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Floating tablets of Nimodipine and its inclusion complex with β-Cyclodextrin for controlled release

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Abstract: Floating tablets of nimodipine(N) alone and its inclusion complex with β-cyclodextrin (βCD) were formulated using gas generating agent (sodium bicarbonate), hydrophilic polymer (different grades of hydroxy propyl methylcellulose) and drug release retarding agent (Eudragit RSPO), with an objective to enhance the solubility, dissolution rate of nimodipine and to control the drug release and restrict the region of drug release to stomach. As nimodipine is practically insoluble in water and aqueous fluids, its inclusion complex with βCD was investigated to improve its solubility and dissolution rate. Inclusion complex of nimodipine with βCD has markedly enhanced the solubility and dissolution of nimodipine. A 7.1-, 7.3- and 7.4- fold increase in the dissolution efficiency of nimodipine was observed with N-βCD in the ratio of 1:1, 1:2 and 1:3 respectively. Floating tablets formulated containing nimodipine alone gave very slow dissolution, whereas those formulated containing its inclusion complex with βCD gave slow, controlled and complete release up to 24 h.
Key words: Nimodipine, β-cyclodextrin, floating tablet, phase solubility, complexation.

Introduction and Experimental:

The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal (GI) tract until all the drug is released for the desire period of time[1]. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose[2]. Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems,[3] swelling and expanding systems,[4,5] floating systems,[6,7] and other delayed gastric emptying devices.[8,9] The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. Nimodipine, a calcium channel blocker is used primarily for its cerebral vasodilator effect. It has also been used for neurological deficits after cerebral ischemia and migraine. It is practically insoluble in water and its absorption is dissolution rate limited[10]. Nimodipine is widely absorbed from stomach and upper part of the small intestine and absorption becomes less as the drug passes beyond this. So it is necessary to restrict the region of drug release to stomach. It has a short biological half life of 1-2 h[11]. The short half life of nimodipine necessitates frequent administration. As such floating drug delivery products are needed for nimodipine to prolong and restrict the release in only stomach and to improve patient compliance. In the present work floating tablets of nimodipine(N) and its inclusion complex with β-Cyclodextrin(βCD) were formulated employing gas

generating agent (sodium bicarbonate), hydrophilic polymer (different grades of hydroxy propyl methylcellulose) and drug release retarding agent (Eudragit RSPO), with an objective to control the drug release and restrict the region of drug release to stomach. As nimodipine is practically insoluble in water, its inclusion complexes with βCD were prepared to enhance its dissolution rate and to evaluate the feasibility of using this inclusion complex in the formulation of floating tablets for controlled release.

Materials:

Nimodipine and β-cyclodextrin were obtained as a gift samples from Micro Labs, Bangalore. Eudragit RSPO, HPMC E15 and Aerosil were obtained as a gift samples from Hetero Drugs Ltd., Hyderabad. HPMC K4M, HPMC K15M were obtained as a gift samples from Micro Labs, Bangalore. Sodium bicarbonate and dicalcium phosphate were obtained from S.D. Fine Chem. Ltd. Mumbai. All other chemicals and solvents used were of analytical reagent grade.

Methods:

All experiments were carried out under subdued light to prevent photo degradation of nimodipine

Phase solubility studies:

Phase-solubility studies were performed according to the method reported by Higuchi and Connors[12]. Nimodipine (50 mg) was added to 15 ml of distilled water containing 3-15 mM of βCD and transferred into 25 ml stopped conical flasks. The mixtures were shaken for 72 h at room temperature (28^0C) on a rotary flask shaker. After equilibrating for 72 h, samples were withdrawn and filtered immediately using 0.45 µ nylon disc filter. The drug content in each sample was analysed after suitable dilution by Elico UV/Visible spectrophotometer at 358 nm. The solubility experiments were conducted in triplicate(n=3).

