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Formulation and Characterization of Bilayer Floating Tablets of Glipizide and Lisinopril

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A B S T R A C T

The purpose of the study is to prepare Bilayer floating tablets containing Glipizide as sustained release and Lisinopril as immediate release which can be used to treat both the diseases concomitantly. Sustained layer were prepared by direct compression method using the release retarding polymer HPMC K4M & HPMC K100M and gas generating agent sodium bicarbonate and citric acid. Immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and pregelatinized starch. Bilayer tablets were prepared with different quantities of polymers like HPMC K4 M and HPMC K100M. A 3^2 Full factorial design was used for optimization of polymers. The quantity of HPMC K4M (X1) and HPMC K100M (X2) were selected as independent variables and Floating Duration, Percentage drug release at 8 h(Q_8) and Percentage drug release at 20 h(Q_{20}) were selected as dependent variables. Tablets were evaluated. The formulations (FT4) showed release of Lisinopril within 30 min followed by sustained release of Glipizide (98.86%) at 20 h. The kinetics release of optimize batch FT4 was best explained by first order and Korsmeyer–Peppas. The IR spectrum revealed that there is no disturbance in the principal peaks of pure drugs Glipizide and Lisinopril. There is no incompatibility of them with excipients.

Keywords: Glipizide, Lisinopril, Floating, Immediate release, Bilayer Tablets.

A R T I C L E I N F O

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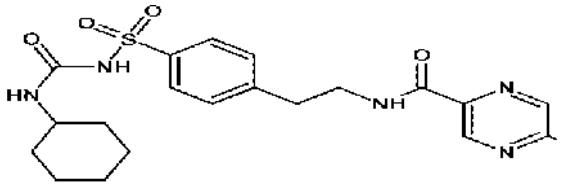
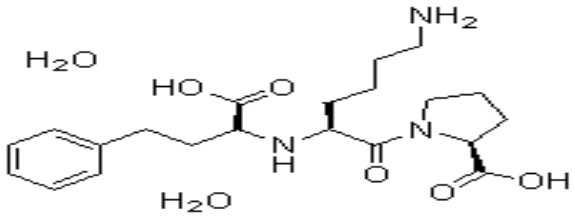
1. Introduction

The gastro retention dosage form has been successfully utilized for drug delivery of narrow absorption window drugs. In addition to retention in stomach region, the drug release can also be controlled for longer duration. Several approaches have been utilized for gastroretention of dosage form like, floating tablets, *in-situ* gelling gums, multiunit systems etc. Bilayer tablets have been successfully developed and evaluated Bilayer tablets contain separate drug release layer and floating layer. Floating layer generally contains mixture of hydrophilic polymer and sodium bicarbonate. Sodium bicarbonate particles provide buoyancy by carbon dioxide bubble formation where as gel matrix of hydrophilic polymer tries to entrap carbon dioxide bubbles. In this research work, floating bilayer tablets using HPMC K4M, HPMC K100M and Carbopol 934P were developed and evaluated [**1]** Chronic diseases such as diabetes mellitus and systemic hypertension have high prevalence all over the world. In majority of cases, Patients with diabetes mellitus have an increased prevalence of hypertension and associated cardiovascular disease (CVD). An international investigation revealed that hypertension affects about 60% of patients with type II diabetes. According to the American Heart Association, it is possible to say that diabetes mellitus is a cardiovascular disease. So, treatment should not only target lowering of blood glucose level, but should also focus on the correction of other non communicable disease risk factors, such as hypertension. Hypertension is one of the major risk factor for diabetic nephropathy and possibly for diabetic retinopathy. A fixed dose combination (FDC) is a formulation of two or more active ingredients combined in a single dosage form and available in certain fixed doses. FDC pharmaceutical products can be used to treat the same disease state, multiple disease states or counteract the negative side-effects. Glipizide is an oral hypoglycemic agent which is rapidly absorbed and completely metabolized.

Its structure is as below:



Its Synonaym and IUPAC name are Glipizidum [Latin], Glydiazinamide & N-[2-(4-{[(cyclohexylcarbamoyl) amino] sulfonyl}phenyl)ethyl]-5-methylpyrazine-2 carboxamide respectively. Its molecular formula and molecular weight are $C_{21}H_{27}N_5O_4S$ &445.535 g/mole respectively. Its appearance is Whitish powder & melting point is around 208-209 ^oC. Glipizide, a second-generation sulfonylurea, is used with diet to lower blood glucose in patients with diabetes mellitus type II. In human, glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Gastrointestinal absorption is uniform, rapid, and essentially complete. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Its half life is 2 - 5 hr. Being a weak acid, glipizide is better absorbed from basic medium; however, at very low pH levels, the solubility of glipizide is Water solubility 37.2 (mg/L), Simulated gastric fluid (pH 1.2) 1.08 (gm/ml), Phosphate Buffer (pH 7.4) 2.41 (gm/ml). [2, 3, 4] Lisinopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Lisinopril may be used to treat hypertension and symptomatic congestive heart failure, to improve survival in certain individuals following myocardial infarction, and to prevent progression of renal disease in hypertensive patients with diabetes mellitus and microalbuminuria or overt nephropathy. Its Structure is as below:



