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Formulation, *In*-vitro evaluation and stability studies of bilayer floating tablets of Trandolapril and nifedipine combinations

Kareem Unnisa, Syed Abdul Azeez Basha and Sana Ahmed

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 Nifedipine. The immediate release layer of Trandolapril consists of a gas generating agent sodium bicarbonate and floating sustained release layer of Nifedipine comprised of low density release retardant polymers like HPMC K4M, K100M. 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 IR6 exhibited 99.2% drug release in 30 min and optimized SR layer SR2 showed 99.5% drug release in 12 hrs with buoyancy lag time of 130 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 final formulation of bilayer floating tablet showed drug release of Trandolapril as 99.6% at 30 min and 99.5% of Nifedipine at 12 hrs. 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. Stability studies revealed no significant changes.

Keywords Bilayered floating tablets, Trandolapril, nifedipine, HPMC k4m, k100m, direct compression

Introduction
Bilayer tablet is better than the traditionally used conventional dosage forms as it is suitable for sequential release of two drugs in combination, Controlling the delivery rate of either single or two different API's, it is also capable of separating the incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property). The bilayer tablet contains two separate release-layers i.e. biphasic delivery system which aims to deliver drug at two different rates or simultaneously releases two drugs at the same rate, by combining two chemically incompatible drugs into a same system, simultaneously releasing two active pharmaceutical ingredients (APIs) with desired release profiles thereby increasing efficacy of API by providing a synergistic effect. Bilayer tablet in which the immediate release layer releases the drug immediately 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 released in a sustained manner for better patient compliance. [1-5] Gastroretentive drug delivery system (GDDS) has been developed to surmount the difficulties of oral drug delivery system. As these systems can remain in the gastric cavity for several hours thereby prolonging the gastric residence time of drugs thereby improving the bioavailability of the drugs, reducing the drug waste, and improves solubility for drugs that are less soluble in a higher pH environment and also provides local drug delivery to the stomach. Floating drug delivery system is considered to be most favorable amongst the other GDDS as it does not affect the motility of gastrointestinal tract (GIT) [6-7].

Hypertension or high blood pressure is a worldwide problem that effects approximately 15-20% of all adults. Hypertension is associated with cardiovascular disease, insulin resistance, obesity, hyperuricacidemia, atherosclerosis 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. [8]

Trandolapril (TLP) is an esterified prodrug of the active metabolite of trandolaprilate and is a nonsulphydryl angiotensin converting enzyme inhibitor.

It is used for the treatment of hypertension and heart failure. TLP have poor oral bioavailability (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 [10].

Nifedipine is a calcium channel blocking agent used in the treatment of various cardiovascular diseases, long term treatment of hypertension and angina pectoris. It has bioavailability of 45-56%, half-life of 2 hours undergoes hepatic metabolism and 60-80% is excreted in urine. It acts by inhibiting the influx of calcium in smooth muscle cells, thus prevents calcium-dependent myocyte contraction and vasoconstriction thereby decreasing the systemic blood pressure [9].

Combination of ACE Inhibitor & Calcium channel blocker is found to be effective for treatment of Hypertension as this combination is helpful for patients with BP and reduces the CV adverse effects. Citing the advantages of this combination for the treatment of Hypertension, and selective advantage of Trandolapril over other ACE Inhibitors and Nifedipine over other Calcium channel blockers, an attempt is made to prepare, develop & optimize Bilayer floating tablets containing Trandolapril as immediate release layer and Nifedipine 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 Nifedipine (SR, floating tablets).

Table 1: Classification of Hypertension

Classification	Systolic Pressure mm Hg	Diastolic Pressure mm Hg
Normal	90-119	60-79
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-119
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	≥120	≥120

Materials and Methods

Trandolapril and Nifedipine were obtained as gift samples from Aurobindo Pharma. Ltd and Suchem Laboratories, India. HPMC K4M, K100M, Carbopol 934LR, Sodium starch glycolate, Crospovidone, Croscarmellose sodium of Pharmaceutical grade was purchased from S.D. Fine chemical Pvt. Ltd.

Formulation

a) Preparation & Optimization of Immediate release layer of Trandolapril

The Immediate release layer contains uniform mixture of Trandolapril, Croscarmellose sodium, sodium starch glycolate, Crospovidone, lactose, talc were weighed.(Table 2) followed by shifting through 40# sieve and mixed well for 10min. finally prepared powder lubricated with magnesium stearate, the well mixed powder were used as upper layer.

