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RESEARCH ARTICLE

Formulation and Statistical optimization of Esomeprazole Non-Effervescent Gastric Floating Matrix Tablets

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ABSTRACT

Esomeprazole is a proton pump inhibitor that decreases the amount of acid produced in the stomach. Esomeprazole is used to treat symptoms of gastro esophageal reflux disease and other conditions involving Zollinger-Ellison syndrome in adults. In the present work, two methods of preparations were employed i.e. direct compression of physical mixtures and compression of melt granules obtained from hot fusion technique. Lactose was employed as channeling agent to study the effect on drug release. In each method, 3^2 full factorial design was employed for design and optimization of Esomeprazole non-effervescent gastric floating matrix tablets (NEGFMT) with an amount of Glyceryl Laurate (X1) and percent of Lactose (X2) as independent variables. Y1(%DR1) and Y2(T100) were selected as dependant variables. Among the two methods of preparation of NEGFMT, melt granulation technique was found to be more useful compared to physical mixture due to intimate distribution of drug in the Glyceryl Laurate. Though both the optimized formulations met the theoretical release profile, the concentration of GL in the melt granulation was found to be less than half required for physical mixture.

Keywords: Esomeprazole, Glyceryl laurate, Lactose, Non-gas generating floating tablets.

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CONTENTS

Introduction

Non-effervescent gastric floating matrix tablets (NEGFMT) were formulated with glyceryl Laurate (GL). GL is hydrophobic, non swellable, matrix forming, wax material originally introduced as a lubricant in the preparation of tablets, which has been recently used as sustained/controlled release agent1-3. It is having low density of 0.933g/cm3 compared to gastric fluid and hence tried for its application in the design of Non effervevescent Gastric Floating tablets of Esomeprazole. Esomeprazole is

a substituted benzimidazole, indicated for the treatment of gastroesophageal reflux disease in adults and children, risk reduction of NSAIDs-associated gastric ulcer, Helicobacter pylori eradication. The stability of esomeprazole is a function of pH, it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25° C and about 8 hours at 37° C.[4] Esomeprazole has a half life of 1.25 ± 0.25 h and has a bioavailability of 48% when administered orally [5-6].

Materials and Methods

Materials

Esomeprazole was received as a gift sample from Aurobindo Pharma Ltd (Hyderabad, India). Glyceryl Laurate was kindly provided by Dr Reddy's Laboratories (Hyderabad, India). Lactose, Aerosil, Magnesium stearate was provided as gift sample from Loba Chemie Pvt Ltd (Mumbai, India). All other chemicals and solvents were of analytical grade or highest quality and were used as such as obtained.

Methods:

Determination of flow properties

Angle of repose[7] (°θ):

Angle of repose was determined by measuring the height and radius of the heap of the powder/granule bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the horizontal plane. Powder was placed in the funnel and allowed to flow freely.

$$\text{Tan } \theta = h / r$$

Where, h = height of heap of powder/granule bed.

r = radius of heap of powder/granule bed.

In each method, 3^2 full factorial design was employed for design and optimization of Esomeprazole non-effervescent gastric floating matrix tablets (NEGFMT) with an amount of Gleceryl Laurate (X1) and percent of Lactose (X2) as independent variables. Y1 (%DR1) and Y2 (T100) were selected as dependant variables as shown in table 1.

Preparation of melt granules:

Preparation of NEGFMT: Floating Melt granules were prepared by hot fusion technique. Glyceryl Laurate was melted with continuous stirring in a porcelain dish on a water bath maintained at 70° C. The required amount of Esomeprazole was added to the molten GL with proper mixing and cooled to room temperature. The solidified mass was ground and passed through #30 mesh (600 µm) to obtain uniform sized granules. Tablets were prepared by direct compression of physical mixtures as well as by compression of melt granules.

Preparation of NEGFMT by direct compression of physical mixtures: All the ingredients sufficient for a batch of 100 tablets according to the formulae shown in Table 2 were passed through the #30 mesh (600 µm). Esomeprazole was geometrically mixed with excipients, except magnesium stearate and Aerosil until a homogenous blend was achieved. Then the resulting blend was lubricated with magnesium stearate and Aerosil passed through #60 mesh (250 µm). The lubricated blend was then compressed into tablets on a 16 station rotary tablet machine (M/s. Cadmach Machinery Co. Pvt. Ltd., India) using 12 mm round (Esomeprazole) , flat plain punches with a sufficient compression force to obtain hardness of 4 to 5 Kg/cm² containing Esomeprazole equivalent to a dose of 130 mg.