Its IUPAC Name is (2S)-1-[(2S)-6-amino-2-{[(1S)-1-carboxy-3-phenylpropyl] amino} hexanoyl] pyrrolidine-2-carboxylic acid. Its molecular formula and molecular weight are $C_{21}H_{31}N_3\ O_5$ & 405.48g/mole respectively. Its appearance is likeWhitish to off - white powder & melting point is 148 ^oC. Approximately 25%, but widely variable between individuals (6 to 60%) in all doses tested (5-80 mg); absorption is unaffected by food. Effective half life of accumulation following multiple dosing is 12 hours.The solubility of lisinopril in water, propylene glycol and ethanol was 98.47 mg/ml, 14.2 mg/ml and 1.01 mg/ml respectively. Indicating a higher solubility in water than propylene glycol and ethanol. [5,6] As per review of literature there is not any Bilayer Floating Tablets of Glipizide and Lisinopril. [7-25] So here it's thought to prepare Bilayer floating tablets for same.

2. Matirials and Methods

Preparation of Bilayer Floating Tablet of Glipizide and Lisinopril By Using 3^2 Factorial Designs

A 3^2 factorial design was used in this study and two factors (HPMC K4M and HPMC K100M) were evaluated, each at three levels; experimental batches were performed at all

nine possible combinations (Table). The amount of HPMC K4M (X_1) and HPMC K100M (X_2) were selected as independent variables. Floating Lag time (Y_1), Drug release at 8 hr Q_8 (Y_2) and % Drug release at 20 hr Q_{20} (Y_3) were selected as dependent variables. The data were subjected to contour and 3-D response surface plot in Design-Expert® 8.0.7.1 (a software developed by Stat-Ease) to determine the effect of polymers on the release of drug and the dependent variable. The values of variables in 3^2 factorial design are indicated in Table 1.

Table 1: 3^2 Full Factorial Design for Floating Tablets of Glipizide

Formulation	HPMC K4M (X_1)	HPMC K100M (X_2)
FT1	-1	-1
FT2	-1	0
FT3	-1	+1
FT4	0	-1
FT5	0	0
FT6	0	+1
FT7	+1	-1
FT8	+1	0
FT9	+1	+1

Table 2: Values of variables in 3^2 factorial design

Coded variables	-1	0	+1
X_1 (HPMC K4M)	20	25	30
X_2 (HPMC K100M)	70	75	80

Formulation of Fast Disintegrating Tablets of Lisinopril

Table 1: Composition of Fast Disintegrating Tablets of Lisinopril

Ingredients (mg)	Batch code							
	F1	F2	F3	F4	F5	F6	F7	F8
Lisinopril	10	10	10	10	10	10	10	10
Dicalcium Phosphate	30	30	30	30	30	30	37.8	42.8
Microcrystalline cellulose PH102	46.8	44.8	42.8	46.8	44.8	42.8	35	30
Partially pregelatinized starch	5	5	5	5	5	5	5	5
Sodium starch glycolate	-	-	-	6	8	10	10	10
Crosscarmellose sodium	6	8	10	-	-	-	-	-
Aerosil	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1
Iron oxide red	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Lisinopril tablets each containing 10 mg of lisinopril were prepared by direct compression as per the formula given in Table 1. All the ingredients were passed through sieve #80 blended with iron oxide red and mixed homogenously to get uniform blend without mottling. This mixed blend of drug and excipients was compressed using single punch tabletting machine to produce tablet weighing 100 mg having a diameter of 9 mm. Following above procedure, eight batches of Fast Disintegrating Tablet (FDT) of Lisinopril in different ratio of superdisintegrants were prepared.

Formulation of Floating Tablets of Glipizide

Glipizide was geometrically mixed with the required quantities of microcrystalline cellulose, HPMC K4M, HPMC K100M, sodium bicarbonate, citric acid and polyvinyl pyrollidon in a mortar and triturated well in a mortar to mix them properly. Magnesium stearate and talc were then passed through sieve #80, mixed and blended with the initial mixture for additional 2-3 minutes. This mixed blend of drug and excipients was compressed using single punch tableting machine to produce tablet weighing 250 mg having a diameter of 9 mm. Compression force of the machine was adjusted to obtain the hardness in the range of 4 kg/cm^2.

Table 2 : Composition of Floating Tablet of Glipizide

Ingredients (mg)	Batch code								
	FT1	**FT2**	**FT3**	**FT4**	**FT5**	**FT6**	**FT7**	**FT8**	**FT9**
Glipizide	5	5	5	5	5	5	5	5	5
HPMC K4 M	20	20	20	25	25	25	30	30	30
HPMC K100 M	70	75	80	70	75	80	70	75	80
Sodium bicarbonate	35	35	35	35	35	35	35	35	35
Citric acid	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Microcrystalline cellulose PH 102	82.5	77.5	72.5	77.5	72.5	67.5	72.5	67.5	62.5
PVP K 30	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Method of Preparation of Bilayer Tablets

Glipizide layer blend 250mg (FT1-FT9) is initially pre-compressed with low hardness and Lisnopril layer blend 100 mg which is optimize earlier same is compressed over all layer using single punch tableting machine to produce tablet weighing 350 mg having a diameter of 9 mm. Compression force of the machine was adjusted to obtain the hardness in the range of 4 kg/cm^2. Before tablet preparation, the mixture blend of all formulations are subjected to pre formulation studies like bulk density, tapped density, compressibility index(%), hausner ratio and angle of repose.

