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Formulation And In-Vitro Evaluation Of Lafutidine Buccal Tablets

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ABSTRACT

The objective of present study was to develop a Lafutidine buccal tablet using polymers such as Sodium Alginate, Eudragit RLPO, Hydroxy propyl methyl Cellulose (HPMC) and Microcrystalline cellulose, Magnesium stearate, Talc, Sodium saccharin in alone and in combination as release retarding agent to prolong the drug release, to increase mucoadhesive strength and to avoid first pass metabolism. The mucoadhesive buccal tablets were prepared by direct compression method. The dry blend of drug and polymers were evaluated for precompression parameters to ensure flow properties during tablet punching. The prepared mucoadhesive buccal tablets were evaluated for physicochemical parameters such as hardness, thickness, uniformity, weight variation, and moisture absorption studies. The prepared buccal tablets were also evaluated for mucoadhesive strength, in vitro drug release. In vitro drug release studies showed that formulation F4 (Eudragit RLPO) in the Polymer concentration of 25mg (F4) is showing better result 99.72% drug release and showed satisfactory bio adhesive strength. DSC analysis shows that the Lafutidine drug exhibited a Sharp endothermic peak at 104.18°C corresponding to its melting point. This observation indicated that the drug was free from impurities. FTIR studies indicated that there is no interaction between the drug and the polymers which confirms the stability of the drug.

KEYWORDS: Lafutidine, Bioadhesive buccal tablets, Polymers, Direct compression, First pass metabolism, Bioadhesion/mucoadhesion.

1. INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self-medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa. (b) A vehicle which release the drug at an appropriate rate under the conditions prevailing in the mouth. (c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery system promotes the residence time and act as controlled release dosage forms. Buccal mucosa composed of several layers of different cells. The Epithelium is similar to stratified squamous epithelia, helps bioadhesion between the formulation and biological tissue by means of interfacial forces.

2. Materials and Methods

Lafutidine was obtained as a gift sample from SURA LABS, Hyderabad,India. The polymers like HPMC K100M, Talc was obtained from Sd fine Chemicals Ltd. Mumbai. Magnesium stearate, MCC was purchased from Chemdie Corporation. Sodium Alginate was purchased from Zydus Cadila, Ahmedabad, India. Eudragit RLPO was purchased from Acurate Pharma. All the ingredients were of laboratory grade. The distilled water used in the process of research work was prepared by double distillation process in the laboratory.

3. METHODOLOGY

3.1 Drug-excipient compatibility studies

3.1.1 Drug characterization by DSC:

About 5-6mg of drug was taken in the pierced DSC aluminium pan and crimped, scanned in the temperature range of 50-150°C. The heating rate was 10°C/min, nitrogen served as purged gas and the system was cooled down by liquid nitrogen. Empty aluminium pan was used as the reference cell **(Himansu *et al.*, 2012).**

3.1.2 Fourier Transform Infrared spectroscopic studies:

A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug: excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4000 cm^{-1}.

3.3 Solubility Studies:

The solubility of Lafutidine in phosphate buffer solution pH 6.8 was determined by phase equilibrium method. An excess amount of drug was taken into 20 ml vials containing 10 ml of phosphate buffers (pH 6.8). Vials were closed with rubber caps and constantly agitated at room temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm Whattman's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 290 nm using a UV spectrophotometer.

3.4 Formulation development of tablets:

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Sodium Alginate, Eudragit RLPO and HPMC K100M are the mucoadhesive polymers used in this preparation of buccal mucoadhesive drug delivery systems. Lafutidine was mixed manually with different ratios of Sodium Alginate, Eudragit RLPO and HPMC K100M and MCC as diluent for 10 min the blend was mixed with talc and magnesium stearate for 3-5 min.

Table 1: Formulation Table

INGREDIENTS (mg)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lafutidine	10	10	10	10	10	10	10	10	10
Sodium Alginate	25	50	75	-	-	-	-	-	-
Eudragit RLPO	-	-	-	25	50	75	-	-	-
HPMC K100M	-	-	-	-	-	-	25	50	75
MCC	141	116	91	141	116	91	141	116	91
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Saccharin sodium	15	15	15	15	15	15	15	15	15
Total weight	200	200	200	200	200	200	200	200	200

3.5 Evaluation of pre-compression blend:

The quality of tablet, once formulated, by rule is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characterization of blends produced. Prior to compression, granules were evaluated for their

characteristic parameter such as Tapped density, Bulk density, Carr's index, Angle of repose, Hausner's ratio. Compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus.

