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DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF GINGER EXTRACT: ANTIULCER ACTIVITY

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ABSTRACT

With an attempt to prolong the residence time of the ginger extract within the gastro-intestinal content, its floating tablets were prepared by using hydrophilic polymers such as hydroxypropyl methyl cellulose (HPMC E15) and Carbopol 934. Six batches of floating tablets were prepared using HPMC E15 (F1-F3) and Carbopol 934 (F4-F6). All the tablets were evaluated for thickness, diameter, hardness, friability and drug content. Among the all batches, F3 and F6 showed a significant increase in release of ginger extract in sustained release manner. F3 and F6 showed 66.4 % and 62.4 % release of ginger extract after 8 h, respectively. Further, F3 and F6 optimized tablets were subjected to gastric ulcer activity. A highly significant ($p<0.05$) antiulcer activity of the optimized treatments were evidenced by lowest ulcer index scores of 2.89 ± 0.12 and 2.27 ± 0.12 for F3 and F6 tablets, respectively.

Keywords: Ginger Extract, HPMC, Carbopol, Sustained Release, Antiulcer Activity

INTRODUCTION

Ginger, also known as zanjabeel is a rhizome of *Zingiber officinale* (Family: zingiberaceae) is a highly consumed dietary substance around the world **[1]**. In the traditional

systems of medicine, ginger extract has been used for a variety of purposes, including treating gastrointestinal (GI) disturbances, excellent carminative and intestinal spasmolytic **[2, 3]**. However, modern scientific research has revealed that ginger extract had a wide spectrum of biological and pharmacological activities such as antioxidant effects, an ability to inhibit the formation of inflammatory compounds and direct anti-inflammatory effects **[4-6]**. The main purpose of floating dosage forms is to prolong the residence time and remain buoyant of the dosage form within the GIT contents **[7, 8]**. Release of drug from the floating dosage form is retained at the pH of the stomach under controlled conditions **[9, 10]**. Floating dosage forms have lower bulk density than stomach fluid to keep remain buoyant to increase the residence time without affecting gastric emptying rate **[11, 12]**. Floating dosage forms offer several advantages over conventional dosage forms such as reduced intra and inter subject variability in plasma drug level, effective delivery of narrow absorption window drugs, reduce dose frequency and increased patient compliance **[13]**. Floating tablets have been prepared by incorporating swellable polymers like hydroxypropyl methyl cellulose (HPMC) and Carbopol 934 etc. When tablets come in contact with gastric fluid, polymers start to become swell and form a gelled barrier around the tablets and hence controlled the release of drug from tablets [14]. Two types of granules (effervescent and non-effervescent) have been used to prepare the floating tablets. Effervescent tablets have been prepared by using swellable polymers with effervescent components like sodium bicarbonate and citric or tartaric acid **[15]**. A thorough literature search reveals that only one floating dosage form i.e., the beads of ginger extract have been reported **[5]**. Low aqueous solubility and low bioavailability limits the use of ginger extract in gastric ulcer. Hence, it is essential to develop a suitable floating drug delivery system for treating gastric ulcers. The purpose of this study was to develop a floating tablet of ginger extract using HPMC and Carbopol 934 as the hydrophilic polymers in order to achieve the objective of antiulcer effect.

MATERIALS AND METHODS

Materials

Ginger rhizomes were purchased from local market of Al-Kharj, Saudi Arabia. HMPC and Carbopol 934 were purchased from Sigma Aldrich (St. Louis, MO). All chemicals and solvents used in this study were of analytical/pharmaceutical grade.

Extraction

Accurately weighed 250 g of the dried whole rhizomes of *Zingiber offi*cinale were refluxed with methanol (500 mL) for 1 h in water bath and filtered through Whatman filter paper (No. 41). The marc left out was refluxed again for three times with 250 mL of methanol for 1 h and filtered. The filtrates were combined and evaporate it in rotary vacuum evaporator till complete dryness **[16]**.

