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Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET USING *HIBISCUS ROSA-SINENSIS* MUCILAGE

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ABSTRACT

Objective: Domperidone is a synthetic benzimidazole compound that acts as a dopamine D_2 receptor antagonist. The main aim of this study was to optimize and evaluate the floating tablets of domperidone that prolongs the gastric residence time using *Hibiscus rosa-sinensis* mucilage.

Methods: The directly compressible floating tablets of domperidone were formulated using varying amount of hydroxypropyl methylcellulose K100 M, carbopol 934P and *H. rosa-sinensis* mucilage. The effervescent components sodium bicarbonate is used for the generation of CO_2 gas. The prepared tablets were evaluated for physicochemical parameters and found to be within range, viz., hardness, swelling index, floating capacity, thickness, and weight variation. Further, tablets were evaluated for *in vitro* release characteristics. The concentration of *H. rosa-sinensis* mucilage with a gas-generating agent was optimized to get the sustained release of domperidone.

Result: The % cumulative drug release of all formulation from F1 to F6 was within the range of 81.37% to 98.62% for 18 hrs. The release kinetics of all the dosage forms was calculated using zero order, first order, Higuchi, and Korsmeyer–Peppas. It concludes that the release followed zero order release, whereas the correlation coefficient (r^2 value) was higher for zero order release. The release mechanism follows Higuchi model, Korsmeyer-Peppas model, and non-Fickian diffusion.

Conclusion: As a result of this study, it may be concluded that the floating tablets using *H. rosa-sinensis* mucilage in optimized concentrations can be used to increase the gastric retention time of the dissolution fluid in the stomach to deliver the drug in a sustained manner. Furthermore, from 1 month stability data shows no significant change compared to initial result.

Keywords: Floating drug delivery, *Hibiscus rosa-sinensis* mucilage, Domperidone.

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INTRODUCTION

Rapid gastrointestinal transit could result in incomplete drug release from the dosage form above the absorption zone leading to diminished efficacy of the administered dose. These considerate have led to the development of a controlled or sustained delivery system. The main purpose for developing these systems was to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for long time. Gastroretentive drug delivery is an approach to prolong gastric retention time, thereby targeting site – specific drug release in the upper GIT for local and systemic effect. Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems and floating systems.

Floating drug delivery or hydrodynamically balanced systems have a sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period [1-4].

Domperidone is a synthetic benzimidazole compound that acts as a dopamine D_2 receptor antagonist. Its localization outside the blood-brain barrier and antiemetic properties other has made it a useful adjunct in therapy for Parkinson's disease. There has been renewed interest in antidopaminergic prokinetic agents since the withdrawal of cisapride, a 5-HT4 agonist, from the market. Domperidone is also used as a prokinetic agent for treatment of upper gastrointestinal motility disorders. Patients receiving domperidone or other prokinetic agents for diabetic gastropathy or gastroparesis should also be managing diet, lifestyle, and medications to optimize gastric motility. After oral administration, domperidone is rapidly absorbed from the stomach and the upper part of the GIT with fewer side effects. It is a weak base with good solubility in acidic pH but significantly reduced solubility in alkaline medium [5-7]. Such a weak base, formulated as an oral controlled release dosage form is exposed to environments of increasing pH with subsequent precipitation of poorly soluble free base within the formulation that is no longer capable of being released from the formulation.

A majority of the investigations on natural excipients in drug delivery systems have centered on proteins and polysaccharides due to their ability to produce a wide range of materials and properties according to molecular structural alterations. In recent years, plant gums and mucilages have evoked tremendous interest due to their diverse pharmaceutical applications such as diluents, binders, disintegrants in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppository, thus making them attractive substitutes for costly semisynthetic and synthetic excipients. India, due to its geographical and environmental positioning, has traditionally been a good source for such products among the Asian countries. Hibiscus is widely grown as an ornamental plant throughout the tropics and subtropics. The plant is available in India in large quantities. Its 250 species are widely distributed in tropical and subtropical regions of the world and are reported to possess various medicinal properties, viz., antitumor, antihypertensive, and antioxidant. In this study, an effort was made to extract the mucilage from the leaves of *Hibiscus rosa-sinensis* Linn. and look at the possibility of using this mucilage as the floating agents and releasing retardant material in the formulation of solid dosage forms [8].

