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Research Article

Development of Mouth Dissolve Tablets of Lamotrigine Using Co-Processed Microencapsulated Polysorbate

Pradnya Palekar Shanbhag[1]*, Sujata Gaikwad S[2]

[1]*Saraswathi Vidya Bhavan's College of Pharmacy, Dombivli, Maharashtra*
[2]*Vivekanand Education Society's College of Pharmacy, Chembur, Maharashtra*

Correspondence: drpradnyaps@gmail.com (Tel. +91-9167528638)

Abstract

Mouth dissolve tablet dosage form has widespread demand especially in geriatric and pediatric patient population. The present research work deals with development of mouth dissolve tablets of Lamotrigine using sodium starch glycolate as superdisintegrant and co-processed microencapsulated polysorbate Sepitrap™ 80 as solubilizer to enhance tablet disintegration and dissolution. Lamotrigine, BCS Class II drug is used in treatment of CNS disorders, particularly epilepsy; pain and psychiatric indications. Mouth dissolve tablets of Lamotrigine were prepared by direct compression method with solid dispersion of Lamotrigine and PEG 6000 in 1:0.5 ratio. Tablets were evaluated using standard tablet evaluation parameters, in vitro and in vivo disintegration times, and in vitro dissolution. Formulation containing sodium starch glycolate (6%) and Sepitrap™ 80 (15%) exhibited the shortest *in vitro* disintegration time (8s), in vivo disintegration time (2s) and the highest dissolution at early time dissolution points with t90% of 52.35s. The optimized formulation was subjected to stability studies for three months as per ICH guidelines and showed physical stability with insignificant change in hardness, in vitro disintegration time, drug content and in vitro dissolution. Our results proposed that solubility enhancement using PEG 6000 for solid dispersion, sodium starch glycolate as superdisintegrant and Sepitrap™ 80 could be promising in development of mouth dissolve tablets for rapid release of drugs with limited solubility.

Keywords: Mouth dissolve tablets; Lamotrigine; Sepitrap™ 80; sodium starch glycolate

Introduction

Researchers in drug development areas focus on newer ways of drug administration to enhance potential of approved drug products and improve patient compliance. Among the dosage forms developed to facilitate patient acceptance and palatability with ease of drug administration, mouth dissolve tablet dosage form is most widely accepted in geriatric, pediatric and bedridden patients [1-5]. Mouth dissolve tablets are expected to disintegrate and dissolve rapidly in the mouth and the dissolved material can thus be easily gulped without need of water. Patient compliance along with improved drug release and enhanced bioavailability make mouth dissolve tablets popular and prevalent in the market. There are several techniques to improve pore structure of mouth dissolve tablets for rapid disintegration such as freeze drying, sublimation, spray drying, mass extrusion, etc [6-10]. Lamotrigine [6 - (2, 3 - dichlorophenyl) - 1, 2, 4 - triazine - 3, 5 - diamine] is an antiepileptic drug shown to be effective in treatment CNS disorders, particularly epilepsy; pain; multiple sclerosis and psychiatric indications including bipolar disorder. It works by inhibiting voltage dependent sodium channels, resulting in decreased release of excitatory neurotransmitters glutamate and aspartate. Treatment of epilepletic seizures demands rapid drug release and onset of action. Lamotrigine, BCS Class II drug shows good absorption but has limited aqueous solubility [11-15]. The objective of present research work was to develop mouth dissolve tablets of Lamotrigine using solid dispersion technique along with superdisintegrant such as sodium starch glycolate and co-processed microencapsulated polysorabate Sepitrap™ 80 for rapid disintegration and dissolution. An attempt was made to formulate mouth dissolve tablets of Lamotrigine to provide rapid effect and improved palatability and acceptability.

Materials and Methods

Lamotrigine was obtained as gift sample from Cipla Ltd., Mumbai. Sepitrap™ 80 was obtained as gift sample from Seppic Air Liquide Healthcare Specialty Ingredients. All other materials were of analytical grade or pharmacopoeial grade and used as received.

