Pharmacophore 2014, Vol. 5 (4), 494-508 USA CODEN: PHARM7 ISSN 2229-5402

Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Original Research Paper

FORMULATION AND *IN VITRO* EVALUATION OF ORAL FLOATING NICARDIPINE HYDROCHLORIDE TABLETS USING POLYETHYLENE GLYCOL 6000 AND VARIOUS HPMC GRADES

Chabria N. B.[1]* and Narayanan N.[2]

[1]Pharmacy Department, Higher College of Technology, Ministry of Manpower, Muscat, Sultanate of Oman

[2]Department of Pharmaceutics, Jaya College of Pharmacy, Thiruninravur -262024, Chennai, Tamilnadu, India

ABSTRACT

The purpose of this research was to formulate floating tablets of Nicardipine hydrochloride so as to prolong its gastric residence time and increase its bioavailability as it has good solubility at low pH values. Melt granulation technique was used for preparing the floating tablets using polyethylene glycol 6000 as bioadhesive hydrophilic meltable polymer and different viscosity grades of direct compressible polymer like hydroxyl propyl methylcellulose, and gas generating agent like sodium bicarbonate and ethyl cellulose as floating enhancer material. Pre-compressional and post compressional parameters were evaluated. The mechanisms of drug release were analyzed using different kinetic models. The concentrations of PEG 6000, HPMC K4M, were selected as independent variables and drug release values at $t_{50\%}$ and $t_{80\%}$ as dependent variables. Formulation P6 was selected as an optimum formulation as it showed more similarity in dissolution profile with theoretical profile (similarity factor, $f_2 = 0.98$). It was also observed that increase in viscosity of the HPMC grade resulted in increased floating lag time with simultaneous increase in floating duration. The *in vivo* studies in albino rabbit showed good floating duration for the optimized formulation. The FTIR/DSC studies revealed no interaction between the drugs and excipients. It can be concluded from this study that the combined matrix system containing combination of high molecular weight hydrophilic polymers with increased viscosity minimized the burst release of drug from the tablet and achieved a controlled drug release which is otherwise difficult to achieve with only single polymer matrix.

Keywords: Nicardipine HCl, Melt granulation technique, HPMC, PEG6000, *In vitro* buoyancy, Kinetic models.

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. 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.[5-7] 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.[4, 8-9] 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.[10-14]

The objective of the present study was aimed to formulate sustained release formulation of Nicardipine using HPMC (different grades) as hydrophilic polymer plasticized with low concentration of PEG 6000 as high molecular weight polymer to help in modifying release rate by granulation technique, besides sodium bicarbonate ($NaHCO_3$) and ethyl cellulose as the floating aid and release modifier and to study the *in vitro* performance (bioavailability) of the intended formulations.

MATERIAL AND METHODS

Materials

Nicardipine HCl was purchased from TCI, Tokyo chemical industries co., ltd, Japan. HPMC (K4M, K15M, K100MCR) were purchased from Loba chemie, India; Sodium bicarbonate- Fischer Inorganic and Aromatics ltd, Chennai, India; PEG 6000, Ethyl cellulose from SD fine chemicals; Other chemicals were of analytical grade.

Experimental

Calculation for the dose of drug in the tablets

The total dose of the drug was calculated as published in our previous work.[8,15,16] Hence, the matrix tablet should contain a total dose of 40 mg for 18 h SR dosage form and it should release 20 – 10.359 = 9.641 (24.11 %) mg in the 1st h like conventional dosage form and the remaining dose (40 – 9.641) in remaining 18 h, i.e. 30.359 (75.90%) mg for remaining time up to 18 h at the rate of 1.68 mg (4.2%) per hour up to 18 h. Hence, the theoretical drug release profile can be generated using the above value which is shown in Table 1.

Characterization of Nicardipine HCl

Nicardipine HCl was characterized by determining its melting point, λmax by UV spectrum and important peaks by FTIR spectrum. It has been published earlier by us.[8]

Fabrication of Nicardipine matrix tablets

Nicardipine floating matrix tablets were prepared by melt granulation method using PEG6000 as plasticizer. The percentage of Nicardipine (NIC) was kept at 20%, polymers including HPMC (different grades) and ethyl cellulose and beeswax were fixed at 60%, $NaHCO_3$ at 18% and excipients sufficient enough for a batch of 50 tablets were kept at 2%. Refer our published work.[10-11] Accurately weighed quantities of NIC, HPMC, ethyl cellulose, $NaHCO_3$ were mixed in geometric progression and tumbled for 15 min. The drug and excipients were mixed with the melted wax (PEG6000) in the petri dish. The mass was removed from the hot plate and subjected to scraping until it attained room temperature. The coherent mass was passed through the mesh with sieve no. 14 to get uniform size granules. The dried granules were later mixed with remaining excipients such as lubricants and glidants. The lubricated blends were compressed into tablets of average weight 200 mg using tablet punching machine- 24

stations (Cadmach) with 10 mm standard concave punches. The hardness of the tablet was maintained in the range of 3.5-6 kg/cm^2. Microcrystalline cellulose (MCC) (1%) was used as diluent. Magnesium stearate, aerosil & talc were used as lubricant and glidant (at 1%) respectively. The composition of formulations was shown in Table 2.

