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Formulation and Evaluation of Novel Drug Delivery System for Treatment of Peptic Ulcer

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ABSTRACT

Oral drug delivery is the most common route of drug administration. Nevertheless, there are some important limitations that reinforce the need for developing new drug delivery systems. Mucoadhesive tablet are promising dosage form that adhere to the mucosa and deliver the drug through it, which present several advantages. The study was designed to develop mucoadhesive tablet of aloe vera powder using chitosan, guar gum and hyaluronic acid as mucoadhesive polymer. Mucoadhesive tablet of aloe vera powder prepared by wet granulation technique. The mucoadhesive tablets were evaluated for diameter, thickness, hardness, friability, weight variation, percentage swelling index, determination of mucoadhesive strength and force of adhesion, drug content, *in-vitro* dissolution study, *in-vivo* animal study and stability study. The physicochemical properties of all the prepared mucoadhesive tablet batches were found to be in limits. The cumulative % of drug release of formulation FAG3 containing guar gum and FACH2 containing chitosan and hyaluronic acid combination were 94.60 and 93.43 respectively. *in-vivo* animal study concludes aloe vera mucoadhesive tablet may be a beneficial dosage form for treatment of gastric ulcer. The stability studies showed that there was no significant change in adhesive strength.

1. INTRODUCTION

Peptic ulcer is defined as disruption of the mucosal integrity of stomach and duodenum leading to a local defect or excavation due to active inflammation. The word 'peptic' refers to pepsin a stomach enzyme that break down proteins. Peptic ulcer located in stomach is called gastric ulcer. Gastric and duodenal ulcers break gastric and duodenal mucosa. Both gastric and duodenal ulcers relate to the corrosive action of pepsin and hydrochloric acid on the mucosa of the upper gastrointestinal tract [1]. Aloe vera can be used as natural remedy in the treatment of stomach ulcer. It appears to have soothing effect on the ulcer and interferes with the release of hydrochloric acid by the stomach. It acts as an anti-inflammatory and offers relief by healing the stomach lining, reducing stomach acid secretions and aiding in prevention of internal bleeding [2]. Mucoadhesion may be defined as the state in which two materials at least one of which is of a biological nature, are held together for extended period of time by interfacial forces. For drug delivery purposes, mucoadhesion term implies the attachment of drug carrier systems to a specific biological location. Mucoadhesive dosage form gives complete release of the drug to the stomach. It provide constant and prolonged therapeutic effect, reduces the dosing frequency and thereby improve the patient compliance, better drug utilization will improve the bioavailability, reduce the incidence or intensity of adverse effects and increases safety margin of high potency drugs due to better control of plasma levels [3].Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, coupling of mucoadhesive properties to tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucous layer mucoadhesive tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs [3].

2. MATERIALS AND METHODS

2.1 Materials

Aloe vera powder was obtained from Research Lab, Islampur (Maharashtra). Chitosan, guar gum, MCC and Magnesium stearate were obtained from Research - Lab Fine Chem. Industries, Mumbai. Hyaluronic acid was obtained from Encube ethical Mumbai, PVP K30 was obtained from Oxford laboratory Thane, Magnesium stearate and Talc were obtained from Thermosil Fine Chem. Industries, Pune. All ingredients used were of analytical grade.

2.2 Methods

2.2.1. Characterization of aloe vera powder

Aloe vera powder was characterized for following parameter: [4,5,6,7,8]

Color, odor, taste, solubility, modified Borntrager test, nitric acid test, determination of total ash value, acid insoluble ash value, loss on drying (LOD), UV- Visible spectrophotometry, IR spectrometry, melting range and HPTLC.

High Performance Thin Layer Chromatography of aloe vera powder:

The methanolic extract was spotted in the form of bands of width of 6 mm with space between bands of 8 mm, with a 100 µL sample syringe (Hamilton, Bonaduz, Switzerland) on pre-coated silica gel aluminum plate 60 F_{254} (5 cm ×10 cm) with 250 µm thickness (E. MERCK, Darmstadt, Germany) using a CAMAG Linomat 5 sample applicator (Switzerland). The slit dimensions 6 mm × 0.45 mm and scanning speed of 20 mm/sec was employed. The linear ascending development was carried out in 10 cm×10 cm twin trough glass chamber (CAMAG, Muttenz, Switzerland) using Ethyl Acetate: Methanol: Water (10:2:1 v/v) as mobile phase. The optimized chamber saturation time for mobile phase was 15 min. The length of chromatogram run was 8 cm and development time was approximately 25 min. TLC plates were dried in a current of air with the help of a hair drier. Densitometric scanning was performed on CAMAG thin layer chromatography scanner at 254 nm and 254 nm operated by WINCATS software version 1.4.2.

Standard sample preparation: 10 mg/8 ml methanol + 2 ml DMSO (1000 µg/ml i.e 1000 ng/µl).Sample preparation: 100 mg/8 ml methanol + 2 ml DMSO (4:1)

2.2.2.Drug excipients compatibility study

IR spectrum of drug and excipients was recorded by FT-IR spectrophotometer (Bruker spectrophotometer Model-220, Germany). 1:3 ratio of sample was placed in contact with the surface of an IR transmitting crystal and readings were recorded peak belonging to major functional group were identified. The scanning range was 450 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

2.2.3. Preparation of granules

Mucoadhesive granules of aloe vera powder were prepared by wet granulation method using different polymers as shown in Table 1. All ingredients were passed through sieve no. 60 and then blended (except magnesium stearate and talc) for 15 min. All ingredients were granulated with PVP K30 binding solution. The wet masses were passed through sieve no. 40 and the resulting granules were dried at 40°C. Finally magnesium stearate and talc was added and mixed for 5 min [9].