Table 2: Table of Composition for Immediate Release Layer

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Trandolapril	2	2	2	2	2	2
SSG	12	15	--	--	--	--
CCS	--	--	12	15	--	--
CP	--	--	--	--	12	15
PVPK 30	7.5	7.5	7.5	7.5	7.5	7.5
Lactose M	120	117	120	117	120	117
Sodium bicarbonate	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total tablet weight	150	150	150	150	150	150

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

The floating sustained release tablets containing uniform mixture of drug, polymers and excipients including gas - generating agent. Nifedipine was mixed using variable amount of SCMC, Carbopol 934 LR and HPMC (K4M, K15M) properly in a mortar with weighed amount of excipients as shown in table 3. The well-mixed powder was compressed by direct compression technique and used as controlled release layer. (Table no.3)

Table 3. Table of Composition for Sustained Release Layer

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Nifedipine	20	20	20	20	20	20
HPMC K4M	120	140	-	50	-	90
HPMCK100	-	80	100	120	100	80
Carbopol 934 LR	50	-	50	-	50	50
SCMC	50	-	50	50	50	-
Sodium Bicarbonate	80	80	80	80	80	80
Citric acid	10	10	10	10	10	10
Mg stearate	3.5	3.5	3.5	3.5	3.5	3.5
Talc	5	5	7	5	7	5
Lactose	11.5	11.5	29.5	11.5	29.5	11.5
Total tablet weight	350	350	350	350	350	350

c) Preparation of Bilayer Floating tablets

Bilayer tablets were prepared by combining of optimized immediate release layer IR6 and sustained release layer SR2. After the compression upper punch was lifted and the blend of

powder for immediate release layer was poured into the die, containing initially compressed sustained release tablet on multi station punching machine using 10 mm round punches, with the hardness of 5.5kg/cm^2.

Preformulation Studies [11]

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 λmax. Of Trandolapril and nifedipine

The construction of 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 concentrations of 2.5µ g/ml, 5µ g/ml, 10 µ g/ml, 15 µ g/ml and 20 µ g/ml and 25 µ g/ml solutions. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 210 nm for Trandolapril and at 235nm for Nifedipine. The standard graph was constructed by taking the absorbance on Y-axis and concentrations on X-axis.

Results and Discussion

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).

