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STUDIES ON THE PREPARATION, CHARACTERIZATION AND SOLUBILITY OF NIMODIPINE INCLUSION COMPLEXES WITH β-CYCLODEXTRIN

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ABSTRACT

Nimodipine, a calcium channel blocker, is a highly crystlline powder which is practically insoluble in water, in aqueous fluids both acidic and alkaline. Because of its limited aqueous solubility it exhibits poor dissolution characteristics and its oral absorption is dissolution rate limited. In this study the effect of β-cyclodextrin (βCD) on the aqueous solubility and dissolution rate of nimodipine was investigated. Phase solubility profiles indicated that the solubility of nimodipine was significantly increased in the presence of β-cyclodextrin and was classified as A_L-type, indicating the formation of 1:1 stoichiometric inclusion complexes with a stability constant of 572 M^{-1}. Solid complexes prepared by kneading method were characterized using differential scanning calorimetry and powder X-ray diffractometry. *In vitro* studies showed that the solubility and dissolution rate of nimodipine significantly improved by complexation with β-cyclodextrin with respect to the drug alone and lends an ample credence for better therapeutic efficacy.

KEY WORDS

Nimodipine, β-cyclodextrin, phase solubility, Complexation, DSC, XRD.

INTRODUCTION

Nimodipine is isopropyl (2-methoxyethyl) 1, 4–dihydro–2, 6-dimethyl–4–(3–nitro phenyl) 3, 5-pyridine-dicarboxylate, used for prevention and treatment of ischemic neuralgic deficits caused by spasm of cerebral blood vessels following subarachnoid hemorrhage[1,2]. It is a highly crystalline and practically insoluble in water and in aqueous fluids both acidic and alkaline. The aqueous solubility of nimodipine was reported to be 0.23mg/100ml[3]. Because of its limited aqueous solubility it exhibits poor dissolution characteristics and its oral absorption is dissolution rate limited. The solubility of poorly soluble drugs can be altered in many ways, such as modification of drug crystal forms, addition of co-solvents, addition of surfactants, preparation of drug dispersions with carriers, preparation of inclusion complexes with cyclodextrins, etc[4]. Among the possibilities, the preparation of inclusion complexes with cyclodextrin is of particular interest.

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Cyclodextrins are cyclic oligosaccharides containing at least six D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds with lipophilic inner cavity and hydrophilic outer surface, and are capable of interacting with a large variety of guest molecules to form non-covalent inclusion complexes (Fig.1) [5-7]

The advantages of drugs complexed with cyclodextrins are increased solubility; enhanced bioavailability; improved stability; the masking of bad taste or odor; reduced volatility; transformation of liquid or gas into solid form; reduced side effects; and the possibility of a drug release system[8-10].

In this study, investigations were performed on the possibility of complexation of nimodipine with β-cyclodextrin (βCD) in order to improve solubility and dissolution rate. The complexes of nimodipine with βCD were prepared by kneading method at stoichiometric ratios. Selective physico-chemical determinations based on phase solubility studies, differential scanning calorimetry (DSC) and powder x-ray diffractometry (XRD) were used to characterize the complexes. *In vitro* dissolution rate profiles of the complexes were performed.

Chemical structure and toroidal shape of the β-cyclodextrin

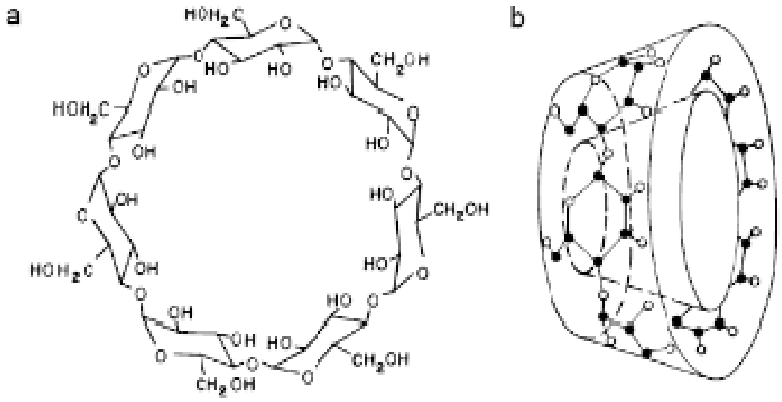

Fig.1.*(a) The chemical structure and (b) the toroidal shape of the β-cyclodextrin molecule.*

