IJPSR (2019), Volume 10, Issue 11 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 February 2019; received in revised form, 27 April 2019; accepted, 17 October 2019; published 01 November 2019

DESIGN AND OPTIMIZATION OF EXPANDABLE GASTRORETENTIVE PATCH OF METRONIDAZOLE FOR *HELICOBACTER PYLORI* INFECTION MANAGEMENT

Snehal Y. Kane [*1] and Munira Momin [2]

RK University [1], Rajkot - 360020, Gujarat, India.
SVKM's Dr. Bhanuben Nanavati College of Pharmacy [2], Mumbai - 400056, Maharashtra, India.

Keywords:

Gastroretentive patch, Expandable patch, Gastroretentive drug delivery, Metronidazole patch, *Helicobacter pylori* infection

Correspondence to Author:
Snehal Yashwant Kane

Ph.D. Scholar,
RK University, Rajkot - 360020,
Gujarat, India.

E-mail: dumbresnehal@gmail.com

ABSTRACT: The aim of the present research was to develop and optimize novel expandable gastro retentive formulation of metronidazole to give local action for the management of *Helicobacter pylori* infection. The formulation contained a drug-loaded sandwich patch prepared by solvent casting method folded into a hard gelatin capsule. Metronidazole being needle shape crystals soluble in 0.1 N HCl, but after drying, the formulation show bursting effect in first 1 h. To avoid this drug-loaded middle layer containing Xanthan gum and HPMC E15 as release retardants was sandwiched between baking layers of HPMC E15. Drug loaded middle layer was subjected to 3^2 full factorial design with concentration of HPMC E15 (X_1) and Xanthan gum (X_2) as independent variables and release of the metronidazole at 1st h and at 4th h as Responses. According to 3^2 full factorial design 9 batches were prepared and evaluated for thickness, folding endurance, mucoadhesion, drug content and % drug release. The thickness of formulations F1 to F6 was found to be in the range of 0.266 to 0.352 mm. Folding endurance, Mucoadhesion, and % of drug content of F1-F9 were found to be between 100 to 250, 2.2 to 4.2 N and 98.35% to 99.65% respectively. *In-vitro* drug release of F1-F9 batches showed bursting effect in F1-F4 batches while optimized batch F6 showed 99.89% release in 12 h. HPMC E15: Xanthan gum with 1.5%: 0.8% concentration (F6) was found to be optimized with good folding-endurance, mucoadhesion, and sustained release till 12 h.

INTRODUCTION: Oral drug delivery is the most preferred route of administration due to ease of administration, patient compliance, and flexibility in formulation [1, 2]. From last few decades number of oral sustained release dosage forms has been developed due to their considerable therapeutic advantages over conventional dosage forms [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(11).5216-23

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(11).5216-23

However, these approaches have not been suitable for drugs with limited and narrow absorption windows and having localized effects in the upper part of the gastrointestinal tract, *i.e.* stomach and small intestine due to relative short transit time of dosage form in the segment [3, 4].

A number of approaches for gastroretentive dosage form (GRDF) have been designed like 1) Floating drug delivery system (low-density drug delivery system), 2) Mucoadhesive drug delivery system 3) Expandable drug delivery system like super porous hydrogels 4) High-density drug delivery system 5) Incorporation of Passage Delaying Food Agents, *etc*. [4, 5, 6]

An alternative strategy is to combine bioadhesion with the ability to expand by unfolding and swelling using levetiracetam initiated by S Sivaneswari *et al.* [1] Gastro retentive drug-loaded polymeric films were also previously investigated and the effect of shape, folding pattern and polymer characteristics on gastric retention has been studied. D Sathish *et al*., Developed bilayer drug-loaded expandable film of furosemide [2]. Klausner *et al*., initiated the research on expandable gastro-retentive dosage form, investigated on Riboflavin and Levodopa expandable GRDFs [4, 5]. Darandale *et al*., designed a controlled-release gastro-retentive mucoadhesive dosage form of Furosemide by unfolding mechanism [6]. Patel T *et al*., developed mucoadhesive gastroretentive patch of glipizide [7].

