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Preparation and Characterization of Lamotrigine Mucoadhesive Tablets with Natural Polymers

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ABSTRACT

Lamotrigine is an anticonvulsant drug and reported lower bioavailability of conventional tablets. Hence it is required to make such a dosage form having improved bioavailability compared to conventional dosage form. The present study was planned to formulate and characterize the mucoadhesive tablets of Lamotrigine employing different proportions of natural polymer acquired from the Okra and *Hibiscus rosasinensis*. The six formulations (L1 to L6) of mucoadhesive tablets were prepared by following direct compression technique. The prepared formulations were evaluated by checking their strength of thickness, friability, hardness, weight variation, drug content, surface pH, mucoadhesive strength, mucoadhesion force, swelling index and *in- vitro* dissolution studies. The findings showed the formulations containing higher amounts of gum Okra and *Hibiscus rosasinensis*have better mucoadhesion strength. The drug release demonstrated 12 hr for the complete release of drug from formulation suggesting sustained release pattern. The mucoadhesive tablets of Lamotrigine enhanced the systemic absorption due to higher permeability with a rich blood supply to mucus layer.

Keywords: *Lamotrigine, Mucoadhesive, Okra, Hibiscus rosasinensis*

Introduction

Administrations of drugs through orally are mostly preferred by patients and more convenient to other delivery systems. The tablets are easy to administer, self-medication properties and controlled drug delivery of drugs to the target site attract physicians to include in their prescription. The oral delivery of drugs has numerous merits over other drug delivery systems like parenteral, transdermal, semisolid dosage form etc. However, gastrointestinal enzymatic degradation, first-pass effect and slow onset of action of oral drug delivery limited their uses. Mucoadhesive drug delivery could be a better approach to solve these downsides[1].

Till date, it has been documented various mucoadhesive drug delivery systems have indeed emerged for both systemic and local effects for nasal,ocular, buccal, oral, rectal and vaginal routes. The mucoadhesive drug delivery is formulated in such a way, it produces small and compact enough to even be convenient to patients and not cause irritation to the mucous membranes.

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There are numerous advantages of mucoadhesive drug delivery systems such as facilitating extended residence time of drugs which increase absorption rate and pharmacological activity of the drug. It also prevents the degradation of drugs from pH and digestive enzymes of the middle gastrointestinal tract. It also avoids the first pass metabolism of drugs. The mucosal membranes have better permeability properties and it improves the onset of action of the drug. This dosage form diminishes fluctuation of drug plasma level [2].

Two plants namely leaves of *Hibiscus rosasinensis* and fruits of Okra (*Abelmoschus esculentus*) are commonly used for the production of natural polymer. Consequently, these natural polymers have been chosen as the polymer for the formulation of mucoadhesive tablets of Lamotrigine. Mostly Indian peoples grow *Hibiscus rosasinensis* as an ornamental plant in different regions. The mucilage of the leaves of *Hibiscus rosasinensis* reported healing of the numerous diseases. It has been reportedin various scientific literature, the mucilage acquired from the Okra pods have potential binder for tablet formulations. The fruits of the Okra are used in the preparation of different curry in Indian diet. Additionally, the fruits of the Okra are used in the treatment of various diseases [3-5]. The mucilage of *Hibiscus rosasinensis* and Okra used as a natural polymer, biocompatible, biodegradable, non-irritant to tissue having good binding properties and better mucoadhesive property.

Lamotrigine is used for the treatment of epilepsy, and it comes under class-II under BCS Classification. Chemically, it is 6-(2, 3-dichlorophenyl)-1,2,4- triazine-3,5-diamine. Lamotrigine regulates partial and secondarily generalized seizures. Lamotrigine demonstrated lesser bioavailability in conventional dosage form due to the narrow therapeutic absorption window in the upper gastrointestinal tract [6,7]. The mucoadhesive drug delivery system is the best option to improve the bioavailability of the Lamotrigine with sustained release effect. Hence, efforts were applied for the formulation and evaluation of the mucoadhesive tablets of Lamotrigine to achieve its better bioavailability. The natural mucilage acquired from the *Hibiscus rosasinensis* and Okra plants were used in the formulation of the mucoadhesive tablets of Lamotrigine.

