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FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE BILAYER FLOATING TABLETS OF LOSARTAN POTASSIUM

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ABSTRACT

The aim of present study was to formulate and evaluate Gastroretentive bilayer floating tablets of Losartan potassium using direct compression technology. Bilayer floating tablets comprised two layers, i.e. immediate release and controlled release layers. The immediate release layer comprised Crospovidone as a super disintegrant and floating layer comprised Sodium carboxy methyl cellulose (SCMC), Metolose SR and Sodium alginate as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. The powder blends were evaluated for pre-compression parameters. Compressed tablets were further evaluated for hardness, friability, weight variation, dimensions, Drug Content Uniformity, *In-vitro* buoyancy and dissolution studies. All the formulations showed good results which were compliance with pharmacopoeial standards. *In-vitro* dissolution studies were performed in USP-XXIII dissolution test apparatus, type II (paddle method) in 1.2pH buffer. More than 99% Losartan potassium of was released from the immediate release layer within 30 min. The results of dissolution studies indicated that formulation BFT8 (drug to polymer[SCMC] 1:0.25), the most successful of the study, exhibited drug release of approximately 98% at 12^{th} hour with more than 12h buoyancy with floating lag time of 93seconds. An increase in drug release was observed on decreasing polymer ratio. The drug release mechanism of all the formulations was found to be Fickian diffusion-controlled drug release.

Keywords: Losartan potassium, Gastroretentive, bilayer floating tablets, Sodium carboxy methyl cellulose, Metolose SR and Sodium alginate.

INTRODUCTION

In the recent years, a great deal of technological and scientific research has been carried out to the develop rate-controlled oral drug delivery systems in order to overcome physiological problems, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Gastro-retentive dosage forms will allow the delivery of restricted 'absorption window' drugs which are absorbed in a particular portion of the GI tract.[1]Floating Bilayer drug delivery system is combined principle of bilayer tablet as well as floating mechanism. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and remain buoyant in the stomach without affecting gastric emptying rate for a longer period of time. Floating drug delivery system provides advantages such as enhanced bioavailability ,enhanced first-pass biotransformation, sustained Drug Delivery / reduced frequency of dosing ,site-Specific Drug Delivery, reduced fluctuations of drug concentration, minimized adverse activity at the colon, absorption Enhancement.[1][2]

Bilayer tablet dosage forms are designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredient(s) (API), to separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer, to administer the fixed dose combinations of different APIs. Bilayer tablets are prepared with one layer of drug for immediate release while second layer

designed to release drug later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of one drug as immediate release and another drug as sustained release, in which one layer is immediate release as initial dose and second layer is maintenance dose. [3]

Hypertension may be defined as a repeated elevation of systolic blood pressure above 140 mmHg or a diastolic blood pressure above 90 mmHg. Hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries (e.g. aortic aneurysm), peripheral arterial disease and is a cause of chronic kidney disease. [4]

Losartan potassium is the first orally active angiotensin-II antagonist used in the treatment of hypertension. Administration of conventional tablets of Losartan potassium may exhibit fluctuations in the plasma drug levels resulting either in manifestation of side effects or reduction in drug concentration at the receptor site. It has low bioavailability due to its first pass metabolism. Systemic bioavailability is about approximately 33% and it has a short biological half-life of 1.5 -2 h ,is eliminated quickly from the body leading to low therapeutic efficacy **.** [5] So the present study is aimed to prepare and evaluate Gastro retentive bilayer floating tablets of Losartan potassium so as to increase the bioavailability , gastric residence time, improve patient compliance and to reduce frequency of administration. These tablets have an immediate release layer leading to a quick rise in blood concentration to a therapeutically effective level and further the concentration is maintained by drug release from the sustained release layer. Floating drug delivery technology was used for Losartan potassium in its sustained release layer.

MATERIALS AND METHOD

Materials: Losartan potassium was obtained from Spectrum pharma, India. Sodium carboxy methyl cellulose(SCMC) was obtained from Oxford Laboratory, Mumbai; Sodium alginate ,Metolose SR, Crospovidone, Lactose monohydrate, Talc and Hcl was obtained from S. D. Fine Chemical, Mumbai. Microcrystalline cellulose(MCC) was obtained from Otto Chemicals, Mumbai. Sodium bicarbonate was obtained from Ranbaxy Fine Chemical Limited, New Delhi. Magnesium stearate was obtained from Central Drug House(p) Limited, New Delhi. Nacl was obtained from Merk Specialities Pvt Limited, Mumbai.

