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New Konjac Gum Based Rapidly Disintegrating Oral Ultra Thin Film of Lamotrigine for Childhood Epilipsy

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ABSTRACT
The study's objective was to develop and characterize an oral thin film (OTF) based on konjac gum for lamotrigine using the solvent casting process. Glass, PEG 400, and aspartame were chosen as the casting surface, water-miscible plasticizer, and sweetener for OTF, respectively, based on preliminary tests. The film was assessed for its overall OTF flavor, physical appearance, surface texture, uniformity of drug content, thickness, in-vitro and in-vivo disintegration times, surface pH, and in-vitro drug release in phosphate buffer at pH 6.8 after 15 minutes. It was determined that batch OTF8's oral thin film (PEG 400, 200 mg; aspartame, 10 mg) was a randomly optimized batch with In-vitro and In-vivo disintegration times of 10 and 12 seconds, drug release of 95.94%, Q15 minutes, thickness of 0.03, surface pH of 6.6, uniformity of weight of 35.4 mg, and easiness to administer. Konjac Gum PEG 400 and aspartame are combined to produce palatable, stable OTF of lamotrigine. This is supported by the smooth mouthfeel, excellent overall taste, FTIR study that showed no interaction between the drug and excipient, even distribution of all ingredients in Konjac Gum OTF (SEM study), and stable film at specified conditions.

Keyword: Lamotrigine, Konjac Gum, aspartame fast dissolving oral film, Epilipsy

I. INTRODUCTION

The oral route of drug delivery is currently the industry standard since it is thought to be the most practical, secure, and cost-effective one. However, there are still certain issues with it that are specific to a group of patients, such as elderly, pediatric, and dysphasic patients who have trouble chewing or swallowing solid dose forms due to a variety of medical disorders. Early in the 19th century, Fast Dissolving Tablets (FDTs) were developed to deal with a variety of issues with swallowing, chewing, and choking [(1)]. Fast-dissolving medication delivery methods have many advantages over traditional dose forms. Due to the drug's fast disintegration and ability to dissolve in saliva without the need for water [(2)]. Because of the thin membrane and high blood flow in the oral mucosa, which is relatively permeable to drugs, fast drug absorption and bioavailability are achievable. The first pass effect and GI tract degradation can be avoided because the drug is directly absorbed into the systemic circulation [(3)]. Furthermore, because this method does not require swallowing like a traditional pill does, it is projected to have higher patient compliance. Patients who have dysphagia or difficulties swallowing can benefit from it. The films' ability to stick to the oral mucosa for improved retention and medication absorption is made possible by the use of mucoadhesive polymers [(4)]. simplicity of organization of measurement structures is of paramount significance, particularly among patients experiencing Alzheimer, Bipolar turmoil, Headache, Parkinson and Schizophrenia. Among a wide range of measurements structure, OTF is exceptionally acknowledged due to its own benefits alongside simplicity of oral conveyance of various drugs (e.g., analgesics, allergy meds, enemies of asthmatics, cardiovascular medications, neuroleptics, and medications for erectile brokenness). As per world organization of nervous system science, headache is a familiar jumble portrayed by repetitive assaults of cerebral pain, widely variable in power, recurrence and span. The WHO ranks migraine as the most in capacitating clinical ailment.

Zolmitriptan (ZMT), a 5-HT receptor agonist of BCS class III, has been broadly pre-

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scribed for patients with headache assaults, no matter what an aura, and bunch cerebral pains. It is immensely viable in lessening migraine symptoms, including agony, queasiness and photograph/phonophobia. It is available as regular oral tablets (2.5, 5 mg), mouth dissolving tablets (2.5 mg), and nasal splashes (5 mg) in the market (5) quick dissolving films are acquiring revenue as a choice to quick dissolving tablets to dispose of patients' apprehension about chocking and conquer patent obstacles. Quick dissolving films are for the most part comprised of plasticized hydrocolloids or mixes made of there of that can be overlaid by dissolvable projecting or hot-meltextrusion [(6)].

Advantages of an oral fast dissolving films

1. Oral thin film is more stable, durable and quick dissolving than other conventional dosage forms.
2. After placing it on the top of the tongue, the film dissolves within seconds, avoiding first pass metabolism and may increase the bioavailability of drug
3. The first pass effect can be avoided, so a reduction in the dose which can lead to reduction in side effects associated with the molecule
4. Oral fast dissolving films can be administered without water, anywhere, any time.
5. Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity
6.Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed
7. Bioavailability, as compared liquid formulations, precision in the administered dose is ensured from each strip of the film.

Disadvantages (27**)**

1. High doses cannot be incorporated.
2. Dose uniformity is a technical challenge
3. It is hygroscopic in nature so it must be kept in dry places.
4. It also shows the fragile, granule property.
5. They require special packaging for the products stability.

Anatomy of oral cavity

The oral cavity presents a surface area of around 100 cm the thickness of buccal mucosa is estimated to be 500-800 µm. Three distinct sorts of oral pit are perceived, Lining mucosa Masticatory mucosa

Lining mucosa (60% of complete oral mucosa) is 500-800µm in thickness and covers lips, cheeks, delicate sense of taste, lower surface of tongue and floor of the oral hole Masticatory mucosa addressing 25% of absolute oral mucosa is 100-200 µm in thickness and covers the gingival and hard sense of taste. It is firmly appended to fundamental construction and exposed to scraped spot and shear pressure during rumination the particular mucosa (15% of complete oral mucosa) is tracked down on dorsum of tongue and associated with taste.

