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Research Article

FORMULATION AND EVALUATION OF HYDRODYNAMICALLY BALANCED FLOATING TABLETS OF *GLYCYRRHIZA GLABRA* EXTRACT

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ABSTRACT

The aim of the study is to formulate, optimize and evaluate *Glycyrrhiza glabra* floating tablets using 2^3 optimization technique for the treatment of asthma. The extract of *Glycyrrhiza glabra* was prepared by subjecting crude drug to hot continuous percolation method using Soxhlet apparatus using distilled water and ethanol. The floating matrix tablets of *Glycyrrhiza glabra* was prepared by wet granulation technique using extract of *Glycyrrhiza glabra*, HPMC K15M as polymer, starch/honey as binder and sodium bicarbonate & citric acid as effervescent agents by 2^3 factorial design. The independent variables are polymer (X1), concentrations of effervescence agents (X2) and binders used for granulation (X3). The dependent variables are hardness (Y1), buoyancy lag time (Y2), total floating time (Y3), and *in-vitro* drug release (Y4). The compatibility studies showed that there is no chemical interaction between the drug, polymer and the excipients used in the tablets. The prepared floating tablets were subjected to all post compression parameters such as hardness, friability, swelling capacity, buoyancy, total floating time, drug content &*in-vitro* drug release and were found to be within normal limits. Based on drug content, buoyancy lag time and *in-vitro* drug release the formulations F8 was found to be the promising system for anti-asthmatic therapy. The present study reports for the development of gastric floating tablet for *Glycyrrhiza glabra* following oral administration.

Keywords: *Glycyrrhiza glabra*, liquorice, floating, herbal, tablet

INTRODUCTION

The phrase "medicinal plant" refers to a variety of plants used in herbal medicine ("herbology" or "herbal medicine"). It is the practise of using plants for medical reasons as well as the study of such practises[1]. Herbal medicines are in significant demand as a source of basic health care in both developed and developing nations, owing to their diverse biological and pharmacological activity, large safety margins, and lower prices[2]. To assess the impact, the herbal system has been reported to be used by numerous communities all over the world[3].

Asthma and chronic obstructive pulmonary disease are both chronic inflammatory airway illnesses that impede airflow. Asthma can occur at any age, and in some cases, it appears to be initiated by a severe respiratory illness. COPD manifests itself in middle to later life; however, it is now thought to have its roots in childhood. COPD is characterised by a progressive increase in dyspnea. Cough, mucus hypersecretion, wheezing, and occasional exacerbations or "flare-ups" are frequent clinical characteristics[4].

Glycyrrhiza comes from the Greek words glykos, which means sweet, and rhiza, which means root. In north India, *Glycyrrhiza glabra* is known as mulaithi. Traditional healers have claimed the efficacy of *Glycyrrhiza* species as a diuretic, choleretic, and insecticide for a variety of pathological disorders, and it is used in traditional medicine for coughs, colds, and uncomfortable swellings[5].

Even though many synthetic chemical formulations are available on the market for the treatment of asthma they may cause some side effects or adverse effects. The herbal formulation is a novel approach which provides good therapeutic effect and also has a safe margin.

MATERIALS AND METHODS

The crude powdered drug of *Glycyrrhiza glabra* analytical grade was purchased from Yucca Enterprises in Mumbai[13]. Yucca Enterprises is a certified herbal drugs manufacturer, retailer and service provider – GST No - 27ACEPL2903R1Z9. HPMC K15M was received as a gift sample from Zydus Cadila Research Center, Ahmadabad. All the other chemicals and reagents used were of analytical grade.

Extraction Method

Glycyrrhiza glabra crude powdered drug was taken. Powdered material was packed in the Soxhlet apparatus and extracted using ethanol as a solvent. The extraction took about 20 hours and was done using a hot continuous extraction process. To remove any impurities, the extract was filtered using Whatman filter paper while it was still hot. The concentrated extract was transferred to a 100 mL beaker and the leftover solvent was collected and dried after being evaporated on a water bath. An airtight container was used to store the dried extract[10].

Wet granulation method

In a mortar and pestle, ethanolic extract of *Glycyrrhiza glabra*, HPMC K15M, citric acid, and sodium bicarbonate (filtered through a #60 mesh screen) were mixed thoroughly. 10 % starch and 50% honey were used as binders according to the formulation

table. The powder mixture was granulated on a #18 mesh screen. The granules were dried at 40-50°C for 2 hours, and the moisture content of the granules was found to be within 0.85 percent to 1.2 percent using an IR Moisture balance. The magnesium stearate and talc were used as lubricant and glidant respectively. The dried granules were then passed through a #22 mesh screen and compressed into tablets in a ten-station rotary small press tablet machine utilising a flat-faced punch[11].

