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FORMULATION OPTIMIZATION OF UNFOLDING GASTRORETENTIVE PATCHES OF ESOMEPRAZOLE

Chintalapati V.S.Raghu Kiran[1] , Chakka Gopinath[2]

[1]Department of Pharmaceutics, Acharya Nagarjuna University, Nagarjuna Nagar, Andhra Pradesh 522510, India

[2]OT & PRI, JNTUA, Ananthapuram, Andhra Pradesh 515001, India

Abstract:

Currently, gastro-retentive dosage forms achieved a remarkable position among the oral drug delivery systems. This is a broadly used technique to hold the drug delivery systems for a long duration in the gastro intestine region, slow drug delivery, and overcome other challenges related to typical oral delivery such as low bioavailability. The current work aimed to formulate and characterize a new expandable gastro-retentive system through Esomeprazole unfolding process for controlled release. The IH-loaded unfolding film formulation was optimized using the Box-Behnken design. Based on desirability criteria, the formulation containing HPMC concentration 60, Stearic acid 25.047 and Xanthan Gum 34.6753 is selected as optimized formulation for further studies.

Keywords:

Esomeprazole, Gastro retentive, Optimization, Design Expert.

Corresponding author:

Chintalapati V.S.Raghu Kiran,

Department of Pharmaceutics,
Acharya Nagarjuna University,
NagarjunaNagar,
Andhra Pradesh 522510, India

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INTRODUCTION:

Recent scientific and patent literature has shown increased interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. The several approaches are currently used to retain the dosage form in the stomach [1, 2]. These include bio-adhesive systems, swelling and expandable systems, floating systems and other delayed gastric emptying devices. The diversity in these systems is owed to the numerous benefits obtained from designing them. These benefits include increased drug bioavailability, decreased side effects and dosing frequency, in addition to increased patient compliance.

The two main factors affecting gastric retention of drug dosage forms are the fed or fasted state, and the size of the delivery system [3, 4]. A system which has dimensions greater than the pyloric sphincter in its relaxed state will have prolonged gastric residence time irrelevant to the fed or fated state. Expandable systems are such kind of systems which will expand, after being folded in capsule, once in contact with gastric fluid. This expansion should provide a system with dimensions greater than the pyloric sphincter in its relaxed state (12.8 ± 7 mm), which ensures mechanical resistance to evacuation [5–7]. Convenience of hard gelatin capsule is the major advantage of such type of dosage forms. In order to modify drug release through polymeric film design, there remain a number of issues including; selection of a polymer with the desired ability to unfold and expand in the stomach and complexity in formulating a drug loaded polymeric film [3, 8, 9]. Combination of floating with the ability to expand by unfolding and swelling using blend of biodegradable polymers (hydrophilic and hydrophobic) is an alternative strategy to increase gastric residence time.

Gastro retentive drug loaded polymeric films was previously investigated and the effect of shape, folding pattern and polymer characteristics on gastric retention has been studied [].A new expandable gastro-retentive system through Itopride Hydrochloride (IH)'s unfolding process for controlled release has been designed by Shaima et al [10].

Yet till date, no attempts were made to prepare unfolding type of gastro retentive system of EH. The purpose of this research is to develop a novel expandable gastro-retentive dosage form, based on unfolding mechanism using EH as a model drug.

2. MATERIALS AND METHODS:

2.1. Materials:

Esomeprazole gifted by Aurobindo Pharma, Hyderabad. HPMC, Stearic acid, Xanthan gum were procured from LobaChemie Pvt Ltd., Mumbai.

2.2. Preparation of EH loaded unfolding film (EH-UF)

The gastro-retentive patch was fabricated by solvent casting technique [19] by using different matrixing agenta such as HPMC, stearic acid and xanthan gum. Hydrophobic polymer ethylcellulose was added commonly in all formulation in order to produce integrity and sustain effect. In polymeric solution the required amount of polymers was dissolved in distilled water and ethyl cellulose solution prepared with ethanol was added. Drug solution of EH was prepared in distilled water. Then the drug solution was incorporated into the polymer solution, propylene glycol used as a plasticizer and mixed thoroughly in the magnetic stirrer. The mixture was then poured in a glass mold and heated in the oven at 70 °C for 2 hours to ensure solvent evaporation and system solidification. The glass mold was covered with an antiadherent plastic bag originally used for cooking prior to mixture addition, in order to assist in dried layer removal. The resultant layer was stored in a desiccator for 2 days then cut to the required dimensions, weighed, folded manually into accordion shape and placed in a "00" sized hard gelatin capsule.

2.3. Experimental design

Preparation of EH-UF is optimized through the statistical method RSM (Response Surface Methodology). The concentration of HPMC (X_1), stearic acid(X_2), and xanthan gum(X_3) were selected as independent variable set three different levels are coded as -1 (low), 0 (medium), and +1 (high). All these variables were studied for their interaction for folding endurance swelling index and bioadhesion strength using the Box Behnken model of Design Expert 12 (Stat Ease Inc., USA), originating 18 experimental trails [11, 12]. Table 1 exhibits the entire plan of the experiment, interns of coded and actual values of chosen variables, and limitations of selected responses. Further, polynomial equations generated were validated using ANOVA (Analysis of variance). Additionally, several statistical tools were applied to all the experimental runs in selecting the best fit model. In each trial, a quadratic design was employed to compute the response and further regression analysis was done.

$$Y_{i(Quadratic)} = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3 + b_7X_1^2 + b_8X_2^2 + b_9X_3^2$$

Where,

Y_i- Selected response or dependent variable,

b_o - Arithmetic response

b_i – Estimated coefficient for main effects (X_1, X_2, X_3); interaction terms of main effects (X_1X_2, X_2X_3, X_1X_3) and polynomial terms of independent variables (X_1^2, X_2^2, X_3^2)

Table 1. Experimental plan for Box-Behnken design in terms of actual and coded values.

