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Formulation and development of mucoadhesive tablets of lafutidine by using design of experiment

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ABSTRACT

The aim of the present work was to prepare and evaluate mucoadhesive tablets of lafutidine to prolong the gastric residence time after oral administration. Formulations were prepared using 3^3 full factorial designs to explore the effects of Gum Kondagogu, Gum Olibanum and Guar Gum (as independent variables) on mucoadhesive strength, drug release and *Ex vivo* residence time (as dependent variables). The tablets were evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, swelling studies, *in vitro* drug release studies, *in vitro* mucoadhesion strength , *Ex vivo* residence time test, *In vivo* tests, bioadhesion test in stomach, bioavailability, X-ray studies and release rate kinetics. The drug-polymer interaction was also studied by conducting FTIR. The *in vitro* release kinetics studies reveal that all formulations fits well with Zero order, followed by Korsmeyer-Peppas, Higuchi and the mechanism of drug release is erosion. After analysis of different evaluation parameters and drug release kinetics, formulation code F22 was selected as a promising formulation for delivery of lafutidine as a mucoadhesive Gastroretentive tablet with best mucoadhesive strength and 99.54% drug release at 12^{th} hour. The main effects and the interaction terms were quantitatively evaluated by quadratic model. The stability studies were carried out at 40°C/75% RH for 180 days. There was no significant change in the physical property and weight variation, hardness, thickness, friability, *in vitro* drug release studies, *in vitro* mucoadhesion strength, and drug content during the study period.

Keywords: Lafutidine, Gastro-retentive tablet, Mucoadhesive tablets, Mucoadhesive strength.

INTRODUCTION

Oral administration is the most convenient, widely utilized, and preferred route of drug delivery for systemic action. However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation and or first pass hepatic metabolism, as a result of which low systemic bioavailability and shorter duration of therapeutic activity. Much attention has been focused, recently on targeting a drug delivery system to a particular region of the body for extended period of drug release, not only for local targeting of drugs but also for the better control of systemic delivery. Gastro retention is also used for achieving local delivery of drug to the stomach and proximal small intestine [4]. Gastro retentive formulations could be designed based on approaches like: (a) floating; (b) high density system;

(c) bioadhesion; (d) lowered motility of the GIT by concomitant administration of drugs or pharmaceutical excipients; (e) swellable and expandable systems. In the current study we have targeted at bioadhesion to the stomach mucosa. The most widely investigated group of mucoadhesive is hydrophilic macromolecules containing numerous hydrogen bonds forming groups. Once the dosage form firmly sticks to the mucosal surface, its gastric residence time is prolonging until it is remove by turnover of mucins or by some other means. Mucus is secreted from both non-specialized and specialized "Goblet" epithelial cells. Mucus glycoprotein chemically consist of large peptide backbone with pendent oligosaccharide side chains whose terminal end is either sialic or sulfonic acid. The presence of sialic acid and sulfate residues and its high charge density play an important role in bioadhesion. Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principal of design of experiments, the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms. Lafutidine,(±)-2-(furfurylsulfinyl)-N-(4-[4-[piperidino-methyl]-2-pyridyl]oxy-(Z)-2-butenyl) acetamide is a newly developed 2nd generation histamine H2-receptor antagonist. It is used in the treatment of gastric ulcers, duodenal ulcers, and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis. It is absorbed in the small intestine, reaches gastric cells via the systemic circulation, and rapidly binds to gastric cell histamine H2 receptors, resulting in immediate inhibition of gastric acid secretion. Lafutidine has been shown to increase the gastric mucosal blood flow and gastric mucus secretion also accelerates sepithelial restitution in rats. Lafutidine has a receptor binding affinity, which is 2-80 times higher than famotidine, ranitidine and cimetidine[12].

MATERIALS AND METHODS

Materials

The Lafutidine was obtained as a gift sample from splendid laboratories, Pune. Gum Kondagogu, Gum Olibanum and Guar Gum were obtained from Girijan Co-operative corp. Ltd, Hyderabad. PVP-K30 was gifted from MSN Labs Ltd, Hyderabad. All other chemicals used were of analytical grade.

Preparation of mucoadhesive tablets

Wet granulation method

Mucoadhesive tablets of Lafutidine were prepared by wet granulation technique using different concentrations of Gum Kondagagu, Gum olibanum and Guar gum. All the ingredients were passed through sieve no 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in isopropyl alcohol). Wet mass was passed through sieve no 12# and dried at 45-55 ^{0}C for 2 hr. Dried granules were sized by sieve no.18# and add Micro crystalline cellulose (Avicel PH 102) magnesium stearate and talc. Granules obtained were compressed with 9mm flat punch (Cadmach, Ahmedabad, India)[3].