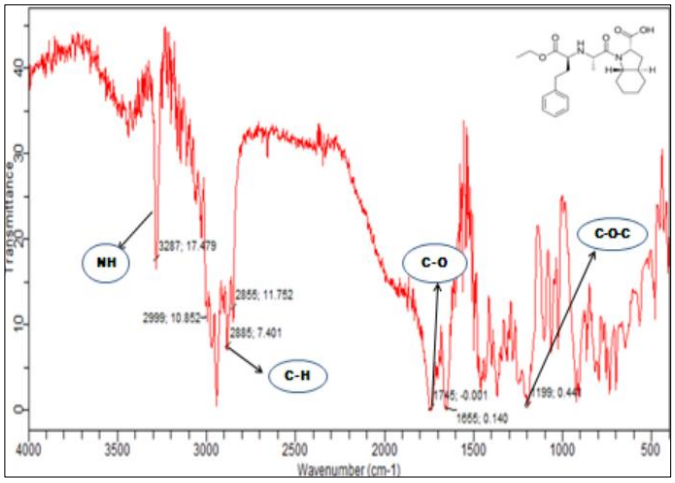

Fig 1: FTIR Spectra of Trandolapril pure drug

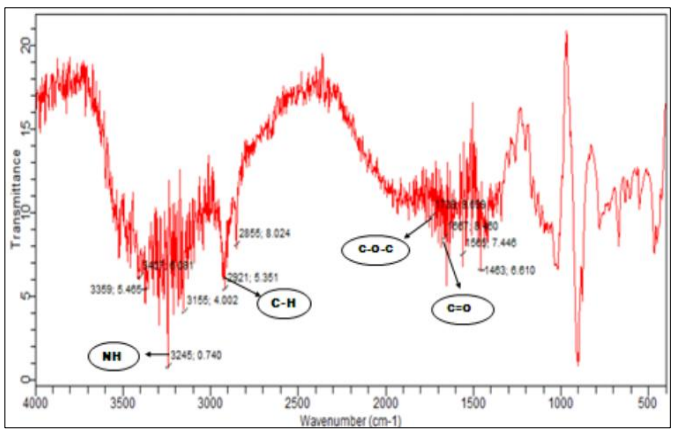

Fig 2: FTIR Spectra of Trandolapril with Excipients

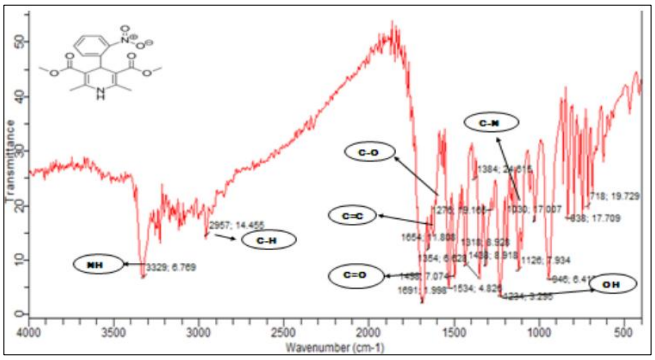

Fig 3: FTIR Spectra of Pure Nifedipine

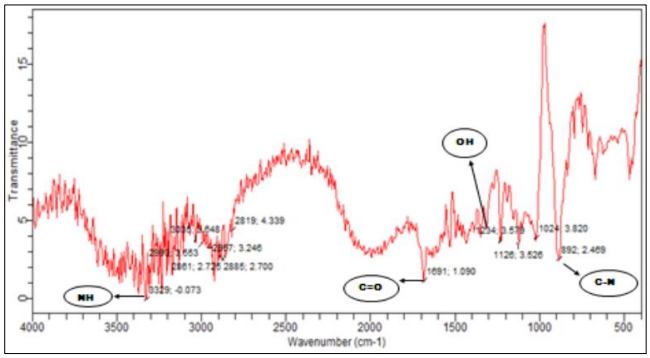

Fig 4: FTIR Spectra of Nifedipine with Excipients

Differential Scanning Calorimetry

DSC thermograms showed that there was no any major difference in onset temperature and peak temperature. The peak was not change endothermic to exothermic or vice versa when compared with pure drug's Thermogram there no interaction was found between drug and polymers. (Fig: 5-7)

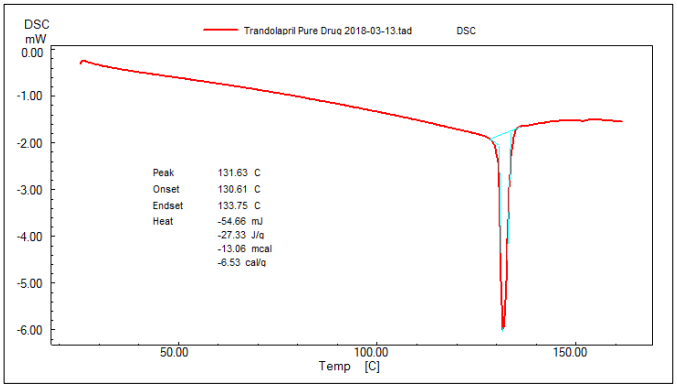

Fig 5: Thermogram of Trandolapril pure drug

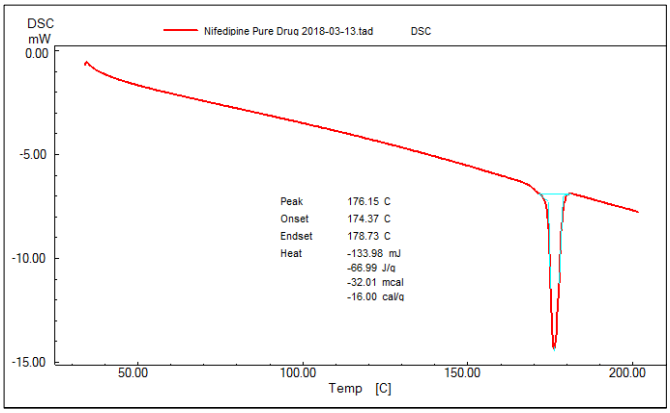

Fig 6: Thermogram of Nifedipine pure drug

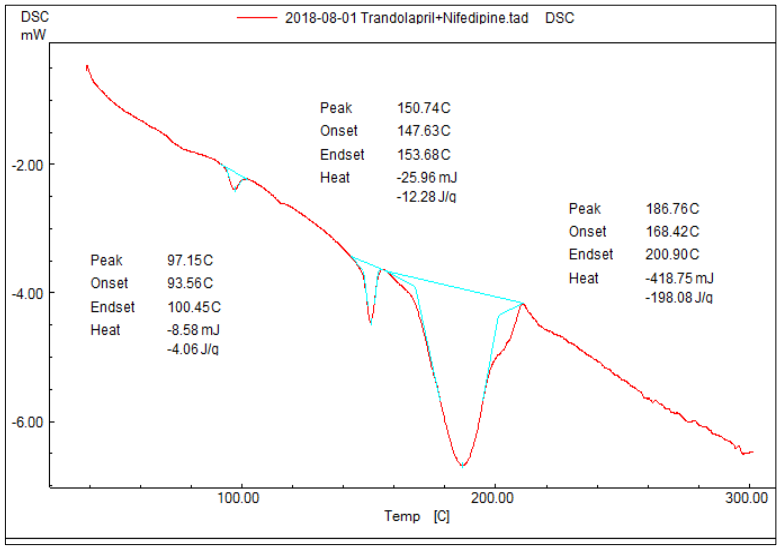

Fig 7: Thermogram of Bilayer floating tablet

Determination of λmax of: The λmax for Trandolapril was found to be at 210nm and for Nifedipine at 235 nm. The standard graph of both the drugs in 1.2 pH showed a good linearity with R^2 of 0.999 (Table: 4, 5 and Figure 8, 9).

