WWJMRD 2022; 8(08): 61-68
www.wwjmrd.com
International Journal
Peer Reviewed Journal
Refereed Journal
Indexed Journal
Impact Factor SJIF 2017: 5.182 2018: 5.51, (ISI) 2020-2021: 1.361
E-ISSN: 2454-6615

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Formulation And Evalution of Bilayer Floating Tablet of Trandolapril and Diltiazem

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Abstract
Hypertension is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. Combination of ACE Inhibitor & Calcium channel blocker is found to be effective for treatment of Hypertension. The present work focuses on the formulation and evaluation of bilayer floating tablets of Trandolapril and Diltiazem. The immediate release layer of Trandolapril consists of a gas generating agent sodium bicarbonate and floating sustained release layer of Diltiazem comprised of low-density release retardant polymers like HPMC. The prepared powder blends were subjected to FTIR/DSC for any interaction Direct compression method was adopted to prepare tablets from optimized layers of immediate release and sustained release and subjected to Pre- and Post-compression parameters and results were found to be reasonably within the limits. The optimized IR layer of formulation F3 exhibited 91.5% drug release in 60 min and optimized SR layer of F3 showed 98.6% drug release in 12 hrs with buoyancy lag time of 190 sec. Optimized layers were compressed together and were subjected to evaluation of post compression parameters whose results were found to be reasonably within the IP limits. The release data were fitted to various mathematical models such as Higuchi, first order and zero order to evaluate kinetics and mechanism of drug release, and it was best fitted to First order and Higuchi's model.

Keywords: Bilayered floating tablets, Trandolapril, Diltiazem immediate release, sustained release, direct compression.

Introduction
Bilayer tablet is superior than the traditionally used conventional dosage forms as it is appropriate for consecutive release of two drugs combination, Controlling the delivery rate of either one or the other single or two distinct API's, it is also able to separate the incompatible of API's with each other, to control the release of one layer by utilizing the utilitarian property of the other layer (like osmotic property).[1] The bilayer tablet contains two separate release-layers for example biphasic delivery system which intends to convey drug at two distinct rates or all the while releases two drugs at the similar rate, by combining two chemically incompatible drugs into an equivalent framework, at the same time releasing two active pharmaceutical ingredients (APIs) with desired release profiles subsequently increasing or expanding the efficacy of API by providing a synergistic effect.[2,3] Bilayer tablet in which the immediate release layer releases the drug promptly for patient's relief and also maintaining therapeutic level to an extended period of time by controlling the release of drug in the second layer which is delivered in a supported way for better persistent consistence. [4,5]
High blood pressure i.e Hypertension is a global problem that effects approximately 15-20% of all adults. Hypertension is associated with cardiovascular disease like atherosclerosis, obesity, insulin resistance, hyperuricacidemia, and affects the structures and functions of small muscular arteries, arterioles and other blood vessels and can cause damage at variable rate to various target organs including kidney, brain and eye, related with the end stage of renal disease and to be the cause of stroke. [6]
Trandolapril (TLP) is a prodrug of the active metabolite of trandolaprilate and is a nonsulphydryl angiotensin converting enzyme inhibitor. It is used to treat high blood pressure and heart failure. Its oral bioavailability is very poor (4–9%; BCS-II), half-life of

about 6 hours. It is metabolism into Trandoprilat in liver. About one-third of Trandolapril and its metabolites are excreted in the urine, and about two-thirds of Trandolapril and its metabolites are excreted in the feces. Serum protein binding of Trandolapril is about 80%. Trandolaprilat, the active metabolite of trandolapril, competes with ATI for binding to ACE and inhibits and enzymatic proteolysis of ATI to ATII. Decreasing ATII levels in the body thus decreases blood pressure by inhibiting the pressor effects of ATII [7] Diltiazem is contained benzodiazepines moiety, belongs to calcium channel blockers class, used in the treatment of hypertension, angina pectoris, and arrhythmia. Reported oral bioavailability of drug is 40%. Formulation of floating tablets containing diltiazem HCL as a drug candidate, which would remain in stomach and/or upper part of GIT for prolonged period of time thereby maximizing the drug release at the desired site within the stipulated time, and The human jejunal permeability to diltiazem and the extent of absorption is low. [8,9]