Material and Methods

Preparation of natural gum

Extraction of *Abelmoschus esculentus* (Okra) gum

The seed were removed from the immature Okra fruits. The quantity of immature Okra fruits was 1 kg. The seedless fruits were cut into small pieces for homogenization. After that samples were extracted with distilled water having sodium metabisulphite (1% w/w). The centrifuge instrument was used for the centrifugation of the crude mucilage at 3000 rpm for 5 min. The gum was precipitated from the supernatant by adding acetone, and washed with numerous times with fresh acetone. The washed gum was dried under vacuum desiccator and finally the light brown coloured gum was acquired. The gums were powdered and stored in a well closed amber coloured container.

Extraction of *Hibiscus rosasinensis* gum

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Hibiscus rosasinensis Linn. leaves were collected from the garden, and shade dried. The dried leaves were coarsely powdered, and dipped in water for 5-6 hr. The preparation was boiled for half an hour, and kept for cooling to produce mucilage. The solution was filtered by squeezing in muslin cloth eight-fold. The gum was precipitated from the mucilage on adding acetone. The gum was dried in an oven and temperature was below 50 °C. The dried gum was powdered and stored in a well closed amber coloured container [8,9].

Formulation of mucoadhesive tablets

Preparation of mucoadhesive tablets of Lamotrigine

The six different tables (F1 to F6) of Lamotrigine were prepared by direct compression technique using Okra gum and *Hibiscus rosasinensis*gum. The composition of formulation is displayed in table 1. Lamotrigine, natural gum and excipient were mixed in a mortar, lubricant was added for proper homogenous mixing. The lubricated mixer was compressed into tablets by the help of a compression machine.

Table 1: Quantity of raw materials for preparation of mucoadhesive tablets of Lamotrigine

Ingredients	L1	L2	L3	L4	L5	L6
Lamotrigine	50	50	50	50	50	50
Okra	30	50	70	-	-	-
Hibiscus rosasinensis	-	-	-	30	50	70
PVP K30	15	15	15	15	15	15
MCC	20	20	20	20	20	20
Talc	1	1	1	1	1	1
Magnesium stearate	50	30	10	50	30	10

Evaluation of Lamotrigine mucoadhesive tablets

Weight variation test

The 20 tablets were weighed separately, and mean on individual weight of tablet was obtained. The whole procedure was performed as mentioned in the Indian Pharmacopeia. Each procedure was repeated three times and their average values were reported.

Thickness test

The vernier calliper was used to measure the thickness of the formulated tablets. The measurement of thickness of the tablets were repeated three times and their average value was reported.

Hardness test

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The Monsanto hardness tester was applied to measure the hardness of the tablets. The measurement of hardness of the tablets were repeated three times and their average value were reported.

Friability test

The twenty tablets were kept in the friabilator chamber of the Roche friabilator, and rotated for the 4 min at speed of 25 rpm. The percentage friability of the tablets were calculated after completion of rotation.

Drug content

The tablets were triturated, and powder equivalent to one tablet wasdissolved in the phosphate solution having pH 6.8. The aliquots of the sample were withdrawn and diluted. The absorbance of the diluted sample was measured at 254 nm, using the UV-Visible Spectrophotometer.

Surface pH

The surface of the pH of the tablet was measured by placing the tablet into 5 ml distilled water (pH 7.0 ± 0.05) at room temperature for 2 h. The tablets were swelled, the pH of the tablets was measured by fetching the electrode of the pH meter at the surface of the tablet and consenting it to equilibrate for 1 min [9].

Mucoadhesion studies

The sheep mucosa as model mucosal membrane was used to determine the mucoadhesion strength of the formulated tablets. The measurement of the strength of the tablets were performed on double beam physical balance. The pan of the left arm of the physical balance was removed and a thick thread of suitable length was attached. The 30 ml capacity of the glass vial was attached and dipped into the 500 ml beaker. Between vial and beaker, the inverted 100 ml capacity of the beaker was placed. The simulated saliva (pH 6.8) was poured into the 500 ml beaker and temperature was maintained at 37.0 ± 0.5 °C during experiment. The physical balance was maintained in such a way that the right-hand-side was exactly 5 g heavier than the left [10-12]. The mucoadhesion strength of the tablet was calculated by applying below formula:

Force of adhesion (N) = Mucoadhesive strength/100 × 9.81.

Swelling index

Firstly, the tablets were exclusively weighed and represented by W1. The weighted tablets were placed into the Petri dish having 5 ml simulated saliva of pH 6.8. The tablet was removed from the petri dish after a specific time interval i.e. 0.5, 1, 2, 4, 6, 8, 10 and 12 hrs. The excess amount of water adhere into tablets was eliminated with the help of filter paper. The weight of the swollen tablet (W2) was measured, and the percentage hydration was estimated by applying the given below [13].

