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Formulation Design, Development, and Characterization of a Hydrodynamically Balanced Gastroretentive System for Sustained Release of Antidiabetic Drugs

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Abstract: The present study aimed to develop and evaluate a hydrodynamically balanced gastroretentive drug delivery system of Mitiglinide to improve therapeutic efficacy in the management of Type II Diabetes Mellitus. A 2^4 factorial design was employed to optimize the formulation variables, including Hydroxypropyl Methylcellulose (HPMC K4M), Hydroxyethyl Cellulose (HEC), hydrophobic fatty base (Cetyl Alcohol), and effervescent agent Sodium Bicarbonate ($NaHCO_3$). A total of sixteen formulations were prepared during the optimization phase and categorized into five groups (Group I–V) for systematic analysis by varying the formulation variables at different levels. The independent variables, namely HPMC K4M, HEC, Cetyl Alcohol, and $NaHCO_3$, were evaluated for their influence on drug release, floating behavior, and overall formulation performance.Pre-compression parameters, including angle of repose, bulk density, compressibility index, and Hausner's ratio, were evaluated to determine the powder flow properties. Post-compression studies included thickness, hardness, friability, weight variation, swelling index, floating lag time, total floating duration, and in vitro drug release. The angle of repose ranged from 24.02° (F4) to 28.38° (F1), indicating acceptable flow characteristics. Bulk density was highest in F9 and lowest in F11. Carr's index was highest in F4 and lowest in F15, suggesting superior compressibility in formulations with lower values. Friability was highest in F9, whereas hardness was highest in F10 and lowest in F11. Swelling studies revealed that formulation F16 exhibited the highest swelling index (22.81), indicating superior matrix hydration and gastroretentive behavior.Floating characteristics of the tablets were evaluated in 400 mL of 0.1 N HCl. In vitro dissolution studies were conducted in a dissolution medium of pH 1.2, and drug release was analyzed at 235 nm using UV spectrophotometry. The results demonstrated that the selected formulation variables significantly influenced tablet buoyancy, swelling behavior, and drug release profile. The main effects of formulation variables A, B, C, and D were determined by evaluating the average response generated by changing one variable from a low to a high level while maintaining the others constant. Interaction effects, including AB, AC, AD, BC, CD, ABC, ABD, BCD, and ABCD, were analyzed to understand the combined influence of multiple independent variables on dependent responses.Factorial analysis confirmed that polymer concentration, hydrophobic matrix composition, and effervescent agent

concentration played significant roles in optimizing gastroretentive performance and sustained drug release. The optimized formulation demonstrated desirable floating characteristics, prolonged gastric retention potential, and controlled drug release, suggesting that the developed hydrodynamically balanced gastroretentive drug delivery system is a promising approach for effective oral antidiabetic therapy.

Keywords: Mitiglinide, Hydrodynamically Balanced Drug Delivery System, Gastroretentive Drug Delivery, HPMC K4M, Hydroxyethyl Cellulose, Factorial Design, In Vitro Evaluation, Type II Diabetes Mellitus.

Introduction

Numerous oral extended drug delivery systems have been developed to prolong the drug release. Since the majority of drugs are preferentially absorbed in the upper part of the small intestine[5], the real challenge in the development of an extended release drug-delivery systems lie in prolong the residence time of the dosage form in stomach or upper part of the small intestine until all the drug is completely emptied from the system in the desired time period.[2, 3]

The biopharmaceutical classification system (BCS) is used to group the API depending upon the solubility and lipophilicity (permeability) characteristics of the drug. BCS Class II compounds are poorly water soluble and highly permeable, and they exhibit bioavailability that is limited by dissolution rate[1]. The dissolution rate of BCS Class II drug substances may be accelerated by improvement of the wetting characteristics of the bulk powder.[4]

In general, drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close proximity to the absorption window is available for absorption. Under this conditions, designing a delivery system that is able to resident in the stomach or preferably prior to the absorption window would increase the absorption of such drugs[1].

Gastroretentive Drug Delivery Systems GRDDS can improve the controlled delivery of drugs that have an absorption window or are absorbed in the proximal intestine by continuously releasing the drug for a prolonged period of time for gradual exposure to the absorption site, thus ensuring optimal bioavailability[1].

