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FORMULATION AND EVALUATION OF LAFUTIDINE EFFERVESCENT TABLETS

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ABSTRACT

In this study, lafutidine effervescent tablets were developed to replace traditional lafutidine tablets in the treatment of gastric and duodenal ulcers, where rapid start of action is advantageous in controlling gastric and duodenal ulcers and aids in bioavailability. Use various acid sources, such as citric acid (F1-F3), tartaric acid (F4-F6), fumaric acid (F7-F9), and carbonate sources (such as sodium bicarbonate) to prepare effervescent tablets using direct compression. The produced tablets are tested for properties after compression, like hardness, friability, thickness, weight change, drug content, CO_2 content, in vitro disintegration time and stability tests. Drug excipient compatibility was investigated using FT-IR and DSC in the preformulation research, suggesting that medicines, acids, bases, and other excipients are compatible. Pre-compressional parameter values were within specified limits, indicating satisfactory free-flowing properties. Except for formulations F1-F3, all post-compressional parameters were tested, and the findings were within acceptable ranges. F11 had the fastest effervescence and disintegration of all the formulations. The produced lafutidine effervescent tablets were stable and kept their medicinal characteristics for 3 months, according to stability testing of the optimised formulation F11. According to the findings of this study, lafutidine effervescent tablets are a viable formulation for the treatment of ulcers.

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INTRODUCTION

The most common way of administering to patients is oral administration due to the simplicity with which it may be given orally, the high level of patient acceptability, and the cost-effectiveness. Effervescent tablets are interesting oral dosage forms that have drawn attention for some unique benefits when compared with simple tablets. Effervescent tablets are carbon dioxide-releasing tablets that dissolve or scatter in water (CO_2). They're made by combining organic acids like tartaric acid or citric acid with sodium bicarbonate and compressing the mixture. When the tablet is submerged in water, a rapid reaction between the acid and the bicarbonate occurs, which lasts around 3 minutes and produces a clear solution containing CO_2. Effervescent tablets are more stable and easily carried than liquid pharmaceutical forms. They are liquidized at the time of administration, so their absorption and onset of action are fast. Furthermore, they have a pleasant taste due to CO_2 production, good stomach and intestinal tolerance, high patient compliance, ease of use, accurate dosing, and the capability to incorporate a larger amount of active ingredients. This dosage form is also easier to use for patients in the intensive care unit, children, people with dysphagia, and the elderly.[1]

Wet granulation, the fusion technique, liquid bed granulation, and direct compression are all methods used to create effervescent tablets. Controlled environmental circumstances are critical in the production of effervescent pills. In order to prevent granulation or adherence of tablets to equipment caused by absorbed moisture, a relative humidity (RH) of 25% or less and a moderate temperature (250C) are necessary in the production area. [2]

H2 antagonists are used to treat gastric ulcers, stress ulcers, gastro esophageal reflux disease (GERD), duodenal ulcers, gastritis, and other conditions. In general, these medicines require a quicker start of action, which is difficult to obtain with traditional formulations. Parenteral H1 antagonists are used to treat vertigo, vomiting, and acute muscular dystopia. In such cases, providing an oral effervescent formulation of H1 antagonist may provide quick relief while also avoiding the intrusive parenteral approach. This necessitates the development of dose formulations with a quicker start of effect. As a result, effervescent dosage forms were used for the development of the histamine antagonist formulation.[3]

Lafutidine,(μ)-2-(furfurylsulfinyl)-N-(4-[4-[piperidinomethyl]-2-pyridyl]oxy-(Z)-2-butenyl) Acetamide is a second-generation histamine H2 blockers that was recently created. It's used to treat duodenal ulcers, gastric mucosal lesions, & gastric ulcers that are caused by acute gastritis or chronic gastritis aggravation. It is absorbed in the stomach, travels via the bloodstream to gastric cells, and instantly binds to histamine H2 receptors on gastric cells, causing gastric acid release. In rats, lafutidine has been found to enhance gastric mucus and stomach mucosal blood flow production while simultaneously hastening epithelial restoration. Lafutidine has a 2-80 times greater receptor affinity than famotidine, ranitidine, and cimetidine.[4]

As a result, the goal of this study was to create a unit dose of effervescent tablets containing lafutidine using various acids and bases in varying concentrations in order to improve patient compliance, achieve a faster onset of action, and provide more effective treatment for gastrointestinal diseases.

