Drug Development and Industrial Pharmacy, 25(4), 543–545 (1999)

COMMUNICATION

Inclusion Complexation of Nimesulide with β-Cyclodextrins

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ABSTRACT

Nimesulide (NM), a nonsteroidal anti-inflammatory drug (NSAID) has poor aqueous solubility. The present study describes the complexation of NM with β-cyclodextrin (β-CD) and its derivative hydroxypropyl β-cyclodextrin (HPβ-CD). The complexation was studied by phase solubility method, Fourier transformed infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffractometry (XRD). The complexes were prepared by a freeze-drying technique. The in vitro dissolution rate of drug–HPβ-CD complex was faster compared to the drug–β-CD complex and drug alone.

INTRODUCTION

Nimesulide, an anti-inflammatory, analgesic, and antipyretic, is used in the treatment of various diseases, such as osteoarthritis, oncological diseases, and postoperative trauma (1). The present work deals with the preparation and characterization of inclusion complexes (ICs) of NM with β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HPβ-CD).

MATERIALS

The NM was supplied by Wave Pharma Limited (Hyderabad, India). The β-CD and HPβ-CD were generously donated by Nihon Shokuhinkako Company Limited, Tokyo, Japan, and AMAIZO, American Maize Products Company, Hammond, Indiana, respectively.

METHODS

Phase Solubility Studies

Solubility measurements were conducted according to the method of Higuchi and Connors (2). The filtrate was analyzed using an ultraviolet (UV) spectrophotometer (Cecil CE 2021 2000 series, Cecil Instruments, Cambridge, England) at 394 nm for NM content.

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Preparation of Inclusion Complexes

The freeze-drying technique (3) (Labconco, Kansas City, MO; Freeze Dry System, Freezone 4.5) was used to prepare ICs of NM and CDs in a 1:1 molar ratio. Physical mixtures (PMs) of NM and respective CDs were also prepared in the same molar ratio by mixing the powders in geometric proportions.

Characterization of Inclusion Complexes

Fourier Transform Infrared Spectral Studies

The Fourier transform infrared (FTIR) spectra of NM, PMs, and ICs were recorded in a KBr pellet using a JASCO FT/IR-5300 (Tokyo, Japan).

Differential Scanning Calorimetry Studies

The NM, PMs, and ICs were subjected to differential scanning calorimetry (DSC) studies using a Perkin Elmer DSC 7 model (Norwalk, CT). Alumina was used as a reference material, and samples were scanned at the rate 10°C/min.

Powder X-ray Diffraction Studies

The X-ray diffraction (XRD) patterns were recorded using a Philips X-ray generator (PW 1729) (Eindhoven, The Netherlands) and automatic X-ray diffractometer model PW 1710.

In Vitro Dissolution Studies

In vitro dissolution studies were conducted for NM, PMs, and ICs using the USP XXIII paddle method. The rotation speed of the paddle was 100 ± 2 rpm, and the water bath temperature was maintained at 37°C ± 0.2°C. Distilled water (450 ml) containing 0.02% w/v Tween 80 was used as a dissolution medium (4). The filtered dissolution medium (250 ml) was removed and replaced with fresh medium after every 30 min. Aliquots of these filtrates were analyzed for NM content at 394 nm using an ultraviolet-visible (UV-Vis) spectrophotometer.

RESULTS AND DISCUSSION

The solubility of NM in water was found to be 0.01 mg/ml. Phase solubility studies of NM confirmed the solubility-enhancement capabilities of the CDs. The solubility curves for β-CD and HPβ-CD systems were classified as the A_L type (2), indicating formation of a 1:1 stoichiometry of these complexes. The stability constants for β-CD and HPβ-CD were found to be 93.78 M^{-1} and 123.15 M^{-1}, respectively. The phase solubility studies indicated that the aqueous solubility of NM was greatly enhanced in the presence of CDs in the order HPβ-CD > β-CD.

The FTIR spectra of the complexes of NM with β-CD and HPβ-CD show the appearance of an intense broad peak at 3364.16 cm^{-1} and 3366.09 cm^{-1}, respectively. These broad peaks indicate possible hydrogen bonding between NM and the CDs.

The DSC thermograms of NM showed a sharp endothermic peak at 159.03°C for NM. This endothermic peak was also observed at 158.36°C and 157.61°C in the PMs with β-CD and HPβ-CD, respectively. The slight shift is probably due to a weak interaction between the host and guest molecules. The ICs showed an absence of NM endotherm, indicating the formation of strong CD complexes.

The XRD patterns of PMs were found to be a combination of NM and respective CDs. However, the XRD patterns of the ICs with β-CD were found to be diffused and different from that of NM, confirming formation of a new solid phase. The XRD pattern of HPβ-CD complex is totally diffused, indicating the complex has an amorphous nature. The peaks of the NM molecule at 5.6°, 12.3°, 19.8°, 22°, 23.6°, and 24.6° present in the PM containing HPβ-CD are not seen in the HPβ-CD complex. This indicates the strong IC formation of HPβ-CD with NM.

In vitro dissolution parameters $T_{25\%}$, $T_{50\%}$, $T_{75\%}$, and $T_{90\%}$ of NM, PMs, and ICs are shown Table 1. The PMs and NM alone show lower dissolution rates compared to ICs. The PMs showed a slight improvement in dissolution rate over that of the pure drug. The dissolution rate of NM from HPβ-CD complex appears to be faster compared with the rate constant from β-CD complexes. This may be due to the increased solubility and wettability, along with the decrease in crystallinity caused by complex formation. The dissolution of NM, PMs, and ICs obeyed the Hixson Crowell cube root dissolution rate equation for powders (5), confirming that the powders consist of uniform size particles.

CONCLUSIONS

The complexation with β-CD and HPβ-CD improved the solubility of NM. The FTIR, DSC, and XRD studies of the complexes showed significant evidence of complexation. The rate of dissolution of NM from HPβ-CD freeze-dried complex was found to be significantly higher

Table 1

Dissolution Parameters of Nimesulide and Its Complexes

Powders	$T_{25\%}$ (min)	$T_{50\%}$ (min)	$T_{75\%}$ (min)	$T_{90\%}$ (min)	*K* (*r*)
Pure nimesulide	30.57	91.22	177.11	297.21	0.0075 (0.9966)
Physical mixture of nimesulide: β-CD	32.79	91.45	187.84	283.60	0.0087 (0.9992)
Physical mixture of nimesulide: HPβ-CD	33.00	104.02	179.69	273.52	0.0089 (0.999)
Complex nimesulide: β-CD	18.00	44.50	102.00	165.00	0.0174 (0.9962)
Complex nimesulide: HPβ-CD	13.50	27.00	60.00	108.56	0.02662 (0.997)

K, Hixson Crowell cube root dissolution rate constant ($\%^{1/3}$/min); *r*, coefficient of regression.

than for β-CD freeze-dried complex. These complexes also follow the Hixson Crowell cube root equation, thus indicating the rate of dissolution is based on the cube root of the weight of the particles.

ACKNOWLEDGMENT

The authors are thankful to Wave Pharmaceuticals, Nihon Shouhinkako Company Limited, and AMAIZO American Maize Products Company for the gift samples of NM, β-CD, and HPβ-CD, respectively.

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