Materials and methods

Mitiglinide was obtained as a gift sample from NATCO Pharma, Hyderabad, India, HPMC K4M obtained from Yarrow chemicals, Mumbai, India. Microcrystalline cellulose was purchased from Rolex laboratories ltd Chennai, India. Microcrystalline cellulose was purchased from Rolex laboratories ltd Chennai, India. Cetyl alcohol was purchased from Loba chemie Pvt ltd, Mumbai, India. All other chemicals and reagents used were of pharmaceutical or analytical grade and were used.

Formulation design by two level-four factor (2^4) Minitab® 15 was used to generate the 2^4 full factorial study designs and to perform the statistical analysis[3]. In factorial designs, the main effects are referred to using single uppercase letters, A, B, C, and D, the main effects of factors respect to HPMC K4M, HEC, Cetyl alcohol and $NaHCO_3$. An interactive effect is referred by a group of letters denoting which factors are interacting to produce the effect, the interactive effect produced by factors A, B, C, & D is referred to as AB, AC, AD, BC, BD, ABC, ABD, BCD, ACD and ABCD.

The magnitude and polarity (direction) of the numerical values of main and interactive effects indicates how it affects the process output. A higher absolute value for an effect means that the factor responsible for it affects the output significantly. A negative value means that increasing level of the factor responsible for that effect will decrease the output of the process[4]. The levels of the factors were shown in Table.1 and the 2^4 factorial design results in the single blocked sixteen formulations coded form run order can see in Table 2.

Preparation of mitiglinide gastroretentive drug delivery system

Accurately weighed mitiglinide, HPMC K4M, HEC and $NaHCO_3$ were mixed by geometric method in a laboratory blender until the homogenization was attained, identified by spectrophotometry assay method. Followed by adding of MCC, Citric acid were mixed with liquefied cetyl alcohol melted at 45°C ensure the proper mixing until the uniform damp mass was formed and screened on 22#, then the screened granules were dried at 45°C. Granules were lubricated with magnesium stearate and tabletted by using 8mm flat shaped punch and die set in 10 station rotary punching machine (Proton R&D press, Mumbai,

India). As mitiglinide was a poor water soluble drug, hydrophilic swellable polymers were added to control the drug release from polymeric matrices. Hydroxypropyl methyl cellulose K4M (HPMC K4M) and hydroxy ethyl cellulose (HEC) were hydrophilic polymers used as they had desirable properties to swell the system.

The drug release mechanism from hydrophilic matrices was depends on size, shape, swelling area and microenvironment surround by the system. In an attempt to study the effect of the amount of HPMC K4M, HEC, Cetyl alcohol and $NaHCO_3$ in alone and/or in combination on the drug release. The compositions of all sixteen formulations were represented in table.2

Statistical optimization technique

A 2^4 full factorial design was created to determine and optimize the effect of the four independent variables using $t_{50\%}$ as response factor. The four factors, in the content of mitiglinide were tested at two levels designated as -1 and +1, respectively. Four variables namely such as HPMC K4M, HEC, Cetyl alcohol and $NaHCO_3$ were kept at two levels. Except the optimization phase whose purpose was validated by extra design check point[7]. Main effects and interaction effects were tested by using statistical methods. The sixteen formulations of optimization phase were categorized into five groups for ease of analysis and comparison as follows:

1. Group I: All variables at low level (Formulation F4).
2. Group II: Any one of four variables at high level (Formulations F11, F7, F12, F14).
3. Group III: Any two of four variables at high level (Formulations F5, F3, F8, F6, F13, and F1).
4. Group IV: Any three of four variables at high level (Formulation F15, F10, F2 and F16).
5. Group V: All variables at high level (F9)

Data obtained from the experimental formulation, analyzed by Analysis of Variance (ANOVA). The polynomial equation of 2^4 factorial models is as follows:

$$Y = b_0 + b_1 A + b_2 B + b_3 C + b_4 D + b_{12} AB + b_{13} AC + b_{14} AD + b_{23} BC + b_{24} BD + b_{34} CD + b_{123} ABC + b_{134} ACD + b_{234} BCD + b_{124} ABD + b_{1234} ABCD.$$

Where, Y is the dependent variable; b0 is the intercept; b_1, b_2, b_3…..b_{1234} are the regression coefficients to respective multiple factors and A, B, C, and D are the independent variables were selected for the experiments.

Flow properties and primary evaluation parameters of BGRDDS

The following parameters of flow properties such as angle of repose, density, compressibility index, hausner's ratio and primary evaluation parameters of such as thickness, hardness, friability, weight variation and swelling index[8] were shown in Table.03.