Preparation of NEGFMT by compression of melt granules: The melt granules obtained from hot fusion technique were geometrically mixed with other excipients and compressed into tablets on a 16 station rotary tablet machine (M/s. Cadmach Machinery Co. Pvt. Ltd., India) using 12 mm round (Esomeprazole), flat plain punches with a sufficient compression force to obtain hardness of 4 to 5 Kg/cm2 containing Esomeprazole equivalent to a dose of 130mg as shown in table 3.

Evaluation of tablets [8-14]: The prepared floating tablets were evaluated for in vitro floating properties, uniformity of weight, hardness, friability, uniformity of content and in vitro drug release studies. The dissolution data was analyzed by model independent and model dependent approaches.

Data analysis, optimization of model: The statistical evaluation of dependent variables, prediction of optimized formulations and cross-validation of model were performed as described. Optimized formulations were prepared with the optimal values and evaluated for uniformity of weight, uniformity of content, hardness, friability, in vitro buoyancy and in vitro dissolution. The experimental values of dependent variables (%DR1 and T100) were determined from the in vitro dissolution data of the optimized formulations.

Table 1: Experimental range and levels of the independent variables in a 3^2 full factorial design

Run No.	Variable no in coded form	
	X_1	X_2
1	-1	-1
2	-1	0
3	-1	+1
4	0	0
5	0	+1
6	0	+1
7	+1	-1
8	+1	0
9	+1	+1

*% w/w to the total weight of drug and Glyceryl Laurate

	Actual values (Esomeprazole)	
Coded Values	**X_1 (Amount GL, mg)**	**X_2 (% of Lactose)***
-1	65	0
0	130	5
+1	195	10

*% w/w to the total weight of drug and Glyceryl Laurate

3. Results and Discussion

NEGFMT were prepared with different ratios of drug-GL (1:0.5, 1:1 and 1:1.5) to examine the effect of GL on the release of Esomeprazole. GL being a hydrophobic polymer, the effect of channeling agent was studied on the drug release and lactose was chosen being soluble in nature.

Hence the concentration of lactose was chosen as an independent variable along with concentration of GL to assess its effect on drug release and studied at three levels viz. 0, 5 and 10%. NEGFMT of Esomeprazole was prepared by direct compression of physical mixtures as well of compression of prepared melt granules in the same ratios of drug-GL in order to study the effect of method of preparation on the drug release.

Flow properties:

The flow of drug (poor flow, θ = 52.1°) was enhanced with the addition of GL. The angle of repose values of all drug-GL physical mixtures were found to be in the range of 26.3-38° (shown in Table 4) which indicated the suitability of physical mixtures of drug with GL for direct compression. The melt granules prepared with drug GL mixtures also exhibited good flow characteristics indicating their suitability for compression.

Table 4: Flow properties of pure drug and physical mixtures with GL (mean, n=3)

DRUG:GL	Angle of Repose(θ)	Inference
1:0(Esomeprazole)	54.3º	Poor
1:0.5	38.0º	Passable
1:1	31.7º	Passable
1:1.5	26.3º	Good

In-vitro floating characteristics:

The results of in vitro floating characteristics are shown in Table 5. All the prepared formulations floated immediately after placing into the beaker and the floating was maintained more than 24 hrs. This might be due to low density of the tablet with the presence of low density waxy material (GL), which produced an upward motion of the dosage form and maintained its floating.

Uniformity of weight, hardness, friability and uniformity of content: The results of uniformity of weight, hardness, friability and uniformity of content are shown in Table 5. All the prepared formulations complied with compendial standards for uniformity of weight. The hardness for all the formulations was found to be in the range of 4 to 5 Kg/cm2. The percentage weight loss in the friability test was found to be less than 1% for all the batches. The content of each individual preparation was found to be within the specified limits of 85 to 115% of the average content indicating that the uniformity of content test complies with the official compendial tests for tablets as per IP. Thus, the nizatidine NEGFMT prepared with GL were found to be of good quality fulfilling all the official and other requirements of tablets.

In-vitro drug release studies: USP XXIV tablet dissolution rate test apparatus with 900 mL of 0.1N HCl as dissolution medium employing paddle stirrer at 50 rpm was used for in vitro dissolution studies of all the NEGFMT. The mean percent of Esomeprazole released at different time intervals and the results are represented in Fig. 1 & 2. Dissolution data indicated that the release of the drug from the prepared NEGFMT depend on the content of glyceryl laurate (GL) and lactose. It was found that as amount of GL increased, release of drug from matrices decreased. It may be due to slower penetration of dissolution medium into the hydrophobic matrices formed by GL. Increased concentration of GL caused relatively more retardation in drug release due to increase in the path length for the diffusion of drug. Presence of lactose in the formulations enhanced the drug release from the hydrophilic matrix. Increasing the concentration of lactose from 0 to 10% increased the drug release from NEGFMT. This behaviour may be due to the rapid and high solubility of lactose in water leading to the formation of pores in the matrix facilitating the diffusion of drug molecules through the pores. It was found that the NEGFMT of the granules prepared by hot fusion technique had a significant and marked effect on decreasing the drug release in comparison with the release from NEGFMT made by direct compression of the physical mixture.

