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Original Article

Formulation and evaluation of bilayer floating tablets of amlodipine besylate and metoprolol succinate

M. Sravanthi*, Dr. K. Abbulu and Aastha Saxena
Department of Pharmaceutics Sciences, Malla Reddy Institute of Pharmaceutical Sciences, Dhulapally, Secunderabad, AP, India

Abstract

In the present study an attempt was made to prepare bilayer floating tablets of Amlodipine Besylate and Metoprolol Succinate floating sustained release layer, which remains in stomach for prolonged period of time in a view to maximize bioavailability of drug, by using various concentrations of polymers, fifteen formulations of Metoprolol having polymers at different concentration levels were prepared of which three formulations F8, F10, F13 showed excellent drug release profiles so these formulations were selected for the preparation of bilayer floating tablets. Amlodipine Besylate layer (immediate release) A1 was prepared by using sodium starch glycolate as super disintegrant, which showed excellent drug release so the composition of immediate release layer is kept constant in all formulations. Best formulations from both the layers were selected and formulated as bilayer tablets i.e (A1+F8), (A1+F10), (A1+F13) and these formulations showed excellent post compression & invitro drug release, hence all the three formulations were selected as optimized formulations.

Keywords: Benecel K200M, Amlodipine Besylate, Metoprolol Succinate, HPMC K100M, HPMC K4M.

***Corresponding Author: M. Sravanthi,** Department of Pharmaceutics Sciences, Malla Reddy Institute of Pharmaceutical Sciences, Dhulapally, Secunderabad. E mail address: sravanthireddy009@gmail.com

1. Introduction

The oral route is the most promising and convenient route of drug administration. Conventional immediate release system achieves as well as maintains the drug concentration within the therapeutically effective range, but one has to take such formulations several times a day. This results in significant fluctuations in plasma drug levels and also the frequency of administration leads to patient non-compliance. Recently, several technical advancements in the pharmaceutical field have led to the development of many novel drug delivery systems that could revolutionize the method of medication and provide a number of therapeutic benefits. [1]

In the present study Amlodipine Besylate which is a calcium channel blocker is combined with beta blocker Metoprolol Succinate to produce the desired effect. Metoprolol Succinate can prevent the potential reflex tachycardia caused by Amlodipine Besylate. Amlodipine Besylate can counteract decrease in cardiac output caused by Metoprolol succinate. Thus both Metoprolol

Succinate and Amlodipine Besylate have different complimentary mechanisms of actions resulting in synergistic anti-hypertensive activity.
However, there are reports of bilayer tablets for the selected combination of drugs but not bilayer floating tablets. Hence the present study was selected.
The objective of the study is to design and evaluate bilayer floating tablets of Amlodipine and Metoprolol using polymers such as HPMC K4M, Benecel K200M, Carbopol 934p, Sodium alginate, Xanthan gum.

2. Material and Method

Amlodipine besylate & Metoprolol succinate was procured as a gift sample from Pharma Train, Kukatpally, Andhra Pradesh; HPMC K100M,Benecel K200M , Xanthan gum, Sodium alginate HPMC K4M and Magnessium stearate were also provided by Pharma Train .The other chemicals used were purchased from Merck chemical. All other chemicals used in our work were of analytical grade.

Method

Formulation of bilayer floating tablets [2,3,4]

Bilayer floating tablets were prepared by taking best formulations from both the individual layers i.e A1 (Amlodipine) & F8, F10, F13 formulations of (Metoprolol Succinate). Metoprolol blend was first introduced into the die cavity, a slight compression was made and then Amlodipine Besylate blend was introduced into the die cavity followed by final compression with optimum hardness to form the bi layer tablets. Here compression was made by using tablet compression machine (Cadmach, India) with 10mm punches.
In total, three formulations containing different combination of polymers were prepared.

Evaluation of Granules [5]

Angle of repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where h and r are the height and radius of the powder cone respectively.

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated by using the following formulas.
LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] /TBD X 100

Evaluation of the Compressed Tablets [6]

Tablets were evaluated for post compression parameters like hardness, weight variation, friability, drug content uniformity etc. The data was presented in (Table 4)

Weight Variation

Weight variation was studied by taking 20 tablets of each formulation, they were weighed on an electronic balance (Shimadzu, AUX 220, Japan), and the test was carried according to the Indian Pharmacopoeia

Hardness and Friability

The hardness and friability were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the friability testing apparatus (Campbell Electronics, Mumbai, India.), respectively.

Determination of Drug Content for Amlodipine & Metoprolol

The drug content was carried out by weighing 10 tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to 5 mg Amlodipine or Metoprolol and dissolved in 100 ml volumetric flask

containing 50 ml of 0.1N HCl and volume was made to 100 ml with solvent. The volumetric flask was shaken using sonicator for 1 hr and after suitable dilution with 0.1N HCl, the drug content was determined using UV-Visible Spectrophotometer at 241, 224nm.