% Swelling Index (S.I) = $[(W_2-W_1)/ W_1] \times 100$

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W_1 = initial weight; W_2= final weight

In-vitro drug release

The drug release from the tablets were performed in USP II apparatus. The apparatus was filled with the 900 ml of phosphate buffer pH 6.8 and paddle were stirred at 50 rpm. The whole process was completed at the temperature 37 ± 0.5 °C. The tablets were placed into the dissolution media and 5 ml samples were withdrawn at specific time intervals. The absorbance of the aliquots were measured at 254 nm using UV-Visible spectroscopy [6,7].

Statistical analysis

The above stated experiments were repeated thrice times, and findings are demonstrated as the mean±S.D.

Results and Discussions

The thickness, friability, hardness, weight variation, drug content, surface pH, mucoadhesive strength, mucoadhesion force, swelling index and *in-vitro* dissolution test were used for evaluation of the prepared formulations to determine the appropriateness of mucoadhesive tablets.

Characteristics of Lamotrigine mucoadhesive tablets

The direct compression technique was employed for the preparation of six different formulations i.e. L1 to L6 and physicochemical properties were assessed. Table 2 expressed the thickness of the formulation L1 to L6 and values were ranged between 2.5±0.02 to 3.4±0.11 mm. The hardness of the formulation L1 to L6 were varied between 3.8±1.21 to 4.7±1.43 Kg/cm^2,which indicates the higher binding capacity between the excipients, polymer and drug (Table 2). Further it also confirms the satisfactory strength of the tablet. The results demonstrated that by increasing the concentration of gum it increases tablet hardness.
The weight of the tablets of L1 to L6 were found to be uniform with low standard deviation values from 165.9±0.28 to 166.8±0.69 mg (Table 2)**.** All the formulated tablets comply with the weight variation evaluation as per IP. All the tablets were circular with no visible cracks and smooth on appearance.

The percentage friability of the formulation L1 to L6 were ranged between 0.39±0.02 to 0.61±0.09 (Table 2). The results expressed percentage friability was less than 1% for all formulations. The findings compiled the official requirement mentioned in the IP.
The percentage of drug content in the formulation L1 to L6 were found in the range of 97.5±0.36 to 99.3±0.18 (Table 2). The values of drug content were under the limit mentioned in the Pharmacopeial.

The outcomes indicate the gel forming property of the gum used in the tablet formulation are similar with the results displayed by the various researchers[12-14]. The results of the tablet hardness endorsed that the tablets can easily resist the mechanical shock and avoid tablets breaking. Moreover, the friability of tablets was less than 1%, confirm the higher strength property of the natural polymer and might be used as a binder in formulation. The findings of

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the physicochemical properties of the tablets show that formulations were within acceptable levels.

Table 2: Evaluation characteristics of Lamotrigine mucoadhesive tablets

Formulation	Tablet Hardness(Kg/cm^2)	Friability (%)	Thickness (mm)	Average weight (mg)	Drug content (%)
L1	4.6±0.74	0.52±0.06	2.7±0.08	166.8±0.69	98.1±0.13
L2	4.1±1.42	0.61±0.09	2.5±0.02	166.1±0.47	97.5±0.36
L3	3.8±1.21	0.47±0.02	2.9±0.05	166.3±0.38	99.3±0.18
L4	4.7±1.43	0.53±0.07	3.4±0.11	166.5±0.71	98.8±0.43
L5	4.2±0.82	0.39±0.02	2.6±0.16	166.2±0.53	98.2±0.22
L6	4.5±1.32	0.45±0.07	3.2±0.09	165.9±0.28	97.9±0.41

Values are mean ± SD, n=3

Surface pH

Table 3 showed the surface pH of the formulations L1 to L6 were in the range of 7.11±0.16 to 7.19±0.27. The formulation of the pH was similar to neutral and endorsed the safety of the formulations which does not produce any local irritation to the mucosal surface.

Mucoadhesive strength

Table 3 exhibited mucoadhesive strength of formulations L1 to L6 ranged from 31.28±0.08 to 42.94±0.19 gm and mucoadhesion force were found to be in the range of 3.334 to 4.212 N. The findings suggest the bioadhesion properties of gum increases on enhancing their concentration. The formulation having higher concentration of gum showed greater bioadhesive strength. The L6 containing *Hibiscus rosasinensis*gum showed higher mucoadhesive strength and mucoadhesion force compared to L3 containing Okra gum.

