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Research Article

Formulation and evaluation of floating bilayer tablets of epleronone

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ABSTRACT

Gastro retentive drug delivery systems have been widely used to prolong retention of dosage forms in stomach. Among the various approaches, the floating bilayer tablets formulation offers sustained drug release as well as prolonged gastric retention, along with the added advantage of liquid oral dosage form. The present study was an attempt to formulate and evaluate floating bilayer tablets of Epleronone by using various polymers like guar gum, ethyl cellulose, SSG, CCS. The prepared floating Bilayered tablets were evaluated for hardness, Weight variation, thickness, friability, drug content uniformity, and in-vitro dissolution studies. Based on various evaluation parameters formulation F3 (IR) & F12 (SR) was selected as optimized formulation. From the above floating buoyancy studies shows that F12 shows higher Total floating time than other formulations. It was observed that Formulations F3 (IR) & F12 (SR) gave maximum drug release within time. All formulations were subjected for drug release kinetics studies viz. Zero order, first order, Higuchi matrix, Peppas model equations and the formulations of sustained release (SR) formulations followed zero order release with non-fickian diffusion mechanism.

Keywords: Epleronone, SSG, CCS, Guar gum, Ethyl cellulsoe.

INTRODUCTION

Gastroretentive Drug Delivery System

After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract.

Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs (Moses AJ et.al.,1993).

Classification of Gastroretentive Drug Delivery System

I. Floating Drug Delivery System: FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

A) Effervescent system: These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides (chitosan), effervescent components (sodium bicarbonate, citric acid, and tartaric acid) and matrices containing chambers of liquid that gasify

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at body temperature (Singh BN et.al., 2000, Kawashima Y et.al.,1992)

a) Gas-generating systems:

b) Volatile liquid containing systems (Osmotically controlled DDS)

B) Non-Effervescent FDDS

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. Non-effervescent systems based on several principles of following types.

a) Low density due to swelling (HBS System)

b) Inherent low density system

i. **Floating Microsphere (Hollow microspheres/Microballons)**
ii. **Floating beads**
iii. **Microporous compartment system (**Kawashima Y et.al., 1992)

Bilayer Tablets: Bilayered Tablets consist of two or more active pharmaceutical ingredients in One unit (Kawashima Y et.al., Park K, et.al., 1984)

Types of bilayer tablet press:

1. Single sided tablet press, 2. Double sided tablet press, 3. Bilayer tablet press with displacement monitoring (Gaurav Singh Gurjar et.al., 2017, Sanjana. A, et.al., 2016, Rakesh Kumar, et.al., 2016)

Types of Different Release Patterns of Bilayer Dosage Forms

Controlled release, Delayed release, Immediate release, Sustained release (Extended-/prolonged-release tablets) (Whitehead L, et.al., 1996, Ramu B, et.al., 2015, Vinay C.H, et.al., 2016)

MATERIALS AND METHOD

Epleronone was obtained as gift sample from BMR Chemicals, Hyd, India. CCS, Sodium Starch gylcolate, Guar Gum was procured from Narmada Chemicals, Hyd. Mg stearate, MCC, Talc, PVP-K30 procurred from SD Fine Chemicals. EC, NaHCO3, Citric acid, Sunset yellow CFC procured from BMR Chemicals, Hyd. Lactose procured from Agastan Bio Cheme Pvt Ltd.

Preparation of Bilayer tablets

a) Preparation of Immediate release layer: The Immediate release layer contains uniform mixture of Epleronone, Povidone, & CCS were weighed followed by shifting through 40# sieve and mixed well for 10min. finally prepared powder lubricated with magnesium stearate and Talc the well mixed powder were used as upper layer (Oth M, 1992)

b) Preparation of Sustained release layer: 20mg of Epleronone, GUAR GUM & ethyl cellulose, variable amount using of MCC, PVP K30, sodium bicarbonate, citric acid, Magnesium stearate and Talc was mixed properly in a mortar with weighed amount of polymers and excipients, The well-mixed powder was compressed by direct compression technique and used as sustained release layer (M. Yasmin Begum, 2014)

c) Preparation of Bilayer tablet: Bilayer tablets were prepared by combining of fast release layer and various formulations of sustained release layer. After the compression upper punch was lifted and the blend of powder for immediate release layer was poured into the die, containing initially compressed matrix tablet on multi station punching machine using flat punches, with the hardness of 6-8 kg/cm2.

