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Original Article

FORMULATION AND EVALUATION OF GARLIC POWDER LOADED FLOATING MATRIX TABLET

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ABSTRACT

Objective: The objective of the present work was to formulate and evaluate a stable, odour free garlic powder loaded floating matrix tablet for the treatment of peptic ulcers.

Methods: A gastro-retentive floating matrix tablet (FMT) formulation of garlic powder (GP) was prepared using various concentrations of hydroxypropyl methylcellulose K4M (HPMC K4 M) and effervescent system (sodium bicarbonate and citric acid in 1:1 % w/w) to achieve desirable floating time (FT), floating lag time (FLT) and drug release. Wet granulation method was selected using ethanol as a binder for preparation of tablet. 3^2 full factorial designs were used for selection of suitable polymer concentration and effervescent system. Nonenteric film coating was applied to mask GP odour.

Results: It was observed that FMT with optimum quantities of HPMC K4M and the effervescent system showed 97 % of drug release in 12 h with FT up to 10 h and minimum FLT of 3 min. There was no significant change in FLT, FT and drug content during the stability study of FMT.

Conclusion: A stable, sustained release FMT of GP tablets using HPMC K4M and an effervescent system was successfully prepared. This formulation can overcome problems of taste and odour masking, gastric irritation, and loss of active constituents present in garlic.

Keywords: Garlic powder, *H. pylori*, Floating time, Floating Lag time, Floating Matrix tablet, HPMC K4M

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INTRODUCTION

Peptic ulcers are chronic, most often solitary, lesions that occur in any portion of the gastrointestinal tract exposed to the aggressive action of acid-peptic juices. As much as 80% of ulcers are associated with *Helicobacter pylori*, a spiral-shaped bacterium that lives in the acidic environment of the stomach [1]. Treatment usually involves a combination of antibiotics, acid suppressors, and stomach protectors i.e.14-tablet/day for a week or more. Although antibiotic therapy has a success rate of 80%-90%, problems including undesirable side effects, high cost and poor patient compliances are associated with significant levels of treatment failure. Development of microbial resistance and contraindications is also observed in some patients [2].

Peptic ulcers can be treated successfully by herbal medicines without any side-effects. The aim of the study was to formulate a stable gastro-retentive dosage form containing garlic for local action in the stomach to treat peptic ulcers caused by *H. pylori*.

Garlic clove, garlic aqueous extracts, garlic powder, garlic oil, and allicin have been proved to be effective against *H. pylori* [3]. The powder form of garlic is the most stable starting material for the formulation, as the antibacterial principle i.e. allicin is formed from alliin present in garlic powder (GP), *in situ* and its biotransformation products are also effective against *H. pylori*. Allicin was found to be more stable in 20% alcohol than in water [4]. However, a patient cannot take garlic powder or raw garlic cloves as such because of gastric irritation and strong odour associated with the high dose needed for antibacterial action. The present work highlights the novel herbal formulation aimed specifically for the treatment of *Helicobacter pylori* infection to heal gastric ulcers. This formulation is very significant for the emerging nutraceutical market as garlic is one of the topmost selling nutraceuticals internationally.

MATERIALS AND METHODS

Garlic was procured from the local market and the whole sample of garlic plant was authenticated (Auth08-022) by Agarkar Research Institute, Pune, Maharashtra, India. Hydroxypropyl methylcellulose K4M (HMPC K4M), cross caramelose sodium, aerosil PH 200, talc, magnesium stearate were received from Himedia Labs, Mumbai, India. Avicel PH 102 was donated by Dow Chemical Company, Mumbai. All other chemicals used in the study were of an analytical grade.

Preparation of garlic powder

Garlic cloves were peeled and kept in a hot air oven, temperature maintained between 50 °C to 55 °C. Dried garlic cloves were powdered with suitable grinder. Moisture loss of garlic cloves was determined by percent weight loss per day till a constant weight was achieved.

Analytical method

The HPTLC method was developed for analysis of the GP in the tablet formulation. The 500 mg GP was weighed accurately and dissolved in 25 ml water containing ethanol as a co-solvent with constant stirring for 15 min. Then the solution was filtered with the help of Whatmman filter paper and dilutions were made to obtain 4-14 µg/ml solutions. 12 µl of each dilution was spotted with the help of HPTLC syringe on HPTLC plate. The area obtained for each ml solution was then presented by CAMAGE software.