Preparation of bilayer tablet: Bilayer floating tablets were prepared by direct compression using Crospovidone as a superdisintegrant, Sodium alginate, SCMC and Metolose SR as the release controlling polymers, Sodium bicarbonate as a gas generating agent, MCC, Lactose monohydrate as diluents and Magnesium Stearate, Talc as lubricant and glidant. The drug, polymers and other excipients used for both immediate (IR) and sustained release (SR) layers were passed through sieve # 60 before their use in the formulation. Preparation of bilayer floating tablets had two steps:

STEP 1: Formulation of the IR Layer: The ingredients **(Table 1)** were collected and accurately weighed. Pre-blend all ingredients (except lubricant-magnesium Stearate) in blender for 15 minutes. Add magnesium Stearate and then again blend for 5-6 minutes and kept in desiccators until further used.

STEP 2: Formulation of the Floating Layer: The SR layer ingredients **(Table 2)** were collected and accurately weighed. Pre-blend all ingredients (except lubricant- magnesium Stearate) in blender for 15 minutes. Add magnesium Stearate and then again blend for 5-6 minutes and subjected for pre-formulation studies.

Compression of bilayer Tablet

Bilayer tablet was prepared manually using Manest 16 Station Punching Machine (Liverpool, England).Accurately weighed amount of SR powder mixture was fed manually into die cavity. SR layer was compressed at mild compression force. After that accurately weighed IR powder mixture was manually fed into the die on SR layer and compressed using 10 mm circular punches**.** Both the layers were identified on the basis of color since the immediate release layer had pink color and the sustained release layer has white color. [6], [7]

Evaluation of Powder Blend

Angle of repose (θ): The angle of repose is the maximum angle that the plane of powder makes with the horizontal surface on rotation. The angle of repose of granules was determined by the fixed funnel and free standing cone method. It is determined by allowing powder mixture to flow through a funnel and fall freely onto a surface. The height and diameter of the resulting cone are measured and the angle of repose was calculated using the following equation. $\tan \theta = h/r$; Where h = height of the powder heap; r = radius of the powder heap; θ = is the angle of repose. [8]

Bulk Density (Db): Apparent bulk density was determined by pouring pre-sieved drug excipient blend into a graduated cylinder and measuring the

volume and weight "as it is". It is expressed in g/ml and is given by
Db = M / V0; Where, M is the mass of powder and V0 is the Bulk volume of the powder.

Tapped density (Dt): It was determined by placing a graduated cylinder, containing a known mass of drug excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by
Dt = M / Vt; Where, M is the mass of powder and Vt is the tapped volume of the powder.

Carr's Index (I): It is expressed in percentage and is expressed by I = (Dt – Db) x100/Dt; Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner ratio: It is expressed by H= Dt / Db Where, Dt is the tapped density of the powder and Db is the bulk density of the powder**.** [9]

Evaluation of tablets
Dimensions:
The thickness and diameter of the tablets was measured using Vernier calipers. It is measured in mm.

Weight Variation
Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in Table- 4 and none deviate by more than twice the percentage shown.

Hardness
The hardness of ten tablets was measured using Monsanto Hardness tester. It was expressed as kg/cm2.

Friability
The friability of the tablets was determined using Roche friabilator. It was expressed in percentage (%). 10 tablets were initially weighed and transferred to the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again.
The % friability was then calculated using the formula:
% friability = Win - Wf / Win x 100
Win=Initial weight WF=final weight. .Acceptance criteria: The friability value should be less than 1.0%. [10]

Uniformity of drug content:
The drug content was performed to check the dose uniformity in the formulation. Randomly ten tablets were weighed and powered. A quantity equivalent to 100mg of Losartan potassium was added in to a 100ml volumetric flask and dissolved in 0.1N HCI, shaken for 10 minutes and made up to the volume with 0.1N HCl. After suitable dilutions the drug content was determined by UV spectrophotometer at 234nm against blank.