Formulation Design

Table-1 Formulation of Immediate release layer (Epleronone).

Ingredients (mg)	**E1**	**E2**	**E3**	**E4**	**E5**	**E6**
Epleronone	10	10	10	10	10	10
CCS	3	6	9	-	-	-
SSG	--	--	--	3	6	9
Lactose	102	100	98	102	100	98
Mg stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Sunset yellow CFC	3	2	1	3	2	1
Total wt	120	120	120	120	120	120

Table 2: Formulation of Bilayer tablets of Epleronone

Ingredients (mg)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
IR formulation (F3)	120	120	120	120	120	120
Epleronone	20	20	20	20	20	20
Ethyl cellulose	30	60	90	--	--	--
GUAR GUM	--	--	--	30	60	90
Sodium bicarbonate	80	80	80	80	80	80
Citric acid	10	10	10	10	10	10
PVP K30	30	30	30	30	30	30
Lactose	124	94	64	124	94	64
Talc	3	3	3	3	3	3
Mg. Sterate	3	3	3	3	3	3
Total	300	300	300	300	300	300

Compression of Bilayer Tablets: The quantity of granules for the sustained-release layer was compressed lightly using 12 stationary double rotary compression machine using 12 inch circular shaped plain punches. Over this compressed layer required quantity of the immediate release granules were placed and compressed to obtain hardness in the range of 6-8 kg/cm^2 to form a bilayer tablet of sustained release of Epleronone and immediate-release of Epleronone. Then the compressed bilayer tablets were evaluated.[62-63]

Evaluation of Tablets[70-78]

Epleronone tablets were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose and moisture content as per the procedures explained above and the results were tabulated in Table

POST COMPRESSION PARAMETERS:

The formulated tablets were evaluated for the following physicochemical parameters.

Thickness: Thickness mainly depends on die filling, physical properties of material to be compressed and compression force. There is bound to be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter were measured by using Vernier calipers. Tablet thickness should be controlled within ± 5% variation of standard value.

Hardness: Tablet requires certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packing and shipping. Ten tablets were randomly picked from each formulation during manufacturing and evaluated for hardness using Monsanto hardness tester. It is expressed in kg/cm^2.Oral tablets normally have a hardness of 4 to 10kg/cm^2.

Friability: The friability test is closely related to tablet hardness it is usually measured by the use of the Roche friabilator. Ten tablets were weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are then dedusted and reweighed and compared with the initial weight. Loss of less than 1% in weight is considered to be acceptable.

$$F\ (\%) \quad \frac{\text{Intial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

Weight Variation Test: Twenty tablets were selected randomly and weighed individually. Average weight was calculated and compared to individual tablet weight. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table-3 Weight variation tolerances for uncoated tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Drug content uniformity: The test is used to ensure that every tablet contains the amount of drug intended with little variation among tablets within a batch. Ten tablets were weighed and crushed in the mortar. The powder equivalent to 20mg drug was dissolved in 6.8pH buffer and volume was made up to 100ml to give a concentration of 250µ g/ml. 1ml of this solution was taken and diluted to 10ml to give a concentration of 50µ g/ml. The absorbance of the prepared solution was measured using UV Visible spectrophotometer (PG Instruments,T60) and the drug concentration was determined from the standard calibration curve by using the regression equation.

$$\text{Concentration } (\mu g/ml) = \frac{\text{absorbance - intercept}}{\text{slope}}$$

$$\text{Drug content } (mg) = \text{concentration X dilution factor}$$

$$\%\ \text{Drug content} = \frac{\text{Drug content}}{\text{Labeled claim}} \text{ X } 100$$

The preparation passes the test if individual drug content is 95-105% of the average content.

In-vitro **buoyancy studies:** The invitro floating behaviour of the tablets was studied by placing them in 100ml beaker 100ml of 6.8 pH buffer The time, tablet required for the emerge on the surface is floating lag time (FLT) or buoyancy lag time (BLT). And the time tablet constantly float on the surface of the medium is called total floating time (TFT). ***In vitro*** **Dissolution Studies:**

Dissolution for Immediate release tablets of Epleronone: The release rate of Epleronone from immediate release tablets was determined using USP dissolution testing apparatus II (paddle). The dissolution test was performed using 900ml of 6.8 pH buffer solution at 37.5± 0.5ºC and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at times 5, 10, 15, 20, 30, 40, 50, & 60 mins and the samples were replaced

with fresh dissolution medium. The samples were observed for absorbance at wavelength of 236 nm.