Formulation development

A 3^2 full Factorial design (Design Expert version 7.1) was constructed where the concentration of sodium bicarbonate and citric acid (A) and amount of polymer (B) were independent variables and floating time (FT) and floating lag time (FLT) were dependent variables.

Three levels (Low, medium and high) for each factor were selected as shown in table 1. All the other formulation ingredients like aerosil PH 200, croscarmellose sodium, talc, magnesium stearate were kept invariant throughout the study for all 9 formulation batches of floating matrix tablet (FMT).

Table 1: Levels of 3^2 factorial design

Variables	Level		
	-1	0	1
A [% w/w of effervescent system(sodium bicarbonate: citric acid 1:1 w/w)]	6	9	12
B (% w/w of HPMC K4M)	7	14	21

All the ingredients (except magnesium stearate, talc) were weighed accurately and mixed along with 50 % of weighed aerosil PH 200 by geometrical proportion. Then ethanol was added in a small fraction to obtain wet mass. The granules were prepared by wet granulation method. Then the accurately weighed magnesium stearate, talc along with the remaining amount of aerosil was mixed and added in a granular mixture. The final blend compressed, using concave punches having length size 21.00 mm and 10.5 mm in width. 5% w/w non-enteric coating of HPMC was applied on FMT. The final weight of tablet after coating for all formulations was 900 mg [9].

Table 2: Composition of FMT formulations

S. No.	Ingredients	Amount (% w/w)								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Garlic Powder	60	60	60	60	60	60	60	60	60
2	HPMC K4M	7	21	7	7	14	14	14	21	21
3	Sodium bicarbonate and citric acid (1:1 w/w)	6	6	12	9	9	12	6	9	12
4	Croscarmellose sodium	1	1	1	1	1	1	1	1	1
5	Avicel 102	20.5	6.5	14.5	17.5	10.5	7.5	13.5	3.5	0.5
6	Aerosil PH200	3	3	3	3	3	3	3	3	3
7	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Talc	2	2	2	2	2	2	2	2	2
9	Ethanol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Physical characterization

All the batches were evaluated for weight variation, hardness, friability, thickness as per USP XXV monograph. The weight variation was determined by taking 20 tablets using electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 20 tablets in a Roche friability tester for 4 min at 25 rpm.

Buoyancy lag time and duration of buoyancy (FLT and FT)

The time interval between the introduction of a tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as FLT and FT was observed visually [10].

Assay

The content of active constituent(s) in garlic powder was determined by HPTLC method. For the preparation of standard solution, 500 mg GP was dissolved in distilled water (25 ml) and ethanol as a co-solvent with constant stirring for 15 min and filtered by Whatmman filter paper (Sample A). For the preparation of test solution, garlic tablet was crushed and dissolved in 25 ml distilled water containing ethanol as a co-solvent with constant stirring for 15 min and filtered by Whatmman filter paper (Sample B). Then the equivalent strength solutions of A and B samples (µl) were spotted by HPTLC syringe on HPTLC plate. Then areas of both were measured to determine % drug content.

***In vitro* drug release**

Drug release was calculated based on HPTLC fingerprint method. 900 ml 0.1 N HCl was selected as dissolution media at 50 rpm, 36.5°C–37.5°C using USP XXIII (Type1). One Gelusil tablet was added in dissolution medium to adjust the pH for maintaining the stability of GP. The 5 ml sampling was taken and replaced with equivalent amount till 12 h with fresh dissolution media.

Evaluation of tablet coating film

The tablet coating film was prepared by spraying the coating solution on a plain glass surface at the flow rate of 3 ml/min for 15 min as required for tablet coating. This film was evaluated for thickness, bursting strength and water vapour permeability.

The thickness of coated FMT was measured using Vernier Calipers, Water vapour permeability was determined at 25 °C using desiccators containing calcium chloride for 72 h.

$$Water\ vapour\ permeability = \left(\frac{Final\ weight - Initial\ weight}{Initial\ weight}\right) \times 100$$

Stability testing

The accelerated stability studies were performed on formulations F8 and F9 as per the protocol. FT, FLT, drug content, tablet thickness, weight variation, and hardness were tested at periodic time intervals.

