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Development and Optimization of Thiolated Polymer-based Gastroretentive Drug Delivery Systems with Enhanced Mucoadhesion

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ABSTRACT

In this study, a novel class of mucoadhesive gastroretentive drug delivery systems (GRDDS) has been developed, focusing on the theory of mucoadhesion. The initial generation of mucoadhesive polymers demonstrated inefficient adhesion to gastrointestinal mucosa, thereby failing to ensure prolonged gastroretention. To address this limitation, thiolated polymers were employed, forming robust covalent bonds through thiol/disulfide exchange reactions with cysteine-rich subdomains of mucus. This innovative approach not only enhanced gastroretention but also facilitated biodegradation. The design of experiments (DOE) methodology was applied, specifically utilizing response surface methodology (RSM) and the Box-Behnken design. Thermo-gravimetric analysis (TGA) (X1) and NaCl-HCl concentration (X2) were selected as critical factors with varying levels (min, mean, max). The mucoadhesion potential, a key response variable, was systematically optimized through experimental runs to identify the ideal conditions. The selected optimal experimental conditions were then translated into the preparation of tablets, which were subsequently evaluated for gastroretention based on in vitro swelling and mucoadhesion studies. The results demonstrated that the developed GRDDS exhibited enhanced mucoadhesion potential, promising extended gastroretention capabilities. This research highlights the significance of thiolated polymers in designing efficient gastroretentive drug delivery systems and provides valuable insights into the optimization of mucoadhesion properties using a systematic experimental approach.

Keywords: Thiolation mucoadhesive properties, drug delivery systems.

INTRODUCTION

The conception of mucoadhesion, as well as mucoadhesion polymers, was developed in the mid 1980s as an intriguing methodology especially for targeting the delivery of drugs at a site or at the absorption window. Mucoadhesive polymers become adhesive on hydration and characterized to have prolonged contact and residence time with the mucous membrane [1]. Despite a few notable exceptions, gastric mucoadhesive systems do not reach their full potential. The success of the majority of the first generation mucoadhesion polymers was limited owing to their insufficient adhesion (such as hydrogen bonds, ionic interactions, and Van der Waals forces etc.) to gastrointestinal tract (GIT), accordingly, cannot assure localization of dosage forms [2].

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Feasible new era of mucoadhesive polymers are thiolated polymers [3], (bearing thiol side chain) alleged thiomers have proven to be a promising new class of polymeric excipients. Instead of entrenched polymers, thiomers can form strong covalent bonds via thiol/disulfide exchange reactions with cysteine-rich subdomains of mucus [4]. As per the need, thiomers ensure the localization of the dosage form for an extended time with good biodegradation. As the oxidation of thiol groups alters their interaction with cysteine-rich subdomains of mucus glycoproteins, thus limiting their mucoadhesive efficacy [5], thiolated polymers were S-protected with mercaptopyridine analogues such as 2-mercapto-nicotinic acid (MA) that increases the reactivity of thiol groups due to the electron shrinkage effect of the pyridine π system [6]. Mucoadhesion, the ability of certain materials to adhere to mucosal surfaces, has gained significant attention in the field of pharmaceutical and drug delivery research. It plays a pivotal role in the design and development of novel drug delivery systems, particularly those aimed at improving the localized and sustained delivery of therapeutic agents to mucosal membranes. One such natural material that exhibits intriguing mucoadhesive properties is "gumghatti," also known as gum tragacanth. Gumghatti, derived from the resin of the Astragalus plant, has been utilized for centuries in various applications, from traditional medicine to culinary arts. However, in recent years, its mucoadhesive potential has been explored, particularly in the realm of pharmaceutical formulations [7]. The mucoadhesive properties of gum tragacanth are attributed to its unique chemical composition, which includes a complex mixture of polysaccharides, proteins, and other bioactive components. These natural compounds enable gum tragacanth to adhere to mucosal surfaces, such as those found in the gastrointestinal tract, nasal passages, and the oral cavity. The adhesive interactions between gum tragacanth and mucosal tissues are a result of various intermolecular forces, including van der Waals forces, hydrogen bonding, and electrostatic interactions.

The utilization of gumghatti as a mucoadhesive agent holds immense promise for drug delivery applications. It can enhance the residence time of pharmaceutical formulations on mucosal surfaces, thus improving drug absorption and bioavailability. Moreover, its natural origin and biocompatibility make it an attractive candidate for the development of safe and effective drug delivery systems. In the forthcoming sections of this research, we delve into a detailed exploration of gumghatti's mucoadhesive properties, shedding light on its potential applications in various drug delivery systems, including gastroretentive formulations [8]. Through comprehensive investigations, we aim to contribute to the growing body of knowledge surrounding mucoadhesion and its role in pharmaceutical science, thereby offering innovative solutions for improved drug delivery and therapeutic outcomes.

MATERIALS AND METHODS

Materials

Aurobindo Pharma of Hyderabad, India, generously donated to Esomeprazole. Tarrow chemicals (India) was contacted for gumghatti, thioglycolic acid and Chitosan, all of which were used in their pure forms. All of the other solvents and compounds are of analytical quality.

Preparation of TGG

Pure gum ghatti (2 g) was firstly dissolved in 50 mL of deionized water, followed by the addition of EDAC (50 mM) and thioglycolic acid (4 g). The aforementioned reaction mixture was kept undisturbed for 3 hr at room temperature. Further, the reaction mixture was added in dialysis membrane and dialyzed against 5 mM hydrochloric acid (HCl) at 10 ± 1 °C for 1 hr, against 5 mM HCl containing sodiumchloride (1%) for 2 hr at room temperature and against 1 mM HCl containing sodiumchloride (1%) for 2 hr at room temperature. Afterwards, the reaction mixture was collected and lyophilized (Allied frost, Delhi, India) at -30 ± 1 °C under 10.01mbar pressure and the mixture were kept at +4 °C [9]. Chemical reaction depicting the synthesis of thiolated polymer is shown in Figure 1.

