DESIGN DEVELOPMENT AND EVALUATION OF MEDICATED LOZENGES CONTAINING LAMOTRIGINE

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ABSTRACT

Lozenges are sweetened base medicated, flavored unit solid dosage form intended to be sucked or heald in the mouth which. These are medicated confections designed for local as well as systemic therapy. Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and neuropathic pain.In the current investigation, Six different formulations of Lamotrigine lozenges were prepared successfully on a laboratory scale by heating and congealing technique. Lozenges dosage formimprove bioavailability and increase patient compliance, especially for those patients who have difficulty in Swallowing. different ingredients i.e sucrose, dextrose, citric acid, coloring agent, and menthol were incorporated with polymer HPMC K100 and HPMC E5 in different ratios. In the lamotrigine lozenges formulatio. All the formulations prepared Lamotrigine hard lozenges evaluated for physicochemical parameters like hardness, friability, content uniformity, weight variation, thickness and drug content and in vitro dissolution studies. Stability studies of selected formulations of batch F5 have also been carried out at 40^{O}C and 75% relative humidity for Three months. There wasn't any substantial interaction between the drug, polymer, flavor and colour and the prepared formulations were found to be stable.

Keywords*: Lamotrigine, Epilepsy, in vitro dissolution, Lozenges, Stability study.*

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INTRODUCTION

Lozenges are solid sugar-based medicated unit dosage forms incorporated with another medicament for local and systemic effect therapy. Oral drug delivery is the most favorable convenient route for dose administration.It Can be given to those patients who have difficulty swallowing.Easy to administer to the geriatric and pediatric populations[1]. It has a pleasant taste. It extends the time of the drug in the oral cavity to elicit a specific effect.Easy to prepare, with a minimum amount of equipment and time.Lozenges dosage form improve bioavaibility by bypassing first pass metabolism hence dosing frequency also reduced and also reduce gastric irritation.It can improve the onset of action.[2]

Lamotrigine it is a antiepileptic drug used in treatment of epilepsy and neuropathic pain.Epilepsy, a serious psychiatric disorder, is defined as the repeated occurrence of excessive, synchronous and sudden discharges in cerebral cortical neurons that lead to disturbance of movements, impairment of cognitive function, and disruption of consciousness.

It is also defined as the recurrent occurrence of seizures. A seizure is a sudden rush of electrical activity in the brain.Epilepsy is a chronic non-communicable disease of the brain that affects people of all ages.Epilepsy is a group of neurological disorders which is characterized by seizures, loss of consciousness and muscular contraction.

Epileptic seizures are episodes that can range from brief, almost undetectable, to lengthy, intense trembling cycles. During epilepsy, seizures appear to recur and the underlying cause is not immediate.[3]

Some cases occur as the result of brain injury, stroke, brain tumors, infections of the brain and birth defects through a process known as epileptogenesis. Known genetic mutations also cause some cases of epilepsy. The diagnosis involves ruling out other conditions such as alcohol withdrawal or electrolyte problems. Epileptic seizures are the result of excessive and abnormal neuronal activity in the cortex of the brain.[4]

The pharmacokinetics of lamotrigine follows first-order kinetics, with a half-life of 29 hours and a volume of distribution of 1.36 L/kg.Lamotrigine is rapidly and completely absorbed after oral administration. Lamotrigine is disarmed by glucuronidation in the liver.Lamotrigine is metabolized mostly by glucuronic acid conjugation. Its major metabolite is an inactive 2-n-glucuronide conjugate.

Lamotrigine is a member of the sodium channel blocking class of antiepileptic drugs.This may suppress the release of glutamate and aspartate, two dominant excitatory neurotransmitters in the central nervous system.[5]

It is generally accepted to be a member of the sodium channel blocking class of antiepileptic drugs, but it could have further actions, since it has a full broader spectrum of action than other sodium channel antiepileptic drugs such as phenytoin and is effective in the treatment of the depressed phase of bipolar disorder, whereas other sodium channel-blocking antiepileptic drugs are not, possibly on account of its sigma receptor activity. In addition,

lamotrigine shares few side effects with other, unrelated anticonvulsants known to inhibit sodium channels, which further emphasizes its unique properties.[6]

MATERIALS AND METHOD

Lamotrigine is received as gift sample from Yarrow chem products. Pvt. Ltd., HPMC K 100 from Research lab fine Industries, Mumbai. HPMC E5 from Ozone International Mumbai, Sucrose,Dextrose of pharmaceutical grade, Citric acid procurd from Himedia laboratories Pvt.Ltd.Nashik and Menthol, Amaranth from Meher chemie, Mumbai.

