Cross-linked *Sterculia foetida* Gum as a Gastroretentive Polymer in High-Density Tablet Formulation: Design and Evaluation

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ABSTRACT

Semi synthetic or Natural materials have been gaining lot of interest in the field of drug delivery as they are readily available, cost effective, eco-friendly and compatible due to their natural origin. The purpose of the present research was to develop gastroretentive high density tablets of diltiazem hydrochloride using modified *Sterculia foetida* gum (SFG). Physicochemical characterization like Viscosity, pH of modified SFG was done. A 3^2 full factorial design (nine runs) was utilized to optimize the formulation wherein the concentration of modified SFG (X1) and concentration of high density agent(X2) were taken as independent variables and Cumulative % drug release upto 12hr (Y1) and tablet density (Y2) were taken as dependant variables. The quantitative, as well as qualitative influence of factor on the response was thoroughly investigated using Design Expert® software (version 13; Stat-Ease, Inc., Minneapolis, MN, USA). It can be concluded from the outcome of the present investigation that modified SFG has good potentials for formulating gastroretentive high density drug delivery system.

KEY WORDS: *Sterculia foetida* gum (SFG), High density drug delivery system (HDDDS), Diltiazem hydrochloride (DH), full factorial design etc.

INTRODUCTION

Oral controlled release drug delivery system has overcome every one of the disadvantages of conventional drug delivery system and for this reason is the mainly ideal route. However, due to a number of physiological difficulties, such as an incapability to restrain and localize the drug delivery system in preferred regions of the gastrointestinal tract (GIT) and the very much changeable nature of gastric emptying process, predictable and increased bioavailability of drugs cannot be achieved. [1-4] A variety of systems such as mucoadhesive, swelling, floating system and high density, have been developed to enhance gastric residence time of a dosage form. Physiological features of the upper

GIT shows significant challenge to develop such systems.

Natural gums or Semi synthetic are often preferred over synthetic materials due to their non-toxicity, low-cost and easy availability. It is the usual balance of economics and performance that determines the commercial realities [8]. SFG seems to be an interesting polymer for preparation of hydrophilic tablets as it may retard drug release due to its higher swelling index [9].

The goal of the present research work was to prepare high density gastroretentive tablet of diltiazem hydrochloride (DH) using modified SFG. DH is a calcium channel blocker used as an antihypertensive as well as anti-anginal was selected as the model drug for the present study. It has short biological half-life of around 3.5 h and has an absorption window in upper part of GIT [10, 11]. A 3^2 factorial design was employed to investigate the effect of two independent variables (factors), *i.e.* concentration of modified SFG and concentration of high density agent, on drug release after 12h and tablet density.

MATERIALS AND METHODS

Materials

DH was received as a gift sample from Glenmark Pharmaceuticals Ltd., Mumbai and *Sterculia foetida* gum (SFG) was received as Vendor M/s Mr. Wagh Brothers, Nagpur. All other chemicals were of analytical grade and purchased from local vendor.

Methods

Synthesis of Modified *Sterculia foetida* Gum

Sterculia foetida gum was cross-linked with tri-sodium tri-metaphosphate (STMP) as follows: STMP (1g) was dissolved in 50ml of 0.1N NaOH in a 200ml beaker with 1g of SFG in a 50ml of water then added slowly with stirring. The reaction mixture was stirred for 2h, poured into each of 5 petridish (20ml each) & dried at 60^0c for 24 h. The dried complex (modified gum) was powdered, passed through a sieve and used for formulation of tablets [12].

Drug-Excipients Compatibility Study

The drug-excipients interaction study was conducted using FTIR spectrophotometer (Jasco IR spectrophotometer, Model: 4100). The IR spectrum of pure DH, SFG, modified SFG and physical mixture of DH: SFG were recorded using KBR pellet method [13].

Characterization of Modified SFG

Initially modified SFG was passed through 160# and used subsequently for characterization studies. Solubility of SFG in water and alcohol was determined. 1 g of modified SFG was dissolved in various amounts of water for solubility determination and for viscosity determination 1% solution was prepared by dissolving 1 g of modified SFG in 99 g of water and pH of the solution was also noted [9,13].

Full Factorial Design

A 3^2 randomized full factorial design was used in this study. In this design two factors, the Concentration of modified gum (X_1) and Concentration of High density agent (Zinc oxide) (X_2) were selected

as independent variables, each at 3 levels and experimental trials were performed at all 9 possible combination. The tablet density and drug release after 12h were selected as dependent variables. All data of optimization study is compiled into Design Expert® software (Design Expert trial version 13) to get one desirable formulation [18- 20]. Table 1 summarizes dependent and independent variables and the resultant formulations are listed in table 2.