Preparation of inclusion complexes:

Inclusion complexes of nimodipine in βCD were prepared by triturating nimodipine and βCD in a mortar in various molar ratios such as 1:1, 1:2 and 1:3, with 10 ml of a solvent blend of water and methanol (6:4). The thick slurry was kneaded for 45 min, dried at 55^0C, pulverized and finally sieved through sieve # 100.

Preparation of floating tablets:

Floating tablets of nimodipine alone and its inclusion complex with βCD were prepared by direct compression method. The composition of formulation is given in the Table 1. Based on the trial basis the composition of the formulation were made by using different swellable polymers to float more than 12 h. HPMC used as swellable polymer i.e. to float but not to retard the release. All the ingredients except magnesium stearate were blended in glass mortar uniformly. After sufficient mixing of drug as well as other excepients, magnesium stearate was added and further mixed for additional 2-3 min. Powder thus obtained was compressed into tablets on a 10 station single punch rotary tablet compression machine (Rimek). A flat-faced punch 12 mm in diameter was used for tableting. Compression force of the machine was adjusted to obtain the hardness of 5-6 kg/cm^2 for different batches.

Estimation of Nimodipine[13]:

Nimodipine content of the complexes was estimated by UV spectrophotometric method. Nimodipine from accurately weighed samples was extracted into methanol and the extracts were suitably diluted with 0.1N HCl and assayed for nimodipine content by measuring the absorbance at 358 nm using 0.1N HCl as blank.

Powder X-ray Diffractometry:

Powder X-ray diffractometry was done to study the powder characteristics of nimodipine and its inclusion complexes with βCD. X-ray diffractograms were obtained by Philips diffractometer (PW 1140) and Cu-Kα radiation diffractograms were run at a scanning speed of 2^o/min and a chart speed of 2^o/ 2cm/ 2θ.

Differential Scanning Calorimetry:

The DSC measurements were performed using a Perkin Elmer Pyris (Shelton, CT) equipped with an intracooler 2P cooling accessory. Samples of 4 mg were placed in standard aluminum pans and sealed with a lid. Heating scans by 10^oC/min were applied with a nitrogen purge of 20 ml/min, over a temperature range of 35^oC to 380^oC. An empty aluminum pan was used as reference.

Table 1: Composition of floating tablets of nimodipine and its inclusion complex with betacyclodextrin

Ingredients (mg/tablet)	F_0	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Nimodipine	50	--	--	--	--	--	--	--	--	--	--	--	--
N-βCD(1:1)*	--	190	190	190	190	190	190	190	190	190	190	190	190
HPMC K_4M	--	120	180	240	--	--	--	--	--	--	--	--	--
HPMC $K_{15}M$	--	--	--	--	120	180	240	--	--	--	--	--	--
HPMC E_{15}	--	--	--	--	--	--	--	120	180	240	--	--	--
HPMC $K_{100}M$	240	--	--	--	--	--	--	--	--	--	120	180	240
Eudragit RSPO	48	24	36	48	24	36	48	24	36	48	24	36	48
Sodium bicarbonate	60	60	60	60	60	60	60	60	60	60	60	60	60
Di-calcium phosphate	196	200	128	56	200	128	56	200	128	56	200	128	56
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6	6	6	6
Total weight	600	600	600	600	600	600	600	600	600	600	600	600	600

*Nimodipine-betacyclodextrin inclusion complex in 1:1 molar ratio equivalent to 50 mg of nimodipine.

Table 2: Drug content and dissolution parameters of inclusion complexes

Inclusion Complexes*	Per cent Drug content# (±SD)	$T_{50\%}$ (min)	Dissolution Rate K_1 $(min)^{-1}$	Dissolution Efficiency DE_{30} (%)
Nimodipine	--	>120	0.007	9.60
N-βCD(1:1)	97.70±0.05	3.9	0.139	67.82
N-βCD(1:2)	99.20±0.04	3.6	0.146	70.47
N-βCD(1:3)	98.20±0.05	3.2	0.179	73.91

*N indicates nimodipine and βCD indicates beta cyclodextrin. #MeanSD, n=3.