Determination of pre-compressed parameters[8,9, 17-23]

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

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

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

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

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

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 3.

Determination of post compressional parameters[17-23]

The thickness, diameter and friability test were measured according to British Pharmacopeia (BP). Uniformity of weight was performed according to USP. The results are shown in Table 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 24 h. Then it was filtered through 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 4.

In vitro buoyancy studies

The buoyancy of the tablets was studied at 37±0.5°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. The evaluation was conducted in triplicate for each batch of tablets. The obtained results are shown in Table 5.

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 percentage water uptake (i.e. degree of swelling was calculated using the following equation.

% Water uptake (Swelling index) =

$$\frac{Wt - Wo}{Wo} \times 100$$

Wo and Wt are weights of dry and swelled tablet at time t, respectively. The obtained results are shown in Table 6 (Figure 1).

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°C. 10 ml samples were withdrawn at different time intervals, filtered through a 0.8 µm filter and assayed by using UV spectrophotometer at a wavelength of 239 nm. The withdrawn volume was replaced with an equal volume of pre-warmed 37°C gastric fluid. Average of three 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 7, 8 (Figure 2, 3). Data obtained from *in vitro* analysis were fitted to various kinetic equations and the obtained results were shown in Table 9, respectively.

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 400 cm^{-1} to determine if there is any interaction between drug and excipients. The results were shown in Table 10 (Figure 4).

Surface morphology studies

The external morphology of the tablet was studied (due to promising physicochemical properties) using Scanning Electron Microscopy (SEM) of intact tablet P6 after dissolution of 24 h. The tablet sample was removed from the dissolution apparatus after 24 h, 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 for studying drug release phenomenon and floating. The microphotograph is shown in Figure 5.

Differential Scanning Calorimetry (DSC) studies

Differential scanning calorimetric measurements were carried out on a Mettler, Star SW 9.01 (AISSMS COP) equipped with a thermal analysis data system. The empty aluminium crucible was kept as reference material and the drug, polymer, physical mixture; formulated microparticles of tablets were all placed individually in the sample cell. Sample of 5-15 mg were placed in aluminium pans (Aluminium crucibles, 40 µl) and sealed. The probes were heated from 20 to 200°C at a rate of 10K/min under nitrogen atmosphere. The DSC measurements were taken to find the Tg and Tm values. The values of Tg and Tm for P6 sample is shown in Figure 6 along with DSC of pure Nicardipine, HPMC grades (HPMC K15 and 100M).

Short-term stability studies

The P6 tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40 ± 2°C / 75 ± 5% RH and a control sample was placed at an ambient condition. Both test and control samples were withdrawn at the end of 30 days and evaluated for active drug content, *in vitro* buoyancy and drug release profile. Table 11 shows the comparison of drug release profile for the optimized batch. (Figure 7)

RESULT AND DISCUSSION

The melting point, Infra-red spectrum and UV-Visible spectrophotometric spectrum for Nicardipine HCl were also carried out and published.[8,9] 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% and sodium bi carbonate at 18% based on initial trials for optimizing floating abilities and integrity. Table 2, shows the composition of different formulations of the drug & polymers. The percentage compressibility was found to be less than 13% in all the formulations which indicated very good flow properties. Besides, angle of repose was found to be less than 27^0 indicating good flow properties (Table 3). The hardness of the formulated tablets was found in the range of 4-6 kg/cm^2, with the friability value between 0.3 and 0.55%. NIC content was found within 100 ± 2% of the labeled amount. The formulated floating tablets complied with the USP requirements for weight variation and friability (Table 4). The *In vitro* buoyancy studies showed that formulations containing HPMC K15M showed short floating lag time of 40-50 seconds and floating duration of more than 20 h in the dissolution medium. But it started losing matrix integrity after the end of 12 h. Rest of the HPMC tablets too hydrated immediately after contact with the medium resulting in decreased tablet density. The maximum floating lag time did not exceed 2 min. 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 20 h. 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 3). From the Stokes – Einstein equation, the diffusion coefficient is inversely proportional to viscosity. Hence, it can be inferred that increasing the viscosity of 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. Diffusional coefficient values obtained from least squares linear regression analysis were 0.5644/0.5891 for 35% / 40% of HPMCK15M and 0.5803/0.9742 for 35% / 40% of HPMCK100M, respectively. This indicates that drug releases from both types of tablets were controlled primarily by non-Fickian diffusion through 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. 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. 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. Table 6 shows the swelling studies of floating tablets, at 8th hour (h) the maximum swelling index for P1 was 150, for P2 119.5, for P3 143, for P4 it was 144.5, for P5 142.5, for P6 141. The % swelling started reducing after this hour for most of the formulations. This may be due to erosion of the polymer, dissolution of the drug in the surrounding area, and increase in porosity. Later the % SI decreased gradually due to dissolution of the outer most gelled layer of tablet, which was slowest for the P6.

