Journal of Inclusion Phenomena and Macrocyclic Chemistry **44:** 123–126, 2002.

Preparation and Investigation of Inclusion Complexes Containing Nifluminic Acid and Cyclodextrins

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(Received: 7 May 2002; in final form: 1 October 2002)

Key words: complexation, dissolution, hydroxypropyl-β-cyclodextrin, nifluminic acid, thermo-analytical investigation

Abstract

Nifluminic acid (N) is a frequently used anti-inflammatory drug, but its poor aqueous solubility is a disadvantageous property. Inclusion complexation with cyclodextrin derivatives (CDs) affords a possibility to increase its solubility properties. For this purpose, different CDs were used, primarily hydroxypropyl-β-CD (HP-β-CD), to prepare products by powder mixing or kneading in four molecular ratios. The dissolution and *in vitro* membrane diffusion of the products were investigated. The wetting angles of pure N and HP-β-CD and of the products, and the *n*-octanol/water partition coefficients were determined. The interaction, leading to complex formation between the components of the products was examined by thermoanalytical methods.

Introduction

Nifluminic acid (N) is an important anti-inflammatory drug and also has a weak analgetic effect. It is primarily used in different forms of rheumatism, e.g., rheumatoid arthritis and arthrosis, and to decrease other inflammatory phenomena. The single dose is 250 mg N for adults, generally in capsules (e.g., *Donalgin® capsule*, G. Richter Pharmaceutical Factory, Budapest, Hungary). It is contraindicated in pregnancy and in individuals supersensitive to N. It has some side-effects, such as nausea or vomiting. In cases of stomach ulcer, it may be used only under medical control [1, 2].

From the standpoint of pharmaceutical technology, its low aqueous solubility is the most significant feature limiting its wider application. Therefore, all pharmaceutical technological possibilities whereby its solubility properties may be improved are of importance. Complexation with cyclodextrins (CDs) is one such possibility.

Consequently, the present aim was an investigation of the solubility properties, with a view to improving the bioavailability of N, and therefore decreasing its dose and side-effects.

Materials and methods

Materials

Nifluminic acid (N): 2-[[3-(trifluoromethyl)phenyl]amino]-3-pyridinecarboxylic acid (G. Richter Pharmaceutical Factory, Budapest, Hungary) (Figure 1); CDs (Cyclolab R&D Laboratory Ltd., Budapest, Hungary); other chemicals (Reanal Co., Budapest, Hungary).

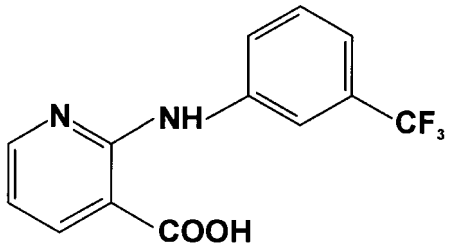

Figure 1. Chemical structure of nifluminic acid.

Methods

USP rotating-basket dissolution apparatus, type DT [3], and kneading mixer, type LK5 (Erweka Apparatebau GmbH, Heusenstamm, Germany); Unicam UV2/Vis spectrometer (Unicam Ltd., England); Sartorius membrane apparatus (Sartorius-Membranfilter GmbH, Germany); Derivatograph-C computing thermal analysis system (MOM, Budapest, Hungary); Mettler Toledo DSC821^e thermal analysis system with STAR^e thermal analysis program V6.0 (Mettler Inc., Schwerzenbach, Switzerland); Leica Q500 MC image processing and analysis system (Leica Cambridge Ltd., Cambridge, UK).

Preparation of products

The products were prepared in four different mole ratios (N:CD mole ratio = 2:1, 1:1, 1:2 and 1:3). *Physical mixtures* (PM): The plain drug and CD were mixed in a mortar and sieved through a 100 μm sieve. *Kneaded products* (KP): PMs of the drug and HP-β-CD were mixed (Erweka LK5) with the same quantity of a solvent mixture of ethanol + water (1:1). They were kneaded until the bulk of the solvent mixture had evaporated. After this, they were dried at room

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temperature and then at 105 °C, and were pulverized and sieved through a 100 μm sieve. Products were stored under normal conditions at room temperature in well-closed glass containers.

Dissolution of nifluminic acid

In the USP dissolution apparatus, the modified paddle method was used to examine 20 mg samples of pure N or products containing 20 mg of drug in 100.0 g of simulated gastric medium (SGM) or simulated intestinal medium (SIM). The basket was rotated at 100 rpm. Sampling was performed after 5, 10, 15, 30, 60, 90 and 120 min. The volume of the samples was 5.0 mL. After filtration and dilution, the N contents of the samples were determined spectrophotometrically ($\lambda_{(SGM)}$ = 256 nm, $\lambda_{(SIM)}$ and $\lambda_{(SPL)}$ = 288 nm).