Development of tablets

Tablets were formulated by wet granulation technique using HPMC E15, Carbopol 934 (polymers) and other ingredients such as sodium biocarbonate, citric acid, methyl cellulose, magnesium stearate and talc. All the ingredients were weighed accurately and passed through sieve no # 60. The ginger extract and all the ingredients were mixed properly in a mortar and pestle to get a uniform powder blend. Granules were prepared manually with a solution of polyvinyl pyrrolidone (PVP K30) in sufficient isopropyl alcohol as binder. The wet mass was passed through a 16 mesh sieve and the wet granules produced were dried in hot air oven for 45 min at 50°C. Finally talc and magnesium stearate were mixed with the granules. The tablet blend was then weighed individually according to the formula and compressed into tablets using single punch tableting machine (Erweka single punch machine, Germany). The different formulations were coded as F1–F6 and their formulae are listed in **Table 1**.

Evaluation of tablet properties

Floating tablets of ginger extract were evaluated for thickness, diameter, hardness, friability and drug content. The thickness, diameter, hardness and weight variation of tablets were measured by Multicheck V (Erweka, Germany). Friability tests were performed using Roche Friabaltor. The drug content in each formulation was determined by taking 20 tablets from each batch, weighed, powdered and analyzed for gingerol at 282 nm by UV spectroscopy **[17]**.

***In vitro* buoyancy/floating study**

In vitro buoyancy studies were performed for all the prepared formulations. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing 0.1N HCl. The time taken for the tablet to rise to the surface and float was taken as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was considered as the total floating time.

Percent swelling index

The swelling behavior of a dosage form was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium simulated

gastric fluid (pH 1.2) at 37 ± 0.5°C. After different time interval, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point. Swelling index was calculated using equation 1 **[18, 19]**.

$$\% \, Swelling \; index = \frac{Weight \; of \; swellen \; tablet - Initial \; weight \; of \; tablet}{Initial \; weight \; of \; tablet} \times 100 \quad \ldots\ldots \textbf{(1)}$$

***In vitro* drug release studies**

The release studies of GE floating tablets were performed by using dissolution testing apparatus USP type II (Paddle type) (Erweka). The studies were done by using 900 ml of 0.1N HCl at 37± 0.5 °C temperature and speed of 75 rpm. At different time intervals, a sample (5 ml) of the solution was withdrawn from the dissolution apparatus, filtered and analyzed spectrophotometrically at 282 nm **[17]**. The studies were performed in triplicate.

Antiulcer activity

The protocols to carry out antiulcer activity were approved by Institutional Ethics Committee of Salman Bin Abdulaziz University, Al-Kharj, Saudi Arabia and their guidelines were followed throughout the study. The gastric ulcers were induced by administration of 90% ethanol orally at a dose of 1 ml/kg in all male Wistar rats weighing 150-250 g. The rats were divided into 6 groups each consisting of six animals. Animals were fasted for 24 h and allowed free access to water.

Group I: (Control) received 90% ethanol orally at a dose of 1 ml/kg

Group II (standard): received pure drug ranitidine suspended in 1% Na-CMC at dose of 20 mg/kg

Group III (ginger extract) received ginger extract pure powder suspended in 1% Na-CMC at dose equivalent to 20 mg/kg.

Group IV received optimized floating tablet of ginger extract (F3) suspended in 1% Na-CMC at dose equivalent to 20 mg/kg.

Group V received optimized floating tablet of ginger extract (F6) suspended in 1% Na-CMC at dose equivalent to 20 mg/kg.