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 molecular weight of HPMC polymers affects the drug release from the matrix tablets. From the dissolution studies, of trial samples it was observed that HPMC K100M showed the slowest release rate compared with others, due to its high molecular weight and viscosity. Thus HPMC k100M and HPMC K15M was used in combination to delay the drug release and improve floating ability. The percentage release at the end of 20 h for P5 was found to be highest at 99.698% and for lowest for P2 at 90.906% (Table 7). P6 had an optimum release of 94.103%. To attain 100% drug release the preferred formulation could be P4 and P6 for 24h duration. Besides, P6 showed the highest swelling index of 109.5% at the end of 14 h in comparison

polymer decreases the release rate of the drug. 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. Therefore all the formulations were prepared using HPMC 15M and HPMC K 100M for attaining long floating duration, intactness and long action and by using 18% sodium bicarbonate for all the batches.

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. 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.[17,18] The coefficients of regression for P1 to P6 were in a range between 0.9077-0.9701 (zero order- P2 with highest value), 0.9631-0.9780 (first order- P1highest), 0.9833-.9925 (Higuchi- matrix- P5 highest), 0.9890-0.9967 (Peppas- P2 highest), and 0.9819-0.9927 (Hix Crowell- P1 highest). 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 (0.5509 to 0.6594) 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 9). The dissolution data of all batches were subjected to find f2 similarity for the selection of optimum batch. Theoretical profile of Nicardipine was taken as reference. P6 batch showed maximum similarity (f2 =0.98) for 70 % of release over 12 h.

Scanning electron microscopy at different magnification of the dried formulation of P6 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 P6. 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. DSC thermograms showed sharp endothermic peaks of drug at 170.97^{o}C and PEG6000 at 64.8^{o} C. In case of HPMC15K and HPMC-K100, broadened endothermic peak at 85.13^{o}C and 75.75^{o} C were observed. Formulations P6 showed endothermic peaks of 70.34/107.5/178.88 (F2). There was no significant difference in the melting point of drug in both samples. It indicated that the drug was present in its characteristic physical and chemical form. These results showed there was no radical thermal interaction between the excipients and drug.[17-23]

The stability study carried on the optimized formulation P6 did not show any change in the morphological condition over the storage conditions. The f2 similarity between the dissolution data's before and after the stability studies was found to be 0.98766.

CONCLUSION

This work has provided a simple approach to formulate oral swellable gastro-retentive floating tablets to deliver Nicardipine HCl over an extended period of time along with a constant drug release. It can be concluded that the combined mix matrix system containing hydrophilic and hydrophobic polymer minimized the burst release of drug from the tablet and achieved drug release by almost zero order kinetic. 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. The optimized formulation P6 showed good swelling and floating ability with maximum drug release over 24 h. It showed more similarity in dissolution profile with theoretical profile (similarity factor, f2 = 0.98).There was no difference observed in the release profile after temperature sensitivity study at 40°C / 75% RH for 1 month. 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.

ACKNOWLEDGMENT

The authors are grateful to Dr. Rajesh Agarwal, Charka College of Pharmacy, Pune; also grateful to Dr. Grace Rathnam, Principal, C L Baid Mehta College of Pharmacy, Chennai, for giving support in carrying out some part of research work at their prestigious institutes respectively.

Table 1: Theoretical drug release profile

Time in (hours)	Amount released (mg)	% Release
0	0	0
1	9.641	24.11
2	11.321	28.31
4	14.681	36.71
6	18.041	45.11
8	21.401	53.51
10	24.761	61.91
12	28.121	70.31
14	31.481	78.71
16	34.841	87.11
18	38.201	95.51
20	~ 40	~100

Table 2: Formulation composition of floating tablets of Nicardipine

Batch code	Drug (%)	HPMCK15M (%)	HPMCK100M (%)	SBC (%)	EC (%)	PEG 6000 (%)
P1	20	40	-	18	05	15
P2	20	-	40	18	05	15
P3	20	25	15	18	05	15
P4	20	15	25	18	05	15
P5	20	30	10	18	05	15
P6	20	10	30	18	05	15

Table 3: Evaluation of pre-compressional parameters

Batch code	Bulk density	Tapped density	Packing factor/ Hausner'sratio	Compressibility% / Carr's Index	Angle of repose
P1	0.69	0.78	1.131	11.530	21.85
P2	0.67	0.76	1.134	11.840	22.65
P3	0.67	0.77	1.149	12.987	23.25
P4	0.65	0.74	1.138	12.162	22.29
P5	0.71	0.80	1.127	11.250	25.04
P6	0.70	0.80	1.143	12.500	22.40