Characterization of Bilayer Floating Tablets of Glipizide and Lisinopril

a) Thickness

Thickness of tablets was determined using Venire caliper in mm. Six tablets was used and average values was calculated**.**

b) Hardness and Friability

Hardness: Hardness of the tablets was determined by Monsanto Hardness Tester. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Friability:

$$\% F = \frac{I_1 \quad w \quad - F \quad w}{I_1 \quad w} \times 1$$

c) Weight variation test:

Weight test as described in the IP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations were determined and recorded.

d) Tablet Density

Tablet density is an important parameter for floating tablets. The tablet will float when its density is less than that of 0.1N HCL (1.004). The density was determined using following formula,

$$V = \pi r^2 h$$

$$d = m\backslash v$$

e) Buoyancy determination

The in vitro buoyancy was determined by floating lag time method described by Dave B.S. The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

f) Drug content of tablet

For the estimation of drugs from the tablets, twenty tablets of glipizide and lisinopril combination was weighed accurately and the average weight per tablet was calculated. Tablets were ground to a fine powder a quantity equivalent to 5mg of glipizide and 10mg of lisinopril was transferred to a volumetric flask and was extracted with 100 ml 0.1N HCl containing 10% methanol. The extract was filtered using whatmann filter paper, and the filtrate was approximately diluted to get a final concentration of 10µg/ml of the formulation. The absorbance of the solution was measured at 205.5nm and 224.5nm. The difference between the two values was taken as the final absorbance to quantify Glipizide and Lisinopril in the sample solution using a calibration curve. The calibration curve for Glipizide and Lisinopril was plotted using the absorbance values of three standard solutions of Glipizide and Lisinopril over a concentration range of 0.5 -15 µg/ml.

g*) In vitro* Drug Release Studies

In-vitro drug release studies were carried out by using USP XXIII Dissolution Apparatus II (Paddle type) [Electrolab Tablet Dissolution Tester] at 50 rpm. The drug release profile was studied in 900 ml of 0.1N HCl containing 10% v/v methanol by maintaining at 37 ± 0.5º C. Dissolution studies were carried out for 24 h. 5ml of the aliquot was

taken at intervals of 5, 10, 15, 20, 25, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, 720 min and last at 24 hr. After collecting the sample, the dissolution medium was replenished with the same volume of fresh medium, and the sample was analyzed spectrometrically at 205.5 nm and 224.5 nm. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

Similarity Factor (f_2)

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. It is used by FOA for comparing similarity between two dissolution profiles.

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Drug Release Kinetics

To know the mechanism of drug release, data obtained from in vitro drug release studies were plotted in various kinetic models. Zero Order as cumulative amount of drug released vs time, First Order as log cumulative percentage of drug remaining vs time, Higuchi's as cumulative percentage of drug released vs square root of time and Korsmeyer as log cumulative percentage of drug released vs log time.

a. Zero Order Release Rate Kinetics

To study the zero-order release kinetics the release rate data are fitted to the following equation,

F= K.t

b. First Order Release Rate Kinetics

To study the first-order release kinetics the release rate data are fitted to the following equation,

Log C = log Co Kt/2.303

c. Higuchi release model:

To study the Higuchi release kinetics the release rate data are fitted to the following equation,

$$F = K . t_{1/2}$$

D. Korsmeyer and Peppas release model

To study the release kinetic the release rate data were fitted to the following equation,

$$M_t/M_\infty = K. t^n$$

E. Hixson–Crowell model

To study the release kinetic the release rate data were fitted to the following equation,

$$W_0^{1/3} - W_t^{1/3} = Ks_t$$

Table 3: Interpretation of diffusional release mechanisms from polymeric films

Release exponent (*n*)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5 < n <1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Stability Studies of Bilayer Floating Tablet of Glipizide and Lisinopril

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time. Under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives. Stability studies were carried out for the selected formulation according to ICH guidelines. An optimize formulation were sealed in aluminium packaging coated inside with polyethylene, and samples were kept in humidity chamber (Remi, India) at 40°C and 75% RH for one month. At the end of the period, samples were analyzed for drug content, floating characteristics, hardness values, and *in vitro* dissolution studies.

