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Research Article

Formulation and Development of Bilayer Floating Tablet of Nifedipine using surface solid dispersion technique

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Surface solid dispersion;
Bilayer tablet;
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Abstract

The aim of the present work was to develop formulation of Nifedipine in the form of bilayer floating sustained release tablet. Bilayer consist of a two layers, immediate release layer and second sustained release layer, compressed in single unit dosage form. Immediate release layer contains surface solid dispersion of Nifedipine and Floating sustained release layer also contain surface solid dispersion of Nifedipine by using HPMC K100M & HPMC K15M as sustained release polymer. Nifedipine is an antihypertensive drug. Surface solid dispersion of Nifedipine was prepared by solvent evaporation method with different super disintegrant as a polymer for improvement of solubility resulting in improved bioavailability. In the present study Nifedipine bilayer floating controlled release tablet were prepared with the help of direct compression method, using sodium bicarbonate and citric acid which generate gas upon contact with gastric fluid. Immediate release layer releases the drug immediately and floating sustained release layer floats on gastric fluid for upto12 hours and releases the drug in sustained manner, subsequently it prolongs duration of action. The tablets were evaluated for various physical parameters, buoyancy studies, dissolution studies and drug released mechanisms. The batch number F5 formulation showed minimum disintegration time of immediate release layer (24 sec) and gave maximum swelling index of the sustained release layer (82.8%) and also maximum drug release duration of Nifedipine spread over 12 hours.

1. Introduction

The bilayer tablet is a concept which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs.[1] Floating Bilayer drug delivery system is combined principle of bilayer tablet as well as floating mechanism. Floating Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.[3] Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. [2] While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.

Bioavailability of poorly water-soluble hydrophobic drugs is limited by their solubility and dissolution rate.[5] The solid dispersion technique shows promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability.[6] The mechanism by which solid dispersion enhances the solubility and dissolution

involves particle size reduction to fine form or molecular level, conversion of crystalline form to amorphous form and by enhancing wettability.

Hypertension

According to WHO, state in which systolic pressure is 150mm Hg or more and diastolic pressure is 95mm Hg or more. Nifedipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through L-type calcium channels. Nifedipine reduces the peripheral arterial vascular resistance and releases coronary artery spasms. Thus it has hypotensive and antianginal properties. The vasodilatory effects of Nifedipine result in an overall decrease in blood pressure. The main objective of developing this system is to prepare sustain release composition which release Nifedipine over prolonged period of time.[7]

2. Material and method

Nifedipine gifted by Pell Tech Health Care Pvt. Ltd., Malad (W) Mumbai. HPMC K 100M, HPMC K 15M, NaHCO3 were gifted by SD Fine Chem. Croscarmellose Sodium, crospovidone, avicel PH102 and starch were purchased from Visual Chem, Mumbai. Sodium starch glycolate, Carbopol 934P, Citric acid, Magnesium stearate were purchased from Research-Lab Fine Chem Industries. Avicel PH102 and Starch were purchased from Hilab Chemicals.

Equipments

Table No.1: List of Equipments used in this study

Sr. No.	Equipment	Mfg. By
1.	Electronic weighing balance	Schimadzu, Japan
2.	Tablet Compression Machine	Emtech
3.	Hot air oven	Bio Techno Lab.
4.	Dissolution apparatus	Electrolab
5.	U.V. Spectrophotometer	Shimadzu 1800
6.	FTIR Spectrophotometer	Perkin Elmer Spectrum 65
7.	Hardness tester	Monsanto
8.	Disintegration Apparatus	Shreeji
9.	Friability Apparatus	Roche Friablator
10.	Stability Chamber	Bio techno lab
11.	Differential Scanning Calorimeter	Miller Star sw 9.01
12.	X-rayDiffraction Spectrometer.	Siemens,Germany D-5000

2. Formulation Development

2.1 Preparation Surface Solid Dispersion of Nifedipine:-

2.2 Preparation of Bilayer Floating Tablet:-

2.1 Preparation Surface Solid Dispersion of Nifedipine:-

Before preparation of surface solid dispersion there was need to select optimized conditions for preparation of surface solid dispersion. The selected drug was light sensitive. The light of wavelength greater than 420 nm was only suitable for stability of drug.[8] Another way was to formulate dosage form in dark background. The formulation was prepared under the light of wavelength greater than 420 nm i.e. in compact fluorescent lamp having wavelength 400-700nm.