Buoyancy studies:
The *in-vitro* floating behavior (buoyancy) of the tablets was determined by floating lag time. The tablets were placed in 100 ml beaker containing 0.1 N HCl (pH 1.2). The floating lag time (time taken by the tablet to reach the surface) and total floating time (floating duration of the tablet) were determined. [5]

In vitro Drug Release Study:
In vitro dissolution studies were performed in a USP XXIII dissolution test apparatus, type II (paddle method) (Disso 2000, Labindia, India) at 37±0.5^{0}C and with a paddles rotation speed of 75rpm.Seperate Dissolution studies were carried out for IR tablets to optimize the super disintegrant before performing the dissolution studies for bilayer tablets .The bilayer floating tablets (BFTs) were then placed into 900ml of 0.1N HCl solution (pH 1.2) which was used as dissolution medium. Dissolution studies were carried out in triplicate. A 5ml aliquot of sample was withdrawn at 15 minutes, 30 minutes and 1 h. Further samples were collected at 1 h interval up to 12 h. The samples were filtered through a 0.45µm membrane filter and diluted if necessary and estimated for Losartan potassium released using UV-visible spectrophotometer at 234nm. At each time of withdrawal, 5ml of fresh medium was replaced into the dissolution flask. The concentrations were calculated using the standard curve prepared using 0.1N Hydrochloric acid as solvent. The cumulative percentage of Losartan potassium released from the tablets was also calculated.

Release kinetics:
The rate and mechanism of release of Losartan potassium from the prepared bilayer floating tablets were analyzed by fitting the dissolution data into the zero-order equation .[11]
$Q = k^0t$
Where Q is the amount of drug released at time t, and k^0 is the zero order release rate constant. The

dissolution data was fitted to the first order equation. [12]

$$\ln (100–Q) = \ln 100 – k_1t$$

Where $k_1$is the first order release rate constant. The dissolution data was fitted to the Higuchi's equation. [13]

$$Q = k_2t^{1/2}$$

Where k_2 is the diffusion rate constant. The dissolution data was also fitted to the well known equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems. [14]

$$Mt/ M_\infty = k_3t^n$$

$$\log (Mt/ M_\infty) = \log k_3 + n \log t$$

where Mt is the amount of drug released at time t , M_∞ is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release.

For a matrix tablet, when 'n' takes the value of ,

- 0.45 - Fickian diffusion-controlled drug release
- 0.89 - Swelling-controlled drug release
- 0.45- 0.89 - Anomalous transport (both diffusion and swelling controlled)

RESULTS AND DISCUSSION

Bilayer floating tablets of Losartan potassium were developed using SCMC, Sodium alginate and Metolose SR as polymers in sustained release layer and Crospovidone as superdisintegrant in immediate release layer. The results demonstrated an initial burst release of immediate release layer was due to super disintegrant.[15]The immediate release tablets were optimized based on dissolution studies. The fastest release of IR layer was observed in tablets containing 8% Crospovidone as superdisintegrant. Hence formula C was used as immediate layer in all bilayered tablets.

The blend of the drug and excipients was evaluated for micrometric properties and were tabulated in Table 3.Angle of repose was found to be between 23.72 to 34.33. Bulk density was found to be between 0.495 to 0.697 gm/ml and tapped density between 0.572 to 0.839 gm/ml for all formulations. Hausner's ratio was found below 1.29 and Carr's compressibility index between 11.44 to 21.94 for all formulations, which indicates that the prepared granules of all the formulations have good flow properties. All batches of tablets were evaluated for various physical parameters and were tabulated in Table 4.The weight variation and drug content of all formulations was within the ranges of 398 to 404 mg and 97 to 102. The hardness of the tablets was within the range of 4.10 to 6.23 kg/cm2.The friability of all tablets below 1% (0.31%-0.82%).The thickness and diameter of all tables was within the range of 6.4 to 6.98 mm and 8.00 to 8.10 mm respectively. Thus all the physical properties of these tablets were satisfactory as specified in the pharmacopoeia (IP, 1996).

In vitro buoyancy studies and in vitro dissolution studies were performed in 1.2 pH 0.1N HCl are tabulated in Table 4, 5 and 6 and graphs were depicted in (Figure1 and 2).All formulations exhibited floating lag time ranging from 87 to 210 secs ;total floating time of 5 to >12 hours was observed in dissolution medium subjected to rotation . The floating time of all formulations was found to be increasing with the increasing amount of polymer concentration. Formulations BFT1, BFT2,BFT4, BFT5, BFT7, BFT8 and BFT10 showed drug release of 73.91, 79.94, 85.98, 89.75, 91.25, 98.80 and 91.63 % respectively at the end of 12 hours. While The formula BFT3,BFT6,BFT9,BFT11and BFT12 showed drug release of 99.55, 99.93, 99.17, 99.17 and 98.04 % respectively at the end of 9,7,5,9 and 8 hours. Among all the formulations, formulation BFT8 was found to be most promising formulation as it has shown most consistent drug release (98.80 %) up to 12 hrs as compared to other formulations. It is evident from the above data that as the proportion of polymer in the formulation decreases, cumulative percentage drug release increases.