Functions of Oral Cavity (28**)**

□ □ As a portal for intake of food material and water
□ □ Identification of ingested material by taste buds of tongue
□ □ To aid in speech and breathing process
□ □ Initiation of carbohydrates and fat metabolism and absorption of catabolic products after
□ □ metabolism catabolic products after metabolism
□ □ To bring chewing, mastication and mixing of food stuff.

Secretions of Oral Cavity

Saliva Spit is intricate liquid containing natural and inorganic materials. It is created by three sets of significant organs viz, parotid, sub mandibular and sublingual organs arranged in external the oral pit and in minor salivary organs arranged in tissues lining the greater part of the oral pit. The outer layer of oral depression is continually washed with a surge of spit roughly 1litre/day by salivary organs. The pH of spit changes from 6.5 to 7.5. It has a low buffering limit and chief support of spit being bicarbonate. Synthetically spit comprises of 99.5% water 0.5% solute incorporates sodium, potassium, calcium, phosphate, bicarbonate, chloride, urea, uric corrosive, serum egg whites, mucin, catalysts and broke up gases.

Mucus: Bodily fluid is a thick liquid made out of chiefly of water, electrolytes and a combination of a few glycoproteins. Bodily fluid is discharged in buccal pit which assists with creating spit. safeguards organic films and goes about as incredible grease. The oral pit might be isolated into two locales, the external oral vestibule, limited by the lips and cheeks and the oral depression itself the lines being, and shaped by the hard and delicate palates, the floor of the mouth and tonsils.

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Tissue	Structure	Epithelial Thickness (µm)	Blood flow (ml/min/cm)
Buccal	Non-Keratinized	500-600	2.40
Sublingual	Non-Keratinized	100-200	0.97
Gingival	Keratinized	200	1.47
palatal	Keratinized	250	0.89

Table 1: Regional variations in the composition of oral mucosa

Theories of muco/Bioadhesion

Many theories have been proposed to explain the forces that under in bioadhesion.

1) Electronic theory:

In this hypothesis different electronic property of the mucoadhesive polymer and the bodily fluid glycoprotein, electron move between these two surfaces happens. Electron move contributes to development of a charged two fold layer at the connection point of the bodily fluid and the polymer, which brings about powers of fascination around here and entombs dispersion of the two surfaces.

2) Adsorption theory:

The essential and optional synthetic obligations of the covalent and non-covalent (electrostatic, Vander walls' powers, hydrogen and hydrophobic bonds) types are framed upon starting contact between the bodily fluid and the mucoadhesive polymer. The majority of the underlying interfacial holding powers is ascribed to non-covalent powers.

3) Wetting theory:

The capacity of a bioadhesive polymer to spread organic surfaces. This hypothesis is prevalently relevant to fluid bioadhesive frameworks decently wettable polymers have been displayed to show ideal grip to human endothelial cells.

4) Diffusion theory:

The essential associated with this hypothesis is chain entrapment between glycoproteins of the bodily fluid and mucoadhesive polymer. Upon beginning contact between these two polymers, dissemination of the bio adhesive polymer chain into the bodily fluid organization makes an ensnared network between the two polymers. Adequate polymer chain adaptability, satisfactory openness for the surface contact of the two polymers, comparable compound designs, and the dispersion coefficient of the bio adhesive polymer are among the component s which impact the bury dissemination of the macromolecule organization.

5) Fracture theory:

It relates the power expected for the unit of polymer s from bodily fluid to the strength of their glue bond. It has been found that work crack is more noteworthy when the organization strands are longer or the level of cross-connecting is reduced.

Product	Active drug	Dose strength (mg)	Application	Company
Triaminic33	Dextromethorphan HBr	5/7.5	Seasonal allergy	Novartis
Triaminic33	Diphenhydramine HCl	12.5	Thin Strip for Long-acting cough	Novartis
Theraflu32	Dextromethorphan HBr	10/20	For Long-acting cough	Novartis
Gas-X32	Simethicone	62.5	Gas-X Thin Strip Anti Gas	Novartis
Sudafed PE34	Phenylephrine HCl	10	Decongestant oral strips	Pfizer
Benadryl32	Diphenhydrami	12.5	Antihistaminic	Pfizer

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	ne HCl		oral strips	
Chloraseptic	Benzocaine: Menthol	3/3	Chloraseptic Relief Strips	Prestige

Table 2 Examples of commercially available Fast Dissolving Oral Films (46,47,48,49**)**

MACHANISM OF ACTION:

To the inactive sodium channel,suppressing the relese of the Lamotrigine likely act by inhibiting sodium current by selective binding excitatory amino acid,glutamate.The mechanism of action of lamotrigine in reducing anticonvulsant activity is likely the same in manageing bipolar disorder .

CLINICAL PHARMACOLOGY:

Absorption:

Lamotrigine is well absorbed with bioavailability approaching 100%. The absorption is unaffected by food and there is no first-pass metabolism. The volume of distribution is between 1.25 and 1.47 L/kg and protein binding is about 55%.

Distribution:

Plasma Protine Binding is about 55%, The volume of distribution is between 1.25 nd 1.47L.

Metabolism:

Lamotrigine is inactivated by glucuronidation in the liver lamotrigine is metabolized predominantly by glucuronic acid conjugation, inactivate 2-n-glucuronide.

Excretion:

Lamotrigine is excreted in both urine and feces following oral administration of 240mg radiolabeledlamotrigine, about 94% of total drug and its metabolites administered is recovered in the urine and 2% is recover in the feces.