In-vitro Dissolution Studies of Bilayer Floating Tablets [7, 8]

The dissolution study of bilayer tablets was performed over a 12 hr period using USP type II (paddle) Dissolution Testing Apparatus (Electrolab) 900ml of 0.1N Hcl was used as dissolution medium agitated at 50 RPM, at temperature of 37O± 0.5OC. 5 ml samples were withdrawn at 5, 10, 15, 30, 45 and 60 min for 1 hr to estimate the release of Amlodipine, and at 1, 2, 4, 6, 8, 10 and 12 hrs for estimating Metoprolol release. The samples were analyzed for Metoprolol and Amlodipine by UV Spectrophotometry at their respective λ max values 224 nm and 241 nm. The samples collected for first hour were analyzed for Amlodipine content at 241 nm in UV spectrophotometer by keeping the solution containing Metoprolol succinate formulation as blank to minimize the interference. The samples collected for 1 – 12 hrs were analyzed for the release of Metoprolol succinate at 224 nm in UV spectrophotometer by keeping the solution containing Amlodipine formulation as blank to minimize the interference.

3. Results and Discussion

Data of Metoprolol Succinate:

- The prepared tablets were evaluated for Weight variation, Hardness, Friability, Thickness, Floating behavior, drug content
- Thickness was found to be in the range of 2.8 to 3.0 mm.
- Hardness of the tablets was in the range of 6.2 ± 0.2 to 6.6 ± 0.2 kg/cm2 which was sufficient for the handling of tablets throughout the shelf life.
- Percentage % friability was between 0.38 – 0.69 % and complies with pharmacopoeial limit of less than 1%.
- Weight variation was less than less than ±7.5% which is a pharmacopoeial limit.

In vitro drug release of Amlodipine besylate tablets:

- The % drug release of sodium starch glycolate (15mg) in formulation A1 was found to be 100.05 ± 1.1 for 45 min.

In Vitro drug release of Metoprolol succinate tablets:

- Formulations F1 – F3 Benecel K200M, as the concentration of Benecel K200M increases % drug release decreased.
- Further the trials were done by taking Carbopol 934p ,Formulations F4, F5, F6 having 50mg, 100, and 200 mg of Carbopol 934p respectively shows more % drug release than same concentrations of Benecel K200M.
- Further in formulations F7, F8 to F9 Sodium alginate (50, 100, 200 mg) In the formulation F8 with the concentration of polymer 100mg showed better release by releasing 98.58% at the end of 12 hrs. In the F9 formulation with the concentration of polymer 200mg the percentage drug release is only 67.56%.
- In formulations F10, F11 to F12 Xanthan gum (50, 100, 200 mg) was used as rate retarding polymer in combination with HPMC K100M (40mg)
- In formulations F13, F14 to F15 HPMC K4M (50, 100, 200 mg) was used as rate retarding polymer in combination with HPMC K100M (40mg) as the concentration of HPMC K4M increases % drug release decreased.
- Hence, F8, F10, F13 were selected as the best formulation for formulation of bilayer floating tablets.
- In vitro dissolution studies of bilayer floating tablets
- Dissolution profile of bilayer tablets was reported in (Table 7) Dissolution was performed in 0.1 N HCl for 12 hrs and % drug release was calculated by UV– spectroscopic method, Amlodipine Besylate release occurred initially for 45 min by giving 100.02 ± 1.24,100.12 ± 1.1.99.96 ± 1.13 % drug release.
- Here, drug release was calculated by measuring absorbance by keeping Metoprolol formulation as blank. Metoprolol drug release was measured up to 12 hrs from first hour by keeping Amlodipine formulation as a blank. Metoprolol gave 98.23 ± 1.24, 98.56 ± 1.21, 98.37 ± 1.11 % drug release at the end of 12 hrs.

Table1: Formulation of amlodipine besylate tablets

Ingredients	A1 (mg) Quantity per Tablet	A1 (mg) Quantity per 100 Tablets
Amlodipine Besylate	5	500
Sodium starch glycolate	15	1500
Micro crystalline cellulose (pH-102)	30	3000
Magnesium stearate	3	300
Iron oxide	1	100
Total weight	54	5400

Table 2: Formulation of metoprolol succinate tablets

	Quantity Per One Tablet														
Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)
Metoprolol Succinate	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75
Benecel K200M	50	100	200	_	_	_	_	_	_	_	_	_	_	_	_
Carbopol 934P	_	_	_	50	100	200	_	_	_	_	_	_	_	_	_
Sodium alginate	_	_	_	_	_	_	50	100	200	_	_	_	_	_	_
Xanthan gum	_	_	_	_	_	_	_	_	_	50	100	200	_	_	_
HPMC K4M	_	_	_	_	_	_	_	_	_	_	_	_	50	100	200
Sodium bicarbonate	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K100M	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Magnesium 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	2.25	2.25	2.25
Micro crystalline cellulose (pH102)	150	100	_	150	100	_	150	100	_	150	100	_	150	100	_
Total weight	286	286	286	286	286	286	286	286	286	286	286	286	286	286	286