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

Table 4: Physico- chemical properties of prepared tablets

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Diameter (cm)	Thickness (mm)	Friability (%)	Drug content (%)
P1	202 ± 4.5	5 ± 0.7	0.8 ± 0.1	0.50 ± 0.05	0.53 ± 0.2	98.55 ± 2.3
P2	202 ± 3.3	4 ± 0.6	0.8 ± 0.1	0.55 ± 0.05	0.45 ± 0.3	99.06 ± 3.5
P3	203 ± 3.5	5 ± 0.7	0.8 ± 0.1	0.53 ± 0.05	0.46 ± 0.2	99.04 ± 2.6
P4	203 ± 3.2	4 ± 0.6	0.8 ± 0.1	0.55 ± 0.05	0.30 ± 0.3	99.05 ± 3.6
P5	205 ± 2.5	4 ± 0.8	0.8 ± 0.1	0.48 ± 0.05	0.42 ± 0.1	98.04 ± 2.2
P6	203 ± 3.5	5 ± 0.4	0.8 ± 0.1	0.47 ± 0.05	0.44 ± 0.1	97.06 ± 2.3

Average of three determinations, ±SD

Table 5: Determination of formulations floating ability with buoyancy

Batch code	Floating lag time (sec)	Floating duration (h)	Matrix integrity
P1	60-70	> 20	+
P2	90-100	> 20	+
P3	45-55	> 20	+
P4	65-75	> 20	+
P5	60-70	> 20	+
P6	65-75	> 20	+

Average of three determinations were reported

Table 6: Percentage swelling studies of floating tablets of Nicardipine

Time	P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	0
1	42	29	39	35	39.5	31.5
2	87	50	70	66	65.5	59
4	111	82.5	110	102.5	109.5	106.5
6	142.5	101	130	126	132.5	125.5
8	150	119.5	143	144.5	142.5	141
10	126	111.5	126	131.5	129	131.5
12	109	100	109.5	120	108	119
14	104	95.5	101	105.5	100	109.5

Average of three determinations were reported

Table 7: *In vitro percentage cumulative d*rug release studies

Time	P1	P2	P3	P4	P5	P6
0	0.000	0.000	0.000	0.000	0.000	0.000
1	18.194	11.615	15.562	14.246	16.878	12.930
2	33.606	21.028	29.269	27.967	31.004	25.799
4	40.948	29.798	37.517	36.230	39.661	34.515
6	48.538	38.363	45.570	42.603	47.266	40.907
8	59.297	44.208	53.010	50.914	55.525	48.400
10	73.520	51.979	65.649	60.678	68.549	56.122
12	85.345	61.602	75.111	72.655	79.614	67.742
18	96.464	83.925	94.037	93.228	95.655	89.588
20	97.300	90.906	97.699	95.302	99.698	94.103

Average of three determinations were reported

Table 8: *In vitro* dissolution studies

Batch code	Response in time t_{50} (hrs) ±SD	Response in time t_{60} (hrs) ±SD	Response in time t_{80} (hrs) ±SD	Response in time t_{90} (hrs) ±SD
P1	5.4	7.6	12.7	15.8
P2	8.7	11.5	17.7	21.2
P3	6.4	8.7	14.2	17.3
P4	6.9	9.3	15.0	18.2
P5	5.9	8.1	13.4	16.5
P6	7.6	10.1	16.0	19.4

Table 9: *In vitro* drug release kinetics of Nicardipine floating tablets

	P1		P2		**P3**		**P4**		**P5**		**P6**	
Models	**R**	**K**	R	k	**R**	**K**	**R**	**k**	**R**	**k**	**R**	**k**
Zero order	0.8820	5.9288	0.9701	4.9077	0.9298	5.6255	0.9414	5.4553	0.9165	5.8053	0.9531	5.2378
T- test	5.293	(Passes)	11.307	(Passes)	7.144	(Passes)	7.891	(Passes)	6.480	(Passes)	8.911	(Passes)
1st order	0.9780	-0.1681	0.9667	-0.1003	0.9524	-0.1525	0.9648	-0.1342	0.8923	-0.1987	0.9631	-0.1194
T- test	13.272	(Passes)	10.685	(Passes)	8.841	(Passes)	10.381	(Passes)	5.590	(Passes)	10.124	(Passes)
Matrix	0.9914	22.3057	0.9765	18.0288	0.9909	20.9535	0.9868	20.2459	0.9925	21.6929	0.9833	19.3655
T- test	21.383	(Passes)	12.823	(Passes)	20.821	(Passes)	17.224	(Passes)	22.964	(Passes)	15.297	(Passes)
Peppas	0.9890	19.7024	0.9967	12.0180	0.9932	16.7468	0.9915	15.5042	0.9929	18.0935	0.9920	14.1452
T- test	18.946	(Passes)	34.505	(Passes)	24.183	(Passes)	21.505	(Passes)	23.573	(Passes)	22.171	(Passes)
H. Crowell	0.9927	-0.0363	0.9898	-0.0254	0.9908	-0.0335	0.9908	-0.0311	0.9819	-0.0375	0.9893	-0.0287
T- test	23.213	(Passes)	19.635	(Passes)	20.738	(Passes)	20.685	(Passes)	14.680	(Passes)	19.200	(Passes)
n	0.5509		0.6594		0.5896		0.6059		0.5727		0.6244	
K	19.7024		12.0180		16.7468		15.5042		18.0935		14.1452	
F2 test	0.58		0.82		0.80		0.89		0.71		0.98	
Best fit	Hix. crowell		Peppas		Peppas		Peppas		Peppas		Peppas	