MATERIAL AND METHOD

Shodhana Laboratories Ltd., Mumbai, provided a free sample of lafutidine. S.D Fines Chem. Ltd., Mumbai, provided the citric acid, tartaric acid, fumaric acid, sodium benzoate, sucrose, lactose, and talc. The rest of the components, reagents, and solvents were all of analytical quality.

Compatibility Studies on Drug Excipients

A proper design and specification of a dosage structure necessitates consideration of the physical, material, and organic qualities of both the active pharmaceutical ingredient and the excipients used in its production. To offer a consistent, strong, appealing, and safe item, similarity should be established between the dynamic fixes and other excipients. If the excipients are novel and there is no prior literature on the use of those exact excipients with a functional fixed, then similarity tests are critical. As a result, prior to providing the true definition, the similarity of lafutidine with other excipients was tested using FT-IR and DSC analyses.

Fourier Transform Infra-Red Spectroscopy (FT-IR)

The FT-IR spectra of the pure medicine & excipient mixtures were taken using an FT-IR spectrophotometer (Shimadzu IR-345, Japan). 2–3 mg tests were combined with 400 mg dry potassium bromide prior being cursed into simple pellet at pressure of 10.000–15.000 psi. The IR spectra were collected in the ranging range of 500–4000nm. [5]

DSC Analysis (Differential Scanning Calorimetric)

In this study, DSC examination was used to assess the similarity between the medicine and selected polymer segments. For lafutidine and the actual mix of details, DSC thermograms were obtained. Tests of 5 mg unadulterated lafutidine and its actual mixes with various excipients were airtight fixed in a level lined aluminium container and heated in the Differential Scanning Calorimetric instrument in a nitrogen environment to eliminate the oxidative and pyrolytic effects. The warming rate was 50^0C per minute in a temperature range of 25–3000C. DSC Thermogrammes were taken and recorded. Thermogrammes were obtained and examined to determine the medicine and formulation's warm changes and Tgs.[6]

Preparation of Effervescent powder blend:

All of the fixes were carefully weighed according to their particular definitions (Table 1). They were sifted through sifter no. 120 and blend for 15 minutes in a double cone blender. [7]

Table 1: Composition of Lafutidine effervescent tablets (F1-F9).

Sl.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
01	Lafutidine	10	10	10	10	10	10	10	10	10	10	10	10	10
02	Citric acid	50	75	100	-	-	-	-	-	-	50	50	50	50
03	Tartaric acid	-	-	-	50	75	100	-	-	-	75	100	-	-
04	Fumaric acid	-	-	-	-	-	-	50	75	100	-	-	75	100
05	Sodium Bicarbonate	150	105	150	150	150	150	150	150	150	150	150	150	150
06	Sucrose	50	50	50	50	50	50	50	50	50	50	50	50	50
07	Lactose	120	85	60	120	85	60	120	85	60	45	20	45	20
08	Sodium Benzoate	10	10	10	10	10	10	10	10	10	10	10	10	10
09	Talc	5	5	5	5	5	5	5	5	5	5	5	5	5
10	Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
	Total	400	400	400	400	400	400	400	400	400	400	400	400	400

Evaluation of powder blends:

The point of rest, compressibility record (Carr's file), and Hausner's percentage were used to characterize the powder mix's stream characteristics (before pressure). Every element of these exams was repeated many times.

