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Dissolution Characteristics of Nifedipine Complexes with β-Cyclodextrins

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ABSTRACT

Formation of nifedipine complexes with β-cyclodextrin, hydroxypropyl-β-cyclodextrin, and DIMEB in solution was studied by the phase solubility method. Solid complexes of nifedipine were prepared by partial and complete solubilization of nifedipine using the freeze- and spray-drying techniques. The complexation led to an improvement in the dissolution rate of the drug. The relative potency of β-cyclodextrins to enhance the dissolution rate of nifedipine was in order: β-cyclodextrin < hydroxypropyl-β-cyclodextrin < DIMEB, which clearly fits the magnitude of stability constant data of the complexes. The dissolution rates of the free drug, complexes, and physical mixture of drug and cyclodextrins from constant surface area disks were also investigated.

INTRODUCTION

There has been a great interest in cyclodextrins (CD) inclusion compounds, as a means of increasing the solubility and dissolution rate of poorly soluble drugs. Water-insoluble drugs are usually characterized by a low bioavailability, because their absorption is dissolution rate limited and consequently slow. The potential use of cyclodextrins as a novel drug carrier material is in controlling the drug release at the desired level. Cyclodextrins were considered as good candidates for the dissolution rate enhancement of insoluble drugs (1).

The oral bioavailability of nifedipine, a calcium channel antagonist, is known to be low due to its poor solubility and the slow dissolution of nifedipine in water (2). Various pharmaceutical preparations have been developed to improve the oral bioavailability of nifedipine. The crystalline nifedipine can be converted to an amorphous form by spray drying with 2-hydroxypropyl-β-cyclodextrin and PVP, and the bioavailability of nifedipine was increased, as shown by oral administration of the complex to dogs (3). Also, the release rate of nifedipine can be modified by the hybridization of hydroxypropyl-β-cyclodextrin and hydrophilic polymers (4,5).

The present study was undertaken to determine whether the solubility and dissolution rate of nifedipine can be enhanced by the formation of inclusion com-

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plexes with cyclodextrins. Among the various cyclodextrins, β-cyclodextrin derivatives are expected to have inclusion properties which differ from those of the parent β-cyclodextrin. Among β-cyclodextrin derivatives, heptakis (2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB) and 2-hydroxypropyl-β-cyclodextrin have been the most extensively studied (6–8). In addition, the experiments were also carried out to evaluate different methods for preparation of nifedipine solid complexes for potential use in development of a suitable oral formulation.

MATERIALS

Nifedipine (Pliva, Zagreb, Croatia) was used without any further purification. β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (average MS value of 0.9 HP-β-CD), and heptakis (2,6-di-*O*-methyl)-β-cyclodextrin, generally known as DIMEB, were kindly supplied by Wacher-Chemie GmbH (Munich, Germany).

All other materials were of analytical reagent grade.

METHODS

All experiments were carried out under light-protected conditions to prevent the photodecomposition of nifedipine.

Phase Solubility Studies

Solubility studies were performed according to the method reported by Higuchi and Connors (9). Excess amount of the drug was added to aqueous solutions containing cyclodextrins, and shaken at 37°C. After equilibrium was attained, filtered aliquots were analyzed spectrophotometrically at 314 nm. The apparent 1:1 stability constants K_s, were calculated from the slope and intercept of the phase solubility diagrams.

Preparation of Solid Complexes

The preparation of solid nifedipine cyclodextrin complexes was performed by complete or partial solubilization of nifedipine in the aqueous solutions of cyclodextrins using the two techniques: freeze and spray drying.

Method 1: Partial Solubilization of Nifedipine

Solid complexes of nifedipine with cyclodextrins were prepared by lyophilizing a solution of the complex. The procedure consisted in adding an excess of nifedipine to an aqueous cyclodextrin solution at 50°C in order to obtain an equimolar amount of the product. The concentrations of the two solutions were calculated to avoid the extemporaneous precipitation of the components during the mixing period. The suspension was stirred for 5 days, filtered, the filtrate lyophilized (Freeze Dryer Alpha 1-4, M Christ, Gefriertrocknungslangen GmbH, Germany), and the solid formed ground with a pestle and mortar.

