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Research Article

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Formulation and Optimization of Gastro retentive Glimepiride Floating Matrix Tablets

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Abstract: The main objective of this research investigational studies is to formulate floating matrix tablets of glimipride by applying simplex centroid design for optimization technique and by direct compression method. The simplex Centroid configuration was drilled as an enhancement strategy by adjusting the amount of three components all the while and holding back their total concentration constant. Ingredients HPMC K15m, Kappa-carrageenan and sodium bicarbonate as X1,X2,X3 independent Variables while response variables Y1 floating lag time Y1, Percentage drug released after 1 hour Y2% and t90 time required for 90% were considered as response variable factors for formulation and optimization of total 14 formulations simplex centroid design was applied. The measures of HPMC K15M (X1), kappa-Carrageenan (X2) and sodium bicarbonate (X3) were utilized as the autonomous factors while coasting slack time (Y1), Percentage drug discharged after 1 hour(Y2) and time required for 90% (t90) were taken as the reaction factors. According to the simplex centroid configuration complete 14 formulations were formulated. Matrices were evaluated for physical parameters, *in-vitro* buoyancy, swelling ability and adhesion retention period. It was inferred that the blend of kappa carrageenan and HPMC K 15 M builds the adaptability in the release pattern of the drug. This examination sets up the utilization of simplex centroid structure in the advancement of coasting network tablets with least experimentation.

Keywords: Optimization**;** gastro retentive; Glimepiride.

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1. INTRODUCTION

The literature review suggested that Glimepiride (GLM) is weakly acidic in nature with pKa value equal to 5.9, which means that the drug remains unionized at acidic pH[1-2]. The unionization is the prerequisite for the drugs to get absorbed by passive diffusion mechanism. Hence, the gastroretentive dosage form of GLM is desired. The elimination half-life of GLM is 2–4 h, which demands frequent administration of drugs, to maintain its level in the body for an extended period of time. Gastroretentive dosage form overcomes that demerit by releasing the drug continuously in the upper part of gastrointestinal tract, thereby achieving the better control of plasma glucose level[3-4]. The exhaustive literature research elucidates that gastro retentive formulations of Glimepiride have been prepared using several approaches[5-8]. Present research involves the development of gastroretentive floating matrix tablets of GLM by effervescence mechanism. Floating matrix tablet of GLM was prepared using the combination of hydrophilic polymer HPMC K15M with anionic and non-ionic polymers. The approach used is the same as that used for the formulation and optimization of floating matrix tablets of metformin. Various anionic and non-ionic polymers used in the present work are sodium alginate, kappa carrageenan, pullulan, xanthan gum and poloxamer 188. The final optimization of floating GLM formulation was done by applying Simplex lattice design (SLD)[9-11] using kappa carrageenan, HPMC K15M and sodium bicarbonate as independent variables. The simplex lattice design for a three-component system is represented by an equilateral triangle in two-dimensional space[12-15]. The levels of the variables were decided from preliminary studies and the tablets were prepared by wet granulation technique using PVP K30.

2. MATERIALS AND METHODS

Tablets containing 4mg of Glimepiride were prepared by wet granulation technique[10,11]. The required quantity of drug, cross linking polymers and gas generating agent, were sieved through sieve number #80 and were thoroughly mixed in a mortar by following a geometric dilution method. Then, the required quantity of microcrystalline cellulose was added and the mixture was filled in a plastic bottle. These bottles were placed in a double cone blender and the equipment was run for 5minutes. After the set time, the powder blend was put in mortar and the granulation was performed using granulating fluid (polyvinyl pyrrolidone, PVP K30, dissolved in alcohol). The mixture was blended properly with granulating fluid to form a dough mass. The mass was passed through mesh No. 10 to obtain wet granules. The wet granules were dried by keeping them in hot air oven at 60°C for an hour. The dried granules were passed through mesh No. 16 to break aggregates and then sieved through sieve no. 40 to separate granules and fines. Magnesium stearate (1%) and (10%) fines were added to dry granules and blended in a double cone blender after enclosing into a closed plastic bottle. The granules were then compressed into tablets on rotary tablet compression machine, using 7 mm round and flat punches with the hardness of 5 kg/sq.cm.

Table 1: Composition (In Mg) of Preliminary Batches of Glimepiride Floating Matrix Tablets

Sr No	Ingredients	G1	G2	G3	G4	G5
1	Glimepiride	4	4	4	4	4
2	PVP K30	16	16	16	16	16
3	HPMC K15M	60	60	60	60	60
4	Sodium bicarbonate	15	15	15	15	15
5	Sodium Alginate	20	-	-	-	-
6	κ-Carrageenan	-	20	-	-	-
7	Pullulan	-	-	20	-	-
8	Xanthan gum	-	-	-	20	-
9	Poloxamer 188	-	-	-	-	20
10	MCC	33.5	33.5	33.5	33.5	33.5
1	Mg stearate	1.5	1.5	1.5	1.5	1.5

2.1 Drug Excipient Compatibility Study[16]

There is always the possibility of drug polymer interaction in any formulation. To check any such kind of interaction, Fourier-transform infrared spectroscopy (FTIR) study was conducted. The FTIR scan of pure drug (Glimepiride), polymers (HPMC K15M and kappa carrageenan) and physical mixture of drug-polymer were taken. The pure drug, polymer and physical mixture were separately mixed with IR grade KBr[13-15]. This mixture was punched to form a disc, which was scanned over a wave number range of 4000 to 400 cm-1.

