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DEVELOPMENT OF FORMULATION AND IN-VITRO EVALUATION OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM FOR NITRENDIPINE BILAYER TABLETS

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ABSTARCT

The developing of formulation for Floating bilayer tablets of Nitrendipine. IR and SR layers were compressed as direct compression method. IR and SR Layers were evaluated for pre and post compression studies. Those all studies were found to be within limits. From the dissolution data of Nitrendipine Immediate release Layer, IR2 formulation was shown maximum drug release at 15 min. i.e., 95.62%. Hence IR2 was concluded as optimized formulation for IR layer. From the dissolution data of floating bilayer tablets of Nitrendipine, FT5 (IR2&SR5) has shown good drug release 97.12% upto 12 hrs. SR_5 contain Locust bean gum. Optimised SR5 Layers were kept for release kinetic studies. SR5 Layer was following Kars mayer peppas release kinetics.

KEYWORDS: Nitrendipine, SR floating layer, Floating bilayer tablets.

AIM AND OBJECTIVE

Aim of the Work

The aim of the study is to formulate and evaluate gastro retentive floating bilayer tablets of Nitrendipine by Effervescent method.

Objective of the Study

The main objective of this study:

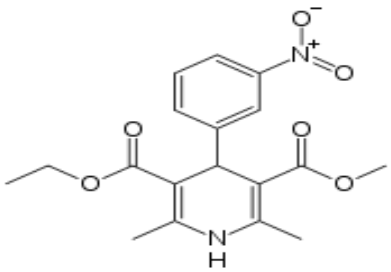
1) The present research work aims to develop a bilayer floating tablet of Nitrendipine

2) To carry out the Drug-Excipient compatibility studies.
3) To evaluate the drug release in developed formulations by *in-vitro* studies.

DRUG PROFILE

Name	:	Nitrendipine
Description	:	A calcium channel blocker with marked vasodilator action. It is an effective antihypertensive agent and differs from other calcium channel blockers in that it does not reduce glomerular filtration rate and is mildly natriuretic, rather than sodium retentive.

Structure



Chemical Name	:	3-ethyl 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
Molecular Formula	:	$C_{18}H_{20}N_2O_6$
Molecular Weight	:	360.3612 gram/mole
Appearance	:	Solid
Solubility	:	Water insoluble.
Melting Point	:	156-160^{0}C
PKa	:	5.43
Category	:	Antihypertensive Agents, Vasodilator Agents, Calcium Channel Blockers

Pharmacokinetic Data

Absorption	:	GI tract
Protein Binding	:	> 99%
Metabolism	:	hepatic
Half-life	:	12–24 hours.
Excretion	:	Renal

Mechanism of Action : By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, Nitrendipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

Uses : For the treatment of mild to moderate hypertension

Side Effects : Heart- Low blood pressure, palpitation, flushing, fast heart rate, chest pain and heart attack. Central Nervous System- Dizziness, drowsiness, fatigue, headache, tingling, irritability and weakness. Gastrointestinal- Nausea, abdominal bloating and diarrhea. Miscellaneous- Muscle/joint pain, breathing problem, blood count changes, increased urination, severe allergic reactions, abnormal liver function tests.

8. RESULTS AND DISCUSSION

8.1. Analytical Method

Graphs of Nitrendipine was taken in 0.1N HCl (pH 1.2)

Table: Observations for graph of Nitrendipine in 0.1N HCl

Conc [µg/mL]	Abs
0	0
4	0.201
8	0.416
12	0.619
16	0.811
20	0.963

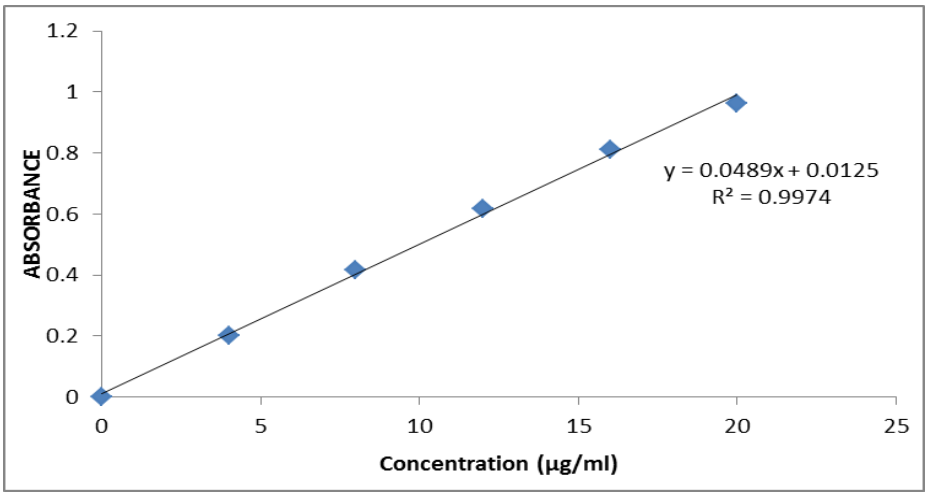


Fig no 8.1: Standard graph of Nitrendipine in 0.1N HCL

Standard graph of Nitrendipine was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Nitrendipine showed good linearity with R^2 of 0.997, which indicates that it obeys "Beer- Lamberts" law.