2.1.1 Procedure:

Required amount of Nifedipine was dissolved in 20 ml of Ethanol. Accurately weighed carrier corresponding to different drug: carrier ratio by weight was dispersed in drug solution. Kept it closed for one hour. Then the solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-42ºC in a protected environmental condition. The dried mass was pulverized and was passed through a #100 mesh sieve. The powder was subsequently dried at 40ºC for 3 hours in a tray drier. The powder was stored in desiccators for further studies.[9]

Table 2: Coding formulations for SSD of Nifedipine

Drug	Nifedipine	Nifedipine	Nifedipine
Carrier	**SSG**	**CCNa**	**CP**
Code	SSD-S1	SSD-C1	SSD-P1
Code	SSD-S2	SSD-C2	SSD-P2
Code	SSD-S3	SSD-C3	SSD-P3
Code	SSD-S4	SSD-C4	SSD-P4
Code	SSD-S5	SSD-C5	SSD-P5
Drug : Carrier ratio	1:1	1:1	1:1
Drug : Carrier ratio	1:2	1:2	1:2
Drug : Carrier ratio	1:3	1:3	1:3
Drug : Carrier ratio	1:4	1:4	1:4
Drug : Carrier ratio	1:5	1:5	1:5

2.3 Preparation of Bilayer Floating Tablet

Tablets were prepared by direct compression technology using 8 stations tablet punch machine. Bilayer floating tablets were prepared in two stages. Both the layers were prepared separately. Bilayer tablets were prepared by double compression technique. First, previously weighed quantity of floating sustained release layer was fed to die cavity as the second layer and compressed very slightly to get uniform layer, then weighed quantity of immediate release layer blend was fed in to the die cavity as the first layer and compressed finally to get bilayer tablet. By this method, the immediate release layer was compressed once, so there is fast disintegration and avoidance of the double compression. The compositions details of Bilayer floating tablets are given in following table.

2.3.1 Dose calculation for bilayer tablet

Dose Calculation: For sustained drug release up to 12 hr, the immediate dose of drug was calculated from total dose of Nifedipine sustained release tablet, which is 20 mg. **Dt = Dose (1 + 0.693 × t/t 1/2)**

Where,

Dt = Total dose; **Dose** = Immediate release dose; **t** = Total time period for which sustained release is required

$\mathbf{t_{1/2}}$ = Half-life of drug (Nifedipine) 2hr

For example, **Nifedipine (20mg) = Dose [1+ (0.693 ×12)/2]**

Dose = 3.87 mg Nifedipine.

According to dose calculation, IR dose of drug is 3.87mg for the preparation of bilayer tablets. The maintenance dose is 16.13mg. Equivalent dose of Nifedipine is taken from surface solid dispersion and added in both layers to form bilayer tablet formulation.[10]

Table No.3: Composition of Bilayer Floating Tablet

Sr No.	Ingredients	Batch code								
	Immediate Release Layer	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**
1	SD of Nifedipine	3.87	3.87	3.87	3.87	3.87	3.87	3.87	3.87	3.87
2	Starch	5	5	5	5	5	5	5	5	5
3	Mg. Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
4	Avicel pH102	78.78	78.78	78.78	78.78	78.78	78.78	78.78	78.78	78.78
Sustain Release Layer		**SR1**	**SR2**	**SR3**	**SR4**	**SR5**	**SR6**	**SR7**	**SR8**	**SR9**
1	SD of Nifedipine	16.13	16.13	16.13	16.13	16.13	16.13	16.13	16.13	16.13
2	HPMC K100M	100	80	60	100	80	60	100	80	60
3	HPMC K15M	10	20	30	20	30	10	30	10	20
4	Carbopol 934P	10	10	10	10	10	10	10	10	10
5	Sod. bicarbonate	30	30	30	30	30	30	30	30	30
6	Citric acid	15	15	15	15	15	15	15	15	15
7	Mg. Stearate	4	4	4	4	4	4	4	4	4
8	Talc	2	2	2	2	2	2	2	2	2
9	Avicel pH102	23.18	33.18	43.18	13.18	23.18	63.18	3.18	43.18	53.18
10	Ferric oxide red	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

*All quantities in ‘mg’ ;*Total Weight of Bilayer Floating tablet: 360mg.;* SD: Solid Dispersion.; *Mg. stearate: Magnesium stearate.; *HPMC: Hydroxy P Propyl Methyl Cellulose.; *Sod.: Sodium.

3. Evaluation

3.1 Pre-compression parameter:[11]

3.1.1 Angle of repose: In this method weighed 10 gm of bulk powder, passed it through sieve no 40 mesh size .then allowed to flow under gravity though funnel and angle of incline of the formed. That is produced is assayed by measuring the height (h) and having a fixed base i.e. radius (r).

$$\text{Angle of Repose } \theta = \tan^{-1} h/r$$

3.1.2 Bulk Density: It is the ratio of total mass of powder (m) to the bulk volume of powder. **Dt=m/Vo**

3.1.3 Tapped Density: It is the ratio of total mass of powder (m) to the tapped volume (Vi) of powder. **Dt = m/Vi**

3.1.4 Compressibility index: It is determined by taking tapped density and bulk density. Which has been put in the formula given below and determined compressibility index.

