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Formulation and *in-vitro* Evaluation of oral Floating *Nicardipine hydrochloride* Tablets

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ABSTRACT

Plan: *The purpose of this research was to develop floating matrix tablets of Nicardipine HCl (NIC) using different viscosity grades of direct compressible polymers with gas generating agent so as to prolong its gastric residence time.*
Preface: *Rapid gastrointestinal transit could lead to incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose.*
Methodology: *The tablets were prepared by direct compression technique. Precompressional and post compressional parameters were evaluated. In vitro dissolution studies were carried out in gastric acid fluid (pH 1.2). The mechanism of drug release from matrix tablets were analyzed kinetically using zero order, first order, Korsmeyer peppas, Higuchi and hixon Crowell models.*
Outcome: *The FTIR studies revealed no interaction between the drugs and excipients. F7 with R^2 value 0.9965 was considered optimized formulation with short floating lag time and long floating duration and release over 24h duration.*
Key words*: Floating tablet; dissolution; Nicardipine HCl; HPMC; kinetic models.*

1. INTRODUCTION

Sustained drug delivery systems have been developed for various routes of administration to provide more efficient therapeutic effects and to reduce the incidence of side effects. Nicardipine HCl (NIC), [1-4] a dihydropyridine calcium channel blocking agent, causes coronary and peripheral vasodilatation by blocking the influx of extracellular calcium across cell membranes. It is effective for treatment of hypertension, angina pectoris and cardiovascular diseases.

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It is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first pass metabolism. It has good solubility at low pH values, but poor solubility at higher pH values. Therefore, Nicardipine HCl is likely to be absorbed only in the stomach and in the upper part of the intestine tract. Because of the poor solubility of NIC or its hydrochloride in biological fluids having pH of 5 to 8, there has been lot of work done for conversion of it to a form having improved solubility in intestinal juices [5-9].

Nicardipine has an extensive hepatic first pass metabolism following oral administration with systemic bioavailability ranging from 20 to 33%. Because of its short half-life (2-4 h), the drug has to be given frequently (30 mg , 3 times daily) further, Nicardipine has some side effects such as nausea, vomiting, flushing, headache, dyspepsia, anorexia and diarrhea, probably due to rapid absorption [1].

Floating dosage forms are retained at the site of absorption and the longer retention enhances the bioavailability. Many approaches have been reported for controlling the residence time of a drug delivery system in a particular region of the gastrointestinal tract, such as intragastric floating systems (FDDS), high-density systems, mucoadhesive systems, magnetic systems, unfoldable, extendable, or expandable systems, and superporous, biodegradable hydrogel systems. Excipients that generate carbon dioxide in the stomach produce effective buoyancy for more than 24h. Hydrocolloids of natural and semisynthetic origin are commonly used for the development of FDDS. Floating matrix systems containing HPMC as the matrix forming excipient swell and form a gel layer with entrapped air around the tablet core after contact with gastric fluid, and this gel layer controls the drug release [10-13].

The objective of the present study was to formulate sustained release formulations of Nicardipine and to study the *in-vitro* performance of the sustained release floating formulations.

2. MATERIAL AND METHODS

Nicardipine HCl was purchased from Tokyo. Hydroxy propyl methyl cellulose (K100LV, K4M, K15M, K100MCR) were purchased from Loba Chemie, Chennai, India. Sodium bicarbonate procured from Fischer Scientific, Chennai, India. All other chemicals and solvents were of analytical grade.

2.1. Characterization of Nicardipine HCl.

The melting point, UV spectrum and FTIR spectrum were determined for Nicardipine HCl.

2.1.1.. Preparation of Nicardipine matrix tablets.

The matrix tablets were prepared by direct compression method. Accurately weighed quantities of Nicardipine (NIC) at 20%, HPMC (different grades) at 78%, $NaHCO_3$ at 18% and excipients sufficient enough (approximately 2%) for a batch of 50 tablets were mixed by geometric method of dilution and tumbled for 15 min. The percentages of polymer and sodium bicarbonate were fixed based on the initial trial for optimizing the floating abilities.