The formulations are made by using design of experiment method (factorial designs)

Study type: **Response surface**
Design type: **central composite**
Design mode: **quadratic**

Table no: 1 Design summary of formulation by natural polymers

F.NO	LAFUTIDINE (mg)	GK (mg)	GO (mg)	GG (mg)	MCC (mg)	PVP K-30 (mg)	TALC (mg)	MAGNESIUM STEARATE (mg)	TOTAL WEIGHT (mg)
F1	10	10	10	10	140	12	4	4	200
F2	10	30	10	10	120	12	4	4	200
F3	10	10	30	10	130	12	4	4	200
F4	10	30	30	10	100	12	4	4	200

F5	10	10	20	10	130	12	4	4	200
F6	10	30	20	10	110	12	4	4	200
F7	10	20	10	10	130	12	4	4	200
F8	10	20	30	10	110	12	4	4	200
F9	10	20	20	10	120	12	4	4	200
F10	10	10	10	40	110	12	4	4	200
F11	10	30	10	40	90	12	4	4	200
F12	10	10	30	40	90	12	4	4	200
F13	10	30	30	40	70	12	4	4	200
F14	10	10	20	40	100	12	4	4	200
F15	10	30	20	40	80	12	4	4	200
F16	10	20	10	40	100	12	4	4	200
F17	10	20	30	40	80	12	4	4	200
F18	10	20	20	40	90	12	4	4	200
F19	10	10	10	60	90	12	4	4	200
F20	10	30	10	60	70	12	4	4	200
F21	10	10	30	60	70	12	4	4	200
F22	10	30	30	60	50	12	4	4	200
F23	10	10	20	60	80	12	4	4	200
F24	10	30	20	60	60	12	4	4	200
F25	10	20	10	60	80	12	4	4	200
F26	10	20	30	60	60	12	4	4	200
F27	10	20	20	60	70	12	4	4	200

GK: GUM KONDAGOGU GO: GUM OLIBANUM GG: GUAR GUM.
MCC: MICROCRYSTALLINE CELLULOSE PVP K-30: POLYVINYL PYROLIDONE K-30.

Experimental design and statistical analysis

In this study, a 3^3 full factorial design was employed to optimize the formulation of mucoadhesive tablets. In order to optimize formulations, three polymers Gum Kondagogu, Gum Olibanum and Guar Gum as factors and amount of polymers (three different concentrations), were taken as independent variables. Selection of response variables was crucial. The target was to obtain the prolong drug release, but simultaneously to achieve the maximum release. Therefore the response variables selected for evaluation of mucoadhesive tablets release were percent of drug release mucoadhesive strength, drug release and *Ex vivo* residence time was selected as dependent variables. The data obtained by experimental design was processed using Design expert 9.0.1.0 software. 3-D response surface curves were constructed to study the effect of three independent variables alone and in combination of percent drug release. All the responses observed were simultaneously fitted to quadratic models and were evaluated in terms of statistical parameters.

Evaluation of lafutidine mucoadhesive Tablets

Thickness

The thickness of the prepared tablets was tested using vernier calipers. The test was done in triplicate and average thickness was determined.

Hardness

Hardness of prepared tablets was determined using Monsanto hardness tester and measured in terms of kg/cm^2.

Weight variation

Formulated tablets were tested for weight uniformity. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\% \text{ Weight variation} = \frac{\text{Average weight - Individual weight}}{\text{Average weight}}$$

Friability

The Roche friability test apparatus (Electrolab) was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percentage friability was calculated according to the following formula.

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

Content Uniformity

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 10 mg was weighed and dissolved in 100ml of 1.2 pH 0.1 N HCl filtered and drug content analyzed spectrophotometrically in UV spectrophotometer at 220 nm.

In Vitro Swelling Studies

The degree of swelling of mucoadhesive polymer is an important factor affecting adhesion. For conducting the study, a tablet was weighed and placed in a petri dish containing 5 ml of 0.1 N HCl buffer pH 1.2 in 6 h at regular intervals of time (1, 2, 4, and 6h), the tablet was taken carefully by using filter paper. The swelling index was calculated using the following formula

Swelling Index (S.I) = (Wt-Wo)/Wo×100

Where S.I = swelling index, Wt = weight of tablet after swollen at time t Wo= weight of the initial tablet.

Microenvironment pH

The microenvironment pH (surface pH) of the Mucoadhesive tablets was determined in order to investigate the possibility of any side effects *in vivo*. 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 method adopted by Battenberg *et al* was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 mL of distilled water (pH 6.5 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min.