The rate and mechanism of release of Losartan potassium from the prepared bilayer floating tablets were analyzed by fitting the dissolution data into the Zero order, First order, Higuchi matrix, Korsemeyer-Peppas ,the results were tabulated in Table 7.The regression co-efficients obtained for Higuchi's plots (R^2:0.960 to 0.891) were higher, when compared with those of Korsemeyer-peppa's plots (R^2:0.930 to 0.779) with slope(n) values 0.301 to 0.376 ,indicating that the release mechanism of Losartan potassium from bilayered floating tablets followed fickian diffusion for all the formulations.

CONCLUSION

The present study discusses the formulation and evaluation of gastro retentive bilayer floating tablets of Losartan potassium. Sodium bicarbonate helped in achieving in vitro buoyancy, while polymers SCMC, Sodium alginate and Metolose SR along with gas generating agent affected the total lag time and drug release. The tablets demonstrated an initial burst release of immediate release layer within 30min was

due to super disintegrant Crospovidone. Formulation BFT8 was determined to be the optimized formula which possessed satisfactory quality parameters both in process parameters and parameters for finished products. It showed short floating lag time(93 ses) with total floating time of more than 12 hours and cumulative % drug release of 98.80 at the end of 12 hours following Higuchi release kinetics. All the formulations followed fickian diffusion. Thus, results of the current study clearly indicate, a promising potential of the Losartan potassium bilayer floating tablets as an alternative to the conventional dosage form.

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Figure 1 - *In vitro* dissolution profile of formulations A to C