Compressibility Index= Tapped density – bulk density / tapped density x 100

3.1.5 Hausner's Ratio:-It is determined by taking Tapped density and it divided by Bulk density by using following formula: **Hausner's Ratio= Tapped density / Bulk density**

3.2 Evaluation Parameter of Bilayer Floating Tablets:

Prepared Floating Bilayer tablets were evaluated for compression parameters such as Hardness, Weight variation, Friability, Drug content, % Drug Release, Buoyancy lag time, Floating time, etc.

3.2.1 Hardness:- Tablet hardness is also known as tablet crushing strength & was determined by Monsanto hardness tester..

3.2.2 Friability:- Friability test is performed to assess the effect of abrasions and shock that may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose.

$$\% F = \{Wo - W / Wo) \times 100$$

Where, **% F**= Friability in percentage; **Wo**= Initial weight of tablet; **W**= Final weight after revolution

3.2.3 Drug content:- The Nifedipine content in tablets was determined by powdering 10 tablets in each batch. Powder equivalent to 100 mg of Nifedipine was dissolved in 0.1 N HCl. 1 ml of filtrate was further diluted to 100 ml with 0.1 N HCl and it was determined by U.V. spectroscopy at 341.2 nm.

3.2.4 Weight variation: 10 tablets of each of formulation were weighed individually using an electronic balance. The average weight was calculated and individual tablet weight was compared with average value and the deviation was recorded.

3.2.5 Thickness: The thickness of tablets was determined using Digital Vernier Caliper, (Mitutoyo, Japan). It is expressed in mm.

3.2.6 Disintegration Time: Six tablets were selected randomly from each batch for the disintegration test. Disintegration test was performed in simulated gastric fluid using disintegration tester. Disintegration time (DT) was measured for immediate release layer.

3.2.7 Determination of Buoyancy lag time: The buoyancy lag is the time required for tablet to rise towards surface & float. The buoyancy of tablets was studied at 37±0.5ºc in 900ml of simulated gastric fluid. The buoyancy lag time was measured by using stop watch and total floating time was observed visually.

3.2.8 Floating time: Floating time was determined by using USP dissolution apparatus-II at 50 rpm using 900ml of 0.1N HCl and temperature was maintained at 37±0.5ºC, throughout the study. The duration of floating (floating time) is the time the tablet floats in the dissolution medium (including floating lag time, which is the time required for the tablet to rise to the surface) is measured by visual observation.

3.2.9 Swelling Index: Swelling study was performed for the floating sustained release layer tablets. The accurately weighed tablets were placed in USP dissolution apparatus II containing 900ml of 0.1N HCl maintained at 37±2ºC and allowed to swell up to constant weight. The tablets were removed, blotted with filter paper, and changes in weight were measured. The experiments were carried out in triplicate. The degree of swelling (Swelling index) was then calculated from the formula.

$$\text{Swelling index} = \frac{(W_g - W_o)}{W_o} \times 100$$

Where, W_o is the initial weight of tablet and W_g is the weight of tablet at equilibrium swelling in the medium.

3.2.10 *In-vitro* drug release study: *In-vitro* dissolution studies of floating tablets of Nifedipine were carried out in USP dissolution test apparatus-II, employing a paddle type apparatus at 50 rpm using 900ml of 0.1N HCl as dissolution medium at 37±0.5ºC. One tablet was used in each test. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5ºC. The withdrawn samples were filtered through membrane filter 0.45µm & analyzed by using UV spectrophotometer at λ max 338.2nm. This test was performed on 9 batches of bilayer tablets.[12]

3.2.11 FITR study of optimized Bilayer Floating Tablet:-About 1mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer USA and the IR spectrum was recorded from 4000 cm-1 to 400 cm-1 in a scan time of 12 minutes. An FTIR spectrum of final optimized formulation was obtained. The resultant spectra were compared for any spectral changes.

3.2.12 Differential Scanning Calorimetry study for optimized Formulation:- Final optimized formulation was assessed by carrying out thermal analysis "Miller Star sw 9.01" differential scanning calorimeter. The sample (1-2mg) was carefully transferred & heated in a crimped aluminum pan for accurate result. The sample was heated from 30-300ºC at the rate of 10ºC /min. Then the inert atmosphere was maintained by purging Nitrogen gas throughout the experiment at the rate of 40ml/min.

3.2.13 Stability Studies and Storage Condition: To check the effect of environmental condition or storage conditions on formulation. Final formulation was kept in environmental stability chamber for accelerated stability condition at 40°C±2℃ temperature and 75 ± 5 % relative humidity for a period one month. The samples were withdrawn after 10 days, 20 days and 30 days intervals and evaluated for physical parameters, drug content, in-vitro drug release and floating behavior etc.