Material and Method

MATERIAL

The following drug, excipients and chemicals were used for the formulation and evaluation of fast dissolving oral film are given in Table

List of drug, excipients, chemicals and its supplier

Drug	**Supplier name**
Lamotrigine	Glenmark Pharmaceutical Industries Ltd, Mumbai, India
Excipient	**Supplier name**
Konjac Gum	Sarda Polymers,India
Glycerol	Sigma Aldrich Gmbh, USA
Propylene glycol	Merck Pvt. Ltd, Mumbai, India
Polyethylene glycol 400	General Market, Shirpur
Aspartame	Loba Chemie Ptd. Ltd, Mumbai, India
Strawberry	Merck Pvt. Ltd, Mumbai, India
Citric acid	Merck Pvt. Ltd, Mumbai, India
Methanol	Qualigens Ltd. Mumbai
-	Qualigens Ltd. Mumbai

Table 3 List of drugs, excipients, chemicals and its supplier

PREFORMULATION STUDY

Preformulation study is one of the important prerequisites in development of any drug delivery system. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies on the obtained sample of drug for identification including solubility analysis, melting point determination and compatibility studies were performed.

I. Identification and confirmation of drug

Confirmation of drug was carried out by melting point determination, FTIR, DSC, Capillary method and UV spectroscopy.

A) Infrared Spectroscopy

IR spectrum of drug was measured in the solid state as potassium bromide mixture. FTIR spectra of Lamotrigine were obtained by using a FTIR spectrometer-8400. The samples were previously ground and mixed thoroughly with potassium bromide (KBr), an infrared transparent

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matrix at 1:100 (sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders, under force of 15 tonnes for 5 min in a motorized pellet press. The obtained peck was compared with the reference standard IR spectrums of the drug.

B) UV Spectroscopy

1. Blank was place (methanol) in U.V. cabinet.
2. Base line determination was carried out
3. The given sample of Lamotrigine was place in UV cabinet and scanned at 400nm 200nm to calculate λmax of Lamotrigine

C) Melting point determination Capillary method

Melting point determination is prime confirmation of drug. In this method, drug whose analysis to be carried out was filled into capillary tube and tied to the thermometer in such a way that it remains dipped in liquid paraffin bath. The temperature range at which the drug starts melting and complete melting was noted.

DSC

The melting temperature of drug was confirmed by DSC. In which thermogram of Lamotrigine was obtained using DSC. The drug was hermetically sealed in perforated aluminum pans and heated at constant rate of 10°C/min over the temperature ranges of 35-280°C.

Standard Calibration Curve

Calibration curve of Lamotrigine in distilled water, methanol, pH 6.8 buffer was determined using UV visible spectrophotometer.

I. Calibration curve in distilled water

10 mg of Lamotrigine was dissolved in 100 mL of distilled water to obtain working standard of 100 µg/mL Aliquots of 0.3 mL to 1.8 mL from the stock solution representing 0.3 to 20 µg/mL of drug concentration were transferred to 10 mL volumetric flask and the volume was adjusted to mark with water. Absorbances of the above solution were takenat λmax 310 nm against the blank solution prepared in the same manner without adding the drug.

II. Calibration curve in methanol

10 mg of Lamotrigine was dissolved in 100 mL of methanol to obtain working standard of 100 µg/mL Aliquots of 0.2mL to 1.2 mL from the stock solution representing 0.2 to 20 µg/mL of drug concentration were transferred to 10 mL volumetric flask and the volume was adjusted to mark with methanol. Absorbances of the above solution were taken at λmax 310 nm against the blank solution prepared in the same manner without adding the drug.

III. Calibration curve in pH 6.8

10 mg of Lamotrigine was dissolved in 100 mL of pH 6.8 buffer to obtained working standard of 100 µg/mL Aliquots of 0.2 mL to 1.2 mL from the stock solution representing 0.2 to 20 µg/mL of drug were transferred to 10 mL volumetric flask and the volume was adjusted to mark with pH 6.8 buffer. Absorbances of the above solution were taken at λmax 310 nm against the blank solution prepared in the same manner without adding the drug.

Solubility studies

The solubility determination is very vital parameter in the development of fast dissolving oral film formulation. Initially solubility of drug in various vehicles should determine, vehicles which shows maximum solubility for drug. The solubility of Lamotrigine in various vehicles i.e.water, methanol and phosphate buffer 6.8pH was determined initially. A total of 5 mL of each of the selected vehicles were added to each cap vial containing an excess lamotrigine.

II. FORMULATION AND DEVELOPMENT

Formulation of oral fast dissolving film (63).

Konjac Gum is known for its good film forming properties and has an excellent acceptability. Glycerin or propylene glycol and polyethylene glycol 400 as a plasticizer. and were used as a super disintegrants. Citric acid as saliva stimulating agent, Aspartame as a sweetening agent and strawberry as a flavoring agent. The fast-dissolving films of Lamotrigine wereprepared by solvent casting technique using Konjac Gum as a film forming polymer. PEG 400 is used as plasticizer. The calculated amount of polymer was dispersed in 40/10 volume of water with continuous stirring using magnetic stirrer and the final volume of 10 ml with distilled water. The calculated amount of Lamotrigine incorporated in the polymeric solutions after levigation with required volume of PEG 400. and oral film solution are completely homogenization solution. The solution was casted on to Petri dish (Anumbra@, area of 66.31cm2) then kept in hot air oven at 40°C

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for 24 h. The films were punched in to size of 2 cm diameter (an area of 6.28 cm2) containing 10 mg of Lamotrigine.

Evaluation and characterization of oral fast dissolving films

Physical appearance and surface texture

Physical appearance by includes visual inspection of films by touching the surface

Weight uniformity

Uniformity three OTF of each batch (2 × 2 cm2) was weighed individually using a digital single pan analytical weigh balance (AUX 120, Shimadzu, Japan) and their mean weight was determined. **Uniformity of thickness** (64,65)

The thickness of each OTF (2 × 2 cm2) was measured in triplicate using a calibrated digital vernier caliper (Mitutoyo 550-203-10, Mitutoyo, Japan) at five points i.e., the four corners and a center of films before evaluations of mechanical properties such as ultimate tensile strength, folding endurance, and elongation at break. Mean thickness values of each OTF were calculated and used indetermination of the ultimate tensile strength of OTF.