Floating ability (Lag time and duration of floating)

The buoyancy test will be done on the formulated gastroretentive tablets by measuring the floating lag time and the duration of floating. The time take to emerge on the buffer surface (floating lag time) and the time constantly float on surface (duration of floating) was evaluated in the dissolution vessels. The floating lag time and duration of floating will also be assessed by placing the tablets in a flask containing media similar to that in the dissolution vessels[9,10]. The floating abilities of single tablets was determined in 400mL of 0.1N HCl, and shaken at 50rpm, 37 ± 0.2°C for 18hrs, using rotatory shaker apparatus (n=3). The floating lag time (time at which tablets start floating) and duration were measured by visual observation[11]. The results were represented in Table.4.

Swelling index

The swelling and erosion behaviour of tablets of all formulations were evaluated gravimetrically. For each time point, two samples of tablets were weighed and subjected to 900mL of 0.1N HCl buffer medium under similar condition to the dissolution studies. At pre-determined time intervals, swollen samples were removed from the dissolution vessel, patted gently with filter paper, weighed and dried at 60°C until constant weight was reached. Percent of weight gain from hydration and weight loss due to erosion were calculated using the following equation:

Figures of the best formulation were showed in Fig 6.1 at regular intervals of 2, 4, 8 and 12hrs of dissolution respectively.

Evaluation of *invitro* dissolution studies for MGRDDS

***In vitro* drug release studies**

The drug release studies were carried out using the dissolution[138] tester USP XXIV apparatus II. The dissolution media was used 900mL of 0.1N HCl buffer (pH 1.2) at 37±0.5°C with a stirring speed of 50 rpm. Samples were drawn at pre-determined time intervals and replaced by a same equivalent volume of fresh dissolution medium. The collected samples were analyzed for its drug content by spectrophotometrically at 244nm.

Release kinetics

In order to study the drug transport mechanism from the formulations used, four models were considered to fit the experimental data[13, 14]. The data were analyzed for the first 50% of the drug release by linear least-squares regression using the DD solver®[,15]. This analysis was used to relate the formulation effects to the mechanism of release and, consequently, with the selection of proper formulation in designing a GRDDS. The swelling behavior of the drug delivery system is characterized by the development of three fronts…

1. Swelling interface- a front that separates the glassy from rubbery state.
2. Eroding interface – a front that separates the matrix from the penetrant.
3. Diffusion front- a boundary that separates either translocation solid or the dissolved drug.

Results and discussions

The angle of repose of F1 and F4 were highest and lowest for 28.38º and 24.02º respectively. The lowest and highest has the high and low flow from hopper. The bulk density id highest for F9 and lowest for F11, while the Carr's index is highest for F4 and lowest for F15, indicating that low value has the highest compressibility. Highest content was loss on friability test for F9.Hardness is highest for F10 and lowest for F11. Swelling index is more observed for F16 as best formulation and these differences were insignificant and the best retards formulation was optimized by factorial plots and it has the swelling ration of 22.81 for F16can be seen in Fig.1. The lowest and highest lag times were observed for the F4 and F7, F13. The lag time of floating tablet depends on tablet weight, amount of effervescent agent was used, and microenvironment pH surrounded by that and water uptake time to response as in the release of carbon dioxide to takes towards to oppose gravitational force. The rotating speed of the shaker easily influences the floating time. The amount of $NaHCO_3$ increases in the matrix caused a reduction of floating lag time in all tablets. However, with $NaHCO_3$, until stable buoyancy was achieved the matrices began an up and down movement, attributed to rapid changes in CO_2 production and loss, leading to changes in matrix density. This may be the time needed for the HPMC matrix to form the gel layer capable of entrapping the formed CO_2. The HPMC and $NaHCO_3$ matrices showed a swollen gel-like structure, with entrapped CO_2, which improved the floating ability of the tablet. The entrapped CO_2 inside the hydrated matrix and caused a decrease in the tablet density caused to buoyant on fluid medium. The pictures of studies for best formulation can observe in Fig.2.

***In vitro* drug release data of MGRDDS**

All the sixteen formulations were prepared by the proposed design in 2^4 full factorial experiments. The results clearly indicate that the content as well as the release of mitiglinide from the tablets is strongly affected by the variables selected for the study. The main effects of A, B, C, and D represent the average result of changing one variable at a time from its low level to its high level. The interaction terms (AB, AC, AD, BC, BD, CD, ABC, ABD, ACD, BCD, and ABCD) show how the dependent variables change when two, three and four independent variables are simultaneously changed. The negative coefficients in the equation represents an inverse relationship between a response and factor where as a positive value represents a favourable response. The release exponent (n) values and drug release mechanisms for all sixteen formulations were depicted in the Table.6. Higuchi plots of Group I,II,III,IV, V are can seen in

fig.2, 6, 10, 14, 18 respectively. The highest and lowest values among the sixteen formulations are 26.362 (F4) and 14.1(F12) respectively.