Table 10: FTIR studies of formulation P6

Functional groups	Wave numbers (cm^{-1})
C-O stretching of 1^o alcohol	1342 (HPMC/EC)
O-H stretching of 1^o alcohol	3255 (HPMC/EC)
Aliphatic C-H stretching	2884 (HPMC/EC/PEG)
C-O stretching of 6 membered ring	1101 (HPMC/EC)
–C-H out of plane vibrations of mono- substituted phenyl ring	638 (Nicardipine)
–CH stretching of aromatic ring	3071 (Nicardipine)
C- N-H stretching	1278 (Nicardipine)
C=O stretching of ester	1618 (Nicardipine/ PEG 6000)
C- NO_2 stretching	1454 (Nicardipine)

Table 11: Comparison of *in vitro* cumulative percent drug release profile initially and after stability studies of P6 Nicardipine tablet

Time	CPR (Initial) P6	CPR (after 40 ± 2°C / 75 ± 5% RH) P6
0	0.000	0.000
1	12.930	15.562
2	25.799	27.534
4	34.515	35.373
6	40.907	42.179
8	48.400	49.657
10	56.122	57.364
12	67.742	66.105
18	89.588	92.015
20	94.103	96.501

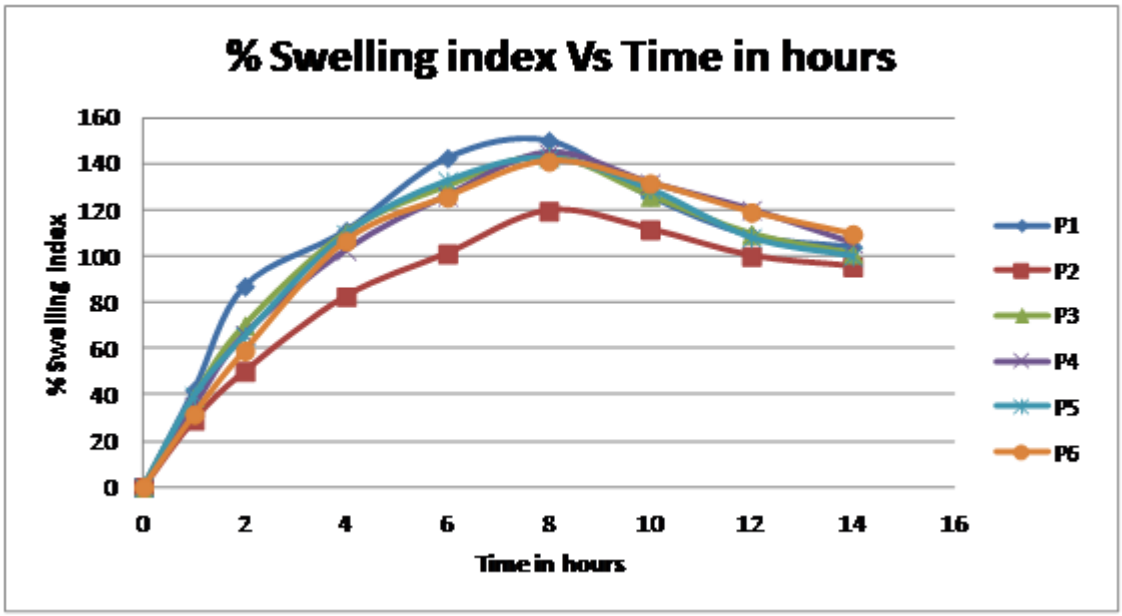

Figure 1: Swelling study of Nicardipine tablet formulations P1 to P6 (for Table 6)

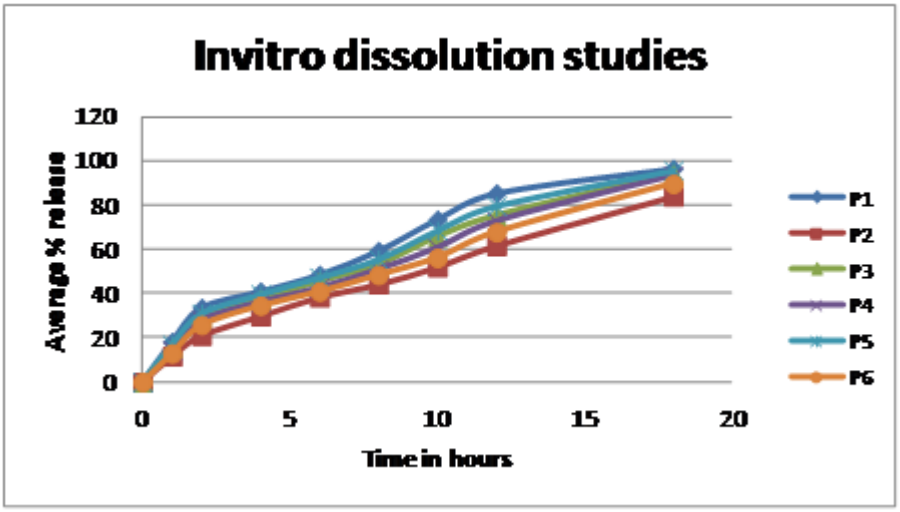

Figure 2: Effect of viscosity grade of HPMC on drug release from floating matrix tablet (for Table 7)

