RESEARCH PAPER

Accepted 11 December 2001
Revised 21 November 2001
Received 7 June 2001
Indian J. Pharm. Sci., 2002, 64(2): 142-146

Complexes of Nifedipine with β-and Hydroxypropyl β-Cyclodextrins in the Design of Nifedipine SR Tablets

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Complex formation of nifedipine with β-cyclodextrin and hydroxypropyl β-cyclodextrin was studied. The possibility of improving the solubility and dissolution rate of nifedipine via complexation with the above cyclodextrins and the feasibility of employing nifedipine cyclodextrin inclusion complexes in the design of mucoadhesive tablets for sustained release were also investigated. The phase solubility studies indicated the formation of a nifedipine-β-cyclodextrin (1:1 M) and nifedipine-hydroxypropyl β-cyclodextrin (1:1 M) inclusion complexes with a stability constant of 121.9 M^{-1} and 253.7 M^{-1} respectively. The solubility and dissolution rate of nifedipine were markedly enhanced by complexation with β-cyclodextrin and hydroxypropyl β-cyclodextrin. Nifedipine-hydroxypropyl β-cyclodextrin (1:3) gave highest enhancement (44.8 fold) in the dissolution rate of nifedipine. Mucoadhesive tablets formulated employing nifedipine alone gave very low dissolution. Whereas those formulated employing nifedipine-β-cyclodextrin and nifedipine-hydroxypropyl β-cyclodextrin complexes gave slow, controlled and complete release spread over a period of 12 h. Drug release from these tablets followed zero order kinetics upto 85-90% release and the release was diffusion controlled. Good sustained release two layered tablet formulations of nifedipine, satisfying the theoretical sustained release need based on its pharmacokinetics, were developed using nifedipine-β-cyclodextrin and nifedipine-hydroxypropyl β-cyclodextrin inclusion complexes.

Nifedipine (N) is used in the treatment of angina pectoris and hypertension[1]. It is practically insoluble in water and its absorption is dissolution rate limited. The very poor aqueous solubility of the drug may lead to variable dissolution rates and bioavailabilities. Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug.[2-4] The objective of the present study was to investigate the possibility of improving the solubility and dissolution rate of nifedipine via complexation with β-cyclodextrin (βCD) and hydroxypropyl β-cyclodextrin (HPβCD). The very poor aqueous solubility of nifedipine also poses problems in the design of nifedipine SR tablets. The feasibility of employing N-βCD and N-HPβCD inclusion complexes in the design of mucoadhesive tablets for sustained release was also investigated. Mucoadhesive tablets of nifedipine and N-βCD and N-HPβCD inclusion complexes were formulated employing sodium CMC as a mucoadhesive polymer and were evaluated with a view to obtain sustained release. The results are reported here.

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EXPERIMENTAL

Nifedipine was a gift sample from M/s Cipla Ltd., Mumbai. β-Cyclodextrin and hydroxypropyl β-cyclodextrin were gift samples from M/s Cerestar Inc., Chicago, USA. Sodium carboxy methyl cellulose (sodium CMC with a viscosity of 1500-3000 cps in 1% w/v aqueous solution at 25°) and methanol GR (Merck) were procured from Loba Chemie Pvt., Ltd., Mumbai. All experiments were carried out under subdued light to prevent photodegradation of nifedipine.

Estimation of nifedipine:

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 238 nm in 0.1 N HCl was used for the estimation of nifedipine. The method obeyed Beer's law in the concentration range 0-20 µg/ml. When a standard drug solution was assayed repeatedly (n=6) the relative error (accuracy) and relative standard deviation (precision) were found to be 0.9% and 1.2% respectively.