Method 2: Complete Solubilization of Nifedipine

Nifedipine and the cyclodextrin (1:1 molar ratio) were separately dissolved in 400 ml of 96% ethanol and 400 ml of purified water, respectively. The solutions were mixed together and sonicated for 15 min to produce a clear solution which was subjected to spray drying using a Büchi 190M Mini Spray Dryer. Under these conditions, spontaneous precipitation on the inclusion did not occur. The drying conditions were as follows: flow rate 1000 ml/hr, inlet temperature 190°C, outlet temperature 80°C, and the air flow rate 700 NI/hr. In order to serve as control, nifedipine was individually treated by spray drying.

The amounts of nifedipine incorporated into the complexes were determined by UV spectrophotometry.

Dissolution Rate Studies

The dissolution behavior of nifedipine and its β-cyclodextrins complexes in water was determined by the flask and paddle method. The samples, adjusted to contain 5 mg nifedipine, were placed into 300 ml of distilled water thermostated at 37°C and stirred at 50 rpm. The samples were withdrawn at various time intervals and analyzed spectrophotometrically.

The release of nifedipine from the compressed tablets (drug content of 5 mg) was measured in the same manner. Avicel PH 102 was used as constituents and talc and Mg-stearate as lubricants. Tablets were prepared by means of a hydraulic press at 300 kg/cm^2 using flat-face punches of 6 mm diameter.

The values of the relative dissolution rate constant, theoretical dissolution time, and dissolution efficiency were calculated by the modified Hicxson–Crowell model according to the following equation (10):

$$Y_i = 3[1 - (1 - x)^{1/3}] = k_{rel} \cdot t \quad (1)$$

where k_{rel} represents relative dissolution rate constant, and x represents the fraction of the dissolved drug. The

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slope in the graphical interpretation Y_i versus time, t, enables the determination of k_{rel}.

Equation (1) enables the calculation of dissolution time, t_{diss}, i.e., the time required for complete dissolution of the drug, as $t_{diss} = 3/k_{rel}$.

The dissolution efficiency, D_{eff}, at chosen time, t_e, can also be determined by:

$$D_{eff} = 1 + 3[(1 - k_{rel}\, t_e/3)^4 - 1]/4 \cdot k_{rel} t_e \qquad (2)$$

RESULTS AND DISCUSSION

The phase solubility diagram for the complex formation between nifedipine and various cyclodextrins is presented in Fig. 1. The solubility of nifedipine ($5 \cdot 10^{-6}$ mol/liter) increased in a linear fashion as a function of β-cyclodextrins concentration, with the slopes less than unity, and the resulting solubility curves can be classified as Higuchi A_L type (9). This indicates the formation of the soluble complexes. The K_s values obtained for β-cyclodextrin, HP-β-cyclodextrin, and DIMEB complexes were 549.2, 637.3, and 2537.1 M^{-1}, respectively.

The solubility studies showed that both hydrophilic β-cyclodextrin derivatives were more effective than the parent β-cyclodextrin in increasing the solubility of nifedipine.

The higher solubility of nifedipine in DIMEB solution than in β-cyclodextrin and HP-β-cyclodextrin indicated a stronger affinity of nifedipine for DIMEB. DIMEB is a good solubilizer for poorly water-soluble drugs, compared to β-cyclodextrin, since its intrinsic aqueous solubility is much higher than that of β-cyclodextrin. Partially methylated β-cyclodextrin exhibits a high solubilizing effect. A factor such as the micellar phenomenon should be considered in the observed increase of K_s value (7).

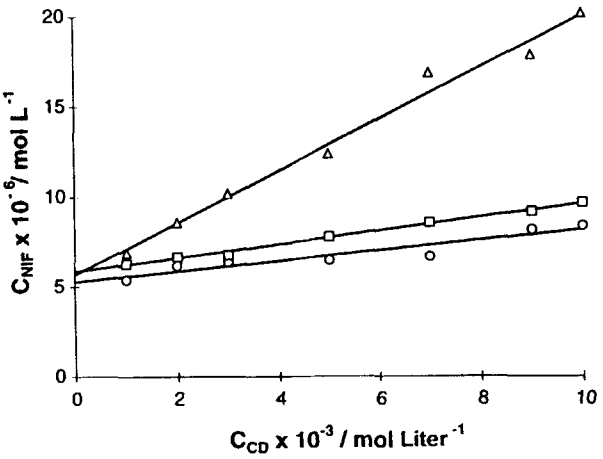

Figure 1. Phase solubility diagram of nifedipine-β-cyclodextrins systems at 37°C: ○, β-CD; □, HP-β-CD; △, DIMEB.