This paper describes the design of a formulation incorporating a metronidazole loaded middle polymeric film sandwiched between backing layers of HPMC E15 to decrease the bursting effect of drug in initial 1 h due to precipitation of drug in to need shape crystals after drying the film and then folded in a hard gelatin capsule developed formulation will provide local action of metronidazole in gastric region for the management of *Helicobacter pylori* (*H. Pylori)* infection. After ingestion, the capsule dissolves and releases the film, which then unfolds in the stomach to a larger dimension resulting in its increased retention in the segment. Mucoadhesion of the film in addition help for gastric retention. This paper focuses on practical aspects of designing and evaluation of dosage form and difficulties appeared during development.

H. pylori is a gram-negative microphilic, flagellated and spiral-shaped organism with a unipolar-sheathed flagella which provides motility. Its spiral shape and high motility help it to penetrate deep in the mucus layer, resist gastric emptying and remain in the host gastric mucosa [8, 9, 10].

Metronidazole is a nitroimidazole antibiotic, chemically it is 2-(2-methyl-5-nitro1*H*imidazol-1-yl) ethanol. Metronidazole is an antibiotic, amebicide, and antiprotozoal used particularly for anaerobic bacteria and protozoa. The unionized metronidazole having the ability to reduce intercellularly, this reduced form covalently binds to DNA, disrupt its helical structure, inhibiting bacterial nucleic acid synthesis and resulting in bacterial cell death [11, 12]. Metronidazole widely used for the treatment of *H. Pylori* eradication therapy, in combination with other antibiotics and one proton pump inhibitor. It is usually taken in a dose of 250 mg / 500 mg two or three times a day. Unionized metronidazole is selective for anaerobic bacteria due to their ability to intracellularly reduce metronidazole to its active form [13, 14].

MATERIALS: Metronidazole was obtained as a gift sample Alkem Laboratories, Mumbai, Maharashtra, India. HPMC E15 and Xanthan Gum were obtained as a gift sample from Colorcon Asia Pvt. Ltd., India. Other excipients and solvents used in the present study were of analytical grade.

METHODS:

Preparation of Gastroretentive Sandwich Patch (GRSP): Metronidazole is available as needle-shaped solid crystals, which are soluble in 0.1 N HCl. While drying the patch (drug-loaded middle layer), metronidazole from the solution precipitate as needle-shaped crystals, which gives bursting effect in an initial 1 h of dissolution study. To avoid this, drug-loaded middle layer is sandwiched between backing layers of Hydroxypropyl methylcellulose (HPMC) E15.

Preparation of Lower and Upper Backing Layer: The objective of preparing backing layers is to retard the busting effect of metronidazole. HPMC E15 which is one of the selected release retardants of the drug-loaded middle layer was selected as polymer to decrease bursting effect of the drug. Propylene Glycol (PG) was used as a plasticizer. Lower and upper backing layers of GRSP were prepared by solvent casting method.

These layers act as release retardant mainly in the first 1 h and in addition provides mucoadhesion to GRSP. The polymeric solution was prepared by soaking 0.4 mg of the HPMC E15 in 15 ml distilled water for 3 to 4 h. PG 0.4 ml was added as a plasticizer and mixture was sonicated for 15 min to avoid any lumps of the polymeric material. This polymeric solution was then poured in the previously lubricated with liquid paraffin glass petri-plate of 5.5 cm diameter as a lower backing layer. Upper backing layer polymeric solution was

also prepared by same method as mentioned for the lower layer using 0.4 mg HPMC E15 and 0.4 ml PG and was poured on semi-dried drug-loaded middle layer containing metronidazole as mentioned in preparation of GRSP.