Statistical optimization technique[12, 13]

The optimization was designed statistically using 2^3 full factorial design. This 2-level full-factorial design consists of 8 full-factorial design points as in following table. This design generally involves independent variables X1, X2, & X4. The dependent formulation variables selected are Y1, Y2, Y3, & Y4. The levels of independent variables and the dependent formulation variables are given in the tables 3 & 4 respectively. The results obtained from the experiment were statistically analyzed for response variables by using Minitab Statistical Software (Version 17). The statistical model incorporating interactive and polynomial terms was used to evaluate the response.

Table 1: Layout of 2^3 Full Factorial Design

F. Code	F1	F2	F3	F4	F5	F6	F7	F8
X1	-1	-1	-1	-1	+1	+1	+1	+1
X2	-1	-1	+1	+1	-1	-1	+1	+1
X3	-1	+1	-1	+1	-1	+1	-1	+1

Table 2: Independent Variables

Code	Variables	Low Level (-1)	High Level(+1)
X1	HPMC K15 M	150	200
X2	Sodium Bicarbonate:Citric acid	100:30	150:45
X3	Binder	10% w/v starch paste	50% v/v honey

Table 3: Dependent Variables

Code	Variables
Y1	Hardness
Y2	Buoyancy lag time
Y3	Total floating time
Y4	In-vitro drug release at 12 hrs

Table 4: Formulation Table

F Code	GG Extract (mg)	HPMC K15M (mg)	Sodium Bicarbonate (mg)	Citric Acid (mg)	Starch % w/v	Honey %w/v	Mag. Stearate (mg)	Talc (mg)	Tablet Weight (mg)
F1	600	150	100	30	10	-	20	10	910
F2	600	150	100	30	-	50	20	10	910
F3	600	150	150	45	10	-	20	10	975
F4	600	150	150	45	-	50	20	10	975
F5	600	200	100	30	10	-	20	10	960
F6	600	200	100	30	-	50	20	10	960
F7	600	200	150	45	10	-	20	10	1025
F8	600	200	150	45	-	50	20	10	1025

Pre compression parameters

Bulk density[7]

A bulk density apparatus was used to determine the bulk density of the formed granules. It is offered in gm/ml and is expressed in gm/ml.

Bulk density = Mass of the powder / Volume of the bulk powder

Tapped density[7]

A graduated cylinder was filled with a weighed quantity of tablet combination. The amount of space occupied by the medicine was recorded. After that, the cylinder was put through 100, 200, and 300 taps in a tap density apparatus.

Tapped density = Mass of the powder / Tapped volume of the powder

Carr's index[7]

The compressibility index was used to assess the compressibility of powder. Changes in volume caused by packing rearrangement during tapping were used to assess the tablet blend's packing ability. Carr's compressibility index was calculated using the following formula.

Carr's index % = Tapped density − Bulk density / Tapped density X100

Hausner ratio[7]

It is a measurement of the tablet blend's frictional resistance. The optimal range is between 1.2 and 1.5. The ratio of tapped density to bulk density was used to determine it.

Hausner's ratio = Tapped density / Bulk density

Angle of repose[7]
It's the highest angle that may be made between a free-standing powder heap and a horizontal plane. The following equation was used to determine it:

$$\tan \theta = h / r$$

Where, θ = Angle of repose, h = of powder heap, r = Radius of the powder cone

Post compression parameters

Tablet thickness: Vernier Calipers were used to determine the thickness of the tablet. From each batch, three tables were chosen at random and the average measurement of three readings was taken[9].

Diameter: Vernier Calipers were used to measure the diameter of the tablet. Three tablets from each batch were chosen at random and the average of three readings was taken[9].

Tablet hardness: Tensile strength (kg/cm^2) is used to measure the strength of a tablet. The tablet crushing load is the amount of force necessary to compress a tablet into pieces. Monsanto hardness tester was used to determine it[6].