Table: Calibration Curve Parameters

Sr. No.	Parameter	Values
1	Correlation coefficient (R)	0.997
2	Slope(M)	0.048
3	Intercept(C)	0.012

8.2. Drug – Excipient compatability studies
Fourier Transform-Infrared Spectroscopy

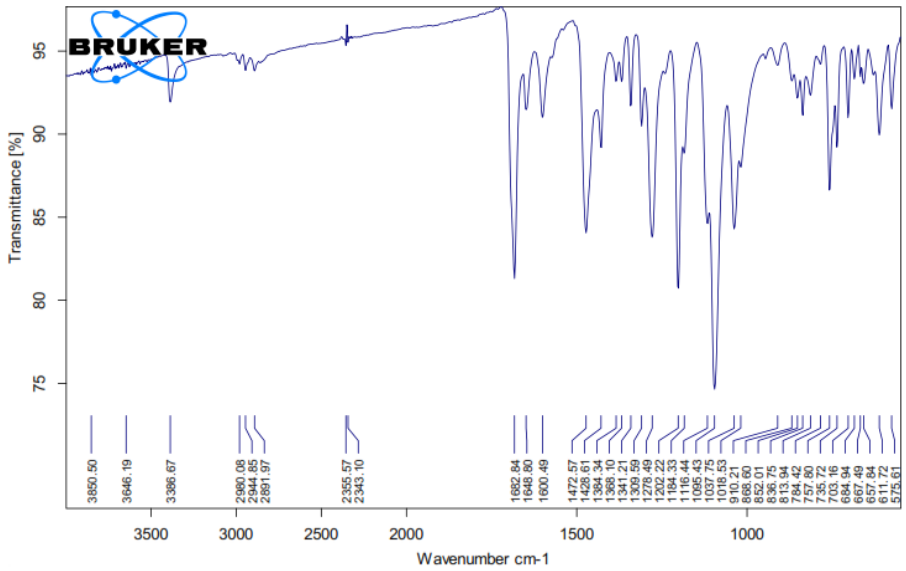


Figure 8.2: FT-IR Spectrum of pure drug.

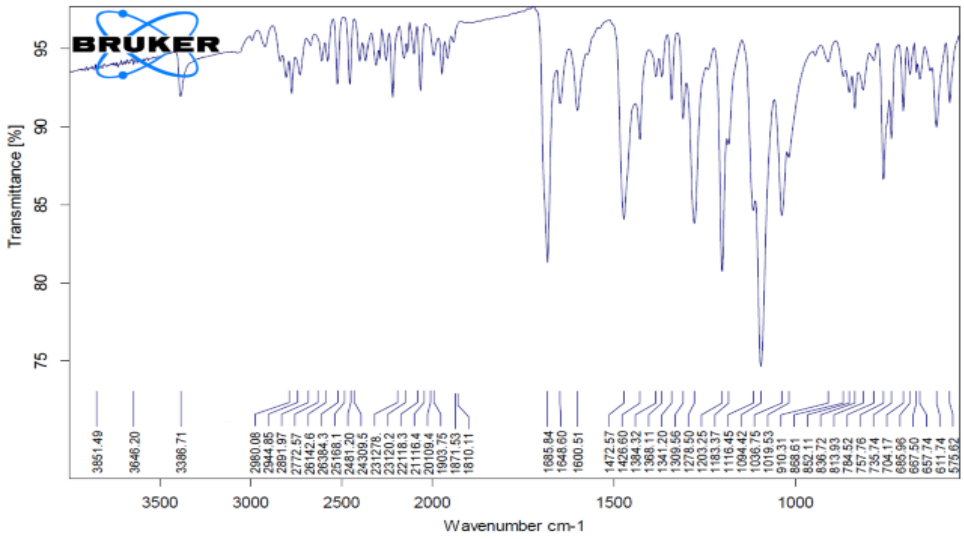


Figure 8.3: FT-IR Spectrum of Optimised bilayer Formulation

It is observed that the peaks of major functional groups of Nitrendipine which are present in spectrum of pure drug. There was no appearance or disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. It means that there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients.

DSC (DIFFERENTIAL SCANNING COLOURIMETRY)