Table 1: Composition of different ingredients used in mucoadhesive tablet

Formulation Ingredients (mg)	FAC3	FAG3	FAH3	FACG1	FACG2	FACH1	FACH2	FAGH1	FAGH2	FACGH
Aloe vera powder	32	32	32	32	32	32	32	32	32	32
Chitosan	100	-	-	50	25	50	25	-	-	25
Guar gum	-	100	-	25	50	-	-	50	25	25
Hyaluronic acid	-	-	100	-	-	25	50	25	50	25
Microcrystalline cellulose	52	52	52	77	77	77	77	77	77	77
Polyvinyl pyrrolidine K30	12	12	12	12	12	12	12	12	12	12
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1	1	1	1
Total weight	200	200	200	200	200	200	200	200	200	200

2.2.4. Evaluation of granules

The angle of repose was measured by using funnel method. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100. Tapped bulk density of the granules was determined by using the formula: TBD= Weight of granule/Tapped volume of granule.[9]

2.2.5. Preparation of mucoadhesive tablet

Mucoadhesive tablet of aloe vera powder prepared by wet granulation method using polymer chitosan, guar gum and hyaluronic acid. The powder mix was granulated with 6% w/w

PVP-K30 in water. The wet mass was passed through sieve 40 and the granules were dried at 40°C for 1 hour in a hot air oven. The dried granules were passed through sieve # 22 and lubricated with magnesium stearate and talc by further blending for 5 min. Tablets were compressed at 200 mg weight on a 10 station mini rotary compression machine with 8 mm flat-shaped punches.[9]

2.2.6. Evaluation of mucoadhesive tablet

All prepared mucoadhesive tablets were evaluated for its diameter, thickness, hardness, friability, weight variations, percentage swelling index, determination of mucoadhesive strength and force of adhesion, drug contents, *in-vitro* dissolution study, *in-vivo* animal study and stability study.

(1) Dimensions

The thickness of ten tablets of each formulation type was determined using a digital vernier caliper.[10]

(2) Weight variation

This test was performed as per I.P. 10 Tablets of each formulation were weighed individually using an electronic balance (0.01mg sensitivity). The average weight was calculated and individual tablet weight was compared with the average value and the deviation was recorded.[10]

(3) Hardness

Hardness of each formulation was determined using Monsanto hardness tester. For this test lower plunger was placed in contact with the tablet and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. The hardness was recorded from the position of the pointer.[10]

(4) Friability

Twenty tablets were weighed and placed in the plastic chamber. The plastic chamber was rotated for 4 minutes or 100 revolutions. During each revolution, the tablets fall from a distance of 6 inches. The tablets were removed from the chamber after 100 revolutions and weighed. Loss in weight indicates the friability. The tablets were considered to be of good quality if the loss in weight was less than 0.8%.[10]

(5) Percentage swelling study

Swelling study of individual batch was carried out using USP dissolution test apparatus-II (rotating paddle) 900 ml of 0.1N HCl solution which was maintained at 37±0.5^{O}C, rotated 100 rpm. Weight and diameter of tablet taken prior to swelling study (W1). Tablet was kept in dissolution medium. The tablet was removed every one hours interval up to 6 hours and excess water was removed carefully using filter paper and diameter of swollen tablets were determined using vernier caliper. The swollen tablets were reweighed (W2); Percentage hydration (Swelling index) calculated by using formula[9,10]

$$\% \text{ Swelling Index} = \frac{W2 - W1}{W1} X100$$

Where, W2- Weight of tablet after particular time interval, W1- Initial weight of tablet.

(6) Determination of mucoadhesive strength and force of adhesion

Mucoadhesive strength was determined by using modified balance method. For this study goat stomach mucosa was collected from local slaughter house and then washed with isotonic phosphate buffer. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media 0.1N HCl pH 1.2, which was then placed below right side of the pan. Stomach mucosa was then tied to Teflon-coated glass slide and this slide was fixed over the protrusion in Teflon block using a thread. The block was then kept in beaker containing pH 1.2 buffer solution at the level that just touches the mucosa. By keeping a 5gm weight on the right pan, the two sides of the balance were made equal. The beaker with the Teflon block was kept below the left hand set up of the balances. The tablet was struck onto the lower side of the left-hand side pan. The 5 gm weight from the right pan was then removed. This lowered the left pan along with the tablet over the stomach mucosa with a weight of 5 gm. This was kept undisturbed for 3 minutes. Then, the weight on the right-hand side was slowly added in an increment of 0.5 gm till the tablet just separated from the mucosal surface. The excess weight on right pan i.e., total weight minus 5gm was

taken as a measure of the mucoadhesive strength. From the mucoadhesive strength, the force of adhesion was calculated using the following formula. [9,10]

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{100} \text{ X } 9.81$$

(7) Drug contents

For this, three tablets of each formulation were finely powdered. Quantity equivalent to 10 mg of Aloe vera powder was dissolved in 100 ml DMSO: Methanol (1:4). It was further diluted to give 10 µg/ml solution. The solution was filtered and the absorbance of filtrate was noted at previously recorded λ max and drug contents were estimated.[12,13]

(8) *In-vitro* dissolution studies

Dissolution studies of all batches were performed employing USP II paddle-type dissolution test apparatus using 900 ml of 0.1 N HCl as dissolution medium at 50 rpm and 37°C ± 0.5°C. A 5 ml aliquot of the sample was withdrawn periodically at 1 hours and the volume replaced with an equivalent amount of the dissolution medium. The samples were analyzed spectrophotometrically at 281 nm using UV-Visible Spectrophotometer (Shimadzu, UV 1800). Drug release experiments were conducted in triplicates.[14]

(9) *In-vivo* animal study of selected formulation of mucoadhesive tablet

Experimental animals

The project proposal was approved by the Institutional Animal Ethical Committee (IAEC) (Approved no16-006) and all the experiments were carried out according to the guidelines of the committee for the purpose of control and supervision of experiments on animals, India (CPCSEA). Healthy adult albino rats weighing between 150-200 gm were used as experimental animals. Animals were housed in polypropylene cages at 24±2 ^{0}C in the animal house and fed with commercial pellet diet. [15,16]

Induction of ulcer

Before experimental study rats were randomly divided into group I, group II, group III and group IV. Animals were starved for 12 hours with free access to drinking water. After 12

hours gastric ulcer was induced by oral administration of 80 % ethanol (10 ml/kg – BW) to each animals except normal control. After 48 hours in group II animals sacrifice and checked for ulcer induction. From the same day group III animals were administered aloe vera powder tablet formulation (medicated mucoadhesive) by oral route 3.2 mg/kg Body weight (BW) once in day for four days. Group IV animals were orally administered pantoprazole marketed formulation (2 mg/kg- Body weight) once in day for four days. On 7 day animals were anesthetic using ether and animals were sacrificed.[15,16]

Stomach of animals opened along greater curvature, rinsed with saline to collect gastric contents and examined by a magnifier lens (10 x) to assess the formation of ulcer. The number of erosions formed on granular portion of stomach was counted and ulcer index was calculated by using following equation.[16]

$$\text{Ulcer index (UI)} = \frac{\text{Total ulcer score}}{\text{No of animal ulcerated}}$$

$$P\% = \text{Control mean ulcer index - Test mean ulcer index / Control mean ulcer index X } 100$$

Where, P%: percentage of ulcer protection.