Dissolution rate studies on inclusion complexes[14]:
Dissolution rate of nimodipine in pure form and from N-βCD inclusion complexes were studied in 900 ml of 0.1N HCl containing 10% v/v methanol. Nimodipine or N-βCD equivalent to 10 mg of nimodipine, a speed of 50 rpm and a temperature of 37±1^{0}C were used in each test. Samples were withdrawn and filtered using 0.45 µ nylon disc filter at different time intervals. The drug content was analysed after suitable dilution at 358 nm. The dissolution experiments were conducted in triplicate.

Evaluation of floating tablets:
The prepared floating tablets were evaluated for weight variation, thickness, buoyancy, and *in vitro* release characteristics. All the formulations were subjected to detailed dissolution study. The hardness of the tablets was measured by Monsanto hardness tester and thickness of the tablets was measured by using Vernier caliper.

Stability studies:
The stability of the drug in the formulation was confirmed by FTIR spectral analysis. FTIR spectra of the pure and all the formulations was determined using Shimadzu FTIR spectrophotometer by KBr disc method.

Buoyancy determination:
Buoyancy time was determined by using USP XXIV paddle dissolution apparatus[15], at 100 rpm using 900 ml of 0.1N HCl and temperature was maintained at 37±0.5^{0}C throughout the study. The duration of buoyancy (buoyancy time) is the time the tablet floats in the dissolution medium (including buoyancy lag time).

***In vitro* drug release studies:**

The *in vitro* release studies were carried by using fabricated equipment called Modified Rossett-Rice test[16]. Tablet was placed in the modified beaker containing 100 ml of 0.1NHCl at 37±0.5^{0}C and at 75 rpm. 5 ml of the sample was collected at regular intervals for 24 h and the same volume of fresh medium was added. The samples withdrawn were filtered and drug content in each sample was analysed after suitable dilution by Elico UV/Visible spectrophotometer at 358 nm.

Table 3: Evaluation data of floating tablets of nimodipine and its inclusion complex with betacyclodextrin

Formulations	F_{Lag} (h)	F_{Total} (h)	Diameter (mm)	Thickness (mm)	Hardness kg/cm^2)	Drug Content(%)
F_0	0.16(0.04)	24.0(0.08)	12.14(0.11)	4.25(0.08)	5.9(0.12)	97.86(0.39)
F_1	0.12(0.04)	16.0(0.06)	12.12(0.09)	4.36(0.12)	5.6(0.05)	99.78(0.42)
F_2	0.14(0.05)	18.0(0.03)	12.21(0.12)	4.14(0.15)	5.7(0.07)	97.56(0.74)
F_3	1.14(0.06)	18.5(0.09)	12.25(0.11)	4.28(0.06)	5.6(0.08)	99.50(0.52)
F_4	0.16(0.03)	20.0(0.09)	12.02(0.07)	4.15(0.13)	5.9(0.12)	96.85(0.61)
F_5	0.09(0.07)	20.5(0.08)	12.07(0.09)	4.61(0.12)	5.7(0.11)	97.23(0.43)
F_6	0.10(0.09)	20.5(0.07)	12.18(0.11)	4.55(0.07)	5.8(0.09)	98.91(0.84)
F_7	0.09(0.06)	21.0(0.08)	12.15(0.13)	4.35(0.09)	6.0(0.10)	96.98(0.51)
F_8	0.10(0.04)	21.5(0.06)	12.08(0.10)	4.18(0.11)	5.8(0.07)	97.12(0.42)
F_9	0.13(0.06)	21.5(0.05)	12.15(0.09)	4.55(0.08)	6.0(0.13)	98.36(0.73)
F_{10}	0.16(0.09)	22.0(0.07)	12.22(0.06)	4.26(0.13)	5.9(0.11)	98.56(0.54)
F_{11}	0.11(0.08)	22.5(0.09)	12.12(0.10)	4.34(0.06)	6.1(0.07)	99.01(0.62)
F_{12}	0.15(0.05)	24.0(0.09)	12.23(0.11)	4.22(0.06)	6.1(0.11)	98.39(0.43)