Combination of ACE Inhibitor & Calcium channel blocker is viewed as compelling for treatment of Hypertension as this combination is useful for patients with BP and diminishes the CV adverse effects. The advantages of this combination for the treatment of Hypertension, and specific benefit of Trandolapril over other ACE Inhibitors and Diltiazem over other Calcium channel blockers, an endeavor is made to prepare, develop & optimize Bilayer floating tablets containing Trandolapril as immediate release layer and Diltiazem as sustained release layer as no work has been undertaken on the proposed topic of floating Bilayer tablet but individually the work is done for Trandolapril (IR) and Diltiazem (SR, floating tablets).

Materials and Methods

Trandolapril and Diltiazem were obtained as gift samples from Aurobindo Pharma. Ltd and Devi's laboratories Ltd, India. HPMC K4M, Sodium starch glycolate, Carbopol, SCMC, CCS, PVP, Lactose, Sod. Bicarbonate, Mg Stearate, Citric Acid, Talc was of analytical grade.

Formulation [10,11]

a) Preparation & Optimization of Immediate release layer of Trandolapril

The Immediate release layer contains a uniform mixture of Trandolapril, Croscarmellose sodium, sodium starch glycolate, Crospovidone, lactose, and talc (Table 1) followed by shifting through 40# sieve and mixed well for 10min. finally prepared powde rlubricated with magnesium stearate, the well mixed powder was used as upper layer.

Table 1: Composition for Immediate Release Layer.

Ingredients	F1(mg)	F2 (mg)	F3 (mg)	F4 (mg)
Trandolapril	2	2	2	2
SSG	15	12	-	-
CCS	-	-	15	12
PVP	7.5	7.5	7.5	7.5
Lactose	117	120	117	120
Sod. Bicarbonate	3	3	3	3
Mg Stearate	3	3	3	3
Talc	3	3	3	3
TOTAL	150	150	150	150

b) Preparation & Optimization of Floating Sustained release layer of Diltiazem

The floating sustained release tablets containing uniform mixture of drug, polymers and excipients including gas - generating agent. Diltiazem was mixed using variable amount of SCMC, Carbopol 934 LR and HPMC properly in a mortar with weighed number of excipients as shown in (Table 2). The well-mixed powder was compressed by direc compression technique and used as controlled release layer.

Table 2: Composition for Sustained Release Layer.

Ingredients	F1(mg)	F2 (mg)	F3 (mg)	F4 (mg)
Diltiazem	20	20	20	20
HPMC K4M	120	140	120	140
Carbopol	50	40	50	40
Scmc	50	40	50	40
Sod. Bicarbonate	80	80	80	80
Citric Acid	10	10	10	10
Mg Stearate	3.5	3.5	3.5	3.5
Talc	5	5	5	5

c) Preparation of Bilayer Floating tablets

Bilayer tablets were prepared by combining of optimized immediate release layer and sustained release layer. After the compression, upper punch was lifted and the blend of the powder for the immediate release layer was poured into the die, containing an initially compressed sustained release tablet on a multi-station punching machine.

Preformulation Studies [11, 12,13]

Drug and Excipient Compatibility Studies Pure drugs, polymers, excipients, drug - excipients mixture and optimized formulation were subjected to FTIR and DSC studies to investigate the drug – excipients interactions.

Determination of λ max. Of Trandolapril and Diltiazem

The construction of the standard calibration curve was done by using 0.1N HCl as the medium. The standard graph was constructed in 0.1N HCl by making the different concentrations. The absorbance of solutions was examined under a UV- spectrophotometer at an absorption maximum of 210 nm for Trandolapril and at 236nm for Diltiazem. The standard graph was constructed by taking the absorbance on Y-axis and concentrations on X-axis.

Pre- compression parameters

It is needed to identify all the solid forms that may exist as a consequence of the synthetic stage such as the presence of polymorphs. Bulks properties such as particle size, bulk density, surface morphology may be changed during the development process and to avoid mislead predictions of solubility and stability which depends on a particular crystalline form. Bulk characterization testing includes bulk density, tapped density carr's index angle of repose were determined.