3. Result and Discussion

Evaluation of Bilayer Tablets of Glipizide and Lisinopril

Physical Parameters of Bilayer Floating tablets of Glipizide and Lisinopril

Table 4: Evaluation of Bilayer Floating Tablets of Glipizide and Lisinopril

Formulation	Thickness(mm)*	Weight variation(mg)**	Hardness (Kg\cm^2)*	Friability(% w/w)*
FT1	4.10±0.05	351.00±0.81	3.93±0.15	0.52
FT2	4.07±0.03	353.33±1.24	4.13±0.11	0.24
FT3	4.09±0.06	349.33±2.05	4.06±0.25	0.27
FT4	4.06±0.09	353.67±1.24	4.06±0.25	0.37
FT5	4.12±0.02	350.00±2.44	4.16±0.25	0.31
FT6	4.15±0.06	349.00±2.05	3.90±0.26	0.22
FT7	4.16±0.03	351.00±0.81	3.90±0.15	0.23
FT8	4.19±0.02	351.00±0.81	4.13±0.11	0.24
FT9	4.20±0.05	351.00±0.40	4.16±0.11	0.14

*All values are mean ± SD, n = 3, ** All values are mean ± SD, n = 20.

Tablet density and Buoyancy study of Bilayer Floating tablets of Glipizide and Lisinopril

Table 5: Tablet density, Buoyancy lag time and Total floating time

Formulation	Tablet density (g\cc)	Buoyancy Lag Time(sec)	Total floating time(hrs)
FT1	0.9	45	17
FT2	0.81	46	18
FT3	0.73	50	19
FT4	0.86	47	20
FT5	0.78	49	21
Ft6	0.7	52	22
FT7	0.84	49	21
FT8	0.75	52	22
FT9	0.67	55	>24

Drug Content of Bilayer Floating Tablets of Glipizide and Lisinopril

The percentage of drug content of Glipizide and Lisnopril was found to be between 95 to 101.38% for Glipizide and 95.04 to 99.95 % for Lisinopril which was within acceptable limits. Table5.15 showed the result of drug content uniformity in each batch.

Table 6: Drug content of Bilayer Floating Tablet of Glipizide and Lisinopril

	Drug content (%)*	
Formulation	**Glipizide**	**Lisinopril**
FT1	101.8±0.30	97.90±1.19
FT2	99.80±0.55	98.90±1.05
FT3	99.78±1.51	96.90±1.51
FT4	96.60±0.62	95.70±0.66
FT5	98.80±1.05	96.80±1.51
FT6	96.20±1.20	96.10±0.55
FT7	96.20±0.30	96.83±1.51
FT8	96.20±1.19	96.50±0.30
FT9	97.40±0.66	96.84±1.25

*All values are mean ± SD, n = 3

***In-vitro* Drug Release Studies of Bilayer Floating tablets of Glipizide and Lisinopril**

In vitro drug release studies of Bilayer Floating tablets of Glipizide and Lisinopril were carried out in 0.1N HCl containing 10% methanol. Cumulative drug release of glipizide was calculated on the basis of drug content of glipizide present in the bilayer tablets. The results obtained in the *in vitro* drug release for the formulations F1 to F9 is shown in Table 7. The plot of cumulative percentage drug release versus time (h) was plotted and depicted as shown in figure 1

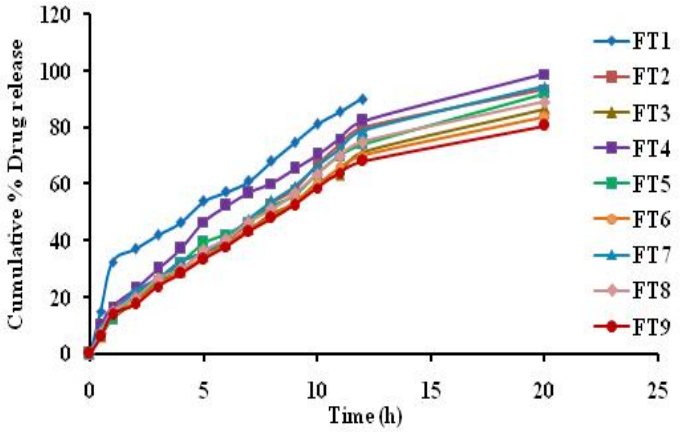


Figure 1: *In-vitro* drug release studies of glipizide in formulation FT1 to FT9 in 0.1N HCl containing 10% methanol