Histopathological evaluation

The gastric tissue samples were fixed in neutral buffered formalin for 24 hrs. Sections of tissue from stomachs were examined histopathologically to study the ulcerogenic and or anti-ulcerogenic activity of Aloe vera powder. The tissues were fixed in 10% buffered formalin and were processed using a tissue processor. The processed tissues were embedded in paraffin blocks and about 5-μm thick sections were cut using a rotary microtome. These sections were stained with hematoxylin and eosin. The slides were examined microscopically for pathomorphological changes such as congestion, hemorrhage, edema, inflammation and epithelium damage using an arbitrary scale for the assessment of severity of these changes.[15]

Statistical analysis was expressed as mean ± SD. The study was performed by one-way ANOVA followed by dunnett test.[15]

(10) Stability study of selected formulation of mucoadhesive tablet

Selected mucoadhesive formulation was subjected to exaggerated conditions of temperature (40 ± 2^0C) and humidity (75±5 % RH) to test effect of various formulation additives on the stability of the drug and as well as that of the dosage form. These formulations were evaluated for contents of aloe vera powder and dissolution profile over a period of one month.[11]

3. RESULTS AND DISCUSSION

3.1. Characterization

Aloe vera powder was dark brown in color, bitter in taste, and having characteristics and disagreeable odor. Aloe vera powder was slightly soluble in methanol, 0.1 N HCl and soluble in dimethyl sulphoxide. In the modified Borntrager test of aloe vera powder was observed pink to red color (C - Glycoside present), nitric acid test- deep brownish red color (C-Glycoside present), bromine test- pale yellow precipitation (C-Glycoside present). In the characterization of aloe vera powder total ash value was found to be 17 %, acid insoluble ash 2.56 %, loss on drying 0.4 mg and melting point146^{0}C-148^{0}C.

UV-Visible spectrophotometry

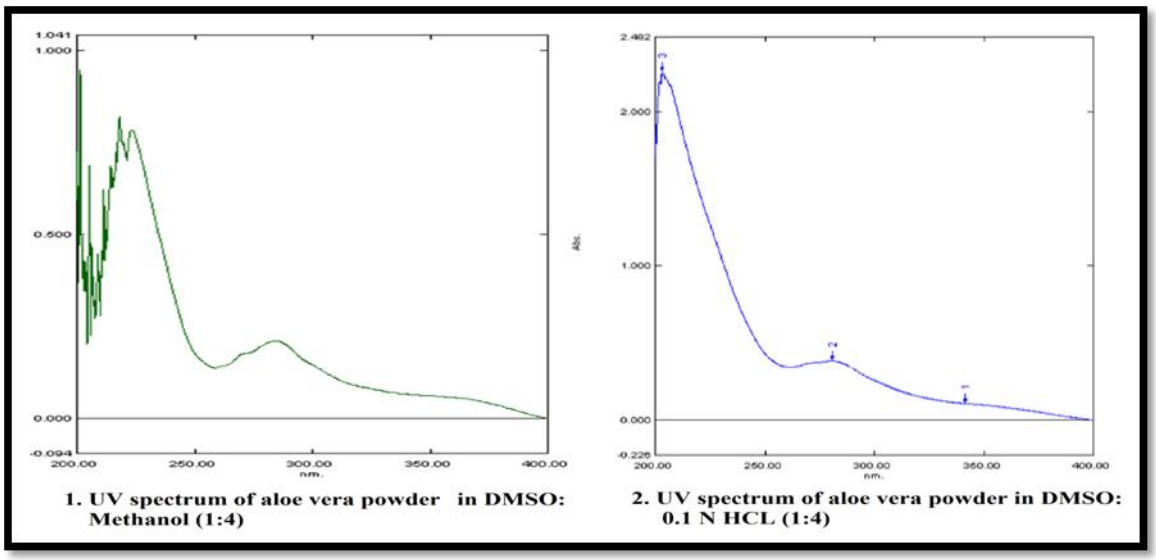

Figure 1: UV spectrum of aloe vera powder

The UV spectrum (λ max) of aloe vera powder in DMSO: Methanol (1:4) indicated λ max at 261nm and UV spectrum (λ max) of aloe vera powder in DMSO: 0.1 N HCl (1:4) indicated λ

max at 281 nm. Hence the observed value is in good agreement with the standard value.

High performance thin layer chromatography

In the chromatogram of aloe vera powder, two well resolved peaks were observed, out of these spots one spot matched with the Rf value shown by aloe vera powder 254 nm. The standard sample found 8.44 % w/v and sample 2.45 % w/v of aloin. The Rf value of standard and sample was found 0.58 and 0.67 respectively.