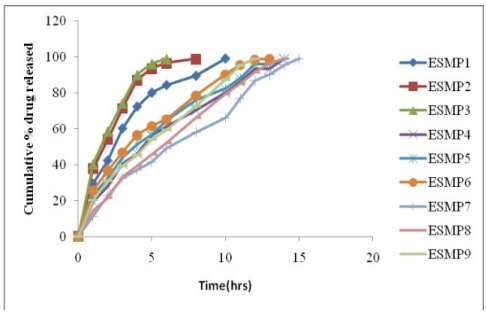

Fig 1: Dissolution profiles of Esomeprazole NEGFMT prepared from physical mixtures

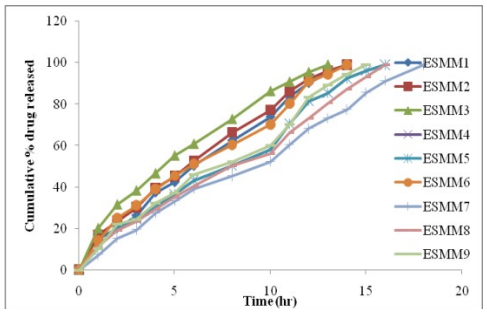

Fig 2: Dissolution profiles of Esomeprazole NEGFMT prepared from melt granulation

Model independent approaches: T_{100} values of all the NEGFMT were represented in Table 6 and those values were found to be in the range of 6hr-15hr for ESMM1-ESMM9 it was in the range 13hr-18hr respectively. T100 values were increased with increase in GL and decreased with increase in lactose content. Relatively higher T100 values were obtained for NEGFMT prepared with melt granules of hot fusion technique than the physical mixtures. The higher T100 values (i.e. slower release of drug) from the NEGFMT prepared with melt granules was due to complete coating of the drug particles by the melted wax. In this case, it was expected that the penetration of the dissolution medium to the matrix will be low compared with direct compression of the physical mixtures and hence, the dissolution and release of the drug occurs at a slower rate.

Model dependent approaches:

Drug release kinetics: The correlation coefficient (r) values of zero and first order of all the NEGFMT were represented in Table 7. It was observed that all the NEGFMT followed zero order release kinetics.

Drug release mechanism:

The drug release mechanism was determined by fitting the dissolution data to Higuchi, Hixon-Crowell and Korsemeyer-Peppas equations and the results were represented in the Table 8. It was found that all the prepared NEGFMT followed diffusion mechanism rather than the erosion. Plots of log fraction of Esomeprazole released versus log time of the all NEGFMT were found to be linear. The 'r' values of these matrices were found to be 0.9891 to 0.9983 indicating that the release also followed Korsmeyer–Peppas model. The release rate exponent values (n) were in the range of 0.54 to 0.86 confirming the anomalous (non Fickian) diffusion release mechanism.

Data analysis, optimization and cross-validation of model:

Data analysis: The summary of statistics along with comparative R^2, adjusted R^2, predicted R^2, PRESS, s.d., F-values and p-values are presented. A suitable model for describing the data was selected based on coefficient of determination (R^2) and PRESS values. Response Y1 was found to follow linear model and response Y2 was found to follow quadratic model for NEGFMT prepared from physical mixtures. The responses Y1 and Y2 were found to follow quadratic and interactive model respectively for NEGFMT prepared from melt granules. These models showed higher R2 and F-values and lower PRESS and p-values. Hence these models were selected for further optimization. ANOVA for measured responses (%DR1 and T100) of batches of both the methods for both the drugs. Higher F-values and lower p-values ($p<0.05$) for all the responses indicated the significance of the models[4-6].