In-vitro dissolution studies

The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 900 ml of 0.1N HCl buffer pH 1.2. The release was performed at 37 ± 0.5°C, with a rotation speed of 100 rpm. 5ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer at 220nm and drug release was determined from standard curve.

Ex-Vivo Residence Time Test

The disintegration test apparatus is used for the study of Ex-vivo residence time of tablets. The intestinal mucosa is collected and is cut in to 2×2 size pieces. These pieces are placed on the glass sides and tied with rubber bands. The formulations are placed on the tissue and kept aside for few minutes. Then all glass slides are fitted to the disintegration test apparatus and the apparatus is allowed to start this process is continued for 12 hours. The residence time of of each formulation is noted as *Ex-vivo* residence time.

Mucoadhesive Strength

Mucoadhesive strength was determined by using modified physical balance method, for which Goat stomach mucosa was collected from local slaughter house and stored in Krebs solution. Mucosa was sticked on glass slide using double sided sticker which was already sticked on the bottom of 100 ml beaker, and this beaker was placed in 1Ltr beaker which already

contained 0.1N HCl of pH 1.2. Tablet were sticked on lower side of left pan of double pan balance using double sided sticker, in both pan of the balance empty beaker were placed and their weight were adjusted, near to the right sided pan arrangement of burette were made for drop wise addition of water, as shown in figure . The mucosal and tablet surface was wetted with few drop of 0.1N HCl and on the left pan tablet 5 gm weight was placed for 5min. to allow the initial contact of mucoadhesion. Then drop wise water was added in beaker of right pan till the detachment of tablet from the mucous membrane was observed. Then weight of water present in right pan beaker was determined, using following formula. Mucoadhesive strength = (Wt.of the beaker + Wt. of the water) – Wt. of the empty beaker. After determination of mucoadhesive strength Force of adhesion was calculated using formula

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

A: Burette B: Beaker for collection of water
C: Wt. adjustment for pan D: 1 lit. Beaker having dissolution medium
E: Glass slide along with mucous F: Modified physical double pan balance
G: focus showing adherence of tablet to mucous membrane

Drug Excipient Compatibility Studies

The drug excipient compatibility studies were carried out by Fourier transforms infrared spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

Stability studies

The stability study of the optimized formulation was carried out under different conditions according to ICH guidelines. The optimized tablets were stored in a stability chamber for stability studies (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The tablets were characterized for hardness, mucoadhesive strength and cumulative % drug released during the stability study period.

RESULTS & DISCUSSION

Physico-chemical parameters of lafutidine Mucoadhesive tablets

The prepared tablets were evaluated for different physico-chemical properties and the results are found to be within the pharmacopoeial limits, which depicted in Table No 2.

Table: 2 Physico-chemical parameters of Lafutidine mucoadhesive tablets

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (Kg/Cm^2)	Friability (%)	Content uniformity (%)
F1	201.65	5	4	0.52	95.23
F2	198.69	5.1	4.1	0.55	97.04
F3	198.04	5.1	4.1	0.63	95.56
F4	201.05	5.2	4.2	0.72	98.11
F5	201.54	5	4	0.62	94.23
F6	200.78	5.3	4.1	0.66	95.45
F7	200.65	5.1	4.1	0.58	94.11
F8	199.57	5.3	4.3	0.69	97.23
F9	200.76	5.3	4.3	0.58	96.13
F10	200.49	5.2	4.2	0.79	95.23
F11	201.53	5.2	4.3	0.76	97.97
F12	202.58	5.3	4.4	0.73	97.45
F13	201.34	5.3	4.8	0.72	97.45
F14	198.67	5.1	4.4	0.74	96.98
F15	199.65	5.4	4.8	0.75	96.45
F16	200.65	5.2	4.4	0.78	96.45
F17	201.79	5.5	4.8	0.79	96.34
F18	201.87	5.5	4.7	0.82	97.56
F19	199.67	5	4	0.84	96.29
F20	199.32	5.2	4.5	0.63	97.18
F21	198.27	5.2	4.3	0.66	96.27
F22	200.27	5	5	0.88	99.78
F23	200.26	5.3	4.8	0.76	96.14
F24	200.10	5.3	4.7	0.73	97.16
F25	199.12	5.1	4.6	0.67	96.23
F26	200.16	5.4	4.7	0.72	97.34
F27	200.29	5.5	4.9	0.89	97.10