2.2 Optimization of Floating Matrix Tablet of GLM by Simplex Lattice Design

The preliminary studies suggested that floating matrix tablets of GLM, prepared with the combination of HPMC K15 M and Î°-Carrageenan, as release retarding polymers, were releasing the drug for 12hrs and had desired floating characteristics. Hence, these polymers were considered for the final optimization of floating matrix tablets of GLM. The levels of the independent variable were decided based on the literature survey and by the experimentation done during the preliminary studies. Mixture design was used to optimize the formulations with HPMC K15 M, Î°-Carrageenan and sodium bicarbonate as independent elements. Simplex Lattice design applied as the technique for optimization by changing the amount of three factors concurrently and keeping their total concentration constant.

Table 2: Factors and their examined levels in Simplex Lattice Design for GLM

Independent Variables /Levels	Amount of HPMC K15M	Amount of k-Carrageenan	Amount of sodium bicarbonate
	X1 (mg)	X2 (mg)	X3 (mg)
Low	50	20	10
High	60	30	20
Dependent Variables	Y1 – Similarity factor % Y2 – Time required for 50% drug release (t50) Y3 - Time required for 90% drug release (t90)		
No. of replicates 4			

In this study, the amounts of matrixing agent [HPMC K15 M (X1)], release retarding polymer [kappa-Carrageenan (X2)], gas-generating agent [sodium bicarbonate (X3)], were chosen as independent variable with the total weight as 90mg. Similarity factor F'2 (%), time required for 50% drug release (t50) and time required for 90% drug release (t90) were claimed as dependent variables (Table 2). The design was applied and evaluated using the Design- ExpertÂ® Software (version- 9.0.6, Stat-Ease) by running 14 experiments. The composition of the batches formulated by using this statistical design is given in table 3.

Table 3: Composition of GLM matrix tablets prepared by applying SLD

Runs	Batch code	Transformed Fractions of Variables*		
		X1	X2	X3
1	G-SLD 1	50	20	20
2	G-SLD 2	56.6667	21.6667	11.666
3	G-SLD 3	55	20	15
4	G-SLD 4	55	25	10
5	G-SLD 5	60	20	10
6	G-SLD 6	60	20	10
7	G-SLD 7	50	20	20
8	G-SLD 8	50	30	10
9	G-SLD 9	51.66	21.66	16.666
10	G-SLD 10	50	25	15
11	G-SLD 11	51.66	26.66	11.666
12	G-SLD 12	55	25	10
13	G-SLD 13	50	**30**	10
14	G-SLD 14	53.33	23.333	13.333

2.3 Validation of Model

Additional three formulations, suggested by the design expert, were formulated to check and validate the reliability of the mathematical models built here with Simple Lattice design. The check point batches were evaluated and experimentally obtained results were compared to those predicted by the mathematical models. Table no. 4 shows the values of the factors used for development of the validation batch, taken from the software, keeping the amount of all other ingredients constant. To validate the chosen experimental design, the experimental values of the responses were quantitatively compared with predicted values and, the relative error (%) was calculated using the following equation[17-19].

$$\text{Relative error (\%)} = \frac{\text{Predicted value} - \text{Experimental value}}{\text{Predictive value}} \times 100$$

Table 4: Formula for validation runs of SLD design for the optimization of GLM floating matrix tablets

Factors	Composition		
	F 1 (mg)	F 2 (mg)	F 3 (mg)
X1 : Amount of HPMC K15M	52.03	55.81	58.51
X2 : Amount of k-Carrageenan	23.33	23.33	21.49
X3 : Amount of sodium bicarbonate	14.64	10.86	10.00

2.4 In vivo Radiographic Studies

The gastroretentive formulation has to be evaluated for its gastroretentive property *in vivo*. There are various techniques like, radiographic study, gastroscopy, gamma scintillography, magnetic marker monitoring, etc. available to confirm the gastroretention of the formulation[24]. The *in vivo* radiographic studies were conducted on healthy albino rabbits (n=3)

weighing 2.0 kg to 2.2 kg. Gastroretentive floating matrix tablet was prepared by incorporating the X-ray opaque material in the optimized formula by replacing MTG with barium sulphate and keeping all other ingredients constant[20-22]. The amount of the X-ray opaque material in the optimized formula was kept sufficient to ensure visibility by X-ray, but at the same time the amount of barium sulphate was low enough to enable the formulation to float. After overnight fasting, the formulation was given to albino rabbit for *in vivo* X-ray imaging study. A radiograph was taken just before the administration of the tablet, at zero hour, to ensure the absence of radio-opaque material in the stomach. During the study the rabbit was not allowed to eat, but water was available freely and the X-ray images were snapped after 4hrs and 12hrs to monitor the gastroretention of optimized floating matrix tablets[22-26].

3. RESULTS AND DISCUSSION

3.1 Evaluation of Preliminary Batches of GLM Floating Matrix tablet

Physical Properties of GLM Tablets Prepared by Wet Granulation Technique. The results of physical evaluation of the prepared dosage forms gave acceptable physical characteristics. Hardness of all the batches was found to be in the range of 4.7-5.3 kg/cm^2. The assay for drug content indicated acceptable content uniformity in the prepared tablets. Drug content of the formulations were in the range of 98.82% to 101.56%, which is within the limits given by Indian Pharmacopoeia (Table 5). The friability was found to be less than 0.25% for all the formulation, hence passed the test for friability.