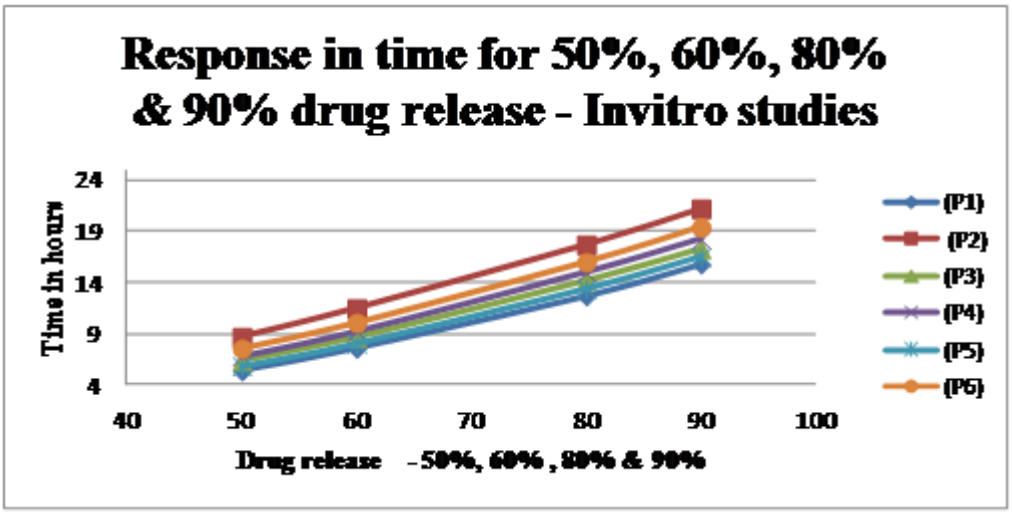

Figure 3: Time for x% release (tx%) for 50%, 60%, 80% & 90% drug release by invitro dissolution studies. (for Table 8)

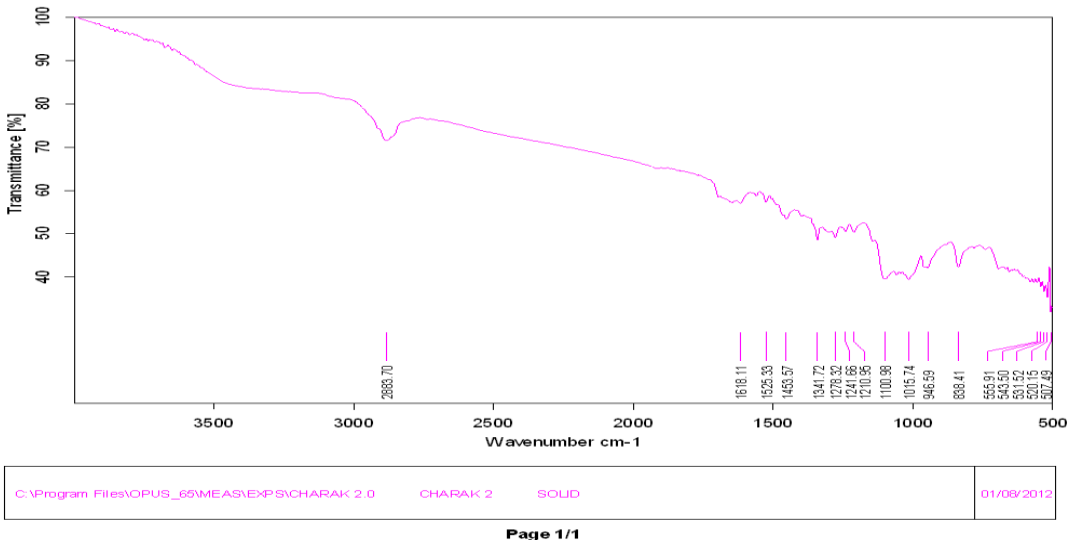

Figure 4: FTIR of Nicardipine + HPMCK15M + HPMC K100M + PEG (For Table 10)

