*Research Article*

**Available Online at: www.ijphr.com**

**International Journal of Pharmaceuticals and Health care Research**

**ISSN: - 2306 – 6091**

# DESIGN AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS OF ANITDIABETIC DRUG-BUFORMIN

[*1]Kranthi Kumar P, [2]Padmabhushanam P

[1,2]Department of Pharmaceutical Analysis, KJR College of Pharmacy, Rajamundry, Andhra Pradesh, India.

[2]Department of Pharmaceutical Analysis, Monad University, Hapur, U.P, India.

**Abstract**

The objective of the present work is to design and evaluate gastroretentive drug delivery systems of buformin to improve the type II diabetic mellitus therapy. In this work gastro retentive drug delivery systems of are prepared by using $2^4$ factorial design employing hydrophilic polymers such as hydroxy propyl methyl cellulose K4M (HPMC K4M), hydroxy ethyl cellulose (HEC), hydrophobic fatty base, cetyl alcohol and effervescent material sodium bi carbonate ($NaHCO_3$). The effects of all independent variables (HPMC K4M, HEC, Cetyl alcohol and NaHCO3) on drug release were determined. The sixteen formulations of optimization phase were categorized into five groups for ease of analysis as Group I, Group II, Group III, Group IV and Group IV by changing all variable at different levels. Parameters of evaluation are 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. The angle of repose of F12 and F15 were highest and lowest for 30.15º and 15.23º respectively. 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 F10 formulation. The floating abilities of single tablets was determined in 400mL of 0.1N Hcl . The drug release studies were carried out using dissolution media 0.1N Hcl buffer pH 1.2 at 235nm. 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.

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

**Author for Correspondence:**
Kranthi Kumar P,
Department of Pharmaceutical Analysis,
KJR College of Pharmacy,
Rajamundry, Andhra Pradesh, India.
Email: krantikumar8793@gmail.com

## 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 $45^0$C to ensure homogenous mass. The wet damp mass was screened to form granules by 22# mesh. The granules were kept under $45^0$C 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 No. 01: 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 No. 02: Formulation composition of $2^4$ full factorial experiment design pattern for BGRDDS**

| Std order | Formulation code | Buformin (mg) | HPMC K4M(mg) | HEC (mg) | Cetyl alcohol (mg) | $NaHCO_3$ (mg) | Citric acid (mg) | MCC (mg) | Mg stearate (mg) | Total weight (mg) |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 No. 03: 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 No. 04: 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 No. 05: Mean cumulative percentage drug release profiles for all formulations**

| Time | 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 No. 06: 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 |