Table 5: Results of the physical evaluation of GLM tablet prepared by wet granulation technique

Batch code	Weight uniformity	Hardness* (kg/cm2)	Drug content* (%)	Friability* (%)	Lag Time*(s)	Floating Time*(h)
G1	Complies	4.7±0.58	98.82±1.04	0.14±0.18	16.39 ± 3.53	8
G2	Complies	5.2±0.43	101.56±1.25	0.15±0.16	27.31 ± 3.41	12
G3	Complies	4.9±0.39	99.76±0.87	0.19±0.10	45.25 ± 2.20	5†
G4	Complies	4.8±0.71	100.06±0.79	0.20±0.18	120.74 ±7.87	12

n=3, average of three determinations ±SD, †Tablet was going up and down during the study

3.2 In vitro Buoyancy Studies

The formulation G1, prepared using sodium alginate in combination with HPMC K15M, had the minimum floating lag time, but it could float for only 8hours. Formulations prepared with k-carrageenan, G2, had the floating lag time as 27.31 ± 3.41seconds and the formulation could float for 12hours, which was desired for present formulation. The formulations prepared with pullulan, G3, had acceptable floating lag time, but it had 5hrs of floating time. Moreover, during the flotation study, the tablet was sinking in between the said duration, which is non-satisfactory. The matrix tablets of GLM prepared with xanthan gum showed the flotation for 12 hours, but it took about 2 minutes to float. Overall, it was apparent from the buoyancy studies that the presence of other release retarding polymer in combination with HPMC K15M had a drastic effect on the flotation behaviour of formulations, as indicated in Table Check the table number table number not correlating.

3.3 Drug Release Studies

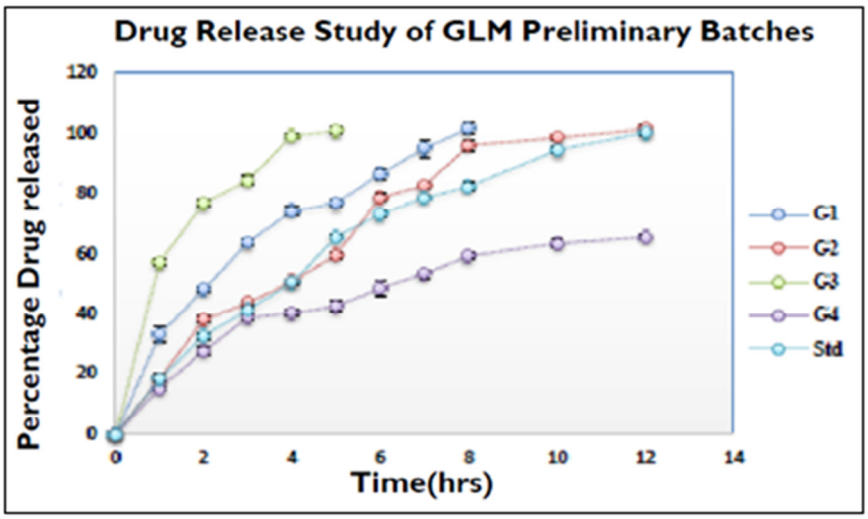
For checking the release pattern of the formulated gastro retentive matrix tablets of GLM, dissolution of marketed formulation of GLM, 4 mg was also performed. The aim was to get the release of the batches similar to that of marketed formulation. The graphical representation of drug release study for the preliminary batches of GLM floating tablets and marketed tablet is shown in Fig.1. The graph indicates that the formulation G1 (formulation with HPMC K15M and sodium alginate) could sustain the release of the drug till 8 hours only, whereas the reference sustained release tablet of GLM gave the sustained release of the drug till 12 hrs. This may be because of less hydration of sodium alginate and also because in acidic pH it doesn't contribute to the matrix erosion and hence release of the drug[27]. Formulations G3, prepared with pullulan could not delay the release of the drug, as the entire amount of drug was released within 4hrs. This means that pullulan doesn't have the ability to sustain the release of GLM from the polymeric matrix system. The formulation G2, (formulation with HPMC K15M and kappa-carrageenan) was giving almost the same release pattern as that of a theoretical release pattern of the drug with 62% similarity factor value. All other formulations couldn't have acceptable similarity factor value.

Table 6: *In vitro* drug release data of preliminary batches of floating matrix tablets of GLM*

Time (hrs)	G1 (%)	G2 (%)	G3 (%)	G4 (%)	STD (%)
0	0	0	0	0	0
1	32.84±2.54	18.22±2.01	56.85±1.04	15.14±0.88	18.23±0.54
2	48.04±0.71	37.96±1.1	76.68±1.11	27.59±1.53	32.61±1.03
3	63.66±1.04	43.67±0.89	84.37±1.43	38.59±0.92	41.31±1.19
4	73.96±1.39	50.65±0.59	98.99±0.71	40.18±1.21	50.41±0.73
5	76.72±1.16	59.45±0.91	100.63±1.04	42.51±1.79	65.39±0.57
6	86.54±1.79	78.58±1.17	-	48.46±2.77	73.01±1.09
7	94.77±2.94	82.53±1.06	-	53.28±1.46	78.42±0.67
8	101.54±1.75	95.72±1.79	-	59.16±0.91	82.24±1.12
10	-	98.32±0.61	-	63.32±1.16	94.21±1.18
12	-	101.2±1.09	-	65.42±0.79	99.95±0.68

n=3, average of three determinations±SD

Studies proved that incorporation of anionic polymers, in HPMC matrices is useful for developing a pH-independent release profile [28]. The present study also revealed that incorporation of kappa-Carrageenan, a poly anionic polymer, in a HPMC matrix of metformin showed the best release pattern. This combination in G2 formulation showed an almost similar release pattern as that of a theoretical release pattern of the drug with maximum F'2 value.



**n=3, average of three determinations ± SD*

Fig 1: Graphical representation of the drug release from preliminary floating tablets of GLM

The formulation G4, prepared with xanthan gum, could sustain the release of the drug for more than 12 hours, the rate of drug release was very slow. This result was similar to that of the study conducted by Sankalia, et al., which states that the higher xanthan gum content in the formulation, diminished the initial drug release and also the drug diffused slowly continuously for more than 12 hrs [29]. Singh et. al., presented the release behavior of drugs from different natural polymers and gums[30]. They found that the presence of xanthan gum in the formulation can retard the release of the drug. In the present study also the researcher got the same result.