This study involved the design of gas generating floating tablets of domperidone as a model drug. The gas generating system consists of hydrophilic matrices prepared with the swellable hydrocolloids such as hydroxypropyl methylcellulose (HPMC) K100 M, carbopol 934P and *H. rosa-sinensis* mucilage. The effervescent components sodium bicarbonate was used for the generation of CO_2 gas. When the dosage form comes in contact with acidity of gastric contents, the CO_2 is entrapped in the polymeric network providing the floating characteristics to the dosage form [9-11].

MATERIAL AND METHODS

Materials

Domperidone was generously gifted by Ajanta Pharma Ltd. Mumbai. *H. rosa-sinensis* leaves are collected from local area of Nagpur, India. Moreover, plant was authenticated at Pharmacognosy Department of Department of Pharmaceutical Science of Nagpur University, India, and mucilage was extracted in Pharmaceutics Research Lab, HPMC K100 M, carbopol 934, sodium bicarbonate, microcrystalline cellulose, magnesium stearate and talc were purchased commercially. All solvents and reagents used were of analytical grade.

Methods

Extraction of H. rosa-sinensis mucilage

The fresh *H. rosa-sinensis* Linn. leaves were collected and washed with water to remove dirts and debries. Leaves were powdered and soaked in water for 5-6 hrs, boiled for 30 minutes and left stand for 1 hr to allow complete release of mucilage into water. The mucilage was extracted using multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the volumes of three times to the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried, in an oven at 40°C, passed through #80 sieve and stored in dessicator at room temperature for further use [9,10].

Purification of H. rosa-sinensis mucilage

The crude mucilage (1%) was obtained after extraction which was centrifuged at 10000 rpm, decanted and precipitated in acetone following 1:2 mucilaginous solution:acetone ratio, washed with isopropyl alcohol with 1:1 volume ratio and finally it was dried [9,10].

Formulation of floating tablet of domperidone by direct compression

Floating tablets of domperidone were prepared by direct compression method employing sodium bicarbonate as gas generating agent. HPMC K100 M and *H. rosa-sinensis* mucilage, carbopol 934 were used as a rate controlling polymers. The concentrations of above ingredients were optimized as shown in Table 1. All the ingredients were weighed accurately. The drug was mixed with the release rate retarding polymers and the mix was blended for 20 minutes to have uniform distribution of drug in the formulation. The blend was lubricated with talc and magnesium stearate and compressed using 8 station compression machines. The tablet weighed for compression was adjusted to 400 mg [11].

Table 1: Formulation batches of floating tablet

Ingredients	Formulation batches					
	F1	F2	F3	F4	F5	F6
Domperidone	30	30	30	30	30	30
HPMC K100 M	200	175	175	175	150	100
Hibscus rosa-sinensis Mucilage	-	-	50	50	100	125
Carbopol	-	75	50	25	25	25
MCC	110	60	35	60	35	60
Sodium bicarbonate	50	50	50	50	50	50
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total weight	400	400	400	400	400	400

All quantities are given in mg. MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methylcellulose

Evaluation of tablets

Precompression parameters and characterization of powders

The flow properties of powders (before compression) were characterized in terms of, bulk density, Hausner's ratio, angle of repose, and Carr's index [4,8].

Physical characterization of tablet

Compressed tablets were then evaluated for shape, diameter and thickness, weight variation, disintegration, hardness, friability study. Diameter and thickness were measured by vernier caliper. Hardness was measured by Monsanto type hardness tester. Friability was determined in friabilator (Electrolab EF-2, USP) [5,6].