Korsmeyer-peppas plots were used to study the drug release mechanism by identifying the release exponent (n) values of Group I,II,III,IV, V are can seen in fig. 4, 8, 12, 16, 20 respectively. The highest and lowest values were 0.6272 (F2) and 0.3480(F13) respectively. F2 showed non-fickian diffusion of drug release due to high level (60mg) of HEC and F13 showed fickian diffusion (30mg at low level of HEC). First order plots of Group I,II,III,IV, V are can seen in fig.4, 8, 12, 16, 20 respectively. Zero order plots of Group I,II,III,IV, V can observe in fig.5, 9, 13, 17, 21 respectively, all results can seen in Table.6.

Table 1: Levels of factors

Independent variables	Coded factor	Low level (mg)	High level (mg)
HPMC K4M	A	30	50
HEC	B	30	50
Cetyl alcohol	C	10	30
$NaHCO_3$	D	10	25

Table 2: Formulation composition of 2^4 full factorial experiment design pattern for MGRDDS

Standard order	Formulation code	HPMC K4M (mg)	HEC (mg)	Cetyl alcohol (mg)	NaHCO3 (mg)	Citric acid (mg)	MCC (mg)	Mg stearate (mg)	Total weight (mg)
6	F1	50	30	30	10	20	100	8	248
15	F2	30	50	30	25	20	100	8	263
4	F3	50	50	10	10	20	100	8	248
1	F4	30	30	10	10	20	100	8	208
10	F5	50	30	10	25	20	100	8	243
7	F6	30	50	30	10	20	100	8	248
2	F7	50	30	10	10	20	100	8	228
11	F8	30	50	10	25	20	100	8	243
16	F9	50	50	30	25	20	100	8	283
12	F10	50	50	10	25	20	100	8	263
9	F11	30	30	10	25	20	100	8	223
3	F12	30	50	10	10	20	100	8	228
13	F13	30	30	30	25	20	100	8	243
5	F14	30	30	30	10	20	100	8	228
8	F15	50	50	30	10	20	100	8	268
14	F16	50	30	30	25	20	100	8	263

Table 3: Data for flow properties and primary evaluation parameters of BGRDD

F. code	Angle of Repose (°)	Bulk Density (g/cm^3)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's ratio (%)	Hardness (Kgf/cm^2)	Friability (%)	Drug content (%)	Swelling index (%)
F 1	28.38±0.02	0.38±0.23	0.51±0.60	26.23±0.51	1.35±0.30	6.5±0.12	-0.10±0.02	92.23±0.20	24.19±0.10
F 2	24.22±0.12	0.39±0.05	0.53±0.32	25.60±0.51	1.34±0.06	6.7±0.10	-0.05±0.02	98.25±0.02	19.01±0.12
F 3	25.25±0.01	0.38±0.55	0.51±0.50	26.23±0.62	1.35±0.06	6.8±0.15	-0.36±0.01	90.56±0.20	28.22±0.20
F 4	24.02±0.01	0.34±0.20	0.47±0.25	27.96±0.25	1.38±0.10	7.4±0.52	-0.09±0.10	98.23±0.62	19.23±0.14
F 5	24.22±0.31	0.37±0.51	0.51±0.62	26.43±0.64	1.35±0.06	7.6±0.51	-0.24±0.02	94.52±0.62	24.69±0.52
F 6	25.26±0.36	0.38±0.51	0.51±0.16	26.23±0.03	1.35±0.02	7.0±0.52	-0.02±0.05	98.62±0.65	20.16±0.52
F 7	24.36±0.36	0.36±0.56	0.49±0.62	27.07±0.52	1.37±0.03	6.2±0.02	-0.04±0.05	96.62±0.01	26.31±0.12
F 8	24.58±0.63	0.37±0.31	0.51±0.50	26.43±0.23	1.35±0.06	7.0±0.06	-0.02±0.05	94.52±0.62	20.57±0.41
F 9	24.35±0.63	0.41±0.51	0.55±0.56	24.89±0.02	1.33±0.21	5.6±0.06	-0.12±0.06	98.56±0.45	24.73±0.95