RESULT AND DISCUSSION

Authentification of garlic sample

The whole sample of the garlic plant was identified as *Allium sativum* Linn (Family-*Liliaceae)*

Physical characterization of FMT

The formulated floating matrix tablets met the pharmacopoeia requirement of hardness, drug content, friability, weight variation and thickness (table 3).

Fig. 1: Floating behaviour of FMT F_9

Formulation and development

The purpose of using 3^2full factorial design was to conduct a comprehensive study of the effect of process parameters like concentration of sodium bicarbonate and citric acid (A) and amount of HMPC K4M (B) and their interactions using a suitable statistical tool (Design expert software version7.1) by applying one-way ANNOVA at 0.05 levels. A mathematical modelling was carried out. Polynomial equation was obtained depending on significant influences among 2 factors on their experimental design.

The fitted equations relating the response FT and FLT to the transformed factor are shown in the equation I, equation II respectively.

$$FT = 5.55556 - 0.5833*A + 2.75*B + 0.41667A^2 + 0.41667B^2 \ldots \text{I}$$

$$FLT = 4.88889 - 1*A - 2.6667*B + 0.16667\,A^2 + 0.6667\,B^2 + 0.5*A*B \ldots \text{II}$$

The values of correlation coefficient indicate a good fit.

The three-dimensional response surface plot was generated by software. The response surface plot is very useful for the determination of main and interaction effects of the independent variables. The response surfaces plots for each response parameter are presented for further interpretation of the results (fig. 2, fig. 3). Formulations F8 and F9 were considered as optimized formulations on the basis of FT and FLT.

The data demonstrated that both factors A and B affect FT and FLT. As the concentration of B increased from 7 % to 21% FT is increased up to 10 h. FLT in increased up to 4 min as sodium bicarbonate and citric acid concentration increases for 6 to 12 % w/w. Desirable FLT i.e. 3 min and FT i.e. 10 h are achieved by increasing concentration of HPMC K4M and maintaining the optimum concentration of sodium bicarbonate and citric acid.

The buoyant delivery systems utilize matrices by swellable polymers such as Methocel (HPMC) or polysaccharides e. g. chitosan and effervescent components e. g., sodium bicarbonate and citric acid or tartaric acid or matrices containing chambers of liquids that gasify at body temperature.

The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in jellified hydrocolloid. This produces an upward motion of dosage form and maintains its buoyancy. Among the gastro-retentive dosage forms, effervescent matrix floating tablet is formulated as it overcomes the problem of acidic degradation of GP and it is able to sustain the release of drug in the stomach with gastric retention.

Table 3: Comparative evaluation of non–enteric coated FMT formulations

S. No.	Formulation code	Thickness* (mm)	Hardness *(kg/cm²)	Weight variation* (%)	Drug content* (%)	Friability* (%)	FLT* (min	FT *(h)
1	F_1	5.2±0.2	3.5±0.2	0.64±0.1	96.45±	0.5±0.8	7±0.2	5±0.5
2	F_2	5.3±0.1	3.5±0.2	0.61±0.1	95.12±	0.6±0.5	5±0.5	5.7±0.3
3	F_3	5.3±0.2	3.4±0.1	0.65±0.1	98.25±	0.7±0.9	6±0.3	4.5±0.2
4	F_4	5.2±0.4	3.5±0.1	0.66±0.2	98.65±	0.8±0.8	5.5±0.2	5±0.4
5	F_5	5.3±0.2	3.2±0.3	0.7±0.2	96.80±	0.7±0.7	3.5±0.5	7±0.2
6	F_6	5.3±0.2	3.5±0.2	0.65±0.3	95.32±	0.7±0.5	3.8±0.3	8±0.5
7	F_7	5.2±0.1	3.4±0.4	0.71±0.3	95.27±	0.8±0.5	3.6±0.4	9±0.5
8	F_8	5.2±0.2	3.5±0.2	0.65±0.2	97.35±	0.8±0.5	3.0±0.5	10±0.2
9	F_9	5.3±0.3	3.5±0.2	0.62±0.2	98.22±	0.8±0.3	3.5±0.5	10±0.2