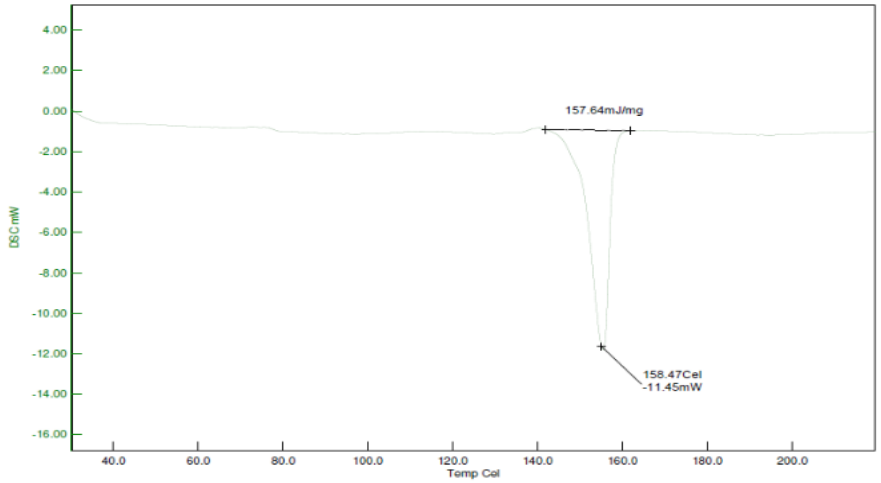


FIGURE : DSC THERMOGRAM OF PURE DRUG

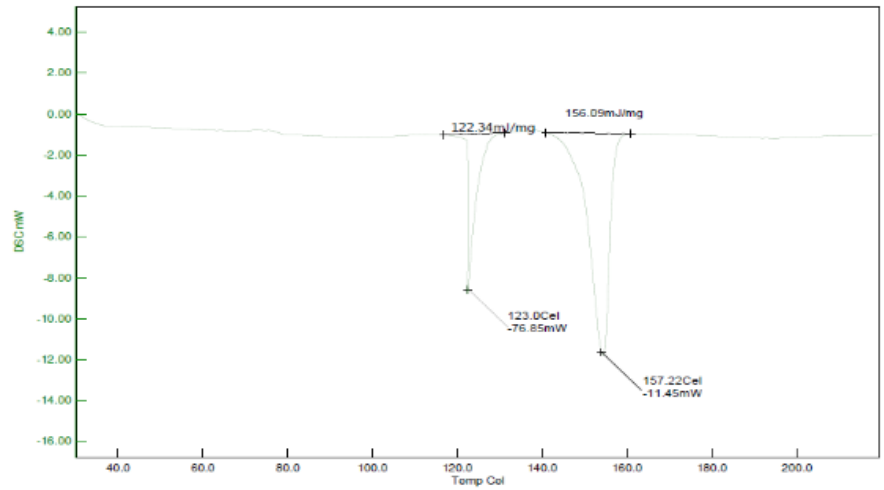


FIGURE : DSC THERMOGRAM OF OPTIMISED FORMULATION

From the DSC studies revealed that there is no incompatibility between drug and polymers.

8.3. Preformulation parameters of powder blend for Immediate Layer

Table: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's Ratio
IR1	24.16	0.63	0.74	14.86	1.17
IR2	23.47	0.72	0.86	16.27	1.19
IR3	27.10	0.66	0.78	15.38	1.18
IR4	24.09	0.54	0.65	16.92	1.20
IR5	25.18	0.63	0.77	18.18	1.22
IR6	24.17	0.65	0.78	16.66	1.2

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.54 to 0.72 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.65 to 0.86 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which show that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Preformulation parameters of powder blend for Sustained Layer

Table: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tappeddensity (gm/cm^3)	Carr's index (%)	Hausner's Ratio
SR1	23.14	0.83	0.96	13.54	1.15
SR2	27.02	0.79	0.91	13.18	1.15
SR3	26.81	0.76	0.89	14.60	1.17
SR4	25.09	0.84	0.98	14.28	1.16
SR5	26.12	0.86	1.02	15.68	1.18
SR6	24.89	0.78	0.95	17.89	1.21
SR7	25.63	0.85	1.00	15.00	1.17
SR8	26.08	0.74	0.87	14.94	1.17
SR9	24.09	0.79	0.98	14.28	1.17
SR10	25.10	0.53	0.59	10.16	1.11
SR11	25.43	0.54	0.60	9.99	1.10
SR12	25.41	0.52	0.58	10.3	1.11
SR13	26.40	0.51	0.61	10.11	1.19
SR14	27.12	0.58	0.63	10.34	1.06
SR15	25.31	0.53	0.64	17.1	1.2
SR16	26.11	0.56	0.63	11.11	1.12
SR17	26.15	0.50	0.58	13.79	1.16
SR18	28.00	0.54	0.61	11.47	1.12

Floating layer powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.74 to 0.86 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.87 to 1.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the Hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

8.4. Optimisation of sodium bicarbonate concentration for SR Layer

Three formulations were prepared with varying concentrations of sodium bicarbonate by direct compression method. The formulation containing sodium bicarbonate in 40mg concentration showed less floating lag time and the tablet was in floating condition for more than 12 hours.

8.5. Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for IR and SR layer tablets.

Table : *In vitro* quality control parameters for IR tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
IR1	96.11	2.3	0.47	3.3	95.61
IR2	100.02	2.4	0.33	3.4	96.11
IR3	95.14	2.2	0.29	3.3	97.28
IR4	96.52	2.4	0.41	3.2	96.14
IR5	100.04	2.2	0.46	3.1	95.28
IR6	101.71	2.3	0.40	3.2	96.17

All the parameters for IR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

Table: *In- vitro* quality control parameters for Floating bilayer tablets

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Duration of floating time(hr)
FT1	301.4	4.0	0.47	4.1	96.28	2.5	<4 hr
FT2	296.8	4.8	0.42	4.3	95.63	2.3	4 hr
FT3	300.8	4.6	0.51	4.0	97.15	2.4	> 6 hr
FT4	298.5	4.7	0.57	4.3	98.06	2.3	9 hr
FT5	301.5	4.5	0.50	4.2	98.12	2.0	> 12 hr