Factors/ Independent Variables	Levels -1	0	+ 1	Responses/Dependent Variables	Constraints
HPMC conc.- X_1	0	30	60	Folding Endurance	Maximum
Stearic acid conc-X_2	0	25	50	Swelling index	Maximum
Xanthan gum conc-X_3	10	25	40	Bioadhesion strength	Maximum

Folding endurance

Folding endurance was determined by repeatedly folding the film at the same place until it breaks. The number of times the film could be folded at the same place without breaking was taken as the folding endurance value. It is an indirect assessment of toughness of film where lower value of folding endurance indicates brittleness of the film [[13]].

Swelling behaviour

Swelling of Patches was examined in triplicates in 0.1 N HCl(pH 1.2) according to the following procedure. After recording the initial weight of the patch (W1), it was immersed in 0.1 N HCl (pH 1.2) buffer solution maintained at 37 ± 0.5 C. The weight at end of 120 min was recorded (W2).

Standardization and validation of optimization outcome

Design-Expert software was employed to instigate the responses provided by all the preparations. The responses were utilized to develop the study methodology and the response surface graph. A numerical standardization method was employed to develop an optimized formula with a specified minimal and maximal limit of every parameter. The results were integrated into a desirability function [14, 15]. The set of solutions was classified with the highest desirability and the solutions which met the specifications are noted. The relation of the independent and dependent parameters was elucidated by the response surface graph. The influence of various factors on the slope coefficients was studied by ANOVA. As a part of design validation, the relative uncertainty was enumerated by using the dissimilarity of predicted and experimental values.Validation of experimental design was done by calculating relative error using the following equation formula.

$$\text{Relative error (\%)} = \frac{\text{Predicted value} - \text{Practical value}}{\text{Predicted value}}$$

2.4. In vitro unfolding study

The prepared polymeric film was folded in two different pat-terns (rolling and accordion pattern) and inserted into 00 size capsules (Fig. 1). In vitro unfolding study was carried out in 900 ml of 0.1 N HCl (pH 1.2) using USP type I apparatus (TDT-08 L, Electrolab, Mumbai, India) at constant temperature of 37 ± 0.5°C at 50 rpm. To examine their unfolding behaviour baskets were removed and tested layers were collected after 10 and 15 minutes to measure their lengths (LTL) [25].

2.5. Evaluation of other parameters

Weight variation

A weight variation test was conducted for ten patches (1 cm × 1 cm). The patches were weighed individually and their average weights and standard deviations were calculated [27]. The mean ± SD (n = 3) values were shown in Table 2.

Thickness

Patch thickness was determined by optical microscopy by taking transverse sections from different points within a patch and observing under ×100 magnification. The mean and standard deviation were calculated [26].

Tensile strength

Tensile strength is the maximum load that a strip specimen can support without fracture when being stretched, divided by the original cross-sectional area of the material. The weight was gradually increased so as to increase the pulley force till the film breaks. The percent elongation before the film breaks was noted with the help of a magnifying glass on graph paper and tensile strength was calculated as kg/cm2[27].

Mechanical strength

Mechanical strength is the force applied manually. Mechanical strength is measured in kg/cm2using paper bursting machine. This machine applies mechanical force on a ball which passes through the film after rupturing it when fixed horizontally in a frame [28, 29].

Degradability test.

This test was performed to inspect the degradability of the optimized formula at intestinal pH using potassium phosphate buffer, pH 6.5. The layer was placed directly in the medium without being first loaded in a

capsule [30]. Its rigidity should decrease at alkaline pH. Rigidity was inspected manually using Young's modulus test. Results will help us predict the layer's behaviour in the intestines in case of premature evacuation.

Drug content

Patches equivalent to 50 mg of EH were taken and placing the patch in 100 ml of 0.1 N HCl (pH 1.2) buffer solution for complete extraction of the drug up to 6 h. The above solution was filtered and then analyzed by UV spectrophotometer at a wavelength of 210 nm [31].

2.6. Gastric retention time and in vitro dissolution studies for optimized formulation

Drug release test was performed using USP apparatus II method. Volume of medium was 500 ml. Sampling was performed at 0, 0.5, 1, 2, 4, 6 hours. Sample withdrawn was 2.5 ml. Sink conditions were maintained. Medium used in performed tests was hydrochloricacid medium (pH 1.2), which represents the lower pH of the stomach. An additional test using acetate buffer medium (pH 4.1) which represents the higher pH of the stomach was performed on the final optimized formula [36]. Paperclips were used to hold the layers to the bottom of the bucket during layers development for the purpose of drug release studies.