METHOD OF PREPRATION

Medicated Lamotrigine lozenges were prepared by heating and congealing technique, at laboratory scale. Composition and quantities are given in table no 1. First of all sucrose was dissolved in one third amount of water and heated on heating mantle at 110^{O}C for 20 minutes. Then dextrose added to it and heated upto 160^{O}C until colour changes to golden yellow. The temperature of the mixture lowered to 90^{O}C, and Lamotrigine, with remaining excipients (polymers, flavour and colour) were added with continuous stirring and the solution was poured into lubricated mould. It was allowed to solidify to shape up, collected and rapped in alum foil and stored in air tight container.[7,8,10,16]

Table 1: Working formula for lozenges

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6
Lamotrigine	25	25	25	25	25	25
Sucrose	1005	997	990	1005	997	990
Dextrose	432	432	432	432	432	432
HPMC K 100	15	23	30	-	-	-
HPMC E5	-	-	-	15	23	30
Citric acid	23	23	23	23	23	23
Flavouring agent	Qs	Qs	Qs	Qs	Qs	Qs
Colouring agent	Qs	Qs	Qs	Qs	Qs	Qs

*Each medicated Lozenges contain a weight of 1500 mg.

*Each medicated Lozenges Contains 25mg of Drug.

EVALUATION OF FORMULATIONS

1. **Measurment of thickness**

   The thickness of lamotrigine lozenges were measured using Vernier calliper. Three lozenges from each batch were used and avarage values were calculated.[8]

2. **Hardness**

   The force required to break the lozenge by compression in diametric direction. The hardness of lmotrigine lozenges are measured by using monsanto Hardness tester, where the force required to break the lozenges was noted. Unit of measuring hardness as kg/cm^2.Ten formulations of each batch were used for the estimation of hardness.[8]

3. **Friability**

   The Rocha friability test apparatus was used to determine the friability of the lozenges. Six pre weighted lamotrigine lozenges were placed in apparatus, for 4min at 25 rpm. Then the lozenges were reweighted. The percentage friability was calculated by using the formula.[8,9]

   % Friability = (Initial weight- final weight)/ Initial weight × 100

4. **Weight variation**

   The Lozenges from each batch check randomly to ensure that uniform weight lozenges were being made. Weighing 20lozenges individually, calculating the average weight and comparing the individual weights to the average.[9]

5. **Drug content**

   An appropriate number of lozenges are crushed and dissolved in an appropriate solvent and therefore the absorbance of the answer is measured spectrophotometrically at 306 nm with blank lozenges extract as the refrences.[9]

6. ***In vitro* dissolution studies**

   *In vitro*dissolution studies of Lamotrigine lozenges were carried out in 900 ml phosphate buffer pH 6.8 using USP dissolution testing apparatus with arotating paddle speed of 100 rpm, and temperature of dissolution medium maintained at 37±0.5 ^{O}C. Aliquots of 5 ml were withdrawn at regular intervals; filtered and same amount of fresh dissolutuion medium was replaced at same temperature. The filtered solutions were analyzed by using (Shimadzu, Japan) UV spectrophotometer at 306 nm.[8,9]

7. **Moisture content analysis**

The sample was weighed and crush in mortar. From this, one gram of the sample was weighed and placed in adesicator for 24 hours. After 24 hours the sample is weighed. Calculated by following formula.[8,9]

% Moisture content = (Initial weight- final weight)/ Initial weight × 100

8. **Disintegration test**

The USP Disintegration apparatus was used to determine how long it took the candy to dissolve fully. Hard-boiled candy Lamotrigine lozenges were put in each tube of the apparatus, and the time it took for the lozenges to dissolve completely was measured using phosphate buffer pH 6.8 at 37 ºC. [9]

9. **Stability test**

For accelerated stability study, selected formulation was kept in airtight container according to ICH guidelines at 40 ºC & 75% relative humidity for 3 months.[9]

RESULT AND DISCUSSION

Result:

1. **Preformulation Study:**

A. Organoleptic Properties (Color, odor, taste and appearance)

Table2: Results of identification tests of drug

Sr.No	Parameter	Property
1	Colour	White to off white
2	Odor	Odorless
3	Taste	Tasteless
4	Appearance	Crystalline powder

