Development and Optimization of Methscopolamine Bromide Gastroretentive Floating Tablets Using 3^2 Factorial Design

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ABSTRACT

Purpose The aim of this study was to formulate methscopolamine floating drug delivery system to increase its gastro retention for further enhancement of absorption and overall bioavailability.

Method Direct compression method was used to formulate floating drug delivery system of methscopolamine bromide**.** Different amount of HPMC, PVP K25, and MCC were used for preparation of tablets.

Result The prepared tablets were evaluated for thickness, hardness, weight variation, floating lag time, swelling index and in-vitro drug release. All the formulations showed less than 10 % of weight variation. The hardness and thickness of all the formulations were within the range of 3.7 – 4.2 kg/cm^2 and 3.63 – 3.83 mm respectively. Floating lag time for all the formulations was reported in seconds. The degree of swelling was reported in range of 82.10 – 85.83 %. In vitro release was carried out for 24 h. The maximum release was shown by F1 (93.947 %) while the minimum release was observed for F4 (90.420 %). The best formulation was optimized on the basis of percentage cumulative drug release, floating lag time and swelling index. F1 found to be the best formulation. Further on analyzing the drug release mechanism, F1 found to exhibit korsmeyer peppas model of drug release.

Conclusion Floating gastroretentive tablet of methscopolamine bromide was successfully developed using direct compression method with potential to enhance the drug absorption and effective treatment of peptic ulcer.

Introduction

A quaternary ammonium derivative of scopolamine named methscopolamine bromide belongs to the class of anticholinergic drugs that inhibits gastric acid secretion. The drug acts by blocking the muscarinic acetylcholine receptors [1] and thus is used effectively for the treatment of peptic ulcer. The quaternary ammonium derivatives show limited absorption of 10 – 25 % [2]. Thus, this poor absorption hinders the efficacy of methscopolamine bromide.

Floating drug delivery system is an approach by which we could retain the drug in stomach for longer period of time to achieve sufficient drug absorption [3–6]. When compared to the aqueous medium the system offers lower bulk density that helps the drug delivery system to float in the gastric fluid. Several approaches like mucoadhesive system, swelling system, high density system, magnetic system and floating system have been developed to increase the residence time of drug in stomach [7–9].

However each of this system seems to offer some drawback like drug induced injuries that may range from local irritation to perforation may occur as a result of mucoadhesive system. On the other hand, patient may suffer from serious implications due to accumulation of swelling system in the stomach [10]. Floating drug delivery system is therefore selected in this research to achieve the desired aim.

Gastric retention will prolong the residence time of the drug in stomach that will eventually results in greater and prolong therapeutic effect. This system will also overcome the problem of frequent dosing associated with the conventional dosage forms and can be used effectively for local stomach disorders [11]. Further this system requires simple and conventional equipment for manufacture and is also suitable for the drugs that are unstable or insoluble at intestinal pH and have absorption window at stomach [12]. After ingestion, these formulations remain confined to the gastric region and releases drug in a sustained and prolonged manner to maintain a continuous supply of the drug to its absorption site in the upper gastrointestinal tract [13, 14].

Thus the motto of this research was to develop a drug delivery system (floating drug delivery system) that will help to retain the drug in stomach for a longer period of time for improving its absorption properties.

Materials and Methods

Materials

Methscopolamine Bromide (assigned purity 99 %) was provided as a gift sample by Alkaloids Private Limited, Kolkata (India). HPMC, MCC and PVPK25 were procured from Thermo Fischer Scientific India Pvt. Ltd.(Mumbai, India)

Methods

Melting point determination

Capillary tube was used to determine the melting point of methscopolamine bromide. The melting point of an organic solid can be determined by introducing a tiny amount into a small capillary tube, attaching this to the stem of a thermometer centered in a heating bath, heating the bath slowly, and observing the temperatures at which melting begins and is complete

Infrared spectral analysis

Infrared spectral analysis is analytical tool to determine the presence of functional group in chemicals. It is identical tool to check authentication of drug. The IR spectra in transmission mode were obtained using KBr disc method in the spectral region 500 – 4000 cm^{-1} (Shimadzu FTIR spectrophotometer), using a resolution of 2 cm^{-1}. Obtained spectrum was compared with reference spectrum of methscopolamine bromide.

