WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 2, 989-1001. Research Article ISSN 2277–7105

FORMULATION AND EVALUATION OF BILAYER TABLET OF SUSTAINED RELEASE NIFEDIPINE AND IMMEDIATE RELEASE CAPTOPRIL AS ANTIHYPERTENSIVE DRUG

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Article Received on
04 December 2024,

Revised on 24 Dec. 2024,
Published on 14 Jan. 2025

DOI: 10.20959/wjpr20252-35341

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ABSTRACT

The aim of present study was to prepare bi-layer tablet of Nifedipine and Captopril for the effective treatment of Hypertension. Nifedipine and Captopril were formulated as Sustained and Immediate release respectively. Wet granulation method was used for the formulation of the both layers. The sustained release layer of Nifedipine was prepared by using different grades of HPMC like HPMC K4M, HPMC K100M. The drug-excipient compatability studies confirmed that both drugs are compatible with excipients by using FT-IR and DSC. The in–vitro dissolution studies were performed by USP–II type dissolution apparatus. The release of Nifedipine from sustained release layer was found to be 99.93% in 12 hours. The release of Captopril for immediate release layer was found to be 99.38% drug release in 60 min. Stability study was carried out at 40 ± 2°C and 75 ± 5% RH up to 3 months. The release kinetics of the optimized tablets showed that it follows zero order release kinetics for sustained release and Matrix release kinetics for immediate release layer.

KEYWORDS: Bilayer tablet, Nifedipine, Captopril, Immediate release, Sustained release, Hypertension.

INTRODUCTION

Bilayer tablets are a new technology for developing controlled release formulations. In order to promote patient convenience and compliance, the pharmaceutical industry has become more interested in creating a dosage form that combines two or more Active Pharmaceutical Ingredients (API). To prevent chemical incompatibilities between APIS by physical separation and to enable the creation of various drug release patterns, bi-layer tablets can be a key alternative. Development of combinations of two or more active pharmaceutical ingredients in a single dose. The form is known as a bilayer tablet. Bilayer tablets are more suitable for the gradual release of the two active ingredients in combination. For bilayer tablets, one layer is released immediately with the aim of achieving high serum concentrations at short term and the other layer is extended release designed for maintain effective plasma levels for a long period of time period. Double-layer tablets became popular, not only a source of attention can be taken orally but have ability to overcome problems with Conventional single-layer tablet. The calcium entry antagonist Nifedipine and the angiotension converting enzyme inhibitor Captopril are well established as effective blood pressure-lowering agent were observed in studies in patients with essential hypertension. The combination of Nifedipine and Captopril may be particularly useful in those patients whose hypertension is not controlled on Captopril and large dose of diuretics as the addition of Nifedipine reduces the need of diuretics. Longer acting converting enzyme inhibitor combined with longer acting calcium entry antagonist should be effective in treatment of moderate to severe essential hypertension.

MATERIALS

Nifedipine and Captopril were purchased from Balaji Drugs, Surat. Starch, Acacia, Microcrystalline cellulose, Magnesium stearate were received from s d fine-chem limited, Mumbai. HPMC K4M, HPMC K100M, Colloidal silicon dioxide were received from Modern Industries, Nashik. Sodium starch glycolate, Croscarmellose sodium were received from Dolphin Chemicals, Mumbai. Dicalcium Phospahte, Talc, HCL were received from Loba Chemie, palghar.

METHODS

Formulation development

Formulation of sustained release granules of nifedipine

Sustained release layer of Nifedipine were prepared by wet granulation technique as per composition of Table 1. All ingredients were weighed and passed through #60 mesh. Mixed all ingredients except lubricant and add binder solution of starch and formed uniform dough mass and pass through # 8 mesh. Dried granules at 60°C in hot air oven for 15 minutes. The dried granules were then sieved with #16 mesh. Then Added Aerosil and starch and mixed for 2 min. Then compressed into tablet.

Table 1: Formulation of sustained release layer.