Table 2: Formulae of Esomeprazole NEGFMT by direct compression of physical mixtures

Ingredients(mg/Tab)	ESMP1	ESMP2	ESMP3	ESMP4	ESMP5	ESMP6	ESMP7	ESMP8	ESMP9
Esomeprazole	130	130	130	130	130	130	130	130	130
Glyceryl Laurate	65	65	65	130	130	130	195	195	195
Lactose	0	9.75	19.5	0	13	26	0	16.25	32.5
Aerosil	5	5	5	5	5	5	3	5	5
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total	203	212.75	222.5	268	281	294	331	349.25	365.5

Table 3: Formulae of Esomeprazole NEGFMT by compression of melt granules

Ingredients(mg/Tab)	ESM M1	ESM M2	ESM M3	ESM M4	ESM M5	ESM M6	ESM M7	ESMM 8	ESM M9
Esomeprazole	130	130	130	130	130	130	130	130	130
Gleceryl Laurate	65	65	65	130	130	130	195	195	195
Lactose	0	9.75	19.5	0	13	26	0	16.25	32.5
Aerosil	5	5	5	5	5	5	3	5	5
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total	203	212.75	222.5	268	281	294	331	349.25	365.5

Table 5: In vitro floating properties and tabletting characteristics of Esomeprazole NEGFMT

NEGFMT	FLT (sec)	TFT (hrs)	Uniformity of weight[a] (mg)	Uniformity of Content[b] (mg)	Hardness[c] (Kg/cm^2)	Friability (%)
ESMP1	0	>24	203.1±0.66	99.9±0.33	4-5	0.08
ESMP2	0	>24	212.75±0.18	99.7±0.14	4-5	0.09
ESMP3	0	>24	222.5±0.77	98.3±0.33	4-5	0.07
ESMP4	0	>24	268.1±0.14	98.5±0.41	4-5	0.05
ESMP5	0	>24	281.5±0.81	99.8±0.17	4-5	0.08
ESMP6	0	>24	294.2±0.11	98.0±0.98	4-5	0.01
ESMP7	0	>24	331.2±0.55	99.5±0.66	4-5	0.02
ESMP8	0	>24	349.25±0.19	99.2±0.71	4-5	0.03
ESMP9	0	>24	365.5±0.41	99.6±0.18	4-5	0.05
ESMM1	0	>24	203.7±0.14	99.1±0.66	4-5	0.08
ESMM2	0	>24	212.1±0.59	98.7±0.41	4-5	0.01
ESMM3	0	>24	222.7±0.44	99.4±0.19	4-5	0.05
ESMM4	0	>24	268.5±0.27	98.5±0.44	4-5	0.05
ESMM5	0	>24	281.9±0.36	99.1±0.36	4-5	0.03

ESMM6	0	>24	294.7±0.59	99.4±0.85	4-5	0.02
ESMM7	0	>24	331.9±0.17	99.1±0.19	4-5	0.04
ESMM8	0	>24	349.5±0.25	99.2±0.54	4-5	0.05
ESMM9	0	>24	365.9±0.33	99.6±0.33	4-5	0.05

ESMP: Esomeprazole Matrix tablets by physical mixture; FLT: Floating Lag Time
ESMM: Esomeprazole Matrix tablets by Melt granulation; TFT: Total Floating Time
a; mean±% deviation, n =20, b; mean±s.d., n=10 c; mean, n=5

Table 6: T_{100} of NEGFMT of physical mixture

Esomeprazole			
ESMP1	10	**ESMM1**	14
ESMP2	8	**ESMM2**	14
ESMP3	6	**ESMM3**	13
ESMP4	14	**ESMM4**	16
ESMP5	14	**ESMM5**	15
ESMP6	13	**ESMM6**	14
ESMP7	15	**ESMM7**	18
ESMP8	14	**ESMM8**	16
ESMP9	12	**ESMM9**	15

Table 7: Co relation coefficient (r) values of NEGFMT for Esomeprazole

NEGFMT	**Zero order**		**First order**	
	K_0	r	K_1	r
ESMP1	9.106	0.951	-0.4	0.906
ESMP2	11.86	0.992	-0.598	0.988
ESMP3	15.73	0.996	-0.743	0.95
ESMP4	6.22	0.932	-0.251	0.849
ESMP5	6.31	0.941	-0.269	0.887
ESMP6	6.82	0.932	-0.251	0.849
ESMP7	6.27	0.986	-0.23	0.8
ESMP8	6.87	0.987	-0.264	0.844
ESMP9	7.6	0.977	-0.309	0.826
ESMM1	6.87	0.993	-0.253	0.811
ESMM2	6.82	0.988	-0.264	0.843
ESMM3	7.018	0.968	-0.283	0.861
ESMM4	5.42	0.966	-0.218	0.789
ESMM5	6.045	0.99	-0.239	0.802
ESMM6	6.59	0.986	-0.244	0.785
ESMM7	5.6	0.994	-0.172	0.728
ESMM8	5.81	0.993	-0.193	0.725
ESMM9	6.2	0.988	-0.221	0.754