Weight variation test: In a single pan balance, 20 pills were randomly picked and weighed individually and together. The average weight was computed, as well as the standard deviation. The IP limit for weight fluctuation in tablets weighing up to 120 mg is 10%, 120 mg to 300 mg is 7.5 percent, and tablets weighing more than 300 mg are 5% [6].

$$PD = (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100$$

Where, PD= Percentage deviation, W_{avg}= Average weight of tablet, $W_{initial}$= Individual weight of tablet.

Friability: In a single pan balance, 20 pills were randomly picked and weighed individually and together. The average weight was computed, as well as the standard deviation. The IP limit for weight fluctuation in tablets weighing up to 120 mg is 10%, 120 mg to 300 mg is 7.5 percent, and tablets weighing more than 300 mg are 5% [6].

Preparation of Simulated Gastric Fluid (Without Enzyme)[12]: 2 gm sodium chloride was dissolved in 7 ml of concentrated hydrochloric acid and the resulting solution diluted to 1000 ml with distilled water. This solution has a pH of about 1.2.

Drug content uniformity: The blend equivalent to 5 mg of medication was weighted and dissolved in a reasonable quantity of pH 1.2 solutions after ten tablets were powered. The drug content was measured spectrophotometrically at 278nm (equivalent to gallic acid) after the solution was filtered and diluted[6].

Total floating time: In a 100 mL glass beaker containing simulated gastric fluid, the tablets were inserted. Floating time was defined as the amount of time the tablet remained afloat on the medium's surface[7].

Buoyancy: The lag time was used to determine the in vitro buoyancy. The tablets were added in a 100 mL beaker containing simulated gastric fluid pH 1.2. The lag time was calculated as the time it took for a tablet to rise to the surface and float [7].

***In vitro* drug release study:** Using USP XXVI type II (paddle) equipment at 37.5^{0}C ± 0.5^{0}C and 50 rpm speed, an in vitro drug release investigation for the produced floating tablets was conducted for 12 hours. The dissolution tests were done in triplicate in phosphate buffer at pH 1.2 under sink conditions for 12 hours. To keep the volume constant, samples of 5 ml were taken from the dissolving medium and replaced with new medium for every sampling. A UV spectrophotometer was used to examine the sample solution after filtering and adequate dilution[7].

Swelling index[8]**:** Before immersing the tablets in simulated gastric fluid pH 1.2 they were weighed. The enlarged tablets were removed and weighed at pre-determined intervals after wiping off the surface water with a filter paper. The swelling index was calculated by using following formula:

$$S.I. = Wt - Wi / Wi \times 100$$

Where, W_i is the initial weight, W_t is the weight at time t

RESULT AND DISCUSSION

The FT- IR Spectrum of pure *Glycyrrhiza glabra* was compared with the FT- IR spectrum of physical mixture of *Glycyrrhiza glabra*, HPMC $K_{15}M$, starch paste/honey, sodium bicarbonate, citric acid, magnesium stearate. There was no appearance or disappearance of any characteristic's peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets. The presence of peaks at the expected range confirms that the materials taken for the study are genuine.

The mixture of all formulations was evaluated for pre-compression parameters before compression into tablets for angle of repose, bulk density, tapped density, Hausner's ratio, compressibility index. The angle of repose value ranged from 25°15" to 28° 75". The results were found to be below 30^0 and hence the blend was found to have good flow ability. Bulk and tapped densities are used for the measurement of Carr's index. The bulk density and tapped density ranged from 0.235 to 0.298 and 0.275 to 0.356 respectively. The compressibility index (%) was then calculated from the bulk and tapped densities and it ranged from 14.91 to 18.47. The blend was found to have good free flowing property as the result were found to be below 20%. The Hausner's ratio ranged from 1.15 to 1.23. The result indicates that the powder has cohesive properties.