Sr. No	Ingredients	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
1.	Nifedipine	30	30	30	30	30	30	30	30	30
2.	Starch	70	70	70	70	70	70	70	70	70
3.	Dicalcium Phosphate	187	169.5	152	187	169.5	152	187	169.5	152
4.	HPMC K4M	52.5	70	87.5	-	-	-	26.25	35	43.75
5.	HPMC K100M	-	-	-	52.5	70	87.5	26.25	35	43.75
6.	Starch	7	7	7	7	7	7	7	7	7
7.	Colloidal silicon dioxide	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
8.	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total (mg)	350	350	350	350	350	350	350	350	350

Formulation of immediate release granules of captopril

Immediate release layer of Captopril were prepared by wet granulation technique as per composition of Table 2. All ingredients were weighed and passed through #60 mesh. Mixed all ingredients except lubricant and add binder solution of Acacia and formed uniform dough mass and pass through #8 mesh. Dried granules at 60□C in hot air oven for 15 minutes. The dried granules were then sieved with #16 mesh. Added Talc and magnesium stearate and mixed for 2 min. Then compressed into tablet.

Table 2: Formulation of immediate release layer.

Sr. No.	Ingredients	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
1.	Captopril	25	25	25	25	25	25	25	25	25
2.	Acacia	30	30	30	30	30	30	30	30	30
3.	Sodium Starch Glycolate	45	60	75	-	-	-	22.5	30	37.5
4.	Croscarmellose sodium	-	-	-	45	60	75	22.5	30	37.5
5.	Microcrystalline cellulose	191	176	161	191	176	161	191	176	161
6.	Talc	6	6	6	6	6	6	6	6	6
7.	Magnesium	3	3	3	3	3	3	3	3	3

	stearate									
8.	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total (mg)	300	300	300	300	300	300	300	300	300

Post compression studies

Weight variation

The weight variation test was taken out to ensure that the weight is uniform. of the tablets in a batch. The total weight of 20 tablets from formulation was determined and the average was calculated.

Hardness

The capacity of tablets to withstand transportation or damage under condition of storage, transportation and handling before usage depends on its hardness.Five tablets from each batch were selected and hardness was measured using Pfizer hardness tester to find the average tablet hardness.

Thickness

Thickness of tablet is important for uniformity of tablet size.Ten tablets were selected at random from individual formulations and thickness was measured by using Digital Vernier Caliper.

Friability

Friability is loss in weight of tablets in the container due to removal of fines from the surface of tablet. Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions.Then tablets were removed, de-dusted and weighed again.

Percentage friability was calculated by using the formula

% Friability = Initial wt- Final wt / Initial wt ×100

Drug content

Preparation of standard stock solution of nifedipine

Nifedipine equivalent to 30 mg was accurately weighed. Methanol was added and sonicated for 10 min. The volume was made up to 100 ml with methanol. 2 ml of the solution was diluted with methanol up to 10 ml. The absorbance of resulting solution was measured at 235 nm.

Preparation of standard stock solution of captopril

Captopril equivalent to 25 mg was accurately weighed. Methanol was added and sonicated for 10 min. The volume was made up to 100 ml with methanol. 2 ml of the solution was diluted with methanol up to 10 ml. The absorbance of resulting solution was measured at 205 nm.

Preparation of sample solution

Twenty tablets were accurately weighed and average weight was calculated. Powdered the tablets. Powder equivalent to 650 mg was weighed and transferred to 100 ml stanadard flask. The powder then dissolved in methanol and sonicated. The volume was made up to 100 ml with methanol. 2 ml of the solution was diluted with methanol up to 10 ml. The absorbance of the resulting solution was measured at 205 nm and 235 nm respectively. The amount of both drugs determined by simultaneous estimation.

$$C_x = A_2a_{y1} - A_1a_{y2} / a_{x2}a_{y1} - a_{x1}ay_2$$

$$C_y = A_1a_{y2} - A_2a_{y1} / a_{x2}a_{y1} - a_{x1}a_{y2}$$

where,

A_1 and A_2 are absorbances of sample at λ_1 and λ_2 respectively.

a_{x1} and a_{x1} are absoptivities of drug X at λ_1 and λ_2 respectively.

a_{y1} and a_{y2} are absoptivities of drug Y at λ_1 and λ_2 respectively.