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MATERIALS AND METHODS

Materials

Nimodipine and β-cyclodextrin were gift samples from M/s Micro Lbs., Bangalore. All other reagents used and chemicals were of analytical grade. USP XXIV dissolution rate test apparatus (M/s. Electro lab) with a paddle stirrer was used for dissolution rate testing

Methods

PHASE SOLUBILITY STUDIES

The phase-solubility technique permits the evaluation of the affinity between cyclodextrin (βCD) and nimodipine in water. Phase-solubility studies were performed according to the method reported by Higuchi and Connors[11]. Nimodipine, in amounts that exceeded its solubility, was taken in to 25ml stoppard conical flask to which were added 15ml of distilled water containing 3-15mM of βCD. The flasks were sealed and shaken for 72hrs at room temperature (28^0C) on a rotary flask shaker. After equilibrating for 72hrs aliquots of 2ml were withdrawn and filtered immediately using 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for nimodipine by measuring absorbance 358nm against blanks. The solubility experiments were conducted in triplicate. The apparent solubility constant (K_c) according the hypothesis of 1:1 stoichiometric ratio of complexes was calculated from the phase-solubility diagrams using following equation[11].

$$K_{a:b} = \frac{\text{slope}}{S_0\ (1\text{-slope})}$$

The slope is obtained from the initial straight line portion of the plot of nimodipine against cyclodextrin concentration, and S_o is the equilibrium solubility of nimodipine in water.

PREPARATION OF SOLID INCLUSION COMPLEXES

The solid complexes of nimodipine-βCD were prepared in 1:1, 1:2 and 1:3 molar ratios by kneading method. Kneading method: Nimodipine and βCD were triturated in a mortar with 10ml of a solvent blend of water-methanol (6:4). The thick slurry was kneaded for 45min., dried at 55^0C, pulverized and finally sieved through mesh no.100.

ESTIMATION OF NIMODIPINE IN INCLUSION COMPLEXES

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 358nm 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.

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DIFFERENTIAL SCANNING CALORIMETRY

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

DISSOLUTION RATE STUDIES

Dissolution rate of nimodipine in pure form and from inclusion complexes was studied in 900ml 0.1N HCl containing 10% methanol. Nimodipine or its inclusion complex equivalent to 10mg of nimodipine, a speed of 50rpm and a temperature of 37°C±1°C were used in each test. Samples of dissolution media (5ml) were withdrawn through a nylon disc filter (0.45µ) at different time intervals. Suitably diluted and assayed for nimodipine at 358nm. The dissolution experiments were conducted in triplicate. The percent of nimodipine dissolved at various time intervals was calculated and plotted against time.

Khan[12] suggested dissolution efficiency (D.E.) as suitable parameter for the evaluation of *in vitro* dissolution data. Dissolution efficiency is defined as the area under dissolution curve upto a certain time 't' expressed as percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution efficiency (DE)} = \frac{\int_0^t Y.dt}{Y_{100}\ t} \times 100$$

DISSOLUTION RATE STUDIES

$T_{50\%}$, $(DE)_{30min}$ values are calculated from the dissolution data and are given in Table 1.

RESULTS AND DISCUSSION

PHASE SOLUBILITY STUDY

The phase-solubility diagram for the complexes of nimodipine with βCD is shown in Fig.2. The phase-solubility diagram was of A_L type according to Higuchi and Connors. 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 diagrams was found to be $572M^{-1}$. This value of stability constant (K_c) indicated that complexes formed is quite stable.