FT6	303.6	4.6	0.41	4.3	96.31	2.7	> 12 hr
FT7	300.7	4.8	0.46	4.1	98.98	2.6	12 hr
FT8	301.6	4.6	0.48	4.0	99.42	2.1	> 12 hr
FT9	300.7	4.1	0.48	4.3	99.12	2.1	> 12 hr
FT10	299.8	4.3	0.47	4.6	99.23	2.3	4 hr
FT11	301.2	4.5	0.45	4.7	99.62	2.7	6 hr
FT12	302.4	4.4	0.44	4.8	99.29	2.9	8 hr
FT13	299.7	4.7	0.43	4.9	99.78	2.8	5 hr
FT14	301.8	4.9	0.42	4.2	99.69	2.7	7 hr
FT15	299.6	4.5	0.49	4.3	99.64	2.5	11 hr
FT16	298.9	4.1	0.44	4.6	99.49	2.3	8 hr
FT17	300.4	4.2	0.43	4.8	99.36	2.3	12 hr
FT18	300.3	4.3	0.41	4.9	99.98	2.2	12 hr

All the parameters for Floating bilayer tablets such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

8.6. In-Vitro Drug Release Studies

Table: Dissolution data of Immediate release Layer

TIME(Min)	IR1	IR2	IR3	IR4	IR5	IR6
0	0	0	0	0	0	0
5	32.51	56.49	29.54	16.38	21.34	32.54
10	57.43	79.16	38.51	29.41	38.76	49.82
15	78.91	95.62	50.73	40.96	52.94	63.94
20	96.31		63.91	59.41	70.87	81.26
30			78.62	81.62	91.63	96.51
45			89.41	96.58	93.54	
60			96.53		93.08	

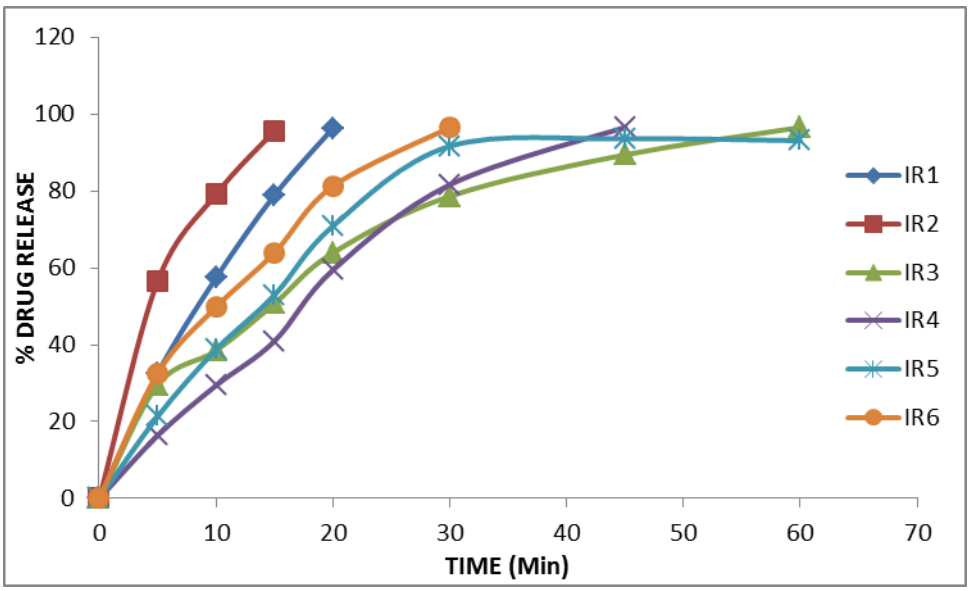


Fig 8.5 : Dissolution data of Immediate release Layer

From the dissolution data of Nitrendipine Immediate release Layer,IR2 formulation was shown maximum drug release at 15 min. i.e., 95.62%. Hence IR2 was concluded as optimised formulation for IR layer.

Table: Dissolution data of Nitrendipine Floating bilayer by using Natural Polymers (Gum karaya, Locust bean gum)

Time (Min)	FT1	FT2	FT3	FT4	FT5	FT6
0	**0**	**0**	**0**	**0**	**0**	**0**
5	56.49	48.17	53.61	54.87	57.43	55.23
10	79.16	63.54	84.17	69.41	89.41	77.65
15	95.62	79.84	94.63	83.59	96.14	94.51
30 (0.5 hr)	32.54	26.48	19.54	15.82	4.56	3.06
60 (1 hr)	63.98	49.31	34.18	26.07	9.14	8.14
120 (2 hr)	79.54	73.62	47.51	39.41	16.59	13.68
180 (3 hr)	95.41	86.59	56.84	49.82	21.28	19.63
240 (4 hr)		95.84	69.41	60.34	26.42	24.51
300 (5 hr)			78.52	72.46	34.91	32.68
360 (6 hr)			86.31	79.63	40.58	39.87
420 (7 hr)			96.37	85.07	52.09	49.62
480 (8 hr)				91.26	64.25	56.17
540 (9 hr)				96.54	76.14	67.28
600 (10 hr)					85.63	76.54
660 (11 hr)					95.11	83.26
720 (12 hr)					97.12	85.62