In-vitro dissolution studies of sustained release layer

The release rate of Nifedipine from Bilayer tablets was determined up to 12 hours using USP-type II dissolution testing paddle apparatus. The dissolution test was performed using the dissolution medium 900 ml containing phosphate buffer 6.8 maintained at 37.0 ± 0.5°C. A 5 ml sample was withdraw at specific time intervals and same volume of fresh medium was replaced. The withdraw samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 235nm. Percentage cumulative drug release was calculated.

In-vitro dissolution studies of immediate release layer

The release rate of Captopril from Bilayer tablets was determined up to 60 minute using USP-type II dissolution testing paddle apparatus. The dissolution test was performed using the dissolution medium 900 ml containing phosphate buffer 6.8 maintained at 37.0 ± 0.5°C. A 5 ml sample was withdraw at specific time intervals and same volume of fresh medium

was replaced. The withdraw samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 205nm. Percentage cumulative drug release was calculated.

Release kinetics

To study release kinetics of the optimized bilayer tablets, various mathematical equations have been proposed namely, Zero order equation, first order equation, Higuchi model(Matrix) and Hixson-Crowell cube root law. In order to verify the release model, dissolution data can further be analyzed by Korsmeyer-Peppas equation. The selection criteria for the best model were based on goodness of fit and residual Sum of Squares (R^2).

Stability study of optimized batch

In the present work, stability study was carried out for the optimized formulation was kept in the stability chmaber at a temperature of 40°C/75% RH for 3 months and samples were withdraw at the end of 0,1,2 and 3 months and evaluated for active drug content.

RESULTS AND DISCUSSION

Drug-excipient compatibility studies

FT-IR study

Drug-Excipient compatibility was carried out by FT-IR analysis. IR spectrum of pure drugs, Nifedipine and Captopril and excipients was obtained. Peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. It indicates no interaction in between drugs and excipients. This indicates that drug was compatible with formulation components.

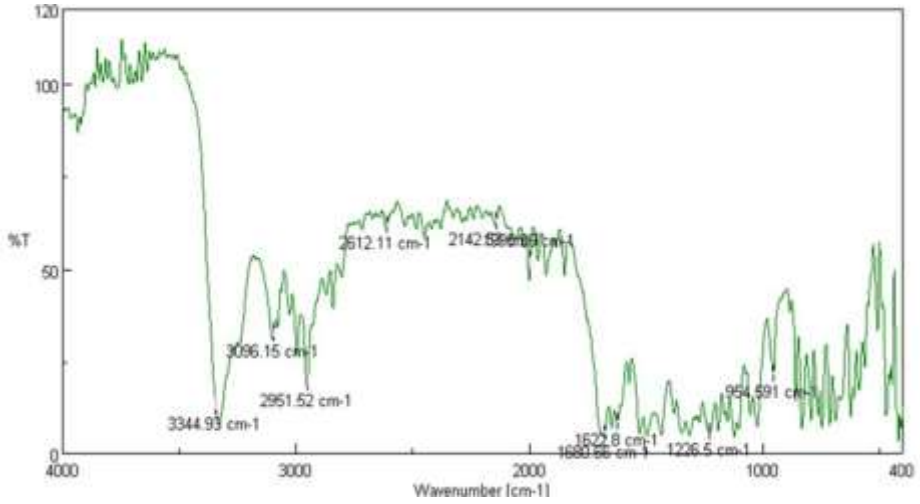

Figure 1: FT-IR spectra of API Nifedipine.

