figure 1: (a) Photomicrograph of freshly prepared lamotrigine oral suspension and (b) photomicrograph of the same suspension after 12 months at room temperature (×100)

take another dose. Replicate this procedure until 10 doses of the suspension have been taken. Calculate assay of 10 doses individually.[14]

Acceptance criteria

The formulation complies with the test if the content of each individual dose is between 85% and 115% of the average content. If the content of more than one individual dose is exceed this limit or if the content of one individual dose is exceed the limits of 75%–125% of the average content, then the preparation is said to be failed.

Viscosity measurement

Viscosity measurements of the suspension were carried out at room temperature on a Brookfield viscometer CAP 2000+ using spindle. Allow 10 min for the cone to come to equilibrium temperature with the plate. At the end of the temperature stabilisation period, disperse approximately 67 µl of suspension in such a way that not enough or too much suspension is outside the spindle. Drive the handle down with care. Allow the cone, plate and suspension to equilibrate to the temperature control setting. Press the run key and allow it to run for 60 s. Record the viscometer reading of the suspension formulation. Repeat the procedure twice more. Note the mean of three analyses.

Uniformity of dosage unit by content uniformity

To ascertain the consistency of dosage units, each and every unit in the batch should have an active pharmaceutical content within a narrow range with the label claim. The definition of dosage units is the dosage form which contains a single dose or a part of a dose of an active pharmaceutical ingredient in each dosage unit. The definition of uniformity of dosage unit is the degree of uniformity in the amount of the active pharmaceutical agent present in dosage units. The uniformity of dosage units can be described by content uniformity or mass variation. The test for content uniformity of prepared formulation in dosage units is dependent on the assay of individual contents of active substance(s) of a number of dosage units to ensure the individual contents are well within pre-defined criteria. Alternately, products that exceed 25 mg or 25% threshold limit may be analysed for uniformity of dosage units by mass variation rather than content uniformity. In our formulation, content exceeds 25% w/w thus, here, we utilised content uniformity for the determination of uniformity of dosage unit.[15]

Content uniformity

Calculate the assay of 10 individual units by a suitable analytical method. Sampling shall be performed on well-mixed material removed from an individual container in conditions of normal use. Express the results as delivered dose. Calculate the acceptance value (AV). Calculate the AV using the formula (1):

$$AV = |M - \bar{X}| + ks \quad (1)$$

Where, M = Reference value

$\bar{X}$ = Mean of individual contents (x_1, x_2,..., x_n), expressed as a percentage of the label claim

K = Acceptability constant

S = Sample standard deviation

Measurement of pH of suspension

Measure the pH of suspension with aid of a pH meter and adjust pH between 6.3 and 7.3 using 1N sodium hydroxide solution.

In vitro drug release studies

In vitro drug release study from lamotrigine oral suspension was carried out using Paddle USP Type-II apparatus as per BP reference under unlicensed medicines (oral suspension). Place 5 ml of lamotrigine suspension into dissolution jar and start dissolution test. Take out 10 ml of test sample with 0.45 µ polyvinylidene fluoride filters after 45 min. Rinse the transferring device with the media in the jar till the entire content is transferred into the jar. The release of lamotrigine from oral suspension was studied for 45 min in 0.1N (pH 1.2) hydrochloric acid containing 900 ml of the dissolution medium, at speed of 50 rpm at 37°C ± 0.5°C. Samples (10 ml) were withdrawn at different time intervals and analysed using HPLC method and replaced with an equivalent volume of the medium. The release was compared to the reference product Lamictal tablets manufactured by GlaxoSmithKline.

RESULTS AND DISCUSSION

Solubility studies of lamotrigine

Lamotrigine exhibits pH-dependent solubility as it demonstrated high solubility at lower pH. The solubility of the drug was found to be very low in 6.8 pH phosphate buffer (0.28 mg/ml) and distilled water (0.29 mg/ml), and was high at pH 1.2 (5.76 mg/ml), at pH 2.0 (3.26 mg/ml) and pH 4.5 acetate buffer (1.52 mg/ml).

Microscopic examination of suspension

The microscopic photographs of fresh (1st day) and 12 months at room temperature of lamotrigine suspension are presented in Figure 1a and b. The micrographs of Figure 1a are freshly prepared lamotrigine oral suspension and Figure 1b is suspension after 12 months. The micrographs indicated almost

similar observations as initials. The above observation suggests the stability of suspension for 12 months at room temperature.

Redispersibility of suspension

The redispersibility of prepared (freshly) lamotrigine oral suspension was found to be 98.68%. This redispersibility test was performed after 12 months at room temperature again, and it was found to be 97.77%, which indicates the stability of suspension for a longer period of time.

Rheological analysis

The viscosity of the suspension was measured at two different rpm (2.5 and 5 rpm) and was found to decrease with increasing rate of shear stress [Table 1], which indicates non-Newtonian flow and shear thinning behaviour. It is concluded that shear stress did not induce irreversible structural changes.

Uniformity of dosage unit by content uniformity

Each dosage unit from multidose container was tested for assay of lamotrigine, methylparaben and propylparaben. The content uniformity was found to be well within the limit as per pre-defined specifications. Assay of lamotrigine, methylparaben and propylparaben from individual dosage units are presented in Table 2.

Measurement of pH

The pH value of suspension was found to be 6.86, when it kept for 12 months of stability study at room temperature, their pH value found to be 6.78. This result indicates that there is no chemical change when kept for a long time.

