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Formulation and evaluation of floating bilayer tablet of clopidogrel bisulfate

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ABSTRACT

Floating bilayer tablet of clopidogrel bisulfate contained two layers, one was immediate release and other was sustained release layer. First immediate release layer quickly released drug with attained quick onset of action and the other layer floated on gastric fluid and released the drug in sustained manner. The optimum batch F7 showed 19 hrs of floating time, 94.25 % of CDR up to 12 hrs. While for immediate release the optimized batch F2 showed 93.55 % of drug content, 92.25 % of CDR at 60 min. So, bilayer floating tablet of clopidogrel bisulfate with all desired attributes were prepared and evaluated. Bilayer floating tablet of clopidogrel bisulfate was prepared successfully by direct compression method. Pre-compression evaluations of powder blend of both layers were performed for tapped density, bulk density, Hauser ratio and Compressibility Index with all tests showed satisfactory results.

Keywords: Bilayer floating tablet, immediate release, sustained release, Clopidogrel Bisulfate.

INTRODUCTION

Drug delivery system has an aim to provide long as well as non-toxic drug delivery system. Now a days various drug delivery systems are available [1, 2]. Solid oral dosage forms are most stable through which tablets are most commonly used dosage forms. Oral drug delivery system is most widely used route of administration among all routes that have been explored for systemic delivery of drug via pharmaceutical products of different formulations. Floating Drug delivery System have bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolong period of time, without affecting the gastric emptying rate [3]. Floating systems can be classified into two distinct categories, non-effervescent and effervescent system. During the development process the formulation under goes the Preformulation studies, formulating the Formulation, optimizing the formulation, and comparing the in vitro dissolution profile of final formulation [4, 5].

MATERIALS AND METHODS

Materials

Clopidogrel bisulfate powder drug was gifted by Artii chemicals, Mumbai and Aerosil, HPMC K4M, Sodium bicarbonate, Magnesium stearate, Talc, Sodium starch glycolate, Crosscarmellose sodium, Dicalcium phosphate, Micro crystalline cellulose, Polyvinyl povidone, Ethyl cellulose all were used of laboratory grade.

Methods

Formulation of Floating Bilayer Tablets

Bilayer tablet containing two layers i.e. immediate release layer and sustained release layer both of Clopidogrel Bisulfate with accurately weighted 100 mg of immediate release layer and 400 mg of floating sustained release layer individually taken. Various batches of bilayer tablets were prepared using direct compression method as per table 1.

Table No.1 Composition of Bilayer Floating Tablet (500 mg)

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Immediate Release layer (100 mg)									
Clopidogrel bisulfate	75	75	75	75	75	75	75	75	75
Sodium starch glycolate	2	5	8	2	5	8	2	5	8
Crosscarmellose sodium	0.5	0.5	0.5	2.75	2.75	2.75	5	5	5
Dicalcium phosphate	19.5	16	13	17	14	11	15	12	9
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Arosil	1	1	1	1	1	1	1	1	1
Floating sustained release layer (400 mg)									
Clopidogrel bisulfate	225	225	225	225	225	225	225	225	225
Sodium bicarbonate	10	10	10	12	12	12	14	14	14
HPMC K4M	40	60	80	40	60	80	40	60	80
MCC	64	44	24	62	62	22	60	40	20
Talc	6	6	6	6	6	6	6	6	6
PVP	20	20	20	20	20	20	20	20	20
Ethyl cellulose	35	35	35	35	35	35	35	35	35

Methods:

A. Pre compression characteristics[7]

Bulk density & Tapped density

$$\text{Bulk density } (\rho_0) = \frac{M}{V_0}$$

$$\text{Tapped density } (\rho_0) = \frac{M}{V_t}$$

Compressibility index & Hausner ratio

$$\text{Compressibility Index} = \frac{\text{Tapped} - \text{Bulk}}{\text{Tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{Bulk}}{\text{Tapped}}$$

Post compression evaluation

Post compression evaluation includes measurement of Thickness, Hardness, and Disintegration time (DT) and dissolution test of prepared formulations.

Hardness test

Tablet units were selected at random and were individually tested for hardness by using Monsanto Hardness Tester.

In-vitro Disintegration Time

Disintegration time for immediate release was determined using USP disintegration apparatus with distilled water. The volume of medium was 900 ml and temperature was 37± 0.2°C. The time in minutes taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured. To comply the test all tablets should disintegrate within 15 minutes.

Drug Content

Units were selected at random and drug content was determined as specified in monograph. The tablet preparation complies with the test, only if each individual content lies between 85 to 115% of the average content.