3. RESULTS AND DISCUSSION:

3.1. Preparation of EH loaded unfolding film

The Box-Behnken design of response surface methodology (RSM) was employed to determine the optimum concentration of the selected factors and their interaction in the ensuing desired folding endurance and LTL. A total of 17 experimental operations were projected and the responses were presented in Table 2. The folding endurance of all the trail preparations was observed between 69 and 114, while LTL was estimated in the range of 9 to 25%. The acquired results were examined for independent responses and the impact of parameters by statistical model fx and ANOVA. For both the responses quadratic model was opted, as per the sum of squares (Type I), model summary statistics, and fit summary [Table 3 and 4]. A quadratic high order polynomial model was chosen, where the auxiliary terms are notable and the model is not aliased.

Table 2. Build Information of the design

File Version	**12.0.1.0**		
Study Type	Response Surface	**Subtype**	Randomized
Design Type	Box-Behnken	**Runs**	18
Design Model	Quadratic	**Blocks**	No Blocks
Build Time (ms)	60.00		

Summary of the Factors and the concetrations

Factor	Name	Units	Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	HPMC conc.	mg	Numeric	0.0000	60.00	-1 ↔ 0.00	+1 ↔ 60.00	30.00	20.58
B	Stearic acid cocn	mg	Numeric	0.0000	50.00	-1 ↔ 0.00	+1 ↔ 50.00	25.00	17.15
C	Xanthan gum conc	mg	Numeric	10.00	40.00	-1 ↔ 10.00	+1 ↔ 40.00	25.00	10.29

Table 3. Projected experimental runs for central composite design and their observed responses.

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Std	**Run**	**A:HPMC conc.**	**B:Stearic acid cocn**	**C:Xanthan gum conc**	**Folding endurance**	**Swelling Index**	**Bioadhesion strength**
		mg	**mg**	**mg**		**%**	**g/cm2**
11	1	30	0	40	65	72	65
16	2	30	25	25	119	69	58
13	3	30	25	25	118	69	57
1	4	0	0	25	35	42	37
17	5	30	25	25	121	68	59
4	6	60	50	25	82	88	74
15	7	30	25	25	124	67	60
9	8	30	0	10	70	46	49
12	9	30	50	40	49	91	58
14	10	30	25	25	118	70	56
5	11	0	25	10	86	28	28
18	12	30	25	25	118	71	57
3	13	0	50	25	38	62	38
10	14	30	50	10	94	48	52
8	15	60	25	40	132	85	72
2	16	60	0	25	92	84	65
6	17	60	25	10	158	57	58
7	18	0	25	40	78	65	39

The Predicted R^2 of 0.8876 is in reasonable agreement with the Adjusted R^2 of 0.9822; i.e. the difference is less than 0.2.Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 37.191 indicates an adequate signal. This model can be used to navigate the design space.In addition to this fit summary data was applied to ensure the effectiveness and fitness of the chosen model. The model repeatability can be assured with the value of the coefficient of variation (CV). CV of the selected quadratic model should to be < 10 %, to confirm the reproducibility. Relatively low CV values (4.85%) were noted in the study which ensures model accuracy and reliability. Adequate Precision quantifies S/N (signal to noise) proportion.Thus, confirming the efficiency of the model to run the design space. Lack of fit can result in an ineffective model to represent the complete data. Therefore, lack of fit is a prerequisite to determining that the equations developed by the model are coherent in forecasting the responses. The lack of fit p values of PS, EE, and SI was observed as insignificant and so the model chosen was appropriate.

A great interconnection was seen with the experimental and predicted values while denoting the selected responses. The probability distribution ensures that residuals are under the regular scattering i.e., straight linearity by the points. The usual methods of statistics aren't applicable, while the visible plot examination is appropriate. In addition, a general residual plot (external studentized residuals Versus usual probability percent) was employed to measure and ensure the accuracy of the adapted model [16]. Further, the effect of test orders on the adapted model was illustrated by the residuals versus test order [17]. In the present work, linear distribution of the external studentized residuals with a slight variation was noted denoting that the selected model was admissible statistically [18]. Figure depicts experimental operations set against the residuals, indeed a working method to recognize the slinking variables which may alter the study results. An arbitrary distribution pattern is noted in the chart that denotes time dependant variables lurking in the framework.

Table 4. Summary of the ANOVA for all the responses

	Intercept	A	B	C	AB	AC	BC	A^2	B^2	C^2
Folding endurance	119.667	28.375	0.125	-10.5	-3.25	-4.5	-10	-6.95833	-50.9583	0.791667
p-values		<0.0001	0.9403	0.0002	0.1933	0.0848	0.0024	0.0131	<0.0001	0.7272
Swelling Index	69	14.625	5.625	16.75	-4	-2.25	4.25	-2.75	2.75	-7.5
p-values		< 0.0001	0.0004	<0.0001	0.0180	0.1339	0.0136	0.0659	0.0659	0.0004
Bioadhesion strength	57.8333	15.875	0.75	5.875	2	0.75	-2.5	-5.54167	1.20833	-3.04167
p-values		<0.0001	0.3503	<0.0001	0.0983	0.5029	0.0476	0.0006	0.2718	0.0178