TABLE 1: EXPERIMENTAL DESIGN: FACTORS AND RESPONSES

Factors (independent variables)	**Levels used**			**Responses**
	-1	**0**	**1**	**(dependent variables)**
X1. Concentration of Modified *Sterculia foetida gum* (% w/w)	20	30	40	Y1= % of drug releases upto 12h
X2. Concentration of High density agent (% w/w)	04	06	08	Y2= Tablet density

TABLE 2: COMPOSITION OF EXPERIMENTAL FORMULATIONS (RUNS)

Batch No.	**Concentration of modified *Sterculia foetida* gum (%w/w)**	**Concentration of high density agent (%w/w)**

HD1	**30**	**04**
HD2	**30**	**06**
HD3	**30**	**08**
HD4	**40**	**04**
HD5	**40**	**06**
M6	**40**	**08**
M7	**50**	**04**
M8	**50**	**06**
M9	**50**	**08**

Preparation of Tablets

The granules were prepared by wet granulation method as per formulae given in the Table 3. The drug, modified polymer, high density agent zinc oxide and lactose, were passed through sieve 40# separately and blended thoroughly. After proper mixing, slowly add the binding solution containing PVP K-30 in IPA till fine uniform granules were obtained. The wet mass was passed through sieve 16# and dried at 50 °C for 30 minutes to get optimum moisture content. Then lubricate the dried granules with magnesium stearate which were already passed through sieve 40#. Then lubricated granules were compressed using a Karnavati rotary tablet press using 10-mm biconvex punch [(14)].

TABLE 3: COMPOSITION OF BATCHES HD1- HD9

INGREDIENTS	**HD1**	**HD2**	**HD3**	**HD4**	**HD5**	**HD6**	**HD7**	**HD8**	**HD9**
DH	15	15	15	15	15	15	15	15	15
Modified Gum	30	30	30	40	40	40	50	50	50
HDA (Zno)	4	6	8	4	6	8	4	6	8
Lactose	41	39	37	31	29	27	21	19	17
PVP K-30	8	8	8	8	8	8	8	8	8
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total % (W/W)	100	100	100	100	100	100	100	100	100

Tablet density

The density (D) of tablets was calculated from tablet thickness, diameter, and weight. All measurements were

performed in triplicates. The averages and standard deviations were calculated and reported.

***In Vitro* Drug Release Studies**

The *in vitro* drug release studies were conducted using USP type II apparatus (TDT-08 L, Electro lab, Mumbai, India). The dissolution media used was 900 mL of 0.1 N Hydrochloric acid (pH 1.2) kept at 37.0 ± 0.5 ^{0}C and 100 rpm. An aliquot of 5 mL sample was withdrawn and replenished with fresh dissolution medium at various time intervals. The contents of DH in sample were determined by measuring absorbance at 237.5 nm in a UV-Visible spectrophotometer (Jasco UV-630). The dissolution data so obtained was then treated using different kinetic models to understand the mechanism of the drug release [17]. The release study was performed in triplicate.

Stability Study

Tablets were packed in aluminium foil and placed in the stability chamber at 40 ^{0}C and 75% RH for a period of 4 weeks. At the end of 4 weeks *in-vitro* drug release study and detachment force were performed [22].

RESULTS AND DISCUSSION

Drug Excipients Compatibility Study:

The IR spectrum of the pure DH, SFG, Modified SFG and physical mixture was recorded to check the possible Drug-Excipients interaction. Pure SFG are associated with 0H group & COO^{-} groups of oleic acid residue. In modified SFG, OH group has been disappears & appearance of new peaks which are absent in Sterculia gum are ascribe to phosphate-I(-C=O Stretching) & phosphate-II(-C-0 bending) of the phosphate group of STMP confirms cross linking reaction. The FTIR Spectra of drug as well as formulation shows characteristics peak of both shows no interaction between drug & excipients.