Drug Loaded Middle Layer: Drug loaded middle layer of the GRSP was prepared by the solvent casting method. The polymeric solution was prepared by soaking required quantity of Xanthan gum and HPMC E15 which act as a release retardant in 20 ml 0.1N HCl for 6-7 h. PG (1.15%) was added as a plasticizer. Accurately weighed quantity of metronidazole was then dispersed in the polymeric solution. The mixture was stir using magnetic stirrer for half an hour and poured on semi-dried lower backing layer of the GRSP in the glass petri-plate. This drug-loaded middle layer was allowed to semi-dry for 2-3 h at room temperature

Preparation of GRSP: The first solution of the lower backing layer of GRSP was cast on the previously lubricated glass petri-plate of 5.5 cm diameter and allowed to dry at room temperature for 2 h. Then the solution of drug-loaded middle layer of GRSP was cast on semi-dried lower backing layer and allowed to dry for 2 h at room temperature. The further solution of upper backing layer was cast on semi-dried drug-loaded middle layer of GRSP and dried at room temperature for 2 h. This GRSP was further dried in a hot air oven at 50 ºC for 3 h for evaporation of remaining solvent. The film was checked for possible imperfections before cutting into size 5 cm × 3 cm. Accurately cut GRSP was filled into hard gelatin capsule size 00 by rolling the patch [6] **Fig. 1**.

FIG. 1: FOLDED GRSP OF METRONIDAZOLE

Optimization of Drug Loaded Middle Layer of GRSP: Lower and upper backing layers were not considered for optimization as they were used only for decreasing the initial bursting effect. The drug-loaded polymeric film was optimized for folding endurance, drug release, mucoadhesion, tensile strength, integrity, and sustained release of drug till 12 h without bursting effect as described below [1, 6, 16].

A 3^2 full factorial design was employed in this study. Two factors (X_1) % concentration of HPMC E15 and (X_2) % concentration of Xanthan gum each at three levels as low(-1), medium (0), and high (+1) individually were selected as independent variables **Table 1**. Nine experimental batches F1 to F9 were prepared as mentioned in **Table 2**. The burst release of metronidazole in 1 h (Y_1) and in vitro drug release in 4 h (Y_2) were selected as Responses or dependent variables. Regression polynomials for the individual dependent variables were calculated with the help of Design Expert 8.0.4.1 software and applied to approximate the response surface and contour plots. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1.X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 \quad \text{(i)}$$

Where Y is the dependent variable, β_0 is the arithmetic mean response of the nine runs, and β_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms ($X_1.X_2$) show how the response changes when 2 factors are simultaneously changed.

The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (*i.e.*, positive or negative).

TABLE 1: CONCENTRATION OF HPMC E15 AND XANTHAN GUM FOR OPTIMIZATION

% Conc. of HPMC E15	-1	0.5
	0	1.5
	+1	2.5
% Conc. of Xanthan gum	-1	0.2
	0	0.5
	+1	0.8

TABLE 2: FORMULATION OF DRUG LOADED MIDDLE LAYER OF GRSP

Layer of sandwich patch	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Backing Lower and upper layer	HPMC E 15 (mg)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
	PG (ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
	water (ml)	15	15	15	15	15	15	15	15	15
Drug loaded Middle layer	Metronidazole (mg)	400	400	400	400	400	400	400	400	400
	HPMC E 15 (%)	0.5	0.5	0.5	1.5	1.5	1.5	2.5	2.5	2.5
	Xanthan gum (%)	0.2	0.5	0.8	0.2	0.5	0.8	0.2	0.5	0.8
	Propylene glycol (%)	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15
	0.1 N HCl (ml)	20	20	20	20	20	20	20	20	20

Dose Calculation: Dose calculation is important as an area of the circular Glass petri-plate was 23.75 cm^2 approx 24 cm^2. Therefore to prepare rectangular GRSP of 5 cm × 3 cm (area 15 cm^2) amount of metronidazole (250 mg dose) required was 400 mg per patch.

Film Integrity and Surface Properties: Film integrity was evaluated visually during dissolution studies to select the most durable patch [2].

Film Thickness: Film thickness was measured using by digital screw gauge (Digital micrometer, Mitutoyo, Japan) at three different places and then mean ± SD values were calculated [1, 2, 15, 18, 19].