Table 7*: In-vitro* Drug Release Data of Bi-layer Floating tablets

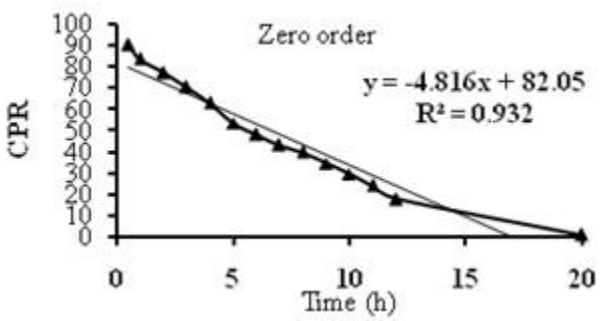
Time (hrs)	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
0.5	15.20± 0.08	9.15±0.07	6.06±0.09	10.08±0.06	7.25±1.00	6.4±1.05	8.91±1.03	7.4±1.07	6.2± 1.03
1	32.53±1.05	15.2±0.99	12.4±1.09	16.66±0.9	12.23±1.0	14.20±1.15	14.52±1.23	15.50±1.2	13.85±1.0
2	37.15±1.03	21.6±1.08	18.54±1.12	22.95±1.0	20.36±1.1	18.1±1.15	22.25±1.12	19.65±1.2	17.46±1.0
3	42.09±1.09	26.1±1.12	25.54±1.08	30.25±1.1	25.4±1.20	24.5±1.09	26.5±1.01	26.5±1.08	23.88±0.9
4	46.38±1.63	32.5±1.54	28.86±1.85	37.03±1.2	31.85±1.9	28.8±2.05	32.5±2.02	30.15±1.98	28.14±2.2
5	53.84±1.46	35.6±1.27	34.4±1.96	46.67±1.2	39.19±2.2	34.5±2.17	36.30±2.35	36.65±1.23	33.45±2.4
6	57.25±1.23	40.1±1.23	38.89±1.10	52.23±1.0	42.23±1.1	38.4±1.09	40.5±1.18	40.5±2.3	37.97±2.1
7	61.16±2.45	46.1±1.20	44.5±1.33	56.85±1.2	46.68±1.9	44.2±2.13	47.76±2.23	46.64±2.1	43.22±1.2
8	68.12±1.05	53.1±0.99	49.69±0.98	60.25±1.0	52.15±1.0	48.6±1.02	54.22±1.09	51.26±1.0	47.84±1.2
9	74.58±1.89	58.1±2.12	53.36±2.19	65.48±2.6	56.14±2.9	53.9±2.23	59.05±1.99	56.65±2.1	52.5± 3.1
10	81.1±1.56	66.6±1.22	60.4±1.29	70.36±2.1	63.36±2.0	59.9±1.93	66.2±1.23	63.36±1.9	58.59±2.3
11	85.65±1.12	74.1±1.15	63.36±1.05	76.2±0.98	70.05±1.2	65.5±1.02	72.56±1.12	69.9±1.09	64.06±0.9
12	90.08±1.33	79.9±1.54	70.86±2.05	82.25±1.9	74.20±1.2	70.1±2.23	78.85±1.85	75.21±2.0	68.40±1.9
20	-	93.4±1.12	86.68±0.98	98.86±1.2	92.10±1.0	83.5±1.23	94.5±0.99	89.15±1.0	80.6± 1.1

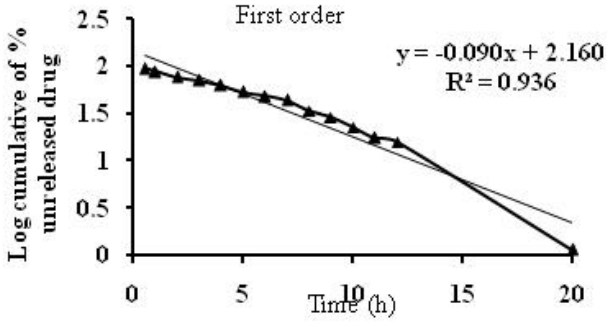
Table 8: Comparision of Regrssion analysis of *in-vitro* drug release of Glipizide in all formulation

Formulations	Zero Order	First Order	Hixon - Crowell	Higuchi	Korsmeyer Peppas
FT	y = -5.782x + 77.61 R^2 = 0.974	y = -0.070x + 1.986 R^2 = 0.937	y = 0.179x + 0.167 R^2 = 0.971	y = 24.93x - 0.163 R^2 = 0.974	y = 0.510x + 1.398 R^2 = 0.958
FT2	y = -4.717x + 86.64 R^2 = 0.941	y = -0.057x + 2.060 R^2 = 0.959	y = 0.107x + 0.043 R^2 = 0.941	y = 24.25x - 13.09 R^2 = 0.964	y = 0.651x + 1.140 R^2 = 0.985
FT3	y = -4.335x + 88.13 R^2 = 0.952	y = -0.042x + 2.017 R^2 = 0.985	y = 0.114x + 0.053 R^2 = 0.985	y = 22.41x - 12.75 R^2 = 0. 992	y = 0.719x + 1.043 R^2 = 0.993
FT4	y = -4.816x + 82.05 R^2 = 0. 932	**y = -0.086x + 2.158** **R^2 = 0.936**	y = 0.169x - 0.007 R^2 = 0.988	**y = 25.22x - 10.20** **R^2 = 0.990**	**y = 0.647x + 1.194** **R^2 = 0.993**
FT5	y = -4.589x + 87.11 R^2 = 0.950	y = -0.052x + 2.045 R^2 = 0.971	y = 0.130x + 0.029 R^2 = 0.994	y = 23.76x - 13.26 R^2 = 0.987	y = 0.712x + 1.077 R^2 = 0.996
FT6	y = -4.213x + 87.46 R^2 = 0.939	y = -0.039x + 2.000 R^2 = 0.988	y = 0.108x + 0.080 R^2 = 0.984	y = 21.86x - 11.59 R^2 = 0.980	y = 0.694x + 1.063 R^2 = 0.988
FT7	y = -4.728x + 86.57 R^2 = 0.949	y = -0.060x + 2.071 R^2 = 0.955	y = 0.142x + 0.006 R^2 = 0.988	y = 24.33x - 13.13 R^2 = 0.973	y = 0.659x + 1.136 R^2 = 0.990
FT8	y = -4.477x + 86.67 R^2 = 0.942	y = -0.047x + 2.023 R^2 = 0.981	y = 0.123x + 0.058 R^2 = 0.987	y = 23.17x - 12.14 R^2 = 0.977	y = 0.677x + 1.104 R^2 = 0.989
FT9	y = -4.079x + 87.58 R^2 = 0.935	y = -0.036x + 1.991 R^2 = 0.987	y = 0.102x + 0.091 R^2 = 0.979	y = 21.22x - 11.07 R^2 = 0.980	y = 0.699x + 1.048 R^2 = 0.985