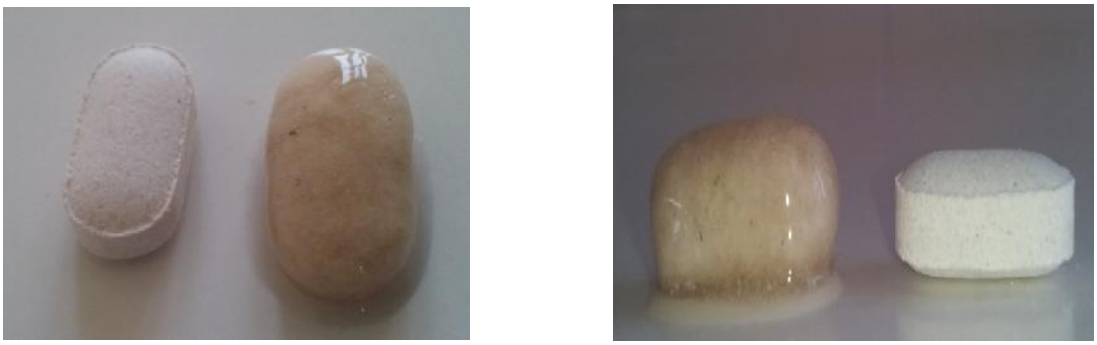

**Fig. No. 01: Shows the swollen tablet of best formulation F10**

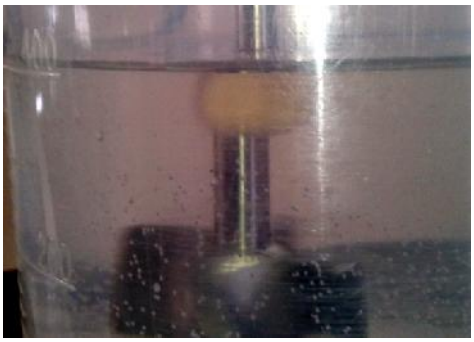

**Fig. No. 02: Floating of optimized F10**

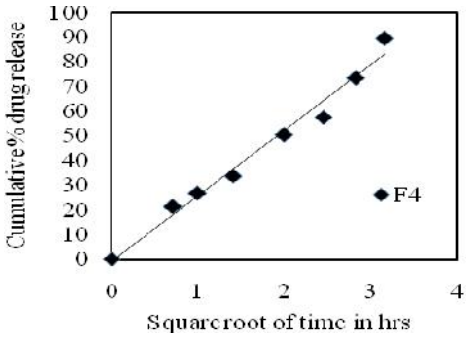


**Fig. No. 03: Higuchi plot for Group I**

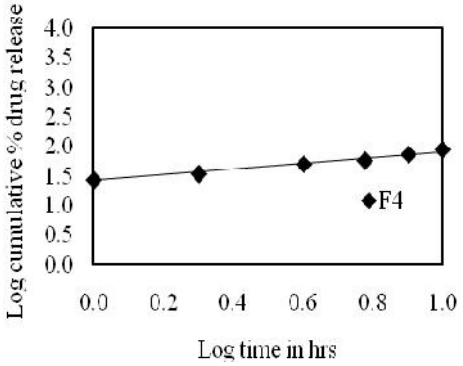


**Fig. No. 04: Korsmeyer-peppas plot for Group I**

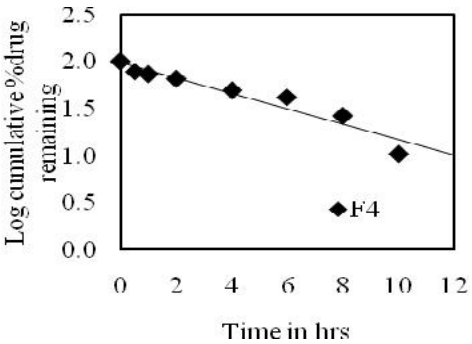


**Fig. No. 05: First order plot for Group I**

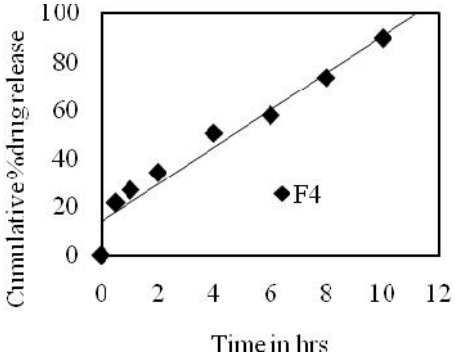


**Fig. No. 06: Zero order plot for Group I**

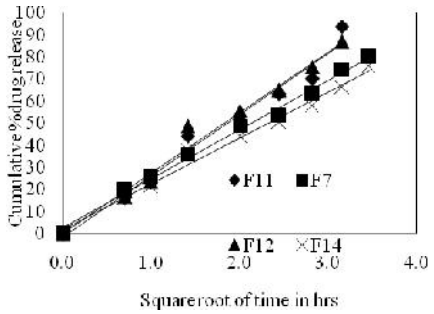


**Fig. No. 07: Higuchi plot for Group II**

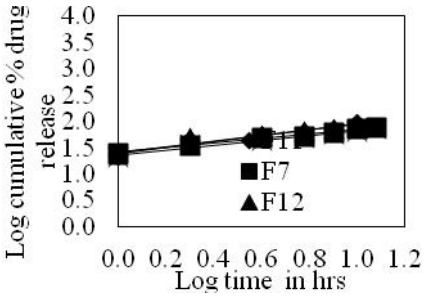


**Fig. No. 08: Korsmeyer-peppas plot for Group II**

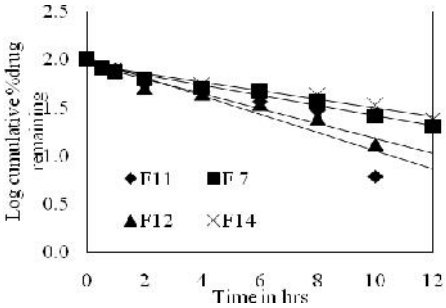


**Fig. No. 09: First order plot for Group II**

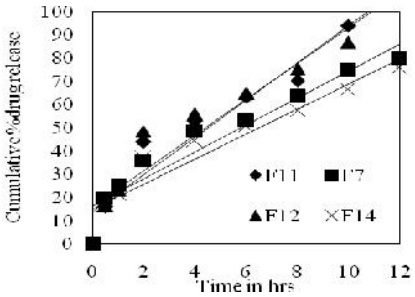


**Fig. No. 10: Zero order plot for Group II**

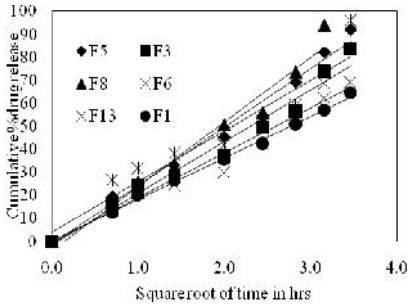


**Fig. No. 11: Higuchi plot for Group III**

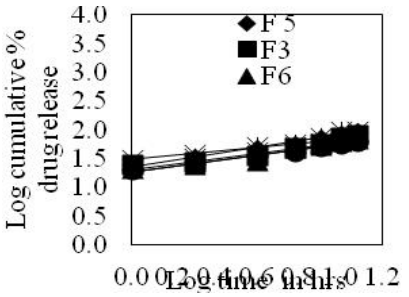