Assay of tablets

Twenty tablets from each batch were weighed and powdered. Powder equivalent to 30 mg of domperidone was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of 0.1 N HCl. The prepared solution was diluted up to 100 ml with 0.1 N HCl and sonicated for 60 min. Five milliliters of the resulting solution was diluted to 100 ml with 0.1 N HCl to get a concentration in the range of 15 µg/ml. A portion of the sample was filtered through 0.45 µ membrane filter and analyzed by Shimadzu UV-1700 UV/Vis double-beam spectrophotometer (Kyoto, Japan) at 284 nm [7,12].

Floating capacity

The *in vitro* buoyancy was determined by floating lag times. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution [13-15].

Swelling index

The extent of swelling was measured in terms of % of weight gained by the tablet. Three tablets from each formulation was weighed and kept in Petri dish containing 50 ml of 0.1 N HCL solution. At the end of specified time interval, tablets were withdrawn from Petri dish and excess buffer was blotted with tissue paper and weighed [13-15].

In vitro dissolution studies

The release rate of domperidone from floating tablets (n=3) was determined as per British Pharmacopoeia (BP) using dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37±0.5° and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 24 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 284 nm using a Shimadzu UV-1700 UV/V is double-beam spectrophotometer (Kyoto, Japan). Duration of time the tablets constantly float on dissolution medium was noted as total floating time [5-7,12].

Kinetic analysis of *in vitro* release rate of floating tablets of domperidone

The rate and mechanism of release of domperidone from the prepared floating tablets were analyzed by fitting the dissolution data into following equations:

Zero order kinetics $F=k_0t$

First order kinetics $(1-F)=-k_1t$

To describe the drug release behavior from polymeric systems, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation.

$M_t/M_\infty=Kt^n$

Where, M_t/M_∞ is the fraction of drug release at time t and k is the kinetic constant, n is the release exponent (indicating the general operating release mechanism) [15,16].

For tablets, depending on the aspect ratios values between 0.43 and 0.5 indicating Fickian (case I) diffusion-mediated release, non-Fickian (Anomalous) release, coupled diffusion, and polymer matrix relaxation, occurs if 0.5<n<0.89, purely matrix relaxation or erosion-mediated release occurs for n=1 (zero order kinetics), and super case II type of release for n>0.89.

Statistical analysis

To evaluate contribution of each factor with different levels on responses, two-way analysis of variance was performed using SigmaStat software (SigmaStat 2.03, SPSS, Chicago, Illinois, USA).

Stability studies

The optimized formulation was kept for short-term stability study. The conditions for stability were 30°C±2°C room temperature and relative humidity of 65% RH±5% RH. All tablets were suitably packed in group of 10 in aluminum foil. At the end of one month, the sealed tablets were opened and evaluated for *in vitro* release and *in vitro* floating.

RESULTS

Precompression parameters

The domperidone powder mixtures obtained during the precompression process were subjected to different parameters and the results were represented in Table 2**.**

Postcompression parameters

Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value. Hardness of the prepared tablets was observed to be within the range of 3.9-4.7 kg/cm^2. Thickness of all the tablets was found in the range of 3.23- 3.45 mm. Friability of all the tablets was found below 1% was shown in Table 3.

The drug content in all the batches of domperidone floating tablets was in the range of 98-100% which is within the specified IP limit. This ensured the uniformity of the drug content in the tablets represented in Table 4.

Swelling index and floating lag time

The swelling index results were depicted in Table 4. It was observed that the swelling indexes were increased with increasing *H. rosa-sinensis* gum concentration with carbopol than that of ones containing HPMC K100 M alone because of the fact that the *H. rosa-sinensis* and carbopol are more viscous in nature and showed good swelling properties in the later periods [8,13]. The formulations had desired floating lag time (<80 seconds) and total floating time between 12 and 18 hrs was found to be the function of concentration of gum.