Preformulation

UV spectrum of Lamotrigine

25 mg of Lamotrigine was dissolved in 30 ml of methanol and volume was made up to 100 ml with phosphate buffer pH 6.8 to get solution of 250 ug/ml. 1ml of this solution was further diluted to 10 ml with phosphate buffer pH 6.8 to get solution of 25 ug/ml. This solution was scanned in the range of 200-400 nm using phosphate buffer pH 6.8 as blank using UV-Visible Spectrophotometer UV- 1800 (Shimadzu) to determine wavelength of maximum absorbance.

Calibration curve for Lamotrigine

100 mg of Lamotrigine was dissolved in 30 ml of methanol and volume was made up to100 ml with phosphate buffer pH 6.8 to get solution of 1 mg/ml. 10 ml of this solution (1mg/ml) was further diluted to 100 ml with phosphate buffer pH 6.8 to get solution of 100 ug/ml. Different concentrations were prepared in the range of 5 ug/ml – 30 ug/ml by appropriately diluting the stock solution with distilled water. The absorbance values were measured using UV-Visible Spectrophotometer (Shimadzu Corporation, Tokyo, Japan) at 307 nm against the blank and calibration curve was constructed.

Fourier Transform Infrared (FT-IR) Spectroscopy

IR spectrum of Lamotrigine was recorded using potassium bromide (KBr) pellet at a resolution of 4 cm-1 over range 4000-400 cm-1 and principle peaks measured using Nicolet FTIR - 380 spectrophotometer.

Differential Scanning Calorimetry scanning

DSC scan of Lamotrigine, PEG 6000 and Lamotrigine-PEG 6000 complex was recorded using Perkin Elmer Pyris series DSC 6000 in scanning range of 30-250 °C at a rate of 10 °C/min.

Preparation of Mouth Dissolve Tablets of Lamotrigine

Formulation Development

Preliminary studies indicated that superdisintegrant sodium starch glycolate was superior compared to other superdisintegrants

(crospovidone and croscarmellose sodium) and hence it was selected as superdisintegrant of choice for present study.

Mouth Dissolve Tablets of Lamotrigine were prepared by direct compression method [8] according to the formulae given in Table 1. Lamotrigine being BCS Class II drug, is insoluble in water. Hence to increase the aqueous solubility, solid dispersion of Lamotrigine was prepared using PEG 6000 as carrier by melt fusion method. Lamotrigine and PEG 6000 were used in the ratio 1:0.5. In melt fusion method, PEG 6000 was melted and solid dispersion with Lamotrigine was formed. This dispersion was cooled to room temperature with constant stirring.

Table 1: Formulations of mouth dissolve tablets of Lamotrigine

Formulations	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)
Lamotrigine: PEG 6000 (1:0.5)	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Mannitol	47	45.75	44	42.75	39	46	41
Sodium starch glycolate	7.5	7.5	8	8	8	6	6
Sepitrap™ 80	7.5	8.75	10	11.25	15	10	15
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5

The solid mass thus obtained was sieved through 60 # to get uniform and free flowing powder. All the ingredients were passed through 60 # mesh separately, weighed and mixed in geometrical order. Then lubricant (200 # mesh) was added and mixed for further 5 min. The blend obtained was directly compressed using 10 mm flat round punches into tablets of 100 mg on a Single Punch Single Stroke compression machine (Royal Artist, Mumbai).

Evaluation of mouth dissolve tablets of Lamotrigine

Hardness test

Monsanto hardness tester was used for measurement of hardness of prepared tablets. Three tablets were selected from each batch for testing and results were expressed in kg/cm2.

Friability Test

It was done in Roche Friabilator and tablets were subjected to combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Preweighed samples of 20 tablets were placed in the friabilator, which was operated for 100 revolutions. The tablets were reweighed. %Friability was determined.

Weight variation

Twenty tablets were weighed individually and average weight was determined. Percent deviation was calculated and checked for weight variation.

Drug content

Three tablets from each formulation were taken and crushed. The tablets were crushed using mortar and pestle and 100 mg powder equivalent to 25 mg of Lamotrigine was weighed and dissolved in phosphate buffer pH 6.8. Volume was made up to 100 ml with phosphate buffer pH 6.8. The solution was then filtered. Appropriate dilutions were made and quantity of Lamotrigine was determined using UV-visible spectrophotometer at 307 nm.