Table 8: Release mechanisms of Esomeprazole NEGFMT

NEGFMT	**Higuchi**	**Hixson Crowell**	**Korsmeyer-Peppas**	
	r	r	r	n
ESMP1	0.934	0.54	0.967	0.543
ESMP2	0.885	0.631	0.958	0.498
ESMP3	0.926	0.867	0.987	0.525
ESMP4	0.936	0.788	0.995	0.622
ESMP5	0.989	0.763	0.997	0.561
ESMP6	0.979	0.797	0.997	0.538
ESMP7	0.976	0.796	0.991	0.762
ESMP8	0.986	0.796	0.997	0.753
ESMP9	0.981	0.779	0.996	0.642
ESMM1	0.956	0.734	0.987	0.76
ESMM2	0.968	0.705	0.991	0.71
ESMM3	0.988	0.638	0.998	0.627

ESMM4	0.94	0.76	0.988	0.783
ESMM5	0.95	0.743	0.99	0.785
ESMM6	0.963	0.702	0.995	0.72
ESMM7	0.943	0.705	0.995	0.874
ESMM8	0.939	0.763	0.99	0.78
ESMM9	0.937	0.753	0.98	0.76

The application of response surface methodology yielded the following regression equations which are an empirical relationship between the logarithm values of $\%DR_1$ and T_{100}.

Table 10: Model coefficients of NEGFMT for Esomeprazole

Factor	Co efficient of Estimate	p-value	SE	95% CI Low	95% CI Low	VIF
NEGFMT prepared from Physical mixture						
Response Y_1 (%DR1): Linear Model						
Intercept	24.63 (β_0)	<0.0001*	0.7413	22.82	26.45	
X_1: Glyceryl Laurate	-10.28(β1)	<0.0001*	0.9079	-12.50	-8.06	1.0000
X_2: Lactose	4.34(β2)	0.0031	0.9.79	2.12	6.56	1.0000
Response Y_2 (T100): Quadratic Model						
Intercept	13.89(β_0)	0.0158	0.6375	11.86	15.92	
X_1: Glyceryl Laurate	2.83(β_1)	0.0039	0.3492	1.72	3.94	1.0000
X_2: Lactose	-1.33(β_2)	0.0316	0.3492	-2.44	-0.2221	1.0000
X_1X_2	-0.2500(β_{12})	0.5999	0.4276	-1.11	1.61	1.0000
X_1X_1	-2.83(β_{11})	0.0184	0.6048	-4.76	-0.9087	1.0000
X_2X_2	0.3333(β_{22})	0.6199	0.6048	-2.26	1.59	1.0000
NEGFMT prepared from Melt granulation						
Response Y_1 (%DR1): Quadratic model						
Intercept	12.10(β_0)	1	0.2380	11.34	12.86	
X_1: Glyceryl Laurate	-3.80(β_1)	< 0.0001	0.1304	-4.22	-3.39	1.0000
X_2: Lactose	1.51(β_2)	0.0002	0.1304	1.10	1.92	1.0000
X_1X_2	-0.2600(β_{12})	0.1444	0.1596	-0.7681	0.2481	1.0000
X_1X_1	1.91(β_{11})	0.0004	0.2258	1.19	2.63	1.000
X_2X_2	0.1567(β_{22})	0.4611	0.2258	-0.5618	0.8752	1.000
Response Y_2 (T100): Quadratic model						
Intercept	14.56(β_0)	0.0007	0.1591	14.15	14.96	
X_1: Glyceryl Laurate	1.67(β_1)	0.0004	0.1948	1.17	2.17	1.0000
X_2: Lactose	-1.17(β_2)	0.0019	0.1948	-1.67	-0.6658	1.0000
X_1X_2	-0.7500(β_{12})	0.0256	0.2386	-1.36	-0.1366	1.0000

%DR1: % drug released in 1 hr; T100: Time to release 100% of drug; SE: Standard error; CI: Confidence interval; VIF: variance of inflation factor * Significant ($p<0.05$)
** Not significant ($p>0.05$)

For Esomeprazole NEGFMT prepared from physical mixtures:

$$\%DR_1 = 24.63 - 10.28X1 + 4.34X2$$

$$T_{100} = 13.89 + 2.83X1 - 1.33X2 - 0.2500X1X2 - 2.83 \quad 0.3333X2X2$$

For Esomeprazole NEGFMT prepared from Melt granulation:

$$\%DR_1 = 12.10 - 3.80\,X1 + 1.51X2 - 0.2600X1X2 + 1.91X1X1 + 0.1567X2X2$$

$$T_{100} = 14.56 + 1.67X1 - 1.17X2 - 0.7500*X1X2$$

Where, X1 and X2 are the coded values of the test variables of the glyceryl laurate quantity and % w/w of lactose to the total weight of drug and glyceryl laurate respectively. The detailed summary of results of multiple regression analysis of dependant variables for both methods and Esomeprazole were shown in Table 10. Main effects of all the selected independent variables like glyceryl laurate quantity and % w/w of lactose were highly significant ($p<0.05$). For NEGMFT prepared by both methods, antagonistic and additive effect was observed for glyceryl laurate (X1) respectively for %DR1 and T100 and reverse situation was observed for lactose (X2). That means increasing the glyceryl laurate decreased %DR1 and increased T100 values i.e. controlled the release of the drug and vice versa observed for lactose.