Table 1: Optimization design summary

Factors/ Independent Variables	Levels			Responses/Dependent Variables	Constraints
	Min	Mean	Max		
TGA conc.- X1	1.17	4	6.83	Thiol content	Maximum
NaCl acid conc-X2	0.5858	2	3.41	Viscosity	Maximum
				Mucoadhesion Time	Maximum

Evaluation of experimental runs

Thiol content

Using Ellman's reagent, the degree of thiol group substitution was measured [10]. The amount of accurately weighed thiolated gum ghatti (50 mg) was dissolved in water (25 ml). Aliquot (2.5 ml) was taken from the above prepared solution and was diluted with 2.5 ml of 0.5 M phosphate buffer (pH 8.0) and was allowed to react with 5 ml of Ellman's reagent for two hours. The absorbance of reaction mixture was measured using UV spectrophotometer at 450 nm. The total number of thiol groups was calculated using the standard curve of thioglycolic acid with Ellman's reagent.

Viscosity

Rheological behaviour of gum ghatti and thiolated gum ghatti was analyzed using rheometer (MCR 92, Anton Paar, Austria).For temperature sweep analysis, samples were analyzed in temperature range of 20 °C to 60 °C with 2 °C/min constant shear rate of 10s-1. The samples were carried out under shear rate sweep analysis ranging from 0.1 to 1000 s-1 to evaluate the flow behavior, with a data acquisition duration varying from 30 sec on a logarithmic scale at a constant temperature of 25°C [11].

Mucoadhesion Time

Individual gastric mucoadhesive tablets were wetted with buffer (0.1 N HCl), then adhere to the freshly excised goat gastric mucosa (which was glued to glass slide by means of cyanoacrylate) by applying little pressure with fingertip for about 25-30 sec and analyzed for mucoadhesion time by placing the glass slide in a beaker, which consists of 200 ml SGF at 37±0.5 °C. Gastric environment was stimulated by applying a moderate stirring rate of 50 rpm and retention of tablets were monitored for about 12 h.

Characterization of gg and TGG

GG and TGG were characterized by FTIR and DSC as explained in section 4.4.2.

Surface morphology

Scanning electron microscopy (SEM) was performed to characterize the surface morphology of the GG and prepared TGG. This was done by using a JSM 6100 JEOL Scanning Electron Microscope at 20 kV. Prior to assessment, samples were gold coated to render them electrically conductive and examined under the microscope.

X-ray diffraction (XRD) analysis [12]

XRD was done on Inxitu Benchtop XRD/XRF Instrument at 250 exposures in an ambient state.

Assessment of mucoadhesion potential of gg and tgg

The mucoadhesive property of the GG and TGG was compared with carbopol (CP) and sodium alginate (SA) through in vitro and ex vivo methods. For ex vivo methods, the stomach portion of a goat was removed immediately after slaughter and preserved in tyrode solution (sodium chloride 8 g/l; potassium chloride 0.2 g/l; calcium chloride 2 H2O 0.134 g/l; sodium bicarbonate 1.0 g/l; sodium dihydrogen phosphate 0.05 g/l; and glucose H2O 1.0 g/l.) until its removal for the experimental use.

Formulation of gastro retentive mucoadhesion tablets

EH gastro retentive mucoadhesion tablets were prepared by using 8%PVP K30 in 80% ethanol solution as granulating medium. Subsequent to being grinded and sifted, required amounts of EH, GG/TGG/Chitosan, and all other excipients (Table 2) were blended thoroughly, consequently passed through sieve #80. Required proportions of granulating medium was added to the powder blend and screened under #10-12 mesh to obtain wet granules. These granules were dried at 55-60°C for about 60 min and dampness was maintained between 3% to 5%. The dried granules which were retained on sieve #14-20, lubricated by adding prescribed amount of magnesium stearate and talc. Finally, the tablets were compressed by using flat faced 8-mm punches in 9-station rotary tablet punching machine (Chamunda pilot press, Ahmedabad, Gujarat, India) and compression force was adjusted to control the hardness within 8-9 kg/cm2 [13].

Table 2: Formulation of EH mucoadhesive tablets*.

	EH-MUCO-1	EH-MUCO-2	EH-MUCO-3	EH-MUCO-4	EH-MUCO-5	EH-MUCO-6
GG	37.5	60	--	--	--	--
TGG	--	--	37.5	60	--	--
Chitosan	--	--	--	--	37.5	60

Each formulation contains EH, magnesium stearate (4 mg), talc (4 mg) and microcrystalline cellulose (MCC) - quantity sufficient to produce 200 mg tablet.

Pre compression parameters

Prepared granules were evaluated for different pre compression parameters like angle of repose, Hausner's ratio and compressibility index.

Ex vivo mucoadhesion time [14,15]

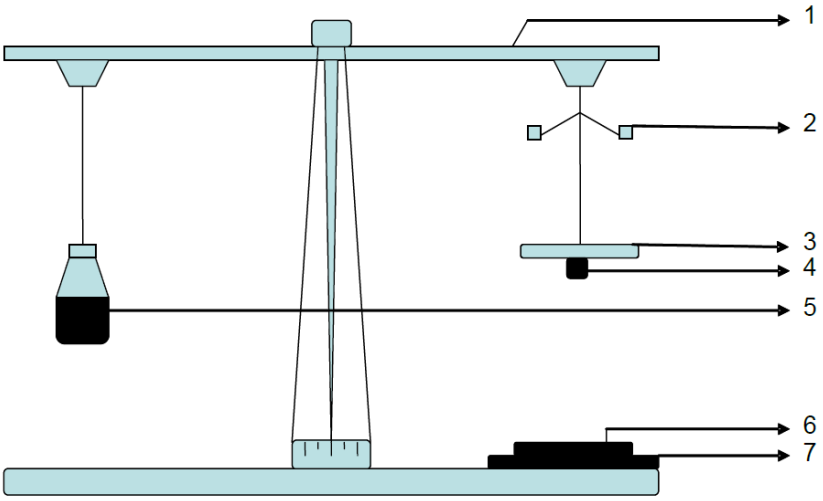
Ex vivo residence time of prepared tablets were also analyzed by modifying dissolution apparatus (TDT-08L-USP type I, Electro lab, India). Freshly excised gastric mucosa was glued to external surface of the basket and the hydrated tablets were attached with a little force. Subsequently, the basket was immersed in the relevant media (0.5 L 0.1N SGF at 37±0.5 °C). The time requisite for detachment was noted after exposing the basket to 100 rpm.