Friability Test

As weight of tablet was less than 650 mg so tablets corresponding to 6.5 gm were taken for the test. All tablets were de-dusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated

about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

Determination of floating capacity:
Three individual tablets from each formulation were put in an individual flask containing 400ml of 0.1N HCL solutions. Then note time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated.

Swelling characteristics:
The swelling properties of matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml 0.1N HCl at 37 ± 0.5°C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation.

$$WU(\%) = \frac{\text{Weight of the swollen tablet - Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

In–Vitro Drug Release Studies:
The dissolution conditions used for studying the drug release from the floating-Bilayer tablet of the for both IR and SR. at wavelength 269 nm by UV-Visible spectrophotometrically all batches (F1-F9) and % CDR of all batches was obtained

RESULTS AND DISCUSSION

Evaluation of formulation

Table 2 . Preformulation characteristics of sustained release layer

Formulation Code	Bulk Density (gm/ml) ±SD	Tapped Density (gm/ml) ±SD	Hausner ratio ±SD	Compressibility Index (%) ±SD
F1	0.87±0.006	1.31±0.018	1.14±0.002	14.6±0.229
F2	0.84±0.003	1.28±0.008	1.15±0.004	14.3±0.969
F3	0.85±0.056	1.31±0.027	1.21±0.007	13.6±0.906
F4	0.88±0.003	1.38±0.002	1.24±0.029	13.2±0.017
F5	0.86±0.004	1.25±0.008	1.25±0.041	12.6±0.008
F6	0.83±0.006	1.30±0.027	1.21±0.026	12.1±0.399
F7	0.79±0.005	1.14±0.002	1.26±0.003	16.3±0.002
F8	0.84±0.008	1.27±0.015	1.20±0.049	15.2±0.176
F9	0.79±0.004	1.28±0.002	1.15±0.08	12.4±0.225

Evaluation of compressed clopidogrel bisulfate floating sustained release layer
The results of Hardness, Disintegration time, Drug content, Friability, Swelling index, Floating time all summarized in the table given below.

Table 3. Post compressed parameter of sustained release layer.

Batches	Hardness (Kg/cm^2± SD	Disintegration (min) ±SD	Drug content (%) ±SD	%Friability ±SD	Swelling index %	Floating Time (min)
F1	2.9±0.06	14.4	78.13±0.63	0.460±0.98	84.57	12.5
F2	2.84±0.08	14.5	77.46±0.71	0.440±0.04	82.22	12.2
F3	2.67±0.82	14.4	75.13±0.81	0.451±0.06	69.21	12.6
F4	2.8±0.04	14.5	76.35±0.82	0.554±0.01	85.29	17.2
F5	3.1±0.051	14.59	79.55±0.63	0.571±0.71	78.80	16.29
F6	2.6±0.012	14.2	70.41±0.94	0.557±0.82	76.47	16.16
F7	2.01±0.04	15.01	74.15±0.92	0.766±0.52	88.80	19.40
F8	2.04±0.08	14.04	60.13±0.97	0.750±0.61	57.85	16.55
F9	1.54±0.04	13.9	64.59±0.78	0.747±0.51	59.21	17.03

Evaluation of Pre -compressed parameters of immediate released layer tablet

Table 4. Pre-compressed characteristics of Immediate released layer tablet

Batches	Bulk Density (gm/ml) ±SD	Tapped Density (gm/ml) ±SD	Hausner Ratio±SD	Compressibility Index %±SD
F1	0.715±0.014	1.51±0.056	1.37±0.002	14.3±0.226
F2	0.813±0.017	1.52±0.064	1.36±0.004	14.5±0.46
F3	0.764±0.010	1.51±0.015	1.35±0.007	14.4±0.261
F4	0.648±0.024	1.49±0.024	1.35±0.029	14.2±0.127
F5	0.704±0.018	1.42±0.61	1.18±0.041	14.4±0.147
F6	0.674±0.028	1.24±0.512	1.09±0.026	14.3±0.265
F7	0.542±0.014	1.18±0.0215	1.19±0.038	14.2±0.268
F8	0.564±0.07	1.25±0.045	1.16±0.049	13.9±0.021
F9	0.571±0.014	1.31±0.81	1.16±0.048	13.2±0.265

Evaluation of compressed clopidogrel bisulfate immediate release layer tablet

Disintegration Time, Friability, Drug content, Hardness was performed on all batches (F1 toF9). The results of all were shown in Table.