Table 3: Precompression Parameters of Metoprolol and Amlodipine Formulations

Formulation Code	Angle of Repose(θ) Degrees ±S.D	Bulk Density (g/cc)±S.D	Tapped Density(g/cc)±SD	Hausner's Ratio±S.D	Carr's Index(%)±S.D
A	25.16±0.11	0.472±0.012	0.564±0.026	1.19±0.17	16.3±0.14
A1	27.18±0.15	0.456±0.013	0.567±0.025	1.24±0.21	19.5±0.12
M	26.18±0.11	0.453±0.012	0.523±0.022	1.15±0.18	13.38±0.11
F1	29.17±0.18	0.448±0.016	0.538±0.026	1.20±0.23	16.72±0.18
F2	28.9±0.12	0.46±0.02	0.56±0.0212	1.21±0.24	17.85±0.12
F3	30.01±0.14	0.46±0.01	0.58±0.02	1.23±0.19	20.69±0.14
F4	28.18±0.12	0.445±0.03	0.565±0.02	1.22±0.16	21.2±0.12
F5	28.69±0.13	0.45±0.01	0.55±0.023	1.22±0.19	18.18±0.13
F6	28.41±0.13	0.45±0.01	0.58±0.025	1.24±0.18	22.4±0.13
F7	28.53±0.16	0.455±0.02	0.567±0.026	1.24±0.18	19.75±0.16
F8	27.96±0.15	0.464±0.012	0.53±0.027	1.14±0.18	17.4± 0.15
F9	29.17±0.13	0.472±0.011	0.55±0.028	1.16±0.23	14.18±0.13
F10	30.01±0.14	0.46±0.011	0.59±0.029	1.24±0.24	22.03±0.14
F11	28.18±0.17	0.476±0.02	0.567±0.024	1.19±0.19	16.04±0.17
F12	28.69±0.13	0.48±0.01	0.599±0.026	1.24±0.16	19.86±0.13
F13	28.41`±0.14	0.465±0.013	0.569±0.028	1.22±0.19	18.27±0.14
F14	28.53±0.16	0.457±0.011	0.587±0.022	1.24±0.18	22.1±0.16
F15	27.96±0.15	0.466±0.011	0.586±0.023	1.23±0.18	20.47±0.15

A=Amlodipine Besylate (Pure drug), A1= (Amlodipine Besylate Formulation), M= Metoprolol Succinate (Pure drug), F1-F15(Metoprolol Succinate Formulations)(n=3,± S.D) (S.D= Standard deviation)

Table 4: Results of Post Compression Parameters of Compressed Tablets

Formulation Code	% Deviation (n=20)	Hardness(kg/cm^2) (n=3)	Thickness(mm) (n=3)	Friability (n=20)	Drug Content (%)
A1	1.56 ±0.26	3.3±0.2	1.1±0.07	0.6	99.21±0.7
F1	0.01 ±1.64	6.3±0.3	2.8±0.05	0.56	99.03±0.31
F2	0.6 ±1.50	6.5±0.2	2.7±0.07	0.49	99.86±0.70
F3	0.04 ±1.43	6.4±0.2	2.8±0.011	0.63	99.27±0.66
F4	0.2 ±2.71	6.2±0.3	2.9±0.10	0.54	100.61±0.73
F5	2.9 ±1.61	6.3±0.4	3.0±0.08	0.56	98.83±0.41
F6	0.3 ±1.86	6.6±0.2	2.8±0.07	0.38	100.83±0.78
F7	0.01 ±1.47	6.5±0.3	2.9±0.13	0.54	98.94±0.42
F8	0.29 ±1.69	6.2±0.4	2.8±0.09	0.69	100.83±0.66
F9	1.00 ±1.82	6.4±0.3	3.0±0.06	0.53	97.56±0.78
F10	0.26 ±1.77	6.1±0.4	2.8±0.08	0.46	99.63±0.62
F11	0.02 ±1.59	6.3±0.3	2.8±0.06	0.41	99.27±0.73
F12	2.45 ±1.73	6.5±0.4	2.9±0.09	0.59	99.83±0.41
F13	0.05 ±1.63	6.2±0.2	2.8±0.08	0.43	98.94±0.42
F14	0.74 ±1.73	6.3±0.3	2.8±0.12	0.57	99.57±0.7
F15	0.01 ±1.83	6.4±0.2	2.8±0.08	0.63	99.21±0.7

*(±S.D)(S.D= Standard deviation)

Table 5: cumulative % drug release of amlodipine tablets

Time (min)	A1 (%)(±S.D)
0	0
5	38.55±1.3
10	72.64±1.4
15	89.64±1.1
30	99.64±1.2
45	100.05±1.1

*(n=3, ±S.D (S.D = Standard deviation).