*All values are Mean ± SD (n=6), F_{Lag} indicates floating lag time, F_{Total} indicates total floating time

Figure 1: X-ray diffractograms of nimodipine (A), nimodipine-βCD in 1:1M ratio (B), nimodipine-βCD in 1:2M ratio (C) and nimodipine-βCD in 1:3M ratio (D)

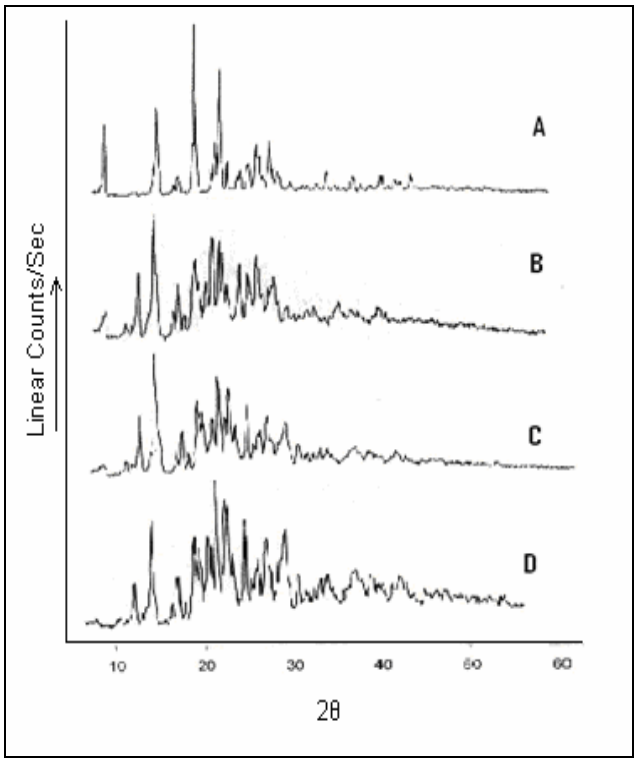
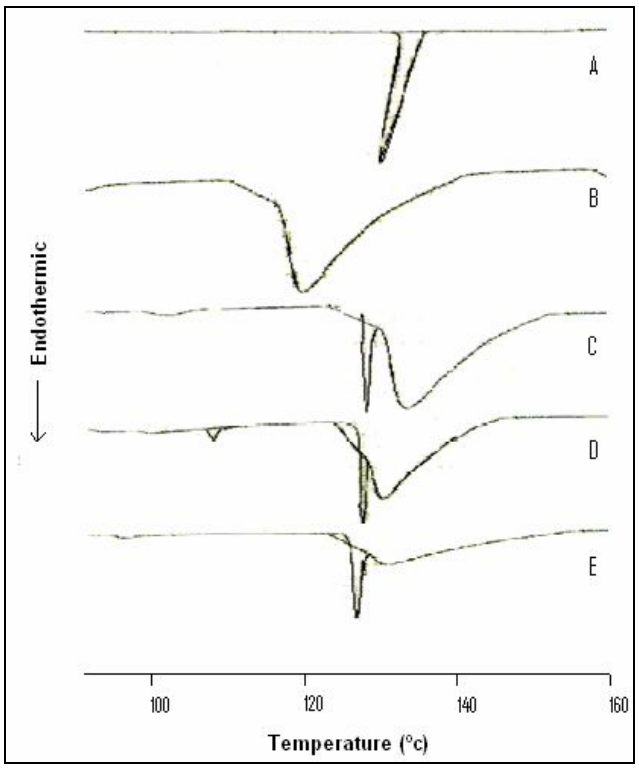


Figure 2: DSC thermograms of nimodipine (A), βCD (B), nimodipine-βCD in 1:1M ratio (C), nimodipine-βCD in 1:2M ratio (D) and nimodipine-βCD in 1:3M ratio (E).