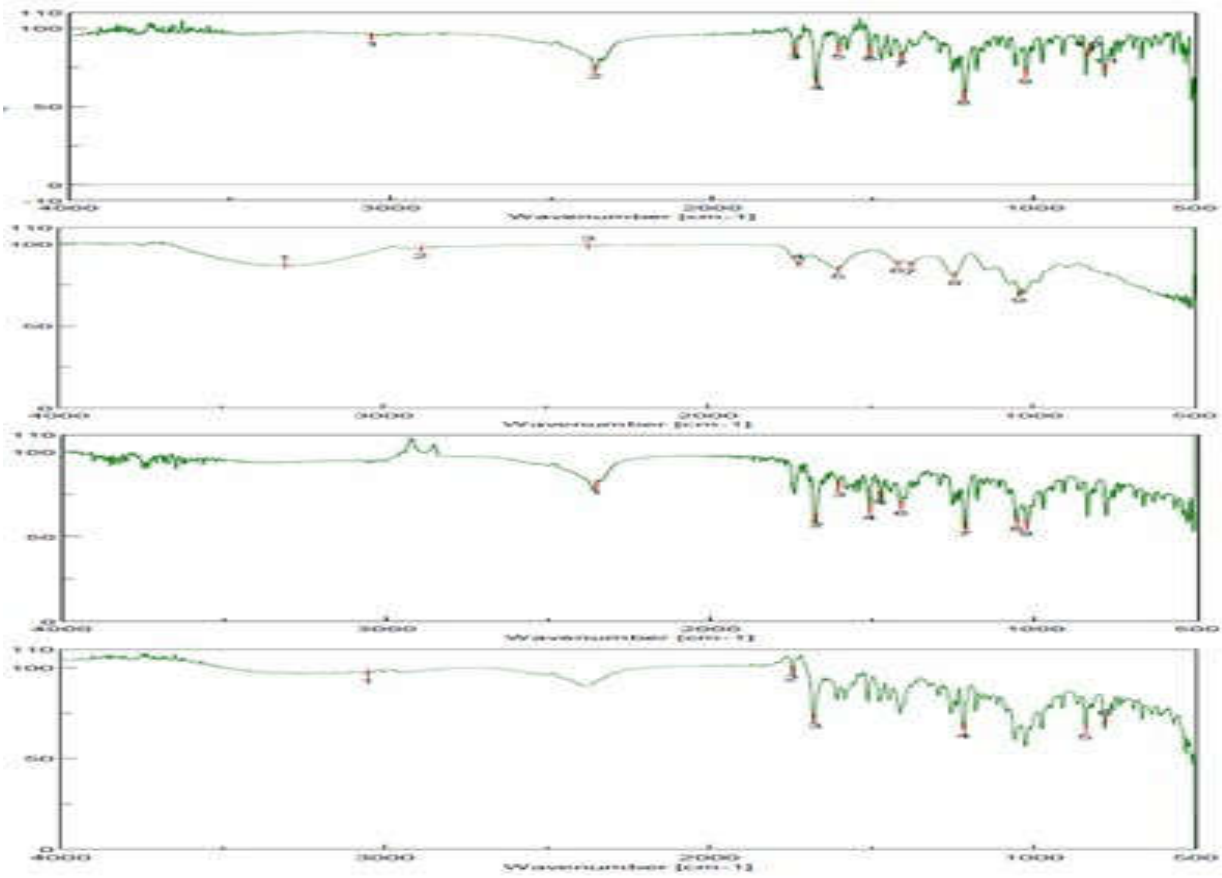

Fig 1: FT-IR spectra of A)Pure drug B) Unmodified *Sterculia foetida* gum C)Modified *Sterculia foetida* gum D) Optimized formulation.

Characterization of modified SFG

Modified SFG is sparingly soluble in water and it dissolves with hydration. It is practically insoluble in absolute ethanol. The viscosity of 1% SFG was found to be 950 centipoises and pH in range of 4–5.

Evaluation Parameters of Factorial Design Batches

The result reveal that the all the evaluation parameters were within the limits as per IP.

Results shown in table 4 & table 5:

Table 4: Evaluation data for gastroretentive high density tablets for formulations HD1-HD9 All values are expressed is mean ± SD, n=3

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
HD1	0.970±0.05	1.131±0.02	14.23±0.19	1.16±0.06	23.68±0.99
HD2	0.966±0.07	1.114±0.01	14.05±0.11	1.14±0.03	23.30±2.04
HD3	0.971±0.02	1.125±0.04	12.91±0.13	1.15±0.05	25.15±2.65
HD4	1.060±0.01	1.180±0.03	13.11±0.10	1.11±0.03	24.68±2.17
HD5	0.976±0.05	1.185±0.04	17.63±0.21	1.21±0.02	26.39±1.49
HD6	0.963±0.06	1.190±0.04	18.73±0.26	1.23±0.04	23.16±1.38
HD7	0.985±0.07	1.104±0.02	10.77±0.15	1.12±0.04	22.19±2.76
HD8	0.981±0.03	1.111±0.01	11.70±0.09	1.13±0.03	26.61±2.09
HD9	0.909±0.02	1.145±0.06	18.61±0.18	1.25±0.01	25.43±2.44