Angle of repose [2,8]

The largest conceivable position between the exterior of a powder heap or granules and the flat surface is shown as the point of rest. The grains were added to flow via a tube attached to a brace of distance tallness. Calculate using the formula.

$$\Theta = \tan^{-1} (h/r)$$

Where,
Point of rest= Θ
Height=h
Radius=r

Bulk density [2, 8]

The apparent bulk density (ρb) was calculated by filling a graduated cylinder with presieved medication excipients mix and measuring the volume (Vb) and weight (M) "as is."

$$\rho b = M/Vb$$

Tapped density [2, 8]

The measuring cylinder containing a known quantity of mix was tapped for a certain length of time. The minimal volume (Vt) of the cylinder and the weight (M) of the mix were both measured. The tapped density was calculated using the formula below

$$(t).\rho t = M/Vt$$

Compressibility index [2, 8]

Compressibility, an indicator of easiness, is the easiest technique to test the free flow attribute of powder. Tapped density of granules (ρt) and untapped bulk density (ρb) of the granules were calculated as follows:

$$C = (\rho t - \rho b)/\rho t \times 100$$

Hausner's ratio [2, 8]

Hausner's ratio is an important to determine the flow property of powder,granules & other solid materials. Tapped density of granules (ρt) and untapped bulk density (ρb) of the granules were calculated by following formula.

$$\text{Hausner's ratio} = \rho t \backslash \rho b$$

Effervescent tablet compression

A mixture of powder was blend with magnesium stearate and talcs about 5 mints. The granule mixes were crushed into 400 mg convex-faced tablets using an 8-station tablet punching machine. Each batch has a minimum of 50 pills in it. [9]

Evaluation of effervescent tablets

The following post compressional parameters of the tablet were conducted to evaluate Physical and chemical properties of the prepared tablets

Friability test [10]

The Roche friabilator was used to assess the tablet's friability. The tablet is abraded and stressed in this equipment, which uses a plastic container that rotates at 25 rpm and drops a tablet from a height of 6 inches after each revolution. A pre-weighted sample of tablets was put into the friabilator and rotated 100 times. The tablets were reweighed after being dusted with a fine cotton towel. The USP limit is between 0.5 and 1%. Friability (F) is calculated as the ratio of the weight of the tablets before the test (W_I) to the weight of the tablet after the test (W_A), as follows:

$$F = (1- W_I / W_A) \times 100$$

Hardness [10]

The pressure required to break a tablet under diametric compression is known as hardness or tablet crushing strength. Monsanto hardness tester or pizer hardness tester is used to determines hardness of tablet. The hardness of tablets determines their resistance during shipment, storage, transportation, and handling prior to use. The force is measured in k/g, and uncoated tablets with a hardness of around 3-5 kg/cm^2 are regarded adequate.

Drug content [10]

Five pills were pulverized, and a 100 mg lafutidine mix was weighed and diluted in an appropriate amount of 0.1 N HCl solutions. A double beam UV spectrophotometer was used to assess the drug content after the solution was filtered and appropriately diluted. Each sample was examined three times.

Effervescence Time [7]

The time it took for a clear solution to appear was called the effervescence period. According to European pharmacopoeia, effervescence time was calculated by allowing one tablet to disperse completely in 100 ml of filtered water at room temperature. A digital stopwatch was used to record the amount of time it took for the effervescence to finish. Six pills were tested for effervescence time, and the findings were positive.

Tablet disintegration [7, 11]

Disintegration studies were determined by using the disintegration tester. The pill was put in a beaker filled with distilled water at 30°C. Before 5 minutes or after the effervescence reaction has subsided, the pill should be dissolved or destroyed.

Taste masking [7]

A sufficient concentration of sugar and flavour was used to conceal the drug's strong salty and slight bitter taste. Human participants were given taste-masked pills to evaluate their mouth feel.

CO_2 gas content [7]

The primary foundation of effervescent preparation is carbon dioxide gas production, which must be calculate and continuously monitored in order to investigate the efficiency of the formulation as well as changes in various factors impacting gas liberation. In 100 ml of 1 N sulfuric acid, one tablet was dissolved. CO_2 content is measured by the weight variation before and after disintegration.

pH [12]

The pH of the produced tablet is measured using a digital pH metre. Using a pH metre, the pH of the solution was determined by dissolving three pills in three beakers containing 200 mL water.

Short term stability study [13]

For short stability testing, the optimised batch EF7 was maintained. The stability investigation was conducted at a temperature of 40°C and RH of 75 %. The optimised tablets were place in glass containers with salt borosilicate glass container. The samples were hold on at 40°C 75 % RH and examined for physical changes & drug content once 15, 30, and 45 days.