F10	25.31±0.61	0.39±0.13	0.53±0.50	25.64±0.10	1.34±0.21	7.9±0.05	-0.11±0.05	90.20±0.51	19.01±0.95
F11	25.28±0.23	0.35±0.34	0.49±0.54	27.28±0.02	1.37±0.20	4.0±0.03	-0.04±0.04	98.62±0.84	17.93±0.75
F12	25.37±0.65	0.36±0.92	0.49±0.73	27.07±0.01	1.37±0.01	7.4±0.06	-0.15±0.05	98.52±0.95	21.92±0.62
F13	25.38±0.65	0.37±0.16	0.51±0.90	26.43±0.03	1.35±0.01	6.9±0.05	-0.02±0.09	98.51±0.95	18.51±0.74
F14	25.00±0.63	0.36±0.51	0.49±0.86	27.07±0.06	1.37±0.05	5.8±0.01	-0.15±0.06	96.54±0.41	17.54±0.51
F15	26.31±0.51	0.40±0.05	0.53±0.54	24.88±0.05	1.33±0.05	6.3±0.03	-0.07±0.09	94.62±0.62	26.11±0.56
F16	26.33±0.52	0.39±0.56	0.53±0.93	26.19±0.06	1.35±0.62	7.3±0.12	-0.28±0.06	97.12±0.84	22.81±0.47

Table 4: Results for floating lag time and duration of floating

Formulation code	Tablet weight (mg)	Lag time (min)	Duration of floating (hrs)
F1	248	1.5	>14
F2	263	1	>14
F3	248	1	>12
F4	208	0.5	< 11
F5	243	1	>14
F6	248	1	>12
F7	228	1.5	>12
F8	243	1	>12
F9	283	1	>14
F10	263	0.55	>14
F11	223	1	>12
F12	228	1	>12
F13	243	1.5	>12
F14	228	1	>12
F15	268	1	>14
F16	263	1	>12

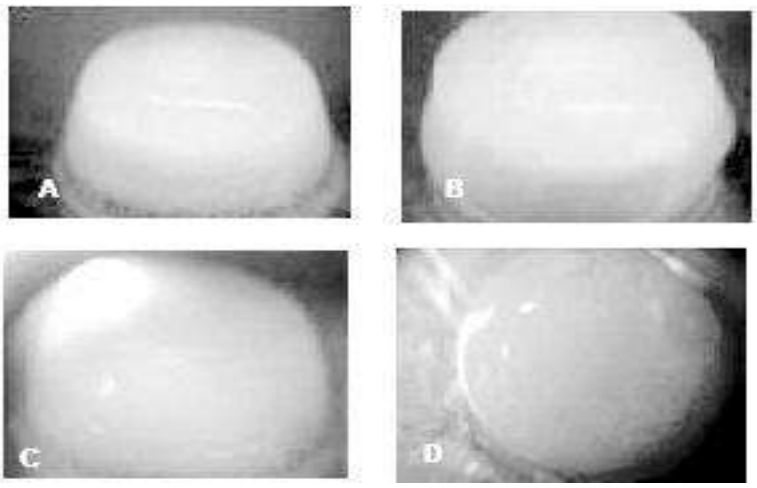
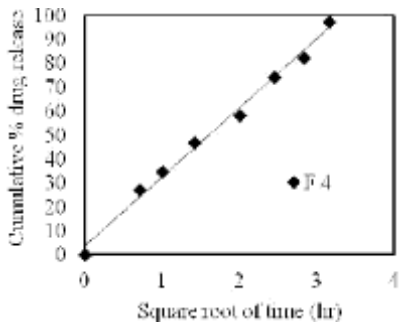


Fig 1: Describes the swelling index of formulation 16 (best formulation) at **A)** 2 hrs **B)** 4 hrs **C)** 8 hrs **D)** 12 hrs.