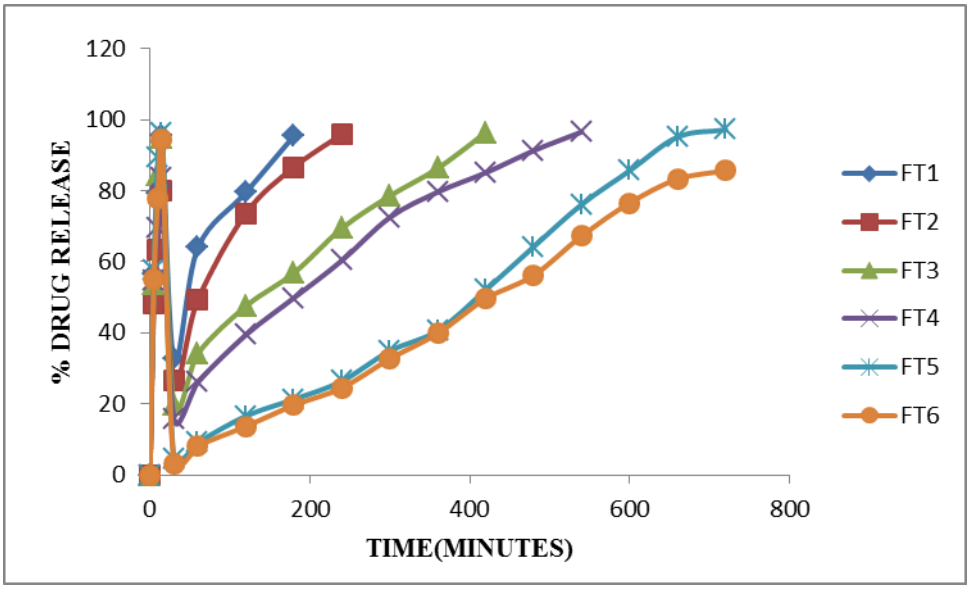


Fig: Dissolution graph of Nitrendipine Floating bilayer tablets by using Natural Polymers(Gum karaya, Locust bean gum)

Nitrendipine Floating bilayer tablets prepared by using Natural gum i.e., Gum karaya formulations were FT1-FT3. 10mg of Gum karaya (drug : polymer ratio = 1:1) was retard the drug release(95.41%) within 3 hours only. 20mg of Gum karaya (drug : polymer ratio = 1:2) was retard the drug release(95.84%) within 4 hours only. 30mg of Gum karaya (drug : polymer ratio = 1:3) was retard the drug release(96.37%) within 7 hours only. Gum karaya was retard the drug release upto 7 hours.

FT4 - FT6 formulations were prepared by using Locust bean gum, in that FT5 formulation was showed good drug release 97.12% in 12 hours. 20 mg of locust bean gum is sufficient to retard the drug release within 12 hours. initially increases the concentration of locust bean gum increases the drug release and finally decrease the drug release.

By Using Natural Gums (Gum karaya, Locust bean gum) FT5 formulation was best formulation because it was showing better result 97.12% in 12 hours.

Table: Dissolution data of Nitrendipine Floating bilayer by using Semi synthetic Polymers (Sodium Alginate, Chitosan)

Time (Min)	FT7	FT8	FT9	FT10	FT11	FT12
0	**0**	**0**	**0**	**0**	**0**	**0**
5	50.31	58.41	50.61	54.87	55.44	57.53
10	68.22	86.52	81.19	69.41	88.48	75.62
15	95.60	94.63	96.61	83.29	96.34	96.58
30 (0.5 hr)	2.61	2.08	5.84	31.24	24.99	16.25
60 (1 hr)	5.12	4.17	14.68	46.83	38.52	27.31
120 (2 hr)	9.63	8.84	27.81	65.76	49.44	36.42
180 (3 hr)	15.97	10.43	31.34	87.34	60.13	45.31
240 (4 hr)	20.84	14.26	37.61	99.08	71.67	54.27
300 (5 hr)	26.59	18.32	48.52		82.78	63.32
360 (6 hr)	35.87	22.51	56.31		90.32	75.42
420 (7 hr)	41.82	29.64	62.37		99.37	87.21
480 (8 hr)	50.61	37.42	68.22			98.41
540 (9 hr)	58.36	46.81	70.54			98.35
600 (10 hr)	65.17	53.06	72.66			
660 (11 hr)	79.14	60.28	81.64			
720 (12 hr)	80.98	62.34	95.6			