B. Melting point determination of Drug: Lamotrigine

Table3: Results of Melting point determination test of drug

DRUG NAME	Melting point
Lamotrigine	216-218ºC

C. Solubility: Soluble in Methanol, DMSO, very slightly soluble in water

D. Standard Calibration Curve In the pre-formulation study, it was found that the λmax of Lamotrigine by thespectrophotometric method in phosphate buffer pH 6.8 was found to be 306nm.The spectrumwere shown in fig.1

Table 4 : Absorbance of Lamotrigine

Concentration	Absorbance
10	0.298
20	0.564
30	0.846
40	1.092
50	1.32

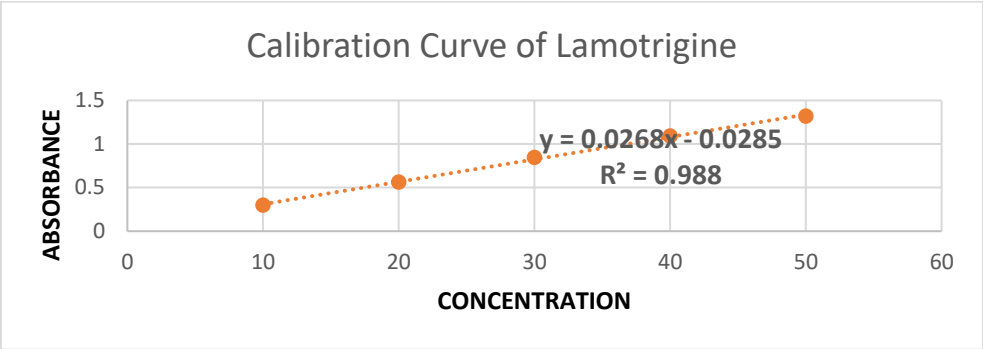

Fig 1: Calibration curve of lamotrigine

2. Identification of drug by FTIR

Identification of drug by FTIR spectroscopy -

FT-IR spectra were recorded in the region of 400–4,000 cm^{-1}. Assign the major absorption bands to change in absorption bands indicates incompatibility between drug & excipients.

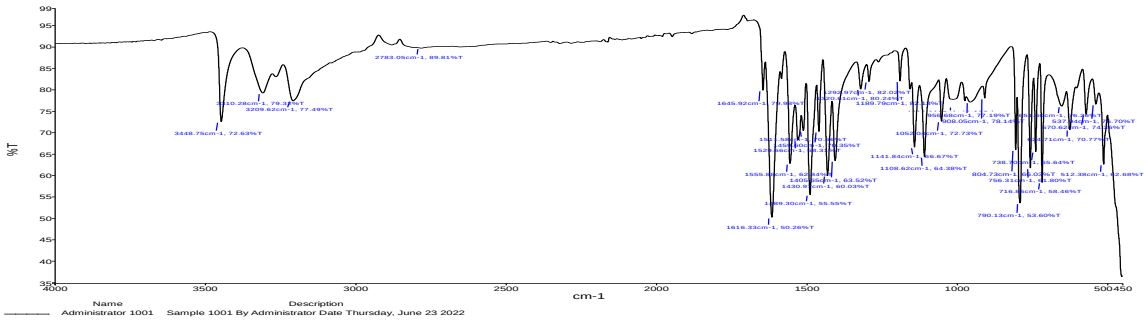

Fig.2: FTIR Of Lamotrigine

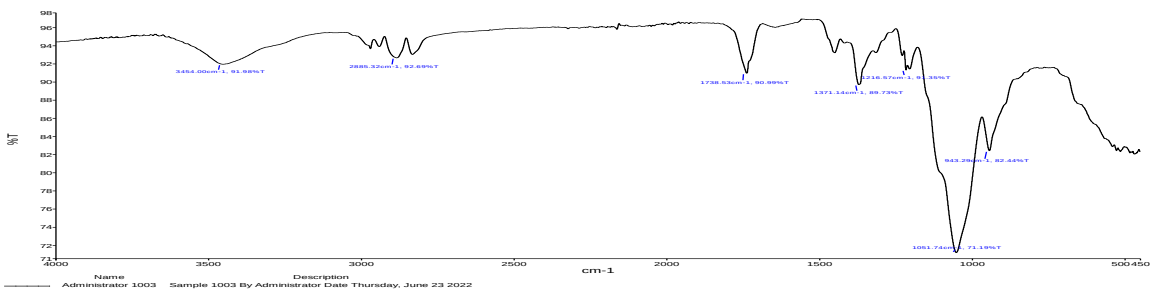

Fig 3: FTIR of Mixture (Drug+ HPMC K100 +Sucrose +Dextrose+Citric acid + Menthol + Suncent+Amaranth)