Table: 3 Physico-chemical parameters of Lafutidine mucoadhesive tablets

Formulation	Swelling index (%)	Surface p^H	Mucoadhesive strength (g)	Residence time (hrs)
F1	73	5.9	05.34	3
F2	79	5.8	12.23	4
F3	78	6.1	13.42	4
F4	88	6	16.39	8
F5	73	5.8	09.45	4
F6	72	5.7	15.24	8
F7	70	5.6	09.78	4
F8	82	6.1	15.34	6
F9	81	6	15.23	6
F10	77	5.8	13.45	6
F11	86	6.1	19.78	7
F12	88	6.2	19.14	8
F13	96	6.1	26.84	10
F14	83	5.8	17.78	9
F15	90	5.9	25.16	9
F16	88	5.7	19.39	8

F17	93	6.2	23.11	10
F18	95	6.3	27.29	10
F19	90	5.7	24.11	8
F20	88	5.7	25.59	9
F21	90	6	25.67	9
F22	98	6.1	29.12	12
F23	88	6	25.12	9
F24	96	6.2	26.78	11
F25	93	6.1	25.16	9
F26	97	6.2	28.28	11
F27	97	6.3	28.33	11

Fig: 1 Percentage drug release of Lafutidine formulations F1-F7

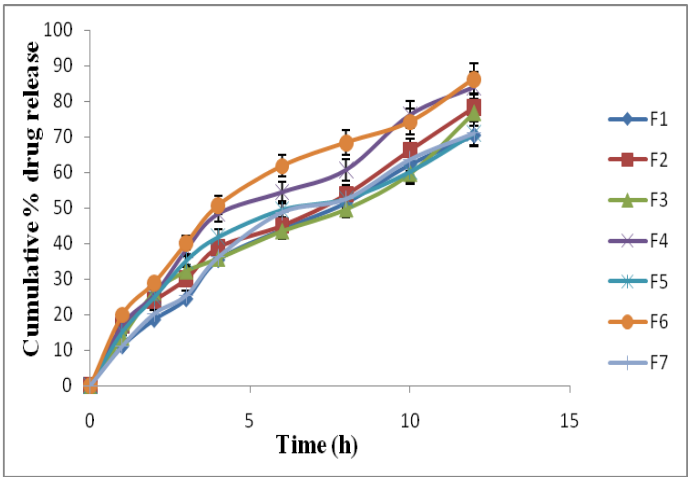

Fig: 2 Percentage drug releases of Lafutidine formulations F8-F14

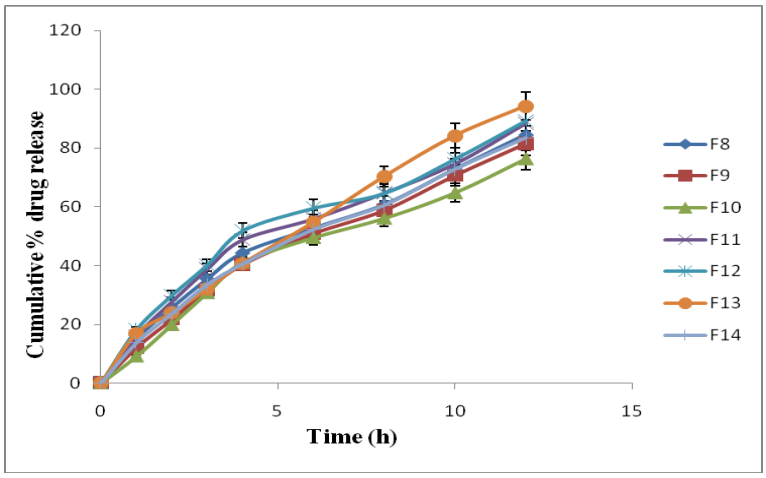

Fig: 3 Percentage drug releases of Lafutidine formulations F15-F21

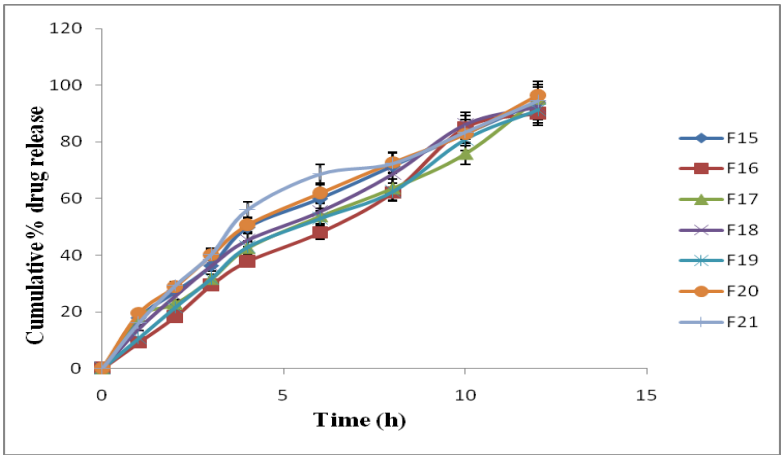

Fig: 4 Percentage drug release of Lafutidine formulations F22-F27

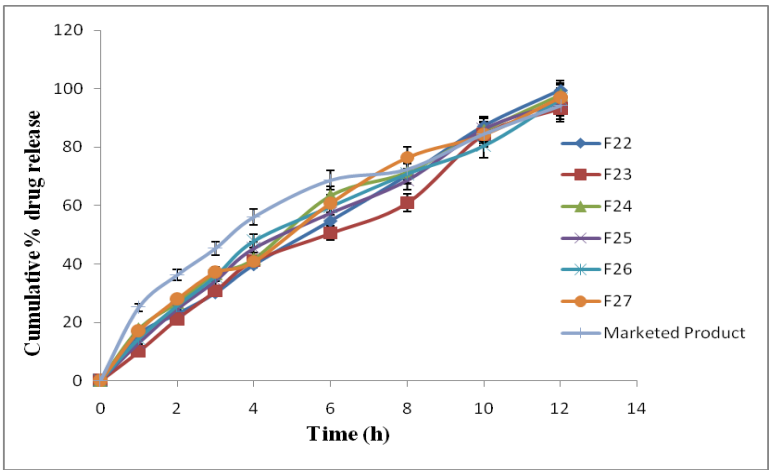

Fig 5: Goat mucous membrane

Fig 6: Optimized Lafutidine mucoadhesive tablet on goat mucous Membrane at 1h

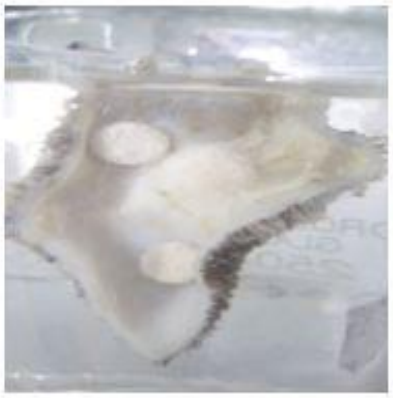

Fig 7: Lafutidine mucoadhesive tablet on goat mucous membrane after 5 h