Table 6**:** Cumulative % Drug Release of Metoprolol Tablets

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	33.27 ±1.2	23.51 ±1.2	18.1 ±1.13	20.42 ±1.22	22.3 ±1.21	16.41 ±1.13	25.43 ±1.22	18.39 ±1.14	11.04 ±1.11	24.66 ±1.12	21.7 ±1.13	18.62 ±1.13	27.48 ±1.2	15.41 ±1.23	20.55 ±1.43
2	35.71 ±1.32	26.91 ±1.22	25.5 ±1.23	31.85 ±1.33	34.09 ±1.43	33.78 ±1.4	31.60 ±1.4	37.59 ±1.5	21.71 ±1.22	34.28 ±1.32	34.15±1.33	26.84 ±1.43	39.05 ±1.23	31.21 ±1.12	29.80 ±1.32
4	52.1± 1.33	45.08 ±1.33	39.6 ±1.32	49.32 ±1.32	56.5± 1.34	75.61 ±1.35	56.53 ±1.24	51.52 ±1.25	40.23 ±1.18	56.93 ±1.19	50.22 ±1.14	42.13 ±1.65	49.96 ±1.32	42.90 ±1.22	42.39 ±1.12
6	55.23 ±1.23	55.75 ±1.33	50.53 ±1.44	62.55 ±1.26	72.32 ±1.28	82.21 ±1.29	61.01 ±1.31	66.13 ±1.32	48.42 ±1.33	67.31 ±1.34	59.98 ±1.29	48.94 ±1.19	63.21 ±1.18	50.35 ±1.17	50.09 ±1.11
8	66.41 ±1.10	64.99 ±1.10	59.21 ±1.33	74.11 ±1.26	88.24 ±1.24	85.80 ±1.28	78.87 ±1.28	79.49 ±1.43	56.90 ±1.25	77.33 ±1.28	70± 1.6	57.54 ±1.23	74.11 ±1.17	65.89 ±1.22	64.04 ±1.33
10	70.12 ±1.18	68.08 ±1.24	62.30 ±1.32	77.58 ±1.28	90.37 ±1.26	91.02 ±1.31	85.36 ±1.34	86.37 ±1.43	61.70 ±1.26	82.21 ±1.37	74.13 ±1.23	69.47 ±1.24	86.07 ±1.18	70.65 ±1.23	69.49 ±1.32
12	95.23 ±1.12	89.62 ±1.23	87.35 ±1.31	94±1.19	95.82 ±1.29	97.37 ±1.32	94.73 ±1.33	98.58 ±1.22	67.56 ±1.29	98.75 ±1.38	91.58 ±1.22	81.44 ±1.25	98.17 ±1.19	91.06 ±1.27	80.30 ±1.31

Table 7: Cumulative % Drug Release of Bilayer Floating Tablets

Time Intervals	A1+F8 (%)		A1+F10 (%)		A1+F13 (%)	
	Amlodipine	Metoprolol	Amlodipine	Metoprolol	Amlodipine	Metoprolol
0 min	0	0	0	0	0	0
5 min	37.51±1.2	-	37.83±1.13	-	36.91±1.21	-
10 min	72.86±1.3	-	74.43±1.22	-	75.86±1.12	-
15 min	88.39±1.12	-	90.13±1.21	-	87.87±1.23	-
30 min	99.18±1.33	-	99.28±1.24	-	98.78±1.24	-
45 min	100.2±1.24	-	100.12±1.1	-	99.96±1.13	-
60 min	-	20.83±1.12	-	23.36±1.3	-	25.86±1.12
2 hrs	-	38.09±1.21	-	34.68±1.2	-	37.43±1.13
4 hrs	-	52.63±1.22	-	58.37±1.3	-	52.86±1.22
6 hrs	-	66.89±1.3	-	65.43±1.2	-	64.86±1.23
8 hrs	-	77.36±1.33	-	78.31±1.11	-	76.96±1.24
10 hrs	-	84.63±1.34	-	83.23±1.23	-	84.47±1.12
12 hrs	-	98.23±1.24	-	98.56±1.21	-	98.37±1.11

*(n=3, ±S.D)(S.D = Standard deviation)

Table 8: Results of Kinetic Studies for Optimized Bilayer Floating Tablets

S.no	Formulation	Zero Order R^2	First Order R^2	Higuchi R^2	Koresmeyer Peppas R^2	n	Mechanism of Drug Release
1	A1+ F8	0.939	0.824	0.994	0.984	0.592	Zero order release, non-Fickian Transport
2	A1+ F10	0.929	0.790	0.991	0.991	0.570	Zero order release, non-Fickian Transport
3	A1+ F13	0.941	0.785	0.997	0.998	0.523	Zero order release non-Fickian Transport

* R2 = Correlation coefficient; n= Diffusional exponent.