In vitro drug release studies of bilayer tablets:
In vitro drug release studies of bilayer tablets were carried out using USP dissolution apparatus type II in 900mL of 6.8 pH buffer up to 720 min. Samples were collected at regular intervals of time and filtered. The collected samples were filtered and observed in UV spectrophotometer.

RESULTS AND DISCUSSION

Characterization of blend (immediate release)

Table: Pre Compression parameters (Immediate release)

Code	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index. (%)	Hausner's ratio
F1	27.54	0.331	0.375	13.97	1.16
F2	26.95	0.319	0.368	15.82	1.19
F3	29.56	0.315	0.385	16.71	1.18
F4	28.62	0.328	0.379	14.87	1.20
F5	29.84	0.335	0.398	16.71	1.17
F6	27.91	0.326	0.384	13.32	1.15

Inference: The angle of repose of different formulations (F1-F6) was found to be in the range of 26.95 to 29.84 which indicates that material had excellent flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.315 to 0.335. Tapped density was found between 0.368 to 0.398. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 13.32 to 16.71 and Hausner's ratio from 1.15 to 1.20 which reveals that the blends have good flow character.

Characterization of Immediate Release Tablets

Table no: Post Compression parameters

Formulation code	Mean Hardness Kg/cm^2	Thickness	Diameter (mm)	Average weight (mg)	Friability % w/w	Disintegration test (sec)	Mean drug content %
F1	3.8	3.22	8.85	150.24	0.80	15	96.47
F2	3.5	2.90	8.54	149.53	0.65	32	99.52
F3	3.2	2.64	8.84	148.35	0.83	23	95.33
F4	4.0	2.84	8.52	150.36	0.96	91	101.14
F5	3.6	2.76	8.49	151.75	0.72	45	97.28
F6	3.9	2.79	8.60	149.68	0.50	15	98.65

Inference: Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3-4 kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±10% of the tablet weight.

Friability values were found to be less than 1% in all the formulations F1 – F6 and considered to be satisfactory ensuring that all the formulations are mechanically stable.

Characterization of blend of Floating SR tablets:

Table : Pre Compression parameters

Formulation code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F7	30.54	0.625	0.737	12.31	1.17
F8	32.16	0.624	0.721	13.57	1.15
F9	29.57	0.653	0.728	15.22	1.18
F10	31.93	0.614	0.749	15.19	1.16
F11	29.61	0.641	0.743	14.93	1.17
F12	30.82	0.628	0.735	13.85	1.14

Inference: The angle of repose of different formulations was ≤ 32.16 which indicates that material had good flow property. So it was confirmed that the flow property of bends were free flowing. The bulk density of blend was found between 0.614g/cm^3 to 0.653 g/cm^3.Tapped density was found between 0.721g/cm^3 to 0.749g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 12.31-15.22 and Hausner's ratio from 1.14 - 1.18 which reveals that the blends have good flow character.

Characterization of tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content.

Table : Characterization of Bilayer tablets

Formulation	Average Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Drug content (%)
F7	299.1	3.96	12.11	6.5	0.54	99.72
F8	291.9	3.58	12.03	6..9	0.72	100.86
F9	298.0	3.68	12.22	6.7	0.43	98.64
F10	291.3	3.78	12.13	7.8	0.28	96.91
F11	289.9	3.58	12.02	7.3	0.92	98.27
F12	287.7	3.92	12.21	6.8	0.67	101.83

Inference: Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 6 - 8 kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of 5% of the tablet weight. Friability values were found to be less than 1% in all the formulations F7 – F12 were considered to be satisfactory ensuring that all the formulations are mechanically stable. The % drug content for all the formulations were close to 100 and varied between 95 to 105%.

Effervescent floating systems:

Table 6.5: In vitro floating buoyancy studies:

Formulation Code	Floating Lag Time (secs)	Total Floating Time (hrs)
F7	123	>10
F8	121	>10
F9	108	>12
F10	106	>10
F11	132	>11
F12	120	>12

Discussion: From the above floating buoyancy studies shows that F12 shows higher Total floating time than other formulations.