Drug polymer stability study

The preliminary interference study was carried out to eliminate the possibility of interaction of methscopolamine bromide with polymers like HPMC and MCC. The drug was kept with each of the above polymers in 1:1 ratio in a humidity chamber at a temperature of 40 ± 20 °C and 65 ± 5 % relative humidity (RH) for one month. The samples were analyzed using FTIR spectroscopy. Pure drug and pure polymers were also kept in similar conditions and analyzed by IR spectroscopy.

Experimental design

A 3^2 randomized factorial design was used and two factors at three levels; were evaluated by experimental trials of nine possible combinations. The concentration of HPMC K15M (X1) and MCC were selected as independent variables as depicted in (▶**Table 1**). Percent swelling index and percent cumulative drug release was taken as dependent variables. The resulting data was fitted into Design-Expert Software (version 12.0 Stat-Ease, Inc., Minneapolis, MN) and analyzed statistically. The 3D response plots were generated to estimate simultaneous influence of HPMC and MCC on dependent variables.

Preparation of floating drug delivery system

The floating tablets were prepared by direct compression method [15]. Methscopolamine bromide, HPMC, PVP K25, and MCC were weighed, sieved through sieve no. 60 separately and homogeneously mixed with each other for half an hour in mortar pestle. Aerosil and Magnesium stearate were mixed at last. The homogeneous blend was then compressed by single punch manual tablet punching machine. The detailed composition of the tablet is detailed as underneath in ▶**Table 1**.

Evaluation parameters for the prepared formulations

Pharmaceutical general parameters for tablet

The prepared tablets were evaluated for official and unofficial parameters of tablets including thickness by Vernier calipers, hardness by Monsanto tester, friability by Roche fibriliator, weight variation and uniformity of content [16–18].

▶**Table 1** 3^2 full factorial design of methscopolamine bromide floating tablets.

Formulation Code	Drug	X1 = HPMC (mg)	X2 = MCC (mg)	PVP K25	Dependent variables
F1	5	55 (−1)	30 (+1)	6	
F2	5	75 (+1)	20 (0)	6	Degree of Swelling
F3	5	65 (0)	20 (0)	6	
F4	5	75 (+1)	10 (−1)	6	
F5	5	75 (+1)	30 (+1)	6	
F6	5	55 (−1)	10 (−1)	6	Percentage Cumulative Drug release
F7	5	65 (0)	10 (−1)	6	
F8	5	55 (−1)	20 (0)	6	
F9	5	65 (0)	30 (+1)	6	
F10	5	65 (0)	20 (0)	6	

