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Research Article

Development and Evaluation of Sustained Release Gastroretentive Minimatrices for Effective Treatment of *H. pylori* Infection

Atul C. Badhan,[1,2] Rajashree C. Mashru,[1] Punit P. Shah,[1] Arti R. Thakkar,[1] and Nitin B. Dobaria[1]

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Abstract. In the present work, sustained release gastroretentive minimatrices of amoxicillin have been designed and optimized using central composite design. Effect of amount of xanthan gum, rate controlling polymers (HPMC K100M CR/PEO coagulant (1:1)), carbopol 974P, and gas generating couple (sodium bicarbonate/citric acid (3:1)) was studied on dependent (response) variables, i.e., buoyancy lag time, drug release at 1 h, time required for 95% drug release, swelling index, and bioadhesive strength. Minimatrices were prepared by non aqueous granulation method using solution of PVP K30 in isopropyl alcohol. All the formulations were found to contain 99.2% to 100.9% of amoxicillin per minimatrix. Optimum formulation (Formulation number AGT09) containing high level of the independent variables was having buoyancy lag time of 7 min and drug release at 1 h was 32.5%. It required 9.39 h for 95% drug release while swelling index and bioadhesive strength were 341 and 17.9 dyn/cm^2, respectively. This formulation was said to be optimum because it has minimum buoyancy lag time, requires maximum time for 95% drug release, and has higher bioadhesive capabilities. *In vitro* results of an optimized formulation indicate its sustained drug release and gastric retention capability, which may be very useful for effective treatment of *H. pylori* infection.

KEY WORDS: central composite design; gastroretentive drug delivery system (GRDDS); *Helicobacter pylori* (*H. pylori*).

INTRODUCTION

For certain drug candidates, prolonging the gastric retention is desirable for achieving greater therapeutic benefit. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract (1) and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention (2–4). In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy and possible reduction of dose size (5–7).

Since its discovery in 1982 by Warren and Marshall (leading to their recent Nobel Prize in Medicine) and its confirmation as a pathogen at the end of the 1980s, researchers have attempted in several ways to efficiently eradicate *Helicobacter pylori* from the stomach. It is well known that long lasting *H. pylori* infections can lead to severe diseases such as gastric cancers and mucosa-associated lymphoid tissue lymphomas. In most countries, *H. pylori* infection is associated with a four- to sixfold increased risk of gastric cancer. This means that the majority of gastric carcinomas in the world are related to *H. pylori* infection (8,9). Since 1994, the International Agency for Research on Cancer and the World Health Organization has been considering that *H. pylori* infection is carcinogenic to humans (group 1 carcinogen). Because of the high level of antibiotic resistance to *H. pylori* and the poor patient compliance, new medicines with better effectiveness and simpler regimens are required. It has been suggested that prolonged local availability of antibacterial agents may augment their effectiveness in treating *H. pylori* infection (10). In particular, *H. pylori* lives deep within the gastric mucus layer, and prolonged local application of drug is needed for its sufficient diffusion to the bacteria. A logical way to improve the effectiveness of therapy is to develop a drug delivery system which can reside in the stomach for longer duration and release drug as long as possible in the ecological niche of the bacterium (11), and Gastroretentive Drug Delivery System (GRDDS) is an ultimate solution for this.

Extensive efforts have been made in both academia and industry towards the development of GRDDS (7). These efforts resulted in GRDDS that were designed in large part based on various approaches which include (a) low density dosage form that causes buoyancy above gastric fluid (12); (b) high density dosage form that is retained in the bottom of the stomach (13); (c) bioadhesion to the stomach mucosa (14,15); (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients (16); (e) expansion by swelling or unfolding to a large size

[1] Centre of Relevance and Excellence in Novel Drug Delivery systems, Pharmacy Department, The M.S. University of Baroda, Fatehgunj, Baroda 390002, India.
[2] To whom correspondence should be addressed. (e-mail: atulbadhan@rediffmail.com)

which limits emptying of the dosage form through the pyloric sphincter (17).

An important discrepancy has always been noted between the very potent activity of amoxicillin against *H. pylori* when tested *in vitro* by conventional methods such as the minimum inhibitory concentration method and the results of *H. pylori* eradication *in vivo*. Eradication is achieved only in approximately 10% to 20% of cases. *H. pylori* infection is a mucosal infection, with bacteria lying in the mucous layer and being strongly attached to the cells. This attachment could modify the susceptibility of bacteria to antibiotics. Moreover, *H. pylori* lives in an environment which does not seem to be favorable to phagocytic cells and therefore, a bactericidal instead of a bacteriostatic effect must be considered (18).

Conventional drug delivery systems cannot maintain effective drug concentration for longer time in stomach due to their short gastric residence time. Hence, objective of the present research work was to develop a GRDDS in the form of minimatrices of amoxicillin. Multiparticulate drug delivery systems usually based on subunits such as minimatrices, granules, or pellets show numerous advantages over monolithic devices (undivided forms) such as higher degree of dispersion in the gastrointestinal tract and reduced risk of systemic toxicity due to dose dumping (19,20). Due to unpredictable gastric emptying associated with migrating myoelectric complex motility pattern, multiparticulate systems are more advantageous than the single unit systems, as the later ones experience ''all or none'' emptying pattern from the stomach (13). Advantageously, minimatrices mostly having a diameter of 2–3 mm can be manufactured with higher reproducibility compared to pellets, especially, regarding their weight and equal dimension (21). The amoxicillin minimatrices developed in the present work would have longer gastric residence time due to floating as well as gastric mucoadhesive property.