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^{2})	Friability (% w/w)	Weight variation (mg)
HD1	4.53±0.01	10.66±0.04	5.8±0.07	0.120±0.03	603.26±1.37
HD2	4.55±0.01	10.60±0.02	5.9±0.09	0.128±0.05	602.56±1.48
HD3	4.60±0.03	10.50±0.01	5.8±0.10	0.198±0.02	598.87±3.55
HD4	4.65±0.02	10.40±0.02	5.2±0.03	0.098±0.01	597.32±2.74
HD5	4.51±0.02	10.30±0.03	6.0±0.11	0.114±0.03	600.94±1.96
HD6	4.20±0.03	10.10±0.02	6.1±0.05	0.105±0.06	599.37±2.54
HD7	4.15±0.03	10.08±0.01	6.0±0.07	0.118±0.05	597.68±2.60
HD8	4.12±0.02	10.06±0.01	6.2±0.04	0.089±0.03	601.62±1.41
HD9	4.08±0.01	10.02±0.03	5.9±0.12	0.131±0.09	598.40±2.58

Table 5: Evaluation data for gastroretentive high density tablets for formulations HD1-HD9 All values are expressed is mean ± SD, n=3

Factorial design

A 3^2 full factorial design was constructed to study the effect of the concentration of modified SFG (X_1) and mucoadhesive agent (X_2) on the drug release as well as buoyancy lag time for the tablets. The two dependent variables chosen were selected i.e. drug release upto 12hr and tablet density. The results were compiled in Table 6**.**

TABLE 6: LAYOUT OF DESIGN ACTUAL

STD	*RUN*	*FACTOR 1* A: CONCENTRATION OF MODIFIED GUM (%)	*FACTOR 2* B: CONCENTRATION OF HIGH DENSITY AGENT (%)	*RESPONSE1* % *CUMULATIVE DRUG RELAEASE UPTO 12HR*	*RESPONSE2* *TABLET DENSITY(GM/CM^3)*
9	1	40	6	87.68	1.75
7	2	40	4	84.88	1.72
8	3	40	8	92.36	1.78
6	4	50	6	79.70	1.85
1	5	30	4		1.58
4	6	50	8	77.1	1.89
5	7	30	6		1.62
3	8	30	8		1.65
2	9	50	4	82.4	1.82

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms.

Various computations for the current optimization study were performed using Design Expert® software (Design Expert trial version 13; State-Ease Inc., Minneapolis, MN, USA). A two-factor three-level full factorial design was used for systemic study of modified (SFG) and gas generating agent (sodium bicarbonate). A 3^2 full factorial design was constructed where the concentration of modified SFG (X1) and concentration of high density agent (X2) were selected as the independent variables i.e. factors. The levels of these factors were selected on the basis of initial studies and observations. All the other formulation aspects and processing variables were kept invariant throughout the study period. Polynomial models including interaction and linear terms were generated for the entire response variable.

Using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented in the Equation

$$Y = b_0 + b_1X_1 + b_2X_2 \quad \text{---------- (1)}$$

Where Y is the dependent variable; b_0 is the arithmetic average of all the quantitative outcomes of nine runs.b_1, b_2, b_{12} are the estimated coefficients computed from the observed experimental response values of Y and X_1 and X_2 are the coded levels of the independent variables. The interaction term (X_1X_2) shows how the response values change when two factors are simultaneously changed. The polynomial terms (X_1^2, X_2^2) are included to investigate nonlinearity.

The polynomial equations can be used to draw conclusion after considering the magnitude coefficient and the mathematical sign that the coefficient carries. A high positive or negative value in the equation represent that by making a minor change in the setting of that factor one may obtain a significant change in the dependent variable.

Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA) provision in the Design Expert software. Level of significance was considered at $p < 0.05$. The best-fitting mathematical model was selected based on the comparison of several statistical parameters, including the coefficient of variation (CV), the multiple correlation coefficient(R^2), the adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual sum of squares (PRESS), provided by the software. PRESS indicates how well the model fits the data, and for the chosen model, it should be small relative to the other models under consideration. The 3-D response surface graphs and the 2-D contour plots were also generated by the Design Expert® software. These plots are very useful to see interaction effects of the factors on responses.