The blend were then lubricated with magnesium stearate for 5 min and directly compressed into tablets of average weight 200 mg using tablet punching machine (Cadmach, India) with 10 mm standard concave punches. The hardness of the tablet was maintained in the range of 3.5- 6 kg/cm^2. Different ratios of polymers were used to achieve the total weight of the tablet as constant. The various polymers grades used were HPMC K100LV, HPMC K4M, HPMC K15M and HPMC K100M. Microcrystalline cellulose (MCC) (1%) was used as diluents. Magnesium stearate, aerosol and talc were used as lubricant and glidant (at 1%) respectively. The composition of the formulations was shown in Table 1.

Table 1: Formulation composition of floating tablets of Nicardipine.

Batch code	Drug (%)	HPMC K100 LV (%)	HPMC K4M (%)	HPMC K15M (%)	HPMC K100M (%)	$NaHCO_3$
F0	20	60	-	-	-	18
F1	20	-	60	-	-	18
F2	20	-	-	60	-	18
F3	20	-	-	-	60	18
F4	20	-	20	40	-	18
F5	20	-	40	20	-	18
F6	20	-	-	20	40	18
F7	20	-	-	40	20	18
F8	20	-	20	-	40	18
F9	20	-	40	-	20	18

Amounts are milligrams per tablet. The excipients used were Aerosil 0.5%, Magnesium stearate 0.5% for all, Talc quantity sufficient (qs) and microcrystalline cellulose (qs) 1%.

2.2. Determination of pre-compressional parameters.

The angle of repose was determined by a fixed funnel method. It was calculated using the following equation [9].

$$\theta = \tan^{-1} h/r$$

Where h and r are the height and radius of the powder cone, and ɵ is angle of repose.

Bulk densities and packed densities (g/ml) of directly compressed powders/ floating microparticles were measured by tapping method. The percentage compressibility was determined for flowability characteristics.

$$\text{Compressibility (\%)} = (Pt-Pb) / Pt \times 100$$

Pt is the tapped bulk density and Pb is the initial bulk density. The packing factor (Hausner's ratio) was calculated as the ratio of bulk density after tapping to bulk density before tapping. The obtained results are shown in Table 2.

2.3. Determination of post compressional parameters.

The thickness and diameter were measured using Vernier caliper. Twenty representative samples were randomly taken for this test. The hardness test was conducting according to British Pharmacopeia (BP) by selecting five tablets randomly and hardness of each tablet was measured using Monsanto hardness tester.

Uniformity of weight was performed according to USP. 20 tablets were weighed accurately to get the total weight.

Table 2: Evaluation of pre-compressional parameters.

Batch code	*Bulk density*	*Tapped density (±SD)*	*Packing factor/ Hausner's ratio*	*% Compressibility*	*Angle of repose*
F0	0.71	0.80	1.127	11.250	23.74
F1	0.67	0.77	1.149	12.987	20.80
F2	0.69	0.80	1.159	13.750	24.22
F3	0.65	0.74	1.138	12.162	22.29
F4	0.67	0.77	1.149	12.987	28.81
F5	0.72	0.80	1.111	10.000	20.80
F6	0.68	0.78	1.147	12.821	21.80
F7	0.66	0.74	1.121	10.811	27.47
F8	0.71	0.81	1.141	12.346	27.02
F9	0.66	0.75	1.136	12.000	24.23

Data is represented as mean ± standard deviation (SD), n=3.

Then average weight was calculated by dividing the total weight of tablets by their number i.e. 20. Then individual tablet weight was taken. The upper control limit and lower control limit was determined based on percent deviation allowed for the given weight range (i.e. ±7.5%). Besides, the % deviation of individual tablet was calculated from the average weight.

For friability test, according to BP, the initial weighed 20 tablets (W_0) were placed in the cylindrical section of the Roche friabilator. The tablets were subjected to 25 rpm for 4 min. The tablets were withdrawn and reweighed (W_1). Percentage friability (% F) was determined using the following formula; the obtained results are shown in Table 3. [9-11]

$$\% F = W_0\text{-}W_1/ W_0 \quad X\ 100$$

2.4. Drug content analysis

The uniformity of drug content was determined by taking 6 tablets. They were crushed in the mortar and weight equivalent to one tablet weight was transferred to a conical flask containing 100 ml of simulated gastric fluid pH 1.2. It was stirred using magnetic stirrer at 50 rpm for 6 h. Then it was filtered through a 0.22 µm filter (Millipore India) and appropriate dilutions were made and absorbance was measured at 239 nm using double beam UV-VIS spectrophotometer (Shimadzu UV- 1601, Japan). The results are tabulated in Table 3.