Table 4: Absorbance of Trandolapril against concentration range of 2-25 µg/ml

Concentration (µg/mL)	Absorbance
0	0
2.5	0.165±0.001
5	0.312±0.002
10	0.469±0.001
15	0.621±0.001
20	0.778±0.002
25	0.925±0.001

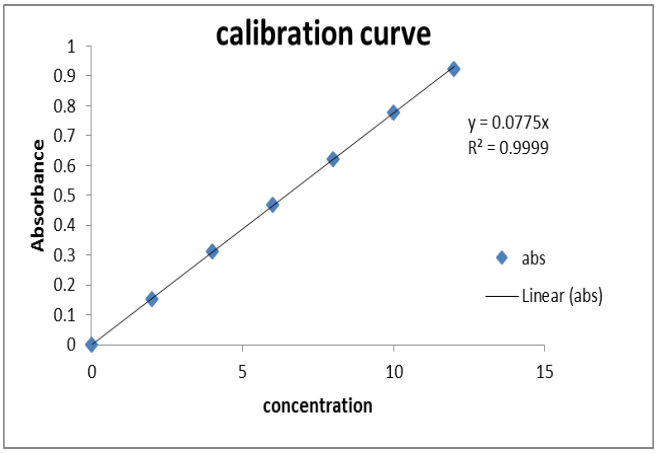

Fig 8: Standard Curve of Trandolapril in 0.1N HCl

Table 5: Absorbance of Nifedipine against concentration range of 2-25 µg/ml

Concentration (µg/mL)	Absorbance
0	0
2.5	0.176±0.001
5	0.339±0.002
10	0.496 ±0.001
15	0.659 ±0.003
20	0.824 ±0.001
25	0.981 ±0.002

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

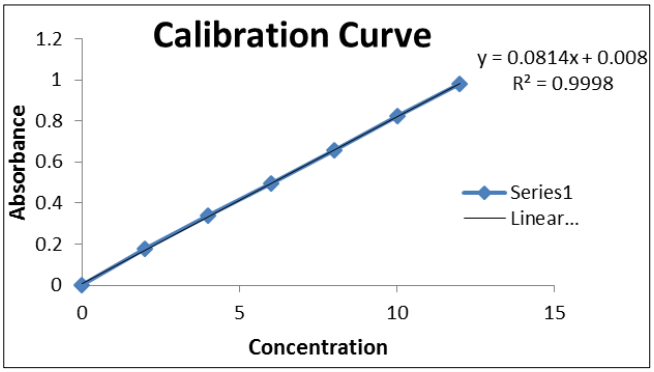

Fig 9: Standard Curve of Nifedipine in 0.1N HCl

Pre-Compression Evaluation

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. Results were calculated and the values ranged as follows, for all formulations of both the layers (Table 6,7). The results of the physical tests of many of the blends were in the limits and comply with the standards.

Table 6: Physical properties of Pre compression blend for immediate release layer

Formulation code	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	26.12^0 ±0.12	0.374±0.01	0.483±0.06	15.15±0.11	1.18±0.08
F2	24.08^0±0.13	0.405±0.04	0.583±0.02	13.48±0.13	1.21±0.02
F3	22.47^0±0.11	0.354±0.07	0.462±0.04	17.46±0.10	1.13±0.05
F4	25.23^0±0.16	0.491±0.05	0.432±0.08	15.26±0.15	1.15±0.03
F5	26.22^0±0.11	0.520±0.04	0.561±0.04	14.23±0.18	1.21±0.06
F6	26.01^0±0.13	0.461±0.03	0.608±0.03	17.91±0.12	1.27±0.04

