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Research

Formulation and Evaluation of a Hydrodynamically Balanced Drug Delivery System for Buformin in Antidiabetic Therapy

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Abstract

The aim of this study is to develop and analyze Hydrodynamically drug delivery systems of buformin to improve the type II diabetic mellitus therapy. Using 24 factorial layouts, such as hydroxy propyl cellulose (HEC), hydrophobic fatty base, cetyl alcohol, and effervescent material sodium bi carbonate are all prepared in this work. (NaHCO3). All independent variables (HPMC K4M, HEC, Cetyl alcohol, and NaHCO3) were tested on drug release, including NaHCO3. According to the sixteen formulations of optimization phase, they were divided into five groups for ease of analysis as Group I, Group II, Group III, Group IV, Group V, and Group VI, with all variables changing at different levels. Examples of evaluation include the angle of repose, density, compressibility index, Hausner's ratio, and key evaluation parameters such as thickness, hardness, friability, and swelling index. The angle of repose of F12 and F15 was both the highest and lowest for 30.15° and 15.23° respectively. The bulk density hit its highs for F8 and low for F4, while Carr's index was the highest for F2 and lowest for F6, meaning that low values have the highest compressibility. In 400mL of 0. 1N Hcl, the floating capabilities of single tablets was determined. The drug testing was carried out at 235nm using dissolution media 0. 1N Hcl buffer pH 1.2. The results show that the design as well as the release of buformin from the tablets is heavily influenced by the variables chosen for the study. Rephrase The main effects of A, B, C, and D were determined by the average result of changing one variable at a time when it was not normal to its high level. The interaction terms (AB, AC, AD, BC, CD, ABD, CD, ABC, ABD, BCD, and ABCD) show how the dependent variables change when two, three, and four independent variables are simultaneously changed.

Keywords: Buformin, Gastro retentive DDS, Hydroxy propyl methyl cellulose, Ethyl cellulose.

INTRODUCTION

Despite of tremendous advancements in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents because of the low cost of therapy, ease of administration, and patient's compliance. Conventional oral dosage forms provide a specific drug concentration in the systemic circulation without offering any control over the rate of drug delivery. Controlled-release drug delivery systems (CRDDS) provide drug release at a pre-determined, predictable, and controlled rate. An important pre-requisite for the successful performance of a once daily oral CRDDS is that the drug should have good absorption throughout the gastro-intestinal tract (GIT) e.g. phenylpropanolamine and nifedipine, preferably by passive diffusion, to ensure continuous absorption of the released drug[1, 2].

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 (Fig.21), thus ensuring optimal bioavailability[1].

MATERIALS AND METHODS

Buformin 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 buformin gastroretentive drug delivery system

Accurately weighed buformin was first mixed with polymers and sodium bicarbonate, citric acid, and microcrystalline cellulose were mixed to form homogenized mass, and on constant mixing it was added to cetyl alcohol previously melted at 45^0C to ensure homogenous mass. The wet damp mass was screened to form granules by 22# mesh. The granules were kept under 45^0C for drying. The dried granules were lubricated with magnesium stearate towards the final mixture. The final blend was then pressed by using Proton R&D ten station tablet press. The first step was to develop a single unit gas-generating gastroretentive dosage form for buformin. As buformin was a water soluble drug, for the controlling of drug release from the dosage form, the hydrophilic swellable polymers should be added[5, 6].

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 buformin 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 3.

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.

Evaluation of *invitro* dissolution studies for BGRDDS

***In vitro* drug release studies**

The drug release studies were carried out using the dissolution tester USP XXIV apparatus II. The dissolution media was 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 and replaced by a same equivalent volume of fresh solvent. The collected samples were diluted twice to 10mL and the absorbance measured spectrophotometrically at 235nm[12]. (Table 5)

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.

Table 1: Levels of factors

Polymers	Individual factor	Low level (mg)	High level (mg)
HPMC K4M	A	300	500
HEC	B	30	50
Cetyl alcohol	C	30	60
$NaHCO_3$	D	30	50