Folding Endurance: Folding endurance was calculated by folding the GRSP of size 5 cm × 3 cm repeatedly in the same place till it breaks. No of times patch could be folded without breaking gives the value of folding endurance [2, 15, 16, 17].

Mucoadhesive Force: Mucoadhesion of GRSP of the metronidazole to the stomach was determined to check their ability to stick to gastric mucosa using double beam physical balance in triplicate [1, 6, 16]. The stomach mucosa of goat used was obtained from a local slaughterhouse washed with ringer solution and was kept in simulated saliva fluid with a pH of 6.8 at 4 ºC till use. Evaluation of mucoadhesive force was calculated within three hours of procurement of the mucosa [16]. The mucosa was tied tightly with the mucosal side upward at the end of cylindrical block of teflon with thread. This Teflon block then kept in glass containers containing 0.1N HCl solution (pH 1.2) at 37 ±1 ºC to just wet the mucosal surface. Then it is placed below the left arm of balance. GRSP of size 2 cm × 2 cm was attached to lower surface of another Teflon block suspended from left arm of the balance. The moist mucosal film was allowed to come in contact with GRSP by removing 5 g weight from the right pan of the balance. The balance was kept in this position for 3 min after which weights were added slowly to the right pan until the film separated from mucosal surface.

The excess weight (total weight minus 5 g) on the pan is the bioadhesive strength required to separate the GRSP from the mucosa. The force of adhesion was calculated using the formula.[18]

Force of adhesion (N) = (Bioadhesive strength/1000) × 9.81

Determination of Drug Content: Sandwich patch of metronidazole of size 5 cm × 3 cm was dissolved in 100 ml methanol and sonicated for 15 min. From this solution 1 ml was diluted to 10 ml with 0.1 N HCl. This solution was then analyzed using UV-Visible spectrophotometer at 276 nm [15, 16, 18].

Tensile Strength Measurement: Tensile strength of Sandwiched patch of 5 cm × 3 cm of each formulation was calculated in duplicate using universal testing machine (UTM, LLOYD) where strip of each patch was attached in between the upper and lower clamps of the apparatus and lower clamed was moved slowly down by keeping upper clamp steady. Force applied just to break the strip was measured. Average was calculated to determine ability to break when force was applied. This may indicate ability to withstand for the force during peristaltic movements [6].

Tensile strength (MPa) = (Force at break / cross-sectional area of sample) × 100

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies are carried out in triplicate using GRSP of 5 cm × 3 cm containing metronidazole 250 mg and USP type I (Basket type) dissolution apparatus [1, 2, 6, 7]. The dissolution study was carried out at 75 RPM using 900 ml 0.1N HCl (pH 1.2) as a dissolution medium. Aliquots of 5ml were removed initially at 15 min, 30 min, and 1 h and then at

regular intervals of 1 h till 12 h and were replaced by same quantity of fresh 0.1 N HCl to maintain the sink condition. Further 1 ml of this solution was diluted to 10 ml with 0.1 N HCl and analyzed using UV- Visible spectrophotometer at 276 nm.

RESULT AND DISCUSSION: Film integrity was observed visually. Formulation F1, F2, F3, and F4 break into pieces after 3 h during dissolution study due to bursting effect of drug. F5, F6, F7, F8, and F9 due to higher concentration of HPMC E15 and Xanthan gum do not break into pieces during dissolution study. This indicates ability of GRSP to withstand for peristaltic movement without breaking.

The thickness of the all formulation F1 to F9 found to be in the range of 0.266 to 0.352 mm. This indicates uniform spreading of polymeric solution of all three layers during preparation **Table 3**.

Folding endurance for all the formulations was checked to check the ability of patch to fold and found to be between 100 to 250 which indicates that patch has good ability of folding **Table 3**.

Mucoadhesion in terms of the force of adhesion for formulations F1- F9 was found to be between 2.2 to 4.2 N. This indicates good ability to adhere to gastric mucosa **Table 3**.