RESULT AND DISCUSSION

Effervescent tablets of lafutidine using fumaric acid, tartaric acid, and citric acid, in three different proportion prepared using direct compression method. The effects of concentration of fumaric acid citric acid, & tartaric acid individually and combination of citric acid with fumaric acid and with tartaric acid on disintegration time, amount of carbon dioxide release were studied and promising formulation was subjected for stability studies.

Drug and excipients compatibility studies

Fourier Transform Infrared Spectroscopy

FTIR spectroscopies were used to confirm the compatibility between drug & polymer. Figure 1 shows the IR spectra of pure drug lafutidine with its peak as (cm^{-1}), 3257.88 (CH stretching), 2947.33 (CH_2 stretching), 1070.53 (S=O stretching) and 759.98 (C-S stretching). Infrared spectral analysis of physical mixes (figures 2, 3, and 4) revealed that the same characteristic bands were present in all spectra, with no new bands or shifts in typical bands. As a consequence, the FTIR data indicated that the medication and the excipients employed in the formulation had no interaction.

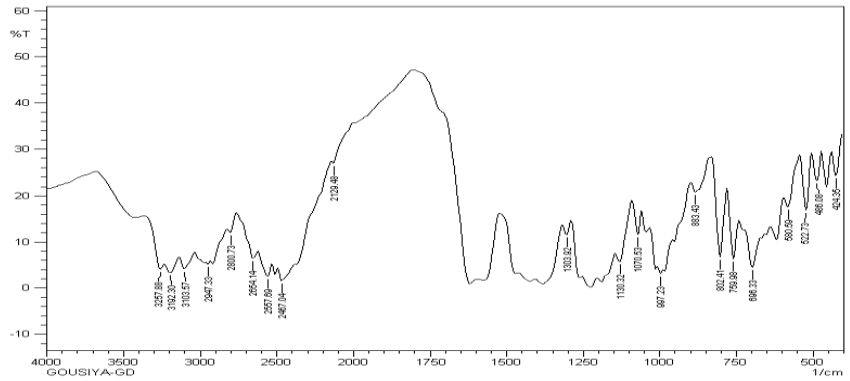

Figure 1: FT-IR of Pure lafutidine.

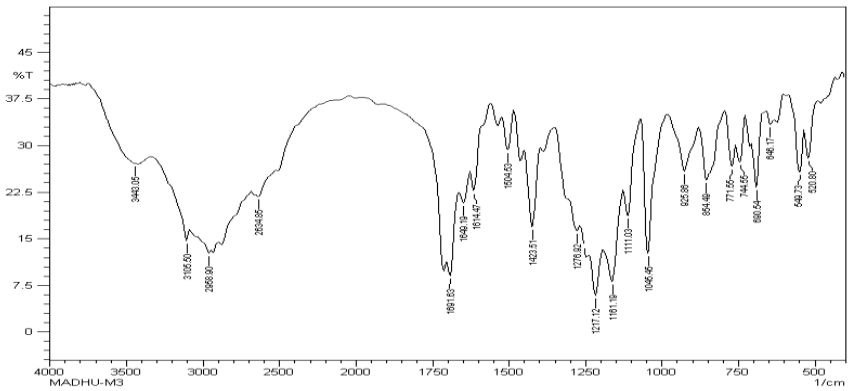

Figure 2: FT-IR of spectrum of physical mixture of drug and citric acid.

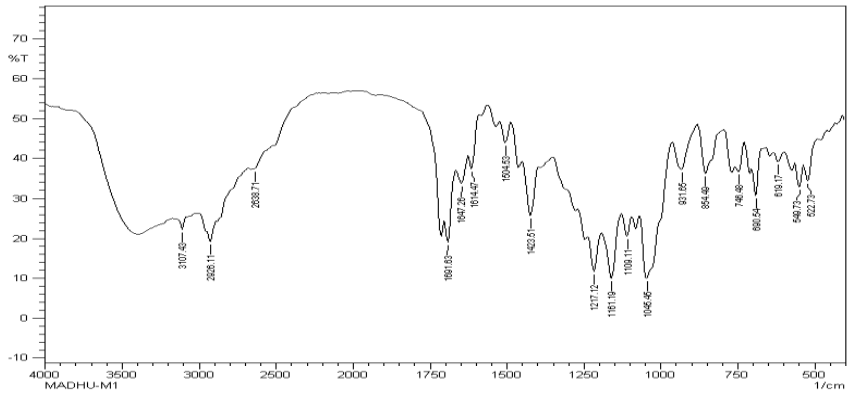

Figure 3: FT-IR of spectrum of physical mixture of drug and tartaric acid.