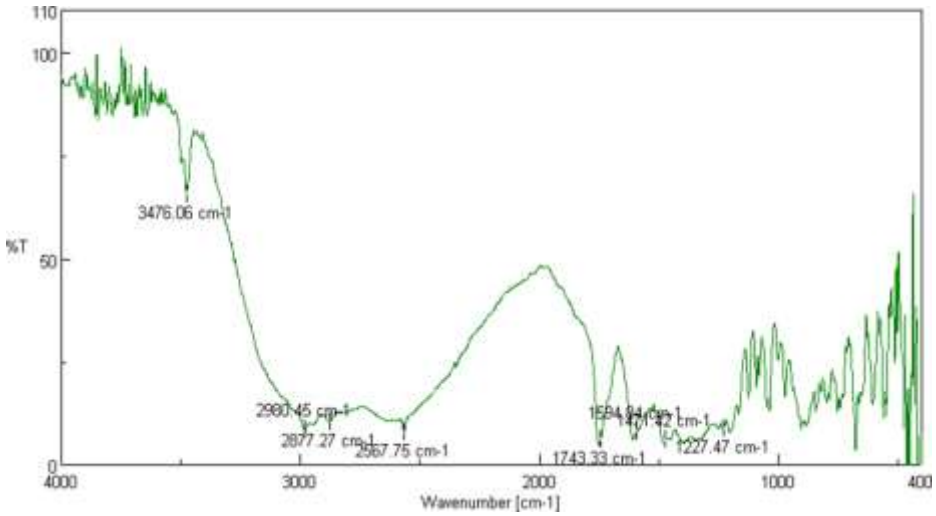

Figure 2: FT-IR spectra of API Captopril.

Differential scanning calorimetry

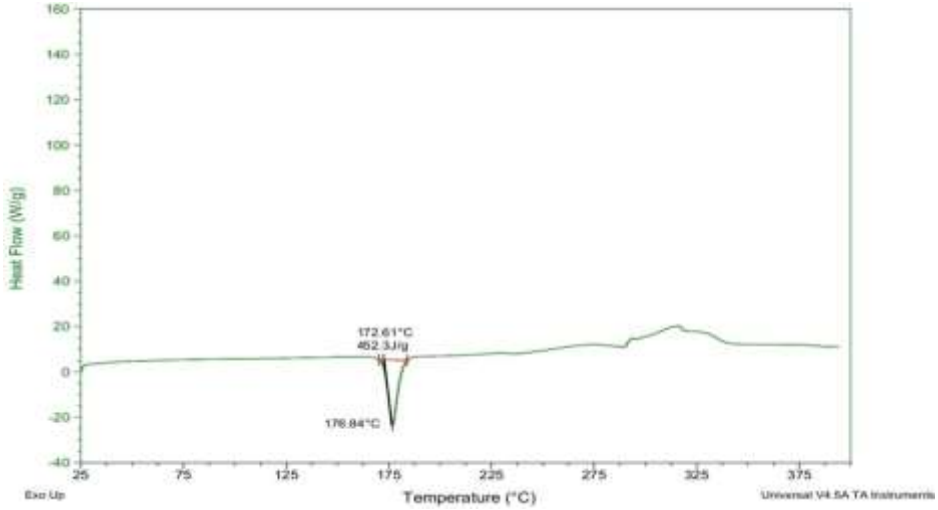

Fig. 3: DSC Thermogram of API Nifedipine.