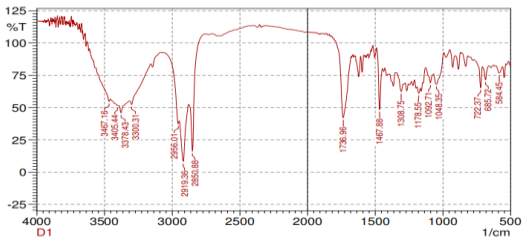

Fig 1: FT-IR Analysis of *Glycyrrhiza glabra* & All Excipients

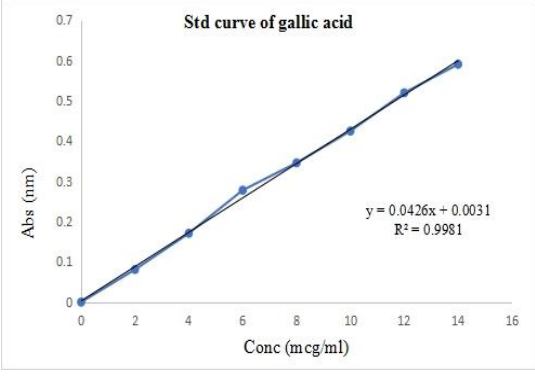

Fig 2: Standard Curve of Gallic Acid

The tablets of all formulation were subjected to various evaluation parameters such as average weight, thickness, diameter, hardness, friability, tablet density, in-vitro buoyancy lag time, total floating time, swelling index, drug content and in-vitro dissolution study. The results of all these tests were found to be satisfactory. The thickness of the tablets was uniform in all formulations and ranged from 6.01 mm to 6.98 mm in formulations F1 – F8. The hardness of tablets ranged from 7.24 kg/cm2 to 7.96 kg/cm^2 and was found to be in permissible limits. The percentage friability of all batches was from 0.10 to 0.84 %, which was well below the pharmacopoeial limit of < 1%.

For a tablet to float on simulated gastric fluid of pH 1.2, the tablet density must be less than 1.004 g/cc. The density of all the formulations were than 1 gm/cc which shows that all the tablets were capable of floating in the simulated gastric fluid. The buoyancy and total floating time of the formulations were from 27 sec to 35 sec and 6.8 to 7.3 hr. As the effervescence excipient concentration has increased the total floating time of the formulations have also increased. The buoyancy has increased because the total weight of the tablet had increased which made the effervescence excipients delay diffusing out of the tablet.

All the formulations using 50% v/v honey as the binding agent showed extended time for drug release when compared to that of the 10% starch as the binder. This shows the more binding capacity of honey than the starch. Formulations using higher amount of effervescence excipients showed more percentage of drug release since the effervescence allowed more amount of solvent to diffuse through the formulation surface. The formulations using higher amount of polymer took extended time for complete drug release up to 12 hours. This is obviously because of increase in tablet weight and lesser diffusivity of solvent into the formulation. Overall, the highest amount of drug release was found as 97.62 % and 99.56 % in 12 hours of the formulations F6 and F8 respectively.

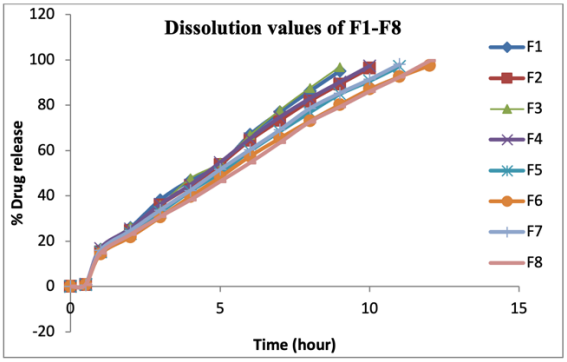

Fig 3: Dissolution Values of F1-F8

To know the kinetic drug release, the data was treated according to different kinetic model equation. The drug release data of F1 – F8 were fitted to all the kinetic equation to find the mechanism of drug release in each formulation. All the formulations exhibited zero-order drug release showing the rate of drug release is independent of the concentration of the drug present in the formulation. Formulations F1–F8 were best fit into Higuchi's indicating that the diffusion is the dominant mechanism of drug release in these formulations. The mechanism of drug release was found to be non-Fickian or anomalous drug release.

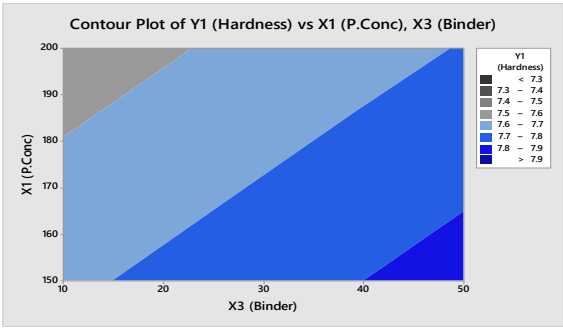

Fig 4: Contour Plot of Y1 (Hardness) Vs X1 (Polymer Concentration) & X3 (Binder)