Measurement of bioadhesion

The ex vivo adhesion studies were conducted using a modified balance method as explained in section (Fig.1).The force in terms of Newton's was calculated by the using following formula,

$$F = \frac{0.00981}{2} \times W$$

Where, W is the amount of water.



[1. Modified physical balance, 2. Counter weights, 3.Upper Glass Slide, 4.Tablet, 5. Conical flask to hold water, 6.Goat intestine, 7. Lower glass slide]

Fig 1: Experimental setup of detachment force measurement.

In vitro drug release studies

Drug release from all the prepared batches were performed using USP dissolution apparatus II (TDT-08L, Electro lab, India) at 50 rpm with 900 ml of SGF buffer as dissolution medium. Constant temperature (37±0.5 °C) was maintained throughout the study period. Aliquots (10 ml) were withdrawn at various time intervals and replaced with same amount of fresh medium, which was maintained at the same temperature. Subsequently, samples were filtered through 0.45 µm millipore filter, followed by suitable dilution and analysed

for drug content by UV Spectrophotometer (Shimadzu UV-18009, Japan) at 223 nm [16-18].

In vitro dissolution studies were further carried out by modified paddle method to mimic the in vivo adhesion of dosage form. A piece of freshly excised gastric mucosa was glued to watch glass and wetted tablet was attached by applying minimum pressure with finger tips. Study was further conducted by placing watch glass in dissolution vessel. Samples were analysed same as paddle method. Both the dissolution methods were compared for resemblance in drug release by calculating difference factor (f1) and similarity factor (f2), considering paddle method as reference and modified method as test [19]. Drug release kinetics were calculated by using MS Office excel work sheet (version-2007). Rate constants, correlation coefficients (r2) for all the kinetics models were calculated and release mechanism can be concluded from peppas model.

RESULTS AND DISCUSSION

Synthesis of thiolated polymer and formulation of mucoadhesive drug delivery systems

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 3. 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 4-9]. A quadratic high order polynomial model was chosen, where the auxiliary terms are notable and the model is not aliased.

Table 3: Experimental runs and responses observed.

		Factor 1	**Factor 2**	**Response 1**	**Response 2**	**Response 3**
Std	Run	A:TGA conc	B:NaCl conc	Thiol content	Viscosity	Mucoadhesion Time
		g	%	mM	mPas	h
4	1	6	3	2.8	38	4.8
13	2	4	2	4.8	48	4.8
6	3	6.82843	2	3.1	21	5
9	4	4	2	4.7	47	4.9
3	5	2	3	2.9	49	5.5
2	6	6	1	3.2	33	6
8	7	4	3.41421	2.6	54	5.5
1	8	2	1	3.2	56	3.7
12	9	4	2	4.8	46	4.4
5	10	1.17157	2	2.8	39	3.9
7	11	4	0.585786	3.8	58	5
11	12	4	2	4.9	47	4.8
10	13	4	2	5	49	4.9