HP-β-cyclodextrin is a better solubilizing agent than the parent β-cyclodextrin, but not as good as DIMEB. The affinity of nifedipine to HP-β-cyclodextrin was comparable to those of the β-cyclodextrins. This could be explained by the steric blockage of the cyclodextrin cavity by the substituents.

Formation of inclusion complexes with cyclodextrins and nifedipine was confirmed by the complete or partial solubilization of the highly insoluble drug in the presence of the aqueous solutions of cyclodextrins.

Freeze drying of the partially solubilized nifedipine in cyclodextrin solutions led to freeze-dried products with very small nifedipine contents. The assayed amounts of nifedipine in freeze-dried β-cyclodextrin, HP-β-cyclodextrin, and DIMEB solid products were 2.1%, 2.3%, and 5.3%, respectively. The assayed amounts of nifedipine in freeze-dried products were well correlated with the stability constants of the complexes. The increased order was β-cyclodextrin < HP-β-cyclodextrin < DIMEB, suggesting that when the stability constant was higher, the entrapment of nifedipine in complex was evidently higher.

The spray drying of the completely solubilized nifedipine in the cyclodextrins solutions (1:1 molar ratio) yielded products of amorphous appearance with the presence of spherical homogeneous small particles. These particles were distinguished by the formation of aggregates, partially broken and hollow, of 5 μm diameter, approximately as observed on image analysis system (Optomax V, Cambridge). It could be assumed that the spray-dried solid products contained a mixture of complex, uncomplexed drug, and cyclodextrins. The structure of cyclodextrin inclusion complexes differs significantly in the solid state and solution. In solution, the guest molecule resides in the cavity and the whole complex is surrounded by a solvate shell of water molecules. In the solid state, the drug can be accommodated not only in the cavity of the cyclodextrins molecule, but between complex molecules as well.

The dissolution profile of nifedipine alone and nifedipine from the cyclodextrin complexes was linearized by plotting $(1 - x)^{1/3}$ versus time, t. Figure 2 presents the nifedipine dissolution from the complexes prepared by the freeze-drying technique. By linear regression analysis, the slopes and intercepts were evaluated. Suitability of the linearization data was shown

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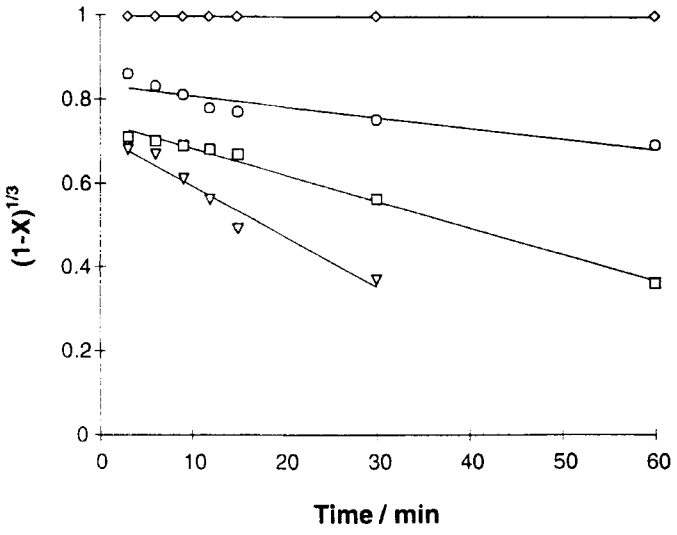

Figure 2. Linearized data of nifedipine dissolution from the complexes prepared by freeze-drying technique in water at 37°C: ◇, commercial nifedipine; ○, β-CD complex; □, HP-β-CD complex; Δ, DIMEB complex.

by correlation coefficients obtained. This mathematical model enables us to calculate relative rate constant, k_{rel}, the dissolution time, t_{diss}, and dissolution efficiency, D_{eff}, at 60 min. Extrapolation to $t = 0$ gives the initial value of the fraction of the dissolved drug, x_0. The values of all these parameters for nifedipine alone and different complexes prepared are shown in Table 1.