Wetting time [8]

For determination of wetting time, a piece of tissue paper folded twice was placed in a small 5 cm diameter petridish containing 6 ml of water. A tablet was placed on the paper and time required for complete wetting was determined.

***In vitro* disintegration test [16]**

In vitro disintegration time was measured using modified disintegration method. For this purpose, a petridish was filled with 10 ml of water at 37 ± 0.5 °C. The tablet was carefully put in the center of the petridish and time for the tablet to completely disintegrate into fine particles was noted.

***In vitro* drug release [17]**

In vitro drug release of tablets was conducted in USP XXIII Type II dissolution apparatus (Electrolab, Model-TDT 08L) employing paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5 °C as dissolution medium. Aliquots of dissolution study samples were analyzed for drug content by measuring absorbance at 307 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.

***In vivo* disintegration time**

Tablets were evaluated in healthy human volunteers with their consent (n = 9; 7 males and 2 females) for in vivo disintegration time and mouth feel in the oral cavity. The protocol for human studies was approved by Local Level Ethical Committee for Scientific Research of Vivekanand Education Society's College of Pharmacy. Each healthy human volunteer was randomly given tablets (single blind design) with a potable water rinse at start. The volunteers were asked to place the tablet on the tongue. Volunteers were not restricted later on with respect to tongue movement.

Stability Studies

Tablets of optimized formulation F7 were stored at storage conditions namely 25°C/60 % RH, room temperature and 40°C/75% RH. Each tablet was wrapped in Alu Alu pouch, which was heat-sealed at the end. The tablets were evaluated for hardness, in vitro disintegration time, drug content and in vitro dissolution after storage for 90 days.

Results and Discussion

UV spectrum of Lamotrigine

The solution of Lamotrigine in phosphate buffer was found to exhibit maximum absorption at 307 nm after scanning in the range of 200 - 400 nm. 307 nm has been reported as λ max in the literature. Thus the given sample of Lamotrigine complied with the standard.

Calibration curve for Lamotrigine

Calibration curve constructed for concentration range of 5 ug/ml - 30 ug/ml obeyed Beer Lambert's law. Slope and regression coefficient are given in Table 2.

Table 2: Results of calibration curve for Lamotrigine by UV-Visible Spectrophotometer

Parameters	Results
Linearity range (ug/ml)	5-30
Slope	0.0219
R2	0.999

Fourier Transform Infrared (FT-IR) Spectroscopy

The identity of Lamotrigine was confirmed by comparing IR spectrum of Lamotrigine with reported spectrum of Lamotrigine shown in Figure 1.

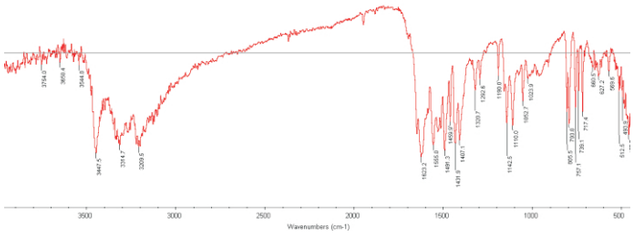

Figure 1: FT-IR spectrum of Lamotrigine

Differential Scanning Calorimetry Scanning

DSC thermograph of solid dispersion of Lamotrigine and PEG 6000 complex indicated that there was no interaction between Lamotrigine and PEG 6000. Lamotrigine was retained in the solid dispersion as shown in Figure 2.

