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Controlled release of nifedipine from mucoadhesive tablets of its inclusion complexes with β-cyclodextrin

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Mucoadhesive tablets formulated with nifedipine (N) alone and its inclusion complexes with β-cyclodextrin (βCD) and the mucoadhesive polymers sodium carboxy methylcellulose and carbopol were investigated with a view to the design of oral controlled release tablets of nifedipine. As nifedipine is practically insoluble in water and aqueous fluids, its complexation with βCD was investigated to improve its solubility and dissolution rate. Complexation of nifedipine with βCD has markedly enhanced the solubility and dissolution rate of nifedipine. The phase solubility studies indicated the formation of a N-βCD inclusion complex with a stability constant of 121.9 M^{-1}. A 20.6 fold increase in the dissolution rate of nifedipine was observed with N-βCD (1 : 2) solid inclusion complex. Mucoadhesive tablets formulated employing nifedipine alone gave very low dissolution, whereas those formulated employing its βCD inclusion complexes gave slow, controlled and complete release spread over a period of 12 h. Drug release from these tablets followed zero order kinetics up to 85–90% release and the release was diffusion controlled. Good controlled release two layered tablet formulations of nifedipine, satisfying the theoretical sustained release requirements based on its pharmacokinetics, were developed using its inclusion complexes with βCD.

1. Introduction

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. Nifedipine has a short biological half-life of 3.4 h and is eliminated rapidly, and its antihypertensive effect lasts only a few hours [2]. Therefore controlled release (CR) products are needed for nifedipine to prolong its duration of action and to improve patient compliance. CR products also avoid the vasodilator related adverse effects such as increase in heart rate, flushing and palpitation associated with conventional nifedipine tablets and capsules. There are a few reports on the formulation of oral controlled release products of nifedipine employing coated granules [3], matrix tablets [4] and microencapsulation [5]. In the present work, mucoadhesive tablets of nifedipine and its inclusion complexes with β-cyclodextrin (βCD) were formulated employing sodium carboxymethylcellulose (sodium CMC) and carbopol as mucoadhesive polymers, and were evaluated with a view to obtaining controlled release for oral use. As nifedipine is practically insoluble in water, its complexation with β-cyclodextrin was tried to enhance its solubility and dissolution rate. Cyclodextrins and their derivatives play an important role in formulation development due to their effect on the solubility, dissolution rate, chemical stability and absorption of a drug [6–8]. The complex formation between N and βCD and the feasibility of using these cyclodextrin complexes in the formulation of mucoadhesive tablet for oral controlled release were also investigated.

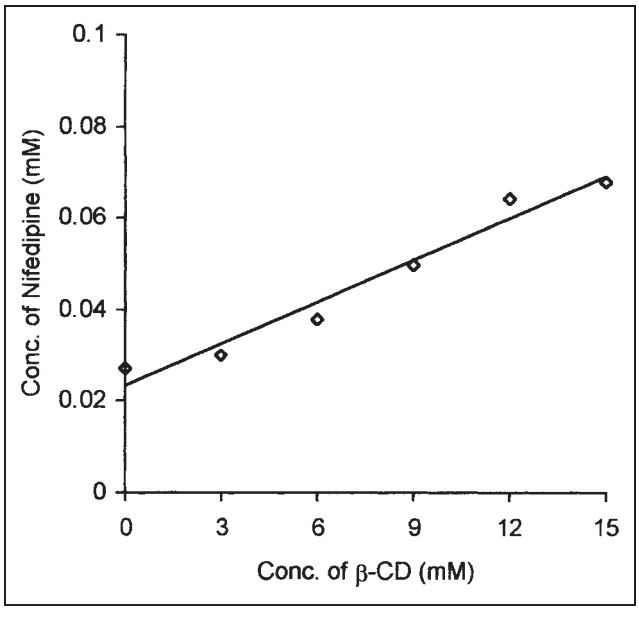

Fig. 1: Phase solubility diagram of N-βCD

2. Investigations and results

2.1. Phase solubility studies

Solubility studies were performed according to the method reported by Higuchi and Connors [9]. The phase solubility diagram for complex formation between nifedipine and β-cyclodextrin is shown in Fig. 1. The aqueous solubility of nifedipine 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 a 1 : 1 M complex. The apparent stability constant (K_C) of N-βCD obtained from the slope of the linear phase solubility diagram was found to be 121.9 M^{-1}.