2.5. In vitro buoyancy studies

The buoyancy of the tablets was studied at 37±0.5^{o}C in 100 ml simulated gastric fluid pH 1.2 (without pepsin).

The time required for tablet to float (lag time), duration of floating and matrix integrity was determined by visual observation [9-11]. The evaluation was conducted in triplicate for each batch of tablets. The obtained results are shown in Table 4.

Table 3: Physico-chemical properties of prepared tablets.

Batch code	*Weight variation (mg)*	*Hardness (kg/cm^2)*	*Diameter (cm)*	*Thickness (mm)*	*Friability (%)*	*Drug content (%)*
F0	203±1.5	4±0.6	0.8±0.1	0.55±0.05	0.4±0.2	99.06±2.3
F1	202±3.5	5±0.7	0.8±0.1	0.50±0.04	0.53±0.2	98.55±2.3
F2	203±3.2	4±0.6	0.8±0.1	0.55± 0.05	0.30±0.3	99.06±3.6
F3	205±1.5	5±0.3	0.8±0.1	0.55±0.05	0.35±0.2	98.06±3.4
F4	206±2.5	4±0.7	0.8±0.1	0.45±0.03	0.60±0.1	99.05±2.5
F5	203±3.5	5±0.4	0.8±0.1	0.47±0.05	0.57±0.1	97.06±2.3
F6	206±2.5	4±0.8	0.8±0.1	0.48±0.04	0.45±0.1	98.06±2.3
F7	202±2.5	4±0.7	0.8±0.1	0.50±0.05	0.35±0.1	99.08±2.3
F8	204±3.5	5±0.7	0.8±0.1	0.53±0.05	0.46±0.1	99.06±2.3
F9	204±3.5	5±0.4	0.8±0.1	0.50±0.05	0.33±0.1	99.06±2.3

Average of three determinations, ±SD

Table 4: Determination of formulations floating ability with buoyancy

Batch code	*Floating lag time (sec)*	*Floating duration (h)*	*Matrix integrity*
F0	40-50	> 16	-
F1	45-55	> 20	+
F2	65-75	> 20	+
F3	90-100	> 20	+
F4	65-75	> 20	+
F5	60-70	> 20	+
F6	80-90	> 20	+
F7	75-85	> 20	+
F8	80-90	> 20	+
F9	70-80	> 20	+

2.6. Swelling characteristics (water uptake studies).

Water uptake studies were performed by placing the weighed tablet matrices in the dissolution vessel containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37± 0.5°C. Speed of rotation was kept at 50 rpm. At regular intervals, the tablets were removed from the dissolution vessel, blotted with tissue paper to remove excess water and reweighed, the results were tabulated Table 5 (fig.1 & 2). The percentage water uptake (degree of swelling was calculated using the following equation. [12-14]

$$\% \text{ Water uptake (swelling index)} = \text{Wt-Wo / Wo X 100}$$

Wo and *Wt* are weights of dry and swelled tablet at time t, respectively. The obtained results are shown in Table 5.

Table 5: Percentage swelling studies of floating tablets of Nicardipine**.**

Time	*F0*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
0	0	0	0	0	0	0	0	0	0	0
1	55	40	36	22.5	35	33.5	27.5	35	37	45
2	82.5	70	52	50	80	87.5	46.5	51	62	67.5
4	125	104	71	77.5	99	111.5	69.5	72.5	89	96
6	147.5	135	112.5	104	127	145.5	97	107.5	119	127.5
8	132.5	147.5	151.5	125	149	136	117.5	160.5	136.5	146
10	105	130	132.5	157	122.5	124	145	150.5	152	135.5
12	72.5	109.5	100	137.5	105	100.5	137	140	137.5	121.5
14	49	72.5	82.5	127.5	97.5	86	126.5	117.5	108.5	101

Average of three determinations were reported

2.7. In vitro dissolution studies.

The *In vitro* release rates of NIC matrix tablets were determined using USP XXIII basket apparatus using 900 ml of simulated gastric fluid (pH1.2) at 50 rpm and at a constant temperature of 37±0.5^{o}C. 10 ml samples were withdrawn at different time intervals, filtered though a 0.8 µm filter and assayed by using UV spectrophotometer at a wavelength of 239nm [15-17]. The withdrawn volume was replaced with an equal volume of pre-warmed 37^{o}C gastric fluid. Average of thee determinations results were reported. The differences in average of data were compared by independent sample t test (by PCP dissolution software). The significance of data was determined at 95% confident limit (α = 0.05). The generated data were shown in Table 6 (fig 3, 4 & 5). Data obtained from *in vitro* analysis were fitted to various kinetic equations [17,18], the obtained results were shown in Table 7, respectively.