Folding endurance

Folding endurance of each batch was determined manually in triplicate by repeatedly folding the OTF (2 × 2 cm2) at the same point until it ruptures. The counting of folding made before the film ruptured was denoted as the mean folding endurance.

Surface pH (66)

The film of each batch (2 × 2 cm2) was placed in a closed petri-plate containing 5 ml of distilled water at room temperature and the surface pH was measured using a digital pH meter (Equiptronics,EQ-611, Mumbai, India) to check whether the film causes an irritation to the tongue or mouth. After moistening of OTF, pH probe was placed in close contact with the wetted film and the surface pH was identified.

In-vitro disintegrating time

It was determined for each OTF (2 × 2 cm2) in triplicate to get mean disintegration time using a glass petri-plate (3.5-inch internal diameter, 1 inch height) containing 10 ml of phosphate buffer of pH6.8 (maintained at 37 ± 0.5◦C) to mimic saliva pH [28,29].

In-vivo disintegration time

This test was measured in triplicate for each batch using a panel of 9 human volunteers. The OTF (2 × 2 cm2) was placed on the tongue of each volunteer and time required for disintegration in mouth was recorded as mean value in seconds.

Uniformity of drug content

This test for each batch OTF was estimated using the UV–spectrophotometer (UV 1700, Shimadzu, Japan). Drug content per film was estimated by random sampling of all batches. The OTF (2 × 2 cm2) was placed in a 100 ml volumetric flask and dissolved using phosphate buffer (pH 6.8). It was suitably diluted and its absorbance was measured at 310 nm. The drug content was determined as mean of three determinations using standard calibration curve represented by five known concentrations of Lamotrigine ranging from 2 to 12_g/ml (r2= 0.9999) in phosphate buffer (pH 6.8).

In-vitro dissolution study

This study was performed in triplicate, employing (Shimadzu 1700, Japan) basket apparatus (type I) using 300 ml phosphate buffer (pH 6.8) at 50 rpm and 37 ± 0.5◦C [34]. Aliquots of 5 ml were withdrawn periodically and replenished with an equivalent volume of the same fresh medium. Samples were filtered through a filter paper (0.45 _, Millipore filter) and the amount of drug released was determined at 310 nm employing a UV–vis spectrophotometer. The cumulative amount of drug release against time was calculated using a standard calibration curve of Lamotrigine in phosphate buffer (pH 6.8).

Scanning electron microscopy (63)

The surface morphology of optimized batch of LMT loaded Konjac Gum based OTF was examined using scanning electron microscope (JEOL-JSM 5610LV, Japan), operating at 15 kV to check even or rough distribution of strawberry (flavors) and aspartame (sweetener) along with PEG 400 (plasticizer) and LMT. Keeping fixed proportion of PEG400, LMT and Konjac Gum, ondansetron hydrochloride loaded pullulan based OTF of batch OTF8samples (A, with flavor and sweetener; B, without flavor and sweetener) were used for this study. Such specimens were mounted on a metal stub with double-sided adhesive tapes and images were taken at 15 kV at two different magnifications.

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Comparison between marketed and lab-scale preparation oral film

The preparation and formulation fast dissolving oral film of Lamotrigine formulation to lab scale and compare to market formulation of oral film and crucial parameter are used in formulation of oral thin film Thickness, drug content, surface pH, weight uniformity, folding endurance, In-vitro disintegration time, In-vivo disintegration time and In-vitro dissolution this are all parameter are compared to lab scale preparation fast dissolving oral thin film.

Stability studies (63)

Stability study of the optimized batch OTF8 was performed at 40 ± 2◦C/75 ± 5% RH in programmable environmental test chambers (Ostwald Scientific Equipment Pvt. Ltd., Mumbai, India) for three months. The samples were packaged in tightly closed rectangular aluminum sachets (3 × 3 cm2) and evaluated for appearance, Thickness, weight variation and Drug content at before and after three months storage.

III. RESULT AND DISCUSSION;

Several methods were described in the previous chapter for the development and evaluation of fast dissolving oral film containing Lamotrigine drugs. These formulations were intended to produce immediate release of drugs in the oral region. The result and discussion under different heading as follows.

Preformulation study

Melting point

Sr.no		BY capillarymethod	Observedmeltingpoints	Methodsused
1		Lamotrigine	216-2180C	By capillary method
			2160C	Electronic melting point apparatus
			2160C	Differential Scanning Calorimetry
2		Konja Gum	2470C	By capillary method

Table4. Melting points determination of drugs and polymer

The DSC thermogram of pure drug and polymer utilized in the system of formulation are presented in following