Table 5. Post compressed characteristics of immediate release layer tablet

Batches	Disintegration Time ±SD	% Friability ±SD	%Drug Content ±SD	Hardness (Kg/cm^2)±SD
F1	2.59±0.26	0.91±0.99	89.67±0.6	2±0.052
F2	2.158±0.43	0.93±0.08	93.55±0.81	2.1±0.064
F3	2.31±0.50	0.90±0.04	91.46±0.68	2.1±0.84
F4	2.56±0.73	0.92±0.07	90.25±0.65	2±0.061
F5	2.21±0.42	0.89±0.76	88.33±0.92	2.2±0.045
F6	2.59±0.18	0.88±0.81	86.96±0.64	2.3±0.095
F7	2.01±0.34	0.82±0.51	85.10±0.48	2.4±0.061
F8	2.10±0.42	0.81±0.53	87.47±0.74	2.3±0.528
F9	3.01±0.76	0.84±0.64	87.69±0.69	2.5±0.624

(All experiment were carried out in triplicates n=3)

Evaluation of precompressed parameters of Floating Bilayer tablet

Table 6. Pre compressed Evaluation of optimized batch of floating bilayer Tablet

Sr. no.	Pre compression parameters	Values (F2+F7)
1	Bulk density(gm/ml)	12.3
2	Tapped density(gm/ml)	1.26
3	Hausner ratio	1.53
4	Compressibility Index	34.67

Evaluation of post compressed parameters of Floating Bilayer Tablet:

Disintegration Time, Friability, Drug content, Hardness, Swelling Index was performed on all batches (F1 toF9) and the results shown in tablebelow.

Table 7. Post compressed Evaluation of optimized batch of floating bilayer tablet

Sr. no.	Post compressed parameters	Values
1	Disintegration	14.09 (Min)
2	Friability	0.920(%)
3	Drug content	92.66(%)
4	Hardness	3.066(tons)
5	Swelling Index	86.50(%)
6	Floating time	13.45(Min)

In-vitro drug release Studies:

The dissolution studies were carried out for all nine formulations (i.e. F1 to F9) of sustained release layer which shown in the table below.

Sustained release layer:

Table 8. Percent cumulative drug release of different formulations (F1-F9) Sustained release layer (n=3)

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1.008	1.36	9.57	7.84	13.39	14.83	**7.63**	11.30	13.39
2	12.72	15.77	12.50	10.19	14.90	16.21	**18.04**	16.55	14.76
3	26.93	23.06	13.22	15.29	15.70	19.32	**28.51**	23.48	17.22
4	32.69	35.42	15.91	22.38	17.23	21.29	**37.98**	29.30	18.46
5	37.69	42.73	17.91	23.17	19.40	22.03	**42.77**	37.51	22.22
6	42.76	43.40	20.99	24.94	20.79	29.68	**51.27**	38.45	32.91
7	43.35	45.40	21.88	29.71	29.66	31.74	**54.27**	45.34	36.73
8	48.49	49.01	23.20	31.76	30.23	42.81	**62.86**	50.28	44.73
9	51.33	51.35	42.60	35.76	32.23	52.53	**73.72**	64.69	52.00
10	52.67	60.60	48.60	42.05	36.77	63.52	**81.75**	72.27	66.70
11	74.15	62.10	52.63	46.29	38.10	83.07	**91.01**	85.35	71.22
12	81.25	83.53	85.37	54.12	53.33	90.44	**94.91**	90.50	88.81

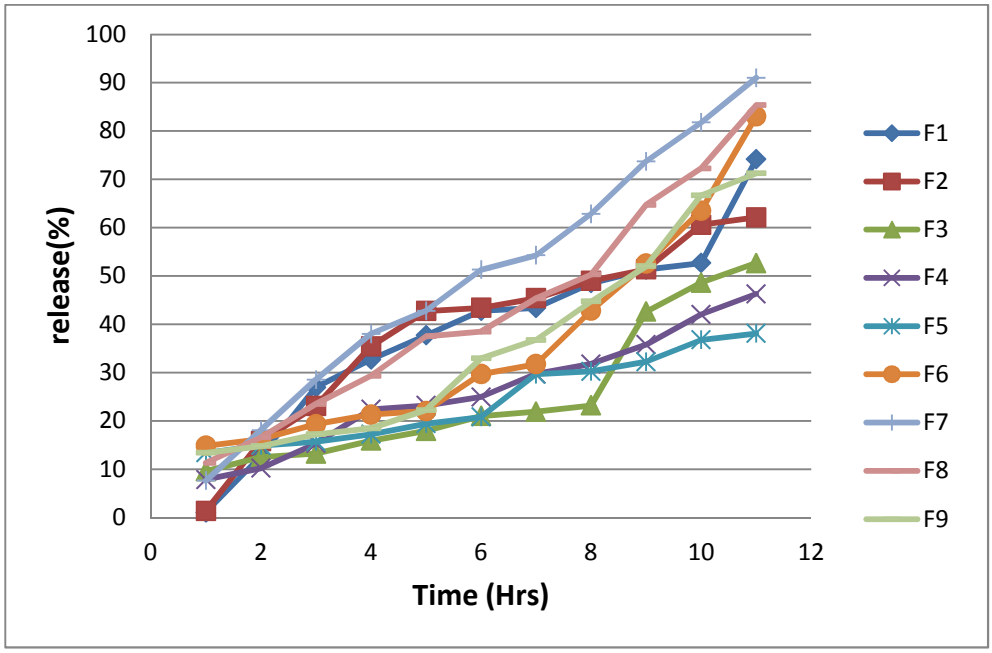

Figure 1: Drug Release Profile of all formulations F1-F9 (sustained release).