It can be seen from the results that the method of complex preparation and the type of cyclodextrin used influenced the dissolution rate of nifedipine. All the nifedipine complexes were dissolved much more rapidly than nifedipine itself. Spray-dried nifedipine exhibited higher dissolution rate than commercial nifedipine. In this case the enhancement of dissolution rate may be attributed to the reduction in crystallinity and the decrease of particle size of the product.

All the inclusion products improve the dissolution rate of nifedipine, but freeze-dried products showed a significant drug dissolution increase. The dissolution rate of nifedipine prepared by method 1, expressed by k_{rel}, t_{diss}, and D_{eff}, was about one order of magnitude higher than the dissolution rate of nifedipine from the complexes prepared by method 2. The better dissolution rate enhancement may be attributed to the increase in the solubility and wettability of nifedipine. This is because of the major interaction between drug and cyclodextrins in the freeze-dried products, containing a small amount of nifedipine. Solid complexes of nifedipine with cyclodextrins were prepared by lyophilizing the solutions of the formed complex. The drug was solubilized by cyclodextrin complexation and only the soluibilized drug fraction was lyophilized. In that way a significantly higher dissolution rate was obtained.

The spray-dried systems showed slower dissolution rates, in comparison with the freeze-dried products. The complexation in solution prior to the spray-drying process was limited due to the stability constants of the complexes which were not high.

The theoretical value for the intercept should be 1, but the values for tested samples were lower. The reason for that is the immediate dissolving of the drug, as seen by data for the initial fraction of dissolved drug, x_0. The relative dissolution potency of β-cyclodextrins was in order of β-CD < HP-β-CD < DIMEB, which clearly fit the magnitude of stability constants of the complexes. β-Cyclodextrin derivatives have higher affinity to nifedipine and could interact more strongly with hydrophobic drug than the parent β-cyclodextrin due to their amphiphilic nature (11).

Table 1

Kinetic Parameters for Dissolution of Nifedipine Alone or from Cyclodextrin Complexes in Water, at 37°C

Parameters	Nifedipine	Nifedipine Spray Dried	Method 1			Method 2		
			β-CD	HP-β-CD	DIMEB	β-CD	HP-β-CD	DIMEB
Slope·10^{-3}	0.11	0.19	2.6	6.3	12.1	0.26	0.63	0.71
r^2	0.985	0.987	0.972	0.992	0.978	0.967	0.971	0.961
k_{rel}·10^{-3} (min^{-1})	0.33	0.57	7.8	18.9	36.1	0.78	1.89	2.13
t_{diss} (hr)	151.5	84.6	6.41	2.63	1.38	64.1	26.3	23.9
D_{eff60} (%)	1.2	1.73	21.1	43.8	65.49	2.21	5.86	6.1
x_0	0.006	0.011	0.42	0.436	0.636	0.15	0.18	0.21

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Since the dissolution rate enhancement may be attributed to the increase in solubility of nifedipine by cyclodextrin complexation, it was of interest to observe if the enhanced dissolution of nifedipine may be obtained with corresponding physical mixture of drug and cyclodextrin. To obtain a constant surface area, and to avoid the increase of particle size as observed for the methods of preparation of the complexes, compressed disks with a drug content of 5 mg were prepared. Microcrystalline cellulose and Avicel PH 102 were used as a tablet diluent and disintegrant. The process formed self-binding tablets which disintegrated rapidly when placed in solution, thus overcoming the problem of significantly decreasing rate of drug release with time.

The dissolution rate profiles of nifedipine—from the tablets prepared with nifedipine alone, physical mixture, and inclusion complexes using HP-β-cyclodextrin—are shown in Fig. 3. It is evident that both the complex and physical mixture in tablets demonstrate a faster dissolution rate than nifedipine alone. The increase in the dissolution of nifedipine physically mixed with cyclodextrin was possibly the result of a local solubilization action operating in the microenvironment or the hydrodynamic layer surrounding the drug particles. Our results suggested that the major contributing factor in the enhancement dissolution of nifedipine from the physical mixture was the ability of these two compound to form a soluble complex during the dissolution process. The extent to which dissolution rate enhancement in the drug–cyclodextrin system is due to soluble complex formation rather than inclusion complex formation in the solid state requires further study.