Kinetics of Drug Release

Data obtained from dissolution studies were fitted to various kinetic models. The kinetic models used were zero order (percentage unreleased vs time), first order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), Hixon-Crowell cube rot law and Korsmeyer (log cumulative percentage of drug released vs log time) equation. The data of average values were described in the Table 8 & Figure 2.





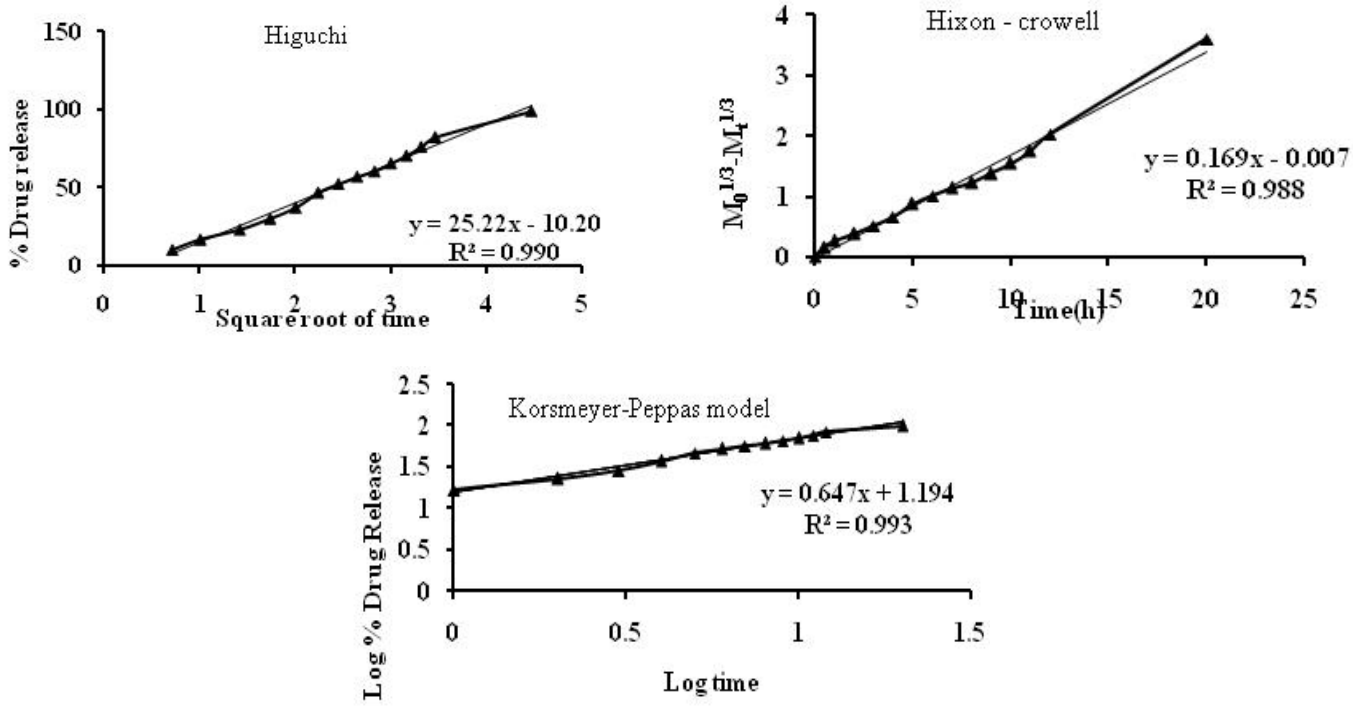


Figure 2: Drug release kinetic model of formulation FT4

Table 8: Comparision of Regrssion analysis of *invtro* drug release of Glipizide in all formulation

Stastical Data Analysis

Experimental design 3^2 Factorial designs has often been applied to optimize the formulation variables with basic requirement of understanding interaction of independent variables. Results for experimental design batches and its ANOVA were shown below.

Table 9: Design Summary

Formulation Code	R_1 Floating Duration* (h)	R_2 Q_8	R_3 Q_{20}
FT1	17	68.12	-
FT2	18	53.15	93.4
FT3	19	49.69	86.68
FT4	20	60.25	98.86
FT5	21	52.15	92.10
FT6	22	48.6	83.5
FT7	21	54.22	94.5
FT8	22	51.26	89.15
FT9	24	47.84	80.6

R_1: Response 1, R_2: Response 2, R_3: Response 3.