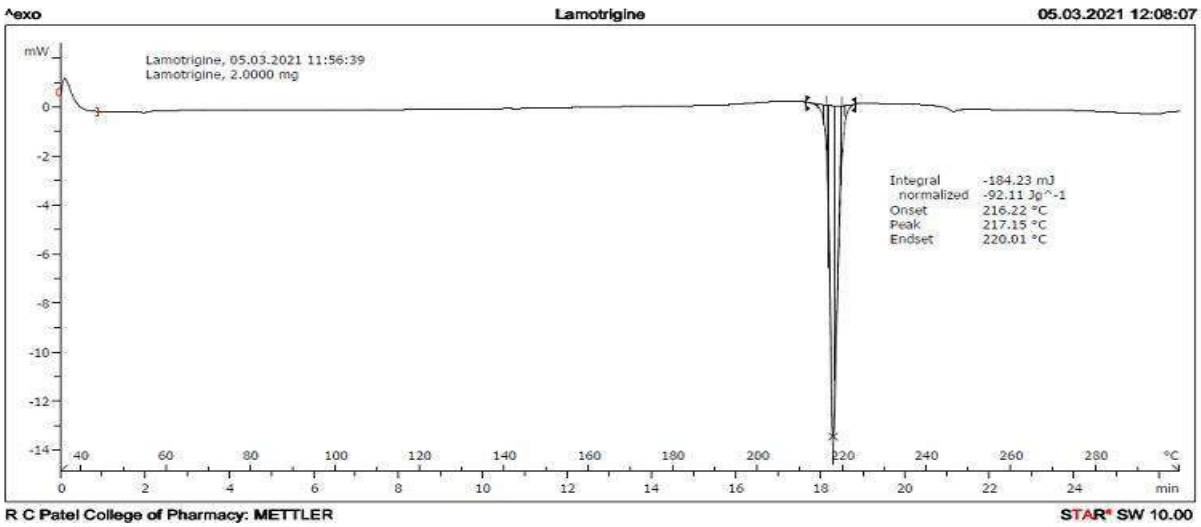

Figure- 1DSC graph of Lamotrigine

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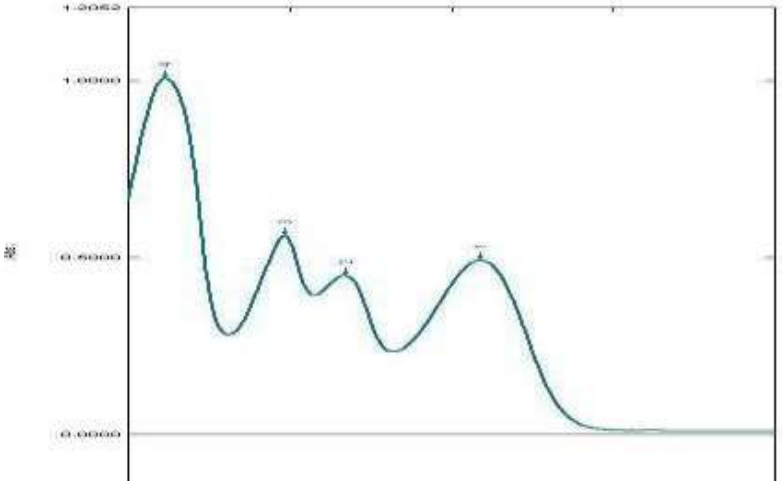
Table 5

Peak	217.15°C
Onset	216.22°C
End set	220.01°C

UV Spectroscopy method

Lamotrigine solution was scanned at 400 nm to 200 nm, an absorbance maximum was observed at 270 nm as shown in **Figure-12** that was reported absorbance maximum of Lamotrigine in methanol.

Figure-2: UV spectrum of Lamotrigine solution in methanol



Calibration curve for Lamotrigine in PBS pH 6.8

Calibration curve of Lamotrigine in PBS pH 6.8 was plotted in belows figure calibration curve of Lamotrigine with the correlation coefficient 0.999 and regression value of y=0.033x+0.007.

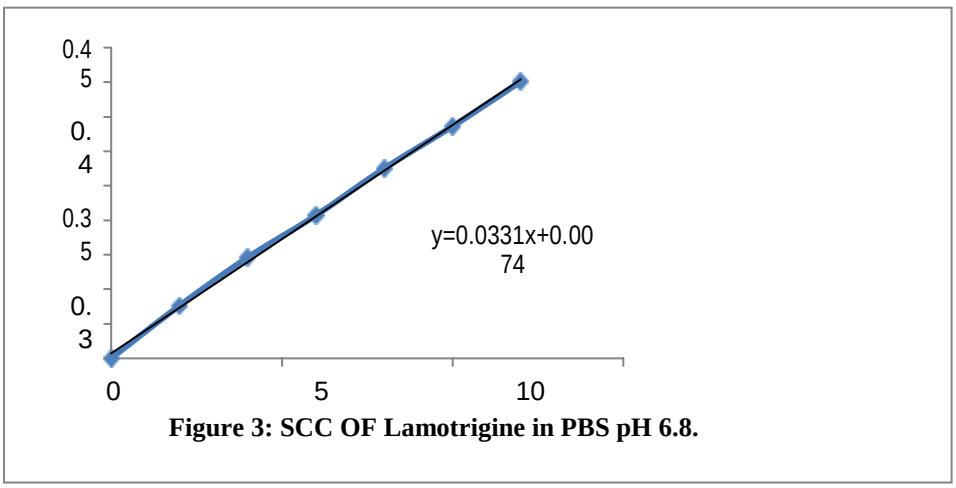


Figure 3: SCC OF Lamotrigine in PBS pH 6.8.