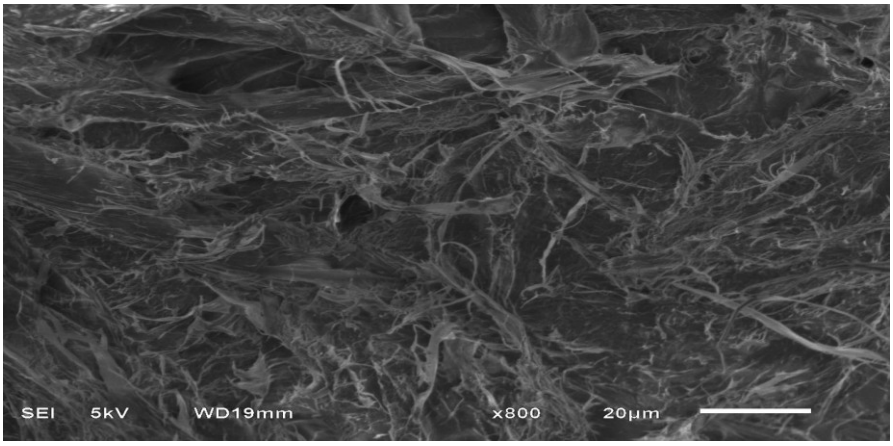

Figure 5: SEM studies of P6 Nicardipine tablet

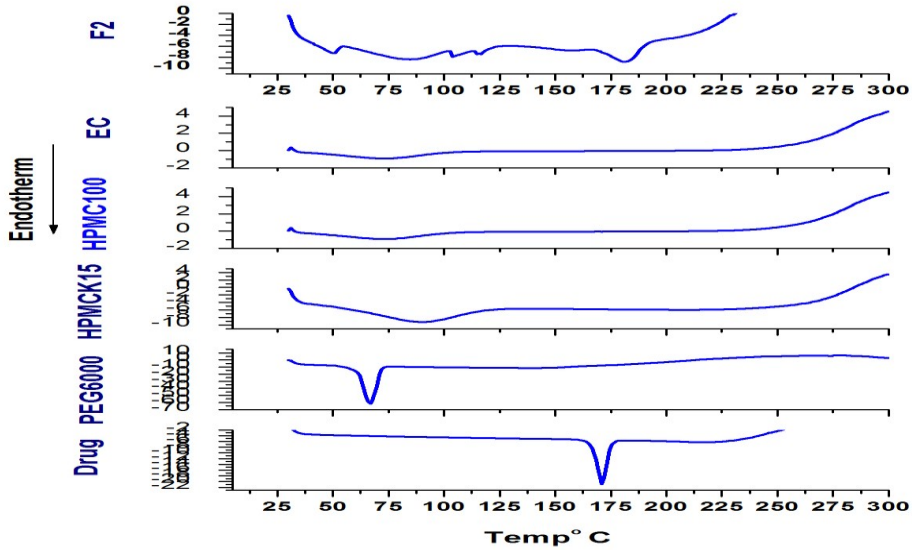

Figure 6: The DSC thermographs of Pure drug, PEG 6000, HPMC15K, HPMCK100M, EC, F2 (i.e. P6)

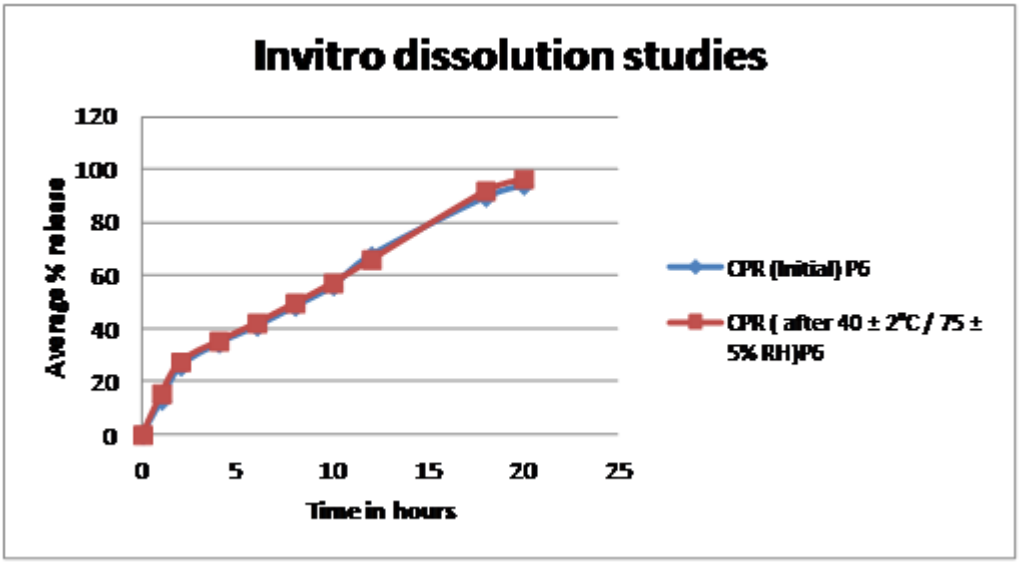

Figure 7: Comparison of *in vitro* drug release profile initially and after stability studies of P6 Nicardipine tablet (for Table 11)