***In vitro* dissolution study**

The % cumulative drug releases of all formulations from F1 to F6 were within the range of 81.37-98.62% for 18 hrs (Fig. 1). From results of *in vitro* drug release studies, it concludes that F6 had better sustained release than the other formulation (Fig. 1). To analyze the domperidone release mechanism, the *in vitro* release data were fitted into various release equations and kinetic models (first order, zero order, Higuchi, Korsmeyer-Peppas) as indicated by the value of r^2, the Higuchi model was found to be efficient in describing the diffusion mechanism. To explore the release pattern, results of the *in vitro* release data of all formulations were fitted to the Korsmeyer-Peppas equation showed "n" value between 0.56 and 0.76 that indicate the drug release occurred via non-Fickian diffusion mechanism (Table 5).

Stability study

The results of stability study indicated that there were no significant changes in drug content, floating lag time, and floating time (Table 6).

Table 2: Precompression parameters of formulations

Formulation code	Angle of repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index	Hausner's ratio
F1	25.32±0.181	0.68±0.042	0.75±0.026	9.45±0.065	1.01±0.013
F2	25.21±0.248	0.69±0.036	0.74±0.029	9.92±0.028	1.12±0.077
F3	26.90±0.713	0.69±0.026	0.80±0.091	10.34±0.022	1.07±0.017
F4	24.47±0.279	0.70±0.061	0.79±0.036	9.32±0.037	1.09±0.051
F5	26.56±0.423	0.68±0.047	0.79±0.047	13.45±0.048	1.11±0.099
F6	26.91±0.576	0.67±0.036	0.78±0.032	12.62±0.053	1.07±0.031

Mean±SD, n=3, p<0.05. SD: Standard deviation

Table 3: Postcompression parameters-I of tablets

Formulation code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability
F1	399.27±1.181	3.24±0.036	4.4±0.381	0.61±0.351
F2	400.02±3.223	3.38±0.091	3.9±0.296	0.59±0.428
F3	400.16±1.293	3.40±0.073	4.2±0.577	0.67±0.138
F4	400.46±1.173	3.43±0.082	4.7±0.122	0.78±0.149
F5	401.03±2.283	3.45±0.069	4.6±0.091	0.82±0.264
F6	399.36±1.132	3.29±0.089	4.7±0.178	0.62±0.381

mean±SD, n=3, p<0.05. SD: Standard deviation

Table 4: Postcompression parameters-II of tablets

Formulation code	Drug content (%)	Floating lag time (s)	Swelling index (%)	Floating duration (h)
F1	98.23±0.15	70	29.29±0.13	12
F2	99.76±0.21	66	30.09±0.15	13
F3	99.81±0.18	64	33.62±0.05	13
F4	98.48±0.07	64	33.68±0.18	15
F5	98.69±0.19	60	35.96±0.19	15
F6	99.57±0.18	55	38.23±0.12	18

Mean±SD, n=3, p<0.05. SD: Standard deviation

Table 5: Dissolution kinetics of domperidone floating tablet

Formulation code	r^2			Korsmeyer-Peppas		Drug release mechanism
	Zero order	First order	Higuchi	r^2	Slope (n)	
F1	0.8205	0.9543	0.9703	0.9553	0.5621	First order non-Fickian diffusion
F2	0.9322	0.9655	0.9630	0.9826	0.5434	First order non-Fickian diffusion
F3	0.9002	0.9555	0.9729	0.9808	0.5368	First order non-Fickian diffusion
F4	0.9509	0.8426	0.9694	0.9791	0.5831	Zero order non-Fickian diffusion
F5	0.9646	0.8724	0.9726	0.9884	0.6238	Zero order non-Fickian diffusion
F6	0.9780	0.8632	0.9484	0.9685	0.7892	Zero order non-Fickian diffusion

Table 6: Drug content and floating behavior of optimized F6 formulation during short-term stability study

Parameter	Result
Drug content	98.42±0.15%
Floating lag time	63 s
Floating time	18 h