In vitro dissolution studies:

Table: Percent Drug Release of Epleronone (IR) Tablets for all formulations (F1-F6)

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	33.49	37.26	42.59	26.54	29.67	33.15
10	41.19	44.02	50.53	33.16	36.82	39.92
15	45.62	48.32	55.36	37.47	41.91	44.78
20	50.32	53.05	60.12	41.28	46.73	50.02
30	59.51	61.89	70.43	49.46	56.19	59.92
40	68.86	71.12	80.28	57.35	66.23	70.62
50	78.31	80.79	90.15	65.91	75.42	81.12
60	87.94	91.47	99.92	74.61	84.69	92.84

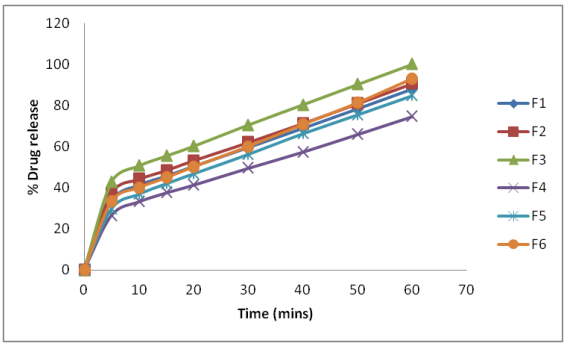


Figure: Percent Drug Release versus Time Plots of Epleronone Tablets F1-F6

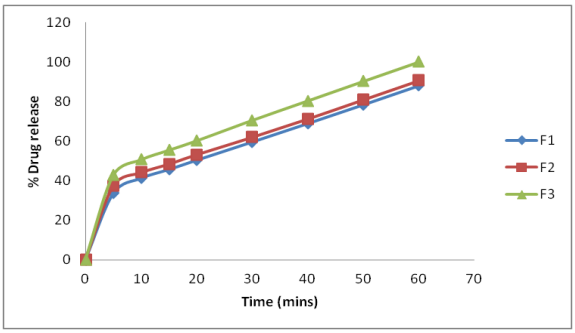


Figure: Percent Drug Release versus Time Plots of Epleronone Tablets for F1-F3

Discussion: F1 shows maximum drug release at the end of 60mins i.e., 87.94 %. While F2 shows 91.47% of drug release at the end of 60mins. Whereas F3 shows 99.92% of drug release at the end of 60mins. By observing the dissolution profiles of F1-F3 increase in the superdisintegrant concentration shows decrease in the drug release time.

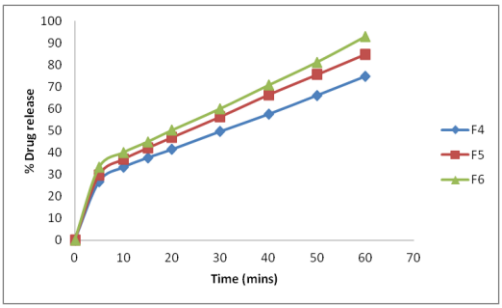


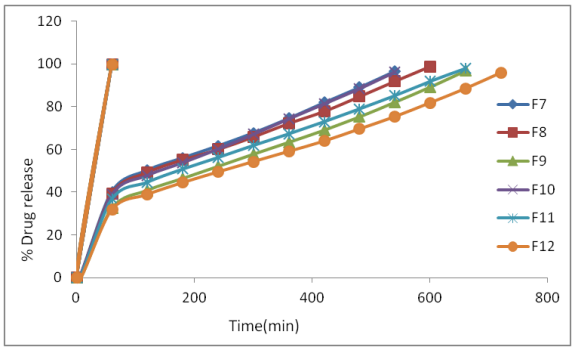
Figure: Percent Drug Release versus Time Plots of Epleronone Tablets for F4-F6

Discussion: F4 shows maximum drug release at the end of 60mins i.e., 74.61%. While formulation F5 shows 84.69% of drug release at the end of 60mins. While formulation F6 shows 92.84% of drug release at the end of 60mins.Above dissolution studies indicate that all the formulations F3 formulation containing higher concentration of CCS as the disintegrant had showed faster drug release in 60mins. So F3 formualtion is considered as optimized formulation.