2.2. Solid inclusion complexes of N-βCD

Solid inclusion complexes of N-βCD were prepared with 1 : 1, 1 : 2 and 1 : 3 ratios by a kneading method. Nifedipine content in the solid inclusion complexes was found to be 100 ± 2% of the labeled amount. In each case low c.v. value (<2%) in the percent drug content indicated uniformity of drug content in the solid complexes.

Table 1: Formulations of nifedipine mucoadhesive tablets as prepared

No. Ingredient (mg/tablet)	Formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
1. Nifedipine	20	–	–	–	20	–	–	–
2. N-βCD (1 : 1)	–	40	–	–	–	40	–	–
3. N-βCD (1 : 2)	–	–	60	–	–	–	60	–
4. N-βCD (1 : 3)	–	–	–	80	–	–	–	80
5. Sodium CMC	172	152	132	112	–	–	–	–
6. Carbopol 934 P	–	–	–	–	172	152	132	112
7. Talc	4	4	4	4	4	4	4	4
8. Magnesium stearate	4	4	4	4	4	4	4	4

The dissolution rate of nifedipine both as such and from N-βCD solid inclusion complexes was studied in 0.1 N HCl. The dissolution of nifedipine from the inclusion complexes followed first order kinetics (r > 0.96). The dissolution efficiency (DE_{30}) values were calculated according to Khan [10]. Solid inclusion complexes of N-βCD exhibited higher rates of dissolution and DE values than nifedipine itself. N-βCD solid complexes gave 90% dissolution within 30 min, whereas for nifedipine done, the dissolution was very low, 28% in 2 h. The dissolution rate increased as the proportion of βCD in the solid complex increased.

2.3. Mucoadhesive tablets

Mucoadhesive tablets of nifedipine were formulated employing nifedipine alone and N-βCD solid complexes and using sodium CMC and carbopol as mucoadhesive matrix materials (Table 1). The tablets were prepared by a conventional wet granulation method and were evaluated for hardness, friability, disintegration time and *in vivo* mucoadhesion property.

Nifedipine release from the mucoadhesive tablets was studied in simulated gastrointestinal fluids for a period of 12 h according to the NF-XIII procedure. The nifedipine release profiles of the tablets are given in Table 2. Release from tablet formulations F1 and F5 which contained pure nifedipine was found to be very low, 33% and 15% respectively in 12 h, whereas tablets formulated with N-βCD complexes gave slow, controlled and complete release spread over a period of more than 12 h.

2.4. Design and evaluation of two layered controlled release tablets of nifedipine

Oral controlled release tablets (CR−1 and CR−2) each containing 20 mg of nifedipine are designed as two layered tablets. CR−1 consists of an immediate release N-

Table 2: Nifedipine release from mucoadhesive tablets in simulated gastrointestinal fluids

Formulation	Composition (Drug & excipient)	Percent nifedipine released at 5 time points (h)					T_{50} (h)	Release rate (mg/h)
		1.0	2.0	4.0	8.0	12.0		
F1	Nifedipine (N) Sodium CMC	4.16 (0.06)	11.21 (0.08)	18.6 (0.14)	26.3 (0.14)	33.0 (0.34)	>12	0.556
F2	N-βCD (1 : 1) Sodium CMC	1.81 (0.15)	4.9 (0.13)	6.5 (0.30)	64.3 (0.66)	86.5 (0.10)	7.4	1.916
F3	N-βCD (1 : 2) Sodium CMC	4.5 (0.30)	7.7 (0.45)	12.5 (0.18)	81.5 (1.22)	92.0 (0.74)	6.6	1.987
F4	N-βCD (1 : 3) Sodium CMC	3.26 (0.29)	8.86 (0.59)	23.2 (0.65)	75.4 (1.06)	100.5 (0.55)	5.5	2.037
F5	Nifedipine (N) Carbopol	2.25 (0.52)	2.33 (0.45)	5.38 (0.62)	11.35 (0.69)	15.18 (1.02)	>12	0.254
F6	N-βCD (1 : 1) Carbopol	2.25 (0.19)	5.20 (0.26)	10.35 (0.52)	28.83 (0.28)	43.88 (0.68)	>12	0.820
F7	N-βCD (1 : 2) Carbopol	2.95 (0.15)	6.80 (0.33)	12.75 (0.41)	32.6 (1.58)	48.70 (0.71)	>12	0.884
F8	N-βCD (1 : 3) Carbopol	3.55 (0.18)	8.18 (0.58)	15.63 (1.14)	36.5 (1.74)	53.8 (1.74)	9.8	0.975
CR-1	Two layered CR tablet designed as described in text	22.7 (0.15)	29.5 (0.45)	44.6 (0.50)	71.7 (0.10)	94.6 (0.20)	5.4	1.697
CR-2	Two layered CR tablet designed as described in text	21.0 (0.91)	28.1 (0.35)	41.9 (1.07)	60.8 (1.97)	83.8 (1.24)	7.4	1.380
Theoretical SR profile needed		23	32	46	73	100	–	1.385

Figures in parentheses are standard deviation values. T_{50} is time for 50% release. F1 to F8 are mucoadhesive tablets of nifedipine. CR-1 and CR-2 are two oral controlled release tablets.