Post –compression parameters [14-18]

The physical parameters of the compressed tablets of Trandolapril and Diltiazem were evaluated for post compression parameters like hardness, weight variation, friability, drug content uniformity, Disintegration time etc

Determination of floating lag time and floating time [19]

The time taken for dosage form to emerge on to the surface of medium is called Floating Lag Time (FLT) and the duration of time by which the dosage form constantly emerges on the surface of medium is called Total Floating Time (TFT). One tablet from each formulation was placed in USP type II dissolution apparatus containing 900 mL of 0.1 N HCl (pH 1.2) using paddle at a rotational speed of 100 rpm. The temperature of medium and the duration of time by which the tablet constantly remains on the surface of the medium were noted.

In vitro dissolution studies [20]

The in vitro dissolution study of floating bilayer tablets was carried out in USP Dissolution Test Apparatus II paddle using 0.1N HCl (1.2 pH) with a volume of 900ml.The samples were withdrawn at predetermined time points the temperature of dissolution media was maintained at 37 ± 0.5oC. The basket rotation speed was kept at 100 rpm. One tablet at a time was weighed and taken for study. Five mL of the sample was withdrawn at every specified time interval for 12 hr. and the same volume was replaced with pre warmed fresh dissolution media and the peak area response was recorded, samples were analysed spectrophotometrically at 236 nm and 210nm.

Percentage drug release was computed from prepared standard curve. The release study was conducted in the triplicate and mean values were plotted.

Kinetic models [21]

To study the mechanism of drug release from the sustained release matrix tablet, the in vitro drug release data of optimized formulation were fitted to various kinetic models like zero order, first order, Higuchi and Koresmayer plot and coefficient of correlation (r) values were calculated for linear curves by regression analysis of the e plot. These models used to explain drug release mechanism of the tablet release.

Results and Discussion

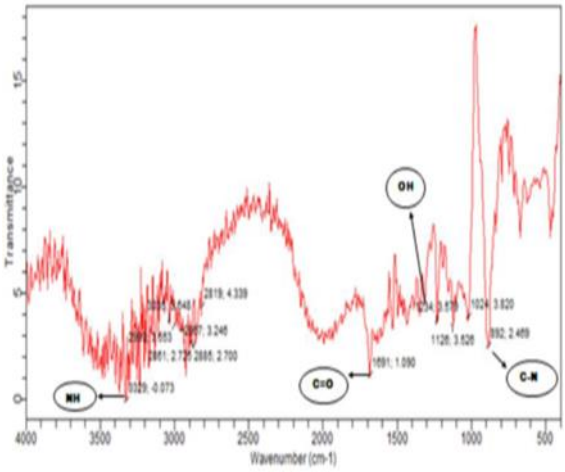
Preformulation Studies

Drug and Excipient Compatibility Studies

Pure drugs, polymers, excipients, drug - excipients mixture and optimized formulation were subjected to FTIR and DSC studies to investigate the drug – excipients interactions.

Drug-Excipients Compatibility

The FTIR spectrum of formulation was compared with that of pure drug spectrum and the results showed that the peaks and functional group are similar to that of drug spectrum. This shows that the drug is compatible with the excipients (Figure 1- 4)



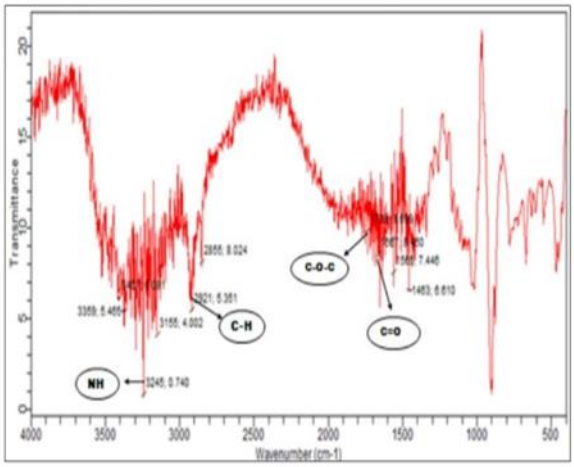
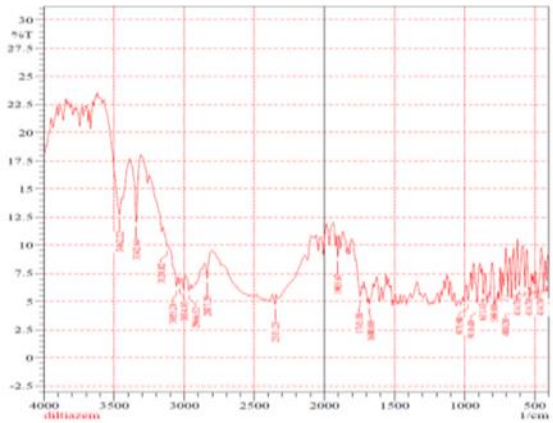