Table I. Formulation Designing by Central Composite Design

	Factor levels[a]			
Formulation no.	X_1	X_2	X_3	X_4
AGT 01	0	0	−1.48	0
AGT 02	1	1	−1	1
AGT 03	1	−1	−1	1
AGT 04	0	0	0	−1.48
AGT 05	−1	−1	1	−1
AGT 06	0	0	0	0
AGT 07	1	−1	1	1
AGT 08	0	0	0	1.48
AGT 09	1	1	1	1
AGT 10	0	−1.48	0	0
AGT 11	−1	1	1	−1
AGT 12	1	1	1	−1
AGT 13	−1	1	1	1
AGT 14	−1	−1	−1	−1
AGT 15	0	0	0	0
AGT 16	−1	1	−1	1
AGT 17	1	−1	1	−1
AGT 18	0	1.48	0	0
AGT 20	1.48	0	0	0
AGT 19	1	1	−1	−1
AGT 21	1	−1	−1	−1
AGT 22	−1	−1	1	1
AGT 23	−1.48	0	0	0
AGT 24	−1	1	−1	−1
AGT 25	−1	−1	−1	1
AGT 26	0	0	1.48	0

[a] −1.48, −1, 0, 1, 1.48 are the coded values for level of formulation variables

Table II. Coded Values and Actual Values of Formulation Variables in Central Composite Design

	Actual values[a]			
Coded values	X_1	X_2	X_3	X_4
−1.48	6.83	4.55	4.55	2.28
−1	9	6	6	3
0	12	9	9	4.5
1	18	12	12	6
1.48	20.17	13.45	13.45	6.72

[a] Actual values indicate % *w*/*w* of final weight of minimatrix

MATERIALS AND METHODS

Materials

Amoxicillin trihydrate was received as a gift sample from Aristo Pharmaceuticals Ltd. (Mumbai, India). Polyethylene oxide (PEO) coagulant and hydroxypropylmethylcellulose (HPMC) K100M CR were gifted by Colorcon Asia Pvt. Ltd. (Goa, India). Microcrystalline cellulose (Avicel PH102) and Carbopol 974P were obtained from Signet Chemical Corporation (Mumbai, India) and BF Goodrich Co. (Clevelend, OH), respectively. Xanthan gum, talc, magnesium stearate, and polyvinylpyrrolidone (PVP) K30 were purchased from S. D. Fine Chemicals (Mumbai, India). Sodium bicarbonate, citric acid, and isopropyl alcohol were purchased from Qualigens Fine Chemicals (Mumbai, India).

Methods

Experimental Design

Design of experiment has been widely used in pharmaceutical field to study the effect of formulation variables and their interaction on dependent (response) variables (22–24). In the present study, central composite design (orthogonal) was used for formulation designing and optimization. The experimental design consists of total 26 experiments (see Table I), which include 16 factorial, eight axial, and two center points. Level of xanthan gum (X_1), rate controlling polymers (HPMC K100M CR/PEO coagulant (1:1)) (X_2), carbopol 974P (X_3), and gas generating couple (sodium bicarbonate/citric acid (3:1)) (X_4) were selected as formulation (independent) variables. The formulation variables and their levels as shown in Table II were chosen from the knowledge obtained from the preliminary studies in our laboratory. In addition to formulation variables, each minimatrix contained amoxicillin trihydrate 40.97% *w*/*w* (equivalent to 12.5 mg of amoxicillin), PVP K30 5% *w*/*w*, talc 0.5%

w/*w*, magnesium stearate 0.5% *w*/*w*, and microcrystalline cellulose as diluent to adjust final weight to 35 mg.

Buoyancy lag time (Y_1), drug release at 1 h (Y_2), time required for 95% drug release (Y_3), swelling index (Y_4), and bioadhesive strength (Y_5) were studied as response (dependent) variables.

All the response variables were fitted to quadratic model and regression analysis was carried out to get a quantitative relationship between dependent and the analyzed independent variables. The equation can be given as

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{11}X_{12} + b_{22}X_{22} + b_{33}X_{32} + b_{44}X_{42} + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{14}X_1X_4 + b_{23}X_2X_3 + b_{24}X_2X_4 + b_{34}X_3X_4 \quad (1)$$

where b_0 is arithmetic mean of 26 runs; b_i is an estimated coefficient for factors X_1, X_2, X_3, and X_4. All experimental results were computed by statistical software DOE v6.0.5 (Stat-Ease Inc., Minneapolis, MN, USA). Response surface plots, showing effect of formulation variables on various response variables, were generated using JMP software v5.1 (SAS Institute Inc., Cary, NC, USA)

Preparation of Minimatrices

Required quantities of amoxicillin trihydrate, xanthan gum, PEO coagulant, HPMC K100M CR, sodium bicarbonate, citric acid, and microcrystalline cellulose (Avicel PH102) were properly mixed and passed through sieve no.30 (Jayant Scientific Sieves, Mumbai, India). PVP K30 solution (5% *w*/*v*) was prepared by dissolving it in isopropyl alcohol. This solution was slowly added to dry powder blend and kneading was done by hand to obtain a granular mass of sufficient strength. Granulated mass was air dried at room temperature for 15–20 min and then was dried at 40°C for 20 min in tray dryer (Shree Kailash Industries, Baroda, India). Dried mass was passed through sieve no. 30 and resultant granules were lubricated by adding carbopol 974P, talc, and magnesium stearate. All the lubricants were previously passed through sieve no. 40. Bulk density of the lubricated granules was determined by using density test apparatus (Electrolab, Mumbai, India) and angle of repose was determined by funnel method.