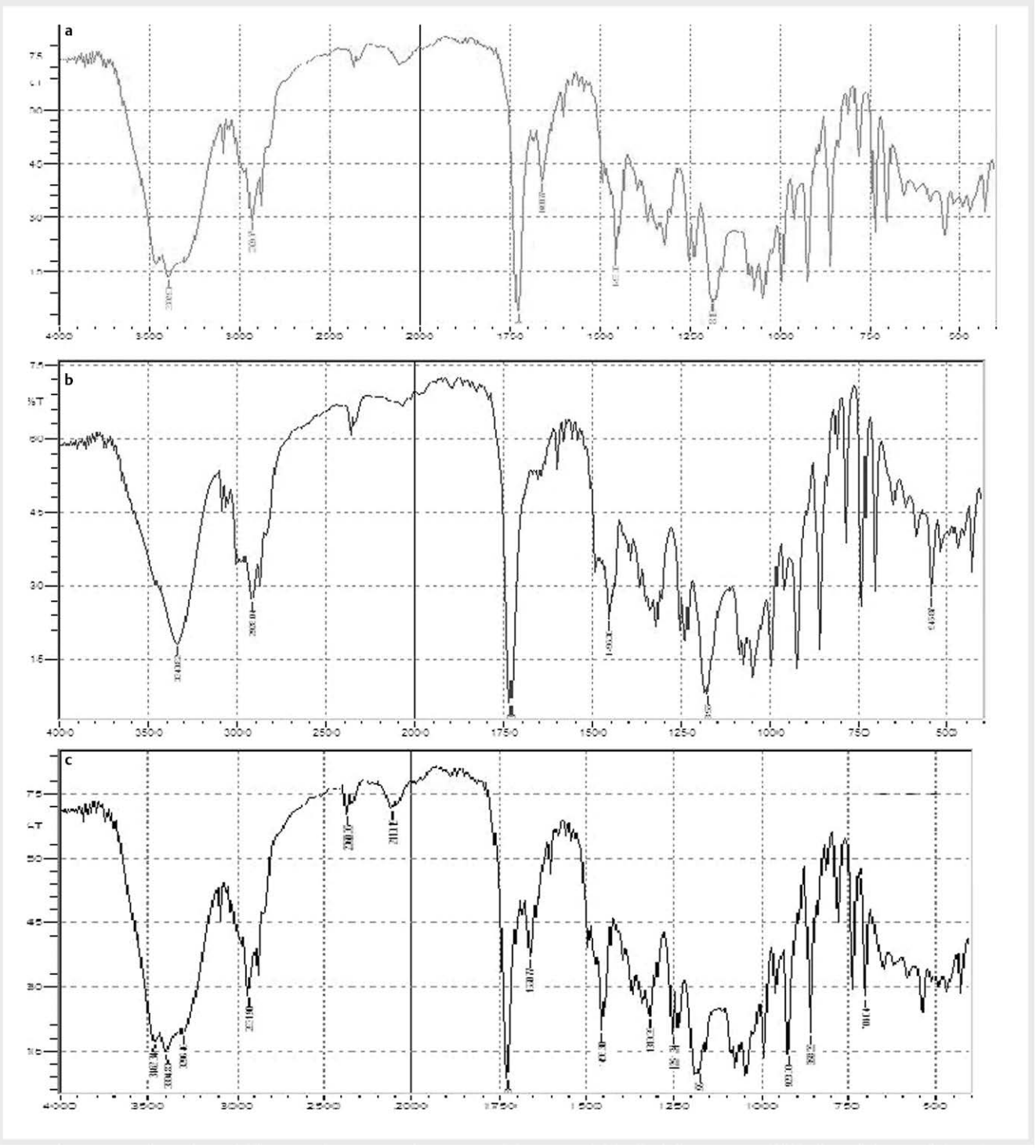
The tablets were further evaluated for their ability to float in the gastric environment by carrying out further evaluation parameters including:

In-vitro buoyancy test

The time taken by the tablet to rise to the surface of the liquid medium and floating lag time (FLT) was noted. The FLT was determined by placing the tablet in 200 ml glass beaker containing 100 ml 0.1N HCl (pH1.2) at 37 °C [19–21].

Total Floating Time (TFT)

The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT)



▶ **Fig. 1** Drug polymer compatibility study **a** Drug, **b** Polymer and **c** Mixture.

[19–21]. The TFT was determined by placing the tablet in 250 ml glass beaker containing 200 ml 0.1N HCl (pH1.2) at 37 °C.

Swelling index

Swelling of hydrophilic polymer such as Hydroxy Propyl Methyl Cellulose greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually influence the release of the drug from the formulation and also the residence time of the formulation in the stomach. One tablet was weighed and placed in a beaker containing 200 ml of distilled water [11]. After each hour the tablet was removed from beaker and weighed again. This procedure was continued until constant weight was observed. The percentage weight gain by the tablet was calculated by using the formula.

$$S.I = Wt–Wo/Wo \times 100$$

Wt = Weight of tablet at time t
Wo = Weight of tablet before immersion

In vitro release studies

In vitro drug release study of formulations were carried out according to USP dissolution apparatus USP XXII with using 900 ml 0.1N HCl (pH1.2) solution at 37 ± 0.5 °C with 50 rpm. 10 ml of aliquot was withdrawn from the dissolution medium at specified time interval and dissolution media was replaced by fresh media. Dissolution studies were continued up to 24 h. Samples were withdrawn and analyzed spectrophotometrically with addition of 0.1 ml sodium picrate solution [22, 23].

Analysis of drug release mechanism

The release mechanism of methscopolamine bromide from prepared non effervescent floating tablets was determined by using different kinetic models like zero order, first order, Higuchi model, Korsmeyer-Peppas model.

Result and Discussion

Drug polymer compatibility study

Drug polymer interference study was carried out to eliminate the possibility of interaction of drug with polymer. FTIR of all the samples were recorded (▶ **Fig. 1**). No predominant drug interaction was detected between drug and polymers along with excipients.