Fig. 1: FTIR of Trandolapril. **Fig. 2:** FTIR of Trandolapril with excipients.



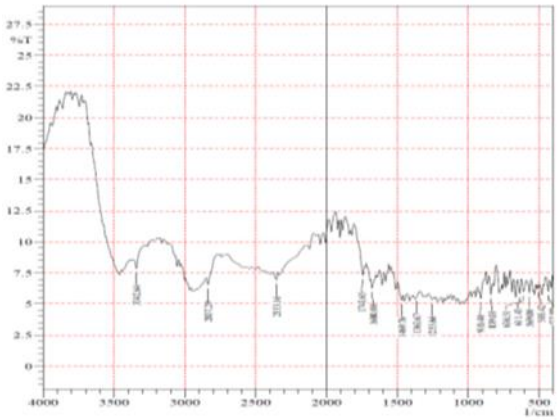


Fig.3: IR Spectra of Diltiazem HCl. **Fig. 4**: IR Spectra of Diltiazem HCl with excipients.

The FTIR spectrum of formulation was compared with that of pure drug spectrum and the results showed that the peaks and functional group are similar to that of drug spectrum. This shows that the drug is compatible with the excipients.

Differential Scanning Calorimetry

DSC thermograms showed that there was no major difference in onset temperature and peak temperature. The peak was not changed from endothermic to exothermic or vice versa when compared with pure drug's Thermogram there no interaction was found between drug and polymers. (Figure5-6)

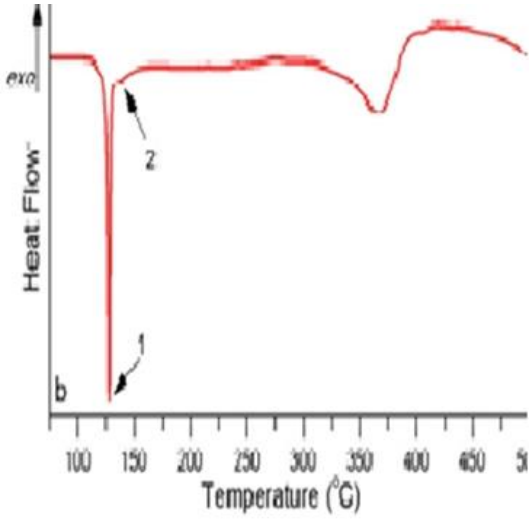


Fig.5: DSC curve of Trandolapril.

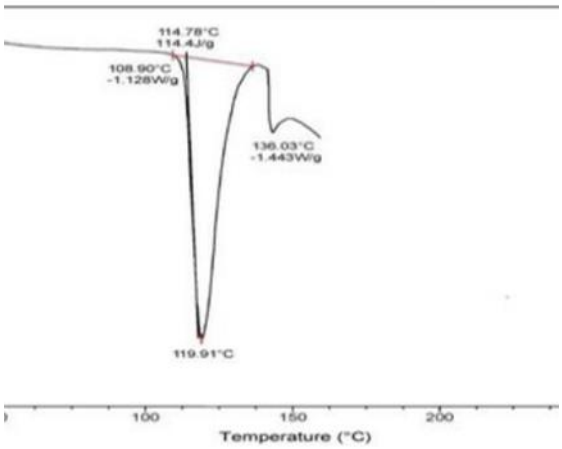
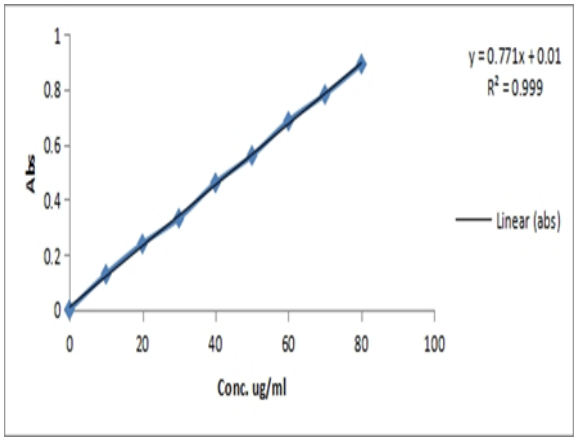


