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COMMUNICATION

Nimesulide and β-Cyclodextrin Inclusion Complexes: Physicochemical Characterization and Dissolution Rate Studies

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ABSTRACT

Complex formation of nimesulide (N) and β-cyclodextrin (βCD) in aqueous solution and in solid state and the possibility of improving the solubility and dissolution rate of nimesulide via complexation with βCD were investigated. Phase solubility studies indicated the formation of a 1:1 complex in solution. The value of the apparent stability constant Kc *was 158.98* M^{-1}*. Solid inclusion complexes of N and βCD were prepared by kneading and coevaporation methods. Differential scanning calorimetry (DSC) studies indicated the formation of solid inclusion complexes of N-βCD at a 1:2 molar ratio in both the methods. Solid complexes of N-βD (1:1 and 1:2 M) exhibited higher rates of dissolution and dissolution efficiency values than the corresponding physical mixtures and pure drug. Higher dissolution rates were observed with kneaded complexes than with those prepared by coevaporation. Increases of 25.6- and 38.7-fold in the dissolution rate were observed, respectively, with N-βCD 1:1 and 1:2 kneaded complexes.*

INTRODUCTION

Nimesulide (N) (chemically, 4-nitro-2-phenoxy methanesulfanilamide) is a relatively new nonsteroidal anti-inflammatory analgesic drug. It is practically insoluble in water (≈0.01 mg/ml), and as such, its oral absorption is limited by the dissolution rate (1). The very poor aqueous solubility of the drug may lead to variable bioavailability. The dissolution rate of nimesulide was earlier improved by a solid dispersion technique (2). The objective of the

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present study was to investigate the possibility of improving the solubility and dissolution rate of nimesulide via complexation with β-cyclodextrin (βCD). In addition, the physicochemical properties of N-βCD systems were also investigated, and the results are reported here.

EXPERIMENTAL

Materials

Nimesulide (gift sample from M/S Aristo Pharmaceuticals, Ltd., Mumbai, India), βCD (Sigma, St. Louis, MO), and methanol (Qualigens) were used.

Methods

Phase Solubility Studies

Solubility studies were performed according to the method reported by Higuchi and Connors (3).

Preparation of Solid Complexes

The solid complexes of nimesulide and βCD were prepared in 1:1 and 1:2 molar ratios by two methods, kneading and coevaporation.

Kneading Method

Nimesulide and βCD were triturated in a mortar with a small volume of water-methanol (1:1) solution. The thick slurry was kneaded for 45 min and then dried at 45°C until dry. The dried mass was pulverized and sieved through 100 mesh.

Coevaporation Method

The aqueous solution of βCD was added to an alcoholic solution of nimesulide. The resulting mixture was stirred for 1 hr and evaporated at a temperature of 45°C until dry. The dried mass was pulverized and sieved through 100 mesh.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was performed with a DSC model 220C (Sieko, Tokyo, Japan). The samples were sealed in aluminum pans, and the DSC thermograms were recorded at a heating rate of 10°C/min from 30°C to 300°C.

Dissolution Rate Studies

In vitro dissolution studies of pure drug, physical mixtures, and the inclusion complexes (equivalent to 50 mg of nimesulide) were carried out in 900 ml of purified water using a USP 21 three-station dissolution rate test apparatus (model DR-3, M/S Campbell Electronics) with a paddle stirrer (50 rpm). Filtered samples withdrawn at different time intervals were assayed for nimesulide by measuring absorbance at 230 nm.

RESULTS AND DISCUSSION

The phase solubility diagram for the complex formation between nimesulide and βCD is shown in Fig. 1. The aqueous solubility of nimesulide increased linearly ($r = 0.9999$) as a function of βCD concentration. The phase solubility diagram (Fig. 1) can be classified as type A_L according to Higuchi and Connors (3). Because the straight line had a slope less than unity, it was assumed that the increase in solubility was due to the formation of a 1:1 complex. The apparent 1:1 stability constant *Kc* of N-βCD 1:1 complex was found to be 158.98 M^{-1}. For A_L type, solid complexes can be prepared by methods such as kneading (4), freeze-drying (5), spray-drying (6), and coevaporation (7). In the present study, kneading and coevaporation methods were used to prepare the solid inclusion complexes of nimesulide and βCD.

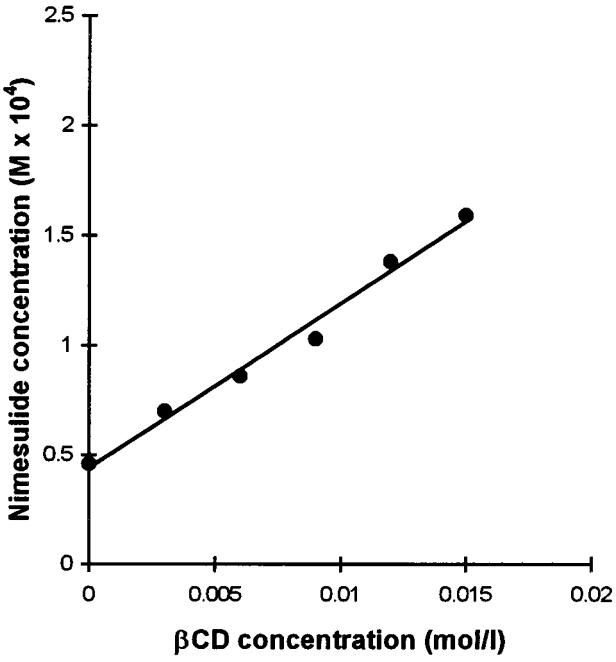

Figure 1. Phase solubility diagram of N-βCD at 28°C.