*values given in the table are the mean±SD of three replicate experiments (n=3)

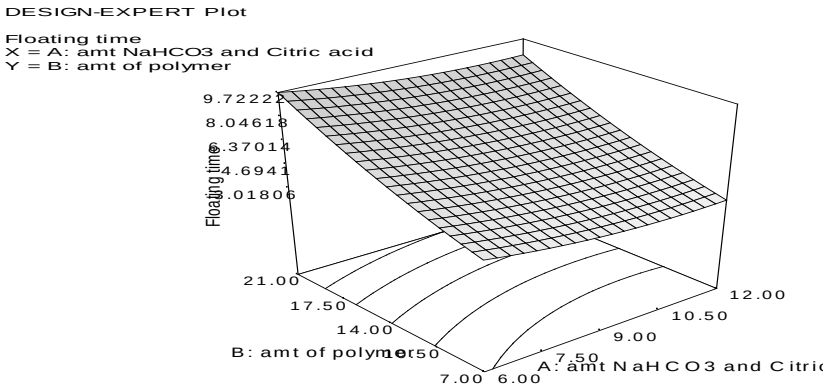

Fig. 2: Response surface plot showing an effect of independent variables (A and B) on response FT (Y)

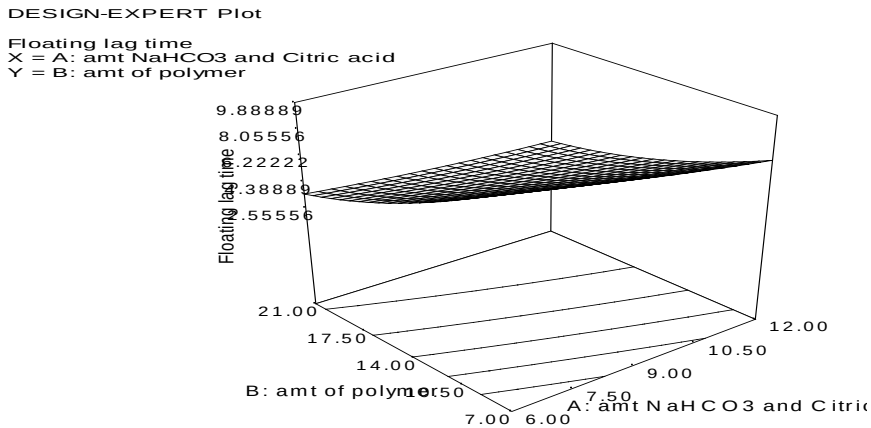

Fig. 3: Response surface plot showing an effect of independent variables (A and B) on response FLT (Y)

In vitro drug release study

Sustained drug release was observed for F_8, F_9 formulations in 0.1 N HCl (fig. 4). The assay of tablets revealed that the total GP content of the F_9 tablet was found to be 94.48% and for F_8 found to release 97% of active constituents in 12 h. Slow drug release is because of swelling of HMPC K4M that delays drug release from the tablet matrix. As a result of the rheology of hydrated product, the swollen particles coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium tablets containing a higher amount of HPMC K4M.

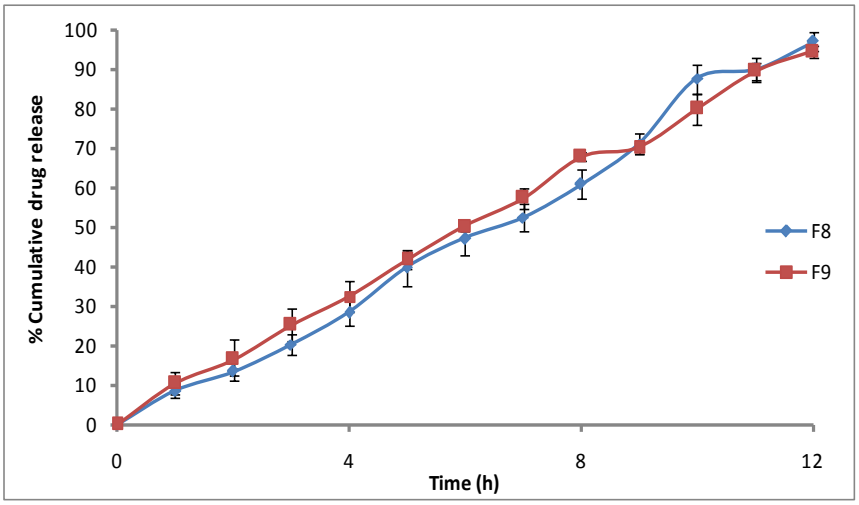

Fig. 4: *In vitro* drug release of FMT formulations F_8 and F_9 (mean±SD of three replicate experiments)