3.2.14 Optimization of Bilayer Floating Tablet: Optimization of formulation variables for preparation of Bilayer floating Tablet of Nifedipine by using 3^2 Full factorial designs. To study the effect of variables, we applied the 3^2 factorial designs. The amount of HPMC K 100M (X1) and HPMC K15M (X2) were kept as an independent variables and Hardness of tablet(Y1), % drug release (Y2) & percent swelling (Y3) were selected as dependent variables.

4. Result and Discussion

Table 4: Result of Bulk density, Tapped density, % Compressibility, Hausner's ratio & Angle of repose of surface solid dispersion of Nifedipine *All values are expressed as Mean ± SD, n

Batch Code	Parameters				
	Bulk Density (gm/cc)	Tapped Density (gm/cc)	% Compressibility (%)	Hausner's Ratio	Angle of repose
SSD-S1	0.424±0.057	0.510±0.034	16.86±0.31	1.20±0.031	25.02±0.71
SSD-S2	0.404±0.048	0.474±0.046	14.76±0.47	1.17±0.074	23.12±0.58
SSD-S3	0.466±0.055	0.556±0.025	16.18±0.52	1.191±0.057	24.27±0.92
SSD-S4	0.480±0.043	0.610±0.047	21.31±0.58	1.27±0.048	24.78±0.83
SSD-S5	0.502±0.040	0.631±0.043	20.44±0.49	1.25±0.038	25.32±1.61
SSD-C1	0.448±0.039	0.533±0.051	15.94±0.73	1.09±0.052	27.59±0.48
SSD-C2	0.525±0.071	0.651±0.058	19.35±0.47	1.24±0.073	27.98±1.39
SSD-C3	0.488±0.045	0.627±0.063	22.16±0.45	1.28±0.068	27.11±0.75
SSD-C4	0.556±0.061	0.699±0.081	20.45±0.53	1.25±0.046	27.32±0.69
SSD-C5	0.410±0.068	0.515±0.042	20.38±0.74	1.25±0.062	25.20±0.64
SSD-P1	0.485±0.028	0.579±0.025	16.23±0.59	1.19±0.047	26.28±0.86
SSD-P2	0.496±0.055	0.556±0.047	10.79±0.38	1.12±0.041	23.43±1.24
SSD-P3	0.499±0.037	0.583±0.062	14.40±0.56	1.16±0.073	27.85±0.65
SSD-P4	0.440±0.025	0.521±0.048	15.54±0.44	1.18±0.061	27.16±1.47
SSD-P5	0.476±0.058	0.581±0.037	18.07±0.48	1.22±0.027	26.84±0.52

***All values are expressed as Mean ± SD, n=3**

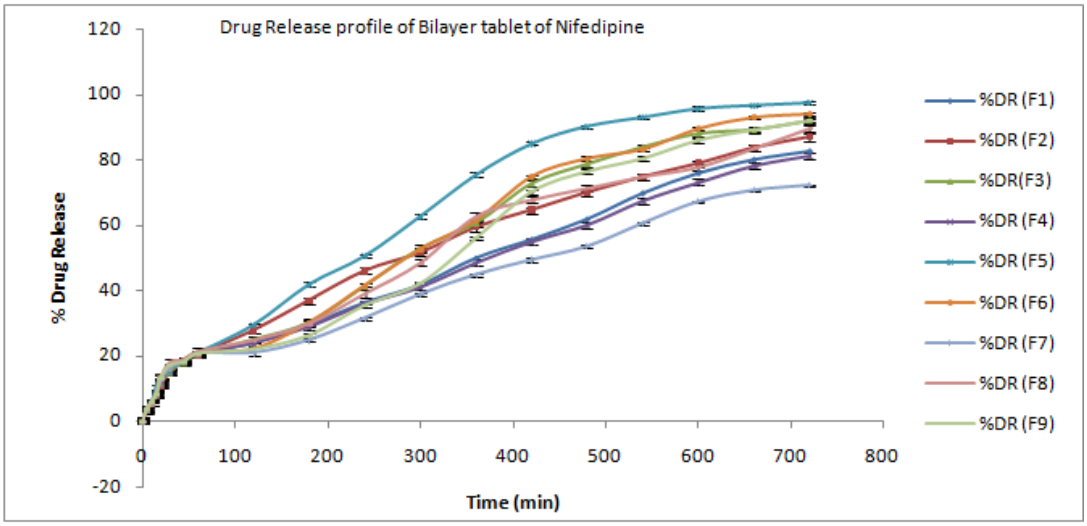
Table 5: Result of Precompression parameter of immediate release and floating sustained release blend of Nifedipine