Physical evaluation of floating tablets

All the tablets of different batches were subjected to various evaluation tests such as thickness, hardness, friability, weight variation and drug content. The results are tabulated in ▶ **Table 2**. It was illustrated by the results that the formed tablets were within the limits prescribed as per weight variation test and uniformity of content test as prescribed by USP. The hardness of all the formulations was found to be in range of 3.7 – 4.2 kg/cm^2. Average thickness was found to be in the range of 3.63 – 3.83 mm and the tablets also passed the friability test as the weight loss of tablets were less than 1 %.

Buoyancy studies

The floating lag time was estimated in seconds for all the batches showing negligible lag time. The variation in total floating time was observed for the different batches. (▶ **Table 3**). With increase in the concentration of HPMC the total floating time was found to be increased. This increase in total floating time with concentration of polymer may be attributed to increase in swelling characteristics due to the entrapment of air [24, 25]. Further in vitro release studies were performed to select the best formulation.

Swelling studies

Appropriate swelling property for FDDS was required for uniform and prolonged release of drug. The floating time and drug release profile were dependent upon swelling behavior of the tablets. Swelling index was calculated with respect to time. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration along with polymer concentration as shown in ▶ **Table 4**. After 10 h no further increase in swelling index was observed. The extensive swelling of formulations will create a thick gel barrier, which retards and increases the path length for the diffusion of the drug molecules. It was found from the studies and confirmed by the design expert software also that selling index was directly proportional to the concentration of HPMC used in the formulation and MCC played a very much negligible role with slight decrease in swelling with increase in concentration as can be seen from ▶ **Table 4** where considering the amount of HPMC (X_1) con-

▶ **Table 2** Physical evaluation of methscopolamine bromide floating tablets.

Formulations	Weight variation ± S.D (n = 20)	Hardness ± S.D (n = 3)	Percentage friability (n = 6)	Percentage drug content ± S.D (n = 3)	Thickness ± S.D (n = 3)
F1	120.2 ± 5.8	3.8 ± 0.03	0.718	98.22 ± 0.07	3.82 ± 0.03
F2	121.2 ± 4.3	3.9 ± 0.09	0.702	98.01 ± 0.06	3.73 ± 0.05
F3	119.7 ± 4.9	4.0 ± 0.07	0.689	97.27 ± 0.01	3.77 ± 0.04
F4	119.9 ± 4.7	3.8 ± 0.12	0.722	97.55 ± 0.05	3.69 ± 0.05
F5	118.5 ± 5.8	3.8 ± 0.03	0.721	96.23 ± 0.06	3.67 ± 0.03
F6	120.1 ± 5.2	3.7 ± 0.09	0.719	95.21 ± 0.29	3.78 ± 0.06
F7	119.7 ± 4.9	4.0 ± 0.07	0.694	94.38 ± 0.04	3.71 ± 0.05
F8	120.2 ± 7.5	3.9 ± 0.06	0.713	93.45 ± 0.07	3.75 ± 0.04
F9	119.9 ± 6.3	3.9 ± 0.06	0.718	93.89 ± 0.10	3.69 ± 0.03
F10	121.1 ± 3.2	3.9 ± 0.09	0.716	96.34 ± 0.05	3.81 ± 0.06

▶ **Table 3** Floating Lag Time (FLT) and Total Floating Time (TFT) of different formulations.

Formulations code	Floating lag time (sec)	Total floating time
F1	0	>20 h
F2	2	>24 h
F3	0	>22 h
F4	4	>24 h
F5	3	>22 h
F6	0	>21 h
F7	5	>23 h
F8	4	>22 h
F9	0	>21 h
F10	0	>22 h

▶ **Table 4** Optimization of data for selection of best formulation.

Formulation Code	X_1 = HPMC (mg)	X_2 = MCC (mg)	Y_1 Degree of swelling (%)	Y_2 Cumulative drug release (%)
F1	55 (−1)	30 (+1)	82.10	93.947 ± 2.1
F2	75 (+1)	20 (0)	85.67	90.635 ± 0.52
F3	65 (0)	20 (0)	84.09	92.660 ± 0.80
F4	75 (+1)	10 (−1)	85.83	90.420 ± 0.40
F5	75 (+1)	30 (+1)	85.52	90.865 ± 0.90
F6	55 (−1)	10 (−1)	82.39	93.102 ± 1.8
F7	65 (0)	10 (−1)	84.26	92.435 ± 1.5
F8	55 (−1)	20 (0)	82.25	93.525 ± 1.2
F9	65 (0)	30 (+1)	83.94	92.825 ± 2.5
F10	65 (0)	20 (0)	84.09	92.660 ± 0.80

stant and increasing the amount of MCC (X_2) as can be seen in batches F2, F4 and F5.