Table 7: Physical properties of Pre compression blend for Floating SR layer

Formulations	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's index (%)	Hausner's ratio
F1	25.18^0±0.11	0.318±0.09	0.340±0.02	13.17±0.12	1.12±0.03
F2	26.42^0±0.13	0.323±0.07	0.483±0.05	16.23±0.16	1.20±0.02
F3	26.16^0±0.11	0.312±0.01	0.391±0.08	14.41±0.15	1.16±0.03
F4	25.73^0±0.14	0.315±0.05	0.417±0.04	14.11±0.13	1.13±0.06
F5	27.58^0±0.15	0.332±0.03	0.342±0.04	13.12±0.14	1.18±0.05
F6	28.16^0±0.12	0.320±0.06	0.396±0.01	15.58±0.11	1.15±0.08

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

Post-Compression Evaluation of tablets

The physical parameters of the compressed tablets of Trandolapril and Nifedipine 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: 8, 9)

Table 8: 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±5.6	4.8±0.12	2.2±0.18	0.45±0.21	98.9±0.01	30 sec
F2	0.3±4.5	4.7±0.25	2.1±0.16	0.50±0.32	98.2±0.01	1 min 10 sec
F3	0.3±5.1	4.7±0.31	2.2±0.21	0.51±0.12	98.5±0.02	1 min 13 sec
F4	0.6±6.8	4.8±0.33	2.1±0.18	0.45±0.41	97.4±0.01	30 sec
F5	1.3±4.4	4.8±0.38	2.1±0.25	0.54±0.54	99.2±0.02	32 sec
F6	0.6±1.2	4.8±0.25	2.1±0.19	0.58±0.32	99.6±0.01	34 sec

Table 9: Physical evaluation of floating SR layer of Nifedipine

Formulations	Weight variation (%)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)
F1	1.3±5.34	3.0±0.21	6.5±0.37	0.46±0.56	98.2±0.01
F2	0.3±4.45	3.1±0.18	6.8±0.20	0.48±0.49	99.6±0.01
F3	0.5±2.28	3.0±0.20	6.6±0.27	0.42±0.41	98.4±0.02
F4	1.1±5.36	3.0±0.11	6.5±0.25	0.49±0.21	96.5±0.01
F5	0.6±4.31	3.1±0.25	6.5±0.33	0.45±0.54	97.3±0.02
F6	1.2±3.24	3.1±0.20	6.4±0.25	0.48±0.42	98.1±0.01

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, F4, F5 and F6 was 4 min 5sec, 2min 10sec, 2min 30sec, 2min 25sec, 2min 20sec, 2min 32sec and 2 min 20sec respectively (Table 5). The total floating time for all the formulations showed sustained release of drug for 12hrs for F2, F4, F5, F6 and 10 hours for F1 and F3.(Table no.10 and figure 10).

Table 10: Buoyancy studies of Nifedipine SR tablets

Formulation	Lag time (min)	Total floating time (hours)
F1	4 min 5 sec	10
F2	2 min 10 sec	12
F3	2 min 30 sec	10
F4	2 min 25 sec	12
F5	2 min 32 sec	12
F6	2 min 20 sec	12

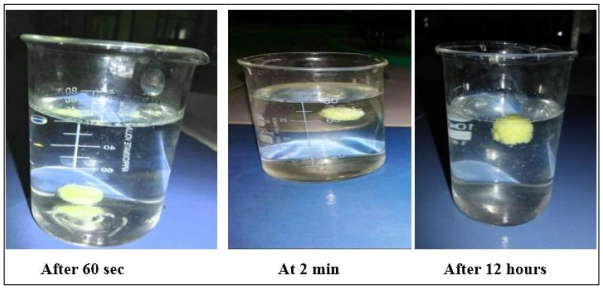

Fig 10: *In* vitro buoyancy studies of Nifedipine SR tablets

Swelling studies of Floating SR layer

Swelling studies were carried out for each batch of tablets for 12 hours. (Table no.11, figure.11)

Table 11: Swelling index of Nifedipine Floating SR tablets

TIME	F1	F2	F3	F4	F5	F6
1	10	25	11	20	22	20
2	19	30	18	28	26	23
3	28	35	25	35	29	27
4	34	40	29	45	36	32
5	43	48	32	48	40	45
6	49	54	38	53	44	51
7	52	64	49	58	52	59
8	57	72	57	60	53	62
9	60	75	64	63	69	67
10	64	79	68	67	73	71
11	67	81	71	69	77	73
12	69	85	75	72	78	76