Batch Code	Parameters				
	Bulk Density (gm/cc)	Tapped Density (gm/cc)	% Compressibility (%)	Hausner's Ratio	Angle of repose
IR	0.612 ±0.008	0.7062± 0.007	13.62 ±0.0019	1.15 ±0.0025	25.64± 1.18
SR1	0.6234±0.031	0.710±0.044	12.19±0.063	1.14±0.04	26.61±0.56
SR2	0.6023±0.053	0.7134±0.047	15.57±0.057	1.184±0.037	27.51±0.72
SR3	0.598±0.047	0.701±0.07	14.69±0.032	1.004±0.032	24.70±0.61
SR4	0.624±0.034	0.731±0.047	14.63±0.039	1.17±0.036	26.56±0.52
SR5	0.614±0.046	0.698±0.062	12.09±0.028	1.13±0.044	24.70±0.54
SR6	0.601±0.062	0.710±0.043	15.35±0.038	1.18±0.026	25.17±0.67
SR7	0.615±0.046	0.720±0.058	14.58±0.052	1.17±0.048	25.45±0.75
SR8	0.6162±0.037	0.7312±0.036	15.72±0.064	1.18±0.063	26.10±0.68
SR9	0.598±0.057	0.678±0.065	11.79±0.049	1.13±0.048	28.22±0.59

Table No.6: Result of Tablet properties of Bilayer Floating tablet formulation.

Sr. No	Parameters	Formulations Code & Results								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Average Weight (360mg)	361±0.06	363±0.08	359±0.05	360±0.05	361±0.06	360±0.06	359±0.05	360±0.06	361±0.07
2	Thickness (mm)	3.02±0.03	3.05±0.04	3.01±0.02	3.01±0.06	3.02±0.01	3.04±0.03	3.07±0.05	3.03±0.03	3.02±0.06
3	Hardness (kg/cm^2)	6.4±0.5	5.4±0.4	5.4±0.2	6.8±0.2	5.8±0.4	5.0±0.4	7.0±0.5	5.2±0.4	5.2±0.7
4	Friability (%)	0.078±0.035	0.071±0.041	0.082±0.032	0.069±0.048	0.062±0.039	0.092±0.023	0.096±0.028	0.083±0.02	0.06±0.049
5	DT of IR layer (Sec)	25±0.82	31±0.23	24±0.27	27±0.75	24±0.17	28±0.37	29±0.47	26±0.33	31±0.12
6	% Swelling Index of SR later tablet	61.2±0.47	64.9±0.58	74.3±0.81	58.4±0.51	82.8±0.36	80.4±0.15	54.2±0.093	70.8±0.39	76.5±0.48
7	Drug Content (%)	96.3±0.9	97.5±0.5	96.1±0.3	96.7±0.3	98.3±0.8	97.5±0.1	98.2±0.4	98.7±0.9	97.5±0.2
8	Floating lag time (Sec)	110±2.1	65±2.5	82±1.3	80±1.6	61±2.5	78±1.8	69±2.7	98±2.9	112±1.3
9	Floating time (hrs)	12.8±0.05	12.3±0.7	12±0.03	12.7± 0.09	12.6±0.05	12.4±0.04	12.6±0.06	13.1±0.03	12.4±0.06

Figure 1: Comparative drug release profile of bilayer tablet of Nifedipine



***All values are expressed as Mean ±SD, n = 3**

From the dissolution profile of the Bilayer tablet formulation (F1-F9) as shown in the Table No 6, from the figure No. 1 it was concluded that F5 batch was considered to be optimized formula, as it had highest percentage drug release of 97.47% of all formulations. Formulation showed drug release up to 12hours. Its hardness was optimum, disintegration time 24sec, floating lag time was 61sec. The reason for this could be the use of HPMC K100M & K15M in adequate proportion

with gas generating agent. HPMC K100M & HPMC K15M showed good swelling property due to which drug release in sustained manner.

4.1 Evaluation of Dependent Variables and Mathematical Modeling:

The values of dependent variables of bilayer tablet formulations are described in Table no.7. These values are necessary to get polynomial equations from Design Expert software for the respective dependent variable.

Table 7: Experimental Runs and Observed Responses for 3^2Factorial Design

Batch	Code		Hardness Kg/cm^2 (Y_1)	% Drug release (Y_2)	% Swelling (Y_3)
	X_1	X_2			
F1	+1	-1	6.4 ± 0.5	82.39 ± 0.61	61.2±0.48
F2	0	0	5.4 ±0.4	86.83 ±0.33	64.9±0.74
F3	-1	+1	5.4 ±0.2	91.92 ±0.51	74.3±0.63
F4	+1	0	6.8 ±0.2	81.35 ±0.57	58.4±0.86
F5	0	+1	5.8 ±0.4	97.47 ±0.42	82.8±0.92
F6	-1	-1	5.0 ±0.4	93.95 ±0.56	80.4±0.73
F7	+1	+1	7.0 ±0.5	72.12 ±0.33	54.2±0.58
F8	0	-1	5.2 ±0.4	89.74 ±0.71	70.8±0.62
F9	-1	0	5.2 ±0.7	92.0 ± 0.47	76.5±0.57