Table 10: Summary of results of regression analysis*

Coefficients	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
			Floating Duration			
FM	20.88	2.166	1.166	-0.833	0.166	0.250
P values	1.7E-06	0.000241	0.0015	0.0189	0.4228	0.1442
RM	21	2.166	1.166	-0.833	-	-
P values	3.79E-06	-	0.005	0.001	-	-
			Q_8			
FM	51.387	-2.976	-5.675	1.123	2.248	3.0675
P values	8.2E-05	0.0506	0.0091	0.5398	0.2612	0.0760
RM	53.635	-	-5.675	-	-	-
P values	1.9E-09	-	0.0119	-	-	-
			Q_{20}			

FM	91.782	-2.971	-7.43	-0.398	-0.493	0.3549
P values	8.687E-07	0.0039	0.00026	0.5768	0.4959	0.4889
RM	91.19	-2.971	-7.43	-	-	-
P values	3.9E-14	9.3E-05		-	-	-

Table 11: Calculation of testing the model in portions*

Floating Duration	**DF**	**SS**	**MS**	**F**	**R^2**	
Regression						
FM	5	38.027	7.605	117.34	0.9949	Fcal = 2.361
RM	3	37.722	12.574	125.74	0.9869	Ftable = 9.5
Error						DF = (2,3)
FM	3	0.194	0.0648	-	0.2545	
RM	5	0.50	0.1	-	0.3162	
Q8	**DF**	**SS**	**MS**	**F**	**R^2**	
Regression						
FM	5	344.33	68.867	19.723	0.9851	Fcal =1.516
RM	3	316.35	105.45	13.707	0.8915	Ftable =199.50
Error						DF = (2,1)
FM	1	15.905	17.048	-	2.3025	
RM	7	119.34	0.8149	-	4.129	
Q20	**DF**	**SS**	**MS**	**F**	**R^2**	
Regression						
FM	5	385.52	77.104	94.61	0.9936	Fcal = 0.535
RM	2	384.21	192.10	307.13	0.9903	Ftable =9.28
Error						DF = (3,3)
FM	3	2.444	0.8149	-	0.9027	
RM	6	3.752	0.6254	-	0.7908	

*FM indicates full model; RM, reduced model

*Response is insignificant at p = 0.05

*DF, degree of freedom; SS, sum of squares; MS, mean of squares; R^2, regression coefficient; FM, full model; RM, reduced model

(A) Effect of formulation variable on Floating Duration (Y_1)

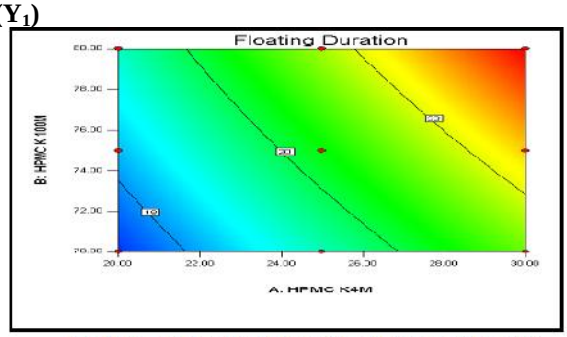


Figure 3: Contour plot showing effect of X_1 and X_2 on floating Duration

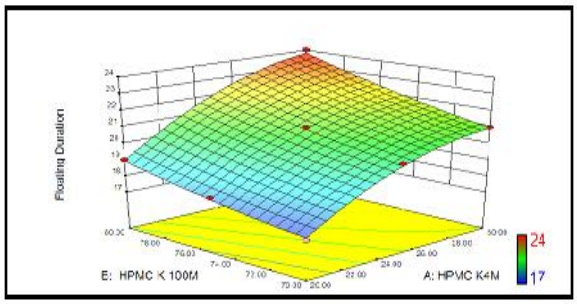


Figure 4: Response surface plot showing effect of X_1 and X_2 on Floating Duration

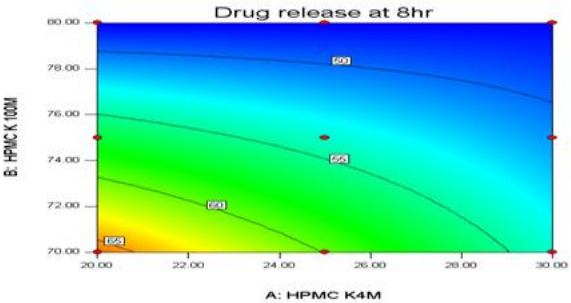


Figure 5: Contour plot showing effect of X_1 and X_2 on drug release at 8 hr

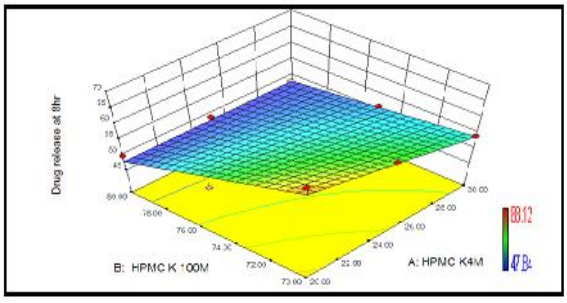


Figure 6: Response surface showing effect of X_1 and X_2 on amount of drug release at 8 h