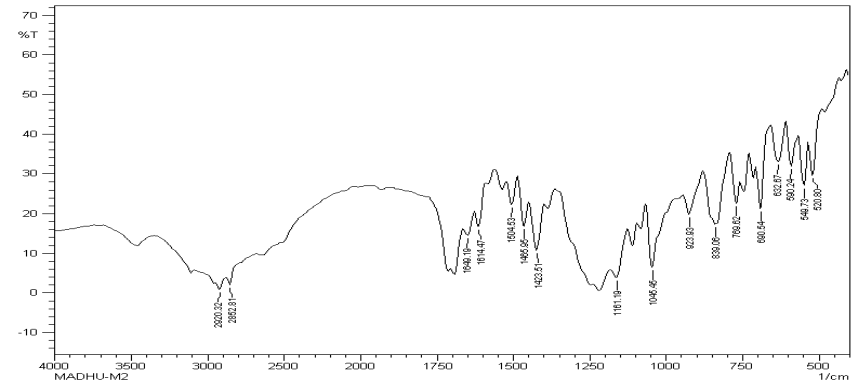

Figure 4: FT-IR of spectrum of physical mixture of drug and fumaric acid.

Differential Scanning Calorimetric (DSC):

The Differential Scanning Calorimetric thermograms of pure form of lafutidine and its mixture with excipients were shown in figure no 5 and 6. The DSC thermograms of pure lafutidine showed a sharp endothermic peak at 141.4^{0}C as its melting point or transition temperature and the physical mixture showed peak (155.78 and 179.18^{0}C physical mixture of drug with citric acid and physical mixture of drug with tartaric acid) There was small increase in the endothermic peak of physical mixture compared to the pure drug. This might be due to the presence of polymer, which alters peak shape and lowers purity as the drug's strength increases. As a result, the slight variation in medication peak values is not indicative of any potential incompatibility. When the drug was physically mixed with fumaric acid, the peak corresponding to the melting of the drug vanished. The development of an amorphous solid dispersion might be to blame.

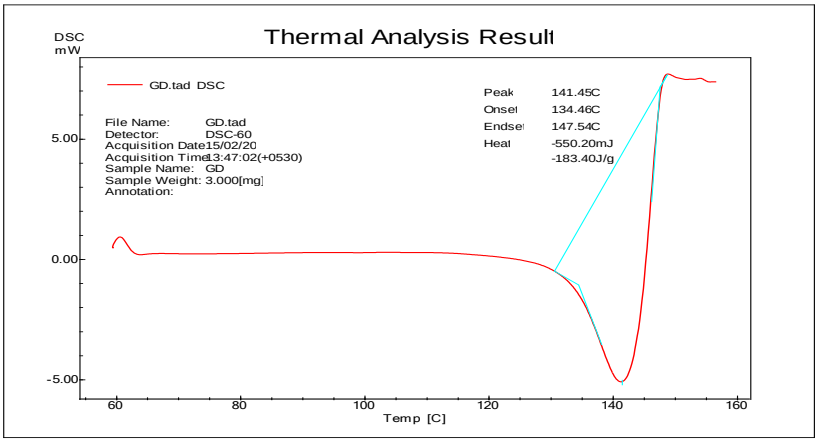

Figure 5: DSC spectrum of Pure lafutidine.