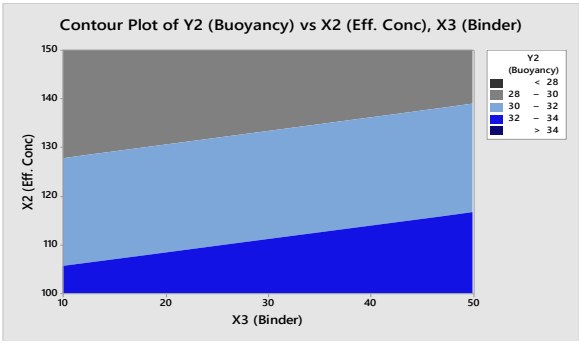

Fig 5: Contour Plot of Y2 (Buoyancy) Vs X2 (Effervescent Concentration) & X3 (Binder)

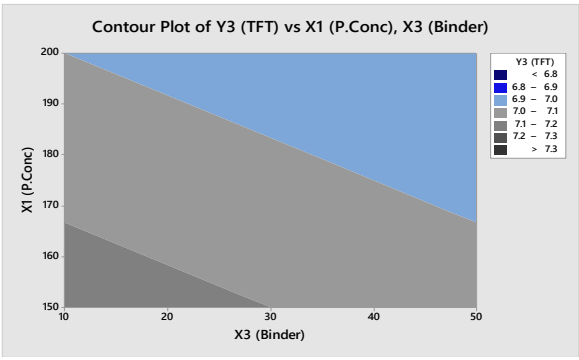

Fig 6: Contour Plot of Y3 (Total Floating Time) Vs X1 (Polymer Concentration) & X3 (Binder)

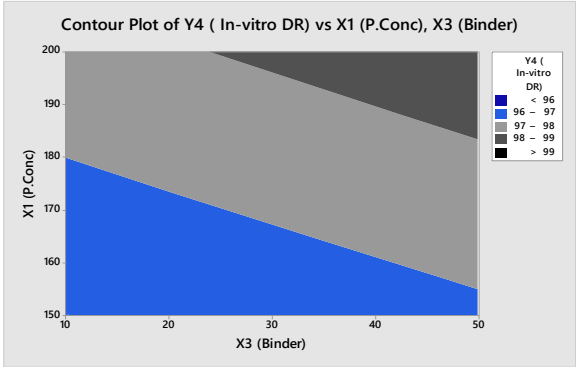

Fig 7: Contour Plot of Y4 (*In-Vitro* Drug Release) Vs X1 (Polymer Concentration) & X3 (Binder)

From the results of ANOVA it was observed that the independent factors X1 (Polymer concentration) and X3 (binder) influences the dependent factor Y1 (hardness). Honey showed more binding capacity than starch. Increase in concentration of HPMC K15M in formulation influences hardness of the tablet in few formulations.

Buoyancy (Y2) is influenced by the amount of effervescent agents (X2). Increase in concentration of effervescent excipients decrease the buoyancy lag time of the formulations. Binders did not influence the buoyancy lag time. Total floating time (Y3) was influenced by both X1 (Polymer concentration) & X3 (binder). Increase in polymer concentration X1 increased the total floating time. The binder also has slight influence by increasing the TFT.

Percentage of drug release was affected by (polymer concentration) X1 and slight influence affected by binder (X3). Increase in polymer concentration has increased the dissolution time. Honey increased the binding capacity of granules, there by decrease the percentage of drug release by time. Increase in concentration of effervescent increased the percentage of drug release very lightly, may be due to the diffusivity of CO^2 out of formulations.

The present study reports for the development of gastric floating tablet for *Glycyrrhiza glabra* following oral administration. The results demonstrated that the release of the drug is dependent on concentration of HPMC K15M and effervescent agents. It can be conclusively stated that the gastric floating tablet (F8) appears to be promising system for the sustained release *Glycyrrhiza glabra* for anti-asthmatic therapy. The release kinetic of all formulations indicates drug release by zero order kinetics with non-fickian or anomalous transport. The dependent variables buoyancy, total floating time was influenced by effervescent agents. The dependent variables hardness and *in-vitro* dissolution are influenced by concentration of polymer and slightly influenced by the binder.

CONCLUSION

It can be conclusively stated that the gastric floating tablet (F8) appears to be promising system for the sustained release *Glycyrrhiza glabra* for anti-asthmatic therapy. The release kinetic of all formulations indicates drug release by zero order kinetics with non-fickian or anomalous transport. The dependent variables buoyancy, total floating time were influenced by effervescent agents. The dependent variables hardness and *in-vitro* dissolution are influenced by concentration of polymer and slightly influenced by the binder.

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