Immediate release layer:

Table 9. Percent cumulative drug release of different formulations (F1-F9) of Immediate released layer (n=3)

Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	4.56	**5.96**	5.01	3.84	4.14	3.18	3.44	3.68	3.84
10	7.22	**10.94**	9.94	8.42	8.27	10.20	10.32	10.36	7.94
15	16.82	**15.90**	13.94	11.82	14.27	14.27	17.58	12.27	12.78
20	26.69	**26.21**	25.81	25.55	18.62	17.90	33.75	27.94	16.19
25	33.67	**35.68**	29.81	36.68	26.34	21.55	36.28	35.41	21.76
30	36.84	**42.57**	33.49	42.58	31.208	34.55	43.58	42.60	26.36
35	51.08	**56.79**	46.30	56.59	50.71	42.50	56.12	52.26	30.50
40	55.28	**69.84**	53.58	62.22	57.81	47.02	67.50	55.26	46.87
45	67.49	**77.14**	58.42	66.86	61.93	55.44	70.04	61.06	52.98
50	76.22	**78.91**	68.41	76.55	65.93	66.31	74.19	68.55	61.27
55	80.35	**83.83**	79.23	81.66	77.01	82.99	77.35	73.67	73.58
60	88.79	**92.29**	90.17	89.19	87.66	85.06	84.83	85.74	86.42

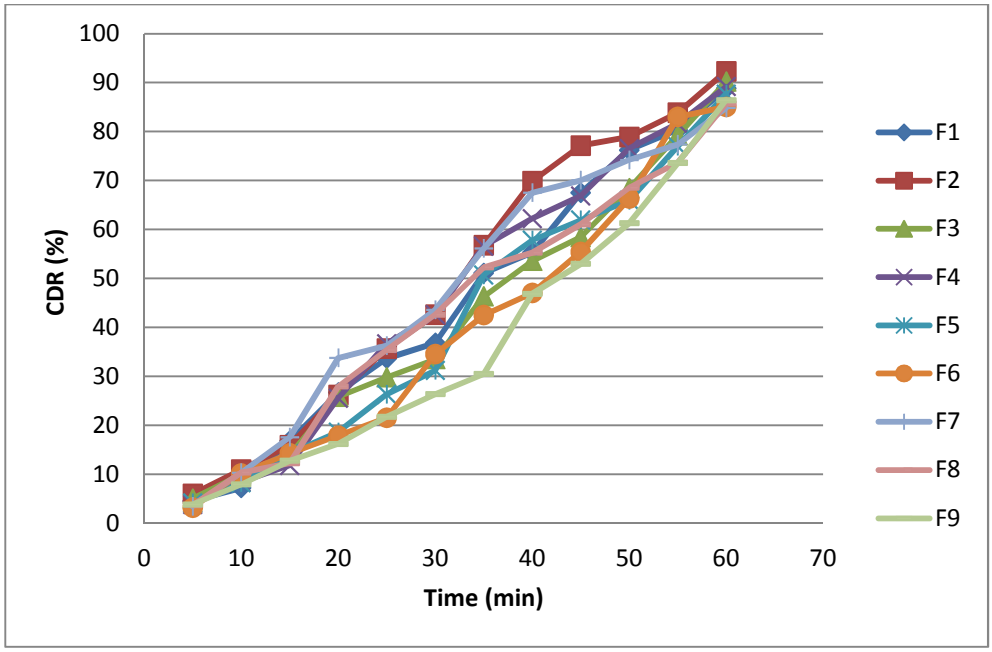

Figure 2: Drug release profile of F1-F9 formulations (immediate release layer)

Floating Bilayer Tablet

Table 10.Percent cumulative drug release of optimized Floating bilayer Tablet (F2+F7)

Time (Hrs.)	Drug release(%)
1	4.14
2	12.15
3	22.42
4	35.56
5	38.88
6	42.60
7	47.88
8	55.86
9	60.05
10	74.67
11	87.18
12	93.64

A. DATA ANALYSIS: (Immediate release layer)

In order to investigate the mode of release from bilayer floating tablet data were analyzed with following mathematical model.