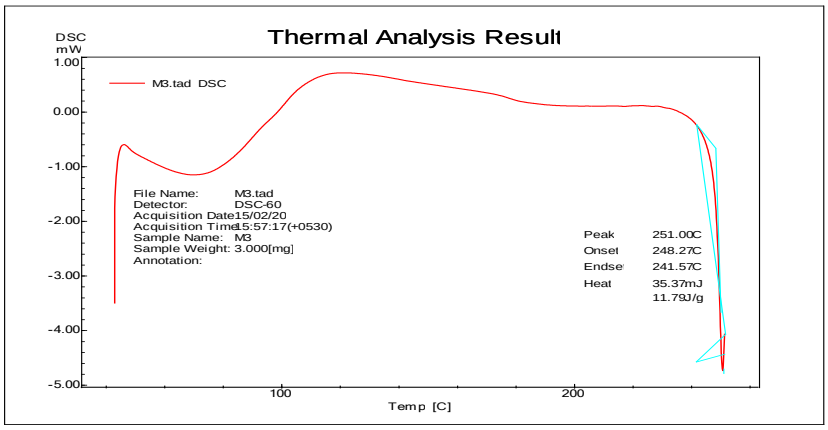

Figure 6: DSC spectrum of physical mixture of drug and citric acid.

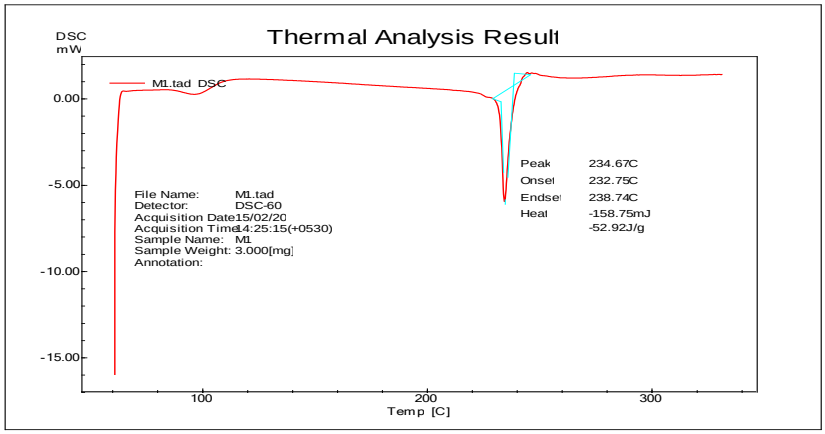

Figure 7: DSC spectrum of physical mixture of drug and tartaric acid.

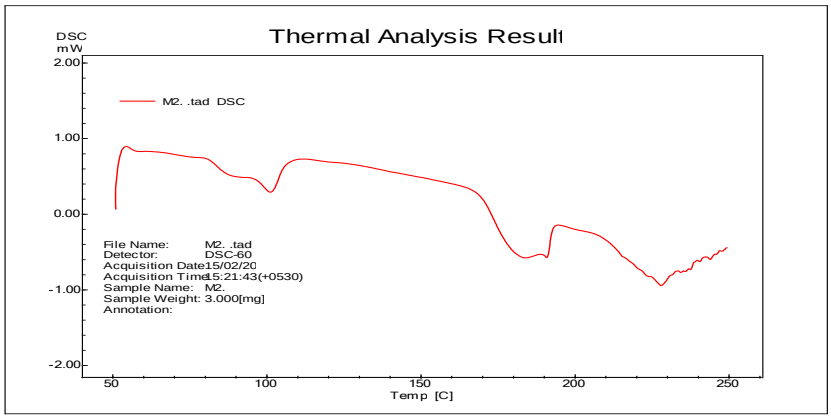

Figure 8: DSC spectrum of physical mixture of drug and fumaric acid.

Evaluation of pre compression parameters of powder blend

All powder mixes were tested, and the precompressional parameter values are listed in Table 2. The powder blend qualities of the formulations F1-F3 were extremely sticky, whereas the powder blend properties of the formulations F4-F9 were non-sticky. It's possible that the sticky character of formulations F1-F3 is related to the presence of citric acid, which is extremely hygroscopic [9]

The bulk density ranged from 0.610.01 gm/ml to 0.950.01 gm/ml, suggesting an average bulk volume of 1.5-2 ml per/g of powder and suitable for unit dose packing. The results showed that the angle of repose for the formulations F1-F3 was not measured because of sticky nature of the powder blend. Whereas the formulations F4-F9 found to be in the range of 21.80±1.21 to 26.56±1.42, this indicates good flow property. Compressibility index was found to be in the range of 16.6 to 37.7%, the result of compressibility index also same as that of angle of repose, which in the formulation containing citric acid showed high % compressibility index. Hence, using of citric acid alone is not suitable for effervescent tablets formulation.