(C) Effect of formulation variable on amount of drug release at 24 hr (Y_3)

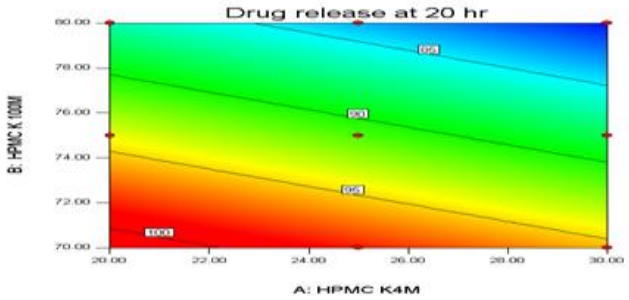


Figure 7: Contour plot showing effect of X_1 and X_2 on amount of drug release at 20 hr

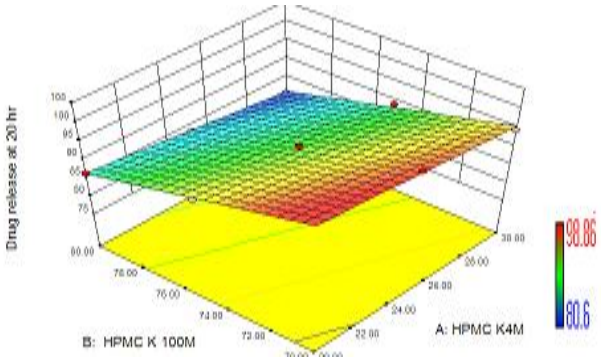


Figure 8: Response surface plot showing effect of X_1 and X_2 on amount of drug release at 20 hr

Table 12: Results of dependent variables of check-point batch

Test parameters	Result
Floating Duration	19.75
Drug release at 8 hrs	59.50±1.02
Drug release at 20 hrs	98.06±1.02

Table 13: Comparison between observed and predicted results of checkpoint batch

Response parameters	Predicted value	Observed values	Relative error (%)
Floating Duration	19.889	19.75	0.6988
Drug release at 8 hrs	59.919	59.50	0.6992
Drug release at 20 hrs	98.413	98.06	0.3586

Stability Study of Optimized Formulation

Table 14: Stability study (40 °C/75%RH) of Optimized Formulation (FT4)

Parameters	Before stability studies	After stability studies
Weight variation(mg)	353.67±1.24	353.67±1.24
Hardness (kg/cm^2)	4.06±0.25	4.05±0.15
Friability (%)	0.37	0.36
Drug content (%)	Glipizide: 96.60 Lisinopril: 95.70	Glipizide: 95.80 Lisinopril: 94.80
Buoyancy Lag Time (Sec)	47	45
Total Floating Time (hrs)	20	19.75
In vitro release (%) 6h	60.25	55.56
In vitro release (%) 20h.	98.86	95.58

Applying the similarity factor f2

Table 15: Comparison of release profile of Reference and Test formulation

Time (h)	CPR*	
	Optimized batch FT4 before stability (Reference)	Optimized batch FT4 after stability (Tested)
0	0	0
0.5	10.8±0.6	7.5±0.85
1	16.6±0.9	13.25±1.2
2	22.95±1.0	17.75±1.5
3	30.25±1.1	27.78±0.55
4	37.03±1.2	34.48±0.8
5	46.67±1.2	43.13±1.3
6	52.23±1.0	47.75±0.96

7	56.85±1.2	51.12±0.85
8	60.25±1.0	55.56±1.15
9	65.48 ±2.6	60.04±0.60
10	70.36 ±2.1	65.5±0.75
11	76.2±0.98	72.24±0.50
12	82.25±1.9	76.56±0.75
20	98.86 ±1.2	95.58±0.95

*All values are Mean±S.D

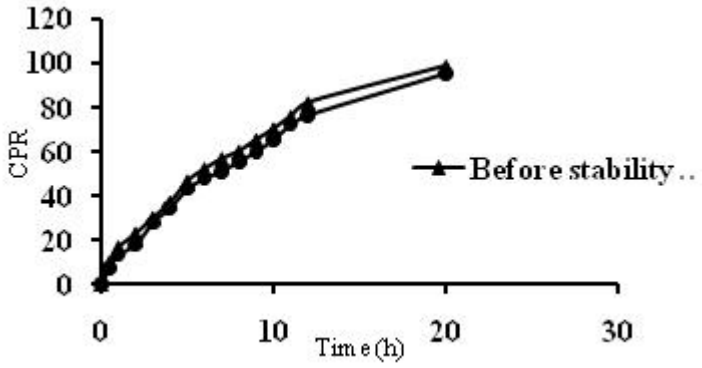


Figure 9: Comparison of release profile of Reference and Test formulation

4. Aknowledgment

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