3.4 Drug Excipient Compatibility Study

The FTIR scan of the drug, polymers and physical mixture of drug and polymer was taken. FTIR scan of Glimepiride showed that all were in the infrared spectra obtained from drug- polymer blend, which demonstrates that there is no significant incompatibility between the drug and the other polymers (Fig. 2).

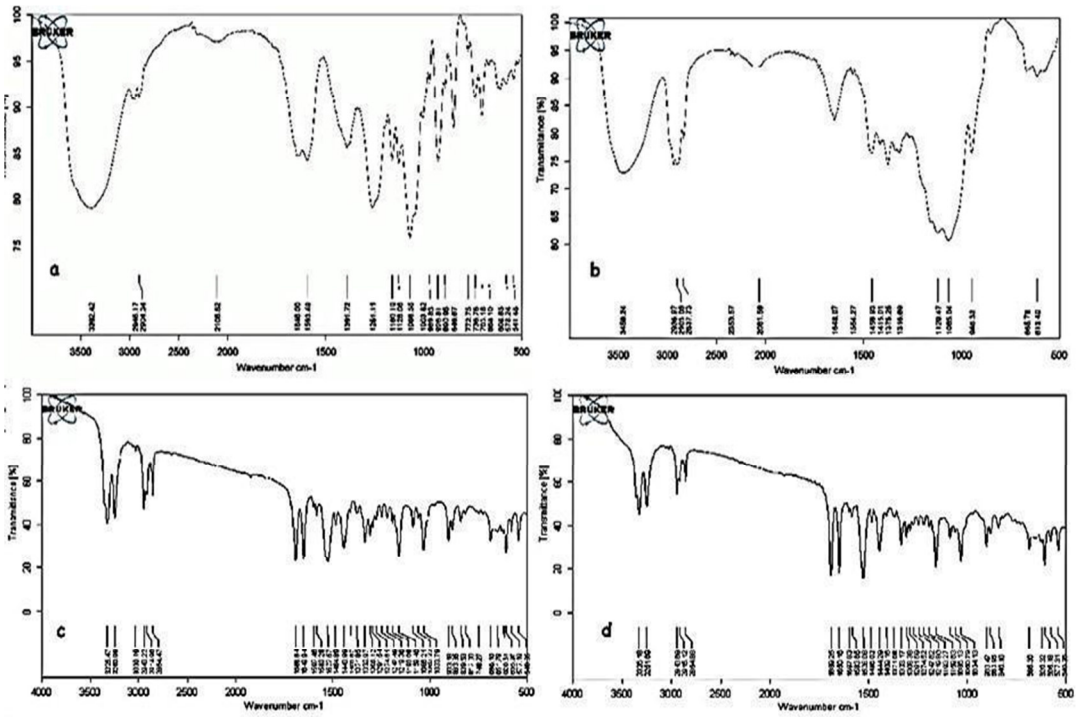


Fig 3: FTIR scan obtained for kappa carrageenan (A), HPMC K15M (B), Glimepiride (C), Optimized formulation, (D), G-SLD 8

3.5 Mixture Design - Simplex Lattice Design

Preliminary studies gave an idea about the polymers and their effect on the release pattern of the drug. The formulation prepared with the combination of HPMC K15M and k-carrageenan gave promising results, so it was decided to optimize the formulation of floating matrix tablets of GLM using these polymers. Mixture design was used to optimize the gastroretentive floating matrix tablet of Glimepiride. A simplex lattice is an arrangement of equally spaced points on a simplex (Lachman et al., 1970). The experiments should be well distributed over the factor space because simplex designs provide an optimal distribution. The design indicates the experimenting points in the factor space that allows an easy estimation of the parameters. When described by a polynomial equation the lattice can be referred to as {q, m}, where, q = Number of components, m = Degree of the polynomial, or in other words, the number of proportions assumed by each part. In a {q,m} lattice, the proportions used for each of the q components have (m + 1) equally spaced values from 0 to 1. All possible mixtures with these proportions for each component were used [31, 32]. The number of points in a {q,m} lattice is equal to the number of parameters or terms in the model.

$$v = \frac{(m+q-1)!}{(m!\,(q-1)!}$$

This equation can be used to calculate the number of design points in the simplex lattice design.

3.6 Physical Properties of Floating Tablet of GLM by applying SLD

The results of the physical properties of GLM floating matrix tablets prepared by applying SLD are shown in table6.

Table 6: Results of the physical properties of GLM floating matrix tablet prepared by applying SLD*

Batch code	Weight uniformity	Hardness (kg/cm^2)	Drug content (%)	Friability (%)	Floating Time (hrs.)	Tablet adhesion retention period (min.)	Lag time (sec.)
G-SLD 1	Complies	5.6±0.25	99.35±0.83	0.25±0.07	> 12	46.34±4.19	12.35±3.21
G-SLD 2	Complies	4.8±0.46	100.91±0.73	0.31±0.10	> 12	84.37 ±3.76	39.16±2.54
G-SLD 3	Complies	4.9±0.17	98.87±0.82	0.22±0.09	> 12	53.32 ±3.43	8.63±2.31
G-SLD 4	Complies	5.2±0.49	100.94±0.93	0.31±0.11	> 12	120.52 ±4.54	90.43±4.52
G-SLD 5	Complies	5.1±0.32	99.43±0.77	0.32±0.07	> 12	63.51±3.56	83.53±5.12
G-SLD 6	Complies	4.9±0.62	100.43±0.54	0.29±0.06	> 12	62.48±4.32	85.53±4.21
G-SLD 7	Complies	5.5±0.53	100.23±0.65	0.19±0.04	> 12	47.52 ±5.26	13.87±1.63
G-SLD 8	Complies	5.1±0.56	99.46±0.43	0.28±0.07	> 12	139.21±5.43	20.42±1.12
G-SLD 9	Complies	4.6±0.85	98.96±0.74	0.38±0.12	> 12	74.55±3.65	9.77±1.43
G-SLD 10	Complies	4.2±0.62	99.38±0.78	0.35±0.08	> 12	104.43±3.95	22.40±2.19
G-SLD 11	Complies	5.2±0.67	99.64±0.79	0.27±0.09	> 12	118.54 ±3.67	40.22±3.55
G-SLD 12	Complies	5.2±0.53	101.27±0.93	0.25±0.08	> 12	119.20 ±4.55	88.46±5.21
G-SLD 13	Complies	5.1±0.57	100.54±0.64	0.36±0.14	> 12	140.22±6.34	22.18±1.47
G-SLD 14	Complies	4.6±0.82	100.16±0.89	0.31±0.11	> 12	97.21±2.87	31.96±2.63