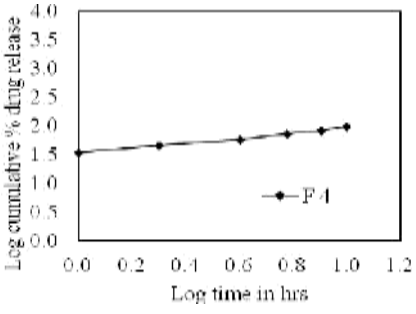


Fig 2: Higuchi plot for Group I

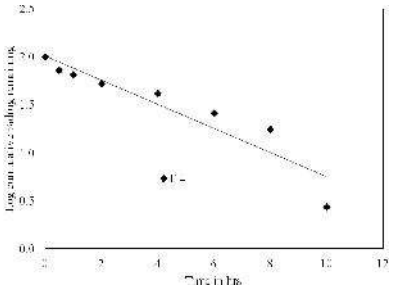


Fig 3: Korsmeyer-peppas for Group I

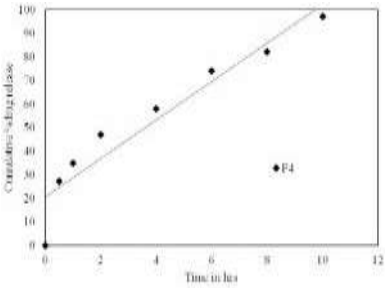


Fig 4: First order plot for Group I

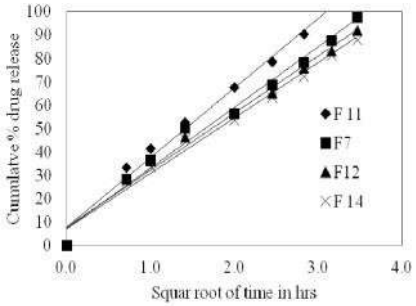


Fig 5: Zero order plot for Group I

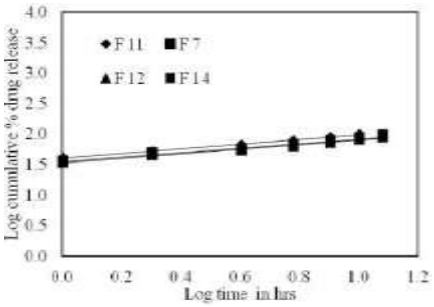
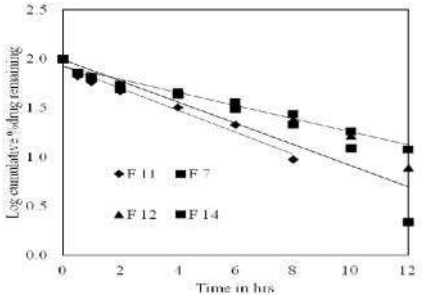


Fig 6: Higuchi plot for Group II

Fig 7: Korsmeyer-peppas plot for Group II



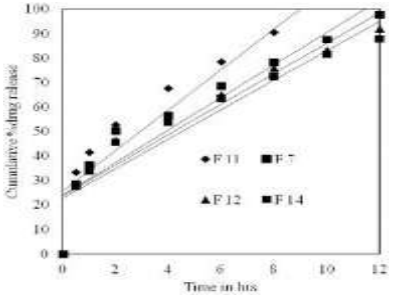
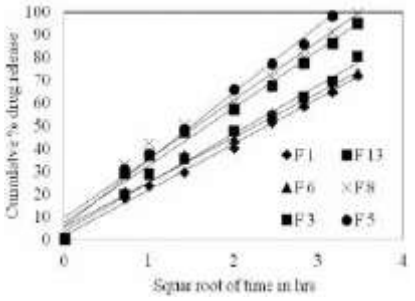


Fig 8: First order plot for Group II

Fig 9: Zero order plot for Group II



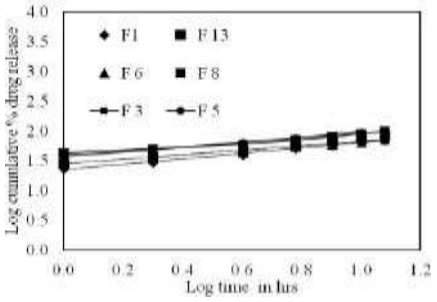
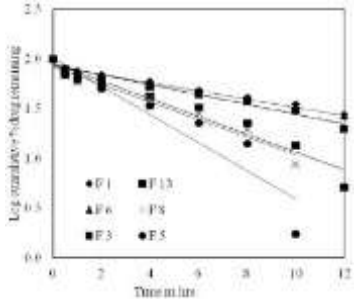