2.8. Fourier Transmission Infrared (FTIR) studies.

FT-IR spectral measurement for pure physical mixtures (1:1 ratio triturated) and selected formulations and were taken at ambient temperature using FT-IR spectrophotometer (Alpha-E, Bruker, Japan). Samples were mixed with potassium bromide (KBr) and vacuum packed to obtain pellets of the material. The samples were analyzed between wavelength 4000 and 400cm^{-1} to determine if there is any interaction between drug and excipients. The results were shown in Table 8 (fig. 6)

Table 6. In vitro percentage cumulative drug release studies.

Time	*F0*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
0	0	0	0	0	0	0	0	0	0	0
1	18.2	16.44	13.81	10.30	15.13	15.56	10.74	14.685	13.375	14.252
2	33.61	30.57	25.80	19.29	28.40	29.27	20.16	24.064	23.636	25.371
4	40.52	38.80	31.51	26.80	33.66	36.23	28.51	31.942	29.374	30.661
6	48.96	47.27	38.79	33.28	41.76	43.88	35.4	40.483	37.52	37.944
8	59.30	56.36	47.98	39.60	50.08	52.59	41.28	50.076	44.213	46.728
10	72.28	69.38	59.44	45.35	63.16	66.06	50.74	58.193	54.469	58.197
12	84.93	77.98	71.02	59.15	74.29	76.75	61.19	68.970	63.244	66.928
18	99.29	96.06	92.82	82.71	94.04	95.25	84.33	89.588	87.569	90.4
20	99.70	98.50	94.90	83.71	96.90	97.70	88.91	92.105	90.909	96

Average of three determinations were reported

2.9. Surface morphology studies.

The external morphology of the tablet was studied (due to promising physicochemical properties) using Scanning Electron Microscopy (SEM) of intact tablet F7 after dissolution of 24 h. The tablet sample was removed from the dissolution apparatus after 24h, and then it was dried to remove water content and placed in a specimen holder. It was then coated for 120 sec with gold using vacuum evaporator for 15 min under argon atmosphere. The coated samples were then observed by using (JEOL JM-6360 scanning electron microscope, UK). The surface morphological characters of these scans were used to drug release phenomenon and floating. The microphotograph is shown in Figure 7.

Table 7: *In vitro* drug release kinetics of Nicardipine floating tablets.