n=3, average of three determinations ± SD

All the prepared formulations compiled the weight uniformity study. The hardness of all the batches was found to be in the range of 4.2 to 5.6 kg/cm^2. Drug content of all the batches was within the limits prescribed by IP. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance. All the prepared batches were floating for more than 12 hours. The tablet adhesion retention time was in the range of 46.34 to 139.21 minutes. It was found that as the amount of kappa carrageenan increased in the formulations, the tablet retention also increased, which was expected because Carrageenan is high molecular weight sulfated polysaccharides and its high adhesion period may be due to hydrogen bonding or ionic interaction with agar[33]. However, increased levels of sodium bicarbonate decreased the tablet adhesion retention period. The findings were the same as that of the results found for the metformin floating matrix tablet, prepared with the combination of same release retarding polymers. The lag time for all the batches was found to be in the range of 8.63 to 90.43 seconds. General observation was that the batches with the minimum amount of gas generating agents had maximum floating lag time.

3.7 *In vitro* Drug Release Study

The *In vitro* dissolution study of all the batches of GLM floating matrix tablet, prepared by applying simplex lattice design was performed in 500ml 0.1N HCl. The drug release data is given in table 7 and the graphical representation of the same is shown in Fig 3.

3.8 *In vitro* Drug Release Kinetics

Model dependent release kinetics describes the mechanisms of overall release of drug from the dosage forms. The model dependent approaches evaluated for the drug release kinetics were zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas. The release from batches G-SLD 1, G-SLD 3, G-SLD 4, G-SLD 8 and G-SLD 9 of GLM floating

matrix tablets was found to follow the RHC model with R2 value close to 1, for the period of 12 hours. RHC model data is obtained from *in vitro* drug release studies plotted as the cube root of drug percentage remaining in matrix versus time[34].

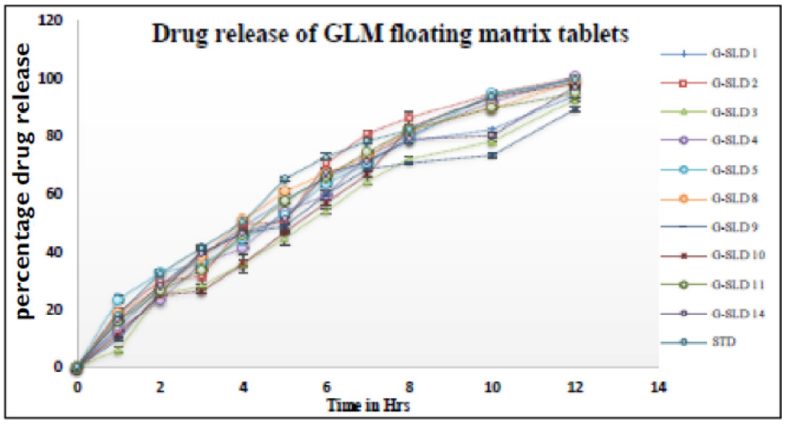


Fig 3: Graphical representation of the drug release from floating tablets of GLP prepared by Simplex Lattice Design

Table 7. Results of *in vitro* release of GLP floating matrix prepared by applying SLD*

Time (hrs)	G-SLD 1 (%)	G-SLD 2 (%)	G-SLD 3 (%)	G-SLD 4 (%)	G-SLD 5 (%)	G-SLD 8 (%)	G-SLD 9 (%)	i-SLD 10(%)	G-SLD 11 (%)	G-SLD 14 (%)	STD (%)
0	0	0	0	0	0	0	0	0	0	0	0
1	13.7±1.09	19.27±1.53	5.91±0.93	12.68±1.02	23.68±1.03	18.75±1.39	9.71±0.79	11.32±1.39	15.85±0.89	16.37±1.18	18.23±0.54
2	27.68±2.67	29.96±2.92	25.13±0.99	23.34±1.02	32.79±0.34	27.23±1.16	26.14±0.49	24.91±1.16	26.54±0.59	28.33±1.53	32.61±1.03
3	38.47±1.12	31.43±2.79	28.22±0.73	36.02±0.52	35.94±1.04	37.95±0.53	39.46±1.32	26.37±0.79	33.71±0.91	39.64±2.02	41.31±1.19
4	48.68±1.18	49.41±0.49	36.01±1.08	41.24±0.91	44.26±1.11	51.02±0.69	46.47±1.6	35.87±2.94	46.03±1.17	46.54±2.54	50.41±0.73
5	58.21±0.92	50.45±1.32	44.64±2.45	54.21±2.42	52.93±0.43	61.18±0.78	48.81±1.18	46.61±0.75	57.9±1.06	51.23±1.79	65.39±0.57
6	65.82±0.82	70.75±1.6	54.37±0.88	59.89±0.89	63.85±0.71	67.44±1.03	60.19±1.53	57.31±1.07	66.17±0.79	67.43±0.92	73.01±1.09
7	72.05±1.53	80.97±1.18	64.71±1.53	73.38±0.67	70.68±1.04	73.26±1.19	68.86±0.92	67.04±1.16	74.61±0.75	71.44±0.88	78.42±0.67
8	78.33±1.29	86.4±2.17	72.24±0.92	80.4±0.88	79.26±1.39	82.2±0.73	70.9±0.57	83.05±0.39	82.16±1.07	78.99±1.49	82.24±1.12
9	82.41±1.42	95.03±0.92	78.33±0.21	92.12±0.45	94.94±1.16	89.91±0.57	73.52±0.79	93.77±0.75	89.98±1.16	80.35±1.03	94.21±1.18
10	94.43±1.11	100.47±0.89	92.87±0.79	100.75±1.02	99.4±0.79	99.16±0.99	89.36±0.82	98.5±0.91	95.19±1.63	97.33±0.98	99.95±0.68