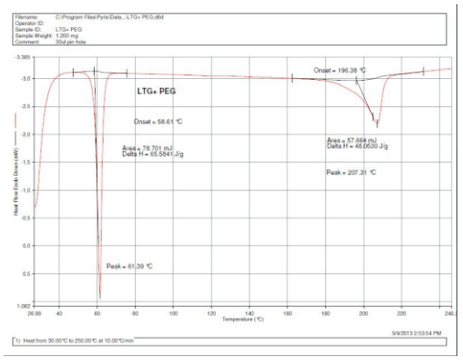

Figure 2: DSC scan of Lamotrigine and PEG 6000

The present work was undertaken to improve solubility of Lamotrigine by using co-processed microencapsulated polysorbate solubilizer Sepitrap™ 80, and to formulate mouth dissolve tablets of Lamotrigine using sodium starch gylcolate as superdisintegrant. All the formulations were evaluated for various parameters like hardness, friability, drug content, wetting time, in vitro disintegration time, in vivo disintegration time and in vitro drug release studies. Hardness of the tablets was found to be 2.5 ± 0.01 to 3.0 ± 0.01 kg/cm2 and friability was found to be below 1% indicating good mechanical resistance. In vitro disintegration time of all batches was satisfactory fulfilling the official requirements (˂3 min) for mouth dissolve tablets [13]. It was observed that in vitro disintegration time of tablets decreased with increase in concentration of sodium starch glycolate. In vitro drug release of all formulations showed above 90% release within 2 minutes. Results of evaluation studies are shown in Table 3. Sepitrap™ 80 helped in rapid drug release

Table 3: Formulations of mouth dissolve tablets of Lamotrigine

S. N.	Parameters	F1	F2	F3	F4	F5	F6	F7
1	Uniformity of weight (mg)	99±0.11	100±0.08	98± 0.01	101± 0.01	99±0.13	101± 0.15	101±0.05
2	Drug content (%)	99.87±0.01	101.0±0.13	101.8±0.12	100.1±0.02	101.04±0.11	99.9± 0.16	101.1±0.14
3	*In vitro* disintegration time (s)	9 ±0.09	9 ±0.08	8.5 ±0.05	8.5 ±0.07	8.75 ±0.04	8.75 ±0.08	8 ±0.06
4	*In vivo* disintegration time (s)	2.75 ±0.02	2.75 ±0.02	2.5 ±0.03	2.5 ±0.02	2.5 ±0.03	2 ±0.02	2 ±0.02
5	*In vitro* wetting time (s)	5.18± 0.16	5.12± 0.11	5 ± 0.15	4.88 ± 0.12	4.57± 0.02	5 ± 0.12	5± 0.08
6	*In vitro* drug release (t90%) (s)	90.55 ±0.12	89.05±0.28	94.74±0.09	119.68±0.10	73.36±0.09	63.77±0.06	52.35±0.05

and sodium starch glycolate reduced dissolution time of the tablets. Mouth dissolve tablets of Lamotrigine showed acceptable palatability with pleasant mouth feel.

Stability Studies

Stability studies on optimized formulation F7 indicated that there are no significant changes in hardness, *in vitro* disintegration time, drug content and *in vitro* dissolution at the end of 3 month period ($P<0.05$) and is shown in Table 4.

Table 4: Data for stability studies

Parameters	Temperature And Humidity Conditions	Three Month
Hardness (kg/cm^2)	40°C/ 75 % RH	2.5 ± 0.02
	Room temperature	2.5 ± 0.03
	25° C/ 60 % RH	2.5 ± 0.01
Drug content (%)	40°C/ 75 % RH	99.1±0.19
	Room temperature	100.1±0.05
	25° C/ 60 % RH	99.1±0.12
In vitro disintegration time (s)	40°C/ 75 % RH	6 ±0.06
	Room temperature	8 ±0.02
	25° C/ 60 % RH	7 ±0.05
In vitro drug release (t90%)(s)	40°C/ 75 % RH	48.21±0.12
	Room temperature	49.14±0.09
	25° C/ 60 % RH	48.11±0.09

Conclusion

A simple and economical technique was adopted for formulation of mouth dissolve tablets of Lamotrigine using solid dispersion with PEG 6000. Novel solubilizer Sepitrap™ 80 has been used to solubilize and enhanced the release of Lamotrigine, BCS Class II drug. Sodium starch glycolate at 6% concentration proved satisfactory superdisintegrant for preparation of mouth dissolve tablets of Lamotrigine with in vitro and in vivo disintegration times of 8 and 2 seconds respectively. A stable, effective and pleasant tasting mouth dissolve tablet dosage form of Lamotrigine was designed using an economic and lab feasible method.

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Conflicts of Interest

The authors have no conflict of interest to declare.

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