	F0		*F1*		*F2*		*F3*		*F4*		*F5*		*F6*		*F7*		*F8*		*F9*	
	R	*k*	*R*	*k*	*R*	*k*	*R*	*k*	*R*	*k*	*R*	*k*	*R*	*k*	*R*	*k*	*R*	*k*	*R*	*k*
Zero order	0.8977	6.0048	0.9169	5.7816	0.9604	5.3478	0.977	4.5906	0.9467	5.5205	0.9351	5.6505	0.9769	4.817	0.9521	5.2326	0.9664	5.0092	0.9618	5.2117
T-test	5.762	(Passes)	6.497	(Passes)	9.746	(Passes)	12.967	(Passes)	8.316	(Passes)	7.464	(Passes)	12.923	(Passes)	8.803	(Passes)	10.627	(Passes)	9.943	(Passes)
1st order	0.9247	-0.2345	0.9504	-0.1704	0.9605	-0.1298	0.9749	-0.0854	0.9551	-0.145	0.9543	-0.1568	0.9713	-0.096	0.9774	-0.1150	0.9689	-0.1056	0.9632	-0.119
T-test	6.87	(Passes)	8.639	(Passes)	9.763	(Passes)	12.397	(Passes)	9.117	(Passes)	9.027	(Passes)	11.554	(Passes)	13.071	(Passes)	11.081	(Passes)	10.13	(Passes)
Matrix	0.992	22.5238	0.9931	21.6066	0.9781	19.7079	0.9651	16.7702	0.9835	20.4449	0.9877	21.0068	0.9699	17.6251	0.9853	19.3621	0.9761	18.4187	0.9781	19.1981
T-test	22.176	(Passes)	23.887	(Passes)	13.293	(Passes)	10.416	(Passes)	15.398	(Passes)	17.892	(Passes)	11.266	(Passes)	16.340	(Passes)	12.712	(Passes)	13.304	(Passes)
Peppas	0.9902	19.5392	0.9935	17.7199	0.9904	14.1668	0.9928	10.5709	0.9895	15.7309	0.9914	16.5012	0.9948	11.115	0.9965	14.5570	0.9918	13.3842	0.9901	14.2725
T-test	20.055	(Passes)	24.687	(Passes)	20.306	(Passes)	23.401	(Passes)	19.339	(Passes)	21.463	(Passes)	27.742	(Passes)	33.685	(Passes)	21.948	(Passes)	19.989	(Passes)
Hix.Crow.	0.9873	-0.0413	0.9922	-0.0358	0.989	-0.0303	0.989	-0.0225	0.9894	-0.0324	0.9908	-0.0341	0.9907	-0.0246	0.9945	-0.0282	0.9898	-0.0263	0.9892	-0.0286
T-test	17.593	(Passes)	22.579	(Passes)	18.906	(Passes)	18.899	(Passes)	19.253	(Passes)	20.759	(Passes)	20.616	(Passes)	26.888	(Passes)	19.643	(Passes)	19.114	(Passes)
n	0.5572		0.5802		0.6274		0.6785		0.6013		0.5952		0.68		0.6111		0.6214		0.6124	
Best fit	Matrix		Peppas		Peppas		Peppas		Hix. Crowell		Peppas		Peppas		Peppas		Peppas		Peppas	

Table 8: FTIR studies of formulation F7.

Functional groups	*Wave numbers (cm^{-1})*
C-O stretching of 1^o alcohol	1270 (HPMC)
O-H stretching of 1^o alcohol	3255 (HPMC)
Aliphatic C-H stretching	
- CH_2 -	2848 (HPMC)
- CH_3 -	2916 (HPMC
C-O stretching of 6 membered ring	1115 (HPMC)
–C-H out of plane vibrations of mono- substituted phenyl ring	608 (Nicardipine)
–CH stretching of aromatic ring	3071 (Nicardipine)
– NH stretching	3179 (Nicardipine)

3. RESULTS AND DISCUSSION

The melting point of Nicardipine HCl was found to be in the range 262°C using Griffins melting point apparatus which was found to be in close agreement with the reported one. The Infra-red spectrum of Nicardipine revealed presence of major functional groups. The UV-Visible spectrophotometric method was developed for Nicardipine HCl. The UV spectrum of Nicardipine HCl was carried out to determine its lambda (λ) max by dissolving known quantity of drug in 100 ml 0.1 N hydrochloric acid using Shimadzu UV-1601. The scanning was done across the entire UV-Visible range and the λ max was found to be 239 nm, slope and intercept was 0.069 and 0.0032. The least linear regression was R^2 was 0.9996, respectively. The tablets were designed to evaluate the best composition of polymer to be used for preparation of floating tablets. The percentages of polymers were fixed at 60% based on initial trials for optimizing floating abilities and sodium bicarbonate at 18% . Table 1, shows the composition of different formulations of the drug and polymers.

The percentage compressibility was found to be less than 15% in all the formulations which indicated very good flow properties. Besides, angle of repose was found to be less than 30^0 indicating good flow properties (Table 2). The hardness of the formulated tablets was found in the range of 4-6 kg/cm^2, with the friability value between 0.12% and 0.65%. NIC content was found within 100 ± 2.5 of the labeled amount (Table 3).

The *In vitro* buoyancy studies showed that formulations containing HPMC K100LV showed short floating lag time of 40-50 seconds and floatation time of more than 16 h in the dissolution medium. But it started losing matrix integrity after the end of 10 h. Rest of the HPMC tablets too hydrated immediately after contact with the medium resulting in decreased tablet density [9]. The matrices were fabricated such that upon contact with gastric fluid, carbon dioxide was liberated by the acidity of gastric contents and was entrapped in the jellified hydrocolloid. This produced an upward motion of the dosage form and maintained the whole tablet buoyant on the surface of the test medium for as long as 18h. It was also observed that increase in viscosity of the HPMC grade resulted in increased floating lag time with simultaneous increase in floating duration with an increase in volume of tablets (Table 4).