A. Zero Order Kinetic

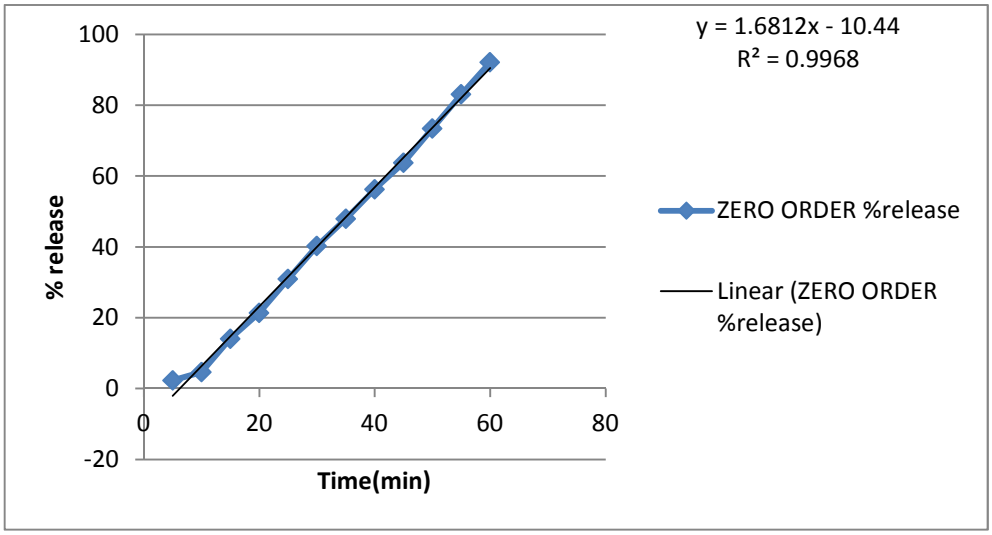

Figure 3: Zero order kinetics of F2 formulation.