Rats were sacrificed 4 h later using ether and the stomach was opened to collect the gastric contents. The stomach was opened along the greater curvature and the length of lesions in the glandular portion was measured **[20]**. The following scores were used to evaluate antiulcer activity:

0.0 Normal (no injury, bleeding and latent injury)

0.5 Latent injury or widespread bleeding

1.0 Slight injury (2–3 dotted lines)

2.0 Severe injury (continuous lined injury or 5–6 dotted injuries)

3.0 Very severe injury (several continuous lined injuries)

4.0 Widespread lined injury or widened injury

RESULTS AND DISCUSSION

Evaluation of tablet properties

All the tablets (F1-F6) were evaluated for thickness, diameter, hardness, friability and drug content **(Table 2)**. Thickness and diameter of floating tablets were observed in the range of 5.21 ± 0.03 to 5.31 ± 0.01 and 12.39 ± 0.05 to12.50 ± 0.03 mm, respectively. However, hardness, friability and drug content of the tablets were observed in the range of 10.92 ± 0.19 to 11.61 ± 0.23 kg/cm^2, 0.0014 ± 0.05 to 0.0032 ± 0.02 % and 97.65 ± 0.18 to 99.54 ± 0.08 %, respectively. These results indicated good uniformity in the prepared formulation.

In vitro buoyancy/floating study

In vitro buoyancy of floating tablets (F1-F6) was observed in the range of 35-60 sec. When a tablet was immersed in beaker containing 100 ml 0.1N HCl, gas generated (effervescence) trapped inside the polymer gel that decreased the density of tablet below 1 that make tablet buoyant. The total floating time of all batches of floating tablet were found more than a day i.e., > 24 h.

Percent swelling index

Swelling studies were carried out for all prepared formulations and the result of swelling index are presented in the **Figures 1 & 2**. It could be seen from **Figures 1 and 2** that swelling of the tablet increases with the time due to gradual absorption of water by polymers HPMC (F1-F3) and Carbopol 934 (F4-F6). Maximum swelling index was observed in formulations F3 and F6. From the results, it was concluded that swelling index increases with increasing the concentration of polymer HPMC E15 and Carbopol 934 used in F3 and F6 formulations, respectively.

In vitro drug release studies

The *in vitro* release studies were carried out for prepared floating tablets of GE (F1-F6) in 0.1N HCl (pH 1.2) and results are presented in **Figures 3 and 4**. The dissolution of floating tablets (F1-F6) was studied at pH 1.2 to gain information about the release of the ginger extract in the stomach. As per these results, release of F3 and F6 tablets was found to be 66.4 % and 62.4 % after 8 h, respectively. As the concentration of polymers (HPMC & Carbopol 934) increased, the release of GE increases with slow rate for

8 h due to water diffusion into the polymer matrix **[17]**.

Antiulcer activity

The results of ulcer index and percent protection are listed in **Table 3 and Figure 5**. All the rats received 1 m/kg 90% ethanol and induced severe gastric mucosal damages. Optimized floating tablets of ginger extract (F3 and F6) significantly suppressed the ethanol induced gastric lesions. F3 and F6 floating tablets showed lowest ulcer index score (2.89 ± 0.12 and 2.27 ± 0.12) with significant increase in protection of gastric mucosa. The percent ulcer protection for F3 and F6 formulations were observed as 47.2 % and 58.7 %, respectively. These values of protection were very close to standard group ranitidine. Thus, it is revealed that ginger extract in the form of floating tablet shown a potential decrease in ulcer and hence it can be used to treat gastric ulcer.

CONCLUSION

Gastroretentive drug delivery system of ginger extract was successfully developed using HPMC and Carbopol. Physicochemical parameters of prepared tablets were found to be satisfactory in terms of hardness, friability and drug content. Formulations F3 and F6 showed 66.4 % and 62.4 % release of ginger extract after 8 h, respectively. Optimized floating tablet of ginger extract (F6) significantly suppressed the ethanol induced gastric lesions. The percent ulcer protection for F6 formulation was observed as 58.7 %. These results indicated that developed floating tablets of ginger extract could be successfully used to treat gastric ulcers.

CONFLICT OF INTEREST

The authors report no declaration of interest. The authors alone are responsible for the content and writing of this paper.