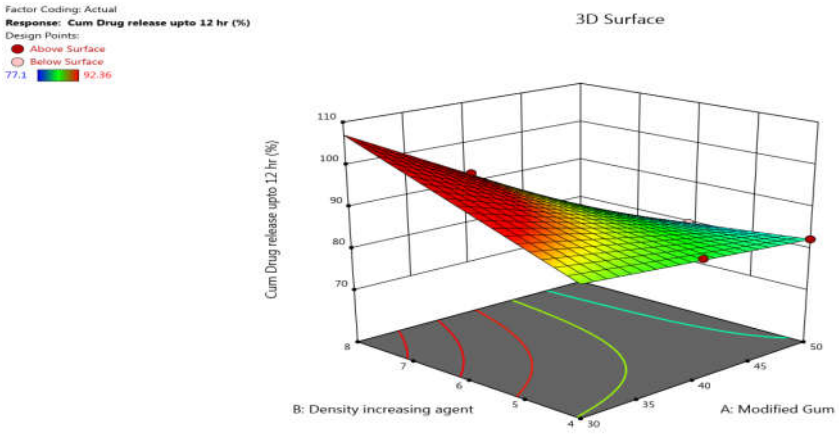

Figure 2: 3D response curve of % CDR upto 12hr for GRDDS High density system

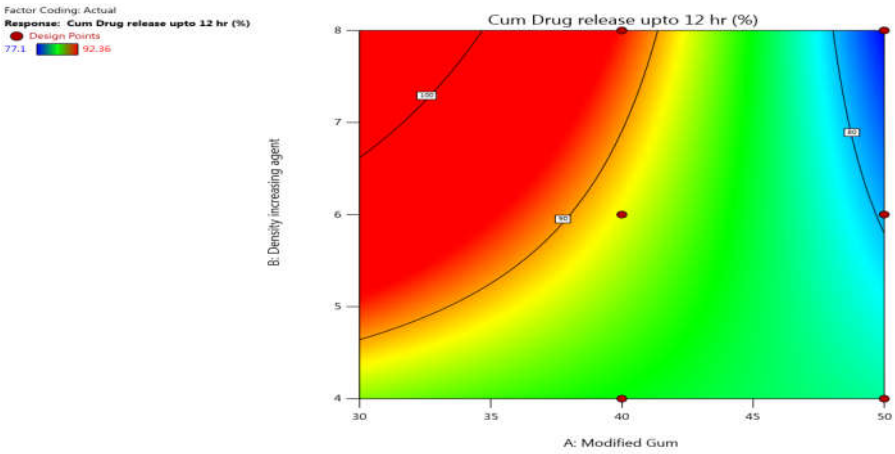

Figure 3: Contour plot of of % cumulative drug release upto 12hr for GRDDS high density system