Fig 10: Higuchi plot for Group III

Fig 11: Korsmeyer-peppas plot for Group III



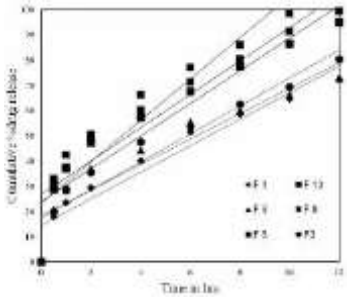


Fig 12: First order plot for Group III

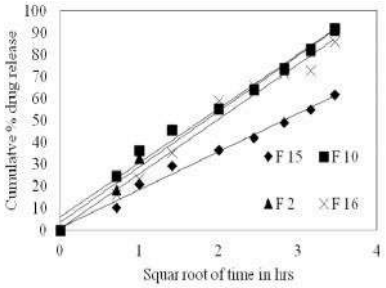


Fig 13: Zero order plot for Group III

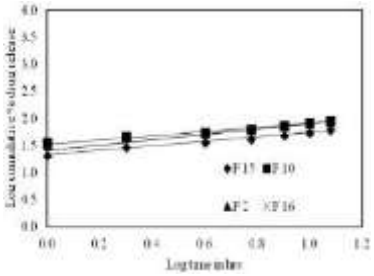


Fig 14: Higuchi plot for Group IV

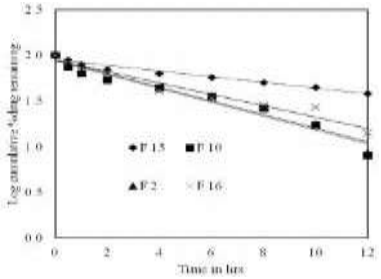


Fig 15: Korsmeyer peppas plot for Group IV

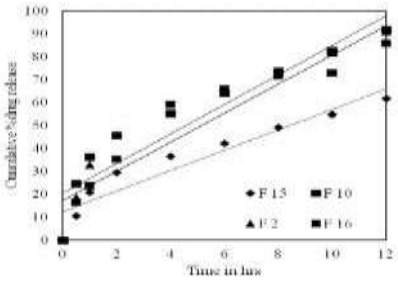


Fig 16: First order plot for Group IV

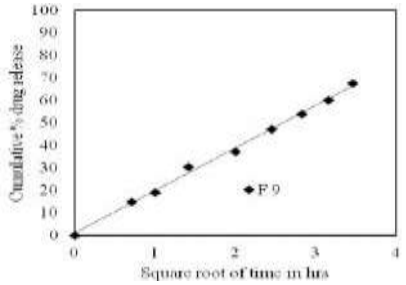


Fig 17: Zero order plot for Group IV

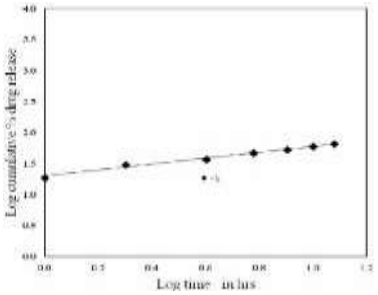


Fig 18: Higuc

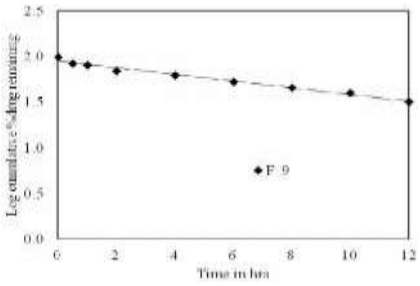
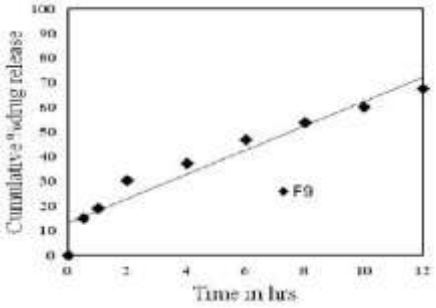


Fig 20: First



Conclusion

Gastro retentive drug delivery systems of mitiglinide were optimized successfully by applying 2^4 factorial designs of four variables at two levels. One-way interactions were significantly affects the drug release. The F10 was followed the fickian diffusion of drug release.

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Table 5: Mean cumulative percentage drug release profiles for all formulations

Mean cumulative percentage drug release ±SD (n=3)