The VIF values for all the models were found to be one, indicating good estimation of coefficient. Contour and response surface plots were generated for %DR1 and T_{100} to demonstrate graphically the effect of GL and lactose are shown in Figs. 3 & 5 respectively for physical mixture formulations and in Figs. 4 & 6 for melt granules formulations. These plots clearly explained the effect of X1 (GL) and X2 (lactose) on the %DR1 & T100 for both the methods i.e. decreased %DR1 and increased T100 with increased X1 (GL) and decreased X2 (lactose) content. These findings suggest that the amount of wax material (GL) and channelling agent (lactose) have got a relationship for achieving a formulation with better controlled drug release.

Optimization:

Optimization was carried out by both numerical optimization and graphical optimization techniques. The desirability and overlay plots are shown respectively in Figs. 7 & 9 and 8 & 10. The desirability function was found to be higher (near to 1) for the optimized formula indicating the suitability of the formulations. The optimal values of independent test variables are presented in Table 11. The optimized formulation of physical mixtures for Esomeprazole ESMPopt it contained 70.3 mg of GL and 9.2 mg (4.6%) of Lactose. Similarly, the optimized formulation of melt granules and for Esomeprazole ESMMopt it contained 79.06 mg of GL and 17.6 mg (8.42%) of Lactose.

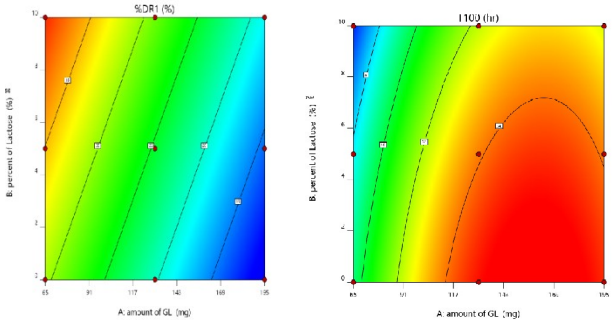

Fig 3: Contour plots for %DR1, T100 of NEGFMT prepared from physical mixtures for Esomeprazole

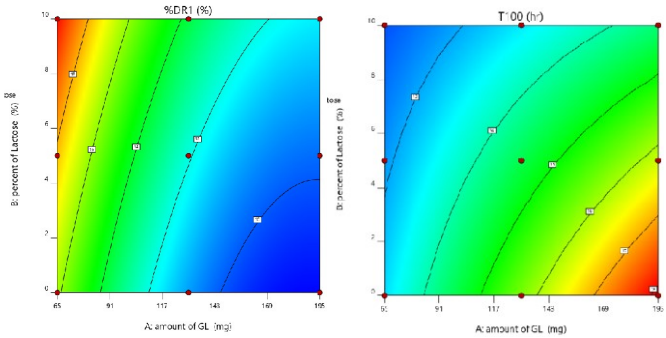

Fig 4: Contour plots for %DR1$T_{100}$of NEGFMT prepared from Melt granulation for Esomeprazole

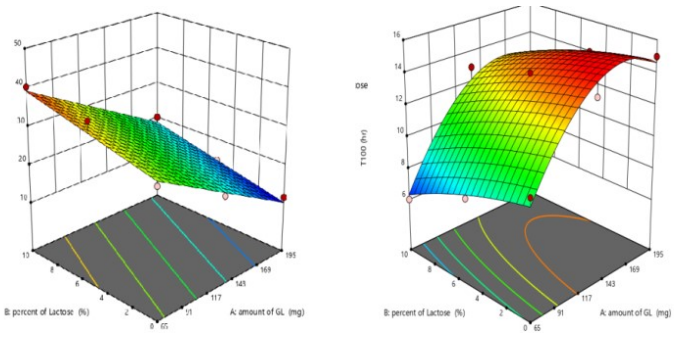

Fig 5: Response surface plot for %DR1, T100 of NEGFMT prepared from physical mixtures for Esomeprazole