Batch code	Hardness (Kg/cm^{-1})	Thickness (mm)	Weight variation	Moisture content (%)	In Vitro Disintegration Time (min)	Friability (%)	Drug Content (%)
F1	9.07	7.12	2.925	0.87	9.02	0.62	96.02

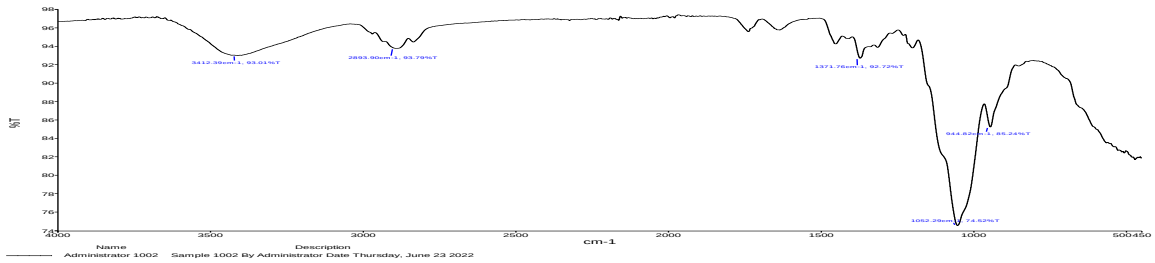

Fig 4: FTIR of Mixture 2 (Drug+HPMC E5 +Sucrose+Dextrose+ Citric acid+ Menthol+ Amaranth)

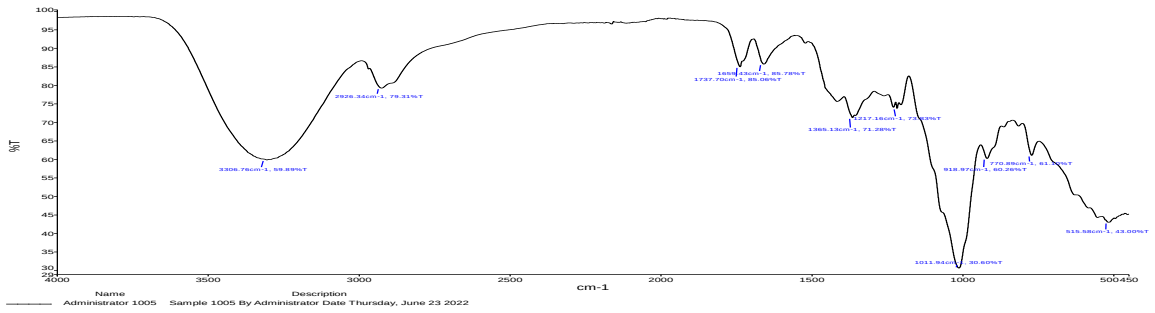

Fig 5: FTIR of formulation(Medicated lamotrigine lozenges)

2. Physicochemical parameter of prepared lozenges.

Table 5: Physicochemical parameter of prepared lozenges.

F2	10.02	7.50	2.981	0.85	9.20	0.78	96.16
F3	10.12	7.13	3.031	1	10.02	0.72	95.55
F4	10.02	7.11	2.923	0.95	9.12	0.50	94.46
F5	10.50	7.20	2.983	0.81	10.18	0.71	97.12
F6	11.00	7.15	2.991	0.90	10.16	0.76	96.10

4. In Vitro release profile of medicated lozenges

Table 6: Cumulative Percent of Lamotrigine was released from lozenges.