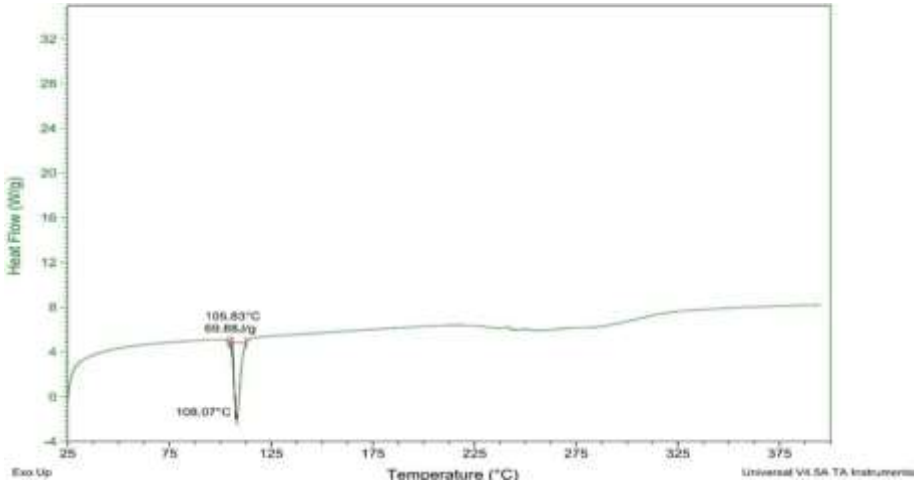

Fig. 4: DSC Thermogram of API Captopril.

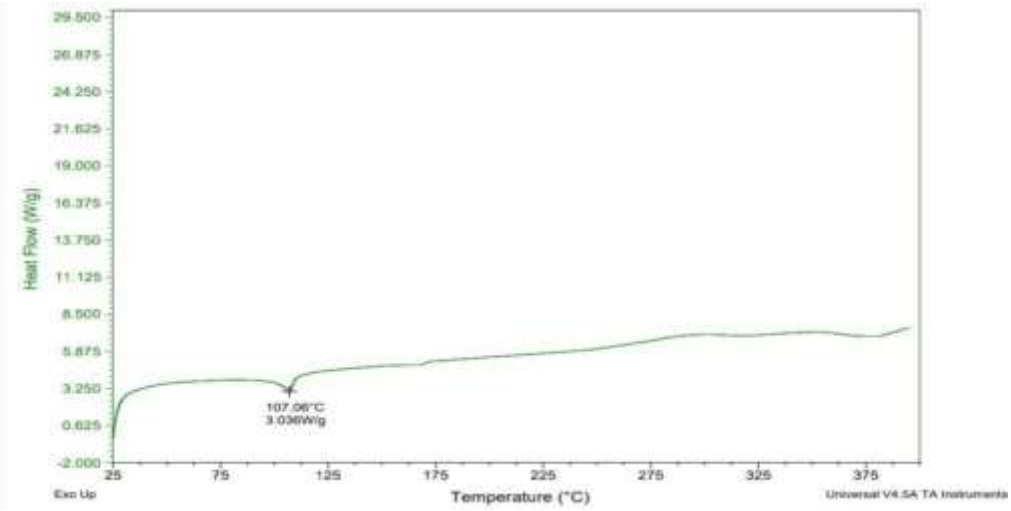

Fig 5: DSC Thermogram of Nifedipine+Captopril+Excipients.

Post compression parameters for bilayer tablet

Table 3: Post compression parameters of bilayer tablet.

Batch	Uniformity of weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)		In vitro disintegration time (Sec) (IRL)
					IR	SR	
F1	650.95±1.5	4.81±0.04	5.1±0.05	0.22±0.04	90.01±0.29	96.66±0.68	30±1.00
F2	649.45±1.6	4.30±0.07	5.5±0.03	0.24±0.06	99.13±0.54	98.45±0.46	27±1.70
F3	649.35±1.5	4.28±0.14	5.3±0.07	0.28±0.02	98.34±0.49	99.56±0.49	29±1.01
F4	649.40±1.3	4.32±0.09	4.7±0.04	0.26±0.03	98.45±0.47	98.45±0.35	48±1.55
F5	650.56±1.3	4.31±0.02	5.9±0.05	0.24±0.02	98.23±0.25	98.23±0.56	59±1.09
F6	651.15±1.4	4.34±0.07	5.2±0.03	0.22±0.06	96.35±0.15	96.64±0.35	34±1.01
F7	649.90±1.5	4.28±0.03	4.5±0.02	0.26±0.04	97.66±0.44	98.26±0.81	29±1.00
F8	648.85±1.6	4.33±0.08	5.8±0.03	0.24±0.03	97.49±0.17	97.23±0.35	28±1.01
F9	650.05±1.6	4.30±0.06	4.1±0.03	0.28±0.06	99.87±0.58	98.47±0.56	30±1.00

In-vitro drug release study

Table 4: In-vitro Drug Release studies formulations (SR1-SR9) (SRL).