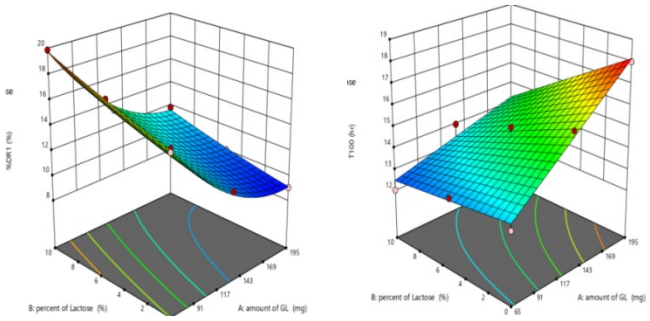

Fig 6: Response surface plot for %DR1 of NEGFMT prepared from Melt granulation for Esomeprazole

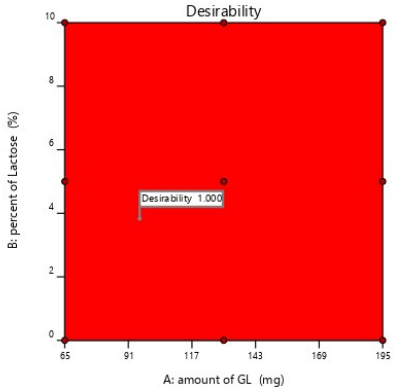

Fig 7: Desirability plot for NEGFMT prepared from physical mixtures for Esomeprazole

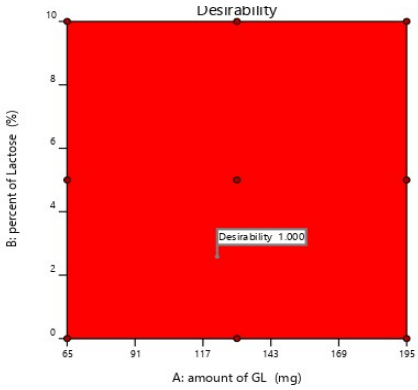

Fig 8: Desirability plot for NEGFMT prepared from Melt granulation for Esomeprazole

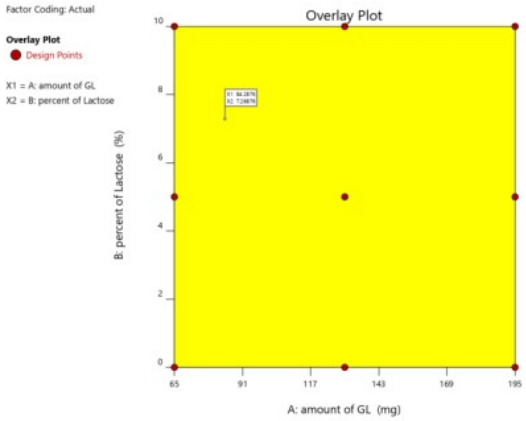

Fig 9: Overplayplot for NEGFMT prepared from physical mixtures for Esomeprazole

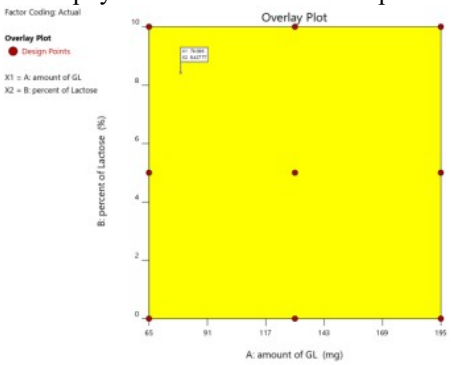

Fig 10: Overplayplot for NEGFMT prepared from Melt granulation for Esomeprazole

Cross-validation of model: Cross-validation of the model was performed by preparing the optimized formulations (ESMPopt and ESMMopt). The prepared optimized formulations were found to be of good quality fulfilling all the official and other requirements of tablet. No lag time observed for floating of the prepared formulations and the floating was remained more than 24 hrs. Photograph was taken during the in vitro floating of optimized formulation and shown in Fig 11.

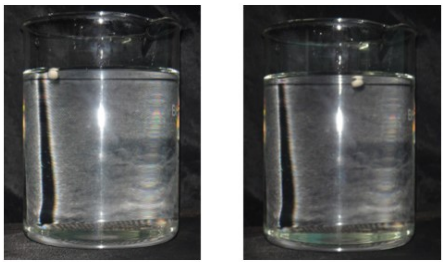

Fig 11: In vitro floating of optimized formulation

The dissolution data of optimized formulations (ESMPopt and ESMMopt) are shown in Table 12 and the comparative dissolution profile is shown in Fig. 12 along with theoretical profile. $f1$ and $f2$ values are represented in Table 13 along with correlation coefficient values of drug release kinetics and release mechanism models.