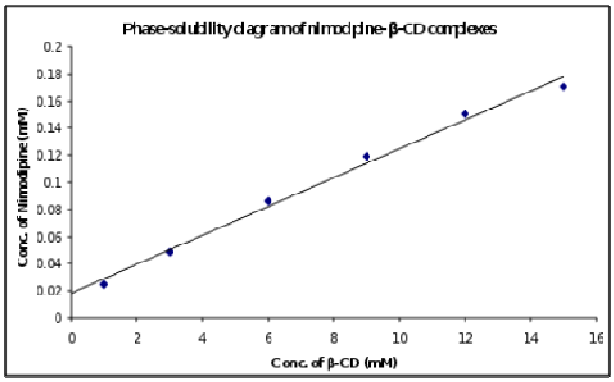

Fig 2. ***Phase-solubility diagram of nimodipine-βCD complexes***

The dissolution profiles of nimodipine and NM-βCD solid inclusion complexes are shown in Fig.3. $T_{50\%}$,

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(DE) $_{30min}$ values are calculated from the dissolution data and are given in **Table no:1** The release rate profiles were drawn as the percentage of the drug dissolved vs time. According to these results, the solid inclusion complexes of NM-βCD exhibited higher dissolution and dissolution efficiency values than nimodipine itself. The dissolution rate and dissolution efficiency valued were increased as the proportion of cyclodextrin (βCD) in the solid complex was increased.

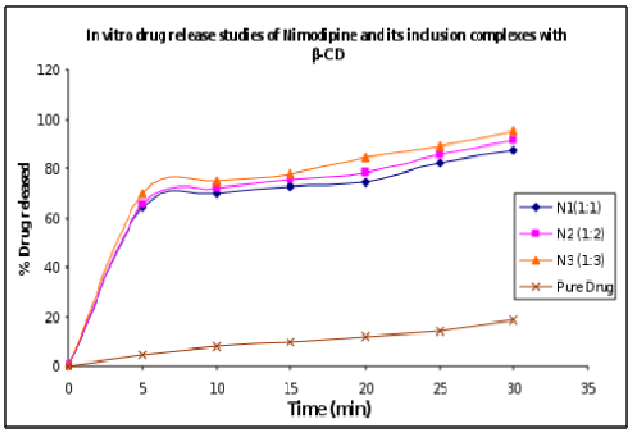

Fig 3. ***In vitro dissolution profiles of nimodipine pure drug and nimodipine-βCD solid inclusion complexes (N_1,N_2 and N_3)***

From the *in vitro* dissolution data, it was found that the drug dissolution from pure form and from different inclusion complexes (N_1-N_3) was 18.45%, 87.55%, 91.30% and 95.40% respectively at the end of 30mins.

The dissolution rate of nimodipine from all complexes was higher than that of pure drug and the dissolution rate increased as proportion of the β-CD increased. The dissolution efficiency of nimodipine was also improved from 9.6% for pure drug to 67.82%, 70.47% and 73.91% in case of inclusion complexes N_1-N_3 respectively.

Table 1. Dissolution parameters

Formu -lation	$T_{50\%}$ (min)	$T_{80\%}$ (min)	$T_{90\%}$ (min)	DE% (30min)
N_1	3.9	23.5	0	67.82
N_2	3.6	21	29	70.47
N_3	3.2	17	26	73.91

$T_{50\%}$, $T_{80\%}$, $T_{90\%}$ and $DE_{(30)}$ of inclusion Complexes (N_1-N_3)

X-RAY DIFFRACTION STUDIES

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To evaluate the mechanism of fast dissolution observed with inclusion complexes. XRD was carried out. The X-ray diffractograms of nimodipine and its inclusion complexes are shown in Fig No: 4. In X-ray diffraction studies nimodipine exhibited characteristic crystalline diffraction pattern where as in case of inclusion complexes with β-CD, the sharp diffraction peaks of nimodipine have disappeared. Absence of diffraction peaks indicates that the drug nimodipine is essentially in amorphous form in these inclusion complexes. β-CD inhibits the crystallization and converting nimodipine into amorphous form, during the preparation of the inclusion complexes.