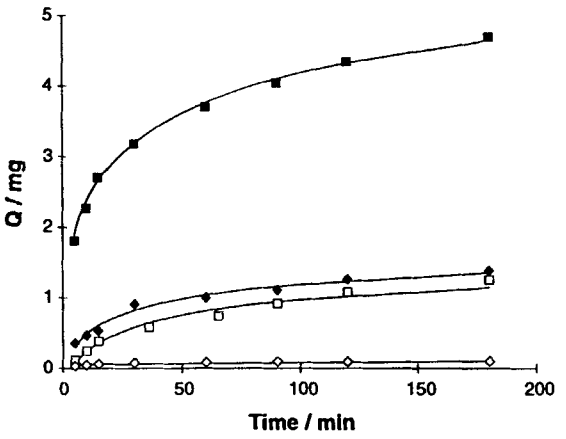

Figure 3. Release profile of nifedipine from tabletes in water at 37°C: ◇, nifedipine; □, nifedipine and HP-β-CD physical mixture; ◆, spray-dried HP-β-CD complex; ■, freeze-dried HP-β-CD complex.

The drug-to-cyclodextrin ratio in the tablet prepared with spray-dried products was the same as in the tablet containing the physical mixture. The drug-to-cyclodextrin ratio in tablet prepared with freeze-dried product was different because of the low nifedipine entrapment in cyclodextrin cavity (2.3% in the case of HP-β-cyclodextrin). The better dissolution of nifedipine in this case could be explained by the major interaction between drug and cyclodextrin in the freeze-dried product containing only soluble nifedipine complex. Drug in the freeze-dried product was probably totally complexed, while the spray-dried complex could contain a mixture of complexed and uncomplexed drug.

The kinetics parameters for the dissolution of nifedipine from the tablets, as calculated by the modified Hicxson–Crowell model, are presented in Table 2. The differences in the dissolution rates of nifedipine between the different methods of complexation were already explained. The dissolution rates of nifedipine from the tablets, expressed by k_{rel}, t_{diss}, and D_{eff}, at 60 and 180 min, were above the values determined for uncompressed solid complexes. This could be explained by the effect of the tablet disintegration on the release rate of the drug.

Therefore, the results obtained from the solubility studies, and the dissolution data for the complexes, indicate that the inclusion complexes may have a considerable potential considering the increased dissolution, and its effects on the drug absorption should be studied further.

CONCLUSIONS

The solubility studies indicated that both hydrophilic β-cyclodextrin derivatives were more effective than the parent β-cyclodextrin in increasing the solubility and dissolution rate of nifedipine. Formation of nifedipine inclusion complexes with β-cyclodextrins was confirmed by complete or partial solubilization using the freeze- and spray-drying techniques. The method of complex preparation and the type of cyclodextrin used influenced the dissolution rate. Drug in freeze-dried products was totally complexed, while spray-dried complexes might be a mixture of complexed and uncomplexed drug. Therefore, the formation of nifedipine inclusion complexes by the partial solubilization, followed by freeze drying, was the chosen preparation method. Improve-

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Table 2

Kinetic Parameters for Dissolution of Nifedipine from Tablets Prepared with Nifedipine, Physical Mixture of Nifedipine and Cyclodextrin, and Nifedipine–Cyclodextrin Complexes in Water, at 37°C

Parameters	Nifedipine	Nifedipine HP-β-CD Phys. Mix.	Method 1			Method 2		
			β-CD	HP-β-CD	DIMEB	β-CD	HP-β-CD	DIMEB
Slope·10^{-3}	0.1	0.5	1.9	2.6	4.2	0.4	0.6	0.69
r^2	0.972	0.986	0.981	0.980	0.987	0.972	0.986	0.995
$k_{rel}\cdot 10^{-3}$ (min^{-1})	0.3	1.5	5.7	7.8	12.6	1.2	1.8	2.07
t_{diss} (hr)	166.6	33.3	8.87	6.4	3.97	41.7	27.7	24.5
D_{eff60} (%)	1.1	4.41	15.8	21.1	31.8	1.96	5.27	5.84
D_{eff180} (%)	2.67	12.7	40.5	50.8	67.04	10.3	15.1	18.7
x_0	0.009	0.06	0.24	0.45	0.47	0.08	0.073	0.098

ment of dissolution rate from complexes, and constant surface area disks, was evaluated; the increased dissolution rate order was β-cyclodextrin < HP-β-cyclodextrin < DIMEB, which fit the magnitude of stability constants of the complexes.

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