3.6 Preparation of Tablets:
The powder blend was compressed into tablets by the direct compression method using 8mm flat faced punches. The tablets were compressed using a ten station LAB PRESS rotary tablet-punching machine. The weight of the tablets was determined using a digital balance and thickness with digital screw gauge.

3.7 EVALUATION OF BUCCAL TABLETS:

3.7.1 Physicochemical characterization of tablets:

A. Weight variation:
The weight variation test is done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage **(mukesh *et al.*.,2019)**

The percent deviation was calculated using the following formula:

% Deviation = (Individual weight – Average weight / Average weight) X 100.

B. Tablet Thickness:
The thickness and diameter of the tablets was determined using a Digital Vernier caliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablets is calculated and presented with standard deviation.**(Amit *et al.*, 2012).**

C. Tablet Hardness:
Tablet hardness is defined as the force required to breaking a tablet in a diametric compression test. Six tablets were taken from each formulation and hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm^2.**(mukesh *et al.*.,2019)**

D. Friability:
Tablet strength is measured by using Roche friabilator. Test subjects to number of tablets to the combined effect of shock, abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution and Operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as

$$\text{Friability (\%)} = \frac{\text{Initial weight of 10 tablets – final weight of 10 tablets}}{\text{Initial weight of 10 tablets}} \times 100$$

E. Assay:
Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 290 nm using pH6.8 phosphate buffer.

3.7.2 In-vitro release studies:
The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 290nm.

3.7.3 Surface pH:

Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.8 phosphate buffers (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3).

3.7.4 Moisture absorption:

Agar (5% W/V) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

3.7.5 Kinetic Analysis of Dissolution Data:

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. Zero – order kinetic model – Cumulative % drug released versus time. First – order kinetic model – Log cumulative percent drug remaining versus time. Higuchi's model – Cumulative percent drug released versus square root of time. Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time.

4. RESULTS AND DISCUSSION

4.1 Drug characterization by DSC

Differential Scanning Calorimetry (DSC) thermogram of lafutidine was shown in figure-1. The DSC thermogram of lafutidine exhibited a sharp endothermic peak at 104.18°C corresponding to its melting point. This observation indicated that the drug was free from impurities.