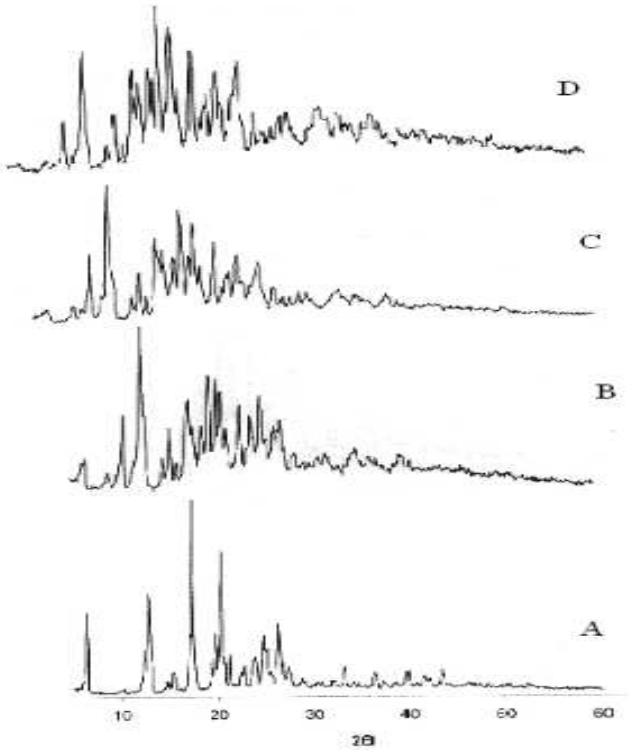

Fig 4. ***X-ray diffractograms of nimodipine (A); nimodipine:β-CD in 1:1M ratio (B); nimodipine:β-CD in 1:2M ratio (C) and nimodipine:β-CD in 1:3M ratio (D)***

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES

The DSC thermograms for the nimodipine and nimodipine-β-CD complexes assayed are represented in Fig 5. Nimodipine exhibits a characteristic endothermic fusion peak at 129.66^{0}C corresponding to its melting point, hence no polymorphs of nimodipine could be found. Further more β-CD shows a broad endothermic peak at 118.84^{0}C.

The DSC thermograms for the nimodipine- β-CD kneaded complexes show the persistence of endothermic peak of nimodipine, indicating that the kneading process didn't substantially affect their solid state properties. For kneaded complexes there is reduction in the peak intensity; this can be explained on the basis of a major interaction between the drug and cyclodextrin. Further more, the characteristic endothermic effect of β-CD is slightly shifted to low temperatures indicating that nimodipine got complexed with β-CD.

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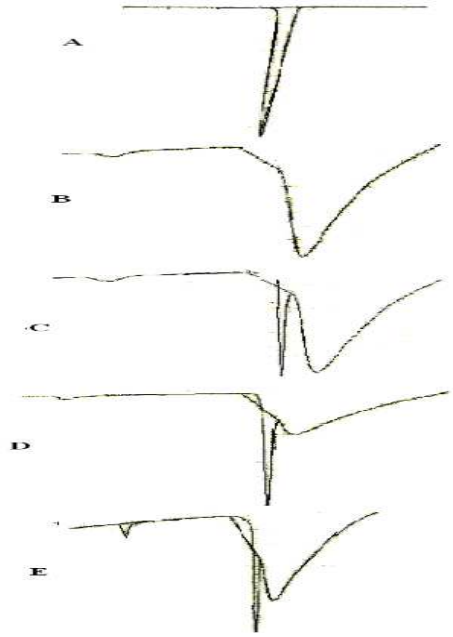

Fig 5. ***DSC thermograms of nimodipine (A); β-CD (B); nimodipine: β-CD in 1:1M ratio (C); nimodipine: β-CD in 1:2M ratio (D) and nimodipine: β-CD in 1:3M ratio (E).***

CONCLUSION

The aqueous solubility and dissolution rate of nimodipine can be increased by inclusion complexation with β-cyclodextrin. The phase-solubility studies indicated the formation of NM- βCD inclusion complexes at 1:1 stoichiometric ratio in solution with stability constant of $572M^{-1}$. The solubility and dissolution rate of nimodipine were significantly enhanced by complexation with βCD. These complexes exhibited higher rates of dissolution and dissolution efficiency values than nimodipine as such. Results obtained by different characterization techniques clearly indicated that kneading method leads to formation of solid state complexes between nimodipine and βCD. The complexation of nimodipine with βCD lends an ample credence for better therapeutic efficacy.

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