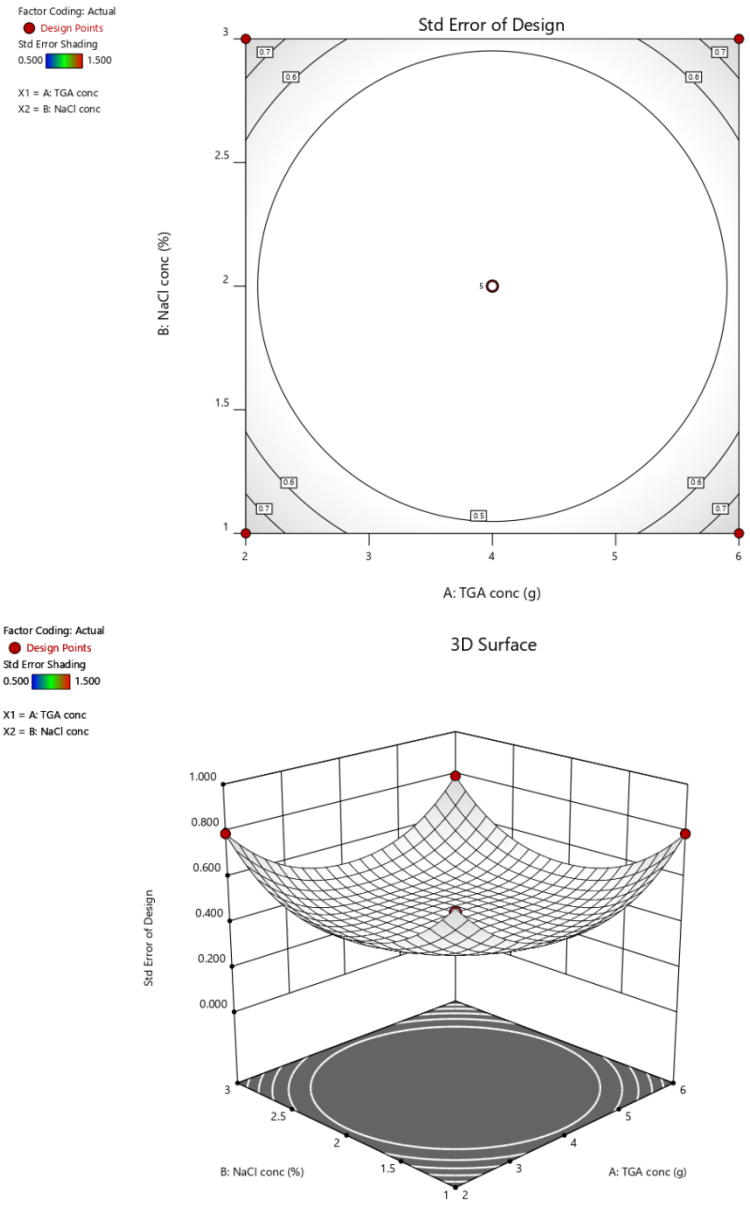


Fig 2: Standard error for design.

Table 4: Fit Summary and ANOVA for Quadratic model

Response 1: Thiol content

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.7059	0.0002	-0.1193	-0.4770	
2FI	0.9635	0.0001	-0.2433	-1.1341	
Quadratic	< 0.0001	0.0998	0.9660	0.8855	Suggested
Cubic	0.0359	0.5687	0.9874	0.9631	Aliased

Table 5: Fit Statistics

Std. Dev.	**0.1755**	**R^2**	**0.9802**
Mean	3.74	Adjusted R^2	0.9660
C.V. %	4.69	Predicted R^2	0.8855
		Adeq Precision	17.6557

The Predicted R^2 of 0.8855 is in reasonable agreement with the Adjusted R^2 of 0.9660; i.e. the difference is less than 0.2. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 17.656 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Thiol content = +4.84 +0.0405 A -0.2996 B -0.0250 AB -0.9575 A^2-0.8325 B^2

Table 6: Fit Summary

Response 2: Viscosity

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.1021	0.0003	0.2397	-0.3699	
2FI	0.5250	0.0002	0.1943	-0.3310	
Quadratic	< 0.0001	0.1405	0.9748	0.9191	Suggested
Cubic	0.1012	0.2826	0.9859	0.8890	Aliased

The Model F-value of 93.97 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, AB, A^2, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The Lack of Fit F-value of 3.28 implies the Lack of Fit is not significant relative to the pure error. There is a 14.05% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Table 7: Fit Statistics

Std. Dev.	1.60	R^2	0.9853
Mean	45.00	Adjusted R^2	0.9748
C.V. %	3.56	Predicted R^2	0.9191
		Adeq Precision	34.7594

The Predicted R^2 of 0.9191 is in reasonable agreement with the Adjusted R^2 of 0.9748; i.e. the difference is less than 0.2. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 34.759 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Viscosity = +47.40 -7.43 A -0.9571 B +3.00 AB -8.45 A^2 +4.55 B^2

Table 8: Fit Summary

Response 3: Mucoadhesion Time

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.1524	0.0162	0.1763	-0.4655	
2FI	0.0012	0.1201	0.7298	0.5461	
Quadratic	0.0060	0.7850	0.9194	0.8708	Suggested
Cubic	0.9809	0.3641	0.8880	0.3230	Aliased

The Model F-value of 28.37 implies the model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The Lack of Fit F-value of 0.36 implies the Lack of Fit is not significant relative to the pure error. There is a 78.50% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