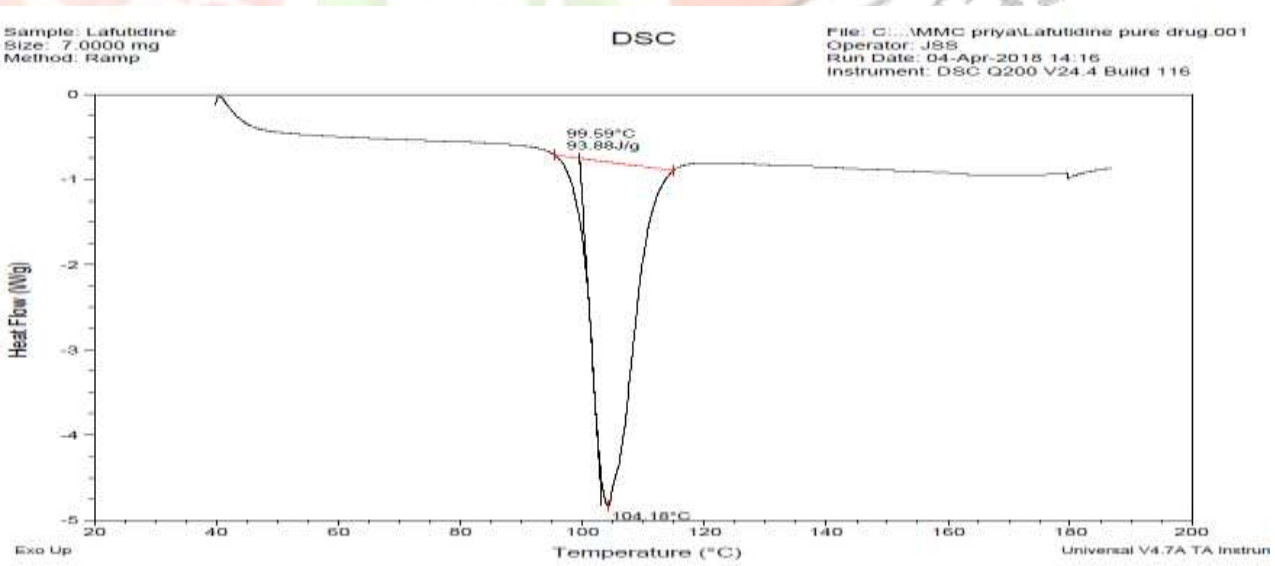

Fig 1:DSC curve of Lafutidine pure drug

4.2 FTIR

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra of pure Lafutidine drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Lafutidine are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug. There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