Membrane diffusion

Stricker's Sartorius apparatus was used [4, 5]. Measurements were performed on 100.0 mL of SGM (pH = 1.1 ± 0.1) or SIM (pH = 7.0 ± 0.1) and simulated plasma (SPL) (pH = 7.5 ± 0.1). 20 mg samples of drug or products containing 20 mg of N were placed in the donor phase in all cases. The artificial membrane type: cellulose acetate (pore size 0.45 μm, diffusion surface 4.6 cm^2). The temperature was 37.5 ± 1.5 °C. 5.0 mL samples were taken five times (after 30, 60, 90, 120 and 150 min) and their N contents were determined spectrophotometrically after filtration and dilution.

Determination of the n-octanol/water partition coefficient

The partition coefficients are important in diffusion processes of dermal dosage forms. Two solvents were prepared: distilled water-saturated *n*-octanol and *n*-octanol-saturated distilled water. Further, N or the products containing N were added to these earlier systems during continuous stirring until the excess drug appeared in suspended form. After filtration, the saturated solutions were diluted with *n*-octanol-saturated distilled water or distilled water-saturated *n*-octanol, and the drug content was determined spectrophotometrically.

Wettability studies

0.25 g powder was compressed under a pressure of 3 tons by a Perkin–Elmer hydraulic press. The diameter and the height of the pressings were 7 mm and 3 mm, respectively. The wetting angles of the pressings were determined after dropping 2 μl dilute methylene blue solution on to the surface of the pressings. The study was carried out in triplicate, using a microscope and Leica Q500 MC analyser.

Thermoanalytical methods

The complex formation between the components of the products was examined by thermoanalytical methods [6]. Approximately 2–5 mg of pure drug or product (in the case of DSC studies) or 50 mg of powder (in the case of the Derivatograph) was examined in the temperature range between 25 °C and 300 °C. The heating rate was 5 °C/min and the flow rate of argon was 10 L/h during the DSC measurements. TG, DTG, DTA and DSC curves were investigated.

Results and discussion

Preliminary experiments

The effects of the different CD derivatives on the solubility properties of N were determined. For this purpose, a mixture of 30 mg N and 50 mg CD derivative (α-CD, β-CD, γ-CD, dimethyl-β-CD, random methylated-β-CD, hydroxypropyl-β-CD or Captisol®) was mixed with water to 20.0 g and stirred for 20 min with a magnetic mixer. The suspension systems were filtered through filter paper and (after suitable dilution) their UV spectra were recorded. A system without CD was used as control. HP-β-CD exerted the highest solubility-increasing effect on N. This CD derivative was therefore chosen for further examinations.

Dissolution studies

The dissolution behaviour of the KPs was better than that of the PMs in both SGM and SIM. In SGM, the dissolution increased in proportion to the CD content in all of the KPs (Figure 2). The maximum solubility increase (nearly 5-fold) was observed for the 1:1, 1:2 and 1:3 KPs in SIM. The 1:3 KP gave the best dissolution result in SGM; the solubility increase was 4.4-fold compared to the pure drug. However, the dissolution increases for the KPs were better in SIM (3.28-fold and 3.53-fold) than in SGM.

For the case of PMs, the dissolution was better in SGM than in SIM, and increased in direct proportion to the CD content.

Membrane diffusion examinations

CD inclusion complexes with relatively high stability constants often have decreased diffusion properties, as in the case of the N complexes. The diffusion of all these products was poorer than that of the active ingredient itself (in SIM, it was about 3 mg/150 min).

n-Octanol/water partition coefficient

The *n*-octanol/water partition coefficients revealed that the water solubility increase was significantly better for the PMs than for the KPs. The concentration of N decreased in *n*-octanol and increased in water (Table 1).

For the four KPs, and especially at the ratio 1:3, the increase in dissolution in SGM was significant, at 4.4-fold. At 1:2 it was 1.74-fold, at 1:1 it was 1.54-fold, and at 2:1 was only 1.20-fold. The results reveal that, on increase of the CD content in the products, the water solubility of N is increased, saturation being reached in all four cases after about 30 min.