Drug content uniformity found to be between 98.35% to 99.65%. This indicates the uniform distribution of the drug in formulations in **Table 3**.

The tensile strength of all formulations was found to be between 2.06 to 6.53 MPa. Tensile strength increases with increase in concentration of HPMC E15 and Xanthan gum moreover Xanthan gum showed more effect on tensile strength due to high viscosity **Table 3**.

TABLE 3: EVALUATION OF GRSP

Formulation	Thickness (mm)	Folding endurance	Force of adhesion (N)	Drug content (%)	Tensile strength (MPa)
F1	0.266 ± 0.0102	102	2.2	98.50 ± 0.103	2.60
F2	0.281 ± 0.0112	115	2.5	98.35 ± 0.125	2.94
F3	0.302 ± 0.0110	132	3.1	98.91 ± 0.112	4.13
F4	0.292 ± 0.0105	154	2.9	99.12 ± 0.125	3.56
F5	0.315 ± 0.0111	178	3.5	99.50 ± 0.106	4.78
F6	0.331 ± 0.0103	190	3.9	99.63 ± 0.113	5.52
F7	0.312 ± 0.0106	210	3.3	99.52 ± 0.110	5.59
F8	0.339 ± 0.0112	235	3.8	99.45 ± 0.104	6.14
F9	0.352 ± 0.0106	250	4.2	99.65 ± 0.111	6.53

Dissolution Rate Profile of the Sandwich Patch: Formulation F1, F2, F3, and F4 showed an initial bursting effect in first 1 h till 42 -50% drug releases even in presence of backing layers and release of complete drug till 8 h due to less concentration of release retardants. F5 showed decrease in the bursting effect till first 1 h to 32.71%, and complete drug release was observed till 11 h. Formulation F6 with HPMC E15 1.5% and Xanthan gum 0.8% showed significant decrease in bursting effect of drug in 15 min, 30 min, and 1 h to 9.17%, 15.32%, and 23.56% respectively. Complete drug release was observed in 12 h. F7 with 0.5% HPMC E15 and 0.2% of Xanthan gum showed less bursting effect in first 1 h but complete drug release was extended for more than 12 h. F8 and F9 with high concentration of HPMC E15 and Xanthan gum showed less bursting effect with drastic decrease in the drug release for more than 12 h **Fig. 2**.

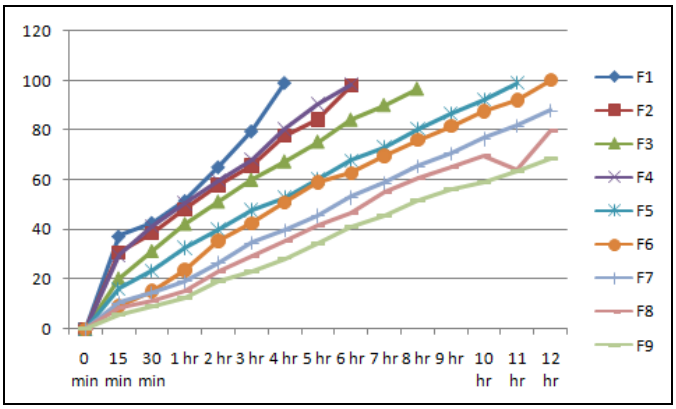

FIG. 2: DISSOLUTION PROFILE FOR FORMULATIONS F1-F9

Optimization of GRSP:

Effect on Response I (Y1): The 1st h burst release follows a linear model shown in equation 2, where the conc. of HPMC E15 and Xanthan gum, both linearly affects the drug release. Thus, with an increase in the concentration of both the polymers,

there is a subsequent decrease in the % drug release. This result is attributed to the swelling behavior of Xanthan gum. In the presence of water, Xanthan gum swells and forms a matrix that slowly releases the drug as the dissolution media penetrates this matrix. Similarly, HPMC E15 sustains drug release through diffusion, erosion, and swelling. Thus, higher the concentration of the polymer, sustained is the drug release. Thus, in order to obtain decrease in initial burst release (25%), an optimum concentration of both the polymers was obtained in batch F6.