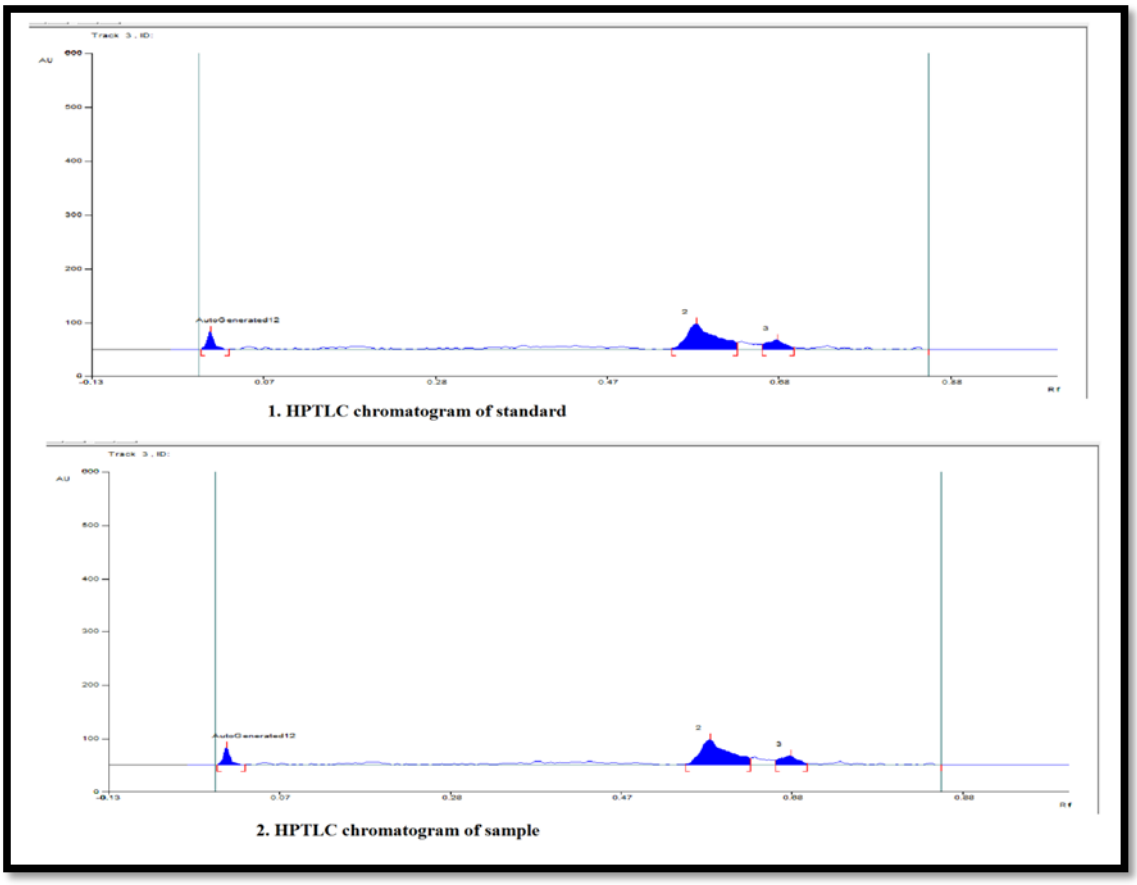

Figure 2: HPTLC chromatogram of standard and sample

Calibration curves:

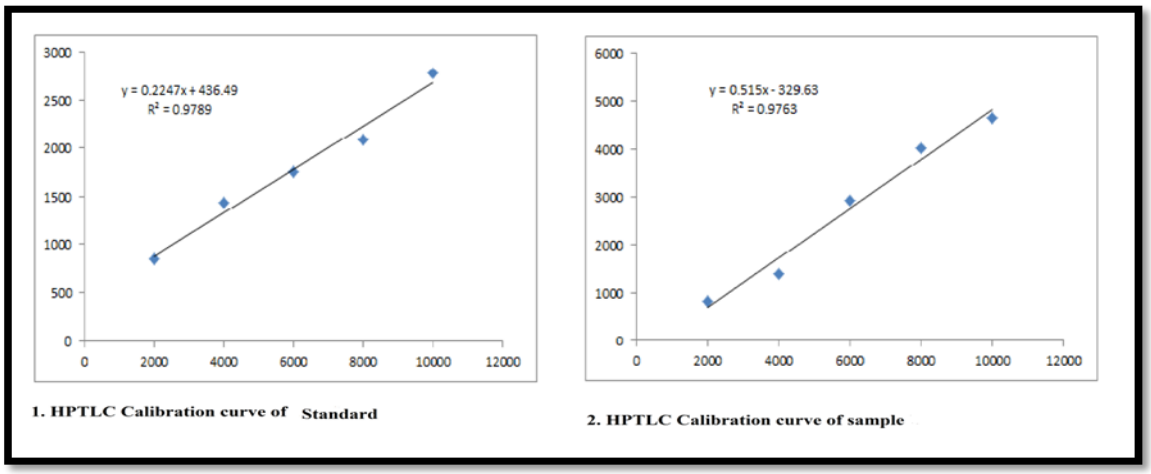

Figure 3: HPTLC calibration curve 1: Standard 2: Sample

Calibration curve was found to be linear over the concentration range 2000-10000µg/spots. Linearity was evaluated by determining seven standard working solutions in duplicate. The peak area and concentration subjected to least square linear regression analysis to calculate the calibration equation. (Standard) y = 0.2247x + 436.49 and regression coefficient was R^2 = 0.9789, (Sample) y = 0.515x - 329.63 and regression coefficient was R^2 = 0.9763.