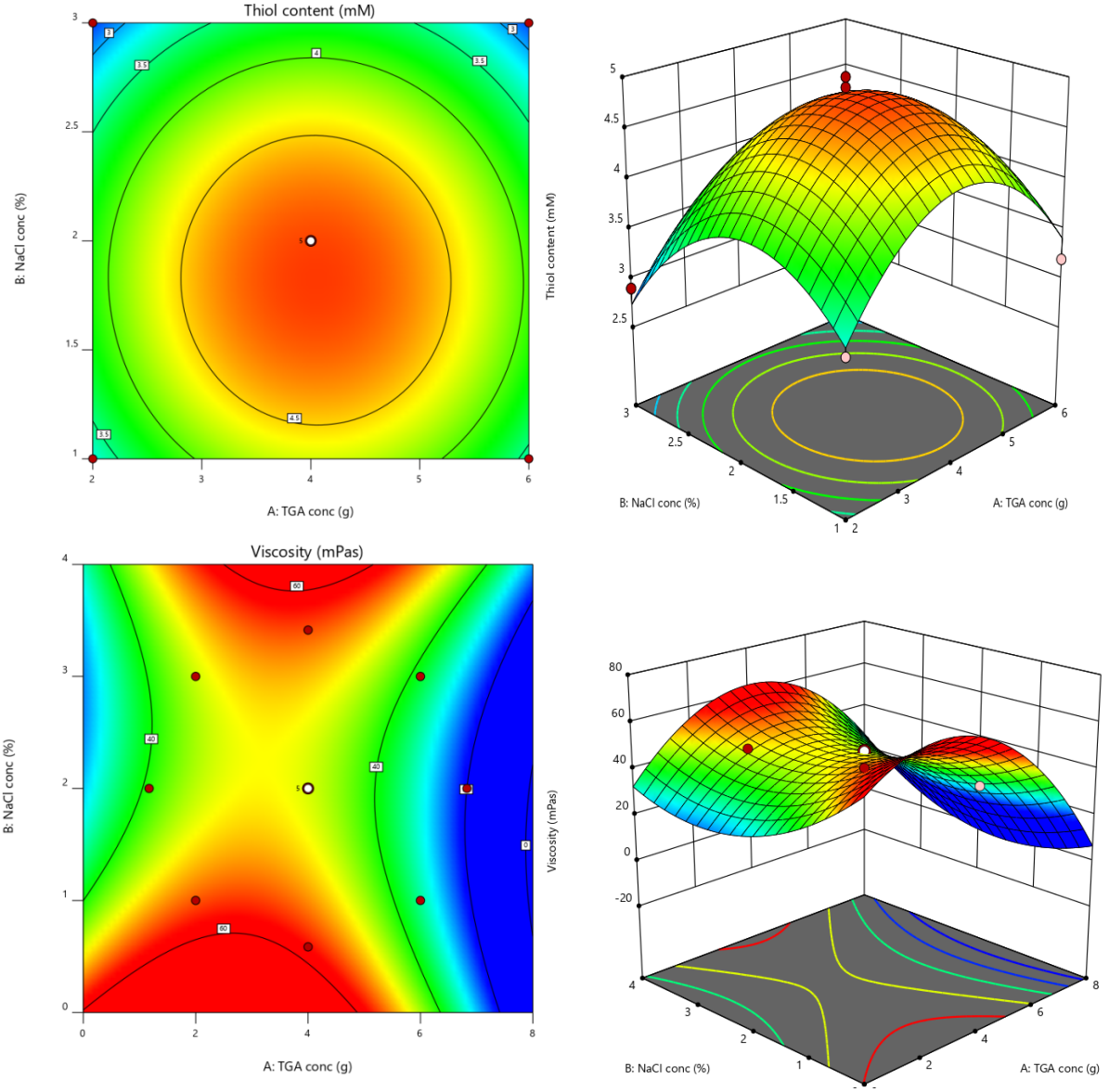
Table 9: Fit Statistics

Std. Dev.	0.1767	R^2	0.9530
Mean	4.86	Adjusted R^2	0.9194
C.V. %	3.64	Predicted R^2	0.8708
		Adeq Precision	19.0620

The Predicted R^2 of 0.8708 is in reasonable agreement with the Adjusted R^2 of 0.9194; i.e. the difference is less than 0.2. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 19.062 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Mucoadhesion Time = +4.76 +0.3945 A +0.1634 B -0.7500 AB -0.1175 A^2 +0.2825 B^2



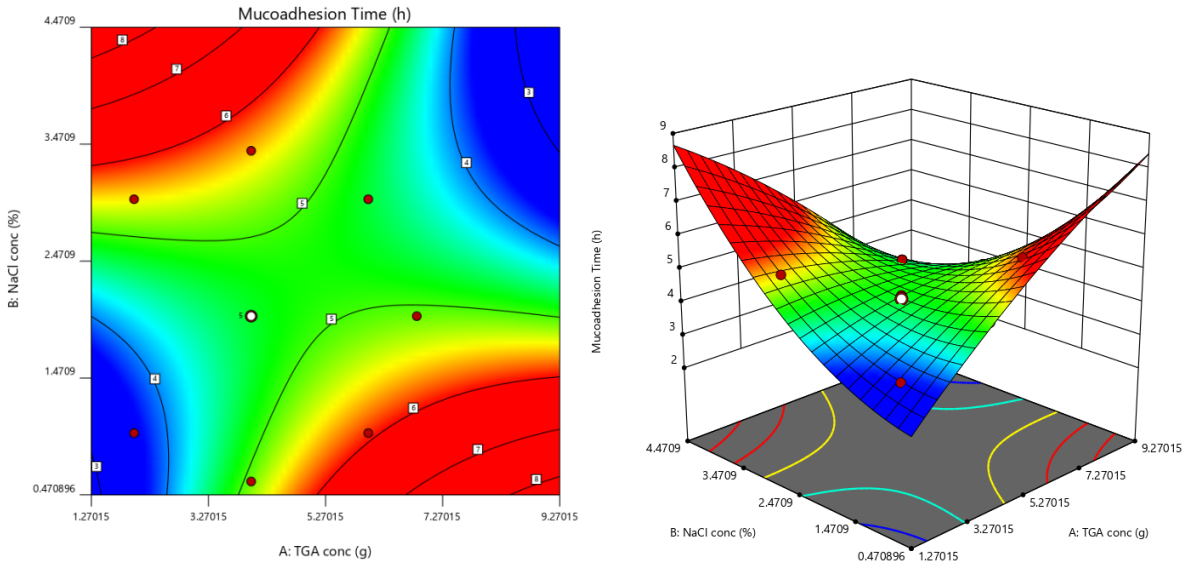
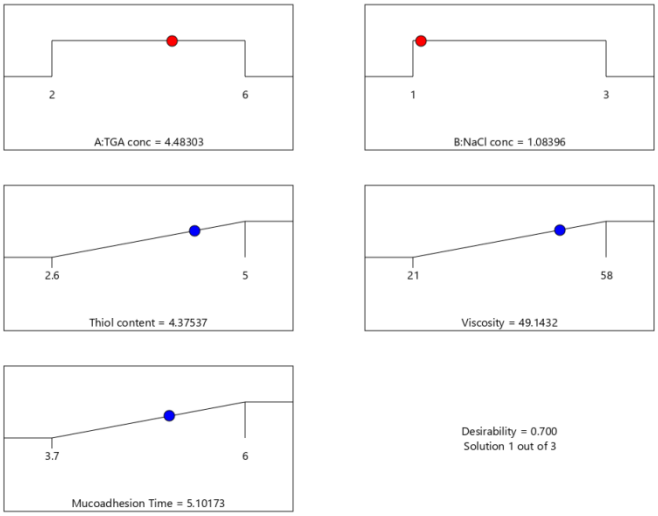


Fig 3: Contour plots and 3-D RSG for response 1, 2 and 3.



Fie 4: Desirability plot.