Time (hr)	Percentage Cumulative Drug Release profile(%)								
	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	10.714	15.616	13.109	14.435	11.931	22.960	20.774	12.009	13.607
2	20.159	26.602	18.821	18.097	14.337	32.125	28.510	16.855	16.828
3	28.981	35.460	31.153	21.071	17.040	36.451	39.556	25.779	21.167
4	38.941	42.265	41.222	28.166	21.043	43.500	51.643	41.143	28.034
5	43.597	47.004	49.975	32.337	26.069	47.778	56.772	45.746	32.325
6	47.135	54.862	58.840	42.325	29.260	58.928	62.145	57.964	41.506
7	53.979	62.805	68.951	50.504	42.650	66.110	70.585	68.081	47.972
8	58.552	68.591	74.629	65.589	50.342	72.904	77.012	76.663	57.390
9	65.599	77.641	81.720	76.824	65.523	78.711	81.022	79.159	63.680
10	76.515	83.538	85.767	85.191	76.181	87.978	86.577	85.141	73.063

11	88.896	87.255	93.514	94.364	86.995	93.581	91.681	91.535	86.700
12	95.833	97.404	99.690	96.605	94.327	98.407	98.422	98.071	99.920

Table 5: In-Vitro Drug Release studies formulations (IR1-IR9) (IRL).

Time (min)	Percentage Cumulative Drug Release profile								
	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
10	35.801	31.711	47.554	27.158	29.977	35.351	31.275	35.801	27.066
20	58.500	40.570	62.231	49.200	40.573	42.986	44.538	49.976	55.275
30	73.330	58.238	71.880	69.193	52.710	60.681	55.452	62.204	68.830
40	85.699	76.996	79.648	79.753	70.484	76.752	77.252	74.274	77.283
50	91.318	88.392	94.935	91.257	85.444	86.585	84.440	83.232	94.636
60	98.025	96.156	99.835	95.661	94.886	97.303	96.537	95.533	98.993

Percent Cumulative Drug Release from batch (SR1-SR9)

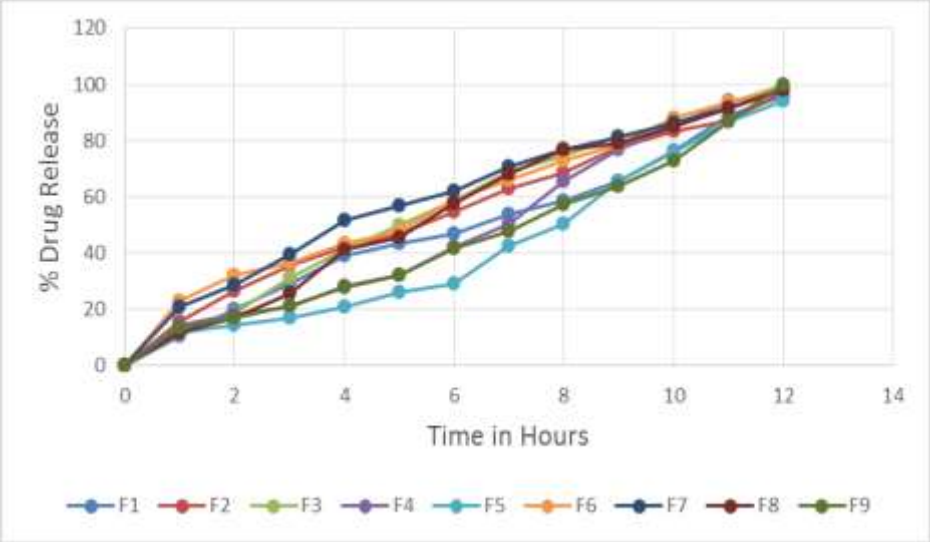

Fig. 6: In-Vitro Release of Nifedipine for batches (SR1-SR9).