Figure 1, a: Zero Order Graph of Optimized Formulation (A1+ F8)

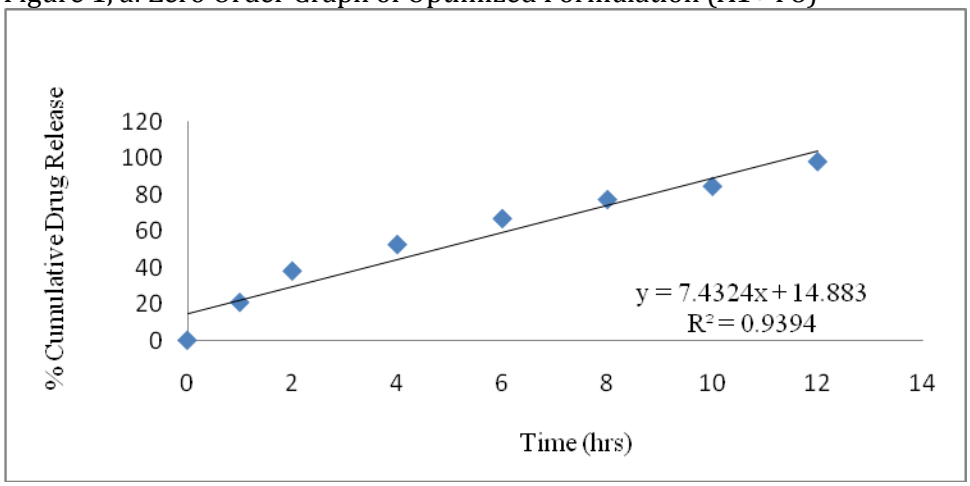


Figure 1.b: Zero Order Graph of Optimized Formulation (A1+F10).

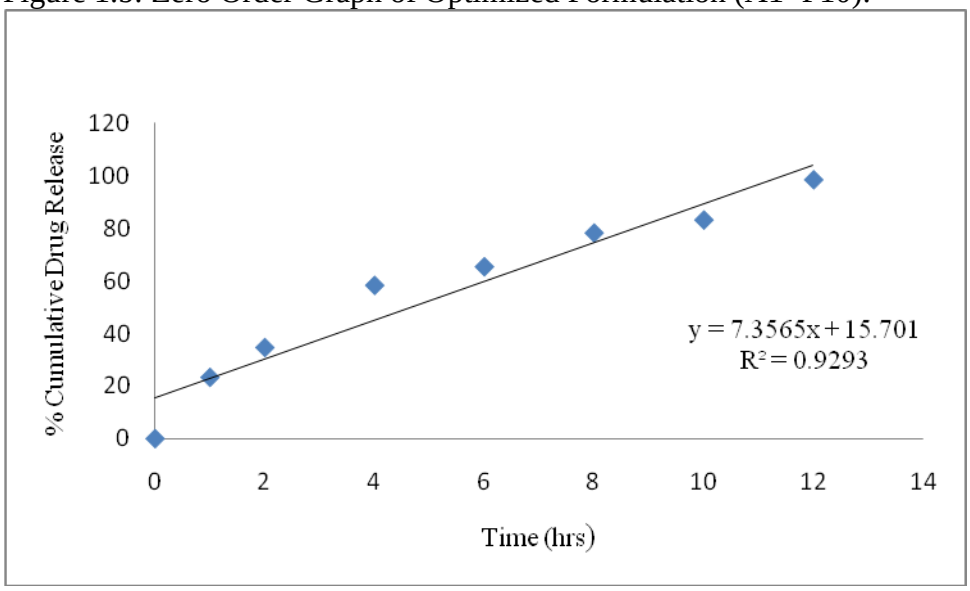


Figure 1.c: Zero Order Graph of Optimized Formulation (A1+F13)

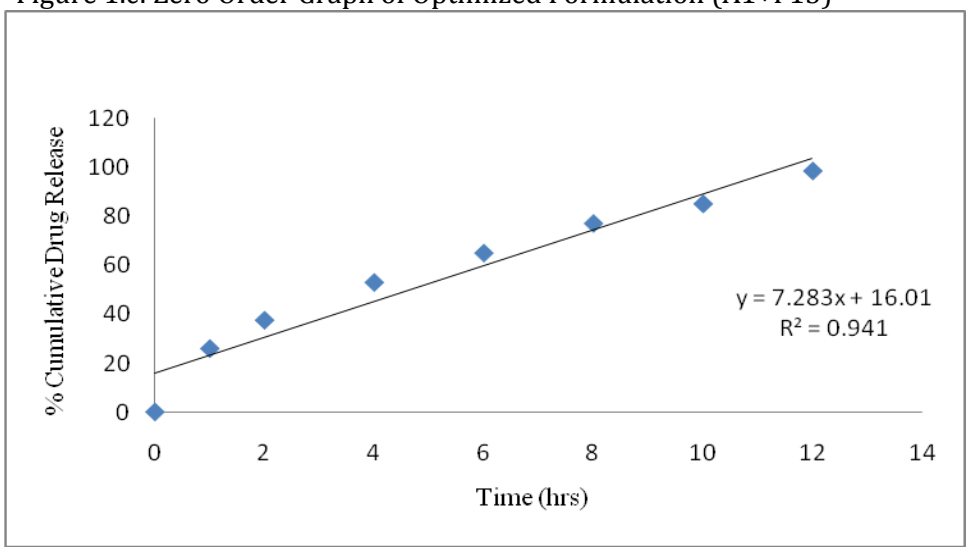


Figure 2a: First order plot for (A1+F8)