Lubricated granules were compressed into minimatrices on eight station rotary tablet compression machine (General Machinery Co., Mumbai, India) using 4-mm circular multi-tip punches. Compressed minimatrices were evaluated for weight variation, thickness, hardness, and friability as in process quality control parameters.

Drug Content

UV spectrophotometric method (UV-1700, Pharmaspec, Shimadzu, Japan) was developed for estimation of amoxicillin content. This method was validated for linearity, specificity, accuracy, and precision. Twenty minimatrices were finely powdered. Powder equivalent to weight of one minimatrix was taken in 100-ml volumetric flask. About 70–80 ml of 0.1 N HCl was added to it and sonication (Vetra, Italy) was done for 20 min. Volume was made up to 100 ml. The solution was filtered using Whatman filter paper type I and appropriate dilutions were done. Drug content was estimated at λmax of 229 nm.

Buoyancy Lag Time

It is the time interval between introduction of the minimatrices in the dissolution vessel to the time when these start floating towards the surface of dissolution medium. It was determined simultaneously during drug release study.

Drug Release Study

Drug release study was carried out in 900 ml of 0.1 N HCl at 37±0.5°C using USP type II dissolution test apparatus (VDA 6-DR, Veego Instruments Corporation, Mumbai, India) at 50 rpm. Sample (5 ml) was withdrawn at 1, 2, 3, 4, 6, 8, 10, and 12 h and was replenished with equal volume of dissolution medium. After suitable dilution, amount of drug released was estimated by UV spectrophotometric method at 229 nm.

Fluid Uptake Study

This study was carried out by a new and convenient method using the baskets of dissolution test apparatus. Five minimatrices were placed in a basket which was immersed in a Petri dish having 100 ml of 0.1 N HCl. Baskets were removed every hour, excess of the 0.1 N HCl was soaked by tissue paper and final weight was measured. The study was carried up to 12 h. Fluid uptake capacity was expressed as swelling index, and it was calculated by Eq. 2.

$$\text{Swelling Index} = [(W_2 - W_1)/W_1] \times 100 \quad (2)$$

where W_1=Initial weight of minimatrices and W_2=Weight of wet minimatrices at 12 h

Bioadhesion Study

This study was performed using Instron tensiometer (Instron 1121, UK). On the upper jaw of tensiometer, single minimatrix was stuck using adhesive tape and on the lower jaw goat stomach tissue (which was freshly collected from local slaughterhouse) was fixed. Upper jaw, having 10 g load cell, was lowered until it came in proper contact with the tissue and was kept as such for 20 s. Afterwards, upper jaw was moved in upward direction at speed of 5 mm/min until the minimatrix was completely detached from the tissue. During the test, goat stomach tissue was wetted by adding 20 µl of 0.1 N HCl. Force in dyn/cm^2 required for this detachment was measured.

RESULTS AND DISCUSSION

Evaluation of Granule Properties

For all the designed formulations, bulk density was found between 0.42 and 0.58 gm/cm^3. Angle of repose was between 30° and 40° which indicates good flow properties (25). Good flow properties are important for avoiding weight variation problems during compression of the minimatrices.

Table III. Values of the Response Variables

Formulation no.	Buoyancy lag time (min) ± SD[a] Y_1	Drug Release at 1 h (%) ± SD[a] Y_2	Time for 95%drug release (h) ± SD[a] Y_3	Swelling index ± SD[a] Y_4	Bioadhesion ($x10^3$ dyn/cm^2) ± SD[a] Y_5
AGT 01	17±1.0	43.4±0.98	4.39±0.36	345.8±10.74	6.8±0.26
AGT 02	16±2.6	41.1±0.95	5.93±0.16	501.2±20.91	7.9±0.36
AGT 03	12±1.0	45.1±0.89	4.51±0.10	317.2±5.79	7.2±0.26
AGT 04	32±2.0	46.3±1.21	4.42±0.14	342.2±12.43	9.3±0.44
AGT 05	21±2.0	48.6±1.39	4.44±0.22	204.9±8.36	12.9±0.26
AGT 06	15±1.0	45.6±1.85	4.44±0.27	296.6±5.98	10.1±0.46
AGT 07	10±2.0	38.1±1.11	6.25±0.19	453.9±13.30	12.2±0.61
AGT 08	8±1.0	46.9±1.64	4.45±0.20	329.5±8.11	9.7±0.46
AGT 09	7±1.0	32.5±1.93	9.39±0.17	341.0±16.46	17.9±0.52
AGT 10	19±2.0	47.1±2.00	3.34±0.22	258.6±8.81	9.2±0.40
AGT 11	23±2.0	42.2±1.82	7.58±0.23	200.2±3.99	15.3±0.70
AGT 12	22±2.0	35.2±1.49	9.20±0.16	412.6±12.25	17.1±0.44
AGT 13	14±1.7	39.5±1.32	7.88±0.55	179.1±5.20	16.9±0.26
AGT 14	25±2.6	53.3±1.75	3.31±0.08	314.0±11.52	7.0±0.26
AGT 15	15±2.0	45.6±1.28	4.44±0.11	296.6±12.50	8.9±0.44
AGT 16	18±2.0	48.1±0.92	5.86±0.14	215.5±5.25	8.7±0.26
AGT 17	21±1.0	40.9±1.83	6.21±0.16	443.0±20.32	17.5±0.40
AGT 18	16±3.0	42.3±1.87	5.85±0.56	393.2±7.51	11.8±0.53
AGT 19	21±1.7	38.5±1.21	7.47±0.45	382.5±6.72	11.2±0.50
AGT 20	22±2.0	31.9±1.56	5.94±0.19	466.8±20.91	8.2±0.30
AGT 21	24±1.0	45.2±0.95	4.51±0.16	423.7±12.13	7.1±0.26
AGT 22	15±2.6	49.2±0.90	4.36±0.44	225.5±11.08	10.2±0.26
AGT 23	18±1.0	50.6±1.41	4.33±0.20	159.0±5.13	8.8±0.36
AGT 24	22±1.0	47.3±0.79	5.97±0.18	289.3±12.93	8.3±0.40
AGT 25	14±1.0	52.6±1.87	3.32±0.14	250.3±6.97	7.0±0.26
AGT 26	16±1.7	45.4±1.14	6.90±0.17	310.0±6.70	18.2±0.78