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Table 1: Formulae of prepared floating tablets

Ingredients (mg/tabs)	F1	F2	F3	F4	F5	F6
Ginger extract	550	550	550	550	550	550
HPMC E15	100	150	200	0	0	0
Carbopol 934	0	0	0	100	150	200
Sod. Biocarbonate	150	150	150	150	150	150
Citric acid	15	15	15	15	15	15
Methyl cellulose	50	50	50	50	50	50
PVP-K30	40	40	40	40	40	40
Mg-stearate	15	15	15	15	15	15
Talc	10	10	10	10	10	10
Total wt/tabs	930	980	1030	930	980	1030

Table 2: Evaluation of floating tablet of GE

Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	5.21 ± 0.03	12.40 ± 0.04	11.32 ± 0.13	0.0018 ± 0.05	98.32 ± 0.11
F2	5.25 ± 0.02	12.43 ± 0.07	10.92 ± 0.19	0.0021 ± 0.04	99.21 ± 0.09
F3	5.31 ± 0.01	12.50 ± 0.03	11.61 ± 0.23	0.0032 ± 0.02	97.65 ± 0.18
F4	5.21 ± 0.03	12.39 ± 0.05	11.24 ± 0.33	0.0024 ± 0.07	99.34 ± 0.21
F5	5.24 ± 0.04	12.41 ± 0.06	11.56 ± 0.29	0.0021 ± 0.02	98.29 ± 0.17
F6	5.29 ± 0.01	12.44 ± 0.08	11.43 ± 0.27	0.0014 ± 0.05	99.54 ± 0.08

Table 3: Effect of GE floating tablets on ethanol induced gastric ulcer

Groups	Treatments	Dose p.o (mg/kg)	Ulcer Index	% Protection
I	90% Ethanol	1 ml/animal	5.50 ± 0.10	-
II	Ranitidine + 90% Ethanol	20	2.30 ± 0.13	58.2
III	Ginger extract + 90% Ethanol	20	3.44 ± 0.10	37.4
IV	F3 + 90% Ethanol	20	2.89 ± 0.12	47.2
V	F6 + 90% Ethanol	20	2.27 ± 0.12	58.7