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	35.71	28.10	27.20	41.67	38.18	36.54
10	53.52	38.43	36.62	55.12	52.12	48.12
15	66.12	55.12	47.12	71.16	68.10	61.08
20	73.10	68.20	56.98	79.91	80.18	70.12
25	81.21	83.16	70.11	87.21	90.06	78.40
30	90.02	91.12	86.20	91.08	94.02	86.29

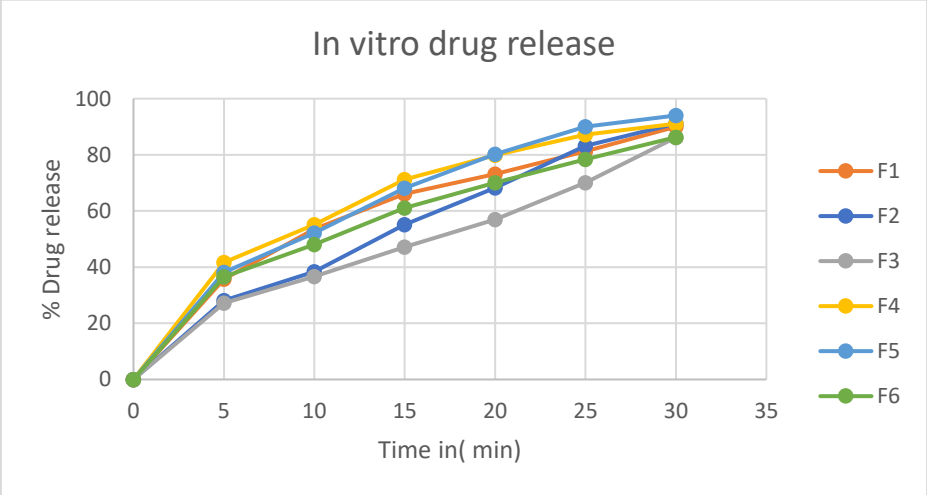

Fig 6 : Invitro drug release study profile of different formulation

5. Stability Study

A stability study was used for establishing assurance of safety, quality, and efficacy of the drug product from early phase development through the drug product. Three month stability study was done, the appearance of lozenges remained clear and no significant variation in pH was observed after subjecting the formulation to stability study for 3 month at 40 °C and 75% relative humidity. There was no significant change in the percentage of drug release after the stability study.[7]

Table 7: Evaluation of optimized formulation after stability

Evaluation parameter	0 day	Stability study after 1 month	Stability study after 2 month	After a stability study of 3 month
Hardness	10.50 kg/cm^2	10. 40 kg/cm^2	10.25 kg/cm2	10.12 kg/cm2
Thickness	7.20 mm	7.18 mm	7.12mm	7.10 mm
% weight variation	2.98 %	2.90 %	2.80 %	2.75 %
% Friability	0.71 %	0.75 %	0.82%	0.95 %
Disintegration time	10.18 min	10.10 min	10 min	9.20 min
Drug content	97.12 %	97.10 %	97.7%	97.05 %
% Drug release	94.12 %	94.02%	93.80%	93.20 %

DISCUSSION

In the current investigation, Six different formulations of Lamotrigine lozenges were prepared successfully on a laboratory scale by heating and congealing technique. Different ingredients i.e sucrose, dextrose, citric acid, coloring agent, and menthol were incorporated with HPMC K100 and HPMC E5 in different ratios. In the lamo. All the formulations prepared Lamotrigine hard lozenges evaluated for physicochemical parameters like hardness, friability, content uniformity, weight variation, thickness and drug content, results are reported in Table 5. The Thickness of the formulations was in the range of 7.12mm to 7.50mm which indicates uniformity for all formulations. Weight variation was found to be in the range of2.925% to 3.031%. The hardness of the formulations was in the range of 9.07 to 11 kg/cm^2 . Friability was between 0.50 and 0.78%. The results of hardness and friability indicated that the lamotrigine lozenges formulations were mechanically stable. Drug content was found to be in the range of 90.02 to 94.12%. The disintegration time of all lamotrigine lozenges formulations lies between 9.02 to 10.18 min. Thus, it can be concluded that all the formulations passed the physicochemical evaluation. An in-vitro release study was performed for 30 minutes, the results are shown in the figure. The percentage of drug release was found in the range of 86.20 to 94.20%. Lamotrigine lozenges formulations of batch F5 showed a release of 94.20% in 30 minutes, which was relatively faster in comparison to the other formulations. During a stability study of 3 months of selected lamotrigine lozenges formulations of batch F5, it was observed that the no change and all evaluation parameter, within the pharmacopeia limits hence formulation is stable.

CONCLUSION

From present study it is concluded that sucrose based medicated lozenges will be an alternative dosage forms. This will have additional advantages of patient compliance, convenience and comfortness for effective treatment including low dose, immediate action,

reduced dosage regimen and economy. That incorporating polymers like HPMC K100 and HPMC E5 can be used to formulate effective medicated Lamotrigine lozenges, especially for patients who cannot swallow solid oral dosage forms like tablets and capsules.

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