3.2. Drug excipients compatibility study

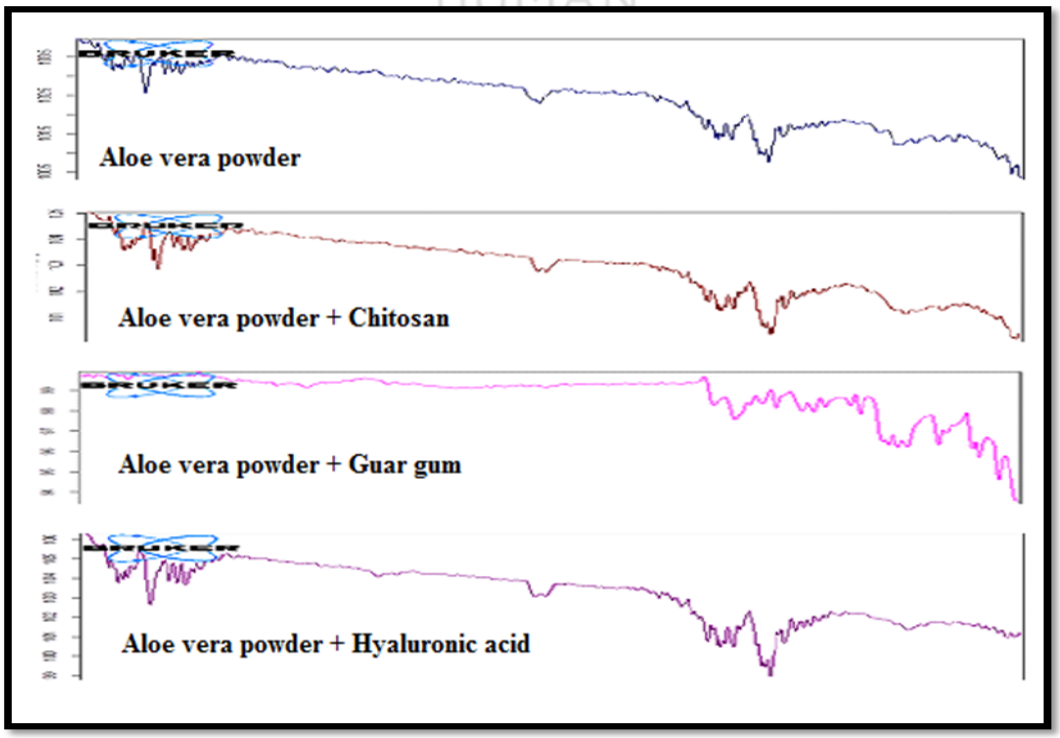

Figure 4: Drug excipient compatibility study

Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational. Frequencies, leading to frequency shifts and splitting in absorption peaks. The FTIR spectrum of samples Figure 4 showed characteristic absorption bands which were comparable with absorption bands of individual sample. The results illustrated there were no chemical instabilities in drug-excipients combinations.

3.3. Evaluation of granules

Carr's index of granules was found to be between 13.25-17.80%. Hausner's ratio was found to be 1.15-1.23.Which was suitable for producing the tablet. Tapped densities of formulations was found to be in between 0.41- 0.62 g/ml. The angle of repose was found to be 22.35^{0} - $27.68^{0.}$

3.4. Evaluation of mucoadhesive tablet

The results of physical evaluation tablets showed that of all batches were found within the limits of the Indian Pharmacopeia. Diameter was found in between 8.2±0.4 mm - 8.4±0.6 mm, thickness was found in between 3.2±0.7mm - 3.9±0.3 mm, hardness was found in the range 3.4±0.1 kg/cm^2 to 3.9±0.28 kg/cm^2, percentage friability was found in between 0.49% and 0.62% and weight variation between 198±2 mg and 200±5 mg.

Percentage swelling index

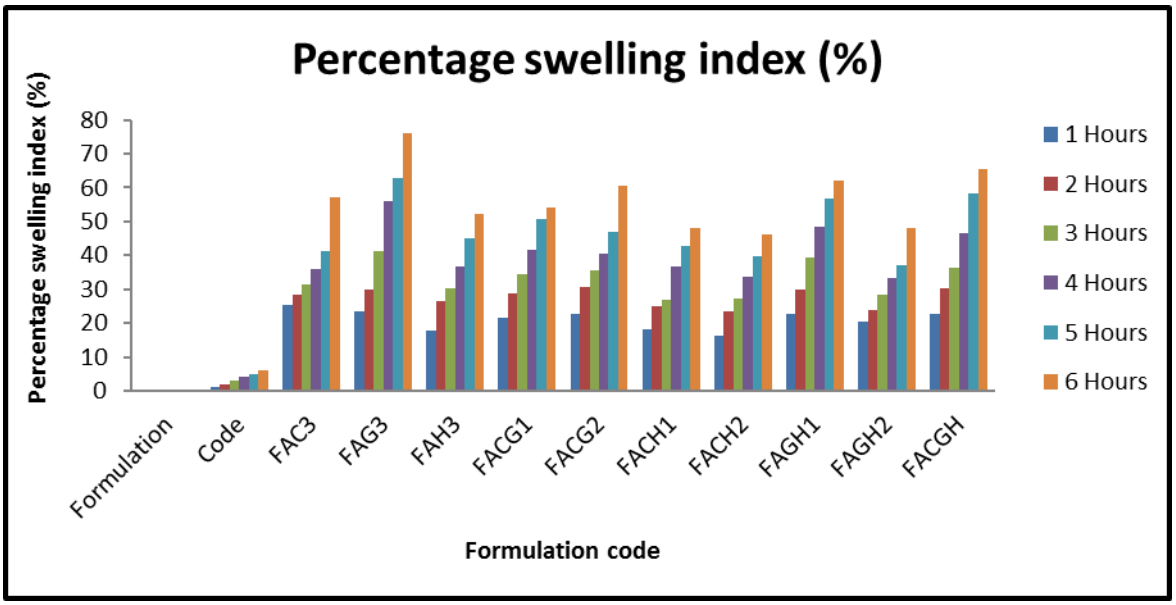

Figure 5: Percentage swelling index (%)

The swelling of the polymer used (Chitosan, guar gum, hyaluronic acid and its combination) could be determined by water uptake of the tablet. Percent swelling of the tablet was determined at different time intervals for 6 hours. The percentage swelling of FAG3 formulation batch guar gum (76.12±0.56%) was found to be higher than other formulations. Formulation FACH2 batch (Chitosan and hyaluronic acid combination) shows lowest swelling index 46.31±0.29% the results was given in Figure 5. The diameter of formulation batch FAG3 (Guar gum) was found to be 9.58 mm within 1 hour during swelling of tablet and after 6 hours diameter of swelling tablet was found to be 12.88 mm. Increasing the concentration of polymer increases the swelling index.

Determination of mucoadhesive strength and force of adhesion

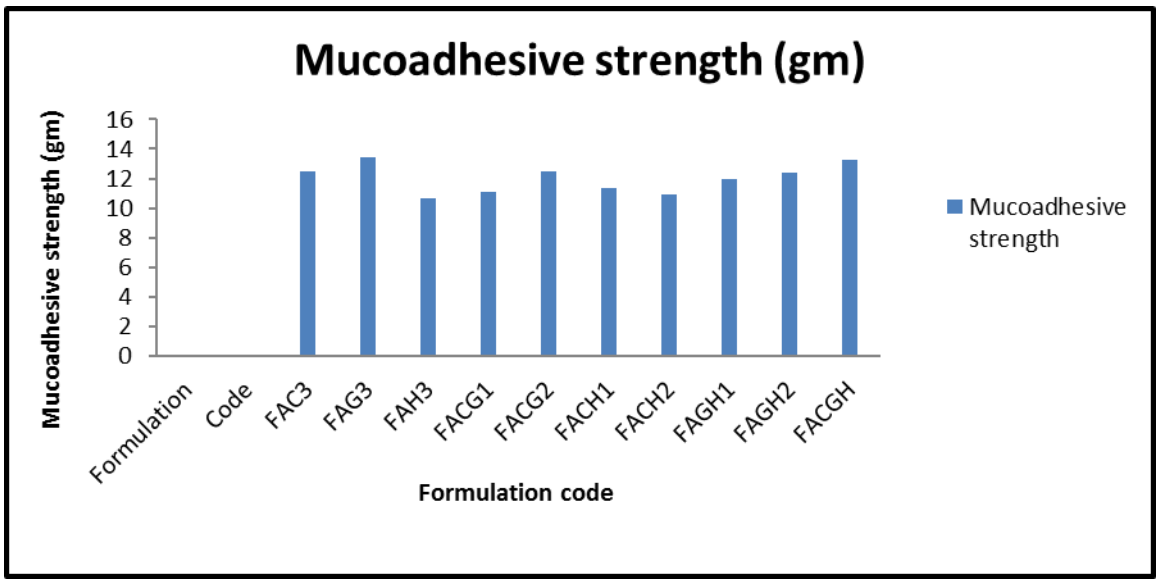

Figure 6: Determination of mucoadhesive strength (gm)