Fig 8: Lafutidine mucoadhesive tablet on goat mucous membrane after 10h

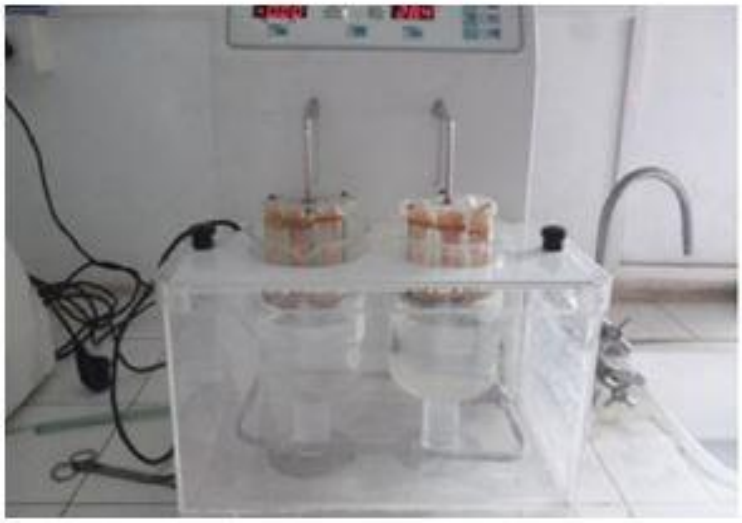

Fig: 9 *Ex-Vivo* Mucoadhesion test of Lafutidine mucoadhesive tablet

Fig: 10 *Ex-Vivo* Mucoadhesion test of Lafutidine mucoadhesive tablet

Kinetic modeling of drug release

To explore the mechanism of drug release from Mucoadhesive tablets, various kinetic models like zero order, first order, and Higuchi and Korsmeyer-Peppas equations were applied to the different formulations. The release kinetics of best formulation (F22) was shown in Table 4. From the data it was concluded that the

Table: 4 Release kinetics of optimized formulation of Lafutidine mucoadhesive tablets:

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F22	0.994	8.020	0.842	0.119	0.946	29.51	0.628	2.155

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.994 indicates that the drug release follows a zero order mechanism (Table no). This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics. Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer-Peppas plots. The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.946 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer-Peppas plots i.e. 0.628 suggest that the drug release from tablets was anomalous Non fickian diffusion