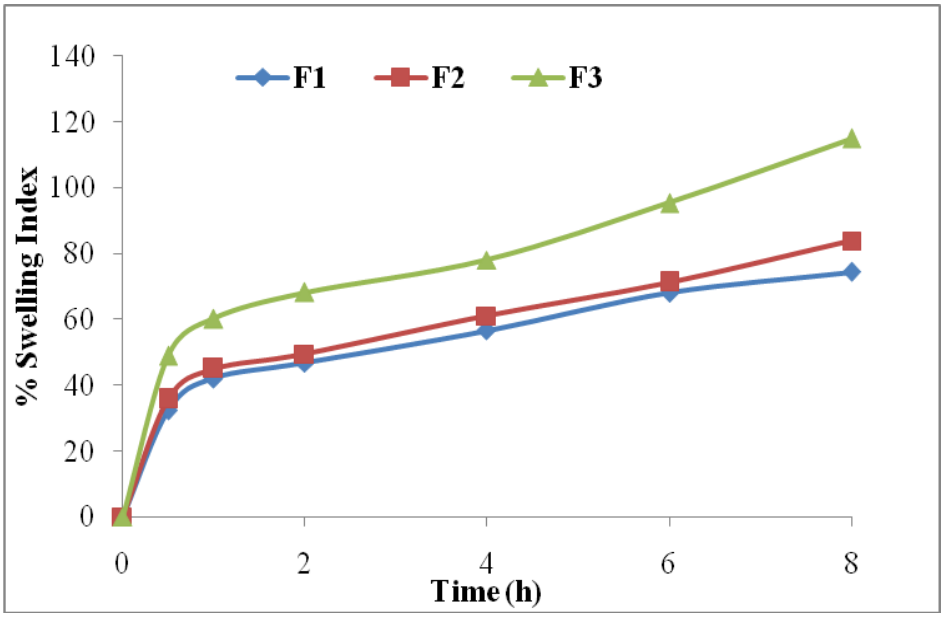

Figure 1: Swelling index of floating tablets prepared using HPMC

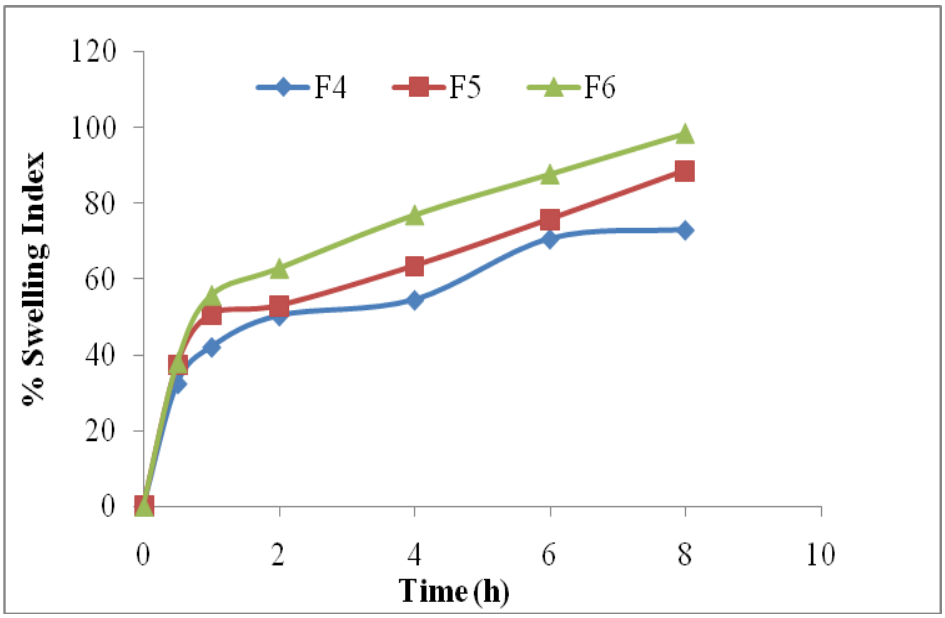

Figure 2: Swelling index of floating tablets prepared using Carbopol 934

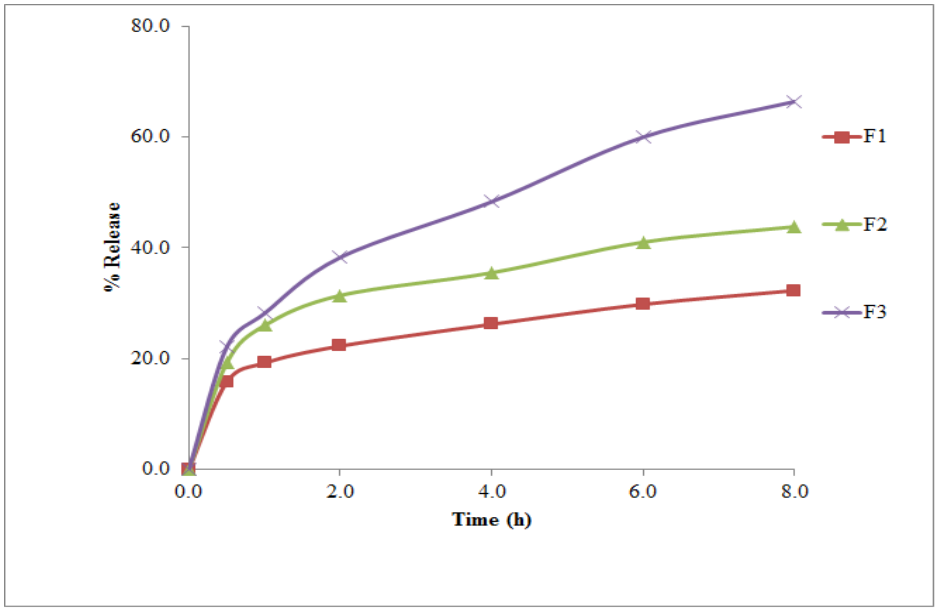