All formulations showed good mucoadhesion. Mucoadhesive strength study was performed on the modified physical balance to measure the force (N) required for detaching the tablet and result are given in Figure 6. Mucoadhesion characteristics were affected by the type of mucoadhesive polymer and viscosity of polymer also affects the mucoadhesive strength of the tablet. In all medicated formulations FAG3 formulation with polymer guar gum shows highest mucoadhesive strength and FACH2 formulation with polymer chitosan and hyaluronic acid shows lowest mucoadhesive strength. The highest force of adhesion was found batch FAG (1.31) and lowest force of adhesion FACH 2 (1.06) results are given in Figure 7.

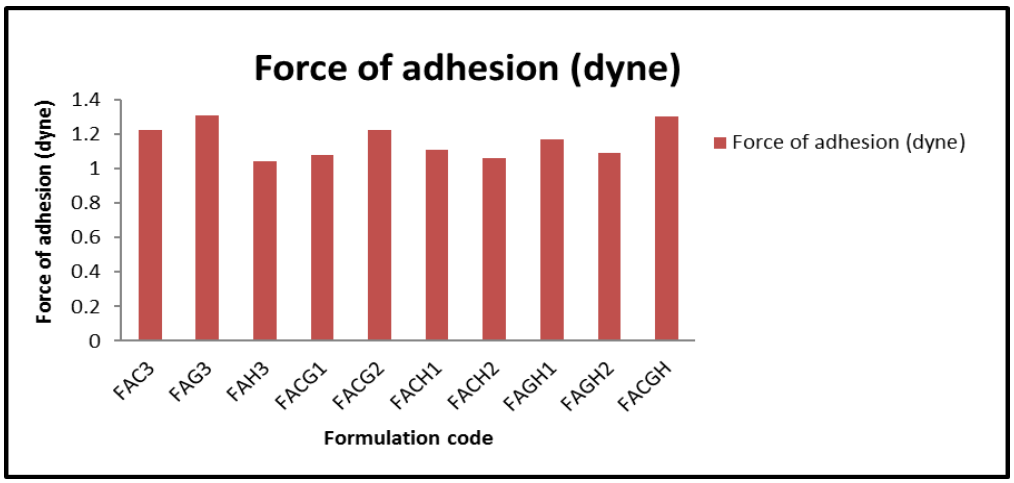

Figure 7: Force of adhesion

Drug contents

The drug contents of all mucoadhesive tablets were found in the range 97.23% to 99.78%.

***In-vitro* dissolution study**

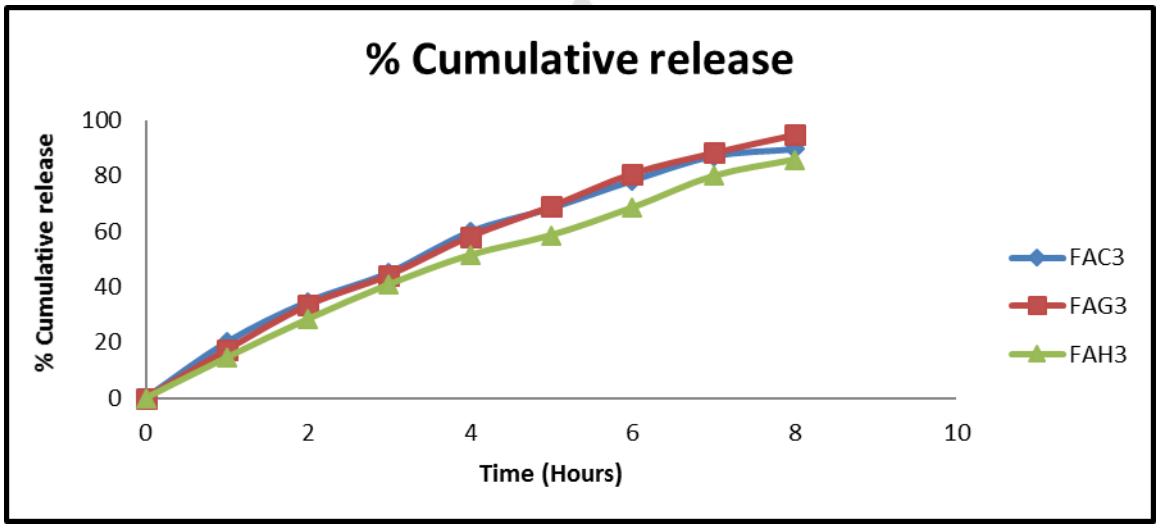

Figure 8: Dissolution plot of aloe vera mucoadhesive tablet in 0.1 N HCl (FAC3-FAH3)