Results and Discussions:

The phase-solubility diagram was of A_L according to Higuchi and Connors[12]. The aqueous solubility of nimodipine was increased linearly as a function of the concentration of βCD with a slope of <1 showing that the increase in the solubility was due to the formation of 1:1M complex. The apparent solubility constant (K_c) obtained from the slope of the linear phase solubility diagram was found to be 572 M^{-1}. This value of stability constant (K_c) indicated that complexes formed is quite stable.

The X-ray diffractograms of nimodipine and N-βCD complexes are shown in Fig No: 1. In X-ray diffraction studies nimodipine exhibited characteristic crystalline diffraction pattern where as in case of inclusion complexes with βCD, the sharp diffraction peaks of nimodipine have disappeared. Absence of diffraction peaks indicates that the nimodipine is essentially in amorphous form in these inclusion complexes. βCD inhibits the crystallization and converts nimodipine into amorphous form, during the preparation of the inclusion complexes.

The DSC thermograms of nimodipine and N-βCD complexes are shown in Fig No: 2. Nimodipine exhibited a sharp endothermic peak at 129.66^0C corresponding to its melting point. In the DSC thermograms of kneaded complexes, the endothermic melting peaks were shifted to 127.62, 126.91 and 126.59^0C for N-βCD 1:1, 1:2 and 1:3 respectively. The intensity of the peak also gradually reduced as the concentration of βCD was increased.

The dissolution of nimodipine as such and from the inclusion complexes followed first order kinetics ($r > 0.97$). Dissolution rate constant (K_1) were calculated from the slope of the first order linear plots of the dissolution data. Dissolution efficiency (DE_{30}) values based on the dissolution data were calculated as per Khan[14]. $T_{50\%}$ (time taken for 50% dissolution) values were recorded from the dissolution profiles. The dissolution profiles are summarized in Table 2. The results of K_1, DE_{30}, $T_{50\%}$ indicate that the inclusion complex gave fast and rapid dissolution of nimodipine when compared to nimodipine pure drug. A 7.06-, 7.34- and 7.69- fold increase in dissolution efficiency was observed with βCD in 1:1, 1:2 and 1:3 respectively. Thus both solubility and dissolution rate of nimodipine were markedly enhanced by

complexation with βCD. N-βCD(1:1) was taken for preparing floating tablets, because N-βCD(1:2) and N-βCD(1:3) results in veterinary products.

The physical parameters (thickness and diameter), hardness, buoyancy time and drug content of all the formulations are shown in Table 3. FTIR spectra analytical reports confirmed that there was no interaction between drug and excipients used (Fig No: 3).

From the results of *in-vitro* release it was noted that the drug release dependent upon the concentration and viscosity grades of HPMC. Different grades of HPMC were chosen as swellable polymer because it is widely used as low-density hydrocolloid system, upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH. Eudragit RSPO is used in combination with HPMC to retard the drug release; Eudragit ability to do this may be caused by the low solubility in gastric pH. Sodium bicarbonate is used as gas generating agent which induces floatability of the tablet and it makes tablet remain to float in stomach.

Carbon dioxide is formed within the tablet containing sodium bicarbonate when the tablet is brought in contact with the acidic dissolution medium. The low density of hydroxypropyl methylcellulose assists in floating the tablet. Moreover, the gelling capacity of HPMC also helps to float the tablet by entrapping carbon dioxide gas in the gel network of HPMC. The gelling capacity of HPMC prevents disintegration of the tablet during the dissolution study.

Tablets containing lower viscosity grades of HPMC controlled the release but could not buoyant for longer time but tablets containing higher viscosity grade of HPMC controlled the release with good buoyancy time.

Release from floating tablets of F_0 was found to be very slow, 58.2% in 24 h. The poor dissolution and low release of nimodipine from F_0 is due to the high crystalline nature and poor solubility of nimodipine. Whereas floating tablets formulated employing N-βCD inclusion complex gave slow, controlled and complete release spread over a period of 24 h.