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

Std order	Std order	Std order	Std order	Std order	Std order	Std order	Std order	Std order	Std order	Std order
6	F1	500	500	30	60	30	50	100	8	1278
15	F2	500	300	50	60	50	50	100	8	1118
4	F3	500	500	50	30	30	50	100	8	1268
1	F4	500	300	30	30	30	50	100	8	1048
10	F5	500	500	30	30	50	50	100	8	1268
7	F6	500	300	50	60	30	50	100	8	1098
2	F7	500	500	30	30	30	50	100	8	1248
11	F8	500	300	50	30	50	50	100	8	1088
16	F9	500	500	50	60	50	50	100	8	1318
12	F10	500	500	50	30	50	50	100	8	1288
9	F11	500	300	30	30	50	50	100	8	1068
3	F12	500	300	50	30	30	50	100	8	1068
13	F13	500	300	30	60	50	50	100	8	1098
5	F14	500	300	30	60	30	50	100	8	1078
8	F15	500	500	50	60	30	50	100	8	1298
14	F16	500	500	30	60	50	50	100	8	1298

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

F 1	22.54 ±0.780	0.24±0.022	0.28±0.053	16.67±0.82	1.20±0.074	6.10±0.27	-0.02±0.023	92.00±0.35	42.25±0.83
F 2	18.54±0.038	0.31±0.028	0.49±0.062	36.11±0.92	1.57±0.035	5.20±0.31	-0.04±0.004	98.00±0.62	38.46±0.84
F 3	24.22±0.280	0.24±0.071	0.28±0.094	13.46±0.25	1.16±0.085	7.00±0.37	-0.04±0.012	90.00±0.23	41.80±0.57
F 4	19.02±0.180	0.20±0.027	0.31±0.062	22.73±0.56	1.29±0.024	7.50±0.61	-0.05±0.001	91.33±0.81	39.12±0.25
F 5	21.35±0.520	0.24±0.037	0.29±0.049	17.31±0.72	1.21±0.056	7.60±0.27	-0.07±0.002	90.33±0.86	39.43±0.84
F 6	20.46±0.350	0.26±0.082	0.28±0.028	07.14±0.82	1.08±0.087	7.10±0.72	-0.12±0.020	89.33±0.82	39.16±0.57
F 7	20.11±0.052	0.26±0.018	0.30±0.073	13.33±0.74	1.15±0.034	6.40±0.85	-0.04±0.003	99.00±0.85	42.47±0.48
F 8	19.50±0.840	0.32±0.015	0.39±0.082	17.95±0.82	1.22±0.054	5.60±0.82	-0.06±0.001	100.00±0.95	38.60±0.83
F 9	19.29±0.043	0.26±0.036	0.39±0.071	32.00±0.73	1.47±0.073	7.52±0.26	-0.19±0.012	101.00±0.73	41.73±0.86
F10	18.29±0.056	0.23±0.042	0.40±0.029	42.86±0.88	1.75±0.065	6.15±0.38	-0.18±0.002	90.00±0.83	42.16±0.83
F11	24.52±0.850	0.31±0.018	0.46±0.037	34.29±0.83	1.52±0.025	4.65±0.82	-0.02±0.018	93.40±0.56	38.39±0.37
F12	30.15±0.874	0.31±0.027	0.41±0.042	23.53±0.38	1.31±0.073	7.03±0.84	-0.05±0.001	92.00±0.85	40.26±0.58
F13	17.26±0.560	0.61±0.034	0.92±0.028	33.33±0.49	1.50±0.058	7.50±0.81	-0.03±0.002	90.60±0.58	37.34±0.82
F14	21.32±0.843	0.47±0.082	0.57±0.011	17.39±0.93	1.21±0.023	5.62±0.85	-0.07±0.004	96.00±0.52	38.03±0.92
F15	15.23±0.830	0.23±0.043	0.28±0.029	17.54±0.83	1.21±0.073	4.52±0.82	-0.07±0.006	90.31±0.37	41.60±0.39
F16	19.29±0.340	0.24±0.084	0.31±0.024	22.22±0.91	1.29±0.063	7.06±0.85	-0.10±0.008	89.21±0.54	39.29±0.81

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

Formulation code	Tablet weight (mg)	Lag time (min)	Duration of floating (hrs)
F1	1278	<1.5	>14
F2	1118	<1	>14
F3	1268	<1	>14
F4	1048	<0.5	< 11
F5	1268	< 1	>14
F6	1098	< 1	>12
F7	1248	< 1	>12
F8	1088	< 1	>12
F9	1318	<1.7	>14

F10	1288	<1.2	>14
F11	1068	<0.3	>12
F12	1068	<0.5	>12
F13	1098	< 0.9	>12
F14	1078	<0.75	>12
F15	1298	<1.4	>12
F16	1298	<1.2	>12