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Table 5. Concentration Vs Absorbance of Lamotrigine

Sr no.	Concentration ug/ml	Absorbance
1	2	0.076
2	4	0.146
3	6	0.207
4	8	0.275
5	10	0.336
6	12	0.401

Standard calibration curve of LMT in water

Figure4:SCCOF Lamotrigine in water

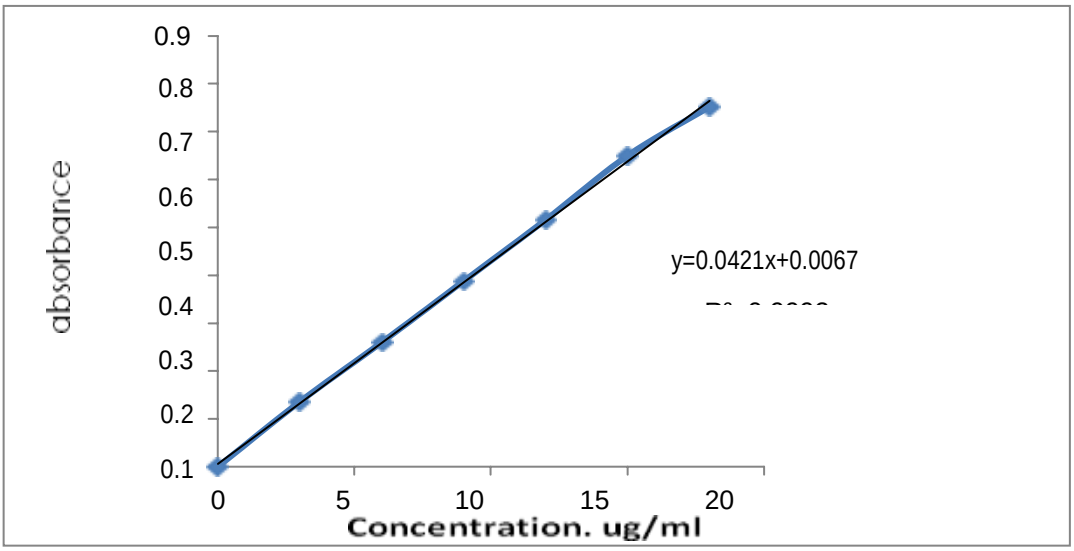

Table 6. Concentration Vs Absorbance of Lamotrigine

Sr no.	Concentration ug/ml	Absorbance
1	3	0.136
2	6	0.260
3	9	0.388
4	12	0.516
5	15	0.650
6	18	0.750

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Figure5:SCCOF Lamotrigine in methanol

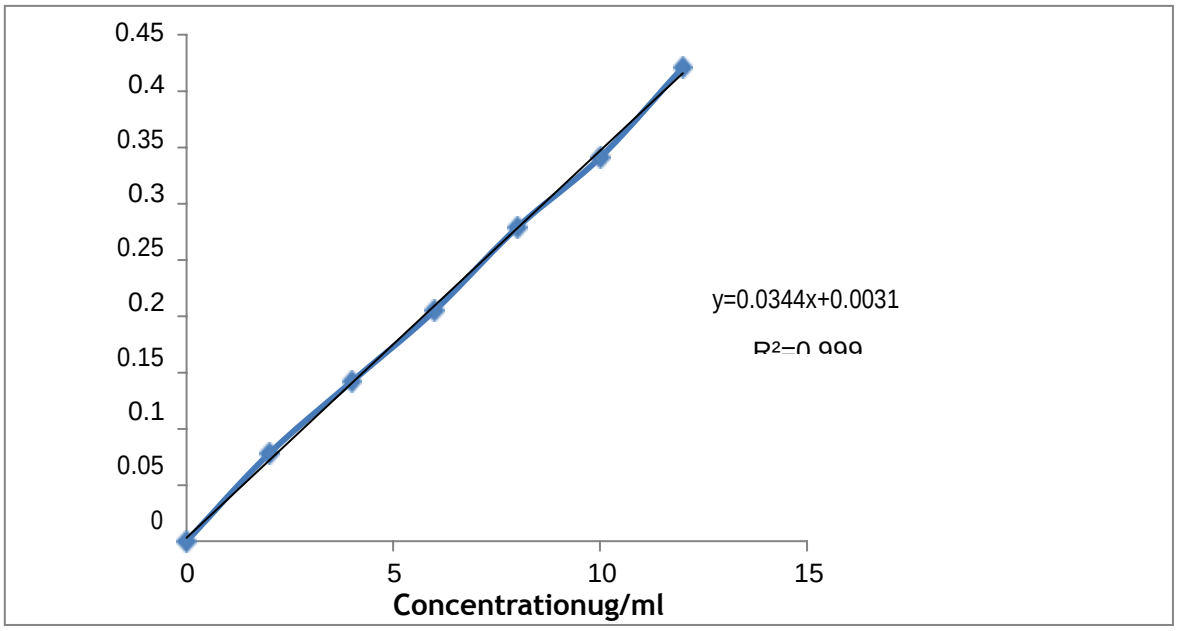

Table 7. Concentration Vs Absorbance of Lamotrigine

Sr no.	Concentration ug/ml	Absorbance
1	2	0.078
2	4	0.142
3	6	0.205
4	8	0.273
5	10	0.341
6	12	0.421

Drug –excipients Interaction studies

As described in the methodology FT-IR studies were carried out on pure drugs Lamotrigine and polymer.IR spectra Lamotrigine with Combination of konjac gum are shown in figures.