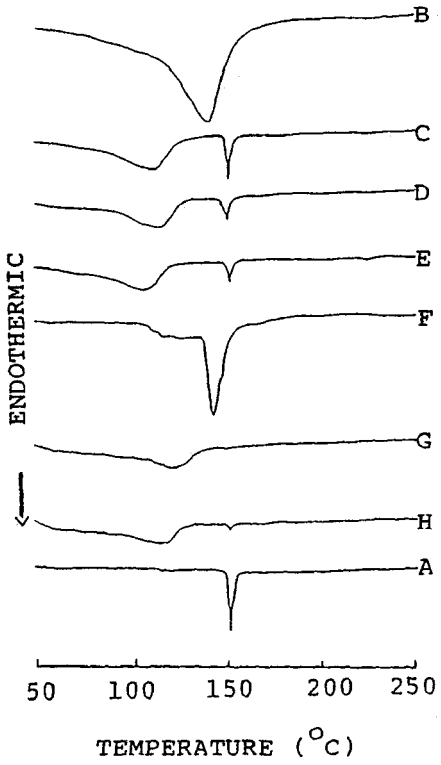

Figure 2. DSC thermograms of (A) nimesulide; (B) βCD; (C) N-βCD (1:1) PM; (D) N-βCD (1:1) KC; (E) N-βCD (1:1) CC; (F) N-βCD (1:2) PM; (G) N-βCD (1:2) KC; (H) N-βCD (1:2) CC.

The thermal behavior of N-βCD inclusion complexes was studied using DSC to confirm the formation of the solid complex. DSC thermograms of nimesulide and N-βCD solid complexes are shown in Fig. 2. The DSC thermogram of nimesulide exhibited an endothermic peak at 150.7°C, corresponding to its melting point. βCD showed a broad endothermic peak at 139.1°C, which may be attributed to a dehydration process. The thermograms of 1:1 N-βCD systems showed the persistence of the endothermic peak of nimesulide at 150°C, indicating that a true inclusion complex had not formed at 1:1 molar ratio in the solid state. The DSC thermograms of N-βCD (1:2) systems prepared by both kneading and coevaporation methods did not show the melting endotherm of nimesulide. The disappearance of the endothermic peak with these systems indicated the formation of a solid inclusion complex of N-βCD at a 1:2 molar ratio.

The dissolution characteristics of nimesulide and N-βCD systems are given in Table 1. The dissolution of nimesulide during the period of 0–10 min followed first-order kinetics (r = 0.90–0.99). Solid complexes of N-βCD (1:1 and 1:2 M) prepared by both the methods exhibited higher rates of dissolution and dissolution efficiency (8) values than the corresponding physical mixtures and pure drug. Solid complexes prepared by the kneading method exhibited higher dissolution rates and efficiency values than those prepared by the coevapora-

Table 1

Dissolution Characteristics of Nimesulide (N) and Its Inclusion Complexes with β-Cyclodextrin (βCD)

Product	Mean Percentage Nimesulide Dissolved					DE_{15} (%)	DE_{60} (%)	$K_1 \times 10^3$ (min^{-1})
	5 min	10 min	15 min	30 min	60 min			
Nimesulide	0.47	0.64	0.89	1.33	2.31	0.5	1.3	0.64
	(2.63)	(3.12)	(2.24)	(3.75)	(1.29)			
N-βCD (1:1 M) PM	1.23	4.07	6.35	6.69	9.65	2.8	6.4	4.16
	(3.69)	(4.17)	(2.20)	(1.79)	(1.45)			
N-βCD (1:1 M) CC	7.57	10.42	11.21	13.37	15.23	7.9	12.2	11.00
	(6.20)	(1.82)	(1.87)	(1.04)	(1.77)			
N-βCD (1:1 M) KC	14.30	15.12	15.20	15.28	15.82	12.3	14.6	16.39
	(1.46)	(0.46)	(0.65)	(0.19)	(0.56)			
N-βCD (1:2 M) PM	4.82	9.22	11.48	13.92	14.93	6.6	12.1	9.69
	(4.77)	(1.08)	(1.39)	(0.59)	(1.07)			
N-βCD (1:2 M) CC	16.35	17.41	19.82	21.22	23.22	14.5	20.0	17.98
	(2.38)	(2.35)	(2.97)	(1.17)	(1.07)			
N-βCD (1:2 M) KC	20.11	21.49	22.32	23.42	25.48	17.5	22.4	24.78
	(1.04)	(2.04)	(1.38)	(0.85)	(1.56)			

Figures in parentheses are coefficient of variation values.
PM = physical mixture; CC = coevaporated complex; KC = kneaded complex.

tion method. Increases of 25.6- and 38.7-fold in the dissolution rate were observed, respectively, with N-βCD 1:1 and 1:2 M complexes prepared by the kneading method when compared to pure drug, nimesulide. The higher dissolution rates observed with kneaded complexes may be due to the better interaction of drug and βCD during the kneading process

Thus, the results of the study indicated the formation of nimesulide and βCD inclusion complexes at a 1:1 ratio in solution with a stability constant of 158.98 M^{-1}, whereas solid inclusion complexes of N-βCD were formed at a 1:2 M ratio. Solid complexes of N-βCD (1:1 and 1:2 M) prepared by kneading and coevaporation methods exhibited higher rates of dissolution and dissolution efficiency values than the corresponding physical mixtures and pure drug.

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