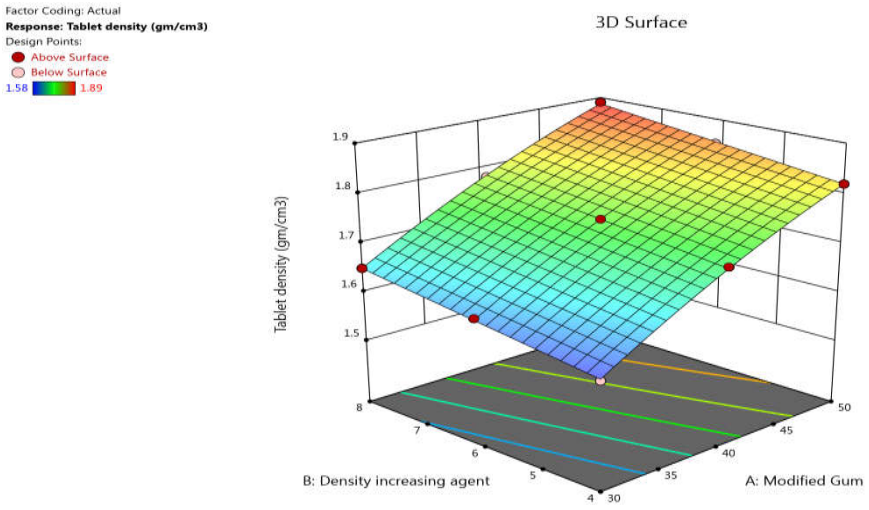

Figure 4: 3D response curve of tablet density for GRDDS high density system

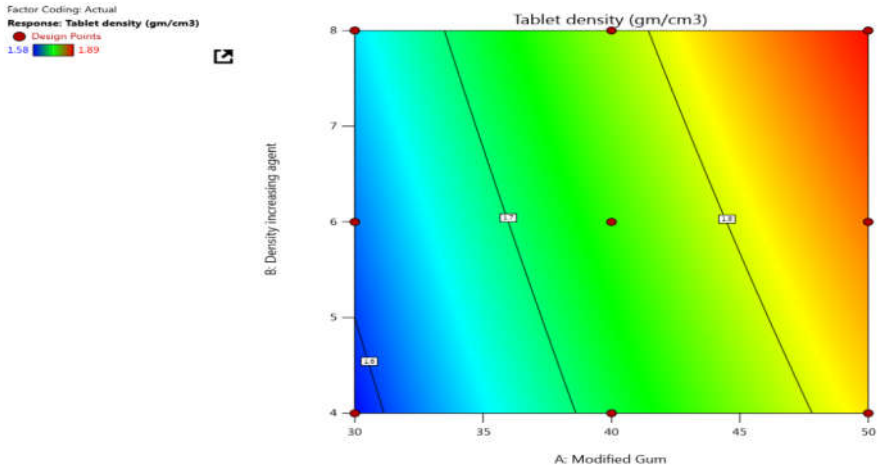

Figure 5: Contour plot of tablet density for GRDDS high density system

Full and Reduced Model assessment for the dependent variables

A) Full Model for % Cum. Drug Release upto 12 hr:

- Full model equation
- % Cum. Drug Release upto 12 hr =+97.69-17.89A+1.02B+1.53B
- A- Modified Gum
- B- High density agent

Statistical validation of the polynomial equations generated by Design Expert and estimation of significance of the models was established on the basis of analysis of variance provision of the software as shown in Table 7.

TABLE 7: ANALYSIS OF VARIANCE FOR RESPONSE % DRUG RELEASE

Source	Sum of Squares	Df	Mean Square	F-value	p-value	Significance
Model	152.27	3	50.76	171.85	0.0058	Significant
A-Concentration of modified gum	110.25	1	110.25	373.28	0.0027	
B-Concentration of density increasing agent	27.98	1	27.98	94.71	0.0104	
AB	40.83	1	40.83	138.24	0.0072	
Residual	0.5907	2	0.2954			

Cor Total	152.86	5				

The Model F-value of 171.85 implies the model is significant. There is only a 0.58% 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 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.

It is observed that increase in polymer concentration retards the drug release, while increase in concentration of zinc oxide dosen't have any impact on drug release.

B) Full Model for Tablet density:

Tablet density =+1.73+0.1067A+0.0217B

Statistical validation of the polynomial equations generated by Design Expert and estimation of significance of the models was established on the basis of analysis of variance provision of the software as shown in Table 8

TABLE 8: ANALYSIS OF VARIANCE FOR TABLET DENSITY

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	0.0911	5	0.0182	820.20	< 0.0001	Significant
A-Concentration of modified gum	0.0840	1	0.0840	3780.75	< 0.0001	
B-Concentration of density increasing agent	0.0067	1	0.0067	300.00	0.0004	
AB	0.0000	1	0.0000	0.0000	1.0000	
Residual	0.0001	3	0.0000			
Cor Total	0.0912	8				

The Model F-value of 820.20 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, B, AB 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.

It is observed increase concentration of zinc oxide increases tablet density, while increase in polymer concentration doesn't have any significant impact on tablet density. After analysis of both independent variables (i.e. factor) and dependant variables (i.e. response) Design Expert® software gives 2 solutions which are shown in Table 9.

TABLE 9: SOLUTIONS FOR OPTIMIZED BATCH

Number	Modified Gum (%)	Density increasing agent (%)	Cum. Drug release upto 12 hr	Tablet density ($gm/cm^{3)}$	Desirability
1	**40.000**	**8.000**	**92.047**	**1.783**	**0.990**
2	38.856	7.909	93.557	1.768	0.941

***In Vitro* Drug release studies of Factorial Design Batches**

In our work, we have shown the effect of polymers on in vitro drug release studies of DH. Formulation batch HD1-HD3 releases drug in 6-9 h due to low concentration of modified polymer. In the later formulations HD4-HD9 use of more concentration of modified polymer in that case it exhibits good drug release up to the 12 h. Formulation HD6 shows maximum drug release 92.36% with controlled manner showed in Table 6.46 and 6.47. A value of coefficient of determination for the optimized gastroretentive high density tablet formulation (OHDS) indicates that release of drug follows Zero order with korsmeyer-peppas kinetic model with non fickian transport.