Both the factors significantly alter the release of the drug linearly with $p<0.001$

$$Y1 = 32.58 - 15.95\ X1 - 7.18\ X2$$

$$R^2 = 0.9131 \text{ and } p=0.0007$$

The above equation iterates that both the polymers negatively affect the drug release and seen in the figure below contour plot **Fig. 3** and **Fig. 4**.

$$\text{Adjusted } R^2 = 0.8841$$

$$\text{Predicted } R^2 = 0.8024$$

The difference between the adjusted R^2 and predicted R^2 signifies that the factor chosen for the response significantly varies with a response. Thus, ideally, the lesser the difference, the better the model is.

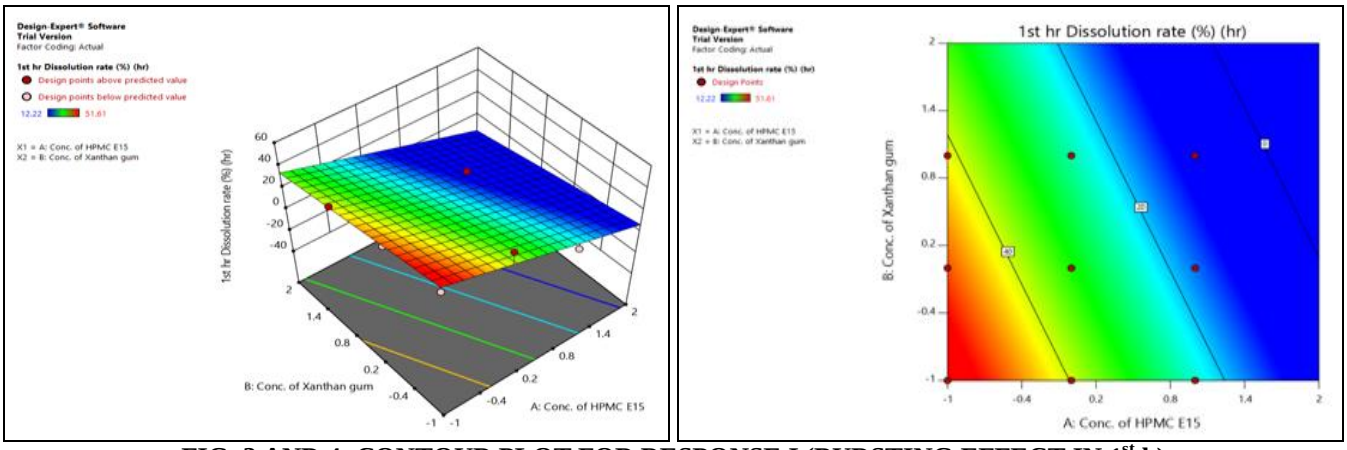

FIG. 3 AND 4: CONTOUR PLOT FOR RESPONSE I (BURSTING EFFECT IN 1st h)