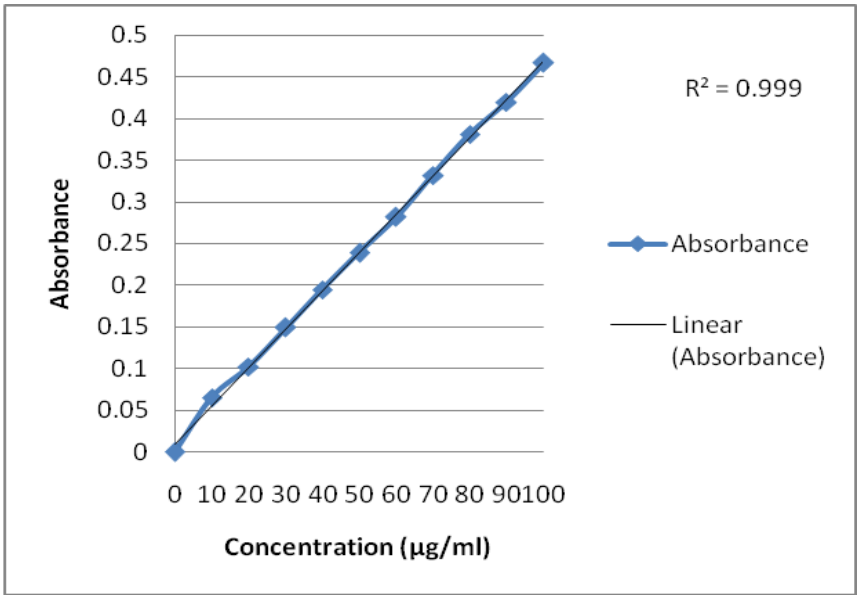

Fig: 11 standard graph of Lafutidine

Drug excipient compatibility studies

FTIR Studies

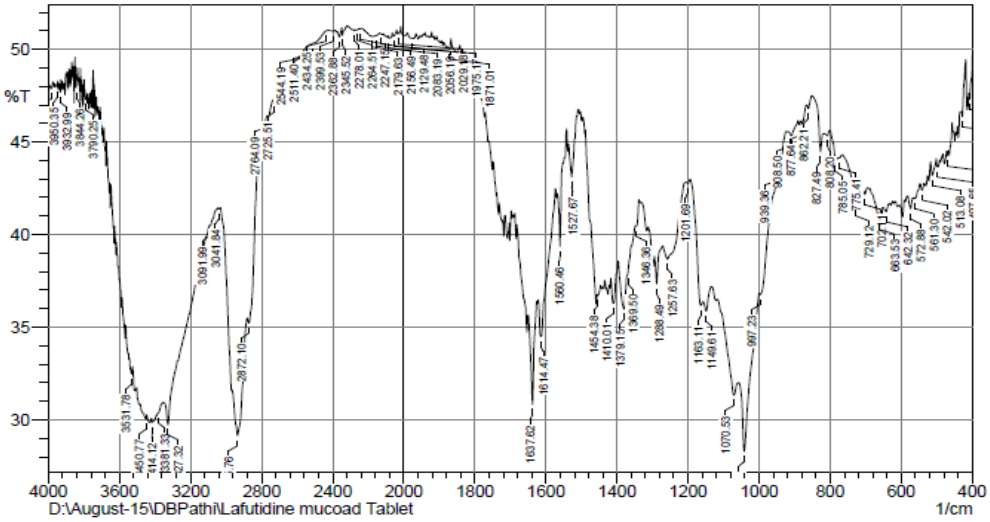

Figure : 12 FT-IR spectrum of pure drug Lafutidine

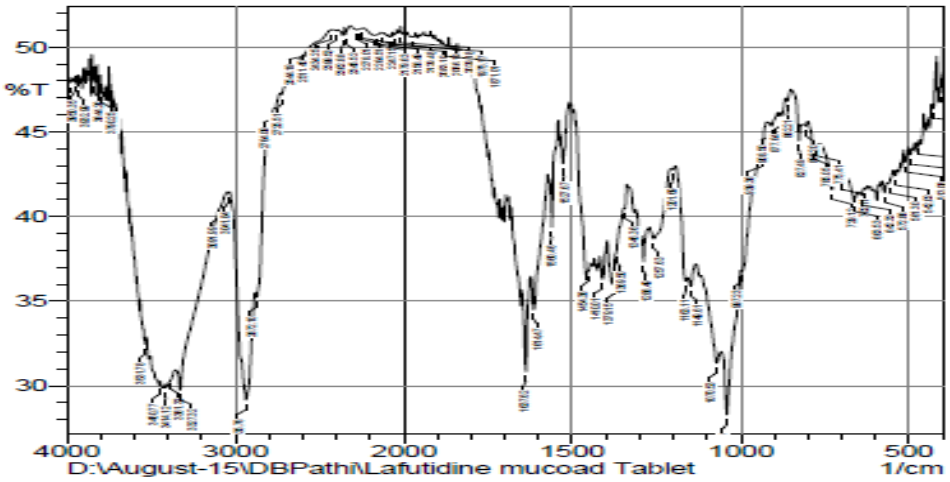

Figure : 13 FT-IR spectrum of optimized formulation F22

Stability Studies

Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties of hardness, bioadhesive strength and *in vitro* dissolution studies with minor differences.

Table: 5 Stability studies of optimized formulation:

Retest Time For Optimized formulation (F22)	Hardness (Kg/Cm^2)	Mucoadhesive strength (g)	*In-vitro* drug release profile (%)
0 days	5	29.12	99.54
30 days	5	29.08	98.56
60 days	5	29.04	97.12
120 days	5	29.00	96.92
180 days	5	28.22	95.68

Design of experiments