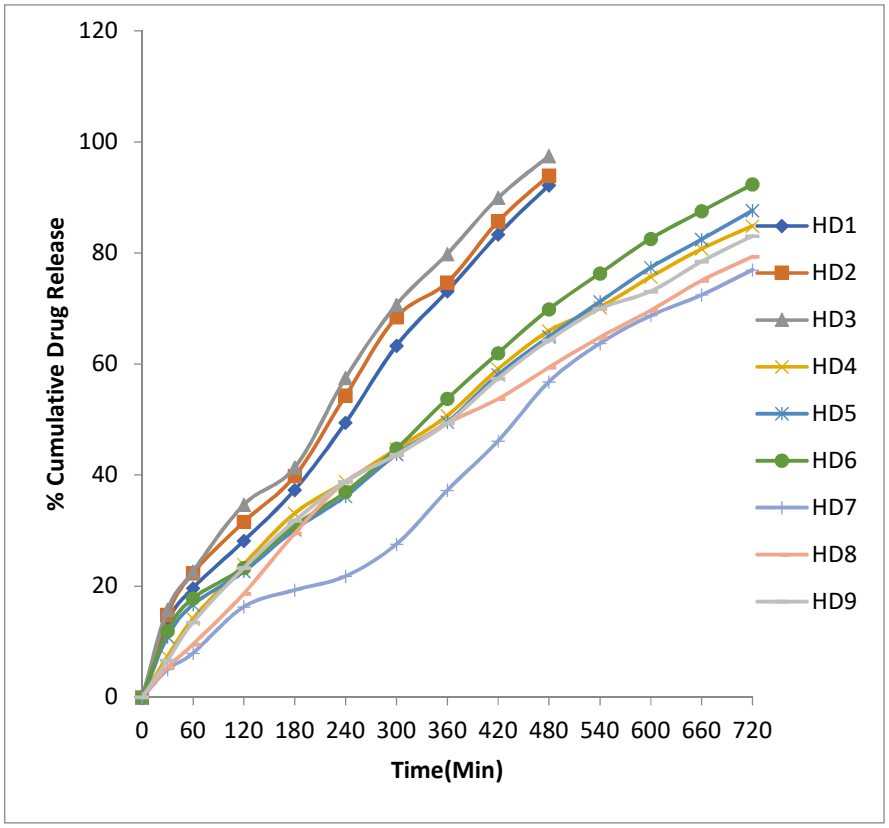

Figure 7: Dissolution profile of Optimized Batches HD1 – HD9

Stability Study

There was no significant change observed in the drug release and tablet density of gastroretentive tablets of optimized batch after 4 weeks.

Conclusion:

Gastroretentive high density tablets of DH using modified SFG were prepared by wet granulation method and all the tablets were found to be good without chipping, capping and sticking. The drug content was uniform in all the formulations. The low values of standard deviation indicate uniform distribution of drug within the Gastroretentive high density tablet. Infrared spectroscopic studies indicated that the drug is compatible with the polymers. Tablets of DH prepared with modified SFG helpful in increasing the bioavailability of drug. Short-term stability studies of optimized formulation (HD6) indicated that there were no significant changes in drug content and dissolution parameter values after 4 weeks of storage at 40±1 ºC. It can be thus concluded that modified SFG has good potentials for formulating gastroretentive high density drug delivery system.

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Declaration of interest: The authors report no conflicts of interest.