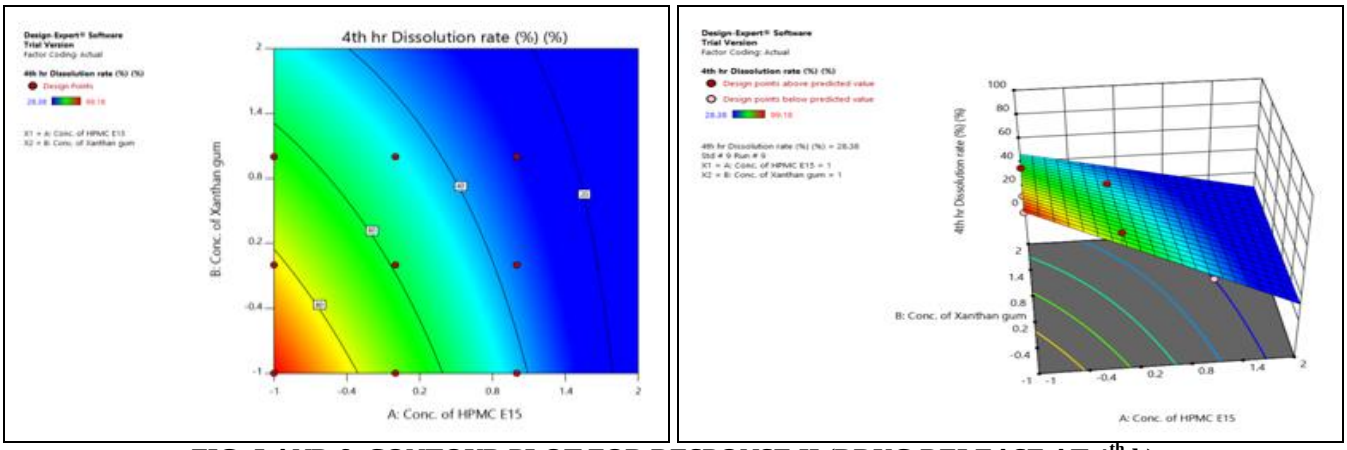

FIG. 5 AND 6: CONTOUR PLOT FOR RESPONSE II (DRUG RELEASE AT 4th h)

Effect on Response II (Y2): The 4th h sustained-release follows a 2FI model where the concentration of HPMC E15 and Xanthan gum and interaction between them helped in sustaining the drug release that effectively transforms to once a day dosing. Thus, at the end of 12th h, most of the drug released aiding in sustaining drug release for once a day. Therefore by increasing the concentration of both the polymers, a sustained % drug release is observed. Again, this is attributed to the swelling behavior of xanthan gum. However, increasing the polymer beyond a certain limit will affect the initial burst release of the drug, and thus, a careful concentration of the polymer was required as in batch F6).

Both the factors significantly alter the release of the drug linearly with $p<0.001$.

$$Y2 = 59.074- 23.46 X1 – 12.08 X2+5.11X1X2$$

$$R^2 = 0.9603 \text{ and } p=0.0006$$

The above equation iterates that both the polymers negatively affect the drug release and seen in the figure below contour plot **Fig. 5** and **6**.

$$\text{Adjusted } R^2 = 0.9365$$

$$\text{Predicted } R^2 = 0.9029$$

The difference between the adjusted R^2 and predicted R^2 signifies that the factor chosen for the response significantly varies with a response. Thus, ideally, the lesser the difference, the better the model in **Fig 5**.

CONCLUSION: In the present investigation, novel expandable gastro retentive sandwich patches of metronidazole were prepared and optimized for the management of *H. Pylori* infection by solvent casting method.

Optimization study with 3^2 factorial design indicates that selected independent variables *i.e.* concentration of HPMC E15 and Xanthan gum significantly affect release rate of the metronidazole in 1 h and 4 h. The response I *i.e.* Bursting effect in first 1 h of metronidazole decreased due to backing of lower and upper layers of HPMC E15. These layers also helped in increasing mucoadhesion and folding endurance of the middle layer. Response II *i.e.* release of metronidazole at 4^{th} h significantly affected by concentration of HPMC E15 and Xanthan gum.

The expandable film shows more gastric retention due larger size and more surface area as compared to other oral gatroretentive dosage forms. Prepared sandwich patches were evaluated for thickness, folding endurance, mucoadhesion, drug content, dissolution profile, and tensile strength.

ACKNOWLEDGEMENT: We would like to acknowledge Alkem Laboratories, Mumbai, Maharashtra, India for providing metronidazole for research work and Colorcon Asia Pvt. Ltd., for gift samples of polymers required.