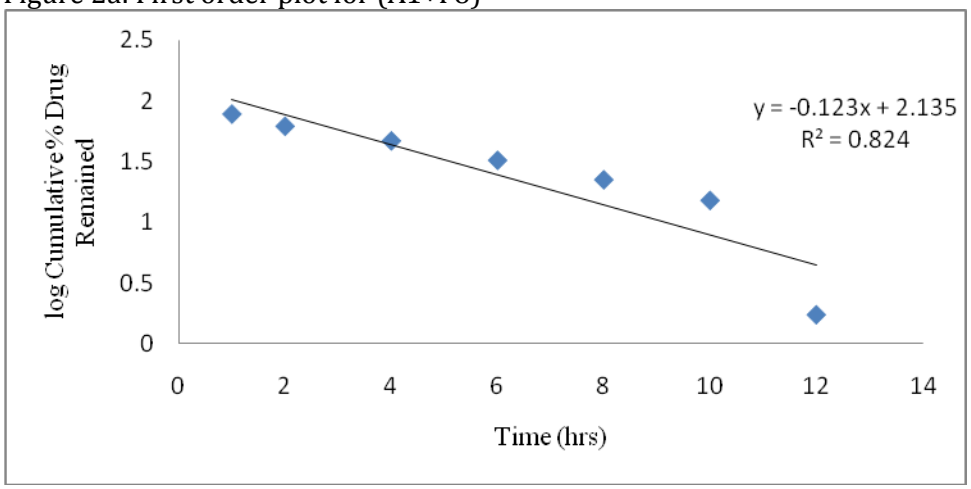


Figure 2 b: First order plot for (A1+ F10)

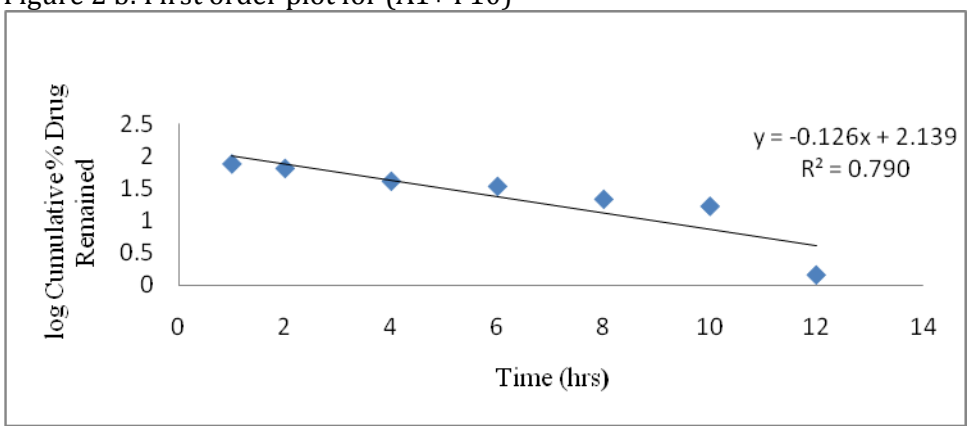


Figure 2 c: First order plot for (A1+ F13).

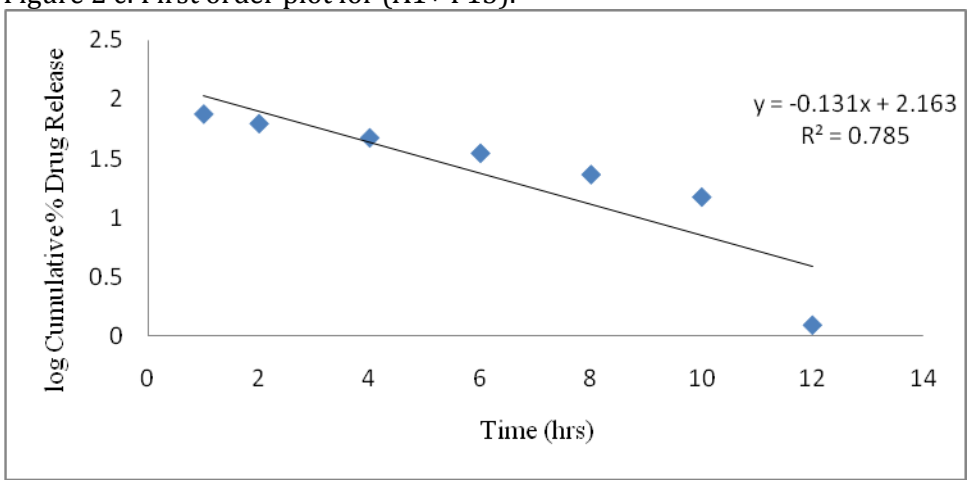


Figure 3 a: Higuchi plot for (A1+F8).