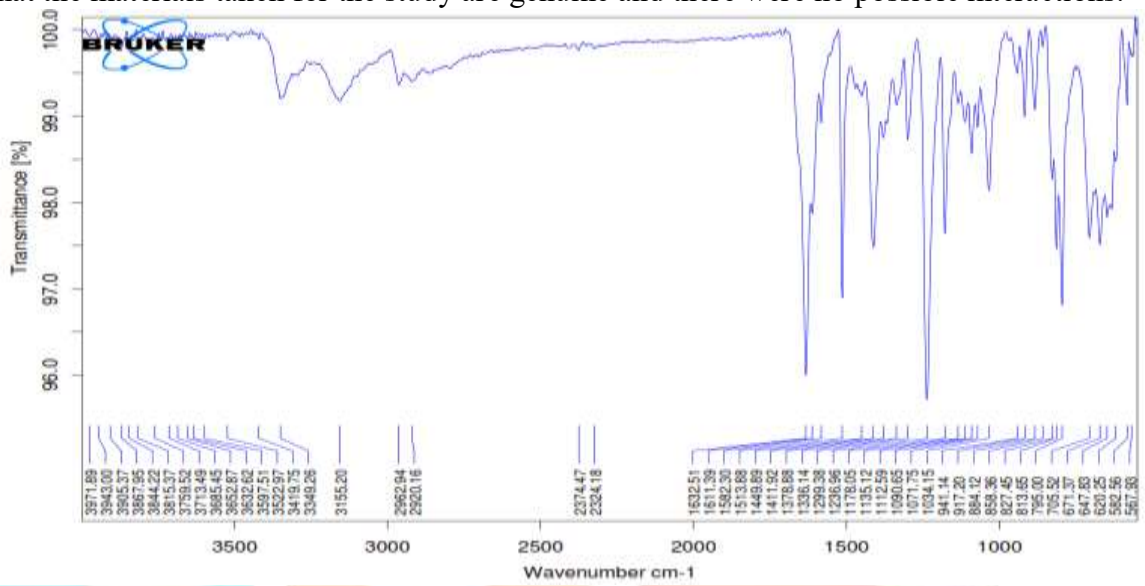

Fig 2: FTIR Peak of pure drug Lafutidine

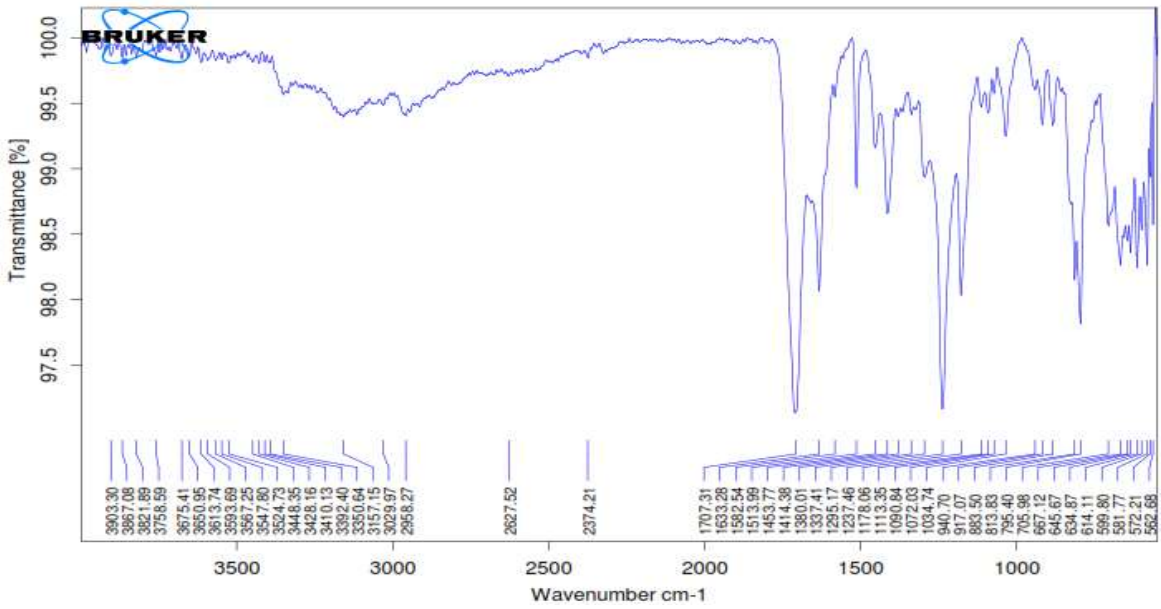

Fig 3: FTIR Peak of Optimised formulation

4.3 Solubility Studies:

Table 2: Solubility studies

S.No	Medium	Amountpresent (µg/mL)
1	Water	24.30±1.97
2	Phosphate pH 6.8 buffer	98.12±0.54
3	Phosphate pH 7.4 buffer	96.53±0.68

Saturation solubility of Lafutidine in various buffers were studied and shown in the Table 2. The results revealed that the solubility of the Lafutidine was increased from pH 6.8 to 7.4. The solubility of the Lafutidine in phosphate buffer pH 6.8 is 98.12µg/mL and it was selected as the suitable media for the release studies because the pH of the phosphate buffer pH 6.8 is nearer to that of buccal mucosa pH.

4.4a) Standard graph in phosphate buffer pH 6.8 (λ_{max} 290 nm)

Standard graph of Lafutidine was plotted in pH6.8 phosphate buffer and it has shown good linearity between 0 to 25 µg/mL showings R^2 value 0.999, which indicates that it obeys "Beer- Lamberts" law.

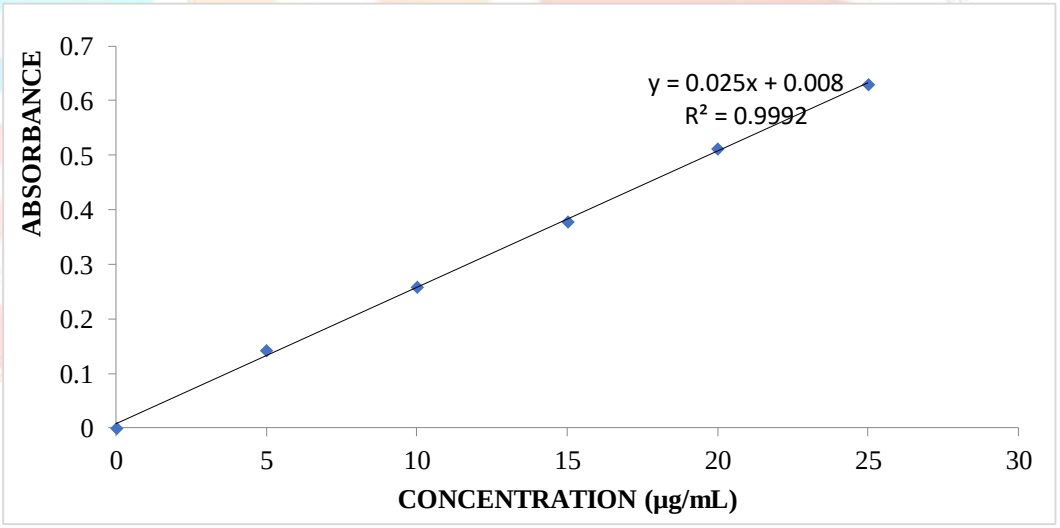

Fig 4: Standard graph of Lafutidine in pH 6.8 phosphate buffer

4.4b) Standard graph in phosphate buffer pH 7.4 (λ_{max} 290 nm)

Standard graph of Lafutidine was plotted in pH 7.4 phosphate buffer and it has shown good linearity between 0 to 25 µg/mL showing R^2 value 0.999, which indicates that it obeys "Beer- Lamberts" law.