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Sivaneswari S, Karthikeyan E and Chandana PJ: Novel expandable gastro retentive system by unfolding mechanism of levetiracetam using simple lattice design - Formulation optimization and *in-vitro* evaluation. Bulletin of Faculty of Pharmacy, Cairo University 2017; 55: 63-72.
2. Satish D, Himbindu S, Kumar P and Rao YM: Preparation and evaluation of novel expandable drug delivery system, British J of Pharmaceutical Research 2003; 3(4): 1079-93.
3. Klausner EA, Lavy E, Friedman M and Hoffman A: Expandable gastroretentive dosage form. J of Controlled Release 2003; 90: 143-62.
4. Klausner EA, Lavy E, Stepensky D, Friedman M and Hoffman A: Novel gastro retentive dosage form: evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. Pharmaceutical Research 2002; 19(10): 1516-23.
5. Klausner EA, Lavy E, Barta M, Cserepes E, Friedman M and Hoffman A: Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharmaceutical Research 2003; 20(9): 1466-73.
6. Darandale SS and Vavia PR: Design of a gastroretentive mucoadhesive dosage form of furosemide for controlled release, Acta Pharmaceutica Sinica 2012; 2(5): 509-17.
7. Patel TB, Patel TR, Suhagia BN and Patel MN: Design and development of novel mucoadhesive gastroretentive formulation of glipizide, Int J Res Ayurveda Pharm 2014; 5(5): 625-31.
8. Garza-González E, Perez-Perez GI, Maldonado-Garza HJ and Bosques-Padilla FJ: A review of Helicobacter pylori diagnosis, treatment, and methods to detect eradication, World J Gastroenterol 2014; 20(6): 1438-49.
9. Diaconu S, Predescu A, Moldoveanu A, Pop CS and Braticevici F: *Helicobacter pylori* infection: old and new. J Med Life 2017; 10(2): 112-17.
10. Gravina AG, Zagari RM, Musis C, Romano L, Loguercio C and Romano M: *Helicobacter pylori* and extragastric diseases: A review. World J Gastroenterol 2018; 24(29): 3204-21.
11. Ribaldone DG, Astegiano M, Saracco G and Pellicano R: Amoxycillin and metronidazole therapy for *Helicobacter pylori* eradication: A 10-Year Trend in Turin, Italy. Balkan Med J 2017; 34(3): 290-91
12. Nohemann L, Almeida M and Ferrari P: Floating ability and drug release evaluation of gastroretentive micro-particles system containing metronidazole obtained by spray drying. Braz J Pharm Sci 2017; 53(1): e15218
13. Loh ZC and Elkordy AA: Formulation and evaluation of different floating tablets containing metronidazole to target stomach. Curr Drug Deliv 2015; 12(4): 425-43.
14. Youssef NA, Kassem AA, El-Massik MA and Boraie NA: Development of gastroretentive metronidazole floating raft system for targeting *Helicobacter pylori*. Int J Pharm 2015; 486(1-2): 297-05.
15. Shidhaye SS, Saindane NS, Sutar S and Kadam V: Muco-adhesive bilayered patches for the administration of suma-triptan succunate. AAPS Pharm Sci Tech 2008; 9: 909-16.
16. Ikram M, Gilhotra N and Gilhotra R: Formulation and optimization of mucoadhesive buccal patches of losartan potassium by using response surface methodology. Adv Biomed Res 2015; 4: 239.
17. Pawar H, Jadhav SM, Jadhav PT and Geevarghese R: Development and evaluation of mucoadhesive patch using a natural polysaccharide isolated from *Cordia diachromata* fruit. J Mol Pharm Org Process Res 2014; 2(3): 120.

18. Singh A, Sharma UK and Prajapati SK: A review on mucoadhesive buccal patches. Int J Res Dev Pharm L Sci 2017; 6(4): 2654-60.

19. Salehi S and Boddoh S: New formulation and approach for mucoadhesive buccal film of rizatriptan benzoate. Prog Biomater 2017; 6: 175-87.

How to cite this article:
Kane SY and Momin M: Design and optimization of expandable gastroretentive patch of metronidazole for *Helicobacter pylori* infection management. Int J Pharm Sci & Res 2019; 10(11): 5216-23. doi: 10.13040/IJPSR.0975-8232.10(11).5216-23.