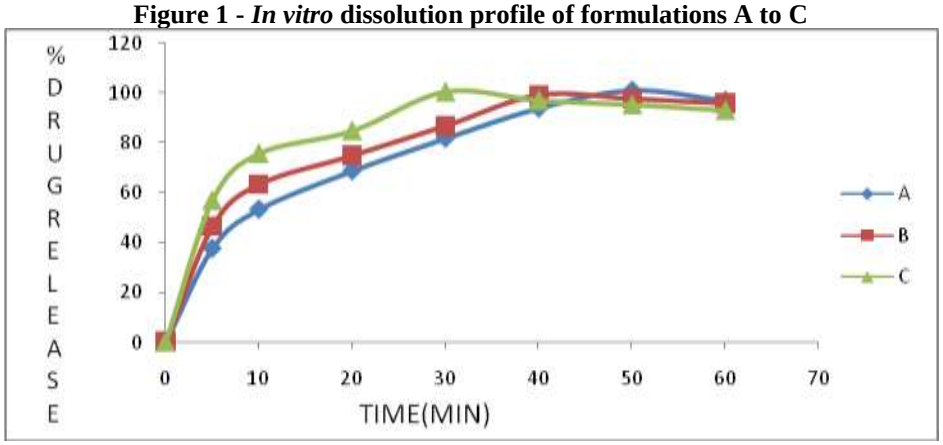

Figure 2 - *In vitro* dissolution profile of formulations BFT1-BFT12

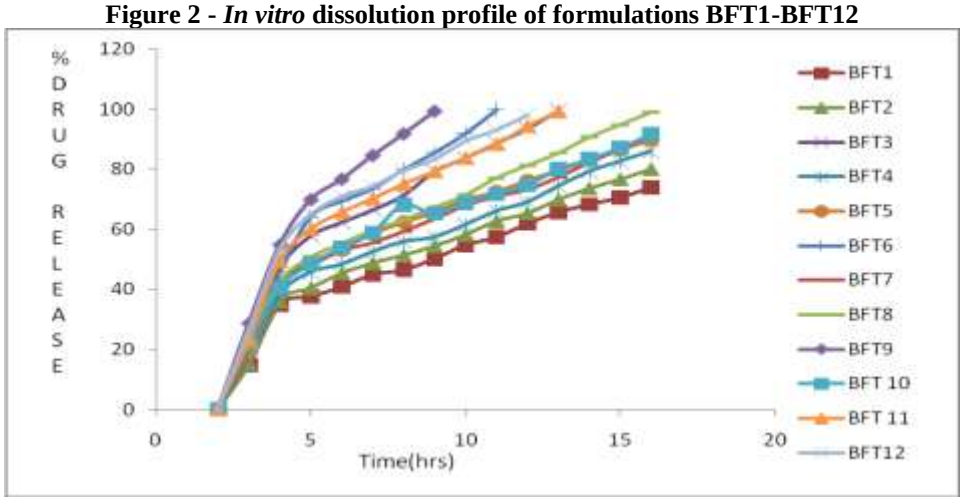

TABLE 1: Formulation development of immediate release layer

Ingredients	A	B	C
Losartan potassium	25	25	25
Crospovidone	6	9	12
MCC	119	110	107
Mg-Stearate	2.25	2.25	2.25
Talc	3	3	3
Color	0.75	0.75	0.75
Total weight	150	150	150

**All values are taken in mg.*

TABLE 2: Composition of bilayer tablets

Ingredients	**BFT 1**	**BFT 2**	**BFT 3**	**BFT 4**	**BFT 5**	**BFT 6**	**BFT 7**	**BFT 8**	**BFT 9**	**BFT 10**	**BFT11**	**BFT12**
FOR IR LAYER												
Losartan potassium	25	25	25	25	25	25	25	25	25	25	25	25
Crospovidone	12	12	12	12	12	12	12	12	12	12	12	12
MCC	107	107	107	107	107	107	107	107	107	107	107	107
Mg-Stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Color	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
FOR SR LAYER												
Losartan potassium	50	50	50	50	50	50	50	50	50	50	50	50
Sodium alginate	50	-	-	37.5	-	-	25	-	-	25	25	-
SCMC	-	50	-	-	37.5	-	-	25	-	25	-	25
Metolose SR	-	-	50	-	-	37.5	-	-	25	-	25	25
Sodium bicarbonate	20	20	20	20	20	20	20	20	20	20	20	20
Lactose monohydrate	122.5	122.5	122.5	135	135	135	147.5	147.5	147.5	122.5	122.5	122.5
Mg-Stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Talc	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total weight	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

TABLE 3: Recompression flow properties of powder blend.

Batch	Angle of repose*(θ)*	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hausners ratio
A	34.33	0.615	0.755	18.54	1.23
B	32.15	0.7	0.839	16.57	1.2
C	29.67	0.697	0.787	11.44	1.13
BFT1	26.43	0.605	0.775	21.94	1.28
BFT2	28.25	0.586	0.741	20.92	1.26
BFT3	30.56	0.526	0.646	18.58	1.23
BFT4	28.32	0.498	0.611	18.49	1.23
BFT5	26.19	0.523	0.648	19.29	1.23
BFT6	32.48	0.613	0.729	15.91	1.19
BFT7	24.33	0.495	0.587	15.67	1.19
BFT8	23.72	0.543	0.633	14.22	1.17
BFT9	28.98	0.502	0.572	12.24	1.14
BFT10	25.47	0.629	0.764	17.67	1.22
BFT11	26.83	0.652	0.75	13.07	1.15
BFT12	27.26	0.561	0.653	14.09	1.16

Table 4: Physical parameters of bilayer floating tablet of losartan potassium

Formulation code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Average weight variation (mg)	Drug content (%)	Floating Lag time(s)	Total Floating time (h)
BFT1	6.4±0.04	8.00±0.05	6.23±0.45	0.31±0.08	398±0.35	97.34±1.3	210	>12
BFT2	6.74±0.03	8.04±0.02	6.00±0.32	0.43±0.04	400±0.29	98.02±0.9	179	>12
BFT3	6.6±0.04	8.02±0.04	4.20±0.28	0.82±0.11	399±0.40	100.10±1.1	150	>9
BFT4	6.81±0.03	8.07±0.08	5.98±0.61	0.46±0.03	402±0.32	98.15±1.4	184	>12
BFT5	6.92±0.08	8.10±0.06	5.28±0.41	0.54±0.08	404±0.22	98.99±0.96	146	>12
BFT6	6.88±0.05	8.08±0.04	4.57±0.25	0.71±0.13	403±0.40	101.39±1.5	102	>7
BFT7	6.79±0.04	8.07±0.07	5.11±0.45	0.58±0.15	402±0.28	99.08±1.6	118	>12
BFT8	6.75±0.09	8.05±0.03	4.90±0.47	0.65±0.09	401±0.23	99.76±1.1	93	>12
BFT9	6.98±0.07	8.09±0.06	4.10±0.62	0.69±0.09	404±0.50	102.54±1.7	87	>5
BFT10	6.81±0.06	8.06±0.05	5.8±0.50	0.41±0.06	402±0.43	98.97±0.8	122	>12
BFT11	6.71±0.08	8.05±0.07	5.04±0.55	0.49±0.10	400±0.25	99.88±1.3	114	>9
BFT12	6.5±0.07	8.03±0.09	4.70±0.32	0.58±0.08	399±0.52	101.03±1.8	106	>8