[a] Values represent Average ± Standard Deviation of three experiments

Experimental Design

Preliminary experiments in the laboratory revealed that independent variables X_1 and X_2 play significant role in sustaining drug release while X_3 was important for maintaining matrix integrity, sustaining drug release and for its bioadhesive feature. Variable X_4 had prominent role for achieving minimum buoyancy lag time. Total buoyancy time depends on the overall entrapment of the gas in the matrix network formed by X_1, X_2, and X_3. Hence, these four

Table IV. Estimation of Regression Coefficients for Different Response Variables

Term	Y_1 EC	Y_1 Prob > F	Y_2 EC	Y_2 Prob > F	Y_3 EC	Y_3 Prob > F	Y_4 EC	Y_4 Prob > F	Y_5 EC	Y_5 Prob > F
b_o	16.80	–	45.36	–	4.12	–	310.40	–	9.17	–
X_1	−0.64	0.4007	−4.51	<0.0001	0.64	< 0.0001	90.84	< 0.0001	0.54	0.1197
X_2	-0.17	0.8220	-2.73	0.0007	1.28	< 0.0001	4.33	0.7316	1.28	0.0020
X_3	-1.00	0.1981	-2.06	0.0048	0.89	< 0.0001	-14.05	0.2781	3.55	< 0.0001
X_4	-5.32	< 0.0001	-0.20	0.7371	-0.06	0.5929	-10.07	0.4310	-0.38	0.2527
X_1^2	1.01	0.3657	-1.81	0.0565	0.54	0.0037	-2.34	0.8982	-0.22	0.6424
X_2^2	-0.13	0.9031	-0.24	0.7811	0.30	0.0693	3.57	0.8454	0.69	0.1623
X_3^2	-0.59	0.5921	-0.38	0.6647	0.78	0.0003	4.49	0.8068	1.60	0.0052
X_4^2	1.01	0.3657	0.62	0.4797	0.23	0.1564	8.10	0.6595	0.24	0.6200
X_1X_2	-0.19	0.8250	0.29	0.6720	-0.08	0.4792	6.88	0.6304	-0.13	0.7336
X_1X_3	-0.44	0.6076	-0.09	0.8971	0.18	0.1529	17.83	0.2260	0.44	0.2473
X_1X_4	-0.81	0.3474	-0.06	0.9264	-0.09	0.4542	5.59	0.6951	-0.44	0.2473
X_2X_3	-0.19	0.8250	-0.39	0.5696	0.20	0.1094	-17.36	0.2378	0.41	0.2737
X_2X_4	0.44	0.6076	0.06	0.9264	-0.07	0.5523	5.68	0.6907	0.46	0.2230
X_3X_4	-0.56	0.5109	-0.64	0.3556	0.13	0.2809	4.01	0.7786	-0.18	0.6346
R^2	0.8442	–	0.9012	–	0.9676	–	0.8466	–	0.9383	–

The terms having Prob > F values very small (<0.0001) indicate that these have significant effect on the response variables
EC estimated coefficient;

formulation variables were selected for systematic optimization studies. Results of the experiments carried out as per central composite design are shown in Table III. The dependent and independent variables related using the mathematical relationships are shown in Table IV. The polynomial equations can be used to draw conclusions by considering sign (positive or negative) and magnitude of the coefficient. High values of coefficient of determination (R^2) indicate good fit. The prediction profiler correlating independent and response variables is shown in Fig. 1.

Drug Content

All the formulations were found to contain 99.2% to 100.9% of added amount of amoxicillin per minimatrix. Drug content was estimated as per the procedure described in "Methods" section. Sonication was necessary in the procedure as the minimatrices contained polymers which have tendency to form matrix and inhibit drug release. Preliminary experiments confirmed 20 min of sonication time to be sufficient for complete drug extraction from the matrix network.

Buoyancy Lag Time

Aim of the present research work was to develop a formulation having gastroretentive capabilities which can be achieved by imparting floating and gastric mucoadhesive properties. Hence buoyancy lag time is very important parameter for the developed formulations. Short lag time may ensure immediate floating of the minimatrices and may further avoid settling of the formulation in lower part of stomach and ultimately avoid escape of the formulation from pyloric sphincter. Buoyancy lag time varied from 7 to 32 min for the developed formulations. Least lag time of 7 min and maximum lag time of 32 min was observed for Formulation no. AGT 09 and AGT 04, respectively. Least lag time might be observed in Formulation no. AGT 09 due to presence of higher amount of gas generating couple (X_4) as compared to other formulations.