This method is mainly used to explain the effect of one factor on other factor. Whether this effect is significant or not. If significant how it influence the response. In this present work the effect of one factor (Guar Gum) on other two factors (Gum Kondagogu, Gum Olibanum) is explained

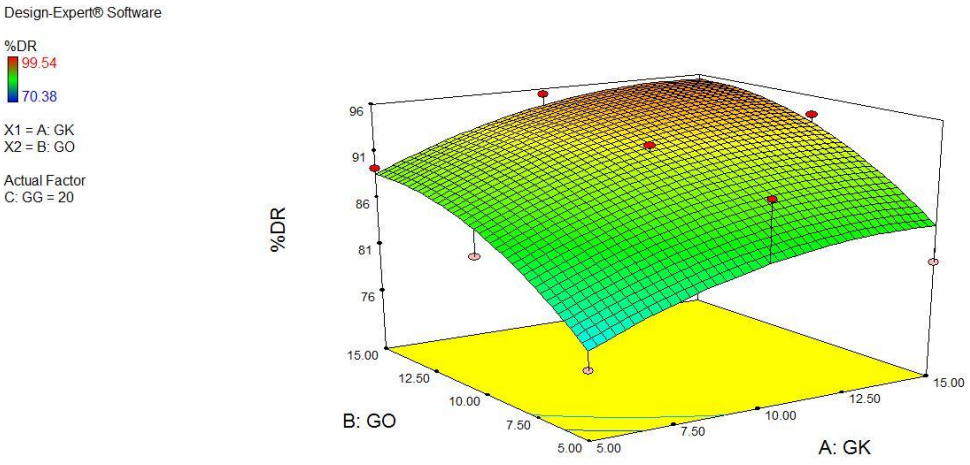

Fig 14: Response surface plot showing the influence of amount of polymer on the release profile of Lafutidine for %CDR

In the above graph the effect of Guar Gum on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of Guar Gum on % cumulative drug release. The formulations with all 3 factors shown % drug release in between 70.38-99.54. but when carbopol is removed from the formulations the maximum % CDR is near 76. This is the effect of factor (carbopol**)** on response