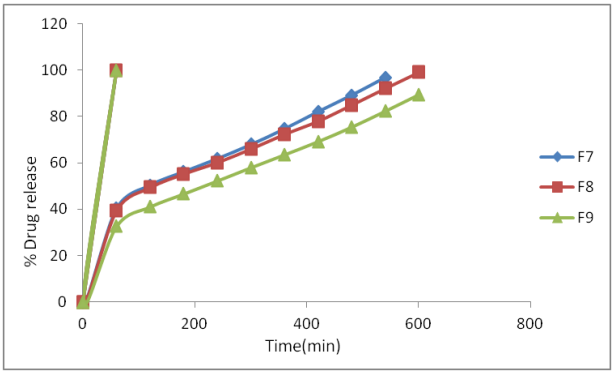
Table : Dissolution profile for Bilayer tablets of all formulations (F7-F12)

Time (MINS)	F7	F8	F9	F10	F11	F12
I.R. Layer						
0	0	0	0	0	0	0
60	99.92	99.92	99.92	99.92	99.92	99.92

S.R. Layer						
0	0	0	0	0	0	0
60	40.25	39.42	32.54	38.87	36.86	31.85
120	50.33	49.32	40.96	47.92	44.78	38.96
180	56.12	55.21	46.53	53.89	50.92	44.53
240	61.75	60.12	52.16	60.23	56.35	49.53
300	67.83	65.96	57.87	67.18	62.02	54.37
360	74.61	72.29	63.45	74.38	67.43	59.16
420	82.02	77.92	69.12	81.41	73.12	63.99
480	89.12	84.88	75.36	88.54	79.13	69.65
540	96.73	92.02	82.23	96.32	85.35	75.42
600		98.96	89.36		92.04	81.95
660			96.95		98.12	88.62
720						96.01

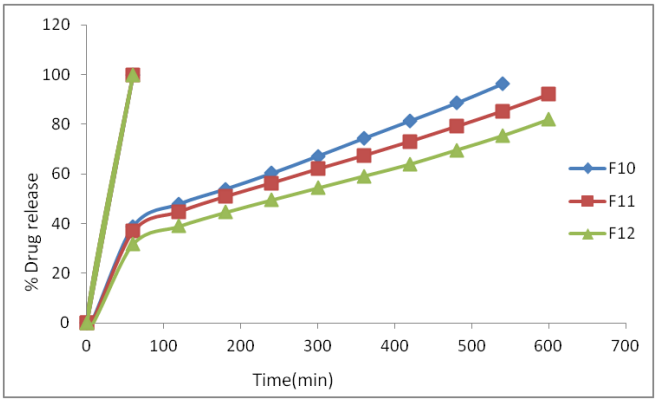


In-vitro drug release profile of Bilayer tablets of Formulation F7-F12.



In-vitro drug release profile of Bilayer tablets of Formulation F7-F9.

From the in vitro dissolution studies of formulaions F7-F9 formulated by using Ethyl cellulose in three different ratios. The F7 formulation containing Ethyl cellulose (30mg) shows 96.73% of drug release at the end of 540mins. While in F8 formulation containing Ethyl cellulose (60mg) shows 98.96 % of drug release at the end of 600mins. While in F9 formulation containing Ethyl cellulose (90mg) shows 96.95% of drug release at the end of 660mins.



In-vitro drug release profile of Floating bilayer tablets of Formulation F10 - F12.

The F10 formulation containing Guar gum (30mg) shows 96.32% of drug release at the end of 540mins. whereas the F11 formulation containing Guar gum (60mg) shows 98.12% of drug release at the end of 660mins. whereas the F12 formulation containing Guar gum (90mg) shows 96.01% of drug release at the end of 720mins. By comparing the in vitro dissolution studies of two polymers like Ethyl cellulose and Guar gum, it was observed that the controlled drug delivery was obtained with the higher concentration of Guar gum in F12 formulation than the remaining formualtion. So the drug release kinetics were performed for the formulation F12 formulation, as it maintains constant drug release in a sustained manner with optimum swelling and gel forming nature.