REFERENCES

1. Sweetman, Sc and Martindale (2009), ***The Complete Drug Reference***, 36th Ed., UK: Royal Pharmaceutical Society, 1348.
2. Mehta, DK(2006), "***British National Formulary (BNF)***" 52nd Ed. UK: Royal Pharmaceutical Society of Great Britain, 110-13.
3. Thomas, F Rice (2009), ***Physicians' Desk Reference***, 63rd Edi., 1093-95.
4. Harvey, R; Camphe, PC and Finkel, R (2008), "***Lippincotts Illustrated Review: Pharmacology***", 2nd Ed., Lippincott Williams and Wilkins, 187-89.
5. Breda, H; Jeny, M; Zdravok, K and Branko, H *et al*. (1992),"Inclusion complex of Nicardipine or its hydrochloride with beta-cyclodextrin and a sustained release pharmaceutical preparation containing the same", ***US Patent 5079237***.
6. Nakamishi, K; Yasuura, H; Fukui, H and Oka; M *et al*.(2001), "Evaluation of a floating dosage form of Nicardipine hydrochloride and HPMC acetate succinate prepared using a twin-screw extruder", ***Int. J. Pharm.***, 218 Vol (1-2), 103 -112.
7. Fernandes, CM and Baptista, FJ (2002), "Effect of the hydrophobic nature of Triacetyl-b -cyclodextrin on the complexation with Nicardipine Hydrochloride: Physico-chemical and dissolution properties of the Kneaded and Spray-dried complexes", ***Chem. Pharm. Bull***, 50(12), 1597-1602 .
8. Chabria, NB and Narayanan, N (2013), "Formulation and *in- vitro* evaluation of oral floating Nicardipine hydrochloride tablets", ***Hygeia. J. D. Med***. Vol 5 (2), 63-75.
9. Chabria, NB and Narayanan, N (2013), 'Formulation and *in vitro – in vivo* evaluation of oral floating Nicardipine hydrochloride tablets using beeswax and various HPMC grades", ***International Journal of Medicine and Pharmaceutical Sciences (IJMPS)***, Vol (3), Issue 3,87-96.
10. Moes, AJ (1993), "Gastroretentive dosage forms", ***Crit Rev Ther Drug Carrier Syst***., Vol 10(2),143- 95.
11. Timmermans, J and Moes, AJ (1990), "How well do floating dosage form float", ***Int J Pharm***, Vol (62),207-16.
12. Arora, S; Javed, Ali; Khar, KR and Ahuja, A(), "Floating drug delivery systems: A Review", ***AAPS PharmSciTech.***, Vol 6(3), E372-E390.
13. Sheth, PR and Tossounian, JL(1979), "Novel sustained release tablet formulations", ***US patent*** 4167558.
14. Baumgartner, S; Tivadar, A; Vrecer, F and Kristl, J (2001), "Development of floating tablets as a new approach to the treatment of Helicobacter pylori infections", ***Acta Pharm***., Vol (51),21-33.
15. Cedillo-Ramirez, E; Villafuerte-Robles, L; Hernandez-Leon, A (2006), "Effect of added pharmatose DCL11 on the sustained-release of metronidazole from methocel K4M and carbopol 971 NF floating matrices", ***Drug Dev Ind Pharm***, Vol (32), 955–65.
16. Babu, VB and Khar, RK (), "*In vitro* and *In vivo* studies of sustained-release floating dosage forms containing salbutamol sulfate", ***Pharmazie***, Vol 45(4),268-70.
17. Ramesh ,CA; Devendra, NR and Pandit, JK(2010), "*In vitro* release kinetics and bioavailability of gastroretentive cinnarizine hydrochloride tablets", ***AAPS PharmSciTech***, Vol (2), No.1, 294-303.
18. Sopimath, SK; Kulkarni, AR; Rudzinski, WE and Aminabhavi, TM (2001), "Microspheres as floating drug delivery systems to increase gastric retention of drugs", ***Drug Metab Rev***., Vol (33),149–60.
19. Rajabi-Siabhoomi, AR; Melia, CD; Davies, MC and Bowtell, RW *et al*.(1992), "Imaging the internal structure of the gel layer in hydrophilic matrix system by NMR imaging", ***J Pharm Pharmacol***, Vol (44),1062-71.
20. Wan, LS; Heng, PW and Wong, LF (1993), "Relationship between swelling and drug release in a hydrophilic matrix drug", ***Dev Ind Pharm***, Vol (19), 1201.
21. Conti, S; Maggi, L; Segale, L; Ochoa, Machiste E *et al*. (2007), "Matrices containing

NaCMC and HPMC: Dissolution performance characterization", ***Int J Pharm.***, 333Vol (1-2),136-42.

22. Timmermans, J and Moes, AJ (1994), "Factors controlling and gastric retention capabilities of floating matrix capsules", ***J Pharm Sci***., Vol (83), 18-24.
23. Ali, J; Arora, S; Ahuja, A; Babbar, A and Sharma, R *et al*.(2007), "Formulation and development of hydrodynamically balanced system for metformin: *in vitro* and *in vivo* evaluation", ***Eur J Pharm Biopharm***, Vol 67(1), 196-201.

Correspondence Author:
Chabria N. B.
Pharmacy Department, Higher College of Technology, Ministry of Manpower, Muscat, Sultanate of Oman
Email : neetusadh@rediffmail.com

Cite This Article: Chabria, NB and Narayanan, N (2014), "Formulation and *in vitro* evaluation of oral floating nicardipine hydrochloride tablets using polyethylene glycol 6000 and various HPMC grades", ***Pharmacophore***, Vol. 5 (4), 494-508.