Table 1: Physical characteristics of lamotrigine oral suspension (mean±standard deviation, *n*=3)

Batch code	Viscosity (cp)		PSD (μm)		
	2.5 (rpm)	5 (rpm)	D (0.1)	D (0.5)	D (0.9)
C1	9542.66	5533	6.43	38.7	120
C2	8914.00	5557	5.95	19.3	94.1
C3	8360.66	5389	6.11	21.1	108

PSD: Particle-size distribution

Table 2: Uniformity of dosage unit by content uniformity

Dosage unit	Percentage assay of lamotrigine	Percentage assay of methylparaben	Percentage assay of propylparaben
N1	96.9	97.8	99.2
N2	97.6	98.2	100.2
N3	97.3	97.8	99.1
N4	98.1	98.5	99.8
N5	97.8	98.8	100.0
N6	97.8	98.3	100.2
N7	98.3	98.8	100.4
N8	98.6	98.7	99.7
N9	97.7	98.0	99.4
N10	97.5	97.9	99.0

In vitro drug release studies

The method was finalised based on the solubility behaviour of the drug substance and the difference in the formulations for which a comparative dissolution profile was to be developed. The *in vitro* release profile of developed lamotrigine oral suspension is shown in Figure 2. From the obtained graph, it was concluded that the release of reference product-Lamictal tablets and test product-lamotrigine oral suspension shows

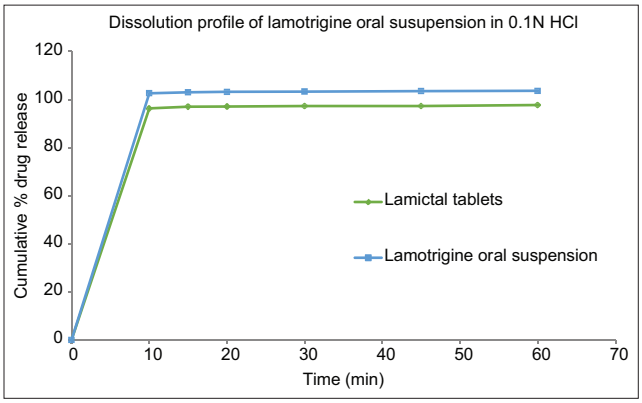

Figure 2: Comparative *in vitro* dissolution profiles of reference product-Lamictal tablets and test product-lamotrigine oral suspension in release media (0.1N HCl)

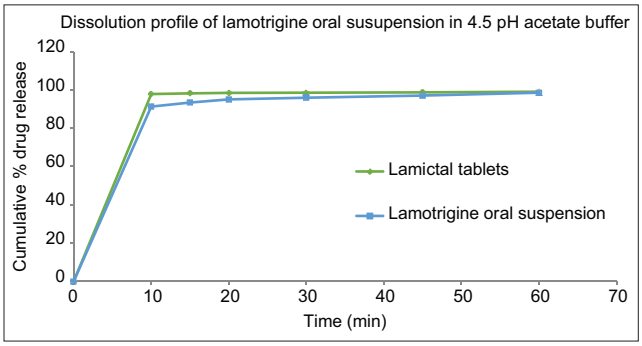

Figure 3: Comparative *in vitro* dissolution profiles of reference product-Lamictal tablets and test product-lamotrigine oral suspension in 4.5 pH acetate buffer

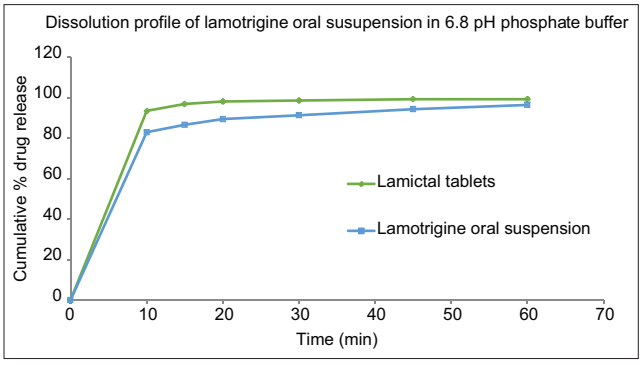

Figure 4: Comparative *in vitro* dissolution profiles of reference product-Lamictal tablets and test product-lamotrigine oral suspension in 6.8 pH phosphate buffer

a complete release profile. The % relative standard deviation observed <10% both the profiles, found well within the limits which indicate that both the profiles were comparable. All three media (0.1 N hydrochloric acid, 4.5 pH acetate buffer and 6.8 pH phosphate buffer) of the reference product and test product formulation released more than 85% within 15 min as per obtained graphs shown in Figures 2-4.

CONCLUSION

In vitro dissolution profile of commercially available tablets and developed lamotrigine oral suspension shows a similar release profile. Moreover, this liquid is bioequivalent to Lamictal tablets proven by clinical trials but that is not a part of this article.

The suspension could give quick onset of action compared to that of the tablet form. Thus, it could be a suitable alternative for children and geriatric population in terms of palatability, stability, flexibility and accurate dosing. However, it is stable at room temperature so patients need not to store in a freeze or refrigerator.

Due to its palatability and sweet taste, the off-white-coloured homogeneous liquid could be a convenient and suitable dosage form for children and geriatric patients and as a result may increase patient compliance.

Lamotrigine should be taken preferably in fasting conditions because the time to reach peak plasma concentration is slightly delayed after food but the extent of absorption is unaffected.[8]

Acknowledgement

The author(s) gratefully acknowledges to Syri Limited (Vadodara, India) for providing excellent support to complete this research work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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