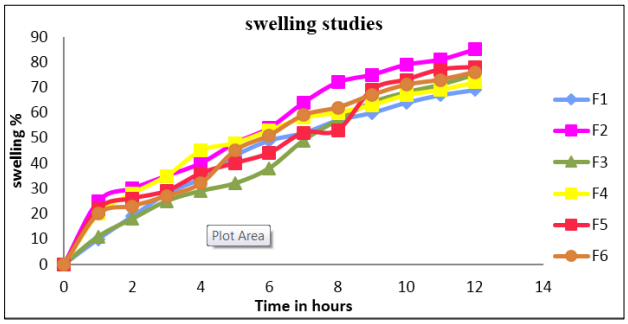

Fig.11: Swelling Studies of Nifedipine SR tablets

Table no.12: Cumulative percentage drug release for immediate layer

Time (Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	18.9	41.4	40.9	45.4	42.7	48
10	32.3	48.2	53.8	70.5	67.4	79.5
15	40.5	55.3	60.9	78.6	80.9	84
20	47.1	61.5	72.5	87.3	93.1	95.3
30	78.5	76.6	78.5	91.5	98.0	99.2
45	85.0	88.7	87.3	97.2	-	-
60	89.1	90.3	91.5	-	-	-

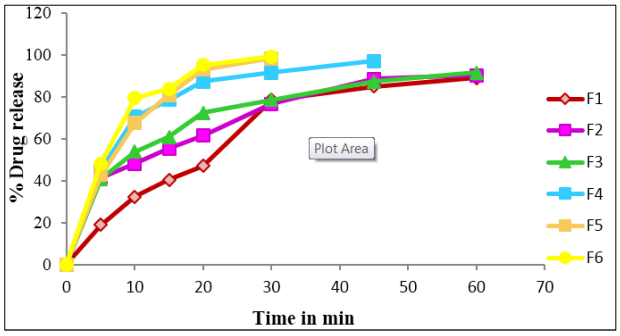

Fig.12: *In*-vitro dissolution Profiles for Trandolapril Immediate layer

Table no.13: In-vitro dissolution Profiles for Nifedipine Floating SR layer

Time (hour)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	11.9	14.01	13.1	7.02	16.33	19.48
2	16.65	27.63	21.46	16.65	20.47	24.39
3	24.79	39.15	37.39	24.79	44.77	30.33
4	36.45	50.58	54.18	34.2	52.56	40.63
5	45.9	61.65	65.02	45.09	67.77	47.16
6	50.4	75.33	70.47	53.64	69.12	53.64
7	62.32	80.76	77.4	60.70	75.6	62.32
8	77.5	84.15	80.77	67.77	80.3	75.33
9	84.15	89.6	88.65	75.15	85.9	82.35
10	97.02	92.7	96.6	86.4	89.41	90
11	-	96	-	96	91.7	93
12	-	99.5	-	-	98	95

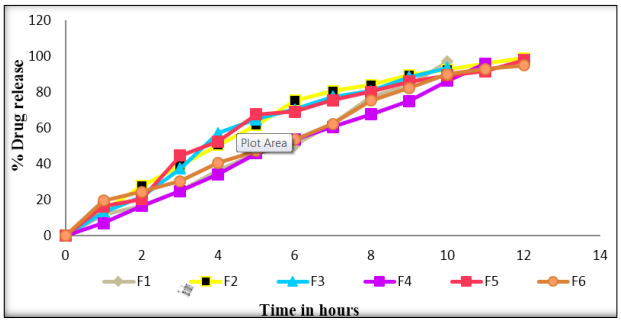

Fig.13: In-vitro dissolution Profiles for Nifedipine floating SR layer

Analysis of drug release mechanism: To understand the rate and mechanism of drug release from optimized SR formulations, dissolution data was fitted into different release kinetic models. The model that best fitted the release data was selected based on the correlation coefficient value (R^2) obtained from various kinetic models. It was observed that both optimized SR formulation and Bilayer floating tablet follows first order and drug release mechanism follows Higuchi model (Figure 13-20, Table: 14, 15)

Table no. 14: comparison of drug release kinetics of different SR formulations

Formulation	Zero order R^2	First order R^2	Higuchi's R^2	Korsmeyer peppas	
				R^2	n
SR1	0.985	0.977	0.976	0.977	0.095
SR2	0.987	0.990	0.980	0.981	0.099
SR3	0.976	0.983	0.962	0.980	0.095
SR4	0.942	0.979	0.968	0.962	0.097
SR5	0.984	0.984	0.967	0.947	0.093
SR6	0.983	0.972	0.977	0.973	0.084