**Fig. No. 12: Korsmeyer-peppas plot for Group III**

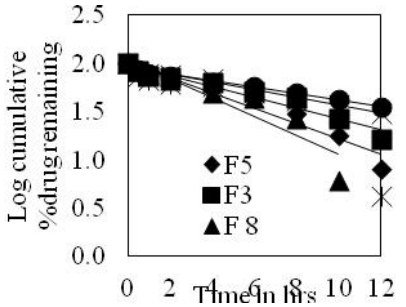


**Fig. No. 13: First order plot for Group III**

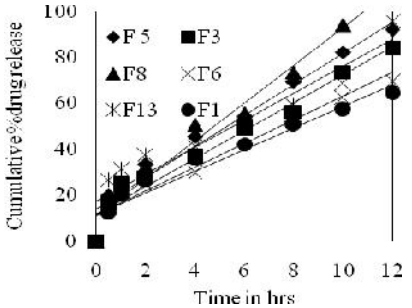


**Fig. No. 14: Zero order plot for Group III**

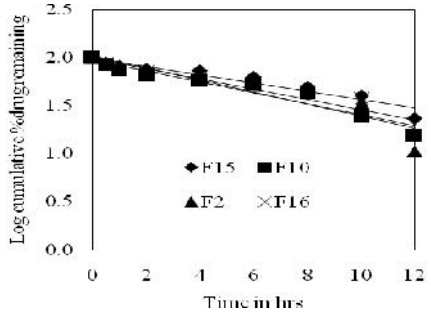


**Fig. No. 15: Higuchi plot for Group IV**

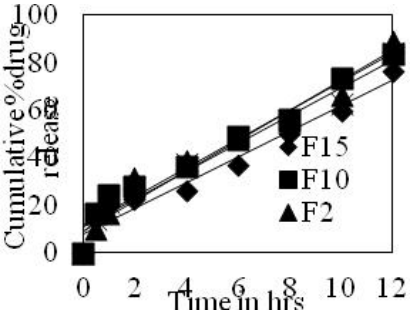


**Fig. No. 16: Korsmeyer- peppas plot for Group IV**

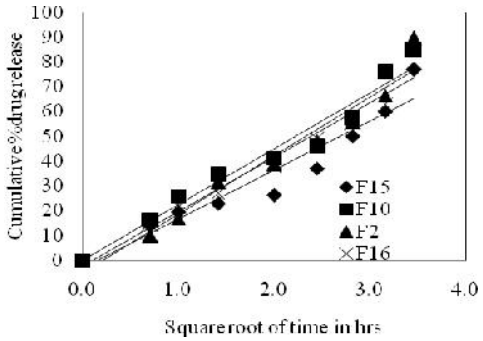


**Fig. No. 17: First order plot for Group IV**

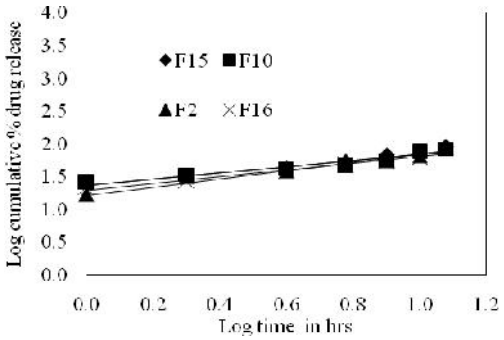


**Fig. No. 18: Zero order plot for Group IV**

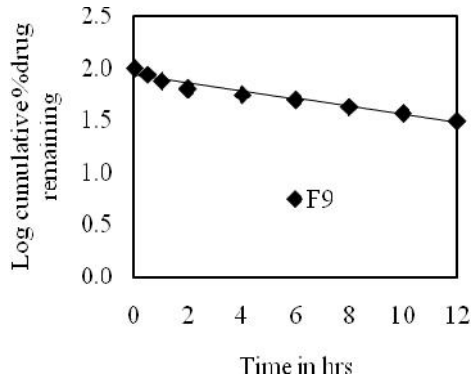


**Fig. No. 19: Higuchi plot for Group V**

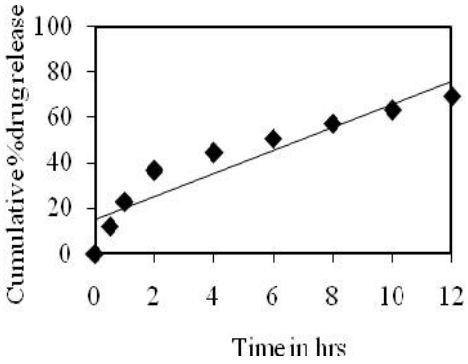


**Fig. No. 20: Korsmeyer-peppas plot for Group V**

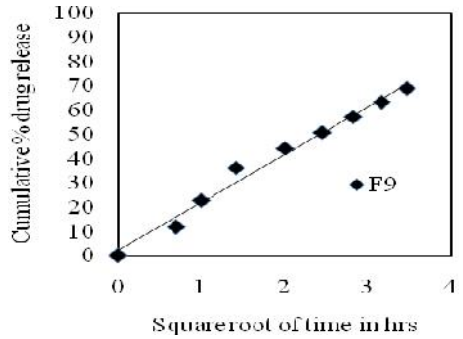


**Fig. No. 21: First order plot for Group V**

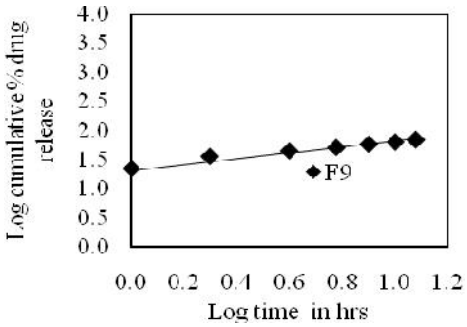


**Fig. No. 22: Zero order plot for Group V**

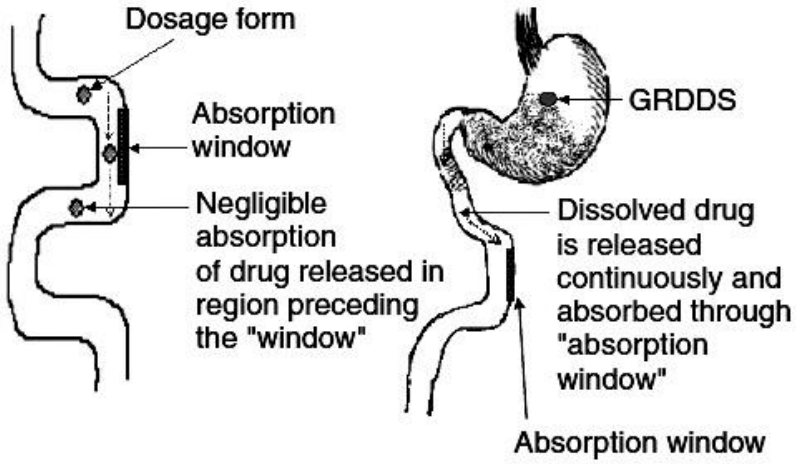