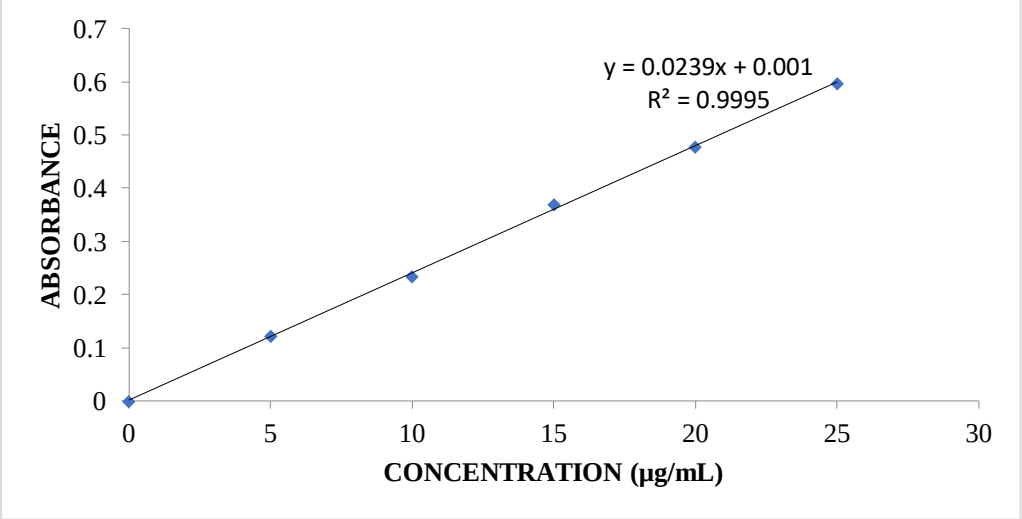

Fig 5: Standard graph of Lafutidine in pH 7.4 phosphate buffer

4.5 Evaluation:

4.5.1 Characterization of pre-compression blend:

The pre-compression blend of Lafutidine buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 27.12º, Carr's index values were less than 10.34 for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.19 for all the batches indicating good flow properties.

Table 3: Physical properties of pre-compression blend

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25.10±0.12	0.53±0.06	0.59±0.24	9.43±0.20	1.11±0.22
F2	25.43±0.11	0.54±0.16	0.60±0.21	9.40±0.15	1.10±0.11
F3	25.41±0.32	0.54±0.33	0.58±0.12	10.01±0.18	1.07±0.17
F4	26.40±0.15	0.51±0.20	0.61±0.18	10.11±0.32	1.19±0.14
F5	27.12±0.21	0.58±0.18	0.63±0.15	10.34±0.36	1.08±0.26
F6	25.31±0.24	0.59±0.15	0.64±0.22	10.12±0.46	1.08±0.21
F7	26.11±0.14	0.56±0.24	0.63±0.10	9.93±0.28	1.12±0.15
F8	26.15±0.23	0.53±0.21	0.58±0.14	10.13±0.22	1.09±0.24
F9	26.10±0.16	0.54±0.14	0.61±0.18	10.2±0.30	1.12±0.18

4.6 Evaluation of buccal tablets:

4.6.1 Physical evaluation of Lafutidine buccal tablets:

The results of the weight variation, hardness, thickness, friability and drug content of the tablets are given in Table-4. All the tablets of different batches complied with the official standards of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.0 to 5.6 kg/cm^2 and the friability values were less than 0.77 % indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 4.01 – 4.92 mm. All the formulations satisfied the content of the drug as they contained 95.38-99.82 % of Lafutidine. Thus all the physical attributes of the prepared tablets were found to be practically within official limits.

Table 4: Physical evaluation of Lafutidine buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content (%)
F1	198.47±0.32	4.01±0.21	4.9±0.23	0.56±0.12	96.10±0.46
F2	196.92±0.12	4.92±0.26	4.0±0.19	0.36±0.11	98.65±0.34
F3	199.30±0.43	4.35±0.12	5.3±0.16	0.24±0.15	99.10±0.18
F4	197.12±0.55	4.87±0.30	4.1±0.24	0.68±0.18	97.34±0.25
F5	198.82±0.40	4.28±0.18	5.2±0.11	0.59±0.12	98.58±0.38
F6	199.27±0.38	4.13±0.28	5.6±0.15	0.32±0.10	96.14±0.32
F7	200.04±0.15	4.79±0.32	4.1±0.26	0.77±0.13	99.82±0.43
F8	198.75±0.28	4.35±0.15	5.0±0.21	0.62±0.15	95.38±0.15
F9	197.80±0.22	4.60±0.11	4.8±0.13	0.43±0.16	98.76±0.22

4.6.2 In vitro release studies:

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Lafutidine from different formulations varies with characteristics and composition of matrix forming polymers.