Fig. 6: DSC curve of Diltiazem.

Determination of λmax of Trandolapril and Diltiazem

The construction of the standard calibration curve was done by using 0.1N HCl as the medium. The standard graph was constructed in 0.1N HCl by making the different concentrations. The absorbance of solutions was examined under a UV- spectrophotometer at an absorption maximum of 210 nm for Trandolapril and at 236nm for Diltiazem. The standard graph was constructed by taking the absorbance on Y-axis and concentrations on X-axis.



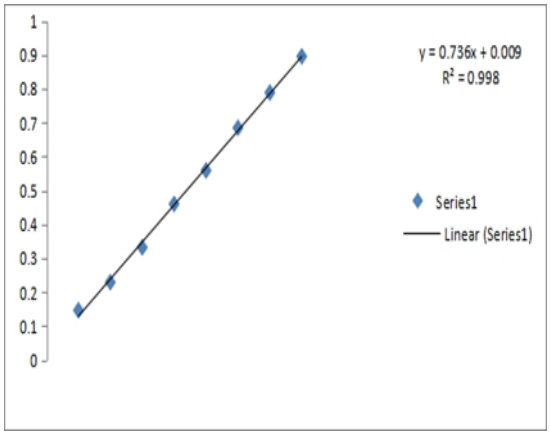


Fig. 7. (a): Standard Curve of Trandolapril in 0.1N HCl.
Fig. 7 (b): Standard Curve of Diltiazem in 0.1N HCl.

Pre-Compression Evaluation

The result of all four formulations of bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose indicates reasonably good flow property. Results were calculated and the values ranged as follows, for all formulations of both the layers (Table 5,6). The results of the physical tests of many of the blends were in the limits and comply with the standards.

Table 5: Physical properties of Pre compression blend for the immediate release layer.

Formulation code	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	25.113 +0.11	0.394+0.03	0.453+0.04	15.35+0.01	1.21+0.07
F2	27.180+0.13	0.425+0.01	0.523+0.03	14.18+0.13	1.19+0.05
F3	22.170+0.21	0.374+0.02	0.472+0.02	13.90+0.18	1.13+0.01
F4	24.150+0.10	0.441+0.05	0.532+0.08	17.16+0.1	1.29+0.08

Table 6: Physical properties of Pre compression blend for Floating SR layer.

Formulation code	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	26.220+0.13	0.353+0.08	0.453+0.02	16.13+0.18	1.18+0.08
F2	27.110+0.11	0.319+0.05	0.381+0.05	17.81+0.85	1.16+0.05
F3	25.130+0.14	0.313+0.01	0.407+0.07	14.31+0.11	1.12+0.03
F4	27.380+0.15	0.382+0.02	0.392+0.03	15.12+0.11	1.19+0.02

All values are expressed as mean ± SD, n=3

Post-Compression Evaluation of tablets

The physical parameters of the compressed tablets of Trandolapril and Diltiazem were evaluated for post compression parameters like hardness, weight variation, friability, drug content uniformity etc. The Nifedipine SR tablets were evaluated for In-Vitro buoyancy test for determining floating lag time, total floating time, swelling study for measuring the percentage water uptake and in vitro dissolution study. Trandolapril IR tablets were evaluated for disintegration study and In-Vitro dissolution study (Table no: 7, 8)

Table 7: Physical evaluation of immediate release layer of Trandolapril.