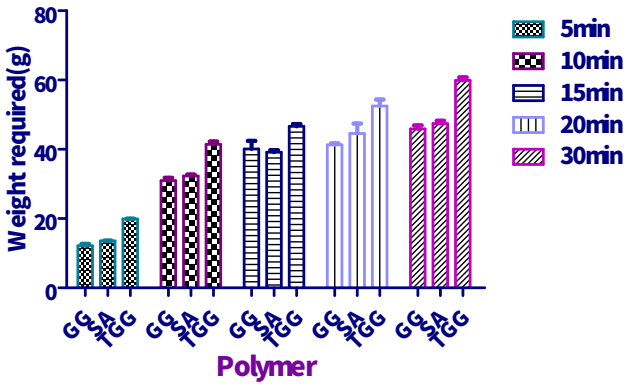


Fig 5: Mucoadhesion strength of 1.5% of polymer solutions determined by shear stress method.

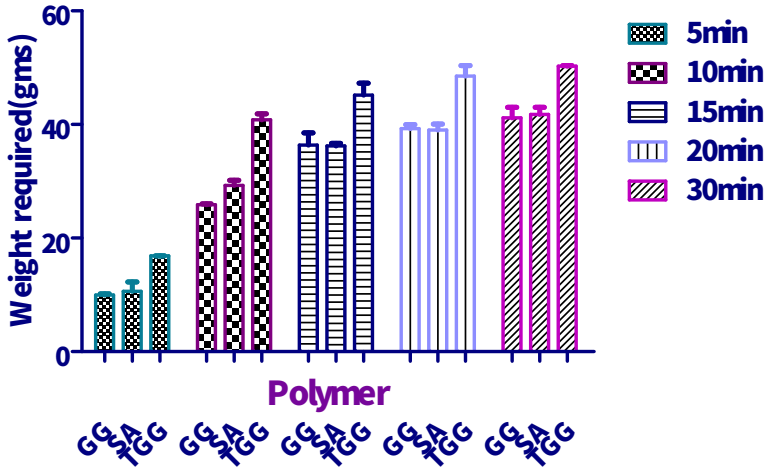


Fig 6: Mucoadhesion strength of 0.5% of polymer solutions determined by shear stress method.

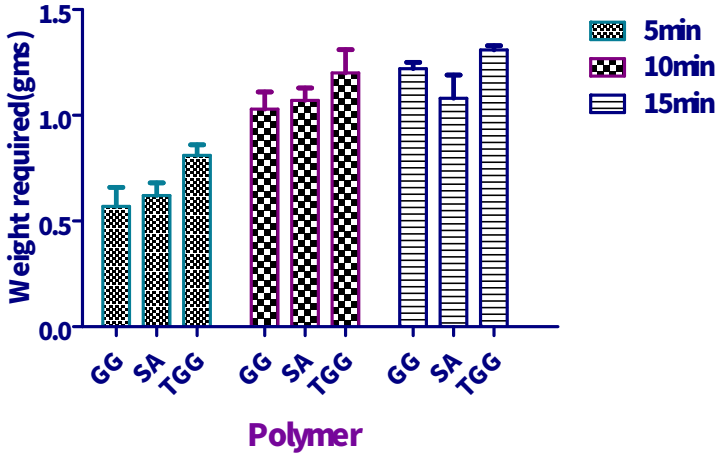


Fig 7: Mucoadhesion strength characterized by Wilhelmy's method.

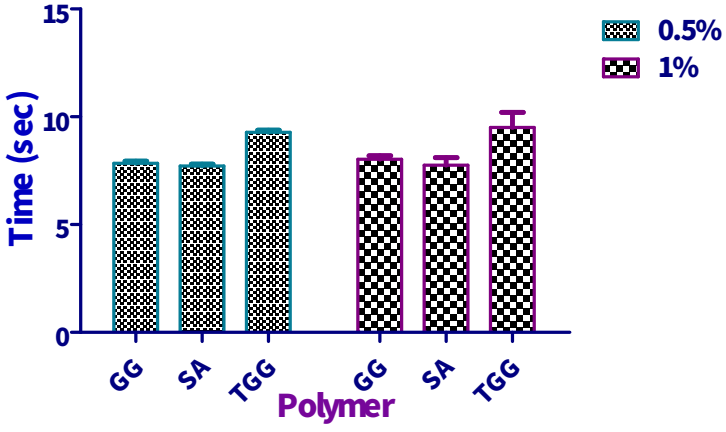


Fig 8: Technological characterization of falling sphere analysis at different concentrations.

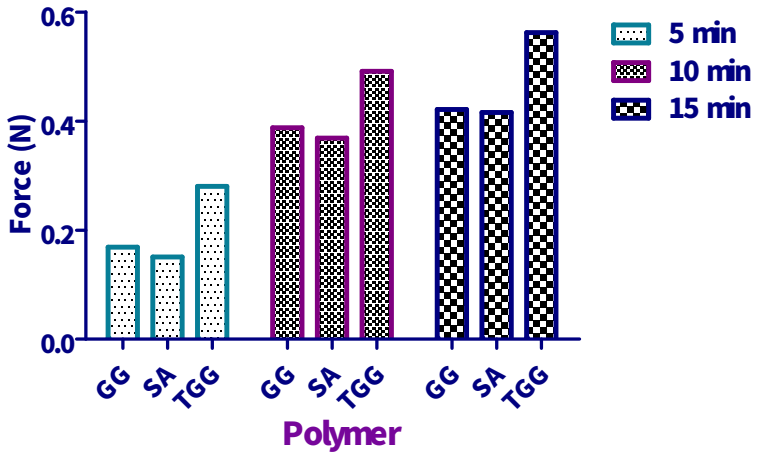


Fig 9: Technological characterization of detaching force measurement at different contact times.

All the result shown that mucoadhesive strength of TGG was more than SA and GG that confirming the application of thiolation of GG in developing mucoadhesive drug delivery systems.

Formulation development of EH mucoadhesive tablets.