The pH of a solution is critical for flavour characteristics of an ingestible substance. All of the formulas have a pH that is closer to neutral. Following the experiment, batches (F1-F9) containing various quantities of acids (citric acid, tartaric acid, and fumaric acid) were made; however, during assessment, it was discovered that these tablets had poor hardness, low CO_2 content, and were difficult to cling to punches and dies. Because a good proportion of citric acid with tartaric acid (F10-F11) and citric acid with fumaric acid (F12-F13) generates good effervescence. Four batches were made with a constant amount of citric acid and gradually rising concentrations of tartaric acid or fumaric acid. The reason for choosing more amount of tartaric acid or fumaric acid compared to citric acid was comparatively less hygroscopic nature, but we cannot use tartaric acid or fumaric acid alone as it needs one antioxidant for stability, thus combination with citric acid was used [9]

Table 2: Data of Pre-compressional parameters of formulation F1-F9.

Test Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Powder blend property	Sticky	Sticky	Sticky	Non sticky	Non sticky	Non sticky	Non sticky	Non sticky	Non sticky
Bulk density (g/cm3)	0.86	0.76	0.74	0.90	0.84	0.8	0.71	0.69	0.95
Tapped density (g/cm3)	1.08	1.03	0.90	1.04	1.05	1.05	0.93	0.94	1.05
Angle of repose **(θ)**	Not measured	Not measured	Not measured	26.56	23.75	21.80	25.64	26.56	24.99
Compressibility index (%)	30.3%	31.5%	37.7%	18.4%	20%	21.8%	16.6%	17%	19.5%
pH	5.86	6.03	6.52	6.48	5.90	6.09	6.36	5.54	5.54

Table 3 demonstrates that formulas F10–F13 produced a good powder mix with less die and punch sticking during tableting. Table 2 indicates that formulation F11 was the best batch in terms of all assessment criteria. It also had better stability due to the two-fold quantity of tartaric acid compared to citric acid, which protected citric acid from being exposed to moisture since tartaric acid could build a coat on it.

Table 3: Data of Pre-compressional parameters of formulation F10-F13.

Test Parameters	F10	F11	F12	F13
Powder blend property	Non sticky	Non sticky	Non sticky	Non sticky
Angle of repose	21.74	20.81	22.22	21.56
Bulk density (g/cm3)	0.86	0.76	0.74	0.90
Tapped density (g/cm3)	1.08	1.03	0.90	1.04
Compressibility index (%)	13.3%	11.5%	15.7%	13.4%
pH	5.86	6.03	6.52	6.48

Compression of lafutidine effervescent tablets:

The concentration of solely acid sources was varied during the investigation, and effervescent tablets of lafutidine were produced by direct compression utilising different acid sources including citric acid (F1-F3), tartaric acid (F4-F6), fumaric acid (F7-F9) and carbonate sources like sodium bicarbonate. All of the postcompressional parameters were applied to the produced tablets. On produced tablets, physicochemical testing such as hardness, friability, thickness, weight variation, assay, CO2 concentration, in vitro disintegration time, and stability studies were performed. All of the formulations, post-compression properties were examined and are included in Table 4. The tablets produced with citric acid alone (F1-F3) at various concentrations had poor hardness, low CO_2 level, and also stuck to punches and dies, which might be owing to the citric acid's hygroscopic nature [9]

Whereas F4-F6 contains tartaric acid & F7-F9 contains fumaric acid tablets have high hardness, low CO_2 concentration and shows fast disintegration time. As a result, a test was conducted to see if a mixture of acids might minimize disintegration time. Citric acid in conjunction with tartaric acid or fumaric acid causes the pills to disintegrate quickly.