ANOVA was conducted to examine the intervention of quantifiable effects of the fact factors. Polynomial equations were derived by subjecting the data to multiple regressions. The equations obtained from the output of the possible optimum model were mentioned below. ANOVA for Quadratic model

Final Equation in Terms of Coded Factors

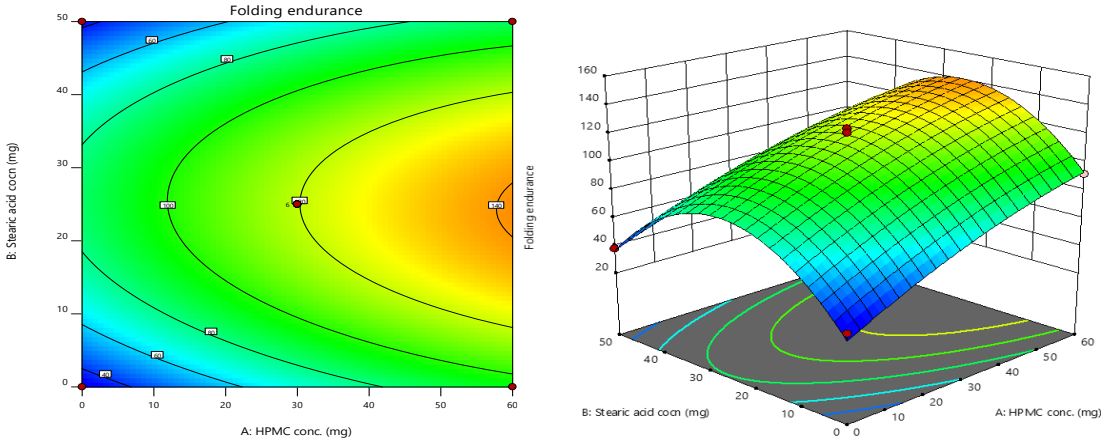
Folding endurance = +119.67 +28.37 A +0.1250 B -10.50 C -3.25 AB -4.50 AC -10.00 BC -6.96 A^2 -50.96 B^2 +0.7917 C^2

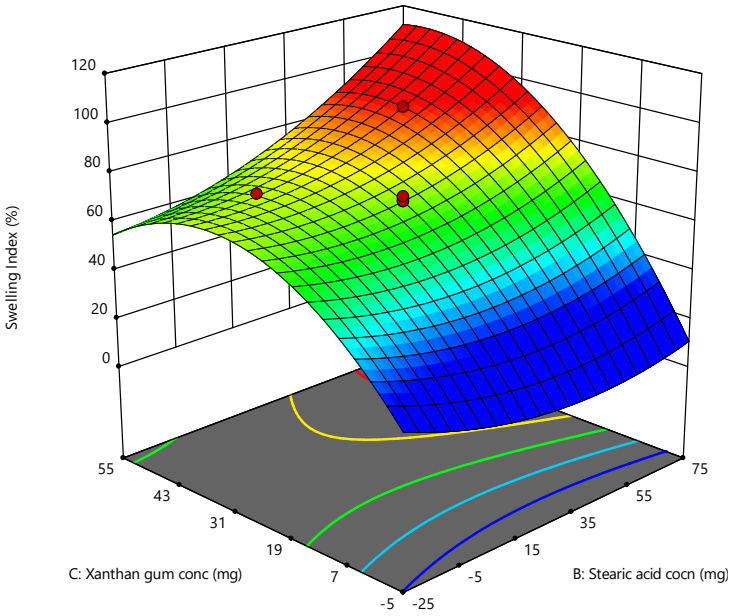
Swelling Index= +69.00 +14.62 A +5.62 B +16.75 C -4.00 AB -2.25 AC +4.25 BC -2.75 A^2

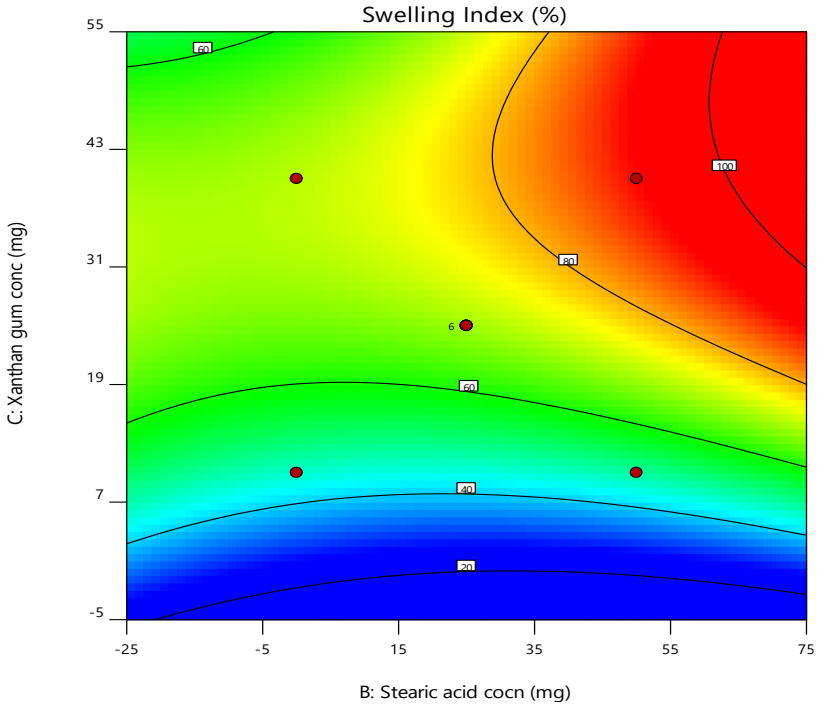
+2.75 B^2 -7.50 C^2

Bioadhesion strength=+57.83 +15.87 A +0.7500 B +5.88 C +2.00 AB +0.7500 AC -2.50 BC -5.54 A^2 +1.21 B^2 -3.04 C^2