*Formulations G-SLD 6, 7, 12 and 13 were duplicate batches of G-SLD 5, 1, 4 and 8, respectively. Hence, their in vitro drug release data is not presented in the table. *n=3, average of three determinations±SD*

Table 8: Results table for *in vitro* drug model-dependent kinetics for GLM Floating matrix tablets

Batch code	Higuchi model (RH)	Korsmeyer Peppas model (RP)	Hixson Crowell model (RHC)	First order (R1)	Zero order (R0)
G-SLD 1	0.9773	0.9956	0.9997	0.7602	0.9897
G-SLD 2	0.9494	0.9335	0.9380	0.8136	0.9563
G-SLD 3	0.9427	0.9232	0.9796	0.6888	0.9749
G-SLD 4	0.9551	0.9942	0.9946	0.7411	0.9892
G-SLD 5	0.9664	0.9563	0.9647	0.7484	0.9437
G-SLD 8	0.9785	0.9870	0.9947	0.7673	0.9858
G-SLD 9	0.9681	0.9542	0.9798	0.7117	0.9623
G-SLD 10	0.9220	0.9689	0.9749	0.7549	0.9823
G-SLD 11	0.9662	0.9915	0.9899	0.8245	0.9930
G-SLD 14	0.9727	0.9902	0.9753	0.7010	0.9756
STD	0.9807	0.9946	0.9908	0.8068	0.9858

This model applies to tablets where dissolution occurs in all the planes equally and the initial geometry of the tablet remains constant. The release from batches G-SLD 2, G-SLD 10 and G-SLD 11, followed R0 model. The data is obtained from in vitro drug release studies, plotted as cumulative amount of drug released versus time. This relationship is used to describe the drug dissolution of the matrix tablets with low soluble drugs. The drug release from G-SLD 2 followed RH model and batch G-SLD 14 and STD formulation of GLM, followed RP model .The results for the analysis of model-dependent drug release kinetics is given in table 8. 3.8 Statistical Analysis .The result of all the dependent variables is given in table 8. A statistical model incorporating 14 interactive terms was used to assess the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X$$

Where, Y is the dependent variable, b0 is the arithmetic mean response of the 14 runs, and bi is the estimated coefficient for the factor Xi. The main effects (X1, X2, and X3) represent the average result of changing one element at a time from its low to high value. The interaction terms (X1X2, X2X3, X1X3, and X1X2X3) give the information about how the response changes when two or more factors are simultaneously modified. The values for Similarity factor Æ'2 (Y1), Time required for 50% drug release (t50) (Y2), Time required for 90% drug release (t90) (Y3) 14 batches (G-SLD1 - G-SLD14) is presented in table 8. The outcomes indicated that the values of subject variables are dependent on independent variables. All the formulations gave satisfactory floating lag time in the range of 8 to 90 seconds, which means that the chosen independent variables had no significant effect on the dependent variables. The formulations released 50% of the drug in the time range of 3.89 to 5.51 hours and released 90% of the drug in the time range of 9.48 to 12.24 hours. Using analysis of variance (ANOVA), the significance (p Ë, 0.05) of the ratio of mean square variation due to the regression coefficient, and the residual error were tested (Table 9). The Special Cubic Mixture model was found to be significant for Y1 and Y2 responses, whereas the special Quartic Mixture model was followed by Y324. The high values of correlation coefficients for similarity factor Æ'2 (R2 = 0.9443), t50 (R2 = 0.9643), and t90 (R2 = 0.9887) indicated a good agreement between the dependent and independent variables. Lack of Fit F-value for Y1, Y2 and Y3 was found to be about 0.5410, 0.1048 and 0.2216 respectively, which suggests the desirable insignificance of Lack of Fit.

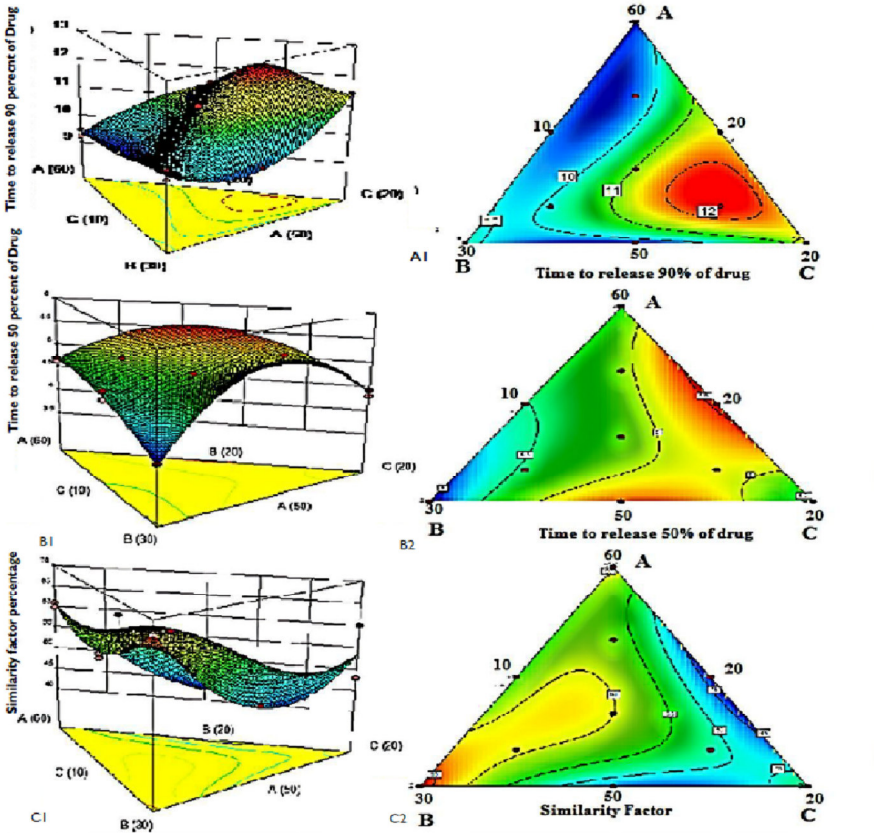
Table 8: Results of dependent factors of GLM floating matrix tablets prepared by applying SLD*