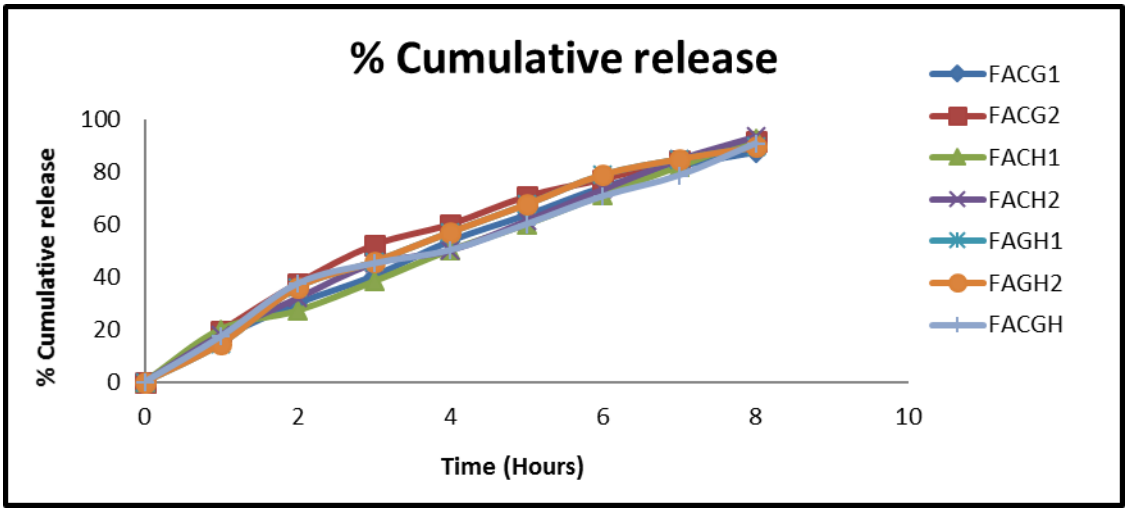

Figure 9: Dissolution plot of aloe vera mucoadhesive tablet in 0.1 N HCl (FACG1-FACGH)

Mucoadhesive tablet showed controlled release behavior with distinct time. Comparative study of the dissolution profiles of the drug in 0.1 N HCl from different formulations of Aloe vera mucoadhesive tablet prepared with drug and various mucoadhesive polymers were studied. The cumulative percentage of drug release was plotted against time is as shown in Figure 8 and Figure 9. From the above results, it was found that formulation FAG3 showed more than 94.60 % and FACH2 showed 93.43 % drug release than other formulations at end of 8 hours. Effect of type of polymer on drug release from mucoadhesive tablets (FAC3, FAG3 and FAH3) showed that drug release from tablets containing guar gum was more as compare to tablets containing chitosan and hyaluronic acid polymers. Guar gum contributes mucosa to the establishment of a more extensive cohesive layer, resulting in superior levels of mucosal retention. In general, the drug release from the tablet may be controlled by gel formation of chitosan and guar gum in acidic environment, diffusion of drug through the gel and finally erosion of gel taking place as a result of dissolution of guar gum and chitosan. The mechanism of drug release from guar gum due to water penetration, gelatinization and diffusion. The drug release mechanism of hyaluronic acid is due to diffusion. From the *in-vitro* dissolution study, it can be noted that the chitosan, guar gum and hyaluronic acid is having ability to control the drug release. Formulation FACG2, FACH1, FACH2, FAGH1, FAGH2 and FACGH containing combinations of polymers do not have significant effect on drug release. Formulation FAG3 contains guar gum as a mucoadhesive polymer. Friability, Hardness, percentage swelling index, mucoadhesive strength and force of adhesion of formulation FAG3 was within acceptable range. Drug release from FAG3 formulation at the

end of 8 hours was higher as compared to other formulation. Hence, FAG3 was selected as best formulation as compared to other formulation.

***In - vivo* animal study of selected formulation of mucoadhesive tablet**

Ethanol-induced gastric ulcer

In positive control animal, oral administration of absolute ethanol produced characteristic lesions in the portion of rat stomach which appeared as elongated bands of thick, black & dark red lesions. Aloe vera powder has shown significant protection index of 82.35% with the dose of 3.2 mg/kg body weight and pantoprazole marketed formulation as reference standard drug shown protection index as 52.83%. (Results are tabulated in Table 2).

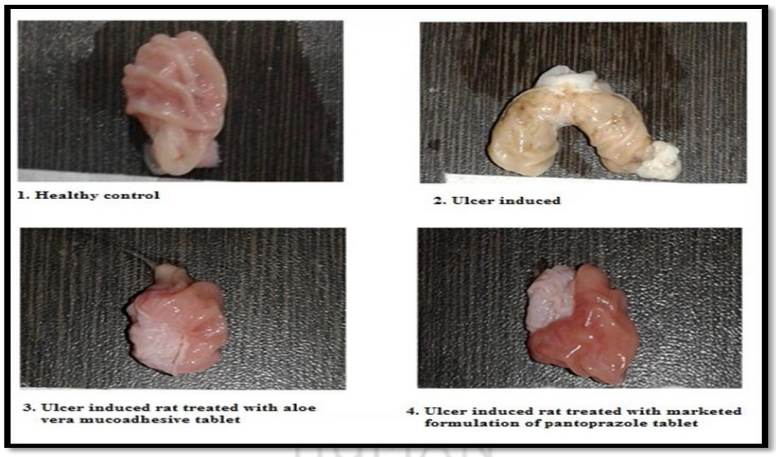

Figure 10: Gross evaluation of rats stomach 1) Healthy control 2) Ulcer induced 3) Ulcer induced rat treated with aloe vera mucoadhesive tablet 4) Ulcer induced rat treated with marketed formulation of pantoprazole tablet.

Table 2: Effect of control, aloe vera and pantoprazole marketed formulation on ethanol induced ulcer in rats.

Treatment	Dose of drug	Ulcer index	% protection
Healthy control	-	-	-
Disease induced	-	11.66±0.35	-
Aloe vera tablet formulation	3.2 mg/kg BW	2.0±0.98	82.35
Pantoprazole marketed formulation	2 mg/kg BW	5.5±0.56	52.83

Histopathological evaluation

Ethanol-induced gastric ulcers are due to many mechanisms, including depletion of gastric mucus and impaired mucosal permeability and lead to increased leakage of hydrogen ions from the lumen and decreased trans-luminal membrane potential difference.

Gastric mucosa of normal control

Histopathological examination of normal control rats stomachs showed normal basic layers of the fundus. The granular mucosa appears darker because of nuclei of epithelial and connective tissue. It contains thin pink strip marks in the muscular is mucosa. Normal animal showed intact mucosa and submucosa. Gastric pits are lined by columnar epithelium. No sign of tissue damage was observed in Figure 11 (1).

Gastric mucosa of positive control

Gastric ulcer was induced by oral administration of 80 % ethanol (10 ml/kg - BW) to each animals except normal control. Histopathology of positive control (ethanol induced) shown edema, severe epithelium damage, hemorrhage and infiltration of cells Figure 11 (2).