Further, the influence of individual parameters on responses was analysed and interpreted by RSM [Figure 3] [43]. The contour plot which gives the association of chosen responses with the variables ensures the variable effects. RSM was employed to estimate and interpret the response of independent parameters against the obtained discrete responses. 3-dimensional surface graphs are crucial to illustrate the interactivity and main effect. The obtained responses are forecasted by contour plots[19].




Swelling Index (%)
120
100
80
60
40
20
0
55
43
31
19
7
-5
C: Xanthan gum conc (mg)
-25
-5
15
35
55
75
B: Stearic acid cocn (mg)


Swelling Index (%)
C: Xanthan gum conc (mg)
55
43
31
19
7
-5
-25
-5
15
35
55
75
B: Stearic acid cocn (mg)
60
80
100
40
20
6

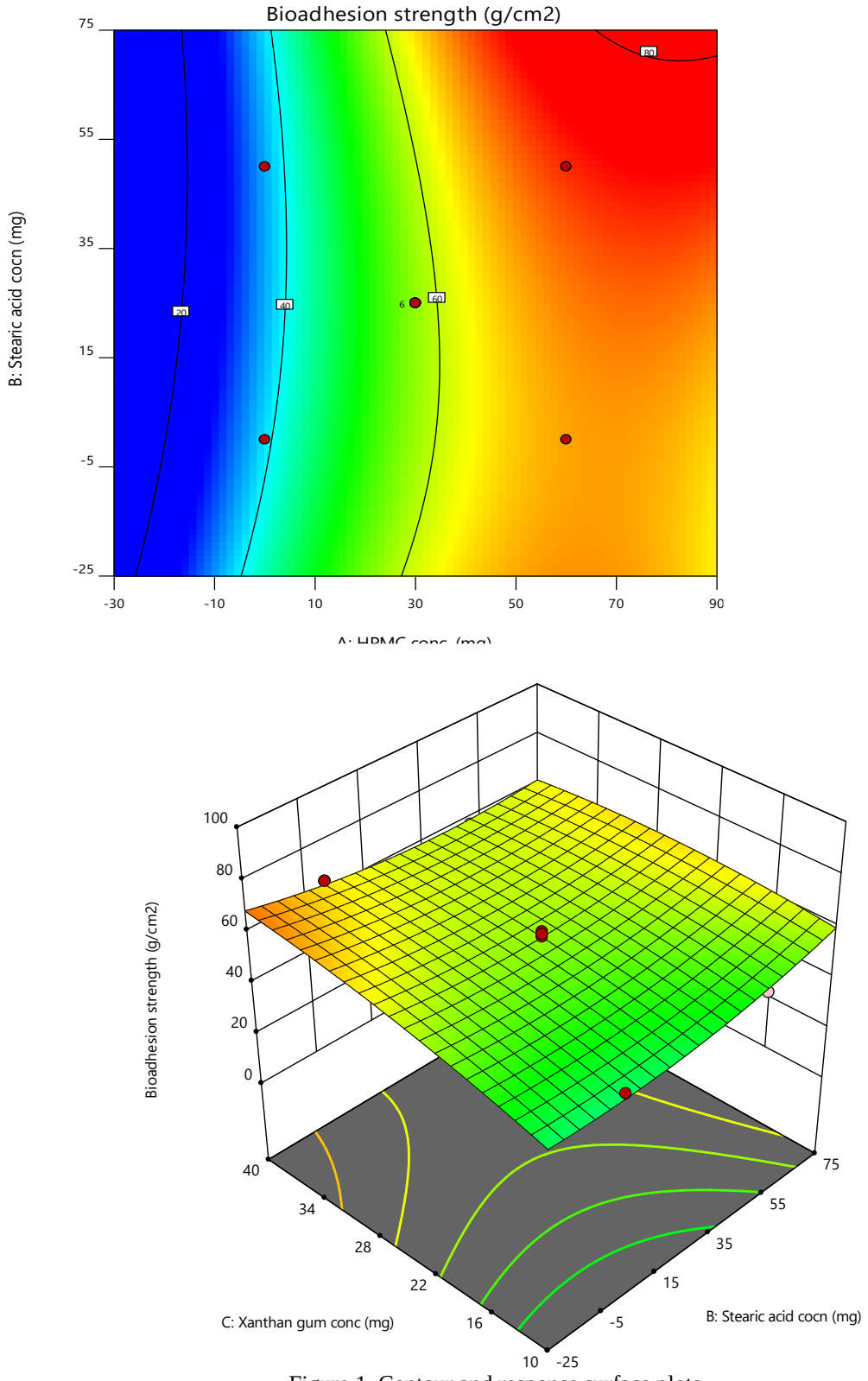


Figure 1. Contour and response surface plots.