Table 5: In vitro dissolution data for formulations F1 – F9

TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	**0**	0	0	0	0	0
0.5	20.89	18.72	18.90	**28.16**	15.82	10.92	15.05	13.53	11.58
1	28.32	38.50	20.35	**36.86**	25.73	21.03	23.19	18.92	20.16
2	36.58	47.93	29.17	**43.57**	33.90	28.51	30.27	28.60	26.09
3	51.91	60.46	36.26	**48.16**	48.17	40.99	36.59	37.18	34.10
4	65.54	67.59	43.83	**54.92**	56.34	46.42	49.01	46.82	53.23
5	76.73	76.98	57.41	**67.34**	63.10	53.60	55.39	52.99	57.42
6	89.15	80.42	61.96	**73.62**	70.09	62.17	75.53	67.76	65.99
7	96.21	86.18	73.63	**82.53**	75.37	70.96	85.89	77.14	76.37
8		90.13	85.57	**99.72**	87.24	75.12	93.73	87.34	81.83

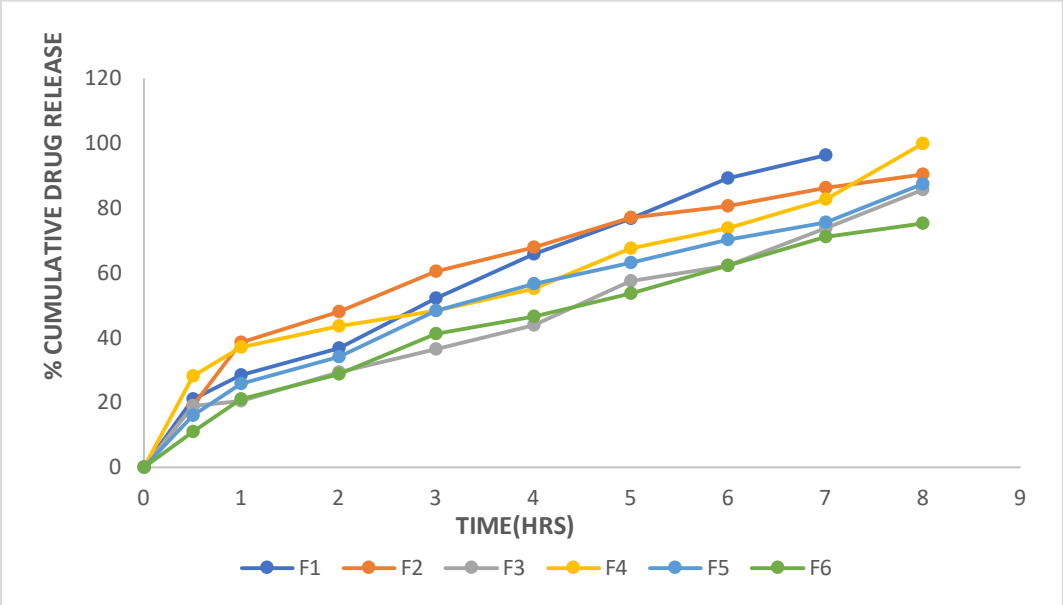

Fig 6: In vitro dissolution data for formulations F1 – F6 by using Sodium Alginate polymer and Eudragit RLPO polymer