REFERENCES

1. Sing BN, Kim K. Floating drug delivery system: An approach to oral controlled drug delivery via gastric retention. Journal of Control Release. 2000; 63, 235-59.
2. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery system: A review. AAPS Pharm SciTech.2005; 6, 47.doi.org/10.1208/pt060347.
3. Ashok M, Kumaran S, & Hiraman H. Development and in Vitro Evaluation of Gastroretentive High Density Tablet of Propafenone HCL. Asian Journal of Pharmaceutical Research and Health Care 2013; *5*(2), 89-99.
4. Bamba M, Puisienx F, Marty JP, Carstensen JT. Release mechanisms in gel forming sustained release preparation. International Journal of Pharmaceutics. 1979; 2,307–315.
5. Lapidus H, Lordi NG. Drug release from compressed hydrophilic matrices. Journal of Pharmaceutical Sciences.1968; 57, 1292–1301.
6. Buri P, Doelker E. Formulation of extended release tablets II hydrophilic matrices. Pharmaceutica Acta Helvetiae. 1980; 55,189–97.
7. Longer M, Ch'ng H, Robinson J. Bioadhesive polymers as platforms for oral controlled drug delivery. III. Oral delivery of Chlorothiazide using bioadhesive polymers. J Pharm Sci. 1985; 74(4): 406-411.
8. Senthilkumaran K. Development of gastroretentive mucoadhesive matrix tablets of propafenone HCL. American Journal of pharmatech research.2013;2(3),1-14.
9. Doelker E, Peppas NA. Water-swollen cellulose derivative in pharmacy. In N. A. Peppas (ed.). Hydrogels in Medicine and Pharmacy. CRS Press, Florida. 1987; 2, 115–160.

10. Taukdar MM, Vercammen JP. Evaluation of Xanthan gum as a hydrophilic matrix for controlled release dosage form preparation. Drug Development and Industrial Pharmacy. 1993; 19, 1037-46**.**

11. Smith F, Montgomery R, Hamor WA. The structure of gum exudates. In F. Smith, and R. Montgomery (eds.), The chemistry of plant gums and mucilage and some related polysaccharides. Reinhold Publishing Corporation, New York.1959; 291-293.

12. Nath B, Nath KL. Evaluation of Sterculia urens gum as novel carrier for oral colon targeted drug delivery system. Journal of Advanced Pharmaceutical Science and Technology. 2013; 1(2), 1-15.

13. Kulkarni GS, Swami S. Formulation and evaluation of sustained release floating tablets of an antihypertensive Diltiazem. International Journal of Pharmaceutical Sciences and Technology. 2017; 10(5), 3844-3852.

14. Patel AN, Patel FM, Rathore KS**.** Formulation and characterization of floating tablets of Diltiazem hydrochloride. Journal of Pharmaceutical and Biomedical Sciences. 2011; 9(9), 1-6.

15. Reddy MM, Reddy JD, Moin A, Shivakumar HG. Formulation of sustained- release matrix tablets using cross-linked karaya gum. Tropical Journal of Pharmaceutical Reasearch.2012;11(1),28-35.

16. Sharma YR. Elementary organic spectroscopy, Principles and chemical applications, 3rd ed., S. Chand and Company Limited. 2008; 211,312,321.

17. Ohara T, Kitamura A, Kitagawa T, Terada K. Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethyl cellulose and hydroxyl propylmethylcellulose. International Journal of Pharmaceutics. 2005; 302:95-102.

18. Kumar R, Patil MB, Patil SR. Formulation and evaluation of effervescent floating tablets of famotidine. International Journal PharmTech Research. 2009; 1(3), 754-763.

19. Rosa M, H Zia, Rhodes T. Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral ingestion. International Journal of Pharmaceutics. 1994;105, 65-70.

20. Korsmeyer R, Gurny R, Peppas N. Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics. 1983; 15, 25-35. Shah NH, Asghar S,

Choudhry MA, Muhammad SHA, Rehman N, Baksh S. Formulation and evaluation of natural gum-based sustained release matrix tablets of flurbiprofen using response surface methodology. Drug Development and Industrial Pharmacy. 2009; 35, 1470–8.

21. Patil SB, Sawant KK. Development, optimization and in vitro evaluation of alginate mucoadhesive microspheres of carvedilol for nasal delivery. Journal of Microencapsulation. 2008; 1–12.

22. Gohel MC, Parikh RK, Nagori SA, Jena DG. Fabrication of modified release tablet formulation of metoprolol succinate using hydroxypropyl methylcellulose and Xanthan gum. AAPS PharmSciTech. 2009; 10(1), 62-68.doi.org/10.1208%2Fs12249-008-9174-1

23. Surana SJ, Belgamwar VS. Floating bioadhesive drug delivery system using novel effervescent agents. Asian Journal of Pharmaceutics. 2009.

24. Sahoo J, Murthy PN, Biswal S, Sahoo SK. Comparative study of Propranolol hydrochloride release from matrix tablets with Kollido$^{n®}$ SR or Hydroxypropyl methyl cellulose. AAPS Pharm SciTec*h.*2008; 9,577-82.