As can be seen from the results of regression analysis in Table IV and prediction profiler in Fig. 1, gas generating couple (sodium bicarbonate/citric acid (3:1)) (X_4) significantly decreased buoyancy lag time. Sodium bicarbonate and citric acid react in presence of acidic dissolution medium and generates carbon dioxide which gets entrapped in polymer matrix and decreases density of the minimatrix (26). Sodium bicarbonate alone can react with gastric fluid to produce carbon dioxide. But citric acid was also included in the formulation to assure that an acidic microenvironment within the swelling matrix is maintained. This may contribute to continuous generation of carbon dioxide in the matrix independent of external changes in the pH environment. Xanthan gum has the tendency to form a viscous gel. Formation of viscous gel entraps the gas bubbles inside the matrix and minimizes chances of bubbles getting escaped from the polymer network channels. This in turn led to floating behavior of the minimatrices for longer duration.

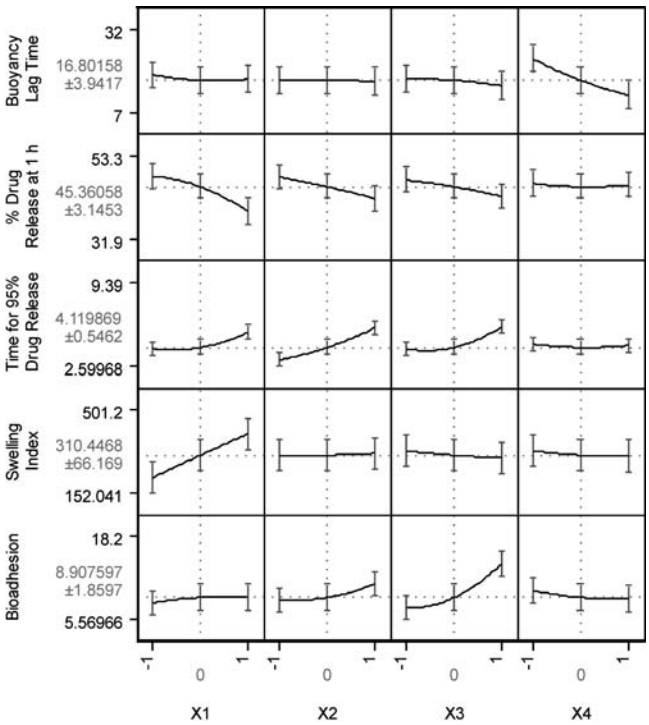

Fig. 1. Prediction profiler correlating independent variables and response variables

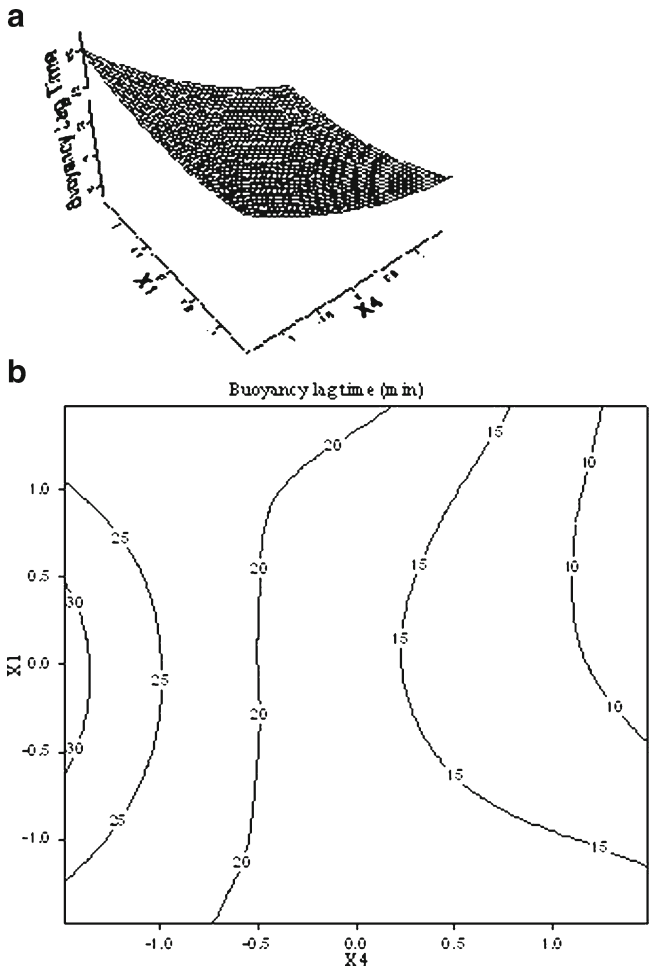

Fig. 2. **a** Response surface plot and **b** contour plot showing effect of X_1 and X_4 on buoyancy lag time

Hence all the developed formulations were found floating up to 12 h. Response surface plot in Fig. 2a and corresponding contour plot in Fig. 2b show effect of different levels of xanthan gum (X_1) and gas generating couple (X_4) on buoyancy lag time (Y_1). Physical integrity of all the formulations was maintained due to presence of carbopol which becomes viscous in presence of water and tends to bind the mixed polymeric system together and reduces matrix erosion (27).

Drug Release Study

Sustaining drug release is very important aspect for maintaining drug concentration for longer time in the stomach, which is residence site of *H. pylori*. Maintaining effective drug concentration for longer time may completely eradicate *H. pylori* infection (11). Hence, core goal of the present research work was to prepare a formulation having gastroretentive capability with sustained drug release feature.

Drug release can be sustained for longer time by retarding initial hour release to maximum possible extent. Xanthan gum (X_1), rate controlling polymers (HPMC, K100M CR, and PEO; X_2) and carbopol 974P (X_3) were found to play important role in decreasing drug release at initial hour (Fig. 1). Drug release at 1 h (Y_2) was 32.5% for Formulation no. AGT 09 which contains high level of gum, polymers, and carbopol while it was 53.3% for Formulation no. AGT 14 containing lowest level of these formulation variables. Results of regression analysis (Table IV), from its negative sign and magnitude and smaller value of Prob>F, indicate that xanthan gum has significant role in retarding drug release at first hour as compared to HPMC, PEO, and carbopol.