The hardness of tablets was found in between range of 2.0 ± 0.25 to 3.9 ± 0.5 kg/cm^2. The loss of % of weight in friability was found to be 0.261± 0.08 to 0.590± 0.06 which is less than 1% which results tablets has good mechanical resistance. In case for formulations F1-F3 which containing citric acid, hardness and friability were affected substantially, the cause of decrease in hardness and increase in friability of tablets was due to liberation of CO_2 which had rendered tablets porous. The weight variation of all prepared formulations was found to be in the range of 329± 0.19 to 345 ± 0.18 mg. The disintegration time of all formulations was found to be in the range of 84± 0.53 to 116 ± 0.65 sec.The drug content of all prepared formulations was found to be in the range of 98.9 ± 1 to 101.5 ± 1.25%. Effervescence times of all formulations were 50-82 sec for the formulations (F1-F13). During this time excipients and medicines were dissolved in water completely. The F11 and F13 formulations had the longest effervescence time (82 and 70 sec, respectively) shown in Table 5.

Table 4: Post compressional parameters of formulation (F1-F9).

Test Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness kg/cm^2	2.4 ±4.2	2.1 ±6.4	2.0 ±5.5	3.3 ±4.1	3.8 ±5.1	3.7 ±3.8	3.3 ±5.1	3.4 ±4.4	3.6 ±3.9
Friability (%)	0.552 ±0.13	0.572 ±0.18	0.590 ±0.20	0.271 ±0.12	0.261 ±0.11	0.282 ±0.13	0.287 ±0.23	0.303 ±0.15	0.309 ±0.20
Weight uniformity (mg)	394 ±0.08	398 ±0.06	401 ±0.015	392 ±0.09	394 ±0.04	390 ±0.08	395 ±0.06	394 ±0.013	399 ±0.016
Disintegration time (sec)	104 ±1.3	114 ±0.88	116 ±0.92	92 ±1.1	90 ±0.82	84 ±2.0	93 ±0.78	88 ±0.82	86 ±1.4
CO_2 content for a single dose	0.07	0.08	0.25	0.11	0.14	0.22	0.18	0.1	0.15
Drug content %	90% ±0.22	97% ±0.82	96% ±0.09	96% ±0.13	98% ±0.21	97% ±0.08	98% ±0.12	96% ±0.22	98% ±0.10
Time of Effervescence (sec)	50 ±1.3	59 ±2.2	64 ±3.1	54 ±2.8	62 ±3.2	68 ±3.4	52 ±4.1	56 ±2.4	56 ±3.2

Table 5: Post compressional parameters of formulation (F10-F13).

Test Parameters	F10	F11	F12	F13
Hardness kg/cm^2	3.4±5.5	3.7±3.8	3.0±3.9	3.3±4.1
Friability (%)	0.252±0.18	0.272±0.11	0.290±0.23	0.271±0.20
Weight uniformity (mg)	398±0.009	394±0.013	391±0.015	393±0.014
Disintegration time (sec)	1040.82	114±2.0	116±0.78	92±1.4
CO_2 content for a single dose	0.07	0.08	0.25	0.11
Drug content %	96%±0.82	98.5%±0.13	97%±0.08	98%±0.22
Time of Effervescence (sec)	50	82	55	70

Stability studies

Stability studies are carried out for the optimized formulation (F11) was selected by storing the formulation at 40±2^{0}C/70±5% RH for three months. The results of drug content after 90 days of stability testing were given in the table no 6. From the stability studies it was confirmed that effervescent tablets of lafutidine remained stable at the above said temperature and humid conditions.

Table 6: Stability study of formulation (F11).

Time(month)	Drug content
	F11
Zero	98.5%±0.26
First	98.1%±0.18
Second	97.8%±0.14
Third	97.2%±0.21

CONCLUSION

It can be concluded from the above experimental report that lafutidine effervescent tablets were developed to replace conventional tablets in the treatment of duodenal ulcers & gastric, where the quick onset of action is beneficial in managing gastric and duodenal ulcers, aiding in the enhancement of bioavailability, and is very easy to administer. The best formulations were chosen based on the findings received at each stage of the formulation process. The medication had no interaction with the polymers employed in the formulations, according to FT-IR and DSC spectra. On the produced tablets, pre- and post-compression tests were performed. All of the provided post compression settings were found to be within pharamacopical limitations. Finally, according to its physicochemical properties, the F11 formulation of lafutidine was chosen as the optimum formulation.

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