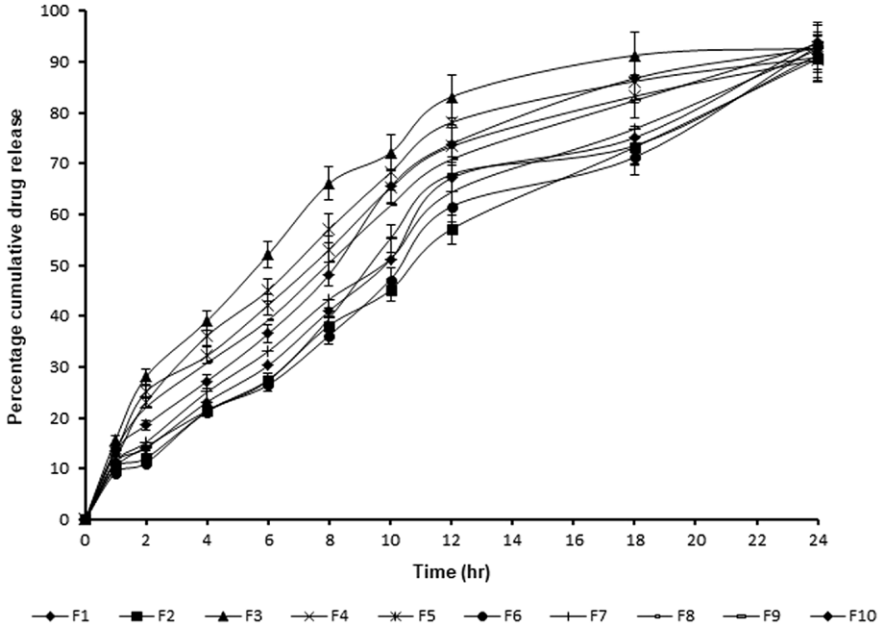
In vitro release studies

In vitro dissolution studies were carried out as per USP procedure by using 900 ml 0.1N HCl solution at 37 ± 0.5 °C and the paddles were rotated at 50 rpm. Under fasted conditions, housekeeper waves clear the digested material from the stomach every 1.5–2 h [15]. When the tablet was taken orally, it remains in the stomach for 2 h and then expelled in the intestine. In case of floating tablets, release of drug was controlled. These studies were carried out for 24 h. In all the formulations the amount of drug was kept constant i. e. 5 mg which was the dose of the drug for controlled release. The concentration of HPMC plays a significant role in determining the rate of release from the floating tablets. It was found and is clear from ▶ **Table 4** that the release rate of drug decreases with increase in concentration of HPMC. As evident from the table comparing formulation F4, F6 and F7 containing constant amount of MCC and varying concentration of HPMC, it was found that the release rate decreased with increase of HPMC concentration (▶ **Fig. 2**).

The above results clearly revealed that an increase in amount of HPMC has a slight effect on drug release. The reason may be the formation of denser hydrogel network which offers more hindrance to the drug release. Also due to extensive swelling with increase and diffusion path length with increase in concentration of polymer may lead to lower cumulative percentage release of drug.

Optimization of formulations

Optimization of prepared batches was done on the basis of floating lag time, swelling index and percentage drug release. An optimized formulation is defined as the one which was having minimum



▶ **Fig. 2** Comparative in vitro drug release versus time graph.

floating lag time, minimum swelling index and maximum drug release. Formulation F1 was found to exhibit all the desired properties of an optimized formulation (▶ **Table 5**).