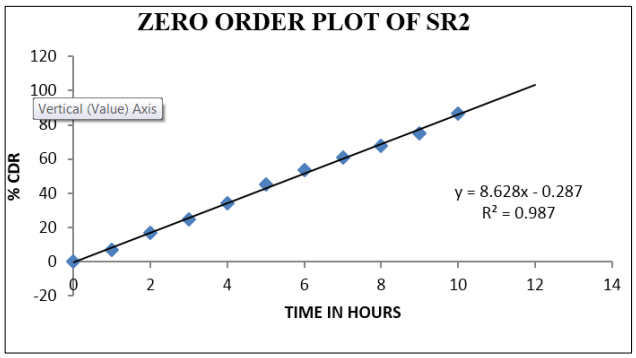

Fig 14: Zero order plot for optimized SR layer

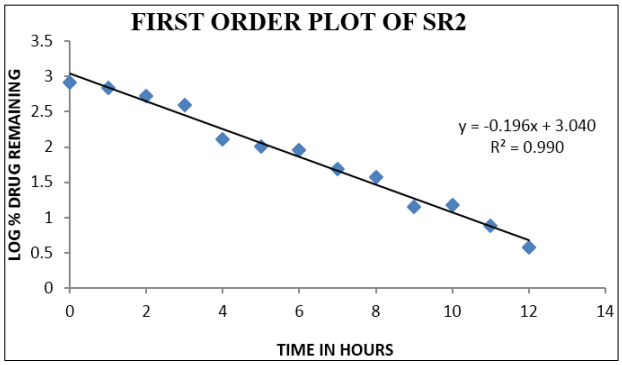

Fig 15: First order plot for optimized SR layer

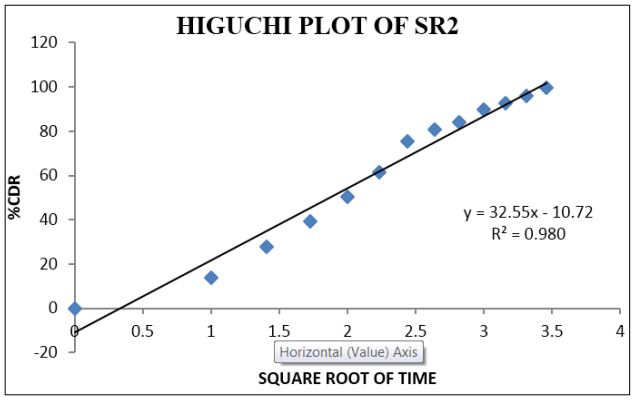

Fig 16: Higuchi plot for optimized SR layer

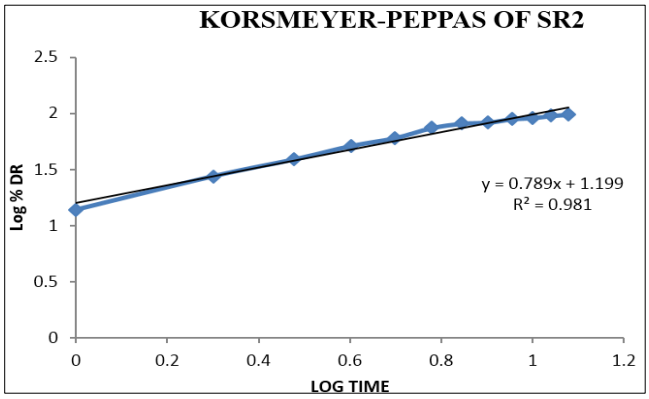

Fig.17: Korsmeyer-peppas plot for optimized SR layer

Table 15: Drug release kinetic studies of Bilayer Floating tablet

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log% Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.01406202	-0.20519636	30.9531307	0.79066715
Intercept	7.480620155	2.169599642	-12.0120347	0.730487873
Correlation	0.982305508	-0.96099032	0.977202195	0.851331954
R 2	0.983924111	0.995502408	0.99192413	0.886766096