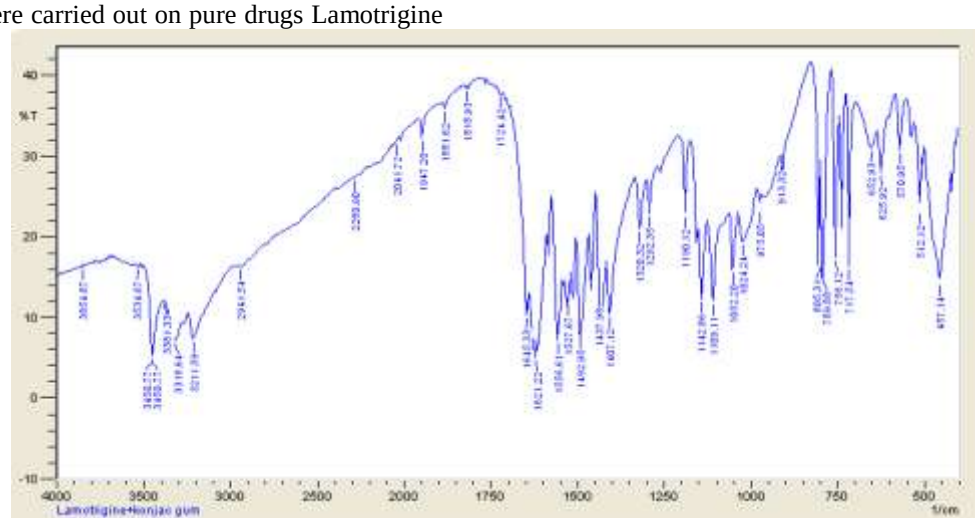

Figure6. Infra –Red spectra of Lamotrigine and konjac gum

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Functional group	Observed peaks	Peak ranges
C-H stretch	2945.40	2850-3000
C-O stretch	1182.40	1125-1205
C=O stretch	1687.77	1640-1690
C-F stretch	1014.59	1000-1350
N-H stretch	3321.53	3310-33350
C-H bend	838.45	690-710

Table 8: Interpretation of IR spectra of drug gum

Formulations of films-

Formulation of oral fast dissolving oral film by solvent casting method.

A B C

Figure7: Formulation of oral fast dissolving oral film by solvent casting method

Evaluation of parameters of prepared films

1. Physical appearance and surface texture

Formulation code	Physical appearance	Surface texture
OTF1	white in color	Smooth
OTF2	White	Very smooth
OTF3	White	Smooth
OTF4	White	Very smooth
OTF5	Light brown	Smooth
OTF6	White	Very smooth
OTF7	Light brown	Smooth
OTF8	White	Very smooth
OTF9	White	Very smooth

Table9. Physical appearance and surface texture

2. Thickness uniformity of films

The thickness of drug loaded film were measured with the help of Digimatic caliper the mean values are shown in table no.16

Formulation code	Mean thickness(mm)
OTF1	0.06
OTF2	0.04
OTF3	0.05
OTF4	0.03
OTF5	0.03
OTF6	0.04
OTF7	0.05
OTF8	0.02
OTF9	0.03

Table 10: Thickness ranges of prepared films

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3. Folding endurance of prepared films

Folding endurance was measured by manually for the prepared films. A strip of film (2×2cm) was cut evenly and repeatedly folded at same place till it broke.

Formulation code	Folding Endurance
OTF1	163
OTF2	180
OTF3	177
OTF4	190
OTF5	196
OTF6	210
OTF7	263
OTF8	289
OTF9	272

Table 11: Folding endurance of prepared films

4. Weight uniformity of prepared films

Drug loaded film was tested for uniformity of weight and the results are given in the table The weight of all the prepared films was found to quite uniform. Standard deviation of all the films ranged between 126-142.The change in the concentration of polymers and plasticizer did not show the difference in the weight of film.

Formulation code	Average weight (mg)
OTF1	52.4
OTF2	54.3
OTF3	54.8
OTF4	51.5
OTF5	49.3
OTF6	48.6
OTF7	40.9
OTF8	35.4
OTF9	41.3

Table 12. Weight uniformity of prepared films

5. In-vitro disintegration time

This study represents an indication of onset of action of drug desired for OTF formulation [26]. Fig. 3a–d illustrates the in-vitro disintegration study of LMY loaded Konjac Gum based OTF in phosphate buffer (pH 6.8) at specific time interval. The mean time for complete disintegration of OTF was obtained below 5sec (Table 19) and completely disappearance into solution was within 10sec indicating that as the concentration of plasticizer increased, the disintegration time of film was also increased.

0sec disintegration 5sec disintegration 7sec disintegration 10sec disintegration

Figure 8: In-vitro disintegration time

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Formulation code	Disintegration time(sec)
OTF1	21
OTF2	23
OTF3	23
OTF4	20
OTF5	18
OTF6	20
OTF7	13
OTF8	10
OTF9	15

Table 13: Disintegration time of prepared films

6. In-vivo Disintegration time (humanvoluntary)

Results of In-vivo disintegration study (Table 20) clearly indicating that as the amount of plasticizer increased an in-vivo disintegration time was also increased. This study correlates well with in-vitro disintegration study of LMT loaded Konjac Gum based OTF. Fig. 3e–j shows the photographic images of in-vivo disintegration study LMT loaded Konjac Gum based OTF (batch OTF8) on a tongue of human volunteer with time.

Formulation code	Disintegration time (sec)
OTF1	30
OTF2	26
OTF3	27
OTF4	21
OTF5	19
OTF6	22
OTF7	15
OTF8	12
OTF9	16

Table 14: In-vivo disintegration time (human voluntary)

7. Surface pH determination

The surface pH of OTF batches was found in the range of 6–7 pH (Table 21), close to neutral pH, indicating that the films were irritation free to tongue, the mucosal lining of oral cavity and easily acceptable for patients.

Formulation code	pH
OTF1	6.7
OTF2	6.2
OTF3	6.7
OTF4	6.4
OTF5	6.5
OTF6	6.3
OTF7	6.5
OTF8	6.6
OTF9	6.7

Table 15: Surface pH determination of prepared films

8. Uniformity of drug content

The content uniformity test is commonly employed for unit dosage forms. In order to make sure about the uniform dispersion of drug in film. The drug content was carried out. The drug content was analysed at 310nm for Lamotrigine by using phosphate buffer 6.8pH. All the formulations showed more than 80% of the drug loading

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indicating much of the drug is not lost. The results indicated that the drug was uniformly dispersed.