Analysis of release mechanism of optimized formulations

All the formulations were subjected to zero order, first order, korsmeyer peppas model, higuchi model to examine the mechanism of drug release. In case of formulations F1 was found that the drugs release mechanism following the korsmeyer peppas model. The n value in case of korsmeyer peppas model suggested whether the diffusion was fickian or non-fickian. The result suggested that drug release from two formulations (F6 and F9) followed fickian diffusion (▶ **Table 5**.) and rest followed non fickian anomalous transport. This shows that both fickian diffusion and non fickian diffusion play an important role in controlling the drug release

A statistical model with individual and interactive terms in the form of second order polynomial equation was used to evaluate the response variables: where X_1(HPMC) and X_2(MCC) are independent variables and Y is the dependent variable. The terms including A and B represent the effect of single factor on the response variable on going from lower level toward higher, while the interactive terms (AB) show the combined effect of the two independent variables on the response parameter. The mathematical equation generated for the quantitative response parameters are expressed as:

$$\text{Cumulative Release} = +92.65 - 1.44\,X1 + 0.2800\,X2 - 0.1000\,X1X2 - 0.5609\,X1^2 - 0.0109\,X2^2 \quad (3)$$

$$\text{Degree of swelling} = +84.09 + 1.71\,X1 - 0.1533\,X2 - 0.0050\,X1X2 - 0.1357\,X1^2 + 0.0043\,X2^2 \quad (4)$$

In Equation (4) negative sign of coefficient of A (X_1) indicates inhibitory effect on the response, and the large magnitude of coefficients showed that the factors pronouncedly reduces the drug release while positive sign of factor B (X_2) indicates positive effect. In Equation (4) the positive sign indicates that HPMC K15M had positive effects on degree of swelling but the negative sign indicates negative impact on degree of swelling of factor B.

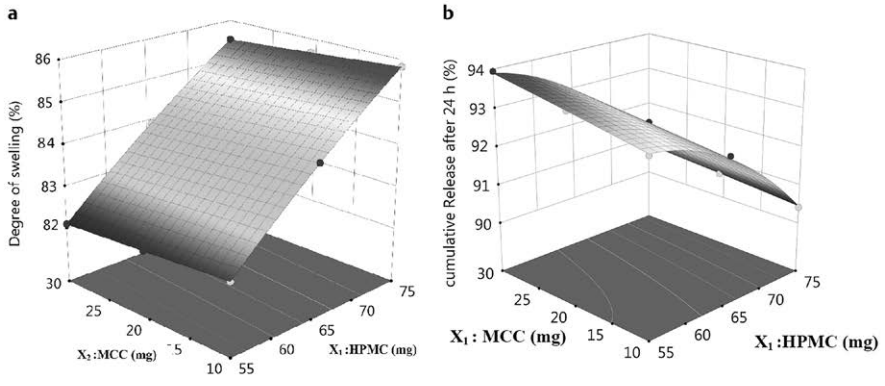
The relationship between variables was further elucidated using response surface plots. 3D bar surface chart drawn for graphical optimization of floating drug delivery system clearly shows the effect of independent variables MCC and HPMC K15M level on the response variables. It was observed that on increasing the levels of HPMC (X_1) and MCC (X_2) simultaneously, the degree of swelling increased in a significant form (▶ **Fig. 3b**). While simultaneous increment of HPMC K15M and MCC has profound inhibitory effect on the drug release from the formulations (▶ **Fig. 3a**).

▶ **Table 5** Regression coefficient values for different release mechanism for developed GRDDS formulations.

Formulation code	Zero order	First order	Higuchi model	Korsmeyer Peppas model
	Regression coefficient (R^2)			
F1	0.792	0.832	0.949	0.920
F2	0.689	0.794	0.923	0.938
F3	0.714	0.728	0.921	0.932
F4	0.681	0.782	0.913	0.929
F5	0.721	0.782	0.937	0.923
F6	0.683	0.832	0.743	0.891
F7	0.745	0.632	0.823	0.937
F8	0.693	0.771	0.895	0.938
F9	0.785	0.821	0.762	0.754
F10	0.693	0.732	0.848	0.932

Conclusion

In the present work floating gastroretentive tablets of methscopolamine using different grades of HPMC were developed. The developed system with enhanced bioavailability will serve as a potential for treatment of peptic ulcer and other stomach related disorders. The tablets were prepared using direct compression method and subjected to various evaluation parameters. Among the various prepared formulations using different HPMC grade, F1 showed best results with respect to floating lag time, swelling index and in vitro drug release.



▶ **Fig. 3** Surface Response Plot **a** Degree of swelling and **b** Percentage Cumulative drug released.

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Conflict of Interest

The authors declare that there are no personal or financial conflicts of interest with individuals or organizations

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