Formulation Code	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Content uniformity (%)	Disintegration Time(min)
F1	0.6+1.6	4.8+0.52	2.3+0.12	0.49+0.31	98.5+0.02	35 sec
F2	0.4+4.5	4.7+0.45	2.4+0.15	0.52+0.35	98.3+0.01	1 min 5 sec
F3	0.3+3.1	4.6+0.11	2.2+0.31	0.41+0.16	98.7+0.01	30 sec
F4	0.5+4.5	4.9+0.13	2.1+0.19	0.48+0.51	97.8+0.02	1 min 15 sec

Table 8: Evaluation of floating SR layer of diltiazem.

Formulations	Weight variation (%)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Content uniformity (%)
F1	1.2+5.14	6.6+0.27	3.2+0.11	0.36+0.46	97.2+0.02
F2	0.9+3.15	6.8+0.25	3.3+0.15	0.38+0.39	98.2+0.03
F3	0.5+2.18	6.4+0.17	3.0+0.10	0.32+0.21	99.1+0.01
F4	1.5+4.36	6.57+0.15	3.5+0.01	0.39+0.11	96.2+0.02

All values are expressed as mean ± SD, n=3

In vitro buoyancy studies of Floating SR layer

From the results, it was observed that the buoyancy lag time for F1, F2, F3 and F4, was 4 min 5sec, 2min 16sec, 3min 10sec, 2min 35secrespectively (Table 9). The total floating time for all the formulations showed sustained release of drug in Table no.10.

Table 9: Buoyancy studies of Diltiazem SR tablets.

Formulation	Lag time (min)	Total floating time (hours)
F1	4 min 5 sec	11
F2	2 min 16 sec	12
F3	3 min 10 sec	12
F4	2 min 35 sec	10

Table 10: Swelling index of Diltiazem Floating SR tablets.

TIME	F1	F2	F3	F4
0	**0**	**0**	**0**	**0**
1	11	14	22	20
2	18	23	28	28
3	25	31	30	35
4	33	40	38	45
5	41	47	46	48
6	48	52	51	53
7	51	60	58	58
8	56	71	64	60
9	60	75	69	63
10	63	78	77	67
11	68	80	81	69

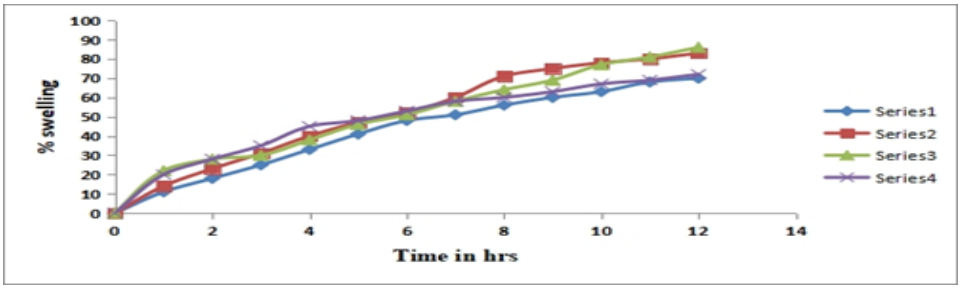


Fig. 8: Swelling Studies of Diltiazem SR tablets.

5.6.8 In vitro dissolution studies [120]

The in vitro dissolution study of floating bilayer tablets was carried out in USP Dissolution Test Apparatus II paddle using 0.1N HCl (1.2 pH) with a volume of 900ml. the peak area response was recorded; samples were analysed spectrophotometrically at 236 nm and 210nm.

Percentage drug release was computed from prepared standard curve. The release study was conducted in the triplicate and mean values were plotted. The results of in vitro release shown in figure 9& 10.

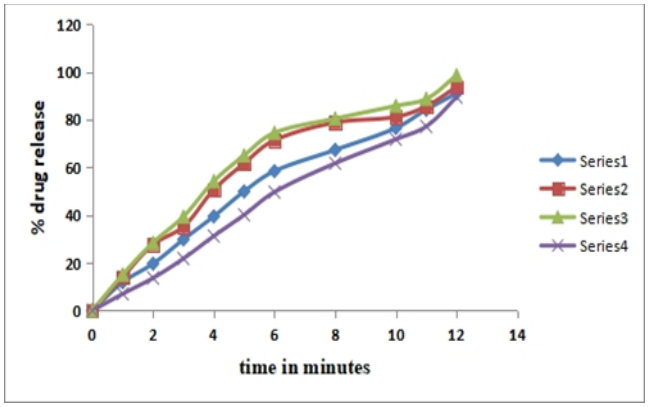


Fig. 9: In-vitro dissolution Profiles for Trandolapril Immediate layer.