Table 3: Evaluation parameters of Lamotrigine mucoadhesive tablets

Formulation code	Surface pH	Mucoadhesive strength (g)	Mucoadhesion force (N)
L1	7.13±0.37	31.28±0.08	3.068
L2	7.16±0.52	33.49±0.13	3.285
L3	7.11±0.16	39.22±0.07	3.847
L4	7.15±0.64	36.64±0.32	3.334
L5	7.19±0.27	39.10±0.43	3.835
L6	7.17±0.14	42.94±0.19	4.212

Values are mean ± SD, n=3

Swelling studies

The swelling index of the formulations L1 to L6 was found in the range of 22 to 79 for 12 hr (Table 4). The results expressed the swelling index of the tablets increasing on increasing the polymer concentration. The gum of the okra increased the swelling index of L3 to 69, while the gum of *Hibiscus rosasinensis*enhances the swelling index of L6 to 79. This may be due to

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the quick hydration of gum on keeping the tablets in contact with water for 1 h to 12 h. An appropriate swelling index is mandatory for the uniform and sustained release of the drug and effective mucoadhesion. Hence the L6 containing *Hibiscus rosasinensis*gum showed higher swelling index compared to L3 containing Okra gum.

Table 4: Swelling index (%) of Lamotrigine mucoadhesive tablets

Formulation code	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs
L1	22	25	30	37	41	46	50
L2	24	29	35	39	45	50	55
L3	28	33	39	48	49	61	69
L4	25	31	37	44	52	56	62
L5	27	35	40	48	57	63	72
L6	32	38	44	51	59	67	79

In-vitro release studies

Figure 1 demonstrated that the release of drug from the formulation was over within 12 hrs. The L3 and L6 released drug 97.25±0.57% and 98.59±0.86% respectively from formulations. It has been observed that the pattern of rate of drug release was varied according to the proportion of natural polymer present in the tablets. The gradual decrease in the percentage of drug release from L1 to L3 and L4 to L6 in 12 hr may be due to the increase in the concentration of gum of Okra and *Hibiscus rosasinensis*, respectively. It may be due to the *in-situ* gelling property of Okra and *Hibiscus rosasinensis*, which slows the dissolution rate of the drug Lamotrigine. The formulation L3 and L6 were remaining intact during the entire 12 h study period.

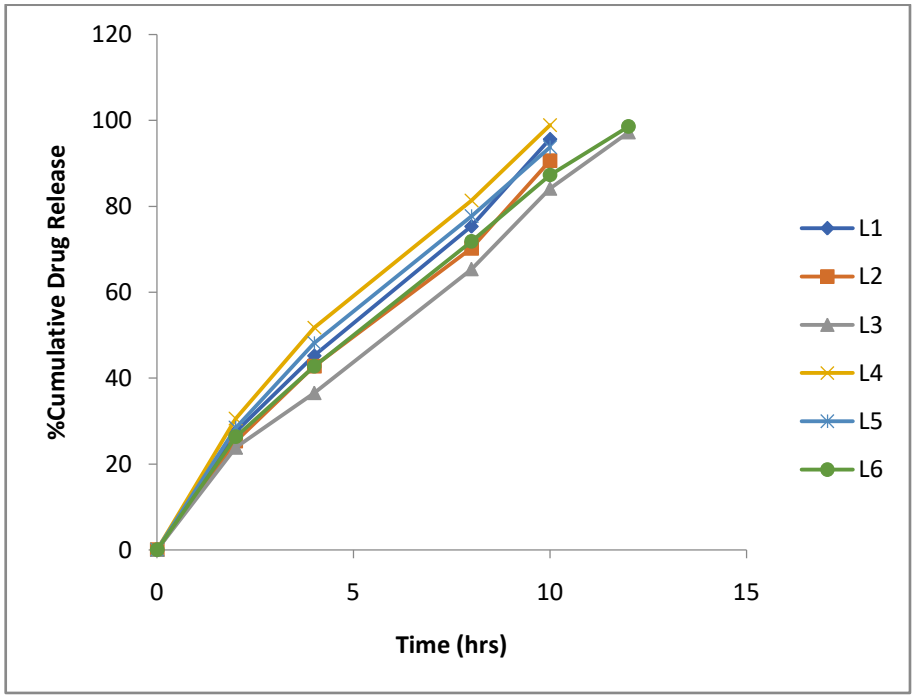

Fig 1: *In-vitro* drug release profile of Lamotrigine mucoadhesive tablets

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Conclusion

The mucoadhesive tablets of Lamotrigine were prepared by using natural polymers namely gum of Okra and *Hibiscus rosasinensis*. The findings of characteristics of the prepared mucoadhesive tablets of Lamotrigine (L1 to L6) showed were acceptable according to Pharmacopoeial limit. The formulation containing higher amounts of gum of Okra and *Hibiscus rosasinensis*reduces the drug release due to greater adhesion strength of the formulation and makes the formulation a sustained release pattern. The above statement assured from the formulation L3 and L6 showed drug release upto 12 hrs. In the future, by the help of Pharmaceutical Manufacturer, these formulations will provide sustained release of mucoadhesive tablets of Lamotrigine with increased bioavailability to the society.