Table 8: Variable in 3^2 factorial Design

Independent Variables	Coded Levels		
	-1	0	+1
	Actual Levels		
X_1= HPMC K100M	60	80	100
X_2= HPMC K15M	10	20	30
Response variable			
Y_1= Hardness Y_2= % Drug release Y_3= % Swelling			

Table 9: Multiple Regression Output for Dependent Variables

Coefficient	Hardness	% Drug release	% Swelling
β_0	5.47	87.53	69.28
β_1	0.77	-7.00	-9.57
β_2	0.27	-0.76	-0.18
β_{11}	0.50	-	-
β_{22}	0.000	-	-
β_{12}	0.050	-	-
r^2	0.9963	0.6115	0.6729
p value(probe>F)	0.0008	0.0224	0.0350

1. Probe >F less than 0.0500 indicate model term are significant.
2. R^2 value less than 1.00 show model terms are significant.

4.1.1 Response 1: Hardness of Tablet

For Hardness of tablet, following equation was obtained from design model,

$$Y_1=5.47+0.77X_1+0.27X_2+0.50X_1^2+0.0000X_2^2+0.050X_1X_2$$

Positive coefficient of X_1 indicated increase in hardness of tablet with increase in HPMC K100M, positive coefficient of X_2 indicated increase in response of Y_1 i.e. increase in hardness with increase in HPMC K15M. In combination it gives positive coefficient effect but less as compared to individual effect. The equation obtained was Quadratic equation.

Surface response plot for Hardness of tablet showed that HPMC K100M (X1) effect was significant on hardness of tablet. As the concentration of HPMC K100M increases from 60-100 (-1 to +1) increase in hardness. HPMC K15M (X2) shows positive effect on hardness. As the concentration HPMC K15M increases from 10-30 then increase in hardness of tablet.

4.1.2 Response 2: Percent drug release

For Percent drug release, following equation was obtained from design model,

$$Y_2= 87.53 - 7.00X_1 – 0.76X_2$$

Negative coefficient of X_1 indicated decrease in % Drug release with increase in HPMC K100M, in the same way

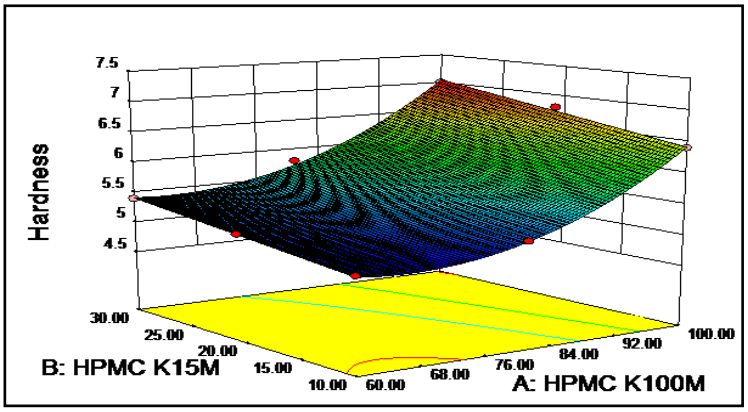
negative coefficient of X_2 indicate decrease in (Y2) i.e. % Drug release with increase in HPMC K15M concentration. 87.53 is the mean response i.e. mean % drug release from tablet.

Surface responses plot for % Drug release shows that HPMC K100M (X1) effect was negative on % drug release. As the concentration of HPMC K100M increases from (-1 to +1) i.e. from 60-100 decrease in percent drug release. HPMC K15M also shows negative effect on response Y2. As we increase the HPMC K15M concentration from 10-30 decrease in % drug release but in slight extend.

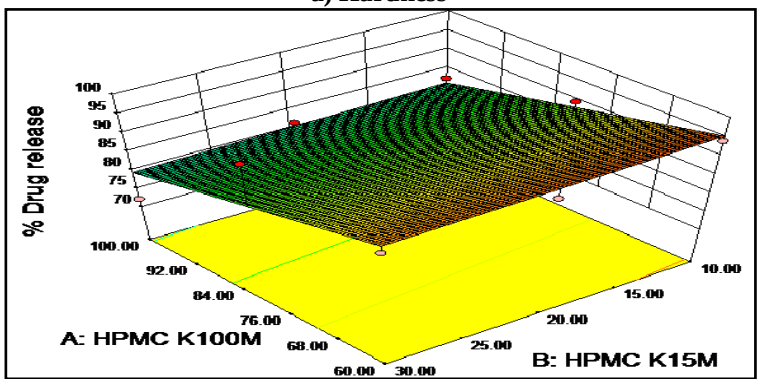
4.1.3 Response 3: Swelling Index: $Y_3 = 69.28 - 9.57X_1 - 0.18X_2$

Negative coefficient of X_1 indicated decrease in % Swelling with increase in HPMC K100M, in the same way negative coefficient of X_2 indicate decrease in (Y2) i.e. % Swelling with increase in HPMC K15M concentration. 69.28 is the mean response i.e. mean swelling index of tablet.