The drug release profile of the tablets having total buoyancy time of 22 h or more are shown in Fig No: 4. Among all the formulations, the tablet containing HPMC K100M and Eudragit RSPO (F_{12}) showed better controlled release over a period of 24 h with the 99.89% drug release.

In conclusion, controlled release floating tablets of nimodipine could be developed using its inclusion complex with Bcd.

Figure 3: FTIR Spectra of Nimodipine (A), Nimodipine+HPMC K_4M (B), Nimodipine+HPMC K_{15}M (C), Nimodipine+HPMC E_{15}M (D) and Nimodipine+HPMCK_{100}M (E)

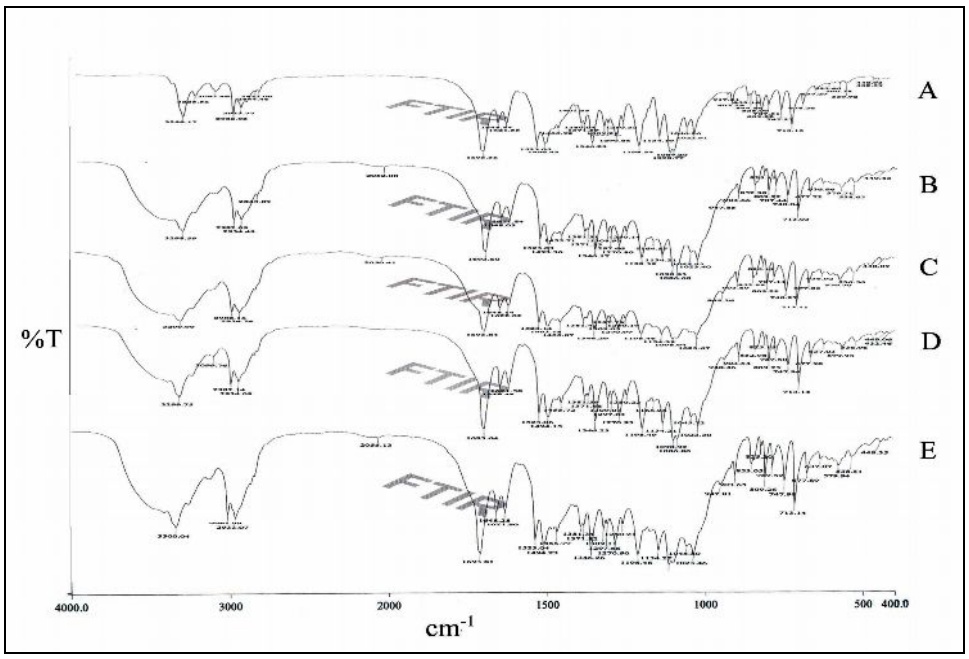
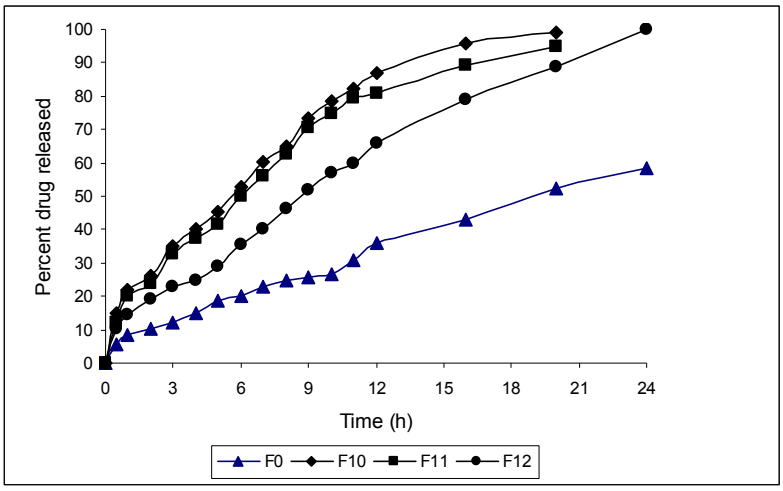


Figure 4: *In Vitro* Drug release of floating tablets.



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