Phase solubility studies:

Solubility studies were performed according to the method reported by Higuchi and Connors[5]. Excess of nifedipine (50 mg) was added to 15 ml of triple distilled water (pH 6.8) containing various concentrations of βCD (3-15 mM) and HPβCD (3-15 mM) taken in a series of 25 ml stoppered conical flasks and the mixtures were shaken for 72 h at room temperature (28°) on a rotary flask shaker. After 72 h of shaking to achieve equilibrium 2 ml aliquots were withdrawn at 1 h interval and filtered immediately using 0.45 µ nylon disc filter. The filtered samples were diluted suitably and assayed for nifedipine by measuring absorbance at 238 nm against blanks prepared in the same concentration of βCD or HPβCD in water so as to cancel any absorbance that may be exhibited by the CD molecules. Shaking was continued until three consecutive estimations are the same. The solubility experiments were conducted in triplicate.

Preparation of N-CD complexes:

Solid complexes of N-βCD and N-HPβCD were prepared in 1:1, 1:2 and 1:3 ratios by kneading method. Nifedipine and cyclodextrin were triturated in a mortar with a small volume of a solvent blend of water-methanol (6:4). The thick slurry was kneaded for 45 min and then dried at 55° until dry. The dried mass was pulverized and sieved through 100 mesh.

Dissolution rate study on N-CD complexes:

Dissolution rate of nifedipine in pure form and from N-βCD and N-HPβCD inclusion complexes was studied using an USP XXIII 3 station dissolution rate test apparatus (model DR-3, M/s Campbell Electronics) with a paddle stirrer. The dissolution fluid was 900 ml of 0.1 N hydrochloric acid containing 10% methanol. Methanol was added to the dissolution fluid to maintain sink condition. Pure drug or inclusion complex equivalent to 10 mg of nifedipine, a speed of 50 rpm, and a temperature of 37±1° were used in each test. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for nifedipine by measuring absorbance at 238 nm. The dissolution experiments were conducted in triplicate.

Preparation of mucoadhesive tablets:

Mucoadhesive tablets each containing 20 mg of nifedipine were prepared by conventional wet granulation method employing nifedipine and its solid inclusion complexes with βCD and HPβCD and sodium CMC as a mucoadhesive matrix material. A blend of all ingredients were granulated with a solvent blend of water and alcohol (6:4). The wet granules (12 mesh) were dried at 60° for 4 h. The dried granules (16 mesh) after blending with lubricants (2% of each of talc and magnesium stearate), were compressed in to 200 mg tablets to a hardness of 6-8 kg/sq.cm. on a Cadmach single punch tablet machine.

Drug release study on mucoadhesive tablets:

Release of nifedipine from the tablets was studied using an USP XXIII 3 station dissolution rate test apparatus (model DR-3, M/s Campbell Electronics) with a paddle stirrer as per NF XIII procedure. Dissolution fluid consisted of 900 ml of simulated gastro intestinal fluids with increasing pH, namely pH 1.2 (0-1 h), pH 2.5 (1-2 h), pH 4.5 (2-3.5 h) pH 7.0 (3.5-5.0 h) and pH 7.5 (5-12 h). The dissolution fluids also contained 10% methanol to maintain sink condition in dissolution rate testing. One tablet containing 20 mg of nifedipine, a speed of 50 rpm and a temperature of 37±1.0 were employed in each test. Samples withdrawn were assayed at 238 nm for nifedipine.

RESULTS AND DISCUSSION

Nifedipine is practically insoluble in water and aqueous fluids due to its highly crystalline nature and exhibits poor dissolution rate. Various attempts made to improve the dissolution rate of nifedipine include solid dispersion in water-soluble carriers such as urea[6], PVP[7], PVP-MCC and HIPC-MCC[8]. In the present work complexation of nifedipine with βCD and HPβCD was tried to improve its solubility and dissolution rate. The phase solubility diagrams for the complex formation between nifedipine and β-CD and HPβCD are shown in fig 1. The aqueous solubility of nifedipine was increased linearly as a function of the concentration of β-CD and HPβCD. The phase solubility diagrams of N-βCD and N-HPβCD complexes can be classified as type A_L according to Higuchi and Connors[5]. Because the straight line had a slope less than unity, the increase in solubility was due to the formation of a 1:1 M complex. The apparent stability constant (K_c) obtained from the slope of the linear phase