Gastro retentive dosage forms are developed to deliver the drug in gastric region. The main intention of this dosage form is to retain drug in a gastric environment for a longer period of time with control release of drug to obtain the desirable local action or drug absorption.

Drug release mechanism

A decrease in release kinetics of the drug was observed by increasing the polymer concentration.

The *in vitro* drug release profile was applied in different mathematical models and was interpreted in the form of graphical presentation and evaluated by the correlation coefficient (R^2) represented in table 4. The highest degree of correlation coefficient determines the suitable mathematical model that follows drug release kinetics [16].

It was concluded that the optimized formulations F_8 and F_9 followed zero order release

Evaluation of tablet coating film

The thickness of the non-enteric film coated FMT was found to be 5.2 mm with hazy appearance having 30% water vapour permeability.

Stability studies

The accelerated stability studies at 40 °C/75% RH were performed on formulation F_8 as per the protocol. Drug content, FT, FLT, hardness and thickness were tested at periodic time intervals. As shown in table 5, F_8 formulation was found to be stable for the tested period under the accelerated storage conditions

Table 4: Results of different models in terms of R^2, slope and intercept for F_8 and F_9.

Model name	F_8			F_9		
	R^2	Slope	Intercept	R^2	Slope	Intercept
Zero order model	0.993	8.330	2.557	0.997	7.895	1.541
First order model	0.8322	-0.4206	2.1673	0.9212	-0.3808	2.1079
Higuchi model	0.991	47.823	0.000	0.9916	48.976	0.0000
Korsmeyer-Peppas model	-4.156	3.1562	0.000	-4.09	3.1875	0.0000
Hixson-Crowell model	0.9586	0.8122	0.0213	0.9897	0.7911	0.0416

Kinetics as it showed the highest linearity ((R^2 = 0.993 and R^2 = 0.997) respectively. Also, the model Korsmeyer-Peppas power law equation states the type of diffusion, which was evaluated by value, n which is higher than 0.89 which implies that the drug release from the system follows Super case II transport [16].

Table 5: Physicochemical analysis of formulation F_8 during stability study

Time interval	Thickness* (mm)	Hardness* (kg/cm²)	FLT* (min)	FT* (h)	Weight variation*%	Drug content* %
Initial	5.3±0.2	3.5±0.5	3.5±0.5	10±0.5	0.62±0.1	85.09±0.8
1 Mo	5.3±0.3	3.5±0.3	3.5±0.8	10±1.5	0.62±0.2	85.09±0.2
2 Mo	5.3±0.5	3.5±0.5	3.7±0.4	10±0.5	0.62±0.1	84.90±0.5
3 Mo	5.3±0.4	3.5±0.5	3.7±0.5	10±0.5	0.62±0.3	84.78±0.3

*Values given in the table are the mean±SD of three replicate experiments (n=3), t-test was performed to verify if any statistically significant changes are noted in tested stability samples against the initial sample. However, there was no significant change in all the parameters during the stability study against initial values.

CONCLUSION

From the study, it was concluded that a stable, sustained release, FMT formulation of GP was successfully prepared. This formulation can overcome problems of taste and odour masking, gastric irritation and loss of active constituents present in garlic. A twice-a-day dosing of the GP tablet (preceded by an antacid) can be a viable substitute to the standard triple therapy for the treatment of peptic ulcers. This formulation may be used in clinical trials to confirm the therapeutic properties of garlic, especially antibacterial activity against *H. pylori* as it is the most reliable dosage form to reap all benefits of garlic.

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AUTHORS CONTRIBUTIONS

I designed and executed the research work

CONFLICT OF INTERESTS

Declared none

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