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	12.31±0.23	9.89±0.52	16.53±0.20	21.46±0.20	19.55±0.10	16.30±0.20	19.79±0.10	16.81±0.10	11.89±0.10	16.38±0.52	16.33±0.20	16.71±0.50	26.38±0.35	16.53±0.12	14.03±0.52	14.49±0.41
1.00	20.09±0.52	16.87±0.20	24.60±0.41	26.86±0.10	25.23±0.20	21.28±0.10	25.76±0.23	21.47±0.72	22.79±0.50	25.96±0.42	23.23±0.63	23.42±0.41	31.49±0.23	21.39±0.51	19.33±0.3	21.19±0.52
2.00	26.44±0.12	31.67±0.22	27.74±0.10	33.98±0.84	33.22±0.10	24.59±0.10	36.18±0.10	32.69±0.95	36.33±0.62	34.46±0.62	43.97±6.23	48.68±0.90	37.67±1.2	37.21±0.62	22.75±0.10	27.21±.62
4.00	35.78±0.21	38.95±0.10	36.67±0.62	50.57±0.41	45.32±0.10	29.66±0.52	48.98±0.52	50.88±0.43	44.37±0.42	41.25±0.41	53.15±0.52	55.86±0.12	41.36±0.41	44.21±0.10	26.15±.45	37.81±0.26
6.00	42.12±0.30	47.66±0.20	49.13±1.02	57.61±0.62	54.26±0.41	48.46±2.03	53.54±0.62	55.83±0.95	50.60±0.62	45.64±0.42	63.21±0.32	65.12±0.50	50.65±0.62	50.75±0.21	37.12±0.62	48.77±0.52
8.00	50.64±0.50	55.68±0.50	56.22±1.05	73.57±0.20	69.30±1.02	55.01±4.02	63.39±0.10	73.55±0.42	57.32±0.92	56.96±0.20	70.16±2.01	75.43±0.41	58.84±0.62	57.62±0.25	50.00±0.45	55.35±0.42
10.00	57.16±0.62	66.48±0.62	73.52±0.63	89.65±0.41	82.18±1.63	62.22±2.01	74.62±0.62	93.85±0.62	63.14±0.01	75.77±0.10	93.88±1.20	86.72±0.62	68.48±0.20	66.53±0.41	59.93±0.41	62.98±0.25
12.00	64.28±0.20	89.41±0.20	83.71±0.10	--------	92.00±0.20	69.31±0.12	79.93±0.42	-------	68.97±0.02	84.56±1.00	--------	--------	95.75±0.30	75.79±0.62	76.86±0.62	84.51±0.56

Table 6: Release kinetics for all formulations of BGRDDS

Formulation Code	Zero order	First order	Higuchi	Korsm eyer-peppas	Drug release mechanism

	r^2	**Slope**	**r^2**	**Slope**	**r^2**	**Slope**	**r^2**	**Slope**	
F1	0.9677	4.7127	-0.9908	-0.0335	0.9983	18.012	0.9965	0.4911	Non- fickian diffusion
F2	0.9785	6.3651	-0.9238	-0.0628	0.978	23.569	0.9887	0.6272	Non- fickian diffusion
F3	0.9811	6.0636	-0.9705	-0.0563	0.9833	22.517	0.9804	0.4805	Non- fickian diffusion
F4	0.9746	7.6724	-0.961	-0.0823	0.9908	26.362	0.9879	0.4665	Non- fickian diffusion
F5	0.9743	7.0861	-0.9806	-0.0649	0.9923	25.474	0.9908	0.4835	Non- fickian diffusion
F6	0.9733	5.1766	-0.9905	-0.0393	0.9878	19.464	0.9733	0.4611	Non- fickian diffusion
F7	0.9566	5.7663	-0.9897	-0.0525	0.9966	22.259	0.9974	0.4359	Non- fickian diffusion
F8	0.9826	8.2485	-0.9284	-0.098	0.9854	27.958	0.9919	0.5624	Non- fickian diffusion
F9	0.9363	5.0471	-0.9789	-0.0385	0.9917	19.805	0.9785	0.5072	Non- fickian diffusion
F10	0.9692	5.9914	-0.9627	-0.0575	0.9802	22.451	0.9801	0.4656	Non- fickian diffusion
F11	0.9614	8.0065	-0.9252	-0.0958	0.9873	27.79	0.9872	0.5505	Non- fickian diffusion
F12	0.9445	7.707	-0.9842	-0.078	0.5171	14.1	0.9809	0.5391	Non- fickian diffusion
F13	0.9453	5.8659	-0.8446	-0.0776	0.9556	21.97	0.9435	0.3480	Non- fickian diffusion
F14	0.9533	5.3719	-0.9843	-0.0444	0.994	20.752	0.9911	0.4640	Non- fickian diffusion
F15	0.9818	5.4257	-0.9572	-0.0434	0.9631	19.718	0.9585	0.4941	Non- fickian diffusion
F16	0.9784	5.8748	-0.9467	-0.0531	0.9832	21.873	0.991	0.5122	Non- fickian diffusion