βCD (1 : 3) complex equivalent to 4 mg of nifedipine and croscarmellose sodium (8 mg) as one layer and the mucoadhesive matrix consisting of N-βCD (1 : 3) complex equivalent to 16 mg of nifedipine and sodium CMC as a second layer. CR−2 consists of an immediate release N-βCD (1 : 3) complex equivalent to 4 mg of nifedipine and croscarmellose sodium (8 mg) as one layer and the mucoadhesive matrix consisting of N-βCD (1 : 3) complex equivalent to 16 mg of nifedipine and carbopol as a second layer. The release profiles of these CR formulations were studied in simulated gastrointestinal fluids for a period of 12 h according to the NF XIII procedure. The release profiles of these CR formulations are given in Table 2 and are shown in Fig. 2 along with the theoretical sustained release needed for nifedipine based on its pharmacokinetic parameters.

3. Discussion

Nifedipine is practically insoluble in water and aqueous fluids due to its highly crystalline nature and exhibits a poor dissolution rate. Various attempts made to improve the dissolution rate of nifedipine have included solid dispersions in water-soluble carriers such as urea [11], polyvinylpyrrolidine (PVP) [12], PVP- microcrystalline cellulose (MCC) and hydroxypropylcellulose (HPC)-MCC [13]. In the present work complexation of nifedipine with βCD was tried to improve its solubility and dissolution rate. The aqueous solubility of nifedipine increased linearly as a function of the concentration of βCD due to the formation of 1 : 1 M complex. The phase solubility diagram of the N-βCD complex can be classified as type A_L according to Higuchi and Connors [9]. The value of the stability constant ($K_C = 121.9\ M^{-1}$) indicated that the N-βCD complex formed is adequately stable.

Solid inclusion complexes of N-βCD exhibited higher rates of dissolution and dissolution efficiency values than nifedipine itself. The dissolution of nifedipine from these complexes followed first order kinetics ($r > 0.96$). The N-βCD (1 : 2) solid inclusion complex gave a 20.6 fold increase in the dissolution rate of nifedipine.

Mucoadhesive tablets of nifedipine were formulated employing sodium CMC and carbopol as mucoadhesive matrix materials. These materials have been reported [14] to have good mucoadhesive properties. Mucoadhesive polymers prolong the residence time of the dosage form in the gastrointestinal tract and hence are more suitable as a matrix material for oral controlled release tablets.

The mucoadhesive tablets prepared were found to be non-disintegrating in water, 0.1 N HCl and phosphate buffer of pH 7.4. Hardness of the tablets was in the range 7–8 kg/cm^2. Percentage weight loss in the friability test was found to be 0.2% in all cases. The tablets of all the batches prepared contained nifedipine within 100 ± 5% of the labeled content. As such all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content.

Drug release from tablet formulations F1 and F5, which contained pure nifedipine, was found to be very low. The poor dissolution and low release of nifedipine from F1 and F5 is due to the highly crystalline nature and poor solubility of nifedipine. However, tablets formulated with N-βCD complexes gave slow, controlled and complete release spread over a period of 12 h (Table 2). Nifedipine release from these tablets followed zero order kinetics ($r > 0.95$) up to 85–90% release. Nifedipine release from these tablets was increased as the proportion of βCD in the inclusion complex was increased. The drug release mechanism from these tablets was diffusion controlled as plots of the amount of the drug released versus square root of time were found to be linear ($r > 0.97$). The higher, but slow and complete, release of nifedipine from these tablets is due to the N-βCD complexes used in their preparation, which exhibited higher and rapid dissolution of nifedipine.

X-ray studies showed that the tablets formulated employing sodium CMC and carbopol were intact and remained in the intestinal region even 10 h after administration indicating good adhesion of the tablets in the intestinal region.

The mucoadhesive tablets formulated employing N-βCD complexes were found suitable for the maintenance portion of oral CR tablets. As the initial release from these tablets was very low, an immediate release loading dose may be provided either as a coating or as a layer on these tablets.