**Fig. No. 23: Drug absorption from CRDDS Vs GRDDS**

## 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.

## References

1. Chawls G, Gupta P, Koradia V, Bansal A. Gastroretention-A means to address regional variability in intestinal drug absorption. Pharm Technol. 2003; 50-68.
2. Hwang S, Park H, Park K. Gastric retentive drug delivery systems. Crit Rev Drug Carrier Syst. 1998; 15(3); 243-284.
3. Deshpande AA, Rhodes CT, Shah NH, Malik AW. Controlled release drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm.1996; 22(6): 531-539.
4. Reddy HVL, Murthy RSR. Floating dosage systems in drug delivery. Crit Rev Drug Carrier Syst. 19(6): 553-585.

5. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Rel. 2000; 63(3): 235-259.
6. Cargill R, Cald-well LJ, Engle K, Fix JA, Porter PA, Gardener CR. Controlled gastric emptying I: Effect of physical properties on gastric residence times of non-disintegrating geometric shapes in beagle dogs. Pharm Res. 1998; 5(8): 553-536.
7. Moes AJ, Gastroretentive dosage forms. Crit rev ther drug carrier syst. 1993; 10(2): 143-95.
8. Maggi L, Seagle L, Torre MI, Ochoa, Machiste E, Conte U. Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides for the controlled release of a water soluble drug: dimensionality study. Biomaterials. 2002; 23(4): 1113-1119.
9. Talukder R, Fassihi R. Gastroretentive delivery systems hollow beads. Drug Dev Ind Pharm. 2004; 30(4): 405-412.
10. Avignon A, Radauceanu A, Monnier L. Non fasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. Diabetes Care. 1997; 20: 1822-1826.
11. Polanski KS, Given BD, Hirsch LJ. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. N Engl J Med. 1998; 318: 231-239.
12. Baily CJ. Metformin, N Eng J Med. 1996; 334: 574-579.
13. Evans AJ, Krenz AJ. Insulin resistance and β-cell dysfunction as therapeutic targets in type 2 diabetes. Diabetes Obes Metab.2001; 3: 219–229.
14. Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in Type 2 diabetes? Eur J Clin Invest.2000; 30 (S2): 3–11.
15. Aburuza S. The development and validation of liquid chromatography method for the simultaneous determination of metformin and glipizide, gliclazide, glibenclamide or glimepride in plasma. J Chromatogr B. 2005; 817: 277–286.