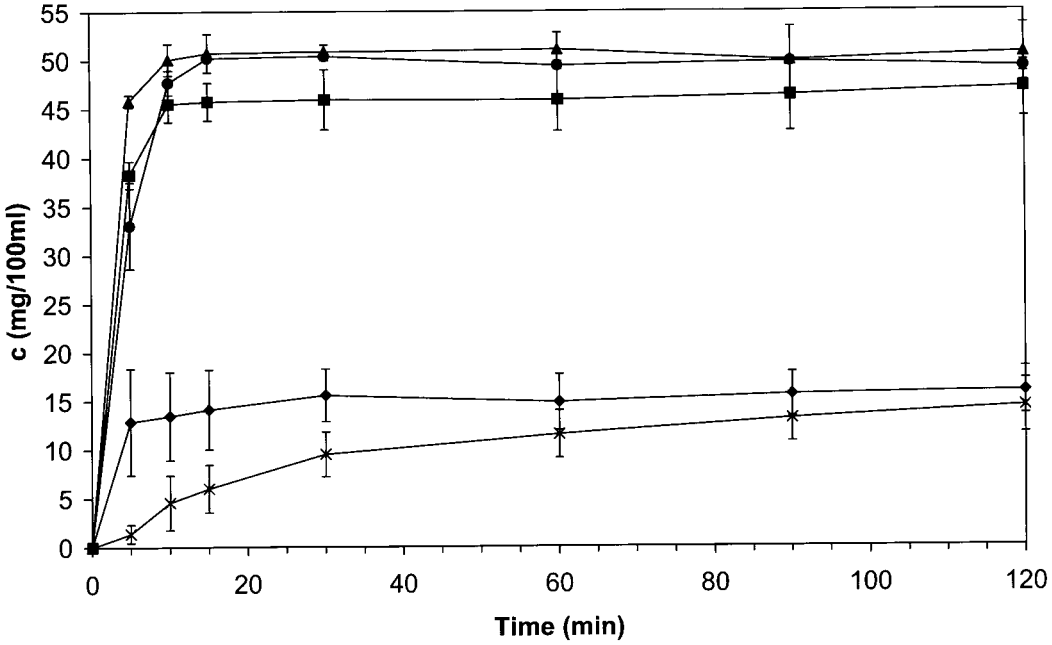

Figure 2. Dissolution of N from KPs (SIM). (♦), KP-2:1; (■), KP 1:1; (▲), KP 1:2; (●), KP 1:3; (∗), N.

Table 1. *n*-octanol/water partition coefficients

Materials	PM			KP		
	c_o (μg/mL)	c_w (μg/mL)	c_o/c_w	c_o (μg/mL)	c_w (μg/mL)	c_o/c_w
N	48439.07	26.75	1810.80	48439.07	26.75	1810.80
2:1	8459.21	177.27	47.72	9466.26	132.51	71.44
1:1	10876.13	311.36	34.93	9466.26	103.84	91.16
1:2	9365.55	162.76	57.54	8962.73	91.43	98.03
1:3	6646.52	243.01	27.35	10775.42	184.61	58.37

For the case of PMs, the increase in the solubility of N was poorer than for the KPs in SGM, and saturation was attained only after 90 min.

In SIM, the dissolution of N depends on the CD content: at ratios of 2:1, 1:1, 1:2 and 1:3, the increase was 1.11-fold, 3.28-fold, 3.53-fold and 3.43-fold, respectively. For the 2:1 product, the quantity of N liberated during 120 min was 15 mg/100 mL, whereas in all other cases it was 47–51 mg/100 mL. It is of interest that there are not such large differences as in the case of dissolution in SGM.

For the PMs, the increase in the dissolution of N was less as compared with the KPs in SIM: at most 1.12-fold.

The presence of CD decreased the solubility of N in *n*-octanol and increased the aqueous concentration of N. The partition coefficients of all products were significantly smaller than that of the active ingredient.

Wettability studies

The wetting angles of N, HP-β-CD and their products were determined. The wetting angle of N was 93°, i.e., it is a very hydrophobic drug (its aqueous solubility is also very small). The wetting angle of HP-β-CD was 52.0° (Table 2).

Table 2. Wetting angle of N, HP-β-CD and their products

Material	PM		KP	
	Wetting angle (°)	SD	Wetting angle (°)	SD
N	93.0	1.0	93.0	1.0
HP-β-CD	52.0	5.2	52.0	5.2
2:1	49.7	1.5	55.7	13.1
1:1	42.7	3.8	55.3	8.5
1:2	45.3	6.5	55.7	6.7
1:3	47.0	3.6	52.0	2.6

For the PMs and KPs, the wetting angles were smaller: 42–50° and 52–56°, respectively.

Thermoanalytical studies

The DSC curve indicates that the melting point of N is at 203.81 °C. An endotherm peak at about 250 °C relates to its decomposition.

The PMs undergo initial water loss as the temperature is raised. The melting point decreases with increase of the CD concentration (189–182 °C).

For KPs, the melting point likewise decreases on increase of the CD content (190–180 °C). In both cases, the 1:3 products give the best result. Partial complexation is presumable.

Conclusions

- HP-β-CD showed the highest solubility-increasing effect on the solubility of nufliminic acid.
- Products of N:HP-β-CD of molecule ratio 2:1, 1:1, 1:2 and 1:3 were prepared by physical mixing and kneading methods.
- The dissolution behaviour of the KPs were higher compared to PMs in both media. In SGM, the dissolution increased proportionally with the increase the CD quantity in all of the KPs. The maximal solubility increase (about 5-fold) was determined with 1:1, 1:2 and 1:3 KPs in SIM.
- The diffusion of all products were smaller than the active ingredient itself (in SIM, it was about 3 mg/150 min).
- The presence of CD decreased the *n*-octanol solubility and increased the water concentration of N. The partition coefficients of all products were significantly smaller than the active ingredient.
- The wetting angle of N was 93°. The wettability of PMs were better than the KPs. The wetting angle of PMs ranged between 42–50° and 52–56° for the KPs, respectively.
- Depending on the thermoanalytical investigations, partial complex formation of KPs can be seen with the CD.

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