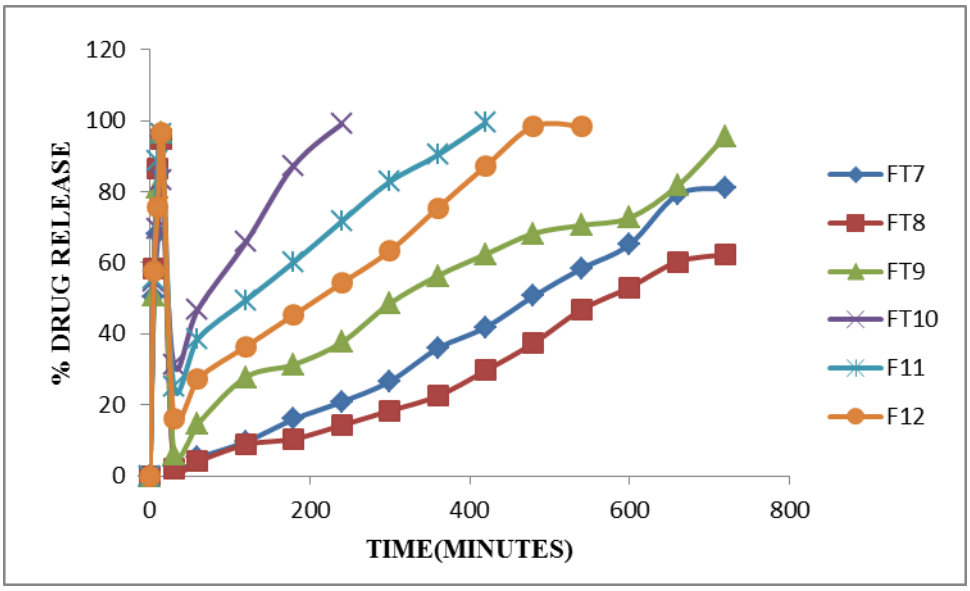


Fig: Dissolution graph of Nitrendipine Floating bilayer tablets by using Semi synthetic Polymers(Sodium Alginate, Chitosan)

F7- F12 Formulations were prepared by using Semi synthetic Polymers (Sodium Alginate, Chitosan). Sodium alginate concentration 30 mg is sufficient to release the drug 95.6% in 12 hours. hence it was considered. Chitosan was not produce the sufficient drug release in 12 hours duration time. Hence they were not considered. FT9 formulation is best formulation by using Semi synthetic polymers.

Table: Dissolution data of Nitrendipine Floating bilayer by using Synthetic Polymers (HPMC K15M, HPMC K100M)

Time (Min)	FT13	FT14	FT15	FT16	FT17	FT18
0	**0**	**0**	**0**	**0**	**0**	**0**
5	52.99	56.44	51.63	54.87	53.45	59.33
10	74.11	86.57	84.16	67.41	88.31	77.95
15	97.72	96.66	94.63	92.59	97.74	98.55
30 (0.5 hr)	40.41	24.51	15.46	34.45	21.26	17.37
60 (1 hr)	51.32	33.32	21.31	48.39	28.27	24.11
120 (2 hr)	63.3	42.11	30.53	56.47	35.52	30.54
180 (3 hr)	79.36	59.47	39.29	62.32	41.49	38.23
240 (4 hr)	80.6	66.36	46.31	70.76	49.08	44.63
300 (5 hr)	99.43	77.17	53.16	78.41	56.34	50.71
360 (6 hr)		84.63	60.27	85.45	62.08	55.63
420 (7 hr)		99.18	69.34	91.67	69.21	60.08
480 (8 hr)			76.41	99.47	75.36	66.34
540 (9 hr)			82.26		81.09	71.04

600 (10 hr)			90.17		87.34	76.12
660 (11 hr)			99.53		94.41	81.34
720 (12 hr)					96.98	87.25

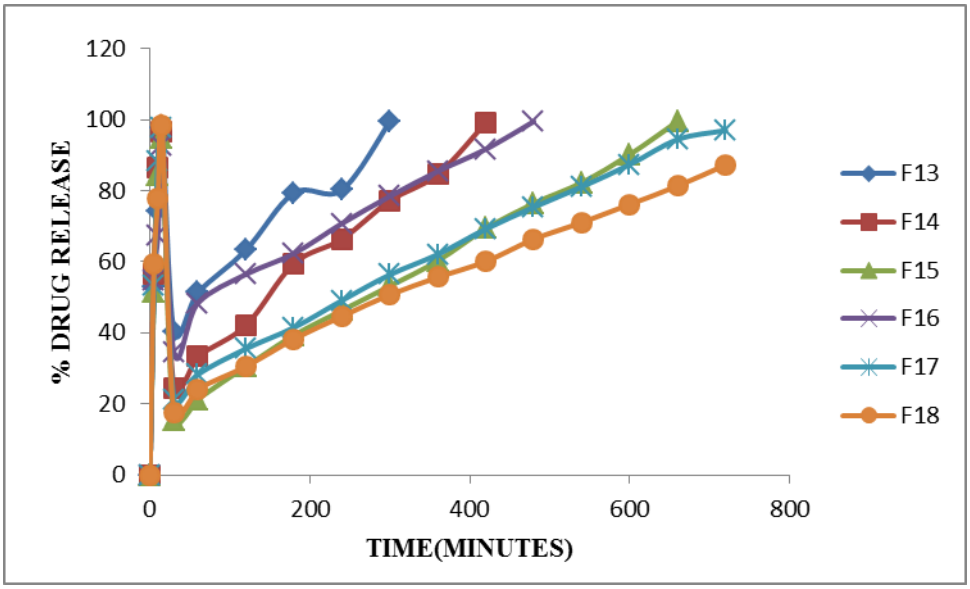


Fig: Dissolution graph of Nitrendipine Floating bilayer tablets by using Synthetic Polymers (HPMC K15M, HPMC K100M)

F13- F18 Formulations were prepared by using Synthetic Polymers (HPMC K15M, HPMC K100M). HPMC K 15M concentration is not sufficient to retard the drug release. hence it was considered. FT17 formulation is best formulation by using HPMC K100M Synthetic polymer. this formulation was 96.98 % drug release in 12 hours. Hence FT17 formulation was considered as best formulation among the synthetic polymers like HPMC K 15M, HPMC K 100M.