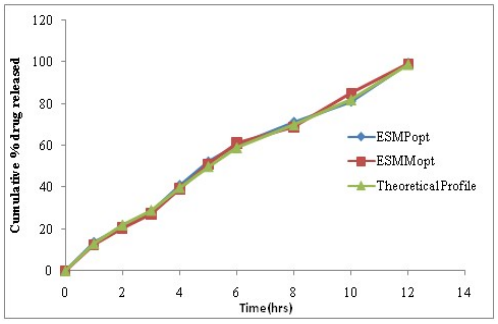

Fig.12: Comparative dissolution profiles of ESMPopt, ESMMopt and theoretical release profile

Both the optimized NEGFMT followed zero order release kinetics with anomalous (non-Fickian) diffusion mechanism. The $f1$ values were found to be near to zero (<5) and the $f2$ values were found to higher (>85) indicating the similarity between the optimized formulations and the theoretical profile.

Table 11: Formulae of optimized NEGFMT and their characteristics for Nizatidine and Esomeprazole

Ingredients(mg/Tab)	$ESMP_{opt}$	$ESMM_{opt}$
Esomeprazole	130	130
Gleceryl Laurate	70.3	79.06
Lactose	9.2 (4.6%)	17.6(8.42%)
Aerosil	4	4
Magnesium Stearate	3	3
Total	216.5	226.6
Characteristics		
FLT (sec)	0	0
TFT (hours)	>24	>24
Uniformity of weight(mg)	216.5±0.32	226.6±0.19
Uniformity of Content (%)	100.4±1.8	99.1±0.66
Hardness	4.0	4.2
Friability	0.02	0.09

a: mean±% deviation, n=20, b: mean±s.d., n=10, c: mean, n=5
d: tablets equivalent to 6.5 gm

Table 12: Dissolution data of optimized NEGFMT for Esomeprazole

Time(hr)	ESMPopt	ESMMopt	Theoretical Profile
1	13.66±0.18	12.54±0.25	13
2	21.02±0.14	20.51±0.58	22
3	28.33±0.35	27.37±0.34	29
4	41.02±0.61	39.33±0.58	40
5	52.30±0.17	51.22±0.17	50
6	60.32±0.59	61.25±0.44	59
8	71.25±0.51	69.00±0.58	70
10	81.33±0.18	85.13±0.66	82
12	99.55±0.41	99.11±0.47	99

Table 13: Correlation coefficients, $f1$ and $f2$ values of optimized NEGFMT for both the drugs

	ESMPopt	ESMMopt
Zero order 'r'value	**0.982**	**0.985**
First order 'r'value	0.758	0.778
Higuchi order 'r'value	0.949	0.942
Hixson crowell'r'value	0.704	0.719
Korsmeyer Peppas 'r'value	0.989	0.990
Korsmeyer Peppas 'n'value	0.823	0.85
***f*1**	2.5	1.89
***f*2**	87.3	93.2

The experimental values, predicted values and percentage relative error of optimized formulation responses (%DR1 and T100) are represented in Table 14. A reasonable agreement between predicted and experimental values was observed as indicated by low values (<5%) of the relative error. This proved the validity of model and ascertained the effects of GL and the amount of lactose on drug release.

Table 14: Cross-validation of model obtained using experimental and predicted results of both optimized NEGFMT

Optimized formulation	Response	Predicted value	Experimental value	%prediction error#
ESMPopt	%DR1	13	12.85	1.15
	T100	12	12	0
ESMMopt	%DR1	12	11.80	1.66
	T100	12	12	0

Percent Error was calculated using the formula :([Predicted value-Experimental value]/Predicted value)x100

4. Conclusion

The present study indicated the suitability of GL in the design of non-effervescent gastric floating matrix tablets as they showed immediate floating without any lag time indicating the suitability of GL as a polymer for the design of NEGFMT. The approach of statistical optimization reduced the number of experimental runs in optimizing the concentration of GL. However GL being a hydrophobic material, the release of drug is dependent on the dissolution of the drug followed by diffusion of drug. Incorporation of a soluble channeling agent like lactose helped in creating channels in the hydrophobic matrix thereby achieving the consistent drug release as per required rate. This assumption was supported by the applied experimental design in which lactose concentration was considered as one of the independent variable and the optimized formulations contained ~8-10% lactose to meet the desired theoretical release profile. Among the two methods of preparation of NEGFMT, melt granulation technique was found to be more useful compared to physical mixture due to intimate distribution of drug in the GL. Though both the optimized formulations met the theoretical release profile the concentration of GL in the melt granulation was found to be less than half required for physical mixture.

5. References

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