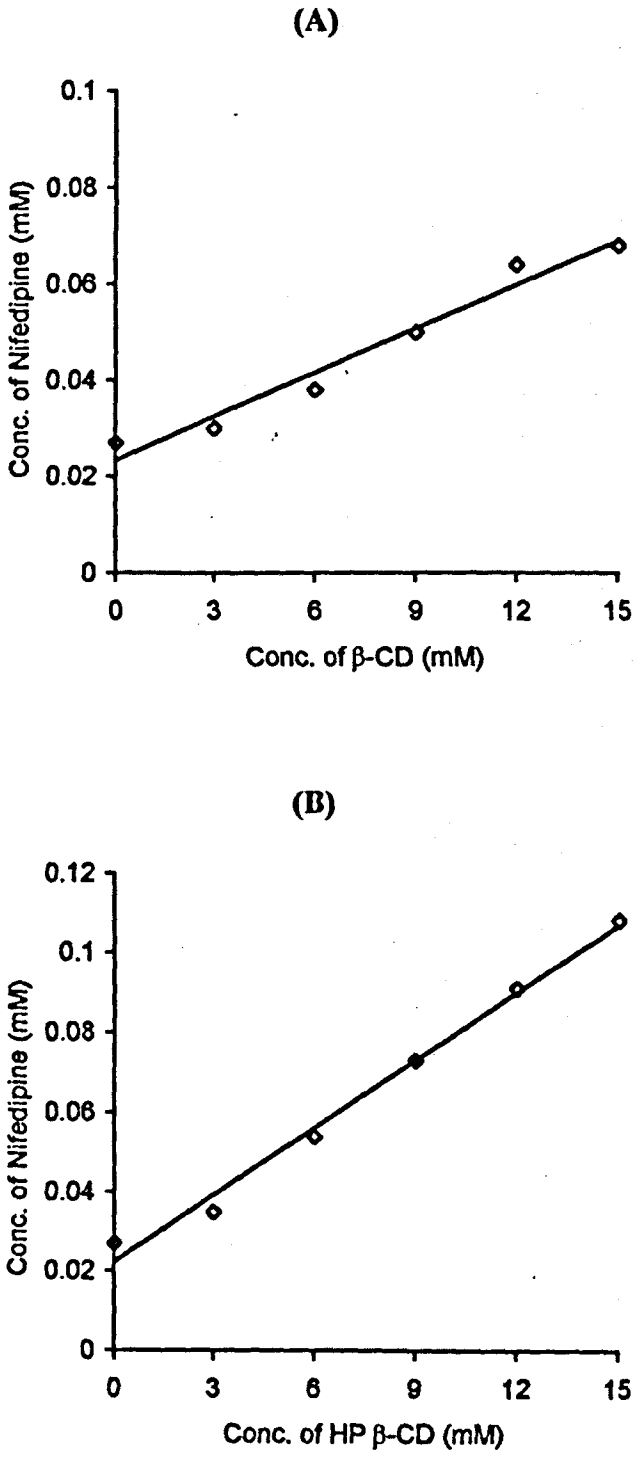

Fig. 1: Phase solubility patterns for nifedipine and cyclodextrin complexes. Phase solubility pattern of N-βCD (A) and N-HPβCD (B).

solubility diagram was found to be 121.9 M^{-1} and 253.7 M^{-1} respectively for N-βCD and N-HPβCD complexes. These values of stability constant (K_c) indicated that the N-βCD and N-HPβCD complexes formed are adequately stable.