B. First-order kinetic:

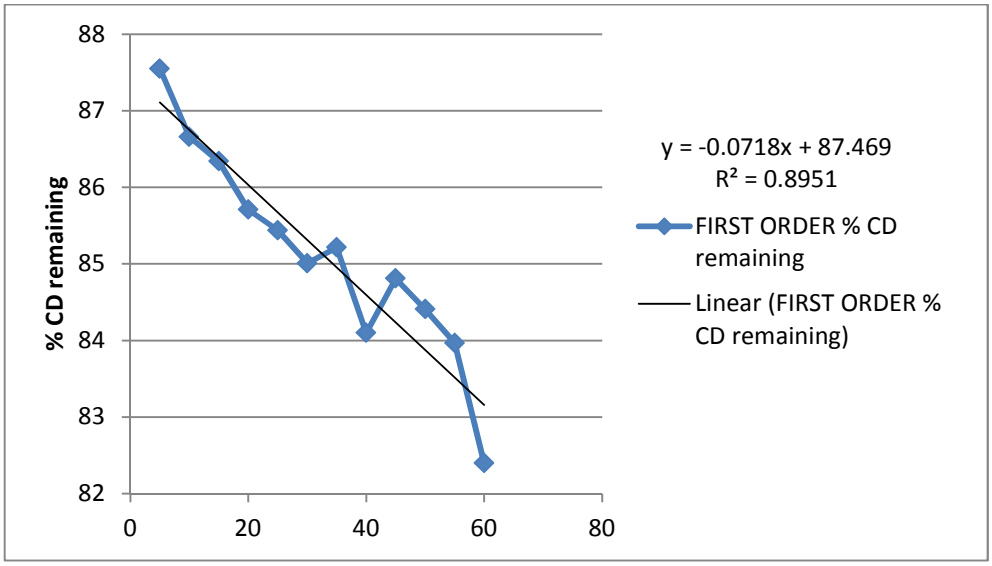

Figure 4: First order kinetics of formulation F2 batch

C. Higuchi equation

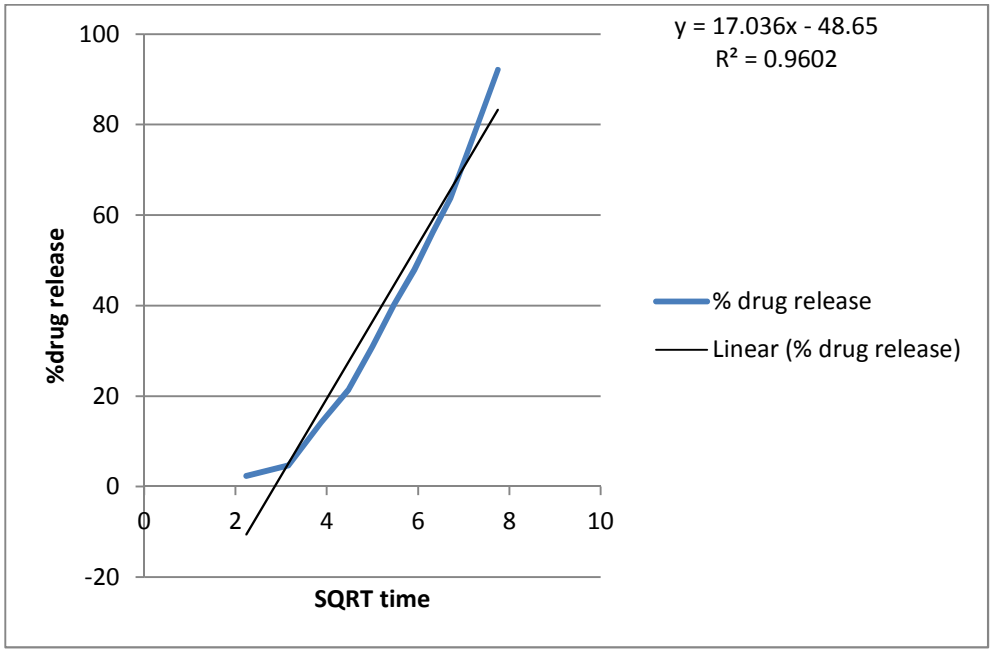

Figure 5: Higuchi model of F2 batch

D. Korsemayer-peppas equation

Table 11. Drug release kinetic for optimized batch

Sr. No.	Model Fitting	R^2 Values	N	K
1.	Zero order	0.9968	1.681	7.68

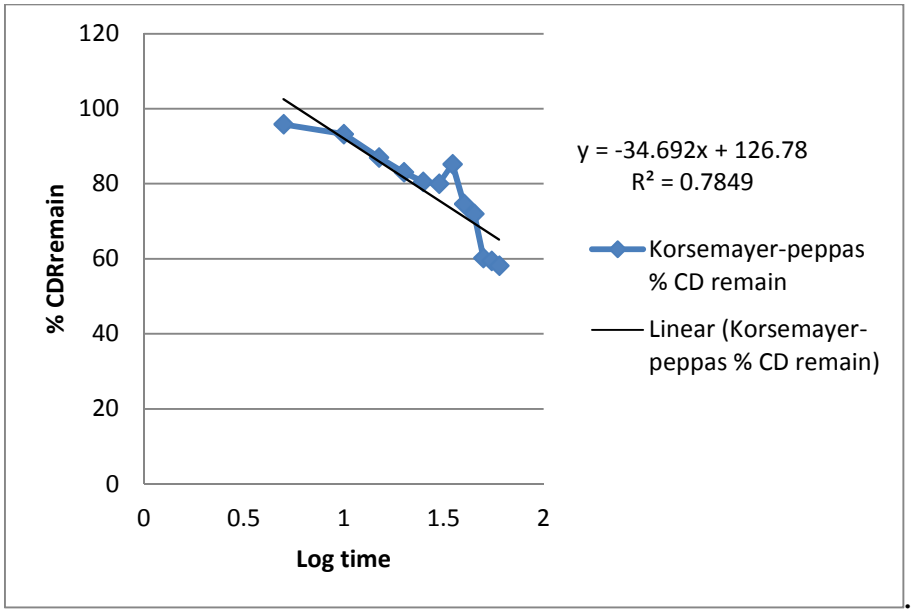