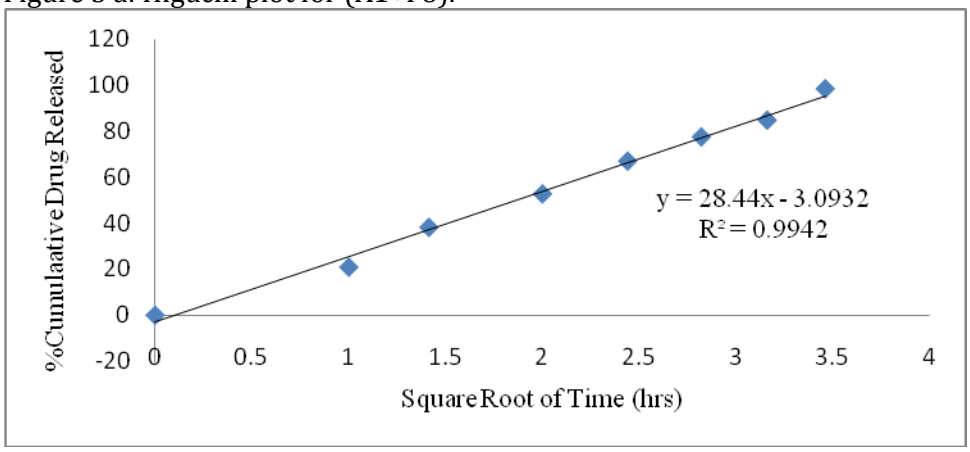


Figure 3 b: Higuchi plot for (A1+F10).

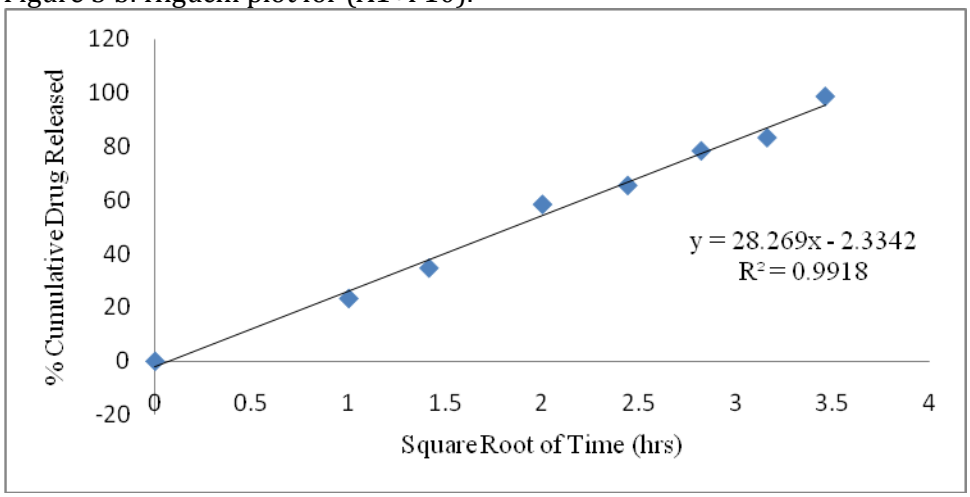


Figure 3 c: Higuchi plot for (A1+F13)

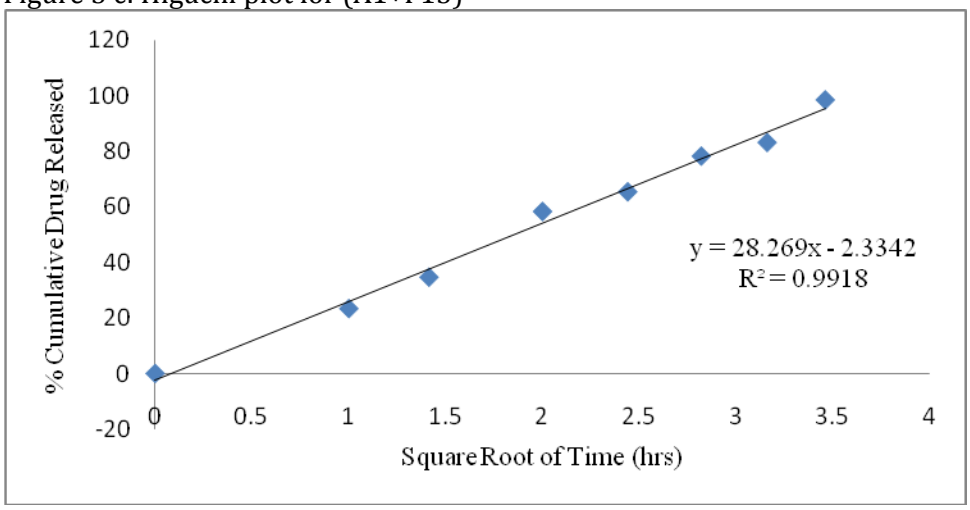


Figure 4 a: Korsmeyer - Peppas Graph for (A1+F8)