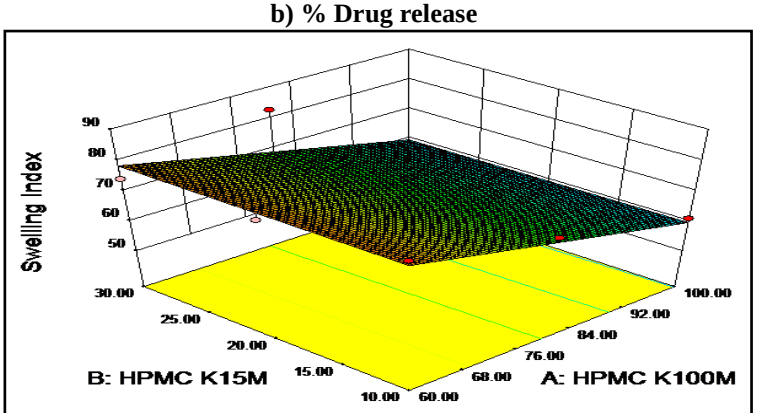
Surface responses plot for % Swelling shows that HPMC K100M (X1) effect was negative on % swelling. As the concentration of HPMC K100M increases from (-1 to +1) i.e. from 60-100 decrease in percent swelling. HPMC K15M also shows negative effect on response Y2. As we increase the HPMC K15M concentration from 10-30 decrease in % swelling but in slight extend.



a) Hardness



b) % Drug release



c) Swelling Index

Figure 2: Response surface plot showing effect of factorial variables on a) Hardness of tablet b) % Drug release c) Swelling Index

Putting all this responses result & after setting goal "seven" solutions were obtained from 9 combinations of categoric factor levels as shown in Table No.9. The best result was shown by the HPMC K100M at 80mg & HPMC K15M at 30mg concentration i.e. F5 batch having highest desirability 0.911.

Table 10: Solutions for 9 combinations of categoric factor levels

Sr. No	HPMC K100M	HPMC K15M	Hardness Kg/cm2	% Drug release	Swelling Index (%)	Desirability
1	**80**	**30**	**5.8**	**97.47**	**82.83**	**0.911**
2	60	30	5.4	91.92	77.06	0.712
3	60	20	5.2	92	77.06	0.647
4	80	10	5.2	89.74	72.83	0.576
5	80	20	5.4	86.83	72.83	0.559
6	100	10	6.4	82.39	57.93	0.364
7	100	20	6.8	81.35	57.93	0.289

From result of Optimization study and the result of various evaluation test like Hardness, Disintegration time, Floating lag time, Total floating time, % drug release, % Swelling it was found that formulation F5 show best result so it was optimize formulation. Formulation F5 then used for further evaluation parameter of tablet.

4.2 FITR study of Bilayer Floating Tablet:-

FTIR study of Bilayer Floating Tablet of optimized batch of Nifedipine in comparison with Pure drug (Nifedipine) was done. The result of study is shown in following figure-

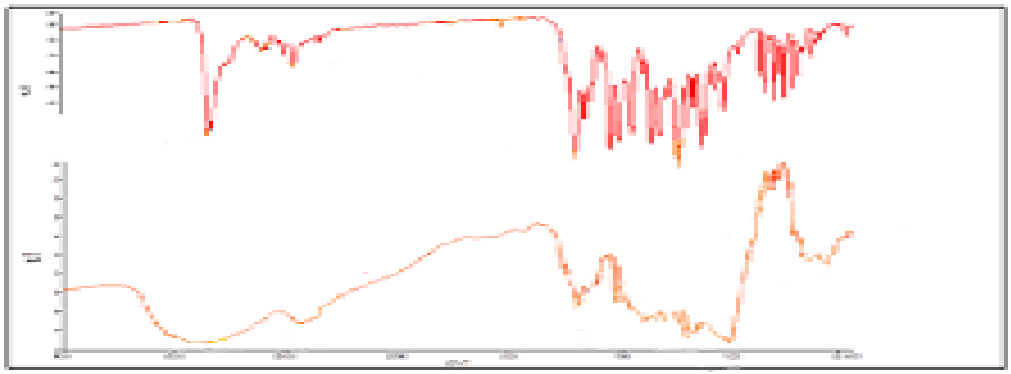


Figure 3: FTIR of Optimize formulation in comparison with Nifedipine

4.3 Differential Scanning Calorimetry study for Final optimized Formulation:-

DSC study for Optimized batch of Bilayer floating Tablet of Nifedipine was done and the result is shown in following figure.