Figure 6: Korsemayer-peppas equation of F2

A. Zero-order Kinetics

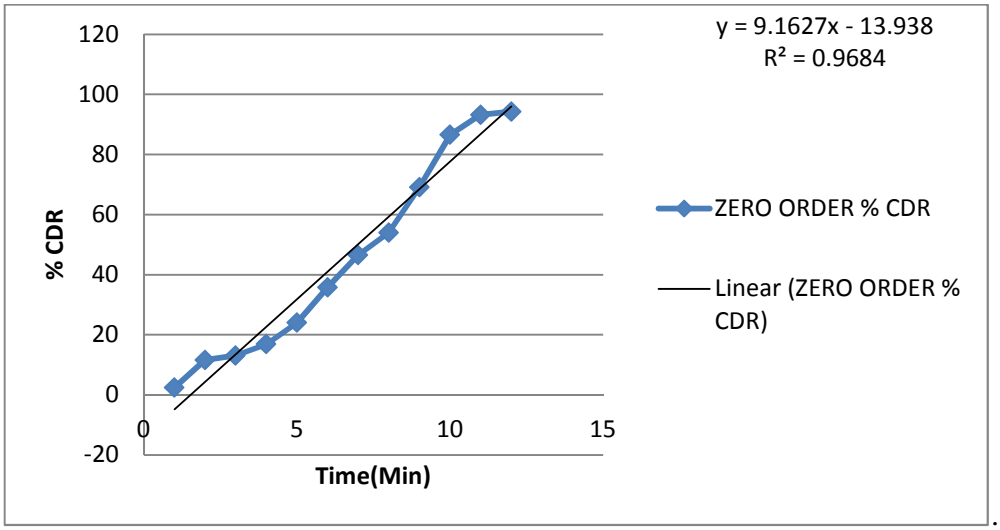

Figure 7: Zero Order kinetic of formulation F7 batch

B. First-order Kinetic

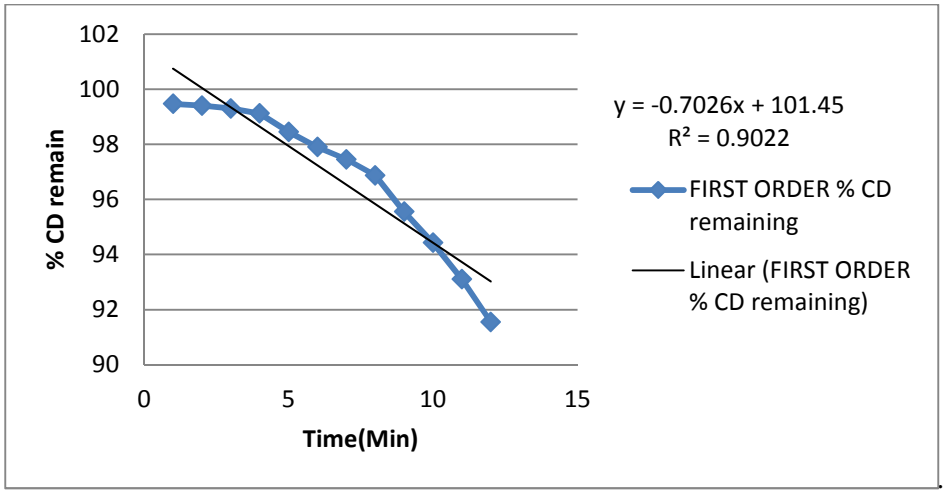

Figure 8: First order kinetic of formulation F7 batch.

B. DATA ANALYSIS

In order to investigate the mode of release from bilayer floating tablet (sustain release) data were analyzed with following mathematical model.