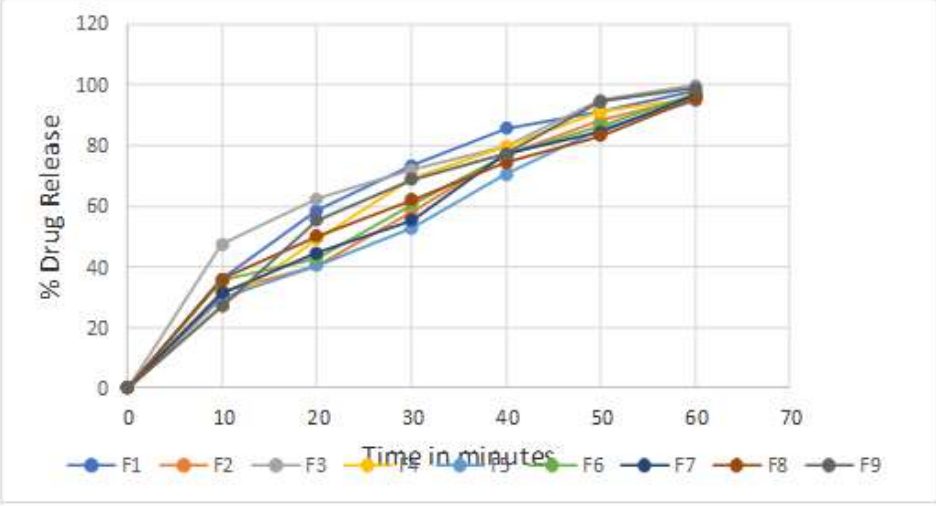

Fig 7: *In-vitro* Release of Captopril for batches (IR1-IR9).

Release kinetics

Release kinetics for sustained release layer

Dissolution data of the optimized batch SR9 was fitted to varoius mathematical models like zero-order, First-order, Higuchi, Korsmeyer-Peppas and Hixson Crowell model in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), PCP dissolution software and best goodness-of-fit test (R^2) were taken as crtieria for selecting the most appropriate mode. Zero order kinetic model were the best fit model for batch SR9.

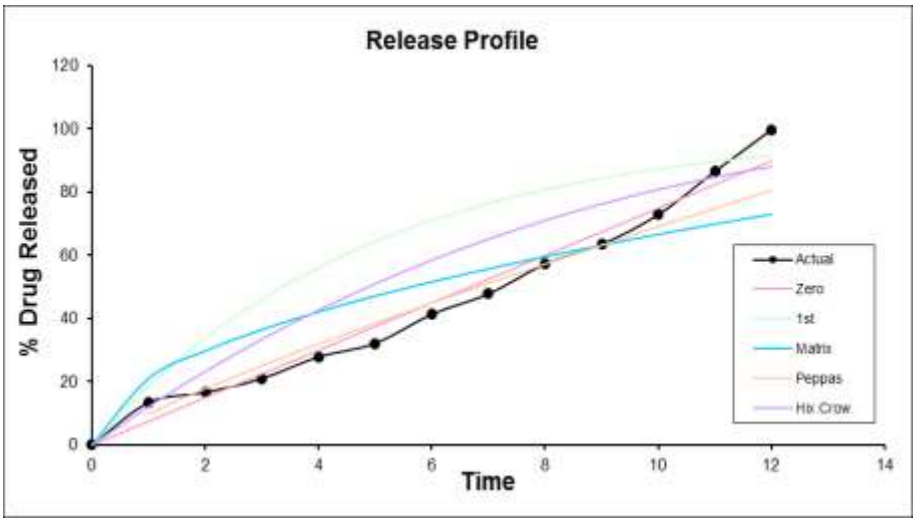

Fig. 8: In vitro Drug Release of SR9 optimize formulation.