Runs	Batch code	Similarity factor *f*2 (%)	Time required for 50 % (hrs)	Time required for 90% (hrs)
1	G-SLD 1	60	4.29±0.09	11.43±0.83
2	G-SLD 2	61	4.95±0.17	9.47±0.16
3	G-SLD 3	43	5.51±0.29	11.49±0.31
4	G-SLD 4	56	4.61±0.18	9.77±0.49
5	G-SLD 5	60	4.72±0.07	9.48±0.29
6	G-SLD 6	61	4.63±0.08	9.21±0.34
7	G-SLD 7	48	4.41±0.17	11.32±0.98
8	G-SLD 8	70	3.92±0.09	10.01±0.72
9	G-SLD 9	48	5.21±0.21	12.24±0.92
10	G-SLD 10	47	5.36±0.15	9.59±0.59
11	G-SLD 11	64	4.32±0.06	10.0±0.48
12	G-SLD 12	55	4.43±0.17	9.71±0.44
13	G-SLD 13	69	3.89±0.21	10.31±0.28
14	G-SLD 14	58	4.88±0.18	11.2±0.28

**n=3, average of three determinations±SD*

Table 9. ANOVA table for response parameters for Simple Lattice design model for GLM gastroretentive floating matrix tablets

Source	Sum of Squares	Degree of freedom	Mean Square	F Value	P-value
Similarity factor % (*f*2)					
Model	643.69	6	107.28	6.33	0.0042
Residual	118.67	7	16.95		
Corrected Total	762.36	13			
Time to release 50% of drug (t50)					
Model	3.05	6	0.51	31.54	0.0001
Residual	0.11	7	0.016		
Corrected Total	3.16	13			
Time to release 90% of drug (t90)					
Model	11.95	8	1.49	54.93	0.0002
Residual	0.14	5	0.027		
Corrected Total	12.09	13			



(In contour plot A, B, C stands for HPMC K15M, k-carrageenan and sodium bicarbonate respectively)

Fig 4: Response surface plot and contour plot for GLM floating matrix tablet prepared by applying SLD

There was an antagonistic effect of variables in two dimensional planes indicating the significant interaction between the variables. This means that on changing the two variables simultaneously, the interaction was observed and that decreased the similarity factor value. However, the most significant coefficient with highest magnitude was when all the three factors were modified simultaneously, it had an agonistic effect on Y1. Observed and predicted values of the similarity factor were found to be comparable, which further validates the suitability of the model. The three dimensional response surface graphs for similarity factor given in Fig 5, shows the obtained contour plot (C2) and response surface plots (C1). This gives the information about the main and interaction effects of the independent components. It can be clearly seen that maximum similarity value, above 65% is obtained in the portion with highest value of k-carrageenan. The results for Y3 could have been better if the higher value of X2 variable would have been increased beyond the existing level.

3.9 Time to Release 50% of Drug

The results of ANOVA for the applied model, time to release 50% of the drug, are shown in Table 9. On looking into the results of F statistics, it was observed that model probability was greater than F value i.e. 31.54, which confirms the significance of the model. There is only a 0.01% chance that an F-value this large could occur due to noise. Significance of the model was also proved by the p-value less than 0.0500. In this case A, B, C, AC, BC, ABC are significant model terms. The result can be expressed for model analysis by special cubic model using following equation:

$$t_{50} = +4.68X_1 + 3.87\,X_2 + 4.87X_3 + 0.86\,X_1X_2 + 4.18\,X_1X_3 + 4.84\,X_2X_3 - 15.17\,X_1X_2X_3$$

3.10 Time to Release 90% of Drug

The results of ANOVA for the applied model on time to release 90% of drugs are shown in Table 4. On looking into the results of F statistics, it was observed that model probability was greater than F value i.e. 54.93, which confirms the significance of the model. There is only a 0.02% chance that an F-value this large could occur due to noise. Significance of the model was also proved by the p-value less than 0.0500. In this case A, B, C, AC, BC, A2BC, ABC2 are significant model terms. As the cubic model was aliased, the result can be expressed for model analysis by Special quartic model using following equation:

$$t_{90} = +9.34X_1 + 10.15\,X_2 + 11.37\,X_3 - 0.081\,X_1X_2 + 4.43\,X_1X_3 - 4.8\,X_2X_3 - 87.10\,X2X_2X_3 + 9.20X_1X2X_3 + 144.92X_1X_2\,X2$$

Table 10: Predicted and actual values of the responses for validation run: SLD for GLM

Responses	F1		F2		F3	
	Predicted values	Actual values	Predicted values	Actual values	Predicted values	Actual values
Similarity factor % $f2$ in %	56.5849	54.23	58.9587	61.54	58.0639	60.35
Time required for 50% drug release (t50) in hrs	4.99175	4.84	4.64653	4.72	4.67158	4.61
Time required for 90% drug release (t90) in hrs	11.8698	11.72	9.2678	9.41	9.44833	9.29

The actual and predicted values of the responses is shown in table no.10. The relative errors (%) between the predicted and experimental values for each response were calculated and the values were found to be within 5%, which confirms the validity of the model. 3.10 Selection of Optimized Formulation. To optimize all the above responses with different targets, a numerical optimization technique by the desirability function and a graphical optimization technique by the overlay plot was used. The overlay plot gives the regions not meeting the specifications as greyed out, leaving an operating window or sweet spot in yellow colour (Fig. 5).