Oral controlled release tablets (CR-1 and CR-2) each contained 20 mg of nifedipine as two layered tablets, an immediately releasing layer consisting of N-βCD (1 : 3) complex along with a superdisintegrant and a second sustained release layer consisting of a matrix of N-βCD and a mucoadhesive polymer.

The theoretical sustained release profile needed for nifedipine was evaluated on the basis of its pharmacokinetic parameters as suggested by Wagner [15]. An oral controlled 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 CR-1 and CR-2 gave release close to the theoretical SR needed for nifedipine (Fig. 2).

Thus slow, controlled and complete of release nifedipine over a period of 12 h was obtained from mucoadhesive tablets formulated with its β-cyclodextrin complexes and sodium CMC and carbopol as mucoadhesive materials, which was not possible with similar tablets formulated employing nifedipine itself. Good oral controlled release two layered tablet formulations of nifedipine could be developed using its inclusion complexes of βCD.

4. Experimental

4.1. Materials

Nifedipine USP was a gift sample from M/s Cipla Ltd., Mumbai, India. β-Cyclodextrin was procured from M/s Cerestar Inc., Chicago, USA. Carbopol 934 P was a gift sample from M/s SmithKline Beecham Pharmaceuticals, Bangalore, India. Sodium carboxymethylcellulose (Sodium CMC with a viscosity of 1500–3000 cps in a 1% w/v aqueous solution at 25 °C), methanol GR (Merck, India) and dichloromethane (Merck, India) were used. All other reagents used were of analytical grade. All experiments were carried out under subdued light to prevent photodegradation of nifedipine.

4.2. Estimation of nifedipine

An UV spectrophotometric method based on the measurement of absorbance at 238 nm in 0.1 N HCl and phosphate buffer of various pHs 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.

4.3. Phase solubility studies

Solubility studies were performed according to the method reported by Higuchi and Connors [9]. Nifedipine (50 mg) was added to 15 ml of triple distilled water pH 6.8 containing various concentrations of βCD (3–15 mM) in a series of 25 ml stoppered conical flasks. The mixtures were shaken for 72 h at room temperature (28 °C) on a rotary flask shaker. After equilibrating for 72 h, aliquots of 2 ml were withdrawn at 1 h intervals and filtered immediately using 0.45 μm nylon disc filters. The filtered samples were diluted suitably and assayed for nifedipine by measuring absorbance at 238 nm against blanks. Shaking was continued until

three consecutive estimations were the same to ensure equilibrium. The solubility experiments were conducted in triplicate.

4.4. Solid inclusion complexes of N-βCD

4.4.1. Preparation

Solid complexes of N and βCD were prepared with 1 : 1 and 1 : 2 and 1 : 3 ratios by a kneading method. N and βCD 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 °C, pulverized and finally sieved through No. 100 mesh.

4.4.2. Dissolution rate studies

The dissolution rate of nifedipine in the pure form and from N-βCD 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. Nifedipine or its inclusion complex equivalent to 10 mg of N, a speed of 50 rpm and a temperature of 37 ± 1 °C 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.

4.5. Mucoadhesive tablets

4.5.1. Preparation

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

4.5.2. Evaluation of tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration times were determined in a Thermonic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the fluids.

4.5.3. Drug release studies

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 gastrointestinal fluids of increasing pHs, namely pH 1.2 (0–1 h), pH 2.5 (1–2 h), pH 4.5 (2–3.5 h) and pH 7.5 (5–12 h). Fluids of pH 1.2, 2.5 and 4.5 were prepared by suitably adjusting the pH of simulated gastric fluid, USP. Fluids of pH 7.0 and 7.5 were prepared by suitably adjusting the pH of simulated intestinal fluid USP. The dissolution fluids also contained 10% methanol to maintain sink condition in dissolution rate testing. One tablet containing 20 mg of N, a speed of 50 rpm and a temperature of 37 ± 1 °C were employed in each test. Samples withdrawn were assayed at 238 nm for nifedipine.

4.5.4. In vivo mucoadhesion testing

The *in vivo* evaluation of the mucoadhesive property of the formulated tablets was performed by X-ray studies in human subjects. For this purpose tablets containing barium sulphate (instead of nifedipine) were prepared employing sodium CMC and carbopol as matrix materials. These tablets were administered to healthy human subjects along with a glassful of water after overnight fasting. X-ray photographs were taken at different time intervals (0, 2, 4, 6, 8 and 10 h) and the position of the tablets was observed.

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