HPMC is a neutral hydrophilic polymer. The polymer molecular chains of HPMC hydrate in contact with water entangle and form a gel matrix. When exposed to water, carbopol becomes viscous and, thus, tends to bind the mixed polymeric system together. During hydration process, channels are formed in the matrix networks which are responsible for drug diffusion. After coming in contact with water, xanthan gum forms very viscous network. This network is particularly built up in the drug diffusion channels formed by

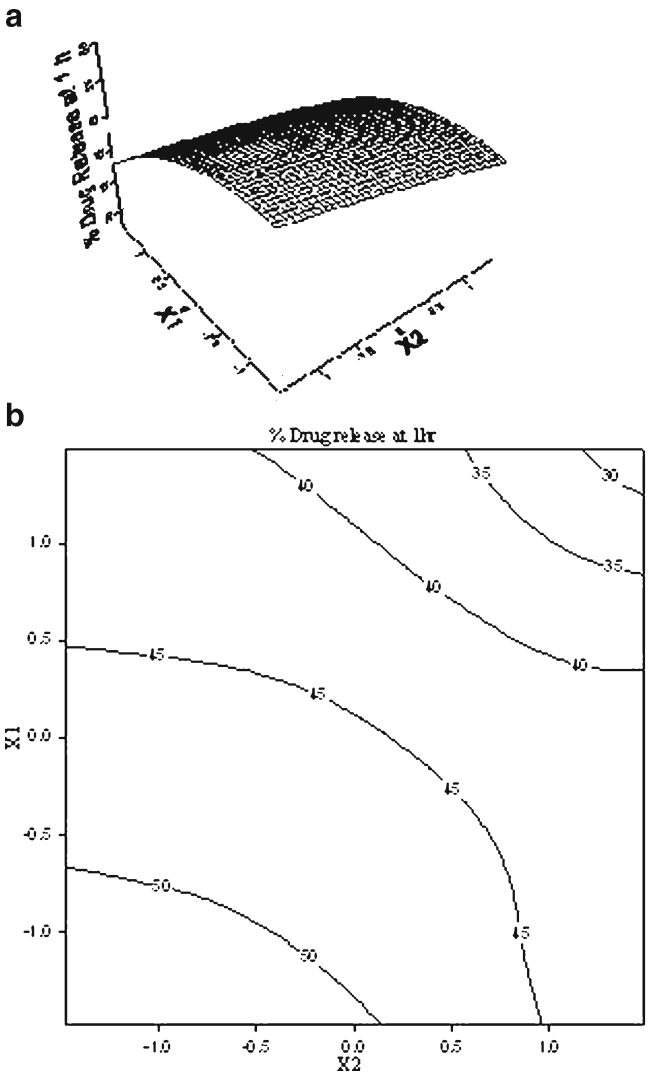

Fig. 3. **a** Response surface plot and **b** contour plot showing effect of X_1 and X_2 on percentage of drug release at 1 h

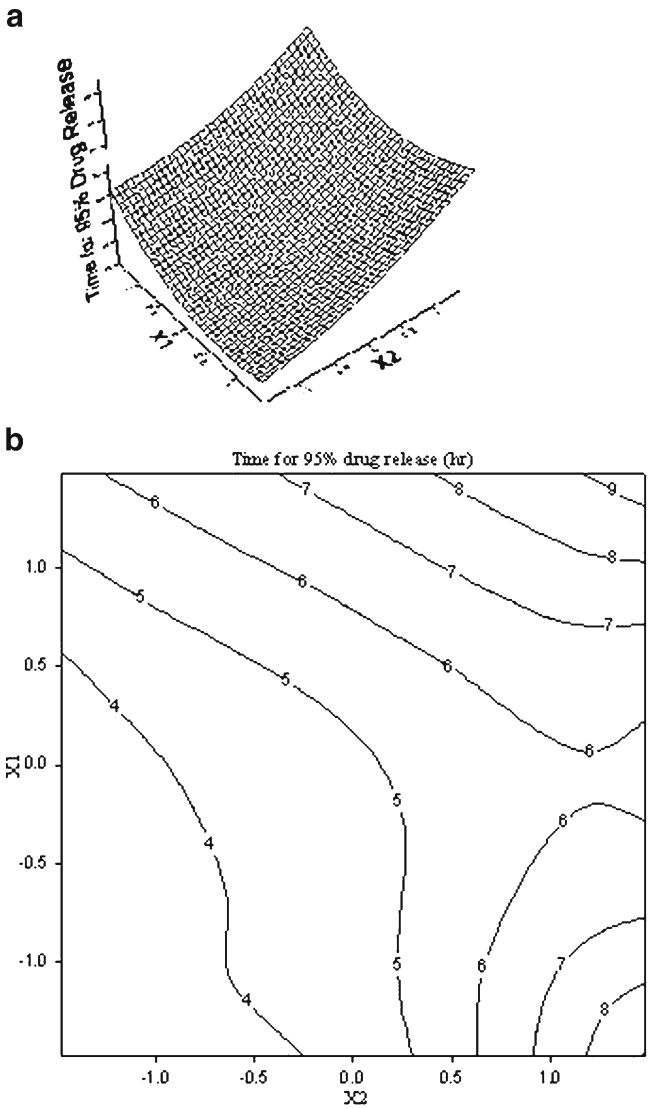

Fig. 4. **a** Response surface plot and **b** contour plot showing effect of X_1 and X_2 on time required for 95% drug release