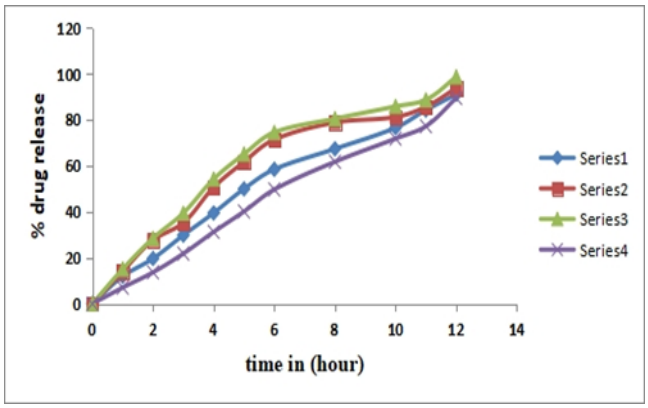


Fig. 10: In-vitro dissolution Profiles for Diltiazem floating SR layer.

Invitro release studies were performed for both immediate release and sustained release layer Formulation F3 from the both IR & SR layer found to be optimized formulation which showed the maximum release.

Analysis of drug release mechanism:

To study the mechanism of drug release from the sustained release matrix tablet, the in vitro drug release data of optimized formulation F3 were fitted to various kinetic models like zero order, first order,Higuchi and Koresmayer plot and coefficient of correlation (r) values were calculated for linear curves by regression analysis of the e plot. These models used to explain drug release mechanism of the tablet release. Shown in figures 11(a, b, c, d).