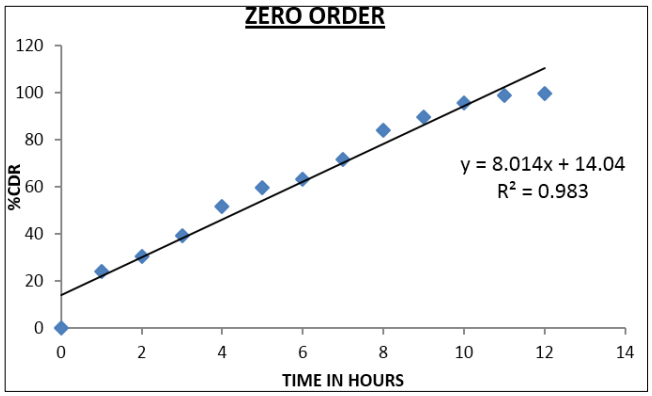

Fig.18: Zero order plot for Bilayer floating tablet

Fig.19: First order plot for Bilayer floating tablet

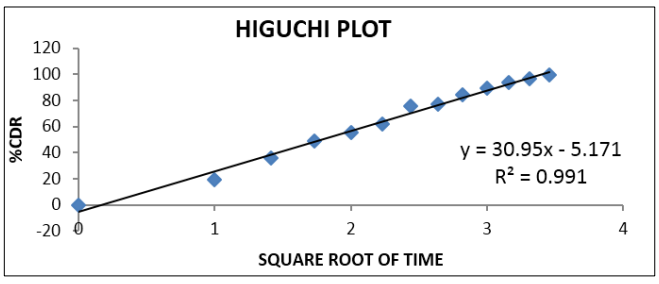

Fig.20: Higuchi plot for Bilayer floating tablet

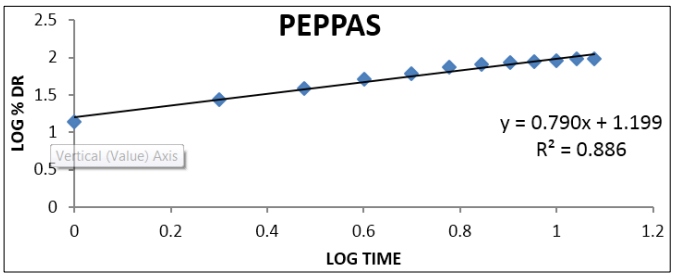

Fig.21: Korsmeyer peppas plot for Bilayer floating tablet

Stability studies of the optimized formulation

The stability studies was carried out for bilayer floating tablets at different temperatures such as room temperature at 25 ± 2ºC / 60 ± 5% R.H and accelerated temperature at 40 ± 2ºC / 75 ± 5% R.H for a period of 3 months and the samples were tested for hardness, thickness, friability, *In vitro* buoyancy, drug content and *In-Vitro* drug release for every month. There was no significant change in the tested parameters.

Discussion

The standard calibration curves of Trandolapril and Nifedipine in 0.1N HCl showed good correlation with regression value 0.999 respectively and λ_{max} was found to be at 210nm for Trandolapril and 235nm for Nifedipine. The polymers and excipients along with the pure drug was found to be compatible when evaluated using FTIR and DSC. The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all formulations

IR formulation IR6 containing Trandolapril, Crospovidone (11%) was nominated to be optimized IR formulation with the average thickness of 2.1 mm, average hardness of 4.8 kg/cm^2, average weight of 150 mg, friability of 0.58%, disintegration time of 34 seconds and %CDR of 99.2% within 30 mins. SR formulation SR2 containing Nifedipine, HPMC K4M(30%), K100M (23%), was nominated to be optimized in SR formulations with the average thickness of 3.1 mm, average

hardness of 6.8 kg/cm^2, average weight of 350 mg, friability of 0.48%, %CDR of 99.5% at 12th hour. The tablets containing HPMC K4M, k100M polymer showed the high degree of swelling. All the formulations remain buoyant up to 10-12hours. The resulted bilayer floating tablet composed of IR2 from Immediate Release & SR6 from release were punched together respectively.

Finally the optimized bilayer floating tablets was further evaluated for hardness, friability, thickness, % CDR. *In vitro* drug release from bilayer floating tablet gave drug release of Trandolapril as 99.6% at 30 min and 99.5% of Nifedipine at 12 hrs.

The drug release from the optimized SR formulation and bilayer floating tablet followed first order and Higuchi's model conforming to be diffusion assisted mechanism. The data for stability studies revealed that no considerable differences in drug content and dissolution rates for a period of 3 months as per ICH guidelines.

Conclusion & Scope

Bilayer floating tablets of Trandolapril and Nifedipine was prepared by direct compression method. The FT-IR study did not show any spectral changes. The powder blends of different formulations have good flow properties. Among the various Immediate release formulations, the formulation IR6 containing Crospovidone (11%) shows maximum release 99.2% is considered as optimized formulation.

Among the floating sustained release formulation, formulation SR2 containing HPMC K4M (30%), K100M (23%) has successfully showed the high degree of swelling. All the formulations remain buoyant up to 12 hrs with lag time of 130 sec, *In vitro* drug release was carried out up to 12 h and showed 99.5% of drug release. IR6 and SR2 were compressed together to obtain bilayer floating tablets which were further evaluated for physical parameters. *In vitro* drug release from bilayer floating tablet gave drug release of Trandolapril as 99.6% at 30 min and 99.5% of Nifedipine at 12 hrs. The drug release from the optimized formulation was found to be first order and best fitted to Higuchi's model conforming to be diffusion assisted mechanism. Stability study was carried out for all the formulations, and it was revealed that there were no significant changes.

From the study, it is evident that the combination of Trandolapril and Nifedipine as bilayer floating tablets can be developed. Further studies are to be assessed for preclinical studies on small animal models.

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