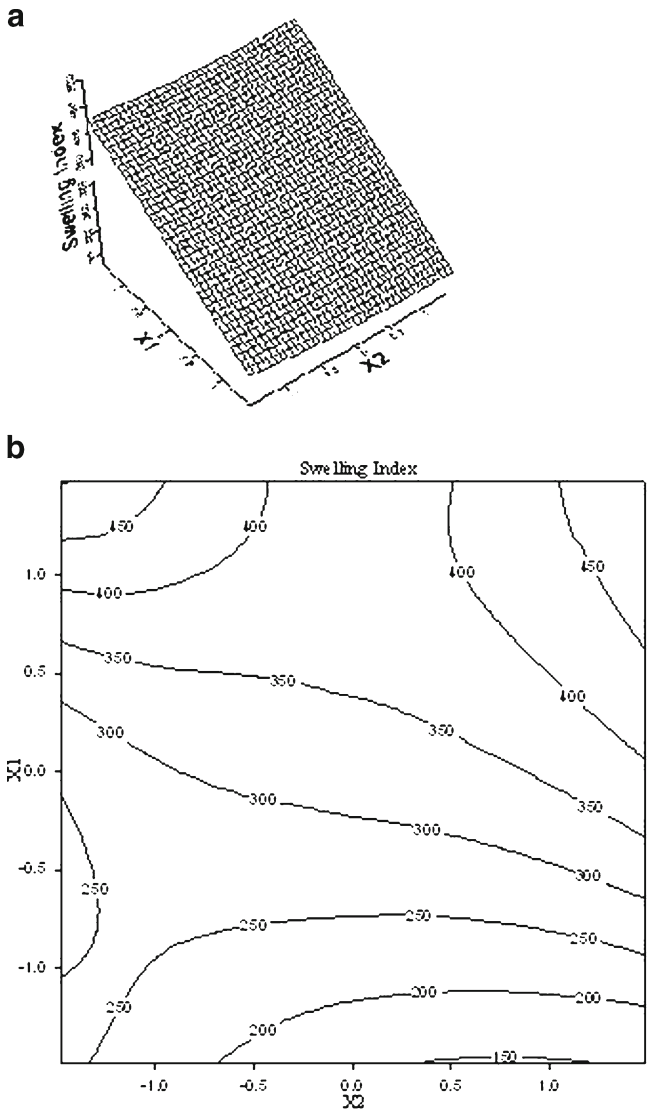

Fig. 5. **a** Response surface plot and **b** contour plot showing effect of X_1 and X_2 on swelling index

polymeric network and ultimately may be responsible for retarding drug release in initial hour. The channel blockage might have enhanced with increasing gum level which might be responsible for decrease in initial hour drug release. Response surface plot in Fig. 3a shows effect of xanthan gum (X_1) and rate controlling polymers (X_2) on the percentage drug release at 1 h (Y_2). It can be clearly interpreted from contour plot in Fig. 3b that for decreasing drug release at initial hour, higher level of X_1 and X_2 is necessary.

Time required for 95% drug release (Y_3) was also increased due to xanthan gum, rate controlling polymers (HPMC, K100M CR, and PEO), and carbopol 974P. Formulation nos. AGT 09 and AGT14 required 9.39 and 3.31 h, respectively, for 95% drug release. Less time may be required for Formulation no. AGT 14 as the matrix may not be capable to sustain drug release for longer time due to low level of X_1, X_2, and X_3 and the observation was vice versa for Formulation no. AGT 09 containing high levels of these formulation variables. Results of regression analysis in Table IV indicate that X_1, X_2, and X_3 have significant effect on Y_3 while magnitude of regression coefficient shows maximum influence of X_2. Similar observation is presented as a prediction profiler in Fig. 1.

Xanthan gum, HPMC, PEO, and carbopol together played crucial role in sustaining drug release. Xanthan gum decreased drug release at initial hour due to its rapid viscolysing property (Fig. 1). HPMC and PEO were particularly responsible for sustaining drug release at later period. So the drug release was found to be high initially and then gradually decreased. The diffusional spaces inside the gelling system are controlled by the molecular weight of the polymer. Diffusion is the predominant drug release mechanism from high molecular weight HPMC and PEO matrices which swell to a higher extent. Swelling phenomenon increases matrix size; therefore, diffusional path length is increased (28). Drug entity present in the matrix core may ultimately be requiring more time to travel towards the matrix surface. This