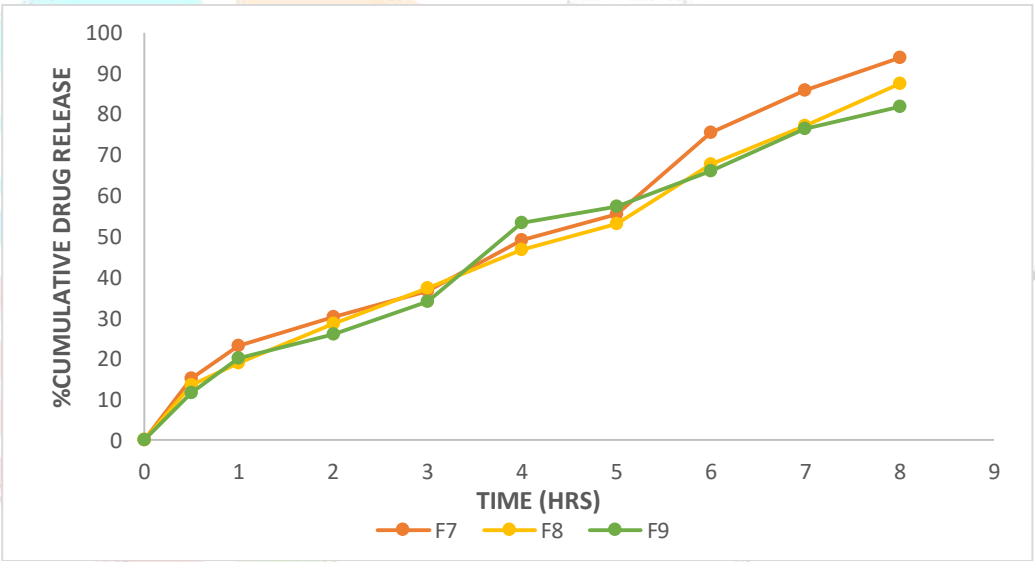

Fig 7: In vitro dissolution data for formulations F7- F9 by using HPMC K100M polymer

From the Fig 6 graph it was evident that Sodium Alginate in the concentration of 50mg of polymer of the total tablet weight (F2) drug with other two Formulations F1, F3. Where as in F2 formulation the quantity of polymer was less hence it showed less drug retardation with more drug release that is 90.13 % in 8 hrs.

From the Fig 6 graph it was evident that Eudragit RLPO in the Polymer concentration of 25mg (F4) is showing better result 99.72% drug release when compared with other two formulations F5, F6, as the concentration of polymer increases the retarding of drug release increased.

From the Fig 7 graph it was evident that HPMC K100M in the Polymer concentration 25mg formulation (F7) is showing better result 93.73% drug release when compared with other two formulations. Where as in F8, F9 formulations the concentration become high and the drug release was less.

Table 6: Moisture absorption, surface pH of selected formulations

Formulation Code	Moisture absorption	Surface pH
F2	88	5.12
F4	98	6.20
F7	96	6.09

4.6.3 Moisture absorption:

The moisture absorption studies give important information of the relative moisture absorption capacities of polymers and it also give information regarding whether the formulations maintain the integrity or not. Among the selected formulations F4 formulation shown good moisture absorption.

4.6.4 Surface pH:

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The surface pH of the selected formulations was found to be 5.12 to 6.20 and the pH was near to the neutral. These results suggested that the polymeric blend identified was suitable for oral application and formulations were not irritant to the buccal mucosa.

Release kinetics:

The data of in vitro release studies of F2, F4, F7 formulations were found to be 90.13 %(F2), 99.72% (F4), 93.73%(F7). Formulation F4 data were subjected to release kinetics models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms. The formulation (F4) was following Higuchi release mechanism with regression value of 0.959.

5) CONCLUSION

The mucoadhesive buccal tablets of Lafutidine could be prepared using Sodium Alginate, Eudragit RLPO and HPMC K100M polymers by using direct compression method. The preparation process was simple, reliable and inexpensive. All the prepared tablet formulations were found to be good without capping and chipping. The physical mixture of powder blend of drug and excipient formulations were studied to drug exicipient compatibility studies and revealed that no interaction with drug and excipients. All the prepared mucoadhesive buccal tablets were evaluated for weight variation, hardness, thickness, friability and drug content and found to be with in pharmacopeial limits. The surface pH of prepared buccal tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation. The in-vitro release of Lafutidine was extended for 8 h. Formulations F4 batch shows good in vitro drug release 99.72%. From the results of present investigation it can be concluded that Lafutidine can certainly be administered through the oral mucosa and Eudragit RLPO is suitable for development of buccoadhesive system. In vivo Bioavailability studies are needed to prove its efficacy.

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