Table 6: Kinetics Release of SR9 optimize formulation.

Models	Zero order	1st order	Matrix	Korsmeyer-Peppas	Hixon- Crowel
R^2 value	0.9885 (Best fit model)	0.6794	0.8979	0.9721	0.8498

Release kinetics for immediate release layer

Dissolution data of the optimized batch IR3 was fitted to varoius mathematical models like zero-order, First-order, Higuchi, Korsmeyer-Peppas and Hixson Crowell model in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), PCP dissolution software and best goodness-of-fit test (R^2) were taken as crtieria for selecting the most appropriate mode. Matrix order kinetic model were the best fit model for batch IR3.

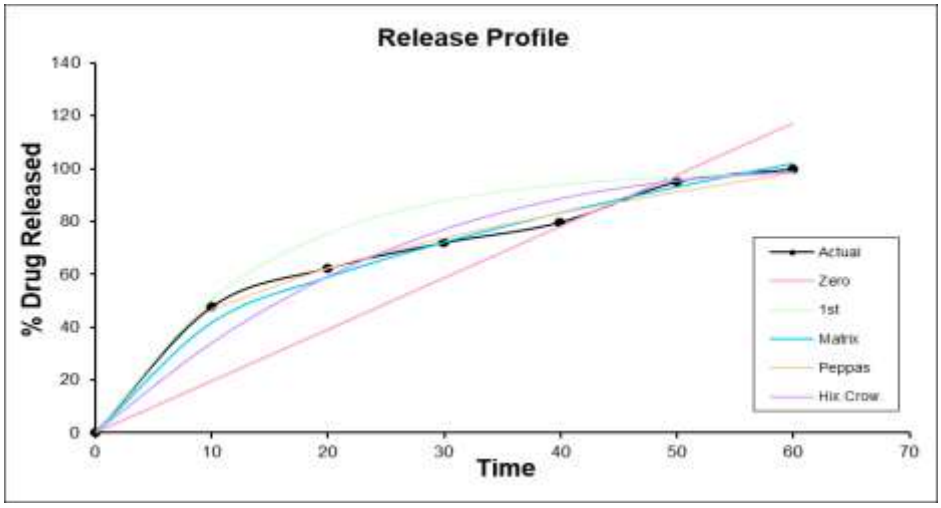

Fig. 9: In vitro Drug release of IR3 optimize formulation.

Table 7: Kinetics Release of IR3 optimize formulation.

Zero order	1st order	Matrix	Korsmeyer- Peppas
0.8587	0.8690	0.9951 (Best fit model)	0.9939

Stability study of optimized batch

Stability study was carried out at 40 ± 2□C and 75 ± 5% RH up to 3 months in stability chamber. At the end of one month, two month, three month tablets were evalauted for drug content. There were no observable significant modifications in any of the studied parameters during the study period.

Table 8: Stability study of optimized formulation.

Time interval	Drug content %	
	Nifedipine	Captopril
0 day	98.76	99.67
30th day	98.69	99.20
60th day	98.78	99.57
90th day	98.56	99.87

CONCLUSION

The present study was carried out to prove that a bilayer tablet of Nifedipine as SR layer and Captopril as IR layer can be formulated. The bilayer tablet were formulated to reduce frequency of administration. The tablets were formulated using superdisintegrant such as Sodium Starch Glycolate in immediate release and polymers such as HPMC k4M and HPMC K100M in sustained release. Bilayer tablets were prepared by wet granulation. The drug-excipient compatability studies confirmed that both drugs are compatible with excipients by using FT-IR and DSC. The formulated bilayer tablet can be used for effective management of

hypertension. To reduce the frequency of administration and to improve patient compliance, a bilayer tablet was prepared sucessfully.

So, from immediate release study formulation IR3 and from sustained release study formulation SR9 were selected as best formulation of each layer.

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