Solid inclusion complexes of N-βCD and N-HPβCD were prepared by kneading method. The dissolution parameters of nifedipine and N-βCD and N-HPβCD solid inclusion complexes are given in Table 1. The dissolution of nifedipine followed first order kinetics ($r>0.96$). Solid inclusion complexes of N-βCD and N-HPβCD exhibited higher rates of dissolution and dissolution efficiency values (calculated as per Khan[9]) than nifedipine itself. N-βCD and N-HPβCD solid complexes gave 90% dissolution within 30 and 20 min respectively. Whereas in the case of nifedipine as such the dissolution was very low, 28% in 2 h. With both βCD and HPβCD the dissolution rate was increased as the proportion of CD in the solid complex was increased. HPβCD gave higher enhancement in the dissolution rate when compared to βCD. An increase of 20.6 and 42.9 fold in the dissolution rate of nifedipine was observed respectively with N-βCD (1:2) and N-HPβCD (1:2) inclusion complexes. Thus both the solubility and dissolution rate of nifedipine were markedly enhanced by complexation with βCD and HPβCD.

Mucoadhesive tablets of nifedipine were formulated employing nifedipine alone and N-βCD and N-HPβCD inclusion complexes and using sodium CMC as mucoadhesive matrix material. Sodium CMC was reported[10] to have good mucoadhesive properties. Mucoadhesive polymers prolong the residence time of the dosage form in the g.i. tract and

TABLE 1: DISSOLUTION PARAMETERS OF NIFEDIPINE AND NβCD AND N-HPβCD INCLUSION COMPLEXES.

Product	Dissolution Parameter	
	K_1 (min^{-1})	DE_{30} (%)
Nifedipine	0.0037	7.12
N-βCD (1:1)	0.0577	69.26
N-βCD (1:2)	0.0778	70.27
N-βCD(1:3)	0.0769	71.01
N-HPβCD (1:1)	0.1404	76.23
N-HPβCD (1:2)	0.1589	77.82
N-HPβCD(1:3)	0.1658	78.41

K_1 is first order dissolution rate constant and DE_{30} is dissolution efficiency up to 30 min as per Khan[9].

hence more suitable as matrix material for oral sustained release tablets.

Nifedipine release from various tablets was studied in simulated gastrointestinal fluids for a period of 12 h. Release from tablet formulation F1 was found to be very low, 33% in 12 h. The poor dissolution and low release of nifedipine from F1 is due to the highly crystalline nature and poor solubility of nifedipine. Whereas tablets formulated employing N-βCD and N-HPβCD solid complexes gave slow, controlled and complete release spread over a period of 12 h (Table 2). Nifedipine release from these tablets followed

TABLE 2: NIFEDIPINE RELEASE FROM MUCOADHESIVE TABLETS IN SIMULATED GASTROINTESTINAL FLUIDS.

Formulation	Composition (Drug & excipient)	Percent nifedipine released with time (h)					T_{50} (h)	Release rate (mg/h)
		1.0	2.0	4.0	8.0	12.0		
F1	Nifedipine(N)	4.16	11.21	18.6	26.3	33.0	>12	0.556
	Sodium CMC	(0.06)	(0.08)	(0.14)	(0.14)	(0.34)		
F2	N-βCD (1:1)	1.81	4.9	6.5	64.3	86.5	7.4	1.916
	Sodium CMC	(0.15)	(0.13)	(0.30)	(0.66)	(0.10)		
F3	N-βCD (1:2)	4.5	7.7	12.5	81.5	92.0	6.6	1.987
	Sodium CMC	(0.30)	(0.45)	(0.18)	(1.22)	(0.74)		
F4	N-βCD (1:3)	3.26	8.86	23.2	75.4	100.5	5.5	2.037
	Sodium CMC	(0.29)	(0.59)	(0.65)	(1.06)	(0.55)		
F5	N-βCD (1:3)	2.91	8.36	22.3	78.5	96.8	6.0	2.008
	Sodium CMC	(0.22)	(0.20)	(0.35)	(1.65)	(1.82)		
	Ethyl cellulose (5%)							
F6	N-HPβCD (1:1)	2.5	6.28	10.9	65.3	85.68	7.0	1.807
	Sodium CMC	(0.18)	(0.38)	(0.13)	(0.73)	(0.55)		
F7	N-HPβCD (1:2)	6.28	10.53	16.5	68.5	92.73	6.2	1.813
	Sodium CMC	(0.25)	(0.34)	(0.63)	(0.57)	(0.56)		
F8	N-HPβCD (1:3)	7.31	12.5	25.5	72.3	100.8	6.0	1.937
	Sodium CMC	(0.22)	(0.69)	(0.98)	(1.62)	(0.68)		
F9	N-HPβCD (1:3)	5.56	10.16	22.06	63.92	90.93	6.8	1.740
	Sodium CMC	(0.25)	(0.40)	(0.71)	(1.11)	(1.21)		
	Ethyl cellulose(5%)							
SR-1	Two layered SR	22.7	29.5	44.6	71.7	94.6	5.4	1.697
	tablet designed as	(0.15)	(0.45)	(0.50)	(0.10)	(0.20)		
	described in text							
SR-2	Two layered SR	22.57	29.8	44.4	68.75	92.5	5.9	1.633
	tablet designed as	(0.15)	(0.86)	(1.14)	(1.35)	(1.02)		
	described in text							
Theoretical SR Profile Needed		25	32	46	73	100	-	1.385