Conflicts of Interest: No

References

[1] Gite SS, Shinkar DM, Saudagar RB. Development and Evaluation of Mucoadhesive Tablets of Atenolol and its B-Cyclodextrin Complex. Asian Journal of Biomedical and Pharmaceutical Sciences, 2014; 04(37): 25-32.

[2] Selvaraj GJ, Balasubramanian A, Ramalingam K. Development of mucoadhesive tablet of pentoxifylline using a natural polymer from *Manilkara zapota* Linn. International Journal of Applied Pharmaceutics, 2019; 11(4): 88-91.

[3] Ameena K, Dilip C, Saraswathi R, Krishnan PN, Sankar C, Simi SP. Isolation of the mucilages from *Hibiscus rosasinensis* Linn. and Okra (*Abelmoschus esculentus* Linn.) and studies of the binding effects of the mucilages. Asian Pacific Journal of Tropical Medicine. 2010; 3(7): 539-543.

[4] Nair AS, Vidhya KM, Saranya TR, Sreelakshmy KR, Nair SC. Mucoadhesive Buccal Patch of Cefixime Trihydrate Using Biodegradable Natural Polymer. Int J Pharm Sci, 2014; 6(6): 366-371.

[5] Ikbal A. M. A, Rajkhowa A, Singh P. C, Choudhury P. D, Sahu R. K. Assessment of Phytochemical and Anthelmintic Activity of Some Selected Ethnomedicinal Plants from Barak Valley Region of Assam. Biomed Pharmacol J 2020;13(4): 1825-1831.

[6] Devi L, Gaba P Sharma N. Formulation characterization and optimization of cefixime trihydrate hydrogel tablet by using design expert. Int J Pharm Sci & Res, 2020; 11(8): 3824-33.

[7] Hayder MA, Ashoor JA, Bader QA, Al-Obaidi Z. Preparation and Evaluation of Cefixime Dispersible Tablets Using Co Processed Excipients. IJPPR, 2015; 4 (2): 424-436.

[8] Mastiholimath VS, Rajendra BA, Mannur VS, Dandagi PM, Gadad AP, Khanal P. Formulation and Evaluation of Cefixime Nanosuspension for the Enhancement of Oral Bioavailability by Solvent-Antisolvent Method and its Suitable Method Development. Indian J of Pharmaceutical Education and Research, 2020; 54(1): 56-67.

[9] Ameena K, Dilip C, Saraswathi R, Krishnan PN, Sankar C, Simi SP. Isolation of the mucilages from *Hibiscus rosasinensis*linn. and Okra (*Abelmoschus esculentus*linn.) and studies of the binding effects of the mucilages. Asian Pacific Journal of Tropical Medicine, 2010; 539-543,

[10] Zaharuddin ND, Noordin MI, Kadivar A. The Use of Hibiscus esculentus (Okra) Gum in Sustaining the Release of Propranolol Hydrochloride in a Solid Oral Dosage Form", BioMed Research International, 2014; 2014: 1-8.
[11] Goswami DS, Choudhury PK, Goyal S, Goyal K, Mittal N. Formulation and Evaluation of Mucoadhesive Tablets of Amoxicillin Trihydrate. Research J. Pharm. and Tech, 2010; 3(2): 540-542.
[12] Balaji A, Radhika V and Goud V: Formulation and evaluation of mucoadhesive buccal tablets by using natural polymer. Int J Pharm Sci & Res 2014; 5(11): 4699-08.
[13] Basani G, Stephenrathinaraj B, Sudharshini S, Reddy AK and Shinde GV: Design and evaluation of baclofen mucoadhesive buccal tablets. Int J Biomedical and Adv Res 2010; 1(1): 25-35.
[14] Fathima N, Das P, Kuchana V. Formulation and Evaluation of Mucoadhesive Tablets of Carvedilol Using Natural Binders. IJRPC, 2015; 5(4): 699-707