This means that within the yellow region the formulation prepared will give maximum similarity factor and better release profile. It is evident from the overlay plot that the minimum amount of HPMC K15 M and gas generating agent, sodium bicarbonate is sufficient to give the desired effect. Whereas, it is clear from the plot that high concentration of kappa carrageenan is required to get the maximum similarity with the release profile of marketed formulation. It was found that the formulation G-SLD 8 and G-SLD 13 (with same composition) fulfilled the desirability criteria and hence can be considered as optimized formulation.

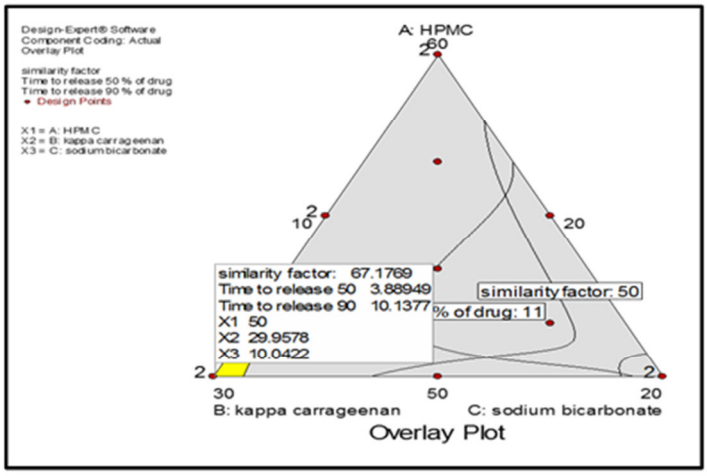


Fig 5 Overlay plot of GLM formulations by SLD

3.11 Radiographic Study

To determine the retention time of the optimized floating matrix tablets of GLM inside the body, radiographic studies were conducted. The barium sulfate loaded tablets, prepared with optimized formula of matrix tablet, were given to rabbits[35]. The X-ray photomicrographs were taken before and after administering the barium sulphate tablet to rabbits. Fig. 6 shows the X-ray images taken at 0, 4 and 12 hrs, time period. The images clearly indicated that the tablets remained afloat in gastric fluid for up to 12 h in the stomach of rabbit. Hence, the study confirms the gastroretentive behavior of the developed floating matrix tablet of GLM.

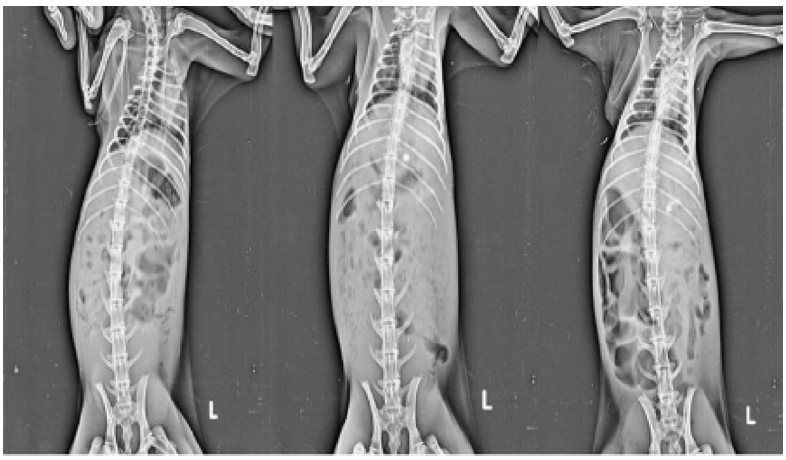


Fig 6. X-ray images showing the presence of barium sulfate-loaded floating matrix tablet in the rabbitâ€™s stomach. a) 0 min b) 4hrs c) 12hrs

4. CONCLUSION

Floating matrix tablet of Glimepiride was a also prepared utilizing the blend of hydrophilic polymer HPMC K15M with anionic and non-ionic polymers. The last improvement of skimming Glimepiride formulation was finished by applying Simplex cross section plan (SLD) utilizing kappa carrageenan, HPMC K15M and sodium bicarbonate as free factors. The degrees of the factors were chosen from preliminary examinations and the tablets were set up by wet granulation strategy utilizing PVP K30. The comparability factor ($f2$), time to deliver half (t_{50}) of medication and time to deliver 90% (t90) of medication were taken as reliant elements. The plan was utilized and assessed utilizing the Design-Expert® Software (adaptation 9.0.6, Stat-Ease) by running 14 examinations. It was apparent from the overlay plot that the base measure of gas producing specialist is adequate to give the ideal impact. Least convergence of HPMC K15M is required, though the measure of kappa carrageenan ought to be greatest. The ideal estimations of chose factors were discovered to be 50 mg of X1, 30 mg of X2 and 10 mg of X3, and this plan indicated highest desirability.

5. AUTHORS CONTRIBUTION STATEMENT

Dr. S.V Gopalakrishna and Dr. G.V Subbareddy conceived the presented idea. They provided intellectual content, performed part of research work and guided the entire work. Kishore did the literature search & performed research work, evaluated the results and reviewed the manuscript.

6. CONFLICT OF INTEREST

Conflict of interest declared none.

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