To standardize the model's order obtained from statistical analysis, the function of global desirability (D) was employed. Every response was laid a limit (PS-Minimum and EE-Maximum) to draft an inlay plot to enhance the independent variables. All the feasible individual parameters were included in the method for standardization. HPMC concentration 60, Stearic acid 25.047 and Xanthan Gum 34.6753

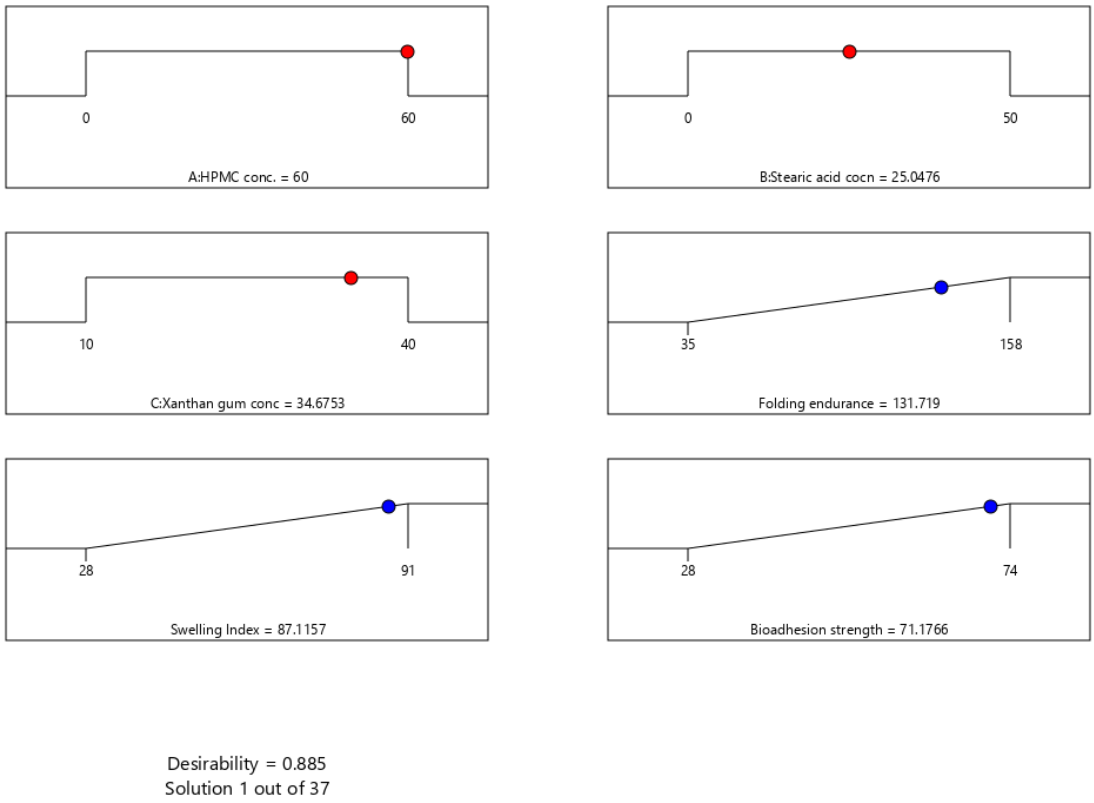


Figure 2. Optimization results.

Evaluation of optimized formulation

O-EH-UF has been evaluated for various physico-chemical properties and the result were summarized in Table 5. The uniformity of weight of the patches was observed in the range of 0.213±0.033 g. The patches were having a thickness of 0.94 ± 0.02 mm. For all the patches folding endurance was more than 100 denoting good flexibility and integrity.

Mechanical strength is the tangential force exerted on the ball through uniform area in the film. Bursting machine was used for the test and positive results were obtained inferring that O-EH-UF has an adequate mechanical strength, which can be credited to the standardized concentrations of plasticizers.

Degradability test (pH 6.5) of the prepared layers illustrate an improvement in rigidity and thickness in wet condition than the dry condition. Samples from standardized formula were tested at pH 1.2 and 6.5 with type II apparatus. Young's modulus for the wet samples tested at pH 6.5 was 0.110 N/mm2 after 5 hours, while for samples tested at pH 1.2 was 0.302 N/mm2 after 6 hours.. The results showed that the alteration in gastric pH due to food intake, disease and drugs will not modify the drug release or the enlargement of the prepared drug system. It was noted that both rigidity and thickness was reduced significantly at intestinal pH (6.5) than the stomach pH (1.2). These results denote that the formulated system is disintegrated quickly and more elastic at intestinal pH and will not remain in the intestines for longer duration, leading to side effects, if preterm eviction occurs.

Table 5. Evaluation tests for optimized formulation.

S. No	Formulation	Test	Result (Avg ±S.D)
1.		Weight variation	0.213±0.033 g
2.		Thickness	0.94±0.02 mm
3.	O-IH-UF	Mechanical strength	1.7±0.03 kg/cm^2
4.		Drug content	101.79±0.10 %
5.		Retention time	> 10 h

A notable change was seen in the length of the optimized preparation by using 30-300 g of weight. These results indictate that PEG offers a good plasticizing effect for polymeric film yet it also increases penetrability of water vapour in the film. O-EH-UF have maximum tensile strength of 270 g (breaking of film was observed at 300 g) [Figure 3].