EH gastro retentive mucoadhesion tablets were prepared by using 8%PVP K30 in 80% ethanol solution as granulating medium.

Table 10: Formulation of EH mucoadhesive formulations*.

	EH-MUCO-1	EH-MUCO-2	EH-MUCO-3	EH-MUCO-4	EH-MUCO-5	EH-MUCO-6
GG	37.5	60	--	--	--	--
Chitosan	--	--	37.5	60	--	--
TGG	--	--	--	--	37.5	60

(Each formulation contains 2 mg of EH, Magnesium stearate (4mg), Talc (4mg) and Microcrystalline cellulose (MCC) -quantity sufficient to produce 200 mg tablet.)*

Evaluation tests

All the formulated tablets were evaluated for thickness, hardness, friability and uniformity of weight. Pre-compression parameters were found to be Angle of repose 26º to 29º, Hausner`s ratio-1.11 to 1.18, Compressibility index values-9%-12%.

In vitro evaluation tests

Hardness: 8-9 kg/cm2

Friability 0.084 % and 0.1%,

eight and thickness variations were maintained at less than 2.5%

Ex vivo mucoadhesion time and mucoadhesion strength were compared and the results were mentioned in Table 10. Results concluded that formulation made with TGG shown superior mucoadhesive properties compared to GG and chitosan.

Table 11: Comparison of ex vivo mucoadhesion time and mucoadhesion strength.

	Ex vivo Residence time		Mucoadhesion strength
	Glass slide method	Modified basket method	(N)
EH-MUCO-1	374	348	0.1582
EH-MUCO-2	415	389	0.1892
EH-MUCO-3	462	459	0.2419
EH-MUCO-4	548	536	0.2935
EH-MUCO-5	>14hrs	>14hrs	0.4289
EH-MUCO-6	>14hrs	>14hrs	0.4308

Each value represents the mean ± standard deviation (n=3)

Swelling study

Formulations have been studied for swelling index and the results were mentioned in Figure 10. Formulations containing TGG shown highest swelling index at the end of 8 h. Other formulations also shown considerable swelling index up to certain extent thereafter disintegration observed [19].

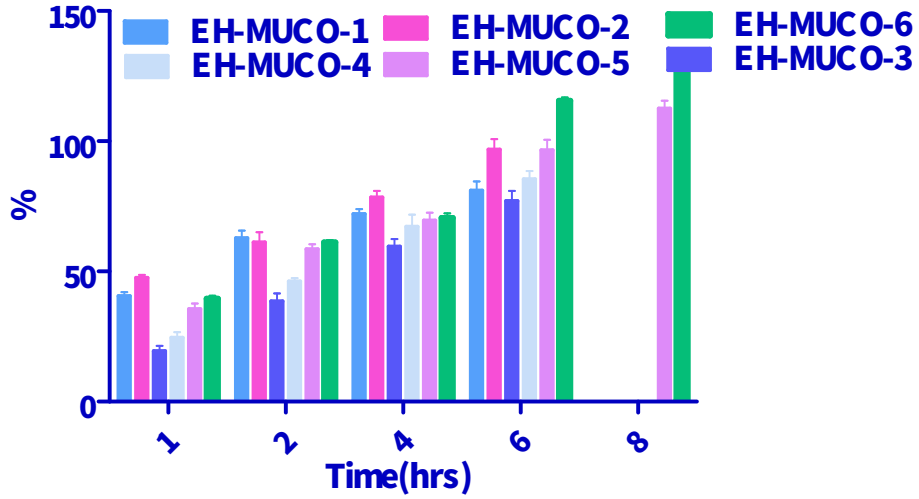


Fig 10: Swelling study of EH mucoadhesive formulations.

In vitro dissolution study

EH-MUCO-6 formulation shown considerable sustained drug release till the end of 24 h. Drug release results were further calculated for drug release kinetics. Thiolation renders information of 3D gel organization and inter-/intrachain disulfide bonds (this could enhance the cross-linkage and cohesive nature of the matrix), therefore improving the passage for the media diffusion. Drug release kinetics of EH-MUCO-6 follows controlled release with anomalous (non-Fickian) diffusion mechanism (slop value of Korsmeyer–Peppas model- n = 0.6979).