TABLE NO 5: Cumulative percentage release of losartan potassium (IR Tablets)*

SR.	TIME(MIN)	A	B	C
1	0	0	0	0
2	5	37.56	46.38	57.01
3	10	53.28	63.35	75.91
4	20	68.67	74.89	84.96
5	30	81.68	86.77	**100.68**
6	40	93.78	99.09	97.17
7	50	100.91	97.63	95.48
8	60	96.84	95.82	93.21

Table no 6: Cumulative percentage release of losartan potassium bfts (bilayer floating tablets)*

TIME (HR)	BFT1	BFT2	BFT3	BFT4	BFT5	BFT6	BFT7	BFT8	BFT9	BFT 10	BFT 11	BFT12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.25	14.74	15.08	21.08	17.04	19.12	21.27	20.36	21.87	28.51	21.53	23.04	26.32
0.5	34.8	35.9	46.76	38.09	40.73	45.63	42.61	42.23	54.68	40.35	49.39	53.17
1	37.56	40.35	57.69	45.63	49.02	64.1	47.89	50.53	69.76	48.27	59.96	64.86
2	40.73	45.25	62.22	48.27	53.17	69.38	52.79	55.05	76.55	53.92	65.61	70.89
3	44.87	48.64	66.37	52.41	58.45	73.53	55.43	59.58	84.47	58.83	70.14	74.29
4	46.38	51.28	71.27	55.81	62.22	79.94	59.2	62.97	91.63	68.09	75.04	79.56
5	50.15	54.3	79.19	57.32	65.61	85.59	63.35	67.12	99.17	65.24	79.19	83.34
6	54.68	58.07	83.71	61.46	69.76	92.01	67.88	71.27		68.63	83.71	89.37
7	57.32	62.6	88.61	65.99	72.4	99.93	70.89	76.93		71.65	88.24	93.14
8	61.84	65.24	93.52	69.01	76.17		73.15	81.07		74.66	94.27	98.04
9	65.61	69.76	99.55	74.29	79.56		77.3	85.22		79.94	99.17	
10	68.25	73.53		79.19	82.96		82.2	90.5		83.34		
11	70.51	76.55		82.58	86.35		86.73	94.65		87.11		
12	73.91	79.94		85.98	89.75		91.25	**98.80**		91.63		

**Average values, n = 3*

Table no 7: *In-vitro* drug release kinetics study of all bilayered tablets

SR NO	Formulation code	**Zero order**		**First order**		**Higuchi**		**Korsmeyer-Peppas**		Best model
		r	K_0	r	K_1	r	K_2	r	n	
1	BFT1	0.909	3.920	0.957	-0.035	0.945	16.29	0.895	0.326	First order
2	BFT2	0.903	4.245	0.967	-0.044	0.946	17.71	0.890	0.333	First order
3	BFT3	0.867	6.894	0.753	-0.173	0.931	25.41	0.886	0.345	Higuchi
4	BFT4	0.901	4.485	0.952	-0.053	0.939	18.64	0.894	0.324	First order
5	BFT5	0.876	4.571	0.966	-0.062	0.946	19.35	0.907	0.317	First order
6	BFT6	0.82	8.952	0.778	-0.227	0.904	29.88	0.873	0.375	Higuchi
7	BFT7	0.902	4.548	0.955	-0.053	0.943	18.95	0.903	0.301	First order
8	BFT8	0.923	5.205	0.819	-0.109	0.960	21.62	0.929	0.317	Higuchi
9	BFT9	0.810	11.94	0.868	-0.327	0.901	34.72	0.886	0.359	Higuchi
10	BFT10	0.788	5.419	0.940	-0.064	0.947	19.18	0.930	0.303	Higuchi
11	BFT11	0.839	6.507	0.625	-0.213	0.916	24.18	0.878	0.321	Higuchi
12	BFT12	0.800	6.879	0.899	-0.155	0.891	24.47	0.779	0.376	First order

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