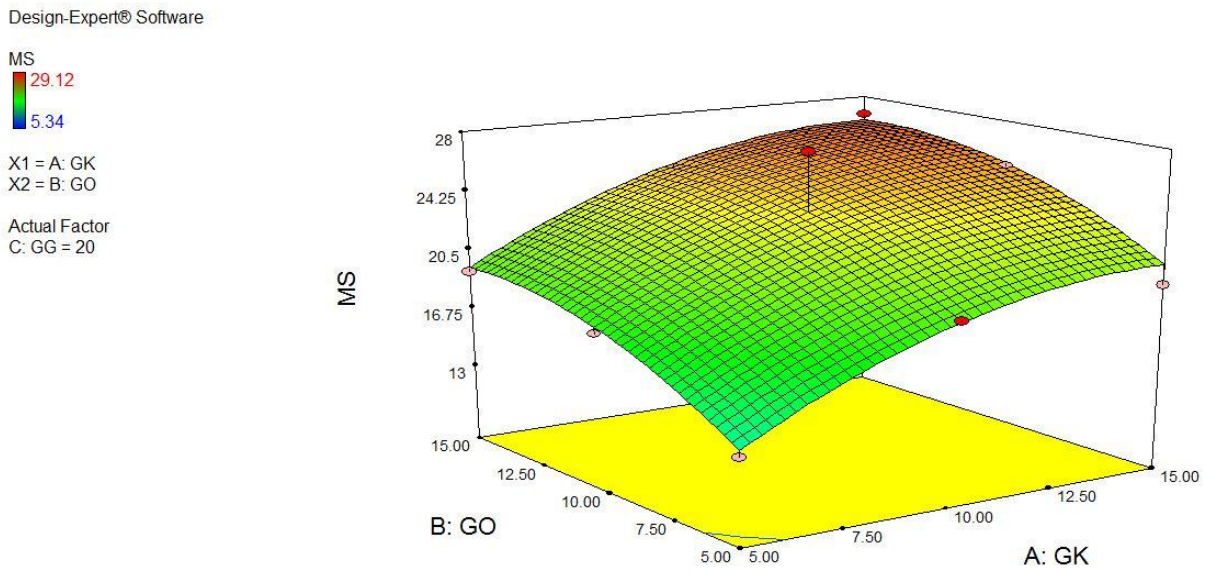

Fig 15. Response surface plot showing the influence of amount of polymer on the release profile of Lafutidine for mucoadhesive strength

There is a negligible effect on mucodhesive strength of formulations because all formulations have excellent mucoadhesive property and there is slightly influence on mucoadhesive strength by Guar Gum.

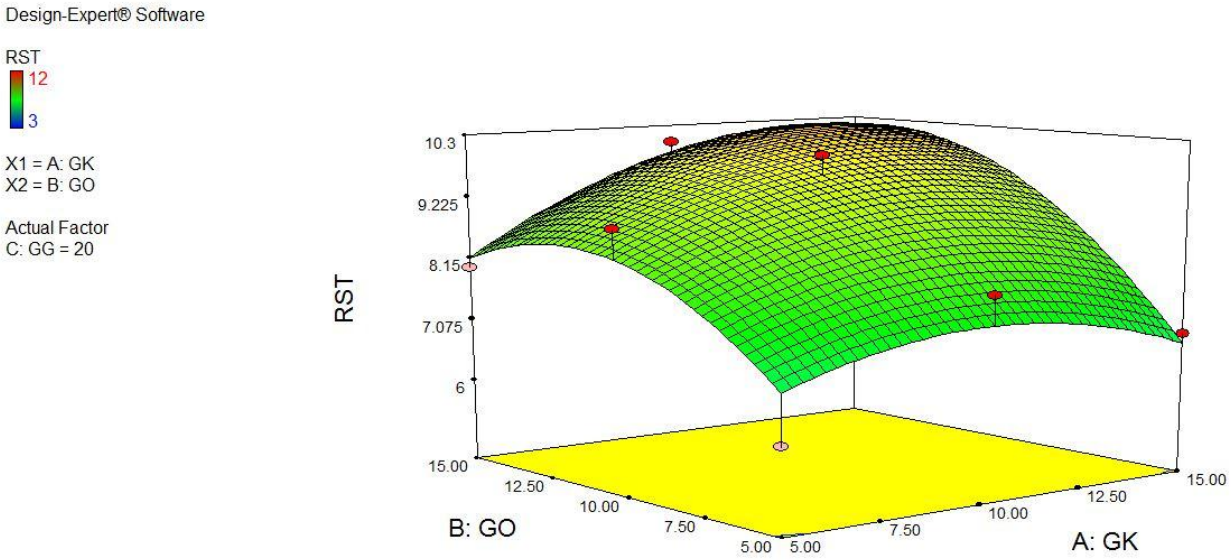

Fig 16. Response surface plot showing the influence of amount of polymer on the release profile of Lafutidine for *Ex vivo* residence time

There is a small effect of Guar Gum on *Ex vivo* residence time of formulations. The formulations without Guar Gum have shown maximum *Ex vivo* residence time is nearly 10 hours.

CONCLUSION

Lafutidine mucoadhesive oral tablets could be formulated using the drug, Gum Kondagogu, Gum Olibanum and Guar Gum with different proportions using 3^3 full factorial designs. It can be seen that there is a synergistic effect when polymers are used in combinations. There is a significant effect of Guar Gum in formulations on drug release rate from the tablets and mucoadhesive strength was also increased. The *in vitro* release kinetics studies reveal that all formulations fits well with Zero order, followed by Korsmeyer-Peppas, Higuchi and the mechanism of drug release is erosion. From the formulations F1-F27 the formulation F22 was selected as optimized formulation because it showed maximum release and the other properties such as swelling index was also low, mucoadhesion force shown good and the Post and pre compression parameters were found to be within the Pharmacopeial limits.

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