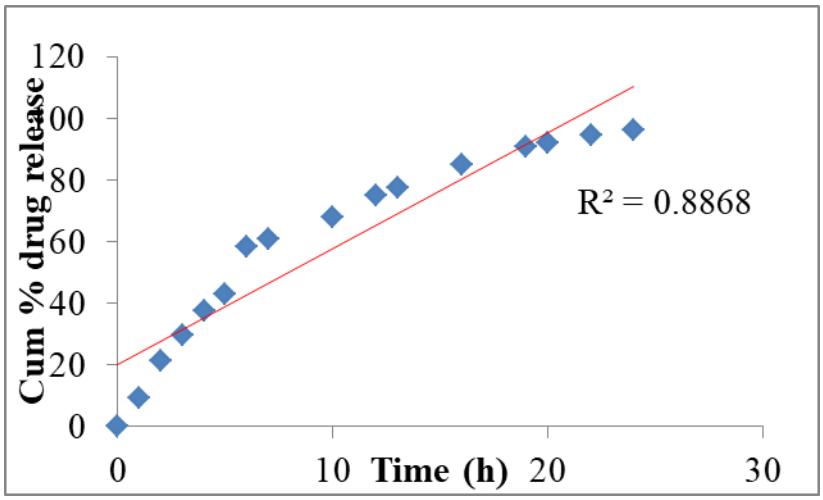


Fig 11: (A) Zero order plot for EH-MUCO-6

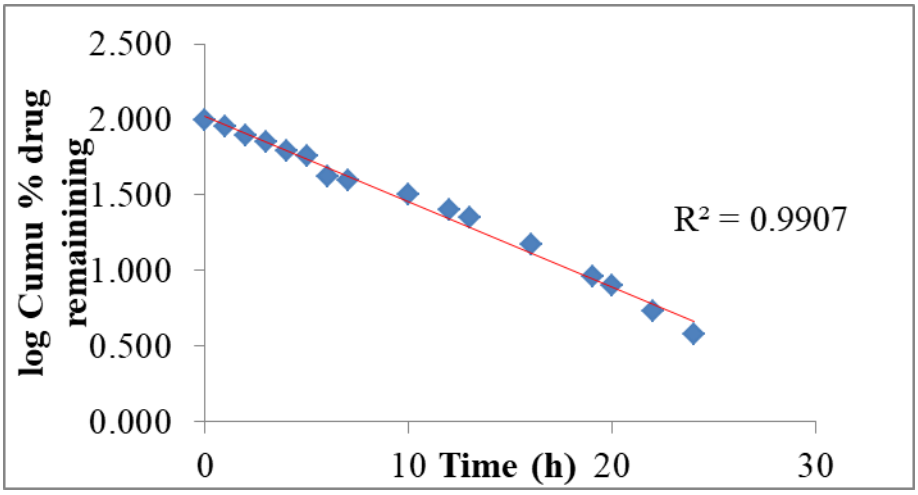


Fig 11: (B) First order plot for EH-MUCO-6

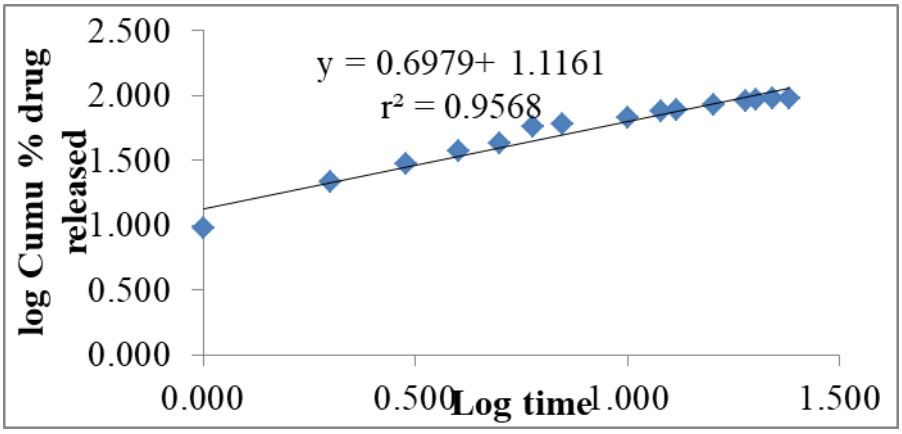


Fig 11: (C) Korsmeyer and Peppas plot for EH-MUCO-6

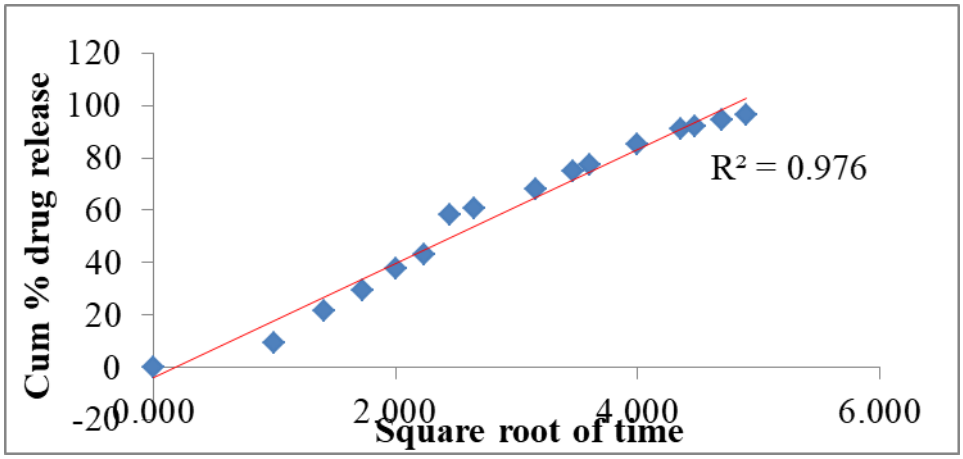


Fig 11: (D) Higuchi plot for EH-MUCO-6

Stability studies

Selected formulation EH-MUCO-6 shown non-significant changes in the test parameters throughout the stability studies at given conditions.

Table 12: Stability studies for EH-MUCO-6

TEST	INITIAL	25o±2º C+60 ±5% RH		40oC ±2º C+75% ±5% RH	
		3 M	6M	3M	6M
Description	Complies	Complies	Complies	Complies	Complies
Hardness	8 kg/cm2	8 kg/cm2	8 kg/cm2	8 kg/cm2	8 kg/cm2
Muco-adhesion time	>14 h	>14 h	>14 h	>14 h	>14 h
Drug content (%)	99.78	99.05	98.72	98.89	98.24

CONCLUSION

Novel Mucoadhesive GRDDS are developed focusing exclusively theory of mucoadhesion where in the first generation of mucoadhesive polymers show inefficient adhesion to GIT mucosa that cannot assure extended gastro retention. Therefore the thiolated polymers that form strong covalent bonds through thiol/di-sufide exchange reactions with cysteine rich sub domains of mucous that ensure enhanced gastroretention and biodegradation are employed and GRDDS are thus prepared by applying design of experimentation to improve the property of mucoadhesion of the polymer by adopting optimization method response surface methodology study type and Box Behnken design with factors TGA(X1), Nacl-Hcl(X2) at levels (min,mean,max) for the desired response of mucoadhesion potential. The suitable experimental run that shows desired response of mucoadhesion potential is transformed into tablets that are evaluated for gastroretention based on invitro swelling and mucoadhesion.

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