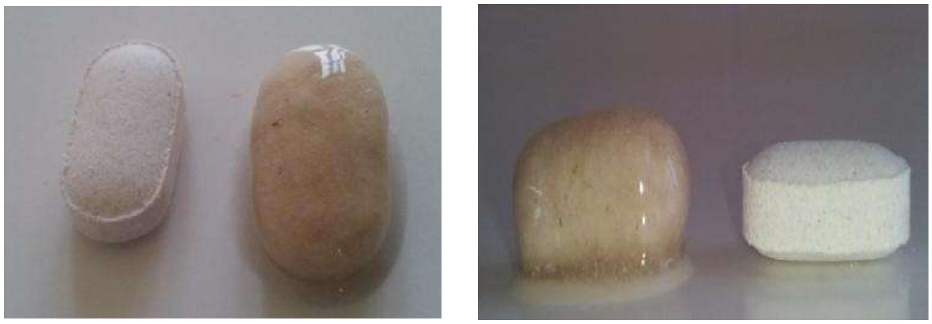
Table 5: Mean cumulative percentage drug release profiles for all formulations

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

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		Korsmeyer-peppas		Drug release mechanism
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)	
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	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	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



g 1: Shows the swollen tablet of best formulation F10

Fig 2: Floating of optimized F10

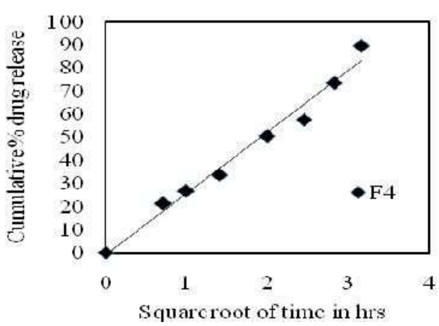


Fig 3: Higuchi plot for Group I

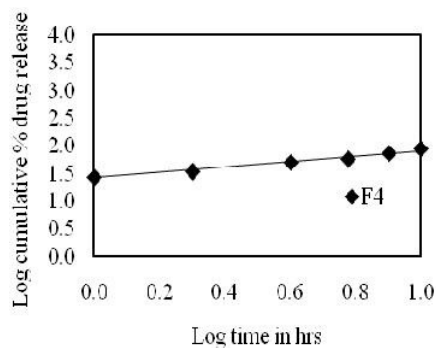


Fig 4: Korsmeyer-peppas plot for Group I

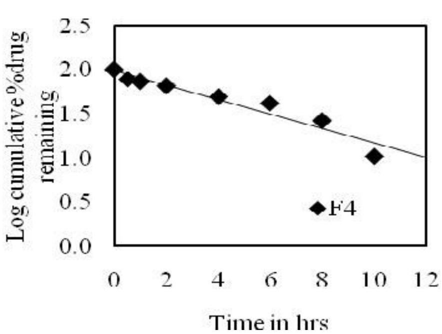


Fig 5: First order plot for Group I

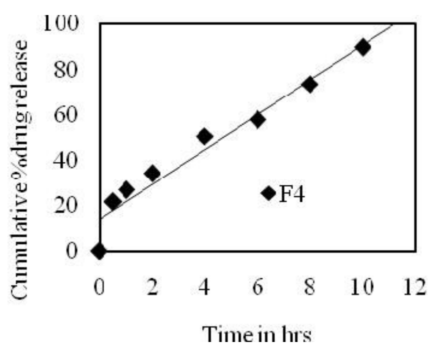


Fig 06: Zero order plot for Group I

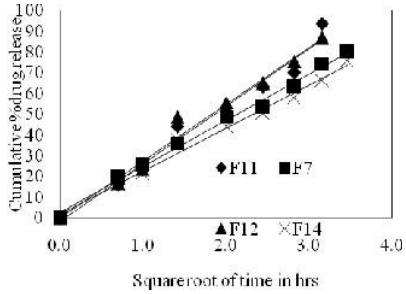


Fig 7: Higuchi plot for Group II

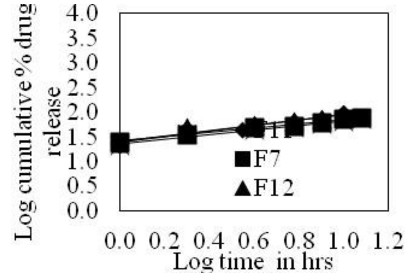


Fig 8: Korsmeyer-peppas plot for Group II

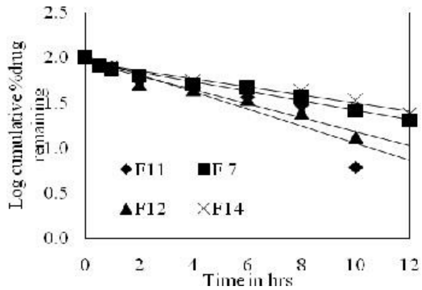


Fig 9: First order plot for Group II

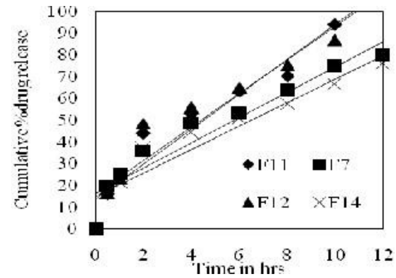


Fig 10: Zero order plot for Group II