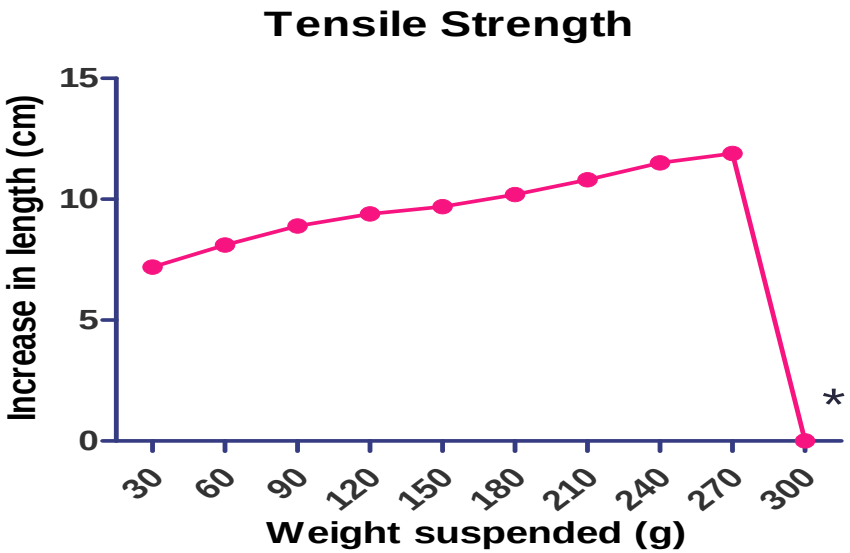


Figure 3. Tensile strength studies

Unfolding test and In vitro drug release studies:

Unfolding test was done using USP II apparatus (Fig. 13) with HCL (pH 1.2) as medium. Also other test was conducted with acetate buffer solution (pH 4.1) on the standardized formula. The capsules were broken down within 3–5 min. Formulated layers must unfold within 10-15 min after intake to avoid preterm eviction. The dimensions of the unfold layer must be greater that the size of relaxed pyloric sphincter [20]. The layers exhibited improved stickiness when got in contact with the test medium. Various anti adhesive agents were employed to avoid the stinking before unfolding.

EH release from pure EH solution and optimized formulation was and the results were shown in Figure 5. Studies were conducted for 24 h. An improper IH release was seen due to solubility issues. Quick release of EH was seen in first 3-4 h, and later a steady-state release was observed till the end of the study. The cumulative IH release from O-EH-UF shows a rapid release (3 h) of around 40-45% of EH from the total amount. The quick release at first is due to the presence of EH at the surface of the film, which allows a great diffusion of water through the liquid matrix, and thus causing quick release. Later a steady phase with constant drug release is seen till 24 h. The total quantity of drugs released from standardized preparation was around 99.24% [Figure 4].

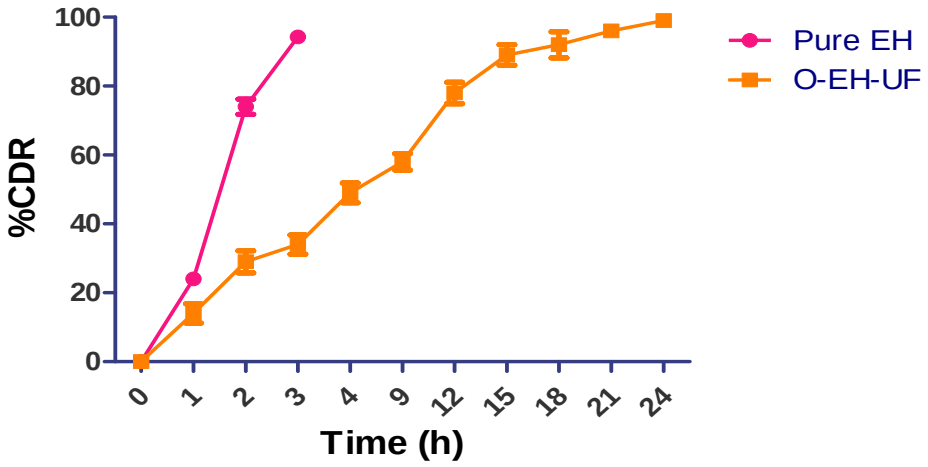


Figure 4. In vitro drug release studies.

CONCLUSION:

The study aimed to formulate an expandable delivery system that can prolong the release of EH for a minimum of 24 h and can be held in the GI system for a longer duration irrespective of fed/fasted conditions. This expansion results in improved bioavailability, reduced dose frequency, and side effects. In this study, a single-layered gastro retentive extendible film loaded with IH was prepared with the design of experiments. Execution of the optimized result achieves good folding endurance. Optimized formulation was found to unfold within 15 min, ensuring preterm eviction avoidance. The developed formulation has shown considerable tensile strength, mechanical strength, and degradability. The in vitro drug release test confirms the complete and sustained release of IH by the end of 24 h. The floating and mechanical performance of the film revealed the gastro retentive potential of the dosage form.