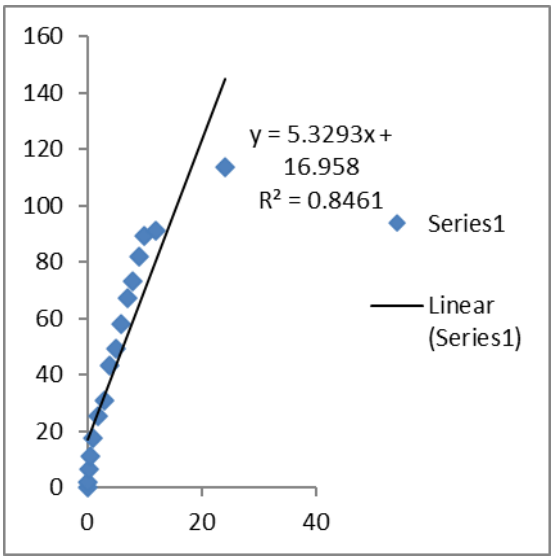


Fig. 11. (a) Zero order

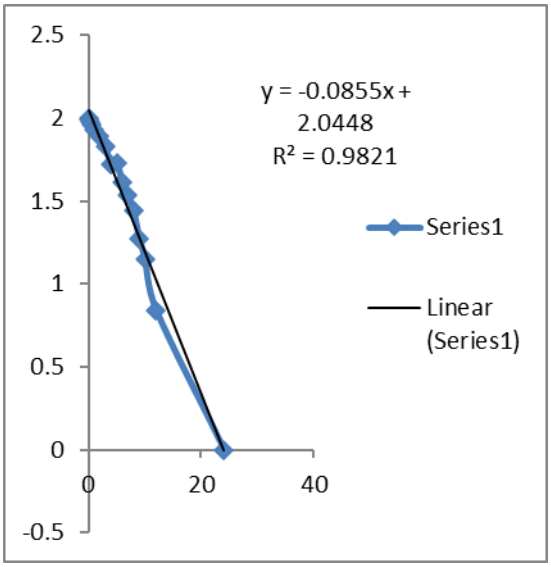


Fig. 11. (b) 1st order

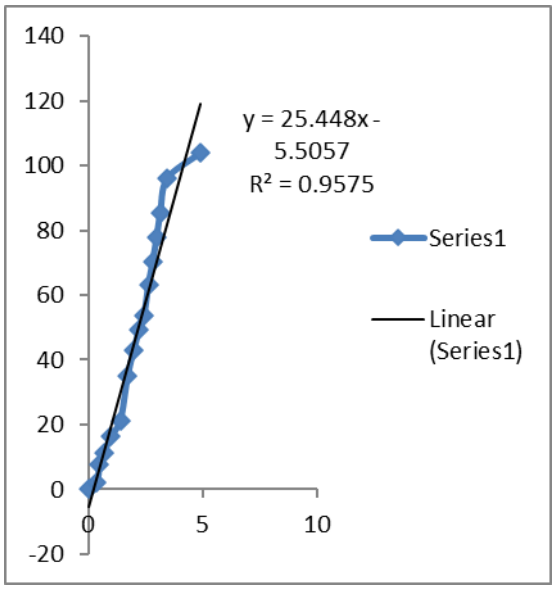


Fig. 11. (c) Higuchi order

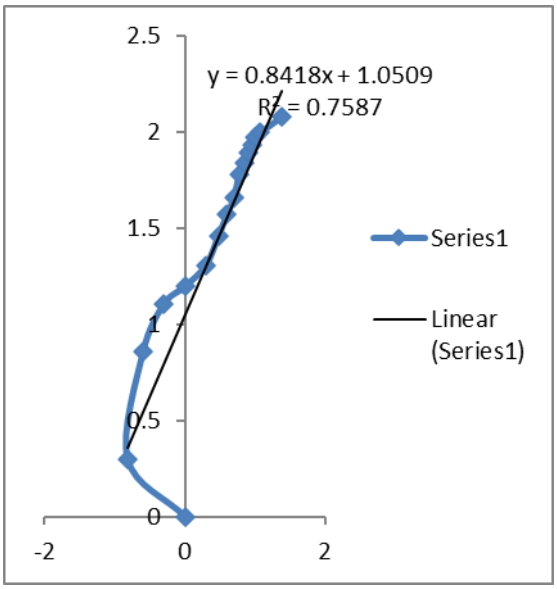


Fig. 11. (d) koresmayer order

The model that best fitted the release data was selected based on the correlation coefficient value (R2) obtained from various kinetic models. It was observed that optimized SR formulation and Bilayer floating tablet follows first order and the drug release mechanism follows the Higuchi model.

Conclusion

In the present research bilayer floating tablets of Trandolapril and Diltiazem were formulated. Preformulation and post evaluation studies were performed. Melting point of the drug was performed by capillary tube method, and it was found to be 171ºC. The construction of standard calibration curve was done by using 0.1N HCL as the medium. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 210 nm for Trandolapril and at 236nm for Diltiazem. The FTIR spectrum of formulation was compared with that of pure drug spectrum and the results showed that the peaks and functional group are similar to that of drug spectrum. This shows that the drug is compatible with the excipients. DSC thermogram showed that there was no any major difference in onset temperature and peak temperature. The result of all six formulations of bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose indicates reasonably good flow property. The Diltiazem SR tablets were evaluated for *In-Vitro* buoyancy test for determining floating lag time, total floating time, swelling study for measuring the percentage water uptake and *in vitro* dissolution study. Trandolapril IR tablets were evaluated for disintegration study and *In-Vitro* dissolution study. All the parameters were found within the range. From the *in* vitro buoyancy studies, it was observed that the buoyancy lag time for F1, F2, F3, and F4 was 4 min 5sec, 2min 16sec, 3min 10sec and 2min 35sec, respectively. The total floating time for all the formulations showed sustained release of drug for 12hrs for F2, F3, and 10 hours for F1 and F4. Swelling studies were carried out for each batch of tablets for 12 hours. Invitro release studies were performed for both immediate release and sustained release layer. To understand the rate and mechanism of drug release from optimized SR formulations, dissolution data was fitted into different release kinetic models. It was observed that both optimized SR formulation and Bilayer floating tablet follows first order and drug release mechanism follows Higuchi model.

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