In fact the buoyancy of the tablet was governed by both the swelling of the hydrocolloid upon contact with the dissolution fluid and the presence of voids in the center of the tablet, which varied from polymer to polymer [10].

Swelling is a very important characteristic of polymers that controls the drug release from the matrix via diffusion mechanism that depends on the rate of penetrant entry into the matrix. Diffusion coefficient values obtained from least squares linear regression analysis were 0.5572 and 0.6785 for HPMCK100LV and HPMCK100M, respectively. This indicates that drug release from former and HPMC K100M tablets were controlled primarily by non-Fickian diffusion though pores and channels in the structure. HPMC tablets upon contact with the dissolution medium swell due to the disruption of hydrogen bindings among the polymeric chains and form a thick gel layer at the tablet surface, which gets eroded over a period of time. These parameters are responsible for controlling drug release rate from HPMC tablets [16]. The penetrating medium fills the voids between the polymer chains and diffuses into denser regions of the polymer, and drug dissolution takes place at the boundary between the infiltrated region and the gel layer. Therefore, dissolved drug release depends upon the diffusion toward the outer most boundary between the swollen matrix and as well as erosion/dissolution of the polymer upon prolonged contact with dissolution medium [13, 14]. It increased as the time progressed because weight gain by tablets was increased proportionally with rate of hydration. Later on it decreased gradually due to dissolution and erosion of the outer most gelled layer of the tablet into dissolution medium. The direct relationship was observed between swelling index and HPMC K100M concentration. Swelling ratio is a function of the network structure, hydrophilicity, and ionization of the functional groups. The pore size is the space available for drug transport. The drug characteristics are as important as those of the gel. The size, shape, and ionization of the drug affect its diffusion though the gel layer [14]. Table 5 shows the swelling studies of floating tablets, at 10^{th} hour (h) the swelling index for F3 was 157, 132.5 for F2, 130 for F1 and 105 for F0. The % swelling started reducing at this hour for F2, F1 and F0 during erosion of the polymer. Maximum swelling for F3 was seen as 157 at 10^{th} h, 151.5 for F2 at 8^{th} h, 147.5 for F1 at 8^{th} h and 147.5 for F0 at 8^{th} h. Similarly comparison of swelling index at 10^{th} h for F4 to F9 showed the F6 to be 145 at maximum, whereas maximum swelling was seen at 8^{th} h for remaining formulations with maximum swelling for F7 with a value of 160.5.

The dissolution studies of all the formulated NIC floating tablets were performed in 0.1N HCl so as to provide them acidic environment of stomach for prolonged periods. The four grades of HPMC (K100LV, K4M, and K100M) differed in their molecular weight. In addition to the effect on the floating lag time, molecular weight affects the drug release from the matrix tablets. Batches F0 to F3 were studied to compare the effect of viscosity of polymer (HPMC) on drug release. There was an apparent difference in NIC release with different viscosity grades of HPMC. From the dissolution studies, it was observed that formulation F3 containing HPMC K100M showed the slowest release rate compared with others, due to its high molecular weight and viscosity.

The percentage release at the end of 20 h for F7 was found to be 92.105%, followed by F6 with 88.911 %, and F3 with % release of 83.716 %. (Table 6).

To attain 100% drug release the preferred formulation could be F6 or F7 over 24h duration. F7 with R^2 value 0.9965 was considered optimized formulation with short floating lag time and long floating duration and release over 24h duration.

Besides, F7 showed the highest swelling index in comparison to others. Among the polymers used in this study, HPMC K100M retarded the drug dissolution rate compared to others. While either swelling or dissolution can be the predominant factor for a specific type of polymer, in most cases, drug release kinetics is a result of a combination of these two mechanisms [13, 14]. Thus, the surface area as well as the hydration of polymer can play an important role in drug releases from matrix tablets. Complete release was reported within 24 h with nearly zero-order release rate. The main emphasis of our study was on different kinetic parameters of formulation.