Gastric mucosa of ulcer induced rats treated with aloe vera tablet

Histopathology of aloe vera tablet treated group shows minimal hemorrhage increases epithelium cells proliferation, edema was not observed. This effect was may be due to increases in IL 10 levels which promote ulcer healing and also acts as gastroprotective effects Figure 11 (3). Aloe vera also has anti-inflammatory effect. Aloe vera can reduce vasoconstriction and improve perfusion of gastric mucosal capillaries, thus promotes ulcer healing. It also inhibits the gastric acid secretion. Aloe vera has antioxidant activity.

Rats gastric mucosa of ulcer induced rats treated with pantoprazole marketed formulation

Histopathology of pantoprazole marketed tablet treated group shown minimal hemorrhage increases epithelium cells proliferation, edema was not observed. Pantoprazole is PPIs which are the suppressors gastric acid secretion and inhibits gastric H^+K^+ ATPase enzymes (proton pump. These drugs reduce daily production of acid Figure 11(4).

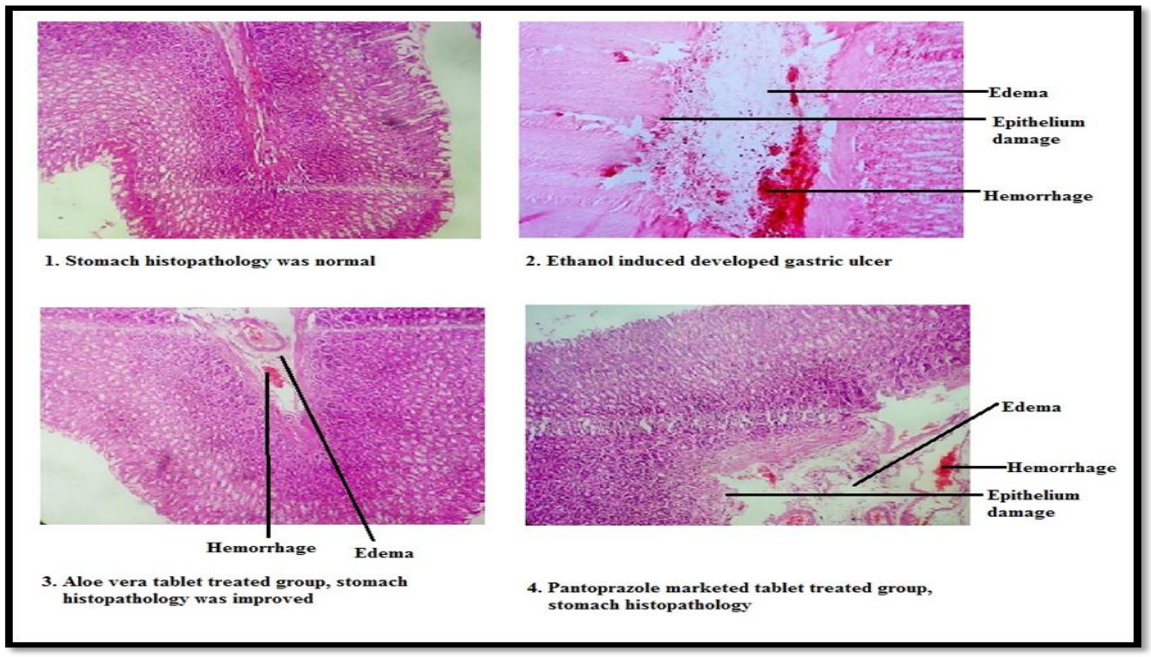

Figure 11: Histopathology of ethanol induced ulcer model 1.Stomach histopathology of healthy control 2.Ethanol induced 3.Ulcer induced rats treated with aloe vera mucoadhesive tablet 4.Ulcer induced rats treated with pantoprazole marketed formulation.

Statistical Analysis

Table 3: Histopathological evaluation of stomach portion of rats

Lesions	**Healthy control**	**Positive control (Ulcer induced)**	**Aloe vera formulation**	**Marketed formulation**
Inflammation	0.33 ±0.51	5.50± 1.04**	0.83±0.40	2.00±0.54
Hemorrhage	0.50±0.54	3.33±1.03**	0.35±0.75	1.16±0.40
Epithelium damage	0.50±0.54	4.50±0.54**	0.94±0.40	1.60±0.51
Edema	0.33±0.51	4.50±0.54**	0.83±0.40	1.16±0.40
Congestion of blood vessels	0.66±0.51	4.00±0.89**	1.00±0.00	1.33±0.51

Value are expressed as mean ±SE

** P<0.001 Vs Healthy control

Severity score: NUD: 0 (No ulcer detected); 1 (very small amount of changes ≤10 %); mild: 2

(ulcer is easily identified but limited severity 11-20%); mild: 3(ulcer is identified but limited severity 21-40%); Moderate: 4(ulcer is prominent 41-60%) Severe: 5 (the degree of changes is 61-80%); 6 Severe: (the degree of changes is 81-100%).In the histopathological study, significant difference observed between healthy control and positive control group. There was no significant difference between healthy control Vs aloe vera treated rats group and marketed formulation treated rats groups. *In vivo* animal study concluded aloe vera mucoadhesive tablet may be a beneficial dosage form for treatment of gastric ulcer.

Stability study of selected formulation of mucoadhesive tablet

The result of the stability study indicated there were not much difference observed in general appearance, friability, mucoadhesive strength, drug content and cumulative percentage drug release before and after the storage period at room temperature and therefore the formulation is quite stable.

4. CONCLUSION

The result for micromeretic properties showed good flow property for physical mixture and the drug content of all formulation. According to result of mucoadhesive strength and percentage swelling index of tablet formulation FAG3 showing best mucoadhesive properties. Among all the tablet formulation FAG3 containing 50% of guar gum was selected based on drug release within given period of time. *In-vitro* release rate studies showed that maximum drug release was observed in FAG3, FACH2, FACH1, and FACG2. Developed mucoadhesive tablets are very reliable to controlled release of aloe vera powder over period of 8 hours. From *in-vivo* animal study, it can be concluded that the mucoadhesive formulation containing aloe vera shows maximum efficacy which can be beneficial dosage form for treatment of peptic ulcer. Formulation was stable at exaggerated condition of temperature and humidity (40 ± 2^{O}C & 75±5%).

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