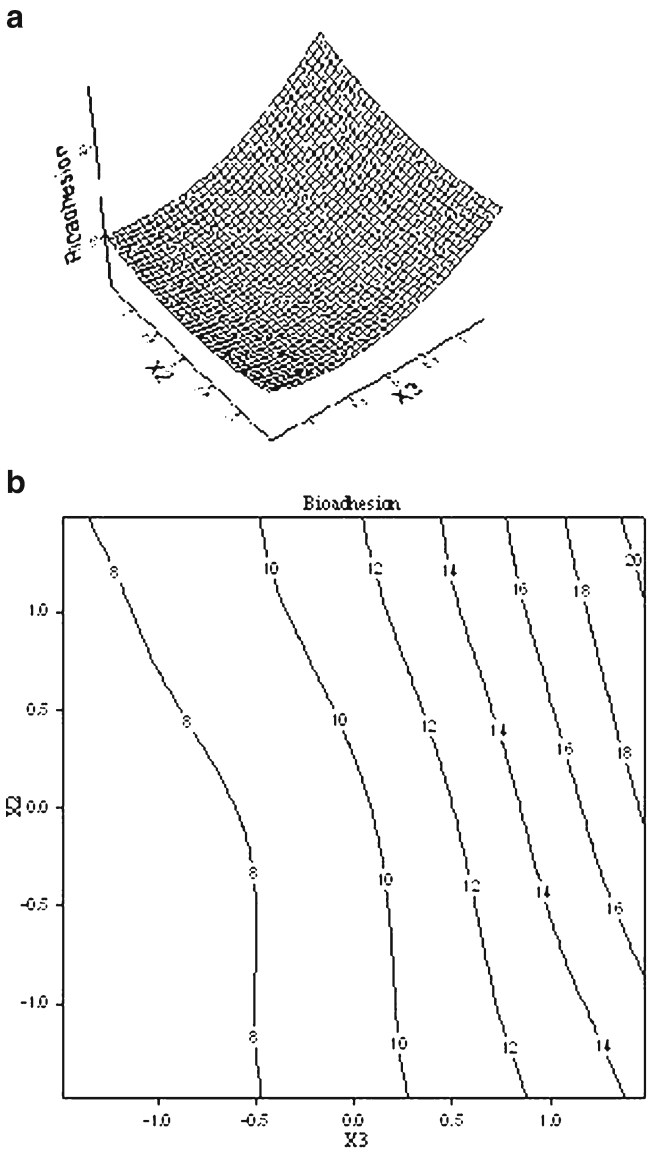

Fig. 6. **a** Response surface plot and **b** contour plot showing effect of X_2 and X_3 on bioadhesion

phenomenon may be responsible for increased time required for 95% drug release. HPMC and PEO take some time to get hydrated and swell. As this process is time dependent, drug release might be sustained in later hours due to these polymers. Sine the swelling capacity depends on amount of polymer present in the formulation, as concentration of X_2 increased from −1 level to +1 level, time required for 95% drug release (Y_3) was significantly decreased as shown in Fig. 1. Effect of combination of xanthan gum (X_1) and rate controlling polymers (X_2) on Y_3 is shown in response surface plot (Fig. 4a) and contour plot (Fig. 4b).

Carbopol is a water-insoluble but water-swellable cross-linked polymer with molecular weight approximately 2×10^6 Da. Swelling occurs due to the uncharged –COOH group that hydrates by forming hydrogen bonds with the imbibing water, thus extending the polymer chains. Swelling of this polymer contributes partially to the floating behavior of the GRDDS. When exposed to water, carbopol becomes viscous and, thus, tends to bind the mixed polymeric system together and reduces erosion of GRDDS (27). This viscous network ultimately results in sustained drug delivery phenomenon.

Fluid Uptake Study

The degree of hydration of the polymer is one of the factors determining the degree and velocity of drug release from the swellable matrices (29). Mobility of the polymer chains and, thus, drug diffusion significantly depends on the water content of the matrix system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling of the system (30). Xanthan gum, HPMC, PEO, and carbopol have the property to absorb water and get hydrated. Thus, percentage of fluid uptake depends on the amount of these components present in the formulation. Results of the fluid uptake study indicate that amount of xanthan gum has prominent effect on this parameter. Formulation containing highest amount of xanthan gum (Formulation no. AGT 20) was having swelling index 466.8 while formulation containing least amount (Formulation no. AGT 23) has value of 159. Significance of the effect of xanthan gum on swelling index can be interpreted from regression analysis values in Table IV and can be observed from prediction profiler in Fig. 1. This effect may be due to water holding and viscolyzing property of xanthan gum. In case of the formulations containing lower amount of xanthan gum, swelling index values may be less because the matrix may not be capable to hold water for longer duration. Maximum swelling index was observed at highest level X_1 and X_2 (Fig. 5).

Bioadhesion Study

Gastroretention can be achieved by imparting floating property to the formulation, but to further strengthen this feature gastric mucoadhesion is also very important. For introducing this feature, carbopol 974P was added in the formulation which is widely used as a bioadhesive polymer. Positive sign and magnitude of regression coefficients in Table IV indicates significant influence of carbopol 974P (X_3) on bioadhesion parameter. The concentration dependent increase in bioadhesive strength can be clearly observed from the prediction profiler in Fig. 1. Carbopols are commonly used as mucoadhesives. These polyacrylates interact with mucus by hydrogen and van der Waals bonds, created between the carboxylic groups of polyacrylates and the sialic acid residues of mucin glycoproteins (31). HPMC, a long-chained and nonionic polymer, has also limited bioadhesive property. It could be due to formation of physical or hydrogen bonding with the mucus components. Presence of this component also enhances overall bioadhesion of the formulation. Response surface plot (Fig. 6a) and corresponding contour plot (Fig. 6b) show effect of combination of X_2 and X_3 on bioadhesive strength. Ultimately, bioadhesive property of the optimized formulation could assist the tablet to stay in the upper part of gastrointestinal tract and enhance the gastroretention along with the floating feature (32).

CONCLUSION

In the present research work, gastroretentive minimatrices, having floating and gastric bioadhesive capabilities, have been developed. The formulation was optimized by using central composite design approach. This is very systematic approach to study influence of level of various formulation variables on different response variables. As minimatrix formulation is multiparticulate drug delivery system approach, it overcomes drawback of all or none principle of gastric emptying of single-unit drug delivery system, and also, there is no risk of burst drug release. The technique implemented for preparation of the minimatrices is cost effective, and formulation can be scaled up on large scale using existing tablet manufacturing facility. Hence, the developed GRDDS may be explored as an effective tool in the management of *H. pylori*-associated gastric complications as it has therapeutic as well as manufacturing advantages.

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