Drug Release Kinetics of Epleronone Bilayer Tablets: (F12)
Zero order release kinetics

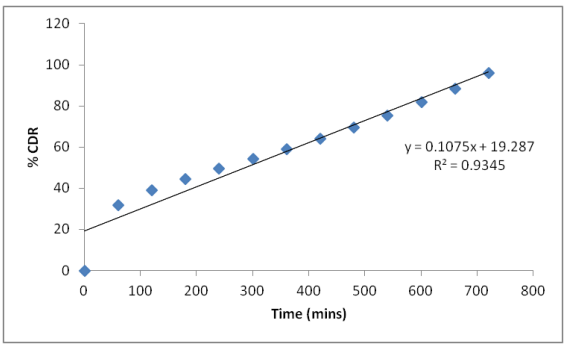


Fig: Zero order release profile of bilayer tablets of Epleronone best formulation F12
First order release kinetics data of FBT of Epleronone best formulation F12

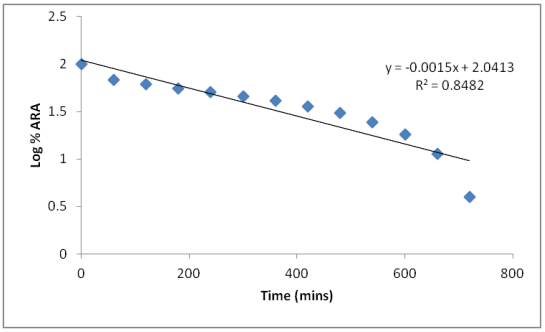


Fig: First order release profile of bilayer tablets of Epleronone best formulation F12

Higuchi Release Kinetics Data of Bilayer Tablets of Epleronone Best Formulation F12

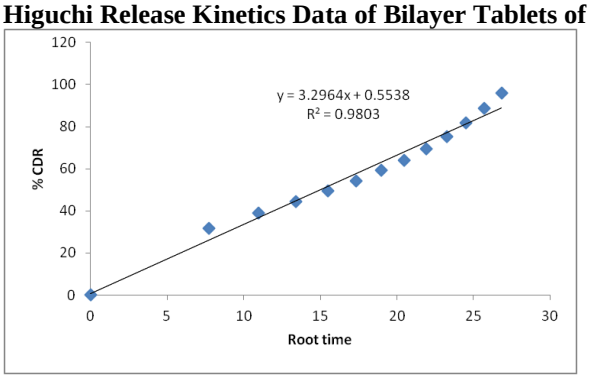


Fig:. Higuchi release kinetics profile of bilayer tablets of Epleronone best formulation F12

Peppas Release Kinetics Data of Bilayer Tablets Of Epleronone Best Formulation F12

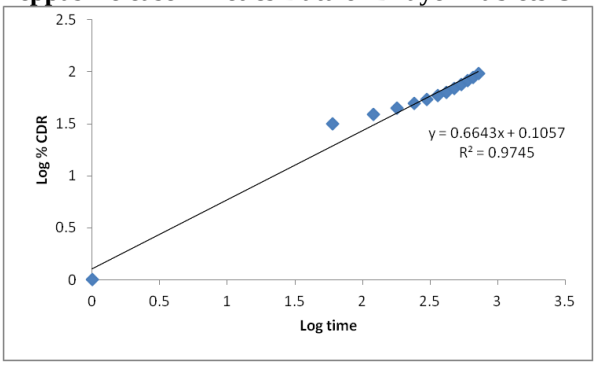


Fig: Peppas release kinetics profile of bilayer tablets of Epleronone best formulation F12

CONCLUSION

The study involves preformulation studies, formulation, evaluation and stability studies of prepared matrix tablets. The physical evaluation of API along with excipients has shown compatibility supporting the choice of excipients. FTIR studies reveal no incompatibility between drug, polymer and various excipients used in the formulations.

CRDDS of a model drug were formulated and evaluated with different polymers. Formulations with higher concentration of GUAR GUM polymers has successfully releases the model drug release upto 12hours and they were formulated by using direct compression. Immediate release tablets of a model drug were formulated and evaluated with different polymers. Formulations with CCS polymers has successfully releases the model drug release within time and they were formulated by using direct compression. The dissolution profiles and kinetic studies (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) indicate that the release of Epleronone follows zero order release and with non-fickian diffusion mechanism.

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