Among All The Formulations F1-F18 Concluded That Best Formulations Are

S.NO	FORMULATION CODE	USED POLYMER	TYPE OF POLYMER	DRUG RELEASE	FLOATING LAG TIME (MIN)	TOTAL FLOATING TIME(HRS)
1	FT5	Locust bean gum	Natural	97.12%	2.0	>12
2	FT9	Sodium alginate	Semi Synthetic	95.6%	2.1	>12
3	FT17	HPMC K100M	Synthetic	96.98 %	2.3	12

From the above dissolution data, Floating lag time, Total Floating Time were taken into the consideration to optimise the formulation. the best drug release, less floating lag time, more total floating time is for the FT5 formulation which contains the Locust bean gum (20mg). Hence FT5 was the optimised formulation.

RELEASE KINETICS

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/ 3	Qt1/ 3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
4.56	0.5	0.707	0.659	-0.301	1.980	9.120	0.2193	-1.341	95.44	4.642	4.570	0.072
9.14	1	1.000	0.961	0.000	1.958	9.140	0.1094	-1.039	90.86	4.642	4.496	0.146
16.59	2	1.414	1.220	0.301	1.921	8.295	0.0603	-0.780	83.41	4.642	4.369	0.272
21.28	3	1.732	1.328	0.477	1.896	7.093	0.0470	-0.672	78.72	4.642	4.286	0.356
26.42	4	2.000	1.422	0.602	1.867	6.605	0.0379	-0.578	73.58	4.642	4.190	0.451
34.91	5	2.236	1.543	0.699	1.814	6.982	0.0286	-0.457	65.09	4.642	4.023	0.619
40.58	6	2.449	1.608	0.778	1.774	6.763	0.0246	-0.392	59.42	4.642	3.902	0.739
52.09	7	2.646	1.717	0.845	1.680	7.441	0.0192	-0.283	47.91	4.642	3.632	1.010
64.25	8	2.828	1.808	0.903	1.553	8.031	0.0156	-0.192	35.75	4.642	3.294	1.347
76.14	9	3.000	1.882	0.954	1.378	8.460	0.0131	-0.118	23.86	4.642	2.879	1.763
85.63	10	3.162	1.933	1.000	1.157	8.563	0.0117	-0.067	14.37	4.642	2.431	2.210
95.11	11	3.317	1.978	1.041	0.689	8.646	0.0105	-0.022	4.89	4.642	1.697	2.944
97.12	12	3.464		1.079								

Table: Application of Release Rate Kinetics to Dissolution Data for optimised formulation (FT5):

KINETICS	SR5 LAYER
Zero order	$R^2 = 0.969$
First order	$R^2 = 0.799$
Kars mayer peppas	**$R^2 = 0.986$**
Higuchi	$R^2 = 0.8762$

Optimised SR5 Layers were kept for release kinetic studies. SR5 Layer was following Kars mayer peppas release kinetics. FT 5 formulation was optimised formulation.