Formulation code	Drug content for LMT (%)
OTF1	87.7
OTF2	80
OTF3	82.3
OTF4	92.5
OTF5	97.5
OTF6	62.5
OTF7	97.5
OTF8	99.2
OTF9	80

Table 16: Uniformity of drug content

9. In-vitro drug release study-

In –vitro drug release study of various formulations was carried out in PBS pH 6.8. The release data of formulations are shown in table no 23

The samples were diluted and analysed using UV-Spectrophotometer at 310nm for Lamotrigine.

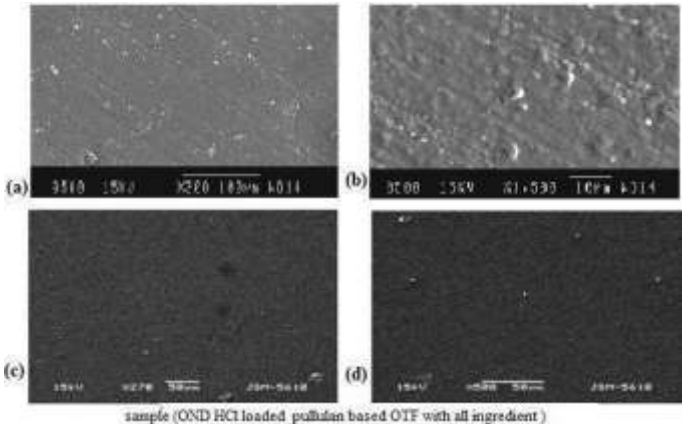
In-vitro drug release study for LMT

Time(sec)	OTF1	OTF2	OTF3	OTF4	OTF5	OTF6	OTF7	OTF8	OTF9
0	0	0	0	0	0	0	0	0	0
5	39.48	58.33	49.08	32.68	57.69	44.10	70.36	71.09	69.35
10	61.77	71.65	61.59	42.38	71.29	60.14	85.32	90.45	77.98
15	71.38	78.36	71.20	49.99	75.73	70.74	91.01	95.94	87.69

Table 17: In-vitro drug release study for LMT

10. Scanning electron microscopy (SEM)

To characterized uniform or rough dispersion of all ingredient in konjac gum based OTF. SEM study was performed for sample LMT loaded konjac gum based OTF with all ingredient batch OTF8) apparent in the morphologies of sample were identified (Fig.22). it shows that proper homogenization solution of all ingredient in konjac gum based OTF before casting on glass petriplates following its subsequent drying.



sample (OND HCl loaded pullulan based OTF with all ingredient)

Figure 9. SEM images of LMT loaded konjac gum based OTF with all ingredients measured at magnifications, (a)X300 (b)X1500 (c) X270 (d) X500

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11. Stability studies-

The optimized formulation of OTF8 was evaluated at the time interval of 30 and 90 days for all the parameters like, Appearance, Weight, Thickness, Drug content. The observations of the stability studies of optimized formulation OTF8 are shown in table and it did not show any significant change in these parameters after stability studies. This confirms the stored film formulation were stable for the storage period.

Duration	Visual Appearance	Weight of films (mg)	Thickness of films (mm)	% Drug content for LMT
0 days	Transparent	35.4	0.03	99.2
30 days	Transparent	35.3	0.03	98.8
60 days	Transparent	35.3	0.03	98.6
90 days	Transparent	35.3	0.03	98.2

Table 18: Evaluation parameters of optimize batch (OTF8) after stability study.

12. Comparison between marketed oral film and lab scale preparation oral film

Parameter	**Marketed oral film**	**Lab scale preparation oral film**
Thickness	0.04mm	0.02mm
In-vitro Disintegration time(sec)	15	10
In-vivo disintegration time(sec)	13	12
Drug content	97.4%	99.2%
Weight uniformity (mg)	43.5	0.02
Folding endurance	254	289
Surface pH	6.6	6.6
In-vitro dissolution	91.83%	95.94 %

Table 19. Comparison between marketed oral film and lab scale preparation oral film

CONCLUSION

Taste masked oral fast dissolving film of Lamotrigine using konjac gum as a natural biodegradable film former, PEG 400 as a plasticizer and aspartame as a sweetener was successfully formulated at lab-scale by solvent casting method. Based on results of preliminary trial batches of konjac gum based OTF, it can be concluded that PEG 400(as plasticizer) and aspartame (as sweetener) are compatible, inert and effective to maintain overall quality, flexibility of resulting konjac gum thin film. They were evaluated successfully for the needful responses and exhibited excellent palatability, very smooth in handling, and administration. PEG 400 showed potential positive influence on the mechanical properties of konjac gum based OTF and negative effect on the drug release rate. PEG 400 and sweetener 'aspartame' showed positive influence on the overall palatability, mouth feel, and handling of the konjac gum based OTF. Randomly Optimized batch OTF8 (konjac gum OTF containing PEG 400, 200 mg; aspartame,10 mg) was identified by formulation of fast dissolving oral film excellent result and exhibiting acceptable excellent mechanical properties of OTF, easy peeling of film from surface of glass, excellent palatability, very easy in handling, very smooth mouth feel and over all excellent stability in tightly closed aluminium sachet stored at40 ± 2◦C and 75 ± 5% RH. Hence, it can be concluded that konjac gum is successfully utilized at lab-scale for the formulation of oral thin film of Lamotrigine using PEG 400 and aspartame as best compatible plasticizer and sweetener, respectively. This types of OTF can be commercially processed easily with consideration of factors influencing on the

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formulation of OTF On the basis of an obtained result Lamotrigine fast dissolving oral dispersible film was successfully formulated and evaluated using polymer konjac gum by solvent casting method.

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