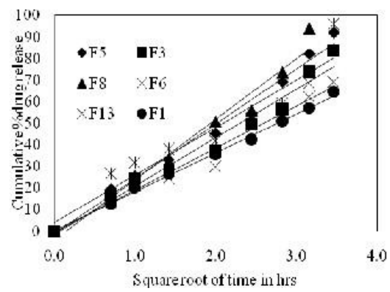


Fig 11: Higuchi plot for Group III

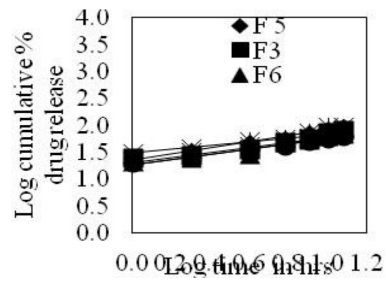


Fig 12: Korsmeyer-peppas plot for Group III

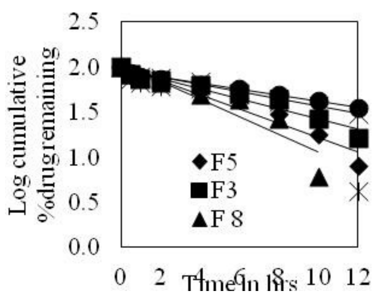


Fig 13: First order plot for Group III

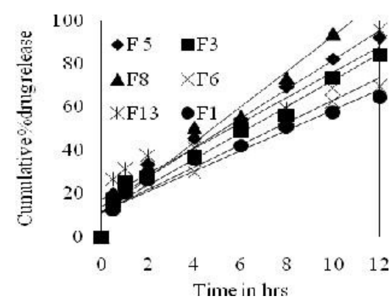


Fig 14: Zero order plot for Group III

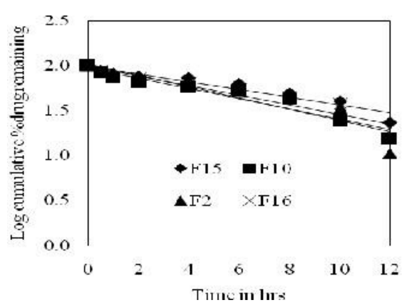


Fig 15: Higuchi plot for Group IV

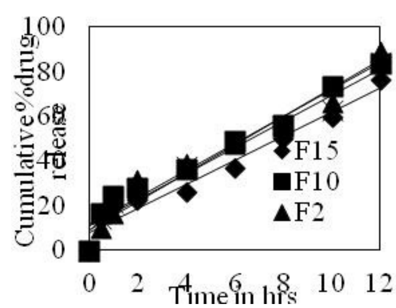


Fig 16: Korsmeyer- peppas plot for Group IV

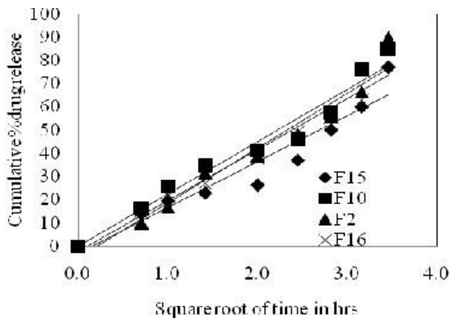


Fig 17: First order plot for Group IV

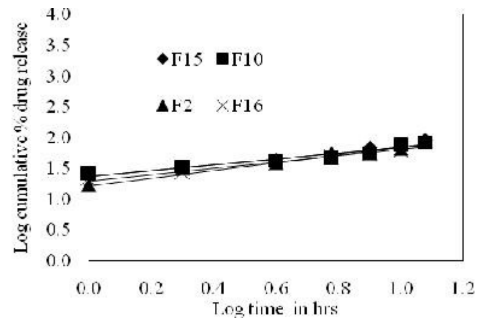


Fig 18: Zero order plot for Group IV

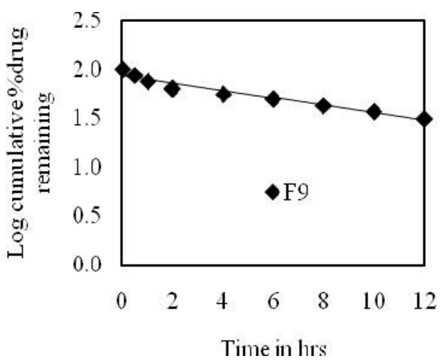


Fig 19: Higuchi plot for Group V

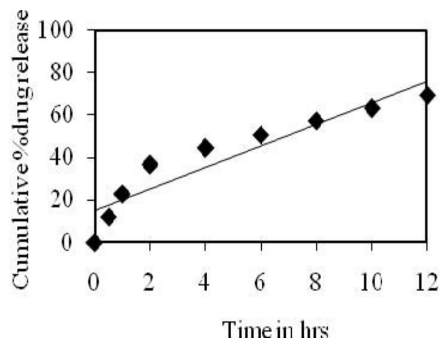


Fig 20: Korsmeyer-peppas plot for Group V

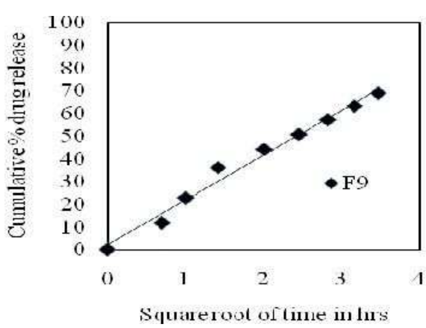


Fig 21: First order plot for Group V

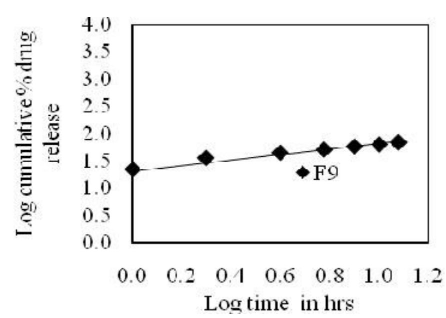


Fig 22: Zero order plot for Group V

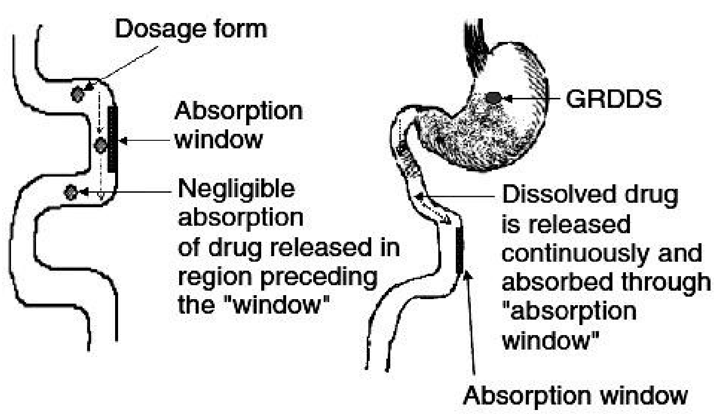


Fig 23: Drug absorption from CRDDS Vs GRDDS

RESULTS AND DISCUSSIONS

The angle of repose of F12 and F15 were highest and lowest for 30.15º and 15.23º respectively. The lowest and highest has the high and low flow from hopper. The bulk density id highest for F8 and lowest for F4, while the Carr's index is highest for F2 and lowest for F6, indicating that low value has the highest compressibility. Highest content was loss on friability test for F9. Hardness is highest for F8 and lowest for F15. Swelling index is more observed for F7 and lowest for F13 and these differences were insignificant and the best retards formulation was optimized by factorial plots and it has the swelling ration of 42.16 for F10can be seen in Fig.1.

The lowest and highest lag times were observed for the F11 and F1. 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.

Results and discussion of *in vitro* drug release data of BGRDDS

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 buformin 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. 3, 7, 11, 15, 19 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.5, 9, 13, 17, 21 respectively. Zero order plots of Group I,II,III,IV, V can observe in fig.6, 10, 14, 18, 22 respectively, all results can seen in Table.6.

CONCLUSION

Gastroretentive drug delivery systems of buformin 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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