C. Higuchi equation:

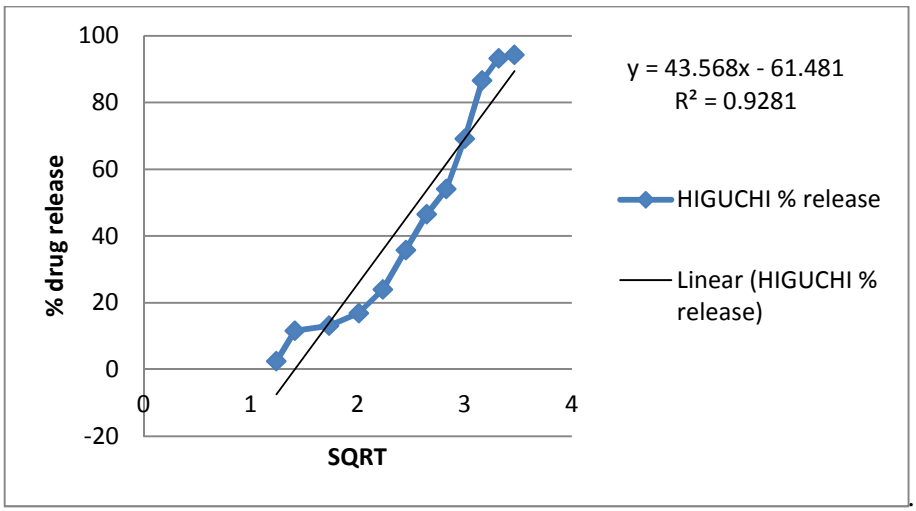

Figure 9: Higuchi model of formulation F7 batch

D. Korsemayer-peppas equation

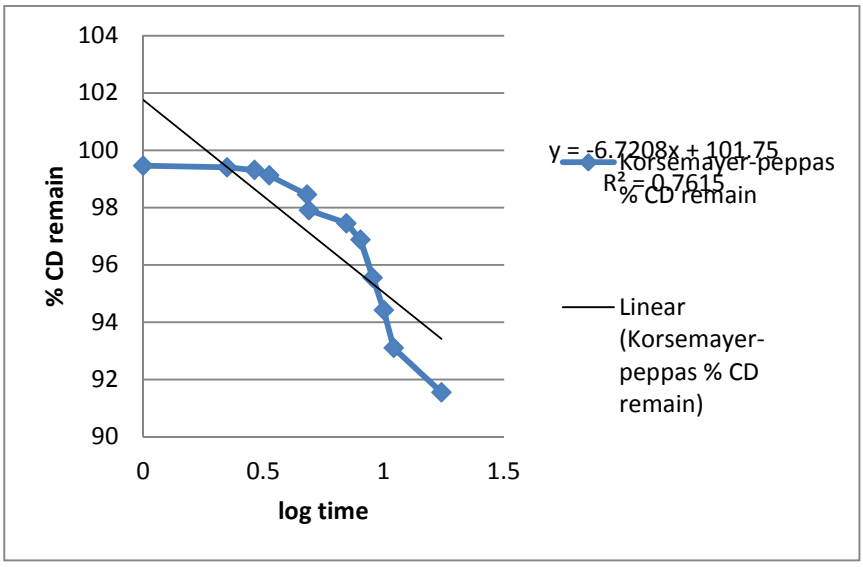

Figure 10: Korsemayer-peppas equation of formulation F7 batch

STABILITY STUDIES:

The samples were withdrawn after 1, 3 and 6 months and subjected to following tests as shown in table below.

Table 12. Result of stability study

Test	Before	After		
	0 month	1 month	3 months	6 months
Drug content	92.66	91.60	91.20	91.58
Drug release	93.64	93.40	93.61	93.50

The accelerated stability studies (carried for 06 months), at temperature of 40^0 C ± 2^0C and % RH 75% ± 5% RH indicated that the developed floating bilayer tablet was unaffected after 03 months storage under accelerated condition as no change was observed in the Drug content, Drug release sign of distinguishable change was observed in the appearance, texture and colour of the formulation. The data of drug content before the study and after the

study shown the change but within limit. On the basis of these results, it may be concluded that the optimized formulation developed is stable under accelerated condition of 06 months.

CONCLUSION

Bilayer floating tablet of clopidogrel bisulfate was prepared successfully by direct compression method. Precompression evaluations of powder blend of both layers were performed for tapped density, bulk density, Hauser's ratio and Compressibility Index. All tests showed satisfactory results. Trial batches were prepared and evaluated to screen Excipients and concentration range of Sodium bicarbonate.Optimization was performed by 3^2 full factorial design where independent variables were concentration of HPMC K4M (X1) and sodium bicarbonate (X2) and dependent variables were Floating Time (Y1), %CDR at (Y2) Based on desirability of dependent variable, batches F4, F5 and F7 were found to be in desirable range, where optimization was performed by design expert. Among F4, F5 and F7 was having most desirable attribute. It was considered as optimum batch. F7 showed 19.29 hrs of floating time, 94.25 % of CDR at 12 hr. So, bilayer floating tablet of Clopidogrel Bisulfate with all desired attributes were prepared and evaluated. Optimization was performed by 3^2 full factorial design where independent variables were concentration of Sodium Starch Glycolate (X1) and Crosscarmellose (X2) and dependent variables were drug content (Y1), %CDR at (Y2) Based on desirability of dependent variable, batches F2, F3 and F4 were found to be in desirable range, where optimization was performed by design expert. Among F2, F3 and F4 was having most desirable attribute. It was considered as optimum batch. F2 showed 93.55 % of drug content, 92.25 % of CDR at 60 minutes. So, bilayer floating tablet of Clopidogrel Bisulfate with all desired attributes were prepared and evaluated.

REFERENCES

[1] Chandira MR, Palanisamy P, Jayakar B. *International Research Journal of Pharmacy*, **2012**; 3(2):257-266.
[2] Charyulu NR, Patil AB, Deepika CH. *Nitte University Journal of Health Science*, **2011**; 9: 38-45.
[3] Pimple S, Maurya P, Joshi A,*World Journal of Pharmacy and Pharmaceutical Sciences*, **2014**; 3(8): 2007-2019.
[4] Rahman Z, Ali M, Khar RK. *Acta Pharm*, **2006**; 56:49-57.
[5] Sravani SK, Kumar AM, Garigeyi PM. *International Journal of Pharmaceutical, Chemical and Biological Sciences*, **2012**;2(1): 38-55.
[6] Solanki PD. *International Journal for Pharmaceutical Research Scholars*, **2012**; 1: 123-134.
[7] Kaur P, Dhiman S, Arora S. *International Journal of Pharmaceutical Sciences Review and Research***, 2013**; 19(1): 112-122.
[8] Parsekar SD, Prabhu S, Shetty A, Azharuddin M, Shabaraya AR. *International Journal of Pharmaceutical and Chemical Sciences*, **2014**; 3(2): 420-430.