Figures in parentheses are standard deviation values. T_{50} is time for 50% release. F1 to F9 are mucoadhesive tablets of nifedipine formulated. SR-1 and SR-2 are two sustained release tablets designed.

zero order kinetics ($r>0.95$) upto 85-90% release. Nifedipine release from these tablets increased as the proportion of βCD and HPβCD in the solid inclusion complex was increased. The drug release mechanism from the tablets was diffusion controlled as plots of the amount of the drug released versus square root of time were found to be linear.

The mucoadhesive tablets formulated employing N-βCD and N-HPβCD solid inclusion complexes were found suitable for maintenance portion of SR tablets. As the initial release from these tablets was very low, an immediately releasing loading dose may be applied either as a coat or as a layer on these tablets.

Sustained release tablets (SR-1 and SR-2), each containing 20 mg of nifedipine, were designed as two layered tablets. SR-1 consists of an immediately releasing N-βCD (1:3) equivalent to 4 mg and Ac-Di-Sol (8 mg) as one layer and the matrix consisting of N-βCD (1:3) complex equivalent to 16 mg of nifedipine, sodium CMC and ethyl cellulose (5%) as a second layer. SR-2 consists of an immediately releasing N-HPβCD (1:3) equivalent to 4 mg and Ac-Di-Sol (8 mg) as one layer and the matrix consisting of N-HPβCD (1:3) complex equivalent to 16 mg of nifedipine, sodium CMC and ethyl cellulose (5%) as a second layer.

The drug release profiles of SR-1 and SR-2 formulations are given in Table 2. Theoretical sustained release profile needed for nifedipine was evaluated based on its pharmacokinetic parameters as suggested by Wagner[11]. A sustained release formulation of nifedipine should contain a total dose of 20 mg and should provide a release of 25% in 1 h, 32% in 2 h, 46% in 4 h, 73% in 8 h and 100% in 12 h. Formulations SR-1 and SR-2 gave release close to the theoretical SR needed for nifedipine (Table 2).

Thus the results of the phase solubility studies indicated the formation of N-βCD (1:1 M) and N-HPβCD (1:1 M) inclusion complexes with a stability constant of 121.9 M^{-1} and 253.7 M^{-1} respectively. The solubility and dissolution rate of nifedipine were markedly enhanced by complexation with βCD and HPβCD. Slow, controlled and complete nifedipine release over a period of 12 h was obtained from mucoadhesive tablets formulated employing N-βCD and N-HPβCD inclusion complexes, which was not possible with tablets formulated employing nifedipine itself. Good sustained release two layered tablet formulation of nifedipine could be developed using N-βCD and N-HPβCD inclusion complexes.

ACKNOWLEDGEMENTS

The authors thank AICTE, New Delhi for financial assistance and to M/s Cipla Ltd., Mumbai for providing a gift sample of nifedipine.

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