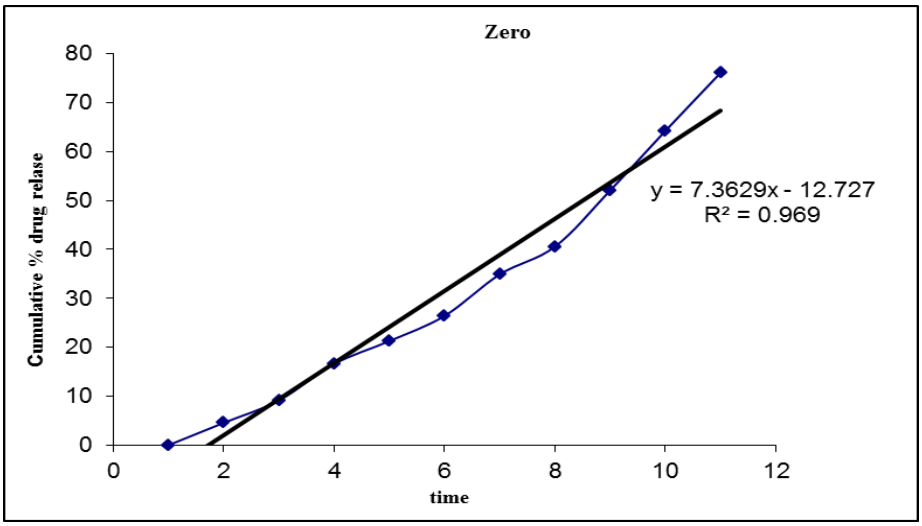


Figure: SR5 Formulation Zero Order Release Kinetics

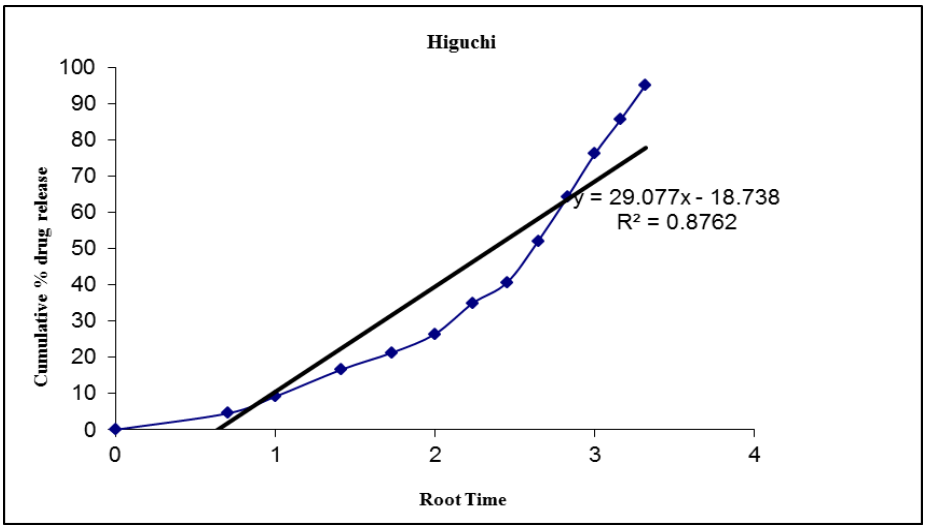


Figure: SR5 Formulation Higuchi graph

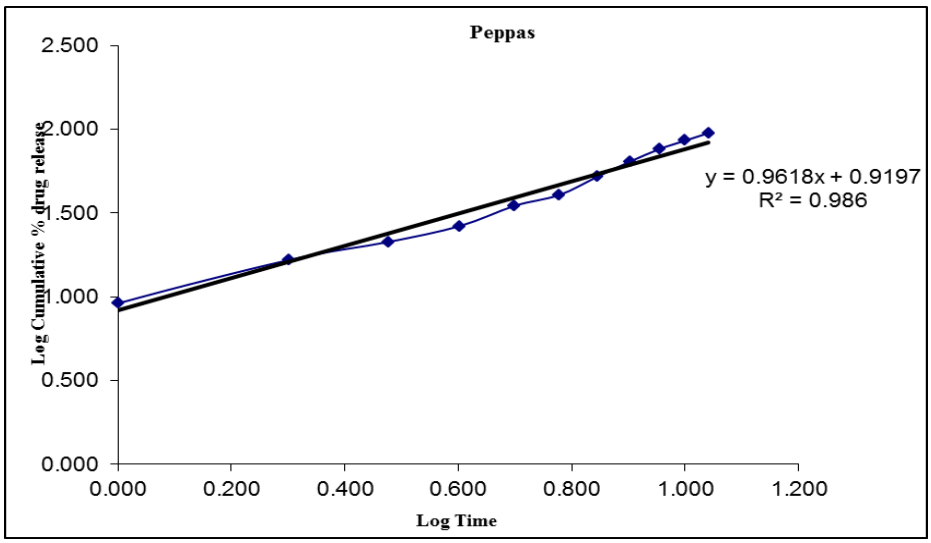


Figure: SR5 Formulation Peppas graph

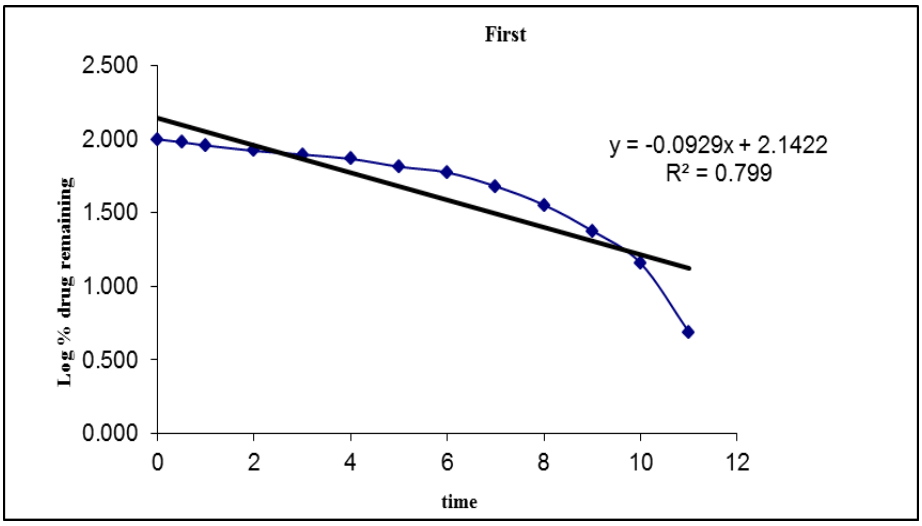


Figure: SR5 Formulation First order graph

CONCLUSION

The present study was carried out for Floating bilayer tablets of Nitrendipine. Both IR and SR layers were compressed using Direct compression method. Immediate powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.54 to 0.72 (gm/Cm^3) showing that the powder has good flow properties.

The tapped density of all the formulations was found to be in the range of 0.65 to 0.86 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which show that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Floating layer powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.74 to 0.86 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.87 to 1.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

All the parameters for IR and floating bilayer tablet such as weight variation, friability, hardness, thickness, drug content, invitro buoyancy (For floating bilayer tablet) were found to be within limits. From the dissolution data of Nitrendipine Immediate release Layer, IR2 formulation was shown maximum drug release at 15 min. i.e., 95.62%. Hence IR4 was concluded as optimized formulation for IR layer. dissolution data, Floating lag time, Total Floating Time were taken into the consideration to optimise the formulation. the best drug release, less floating lag time, more total floating time is for the FT5 formulation which contains the Locust bean gum (20mg). Hence FT5 was the optimised formulation. Optimised SR5 Layers were kept for release kinetic studies. SR5 Layer was following Kars mayer peppas release kinetics. FT 5 formulation was optimised formulation.

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