Figure 3: Release profile of gingerol from floating tablets prepared using HPMC

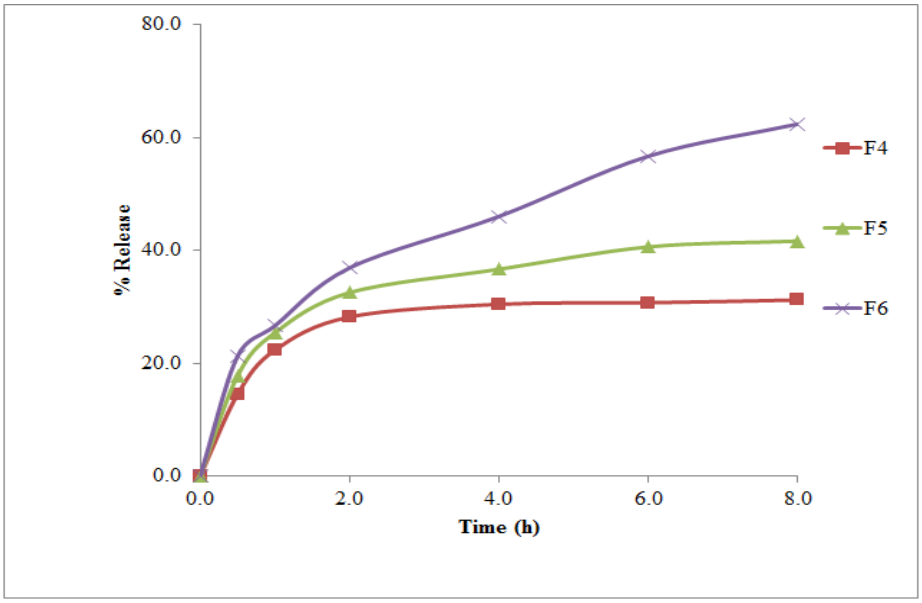

Figure 4: Release profile of gingerol from floating tablets prepared using Carbopol 934

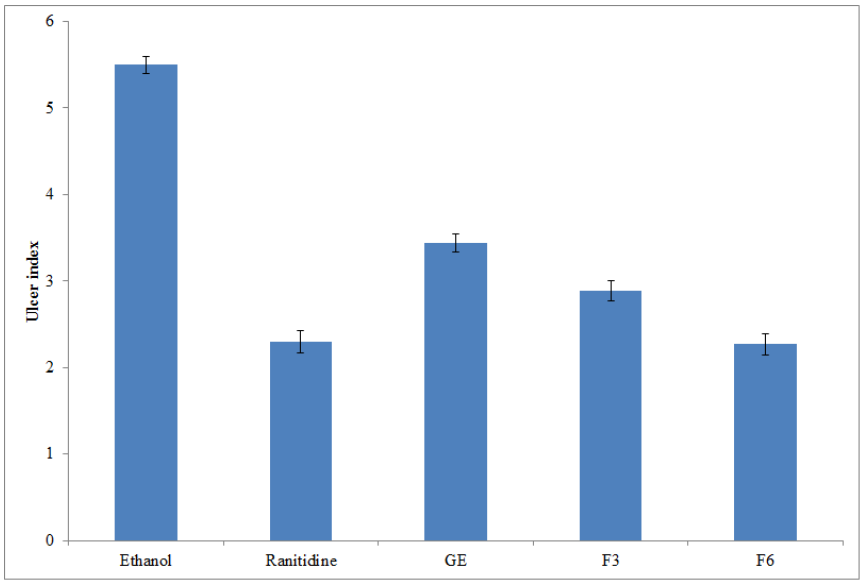

Figure 5: Comparative ulcer index score