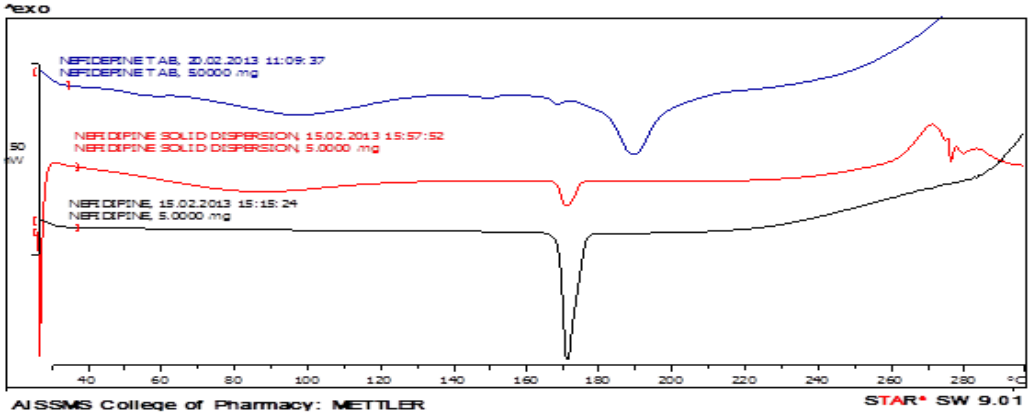


Figure 4: Comparative DSC study of Nifedipine with Surface solid dispersion & Optimized formulation

4.4 Result of stability studies

After storage the formulation was analyzed for various physical parameters, results shown in Table 11. No major differences were found between evaluated parameters before and after ageing / storage and all were in acceptable limits.

Table 11: Evaluation parameters of stability batch

Evaluation Parameters	Before stability storage (25±2℃ & 60±5%RH)	After 10 Days	After 20 days	After 30 days
		Temperature 40±2℃ & 75 ± 5 % RH		
Hardness(kg/cm^2)	5.8±0.4	NC	NC	NC
% Friability	0.062±0.039	NC	NC	NC
Average Weight (mg)	361±0.06	NC	NC	NC
Drug content (%)	98.3±0.8	98.7±0.4	98.4±0.5	98.6±0.2
Disintegration time (sec)	24±0.17	27±0.23	26±0.14	27±0.37
Drug release (%)	97.47±0.42	97.20±0.48	97.60±0.33	97.23±035
Swelling Index (%)	82.8±0.36	82.7±0.76	81.5±0.58	81.9±0.28
Floating lag time (sec)	61±2.5	64±1.2	64±0.9	67±1.3
Total floating time (hrs)	12.6±0.05	12.6±0.07	12.5±0.07	12.6±0.08

The data are presented as mean value ± S.D
(n = 3)
NC- No Change.

5. Conclusion

Nifedipine is Calcium channel blocker fall under BCS class II (Low solubility & High permeability). Nifedipine is rapidly absorbed with a time to maximum concentration (T_{max}) of approximately 30 minutes following oral administration of capsule, immediate release tablet.

Nifedipine has Low Solubility, Low Bioavailability (45-56%) and Low Half life (2hr). Frequent dosing of conventional dosage form Nifedipine is required to attain therapeutic level.

To overcome the solubility problem surface solid dispersion was prepared by Sodium starch glycolate, Croscarmellose sodium & Crospovidone as polymer. The optimized batch is used for further preparation of bilayer tablet of Nifedipine in which one layer is Immediate release act as loading dose as well as for patient comfort & second layer (sustain release floating layer) which enables the prolong and continuous input of the drug to the gastro intestinal tract and improve the bioavailability of the medication.

Sustained release floating layer prepared by HPMC K100M & HPMC K15M & Carbopol 934 P as a controlled release agent, sodium bicarbonate & citric acid act as effervescent agent.

The identity of drug was confirmed by physical characteristics, spectrophotometric analysis such as UV spectrophotometric and FTIR and thermal behaviour by DSC. Bilayer tablet prepared by direct compression technique. Optimization of Bilayer floating formulations carried out using 3^2 Factorial designs. Two independent variables X_1 (conc. of HPMC K100M) and X_2 (conc. of HPMC K15M) for floating sustained release tablets was selected and then prepared nine batches of bilayer tablets.

From the results of dependent variables (Responses) like Hardness, Swelling index, % drug release and from result of evaluations of bilayer formulations like Floating lag time, Total floating time, Disintegration time etc of nine batches F5 was selected as optimized batch.

The optimized formulation was then use for FTIR & DSC study for determination of interaction & stability of formulation. Then comparison of final bilayer formulation with marketed formulation was done. Then stability study as per ICH guideline was done at 40°c± 2°c & 75% ±5% RH condition.

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