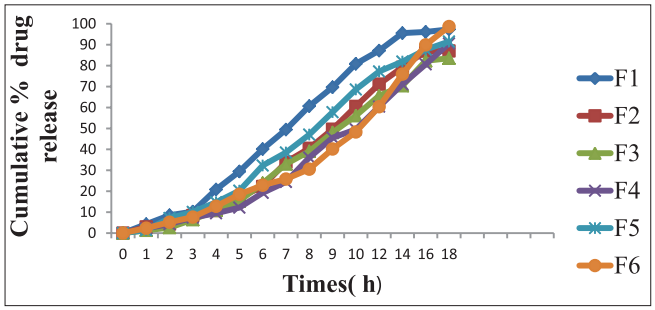

Fig. 1: Cumulative *in vitro* drug release profile of domperidone (mean±standard deviation, n=3, p<0.05)

DISCUSSION

From the results of precompression parameter of tablet it was observed that the bulk density was found to be between 0.672 and 0.703 g/ml and the tapped density ranged between 0.747 and 0.824 g/ml, which make them floatable in the gastric fluid. The other micromeritic properties such as Carr's index, Hausner's ratio revealed no significant differences. Angle of repose was to be between 24.35 and 26.91 indicating good flow properties. Hardness, friability, weight variation, thickness, disintegration time of tablet formulation were within acceptable limits and the drug content in all the batches of domperidone ensured the uniformity of the drug content in the tablets.

The result of floating lag time demonstrates that the tablets containing *H. rosa-sinensis* gum alone showed longer floating lag time as the tablets tend to disintegrate due to the fast release of CO_2 gas. This may be because of the fact that at lower concentrations, the gum has lesser ability to form as gel. This was mainly due to the evolution of CO_2 entrapped into the matrix of swollen polymer of the matrix and well protected by gel formation by the hydrated polymer resulting from interaction between the gas generating agent (sodium bicarbonate) and dissolution medium (0.1N HCl with pH 1.2) that leads to lowering the density and enabling the tablet to float [13,14].

The results revealed that as the amount of *H. rosa-sinensis mucilage* increased, the % swelling increased. This result may be explained by the hydrophilic nature *H. rosa-sinensis* gum which when present at optimum concentration with HPMC, rapidly hydrates leading to expansion and consequently an ordering of the polymer chains. Tablets containing carbopol 934 as copolymer (especially F6) showed higher % swelling. It was reported that carbopol swells in simulated gastric fluid, pH 1.2. The amount of effervescent mixture incorporated had a significant effect on swelling properties of tablet. This may be due to the increased reaction of sodium bicarbonate with the dissolution medium that increased the release of CO_2 and consequently, the number of pores and swelling index was increased [16-19].

In vitro dissolution data of formulation (F1 to F6) reported in Fig. 1. The overall drug releases from these tablets are governed by burst effect followed by gel layer formation, drug diffusion into the gel layer and to the dissolution media. These considerations indicate that hydrophilic polymers have the potential to sustain the release of drug from tablet. Polymer HPMC K100 yielded a faster initial burst effect with desirable drug release. The additional use of carbopol and *H. rosa-sinensis* mucilage decreased the release of domperidone from the tablet. Likely due to the fact that carbopol and *H. rosa-sinensis* are cross-linked polymers when contacted with water, it would swell and hold water inside its microgel network. By increasing the mucilage percentage, a viscous gel layer is formed and diffusion of the drug is controlled primarily by the gel viscosity. The viscosity of mucilage solutions strongly increases with increasing concentration of the mucilage. The behavior is attributable to the intermolecular interaction, increasing the effective macromolecule dimensions and molecular weight [5,6].

CONCLUSIONS

In this study, gastroretentive floating tablets of domperidone were successfully prepared by direct compression method using *H. rosa-sinensis* mucilage. Fabricated tablets showed acceptable weight variation, hardness, and uniformity of drug content. The overall results explained that the tablets prepared by combination of *H. rosa-sinensis* mucilage, HPMC K100 M, carbopol and gas-generating agent sodium bicarbonate, could be more efficient on floating and sustained release of domperidone as compared to the tablets prepared using HPMC K100 M and carbopol only. Thus, proper selection of the ratio of desired drug release was achievable.

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