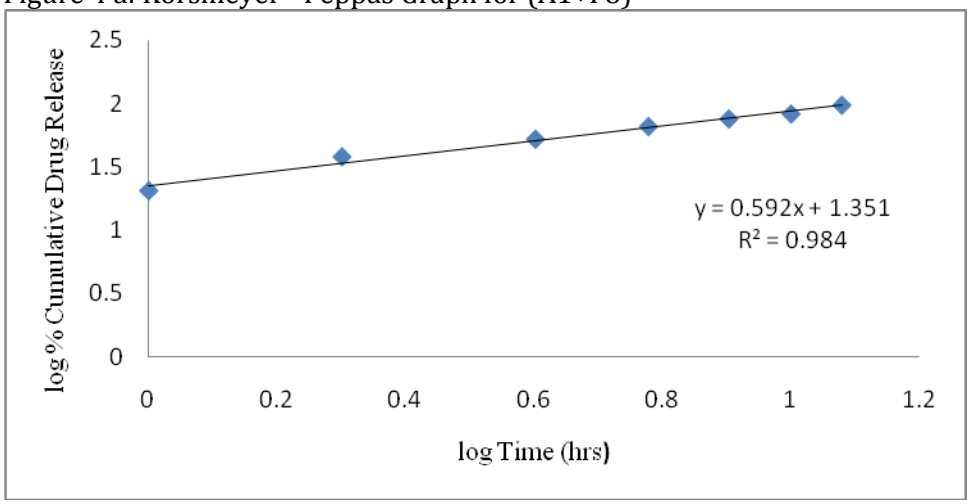


Figure 4 b: Korsmeyer - Peppas Graph for (A1+F10)

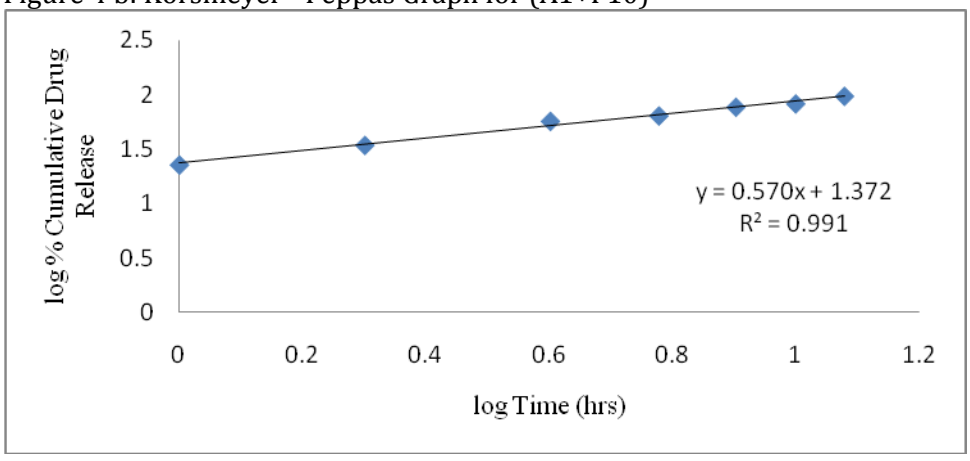
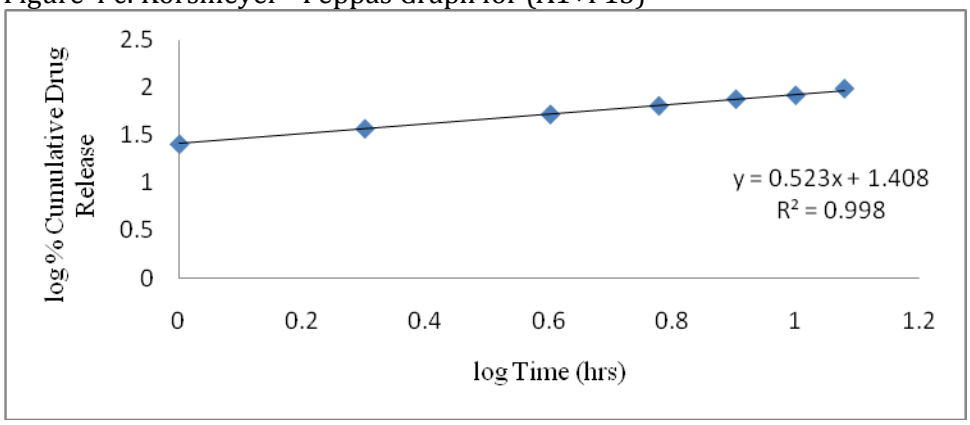


Figure 4 c: Korsmeyer - Peppas Graph for (A1+F13)



Conclusion

From this study by preparing bilayer floating tablets by direct compression technique, it was concluded that we could reduce the total dose, dosage frequency, dose related side effects, and improve the bioavailability of Metoprolol Succinate which in turn improves the patient compliance. Thus a fixed dose combination tablet of Metoprolol and Amlodipine were designed as bilayer floating tablets which will have good patient compliance. However, further clinical studies are needed to access the utility of this system.

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