REFERENCES:

[1] Naveen NR, Gopinath C, Rao DS. Design expert supported mathematical optimization of repaglinide gastroretentive floating tablets: In vitro and in vivo evaluation. *Futur J Pharm Sci*. Epub ahead of print 2017. DOI: 10.1016/j.fjps.2017.05.003.

[2] Garg R, Gupta G. Progress in Controlled Gastroretentive Delivery Systems. *Trop J Pharm Res*; 7. Epub ahead of print 2008. DOI: 10.4314/tjpr.v7i3.14691.

[3] Naveen NR, Gopinath C, Rao DS. Isolation and assessment of natural mucoadhesive agent isolated from Abelmoschus esculents. *J Pharm Res* 2017; 11: 438–443.

[4] Mahor S, Chandra P, Prasad N. Design and in-vitro Evaluation of Float-adhesive Famotidine Microspheres by using Natural Polymers for Gastroretentive Properties. *Indian J Pharm Educ Res* 2021; 55: 407–417.

[5] Sreeharsha N, Naveen NR, Anitha P, et al. Development of Nanocrystal Compressed Minitablets for Chronotherapeutic Drug Delivery. *Pharmaceuticals (Basel)*; 15. Epub ahead of print 4 March 2022. DOI: 10.3390/ph15030311.

[6] Rizg WY, Naveen NR, Kurakula M, et al. QbD Supported Optimization of the Alginate-Chitosan Nanoparticles of Simvastatin in Enhancing the Anti-Proliferative Activity against Tongue Carcinoma. *Gels (Basel, Switzerland)*; 8. Epub ahead of print 1 February 2022. DOI: 10.3390/GELS8020103.

[7] Aj R, Hn Y, Sb S. Natural gums as sustained release carriers: Development of gastroretentive drug delivery system of ziprasidone HCl. *DARU, J Pharm Sci*; 20. Epub ahead of print 2012. DOI: 10.1186/2008-2231-20-58.

[8] Naveen NR, Nagaraja TS, Bharathi DR, et al. Formulation Design and In Vitro Evaluation for Stomach Specific Drug Delivery System of Anti Retroviral drug–Acyclovir. *Int J Pharm Life Sci* 2013; 4: 2506–2510.

[9] Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro-in vivo evaluation in healthy human volunteers. *Eur J Pharm Biopharm*; 74. Epub ahead of print 2010. DOI: 10.1016/j.ejpb.2009.11.010.

[10] Alaithan S, Naveen NR, Goudanavar PS, et al. Development of Novel Unfolding Film System of Itopride Hydrochloride Using Box-Behnken Design—A Gastro Retentive Approach. *Pharm 2022, Vol 15, Page 981* 2022; 15: 981.

[11] Rizg WY, Naveen NR, Kurakula M, et al. Augmentation of Antidiabetic Activity of Glibenclamide Microspheres Using S-Protected Okra Powered by QbD: Scintigraphy and In Vivo Studies. *Pharmaceuticals* 2022; 15: 491.

[12] Naveen NR. Design and characterization of sustained release matrix tablets of glimepiride by using synthetic and natural polymers. *Int J drug Discov Herb Res* 2013; 3: 573–578.

[13] Madgulkar AR, Bhalekar MR, Kapse SB, et al. Transdermal permeation enhancement of valsartan using solid lipid nanoparticles. *Res J Pharm Technol*; 4.

[14] Aldawsari HM, Raghavendra Naveen N, Alhakamy NA, et al. Compression-coated pulsatile chronomodulated therapeutic system: QbD assisted optimization. *https://doi.org/101080/1071754420222094500* 2022; 29: 2258–2268.

[15] Islam MM, Ramesh VH, Bhavani D, et al. Optimization of process parameters for fabrication of electrospun nanofibers containing neomycin sulfate and Malva sylvestris extract for a better diabetic wound healing. *https://doi.org/101080/1071754420222144963* 2022; 29: 3370–3383.

[16] I S, K K, N S. Interaction pattern and in vitro, in vivo release behavior of simvastatin-loaded chitosan nanoformulation. *Drug Dev Ind Pharm* 2019; 45: 1725–1739.

[17] Ahmed OAA, Kurakula M, Banjar ZM, et al. Quality by design coupled with near infrared in formulation of transdermal glimepiride liposomal films. *J Pharm Sci*. Epub ahead of print 2015. DOI: 10.1002/jps.24448.

[18] Singh B, Kapil R, Nandi M, et al. Developing oral drug delivery systems using formulation by design: Vital precepts, retrospect and prospects. *Expert Opinion on Drug Delivery*. Epub ahead of print 2011. DOI: 10.1517/17425247.2011.605120.

[19] Adetunji AI, Olaniran AO. Statistical modelling and optimization of protease production by an autochthonous Bacillus aryabhattai Ab15-ES: A response surface methodology approach. *Biocatal Agric Biotechnol*. Epub ahead of print 2020. DOI: 10.1016/j.bcab.2020.101528.

[20] Sivaneswari S, Karthikeyan E, Chandana PJ. Novel expandable gastro retentive system by unfolding mechanism of levetiracetam using simple lattice design – Formulation optimization and in vitro evaluation. *Bull Fac Pharmacy, Cairo Univ* 2017; 55: 63–72.