A tablet composed of a polymeric matrix on contact with water builds a gel layer around the tablet, which governs the drug release. In order to establish the mechanism of drug release and swelling kinetics, the experimental data were fitted to zero-order, first, Higuchi, Korsmeyer–Peppas and Hixon–Crowell models [14,17,18]. The coefficients of regression for F1 to F9 were in a range between 0.9169-0.9770 (zero order), 0.9247-0.9774 (first order), 0.9651-0.9931 (Higuchi- matrix), 0.9895-0.9965 (Peppas), and 0.9873-0.9908 (Hix Crowell). However, the exponential equation is recommended to be used only for data corresponding up to 70% of drug release. The n values for the Peppas model ranged from (0.5572 to 0.68) for all the batches indicating that the release of the drug from the floating tablets followed non-fickian diffusion from the batches prepared from various grade of HPMC (Table 7).

The drug release from these batches involved two mechanisms, diffusion though swelling and release via polymer dissolution, thus indicating that swelling and erosion of polymer governs the release kinetics. As expected, an increase in the polymer content brought about a corresponding decrease in drug release rate.

Drug- excipient compatibility studies using FTIR studies revealed that there were no change in these peaks in the IR spectra of a mixture of drug and excipients in the formulation F7. (Table 8)

Scanning electron microscopy at different magnification of the dried formulation of F7 kept dispersed in 0.1N HCl in a beaker after 24 h swelling showed that HPMC K15M/ HPMC K100M produces increase porosity on swelling on absorption of Gastric fluid. Hence, the preparation remained floated for a long duration of time due to large intact surface area. The SEM images of samples have been displayed in the (Figure 7). The surface was irregular in shape highly porous and good intact crosslinking of polymer chains. The open cell structure is clearly visible with some of the pores being closed by the polymer. It further confirmed both swelling and diffusion mechanisms to be functioning during drug release from the optimized formulation of batch F7. The figure showed the close aggregate of polymer mesh after 24 h. This might be due to the higher viscosity and high quantity of the polymer added. The higher viscosity hinders the entrance of the liquid phase into the inner pores of the system, thus delayed the release of drug for an extended period.

4. CONCLUSION

This work has provided a simple approach to formulate an oral swellable gastroretentive floating tablets to deliver Nicardipine HCl over an extended period of time along with a constant drug release. Tablet containing HPMC K15M and HPMC K100 M showed good buoyancy with long floatation time of more than 18 h in simulated gastric fluid. The matrix and the size of matrix were intact till the end of 24 h. *In vitro* release of tablets was obtained for more than 18 h.

In vitro release data when fitted to various kinetic models and drug release predominantly followed non-Fickian diffusion and zero order release. The optimized formulation F7 showed good swelling and floating ability with maximum drug release over 24 h. Overall, this study concludes that viscosity is a major factor affecting the drug release and floating properties of FDDS. Further studies are needed to improve the intactness of the tablet over an extended period of time.

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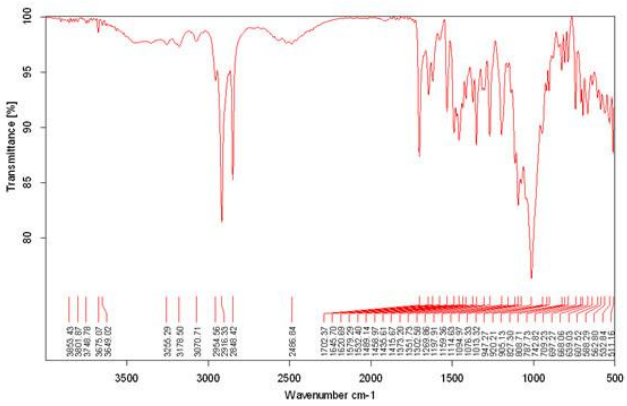

Figure 1: FTIR studies of formulation F7

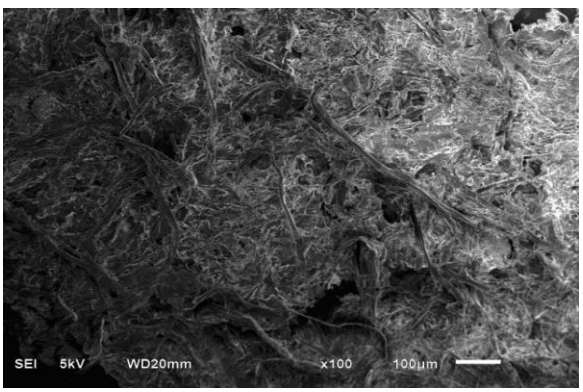

Figure 2: The SEM microphotograph of formulation F7

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