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European Journal of Pharmaceutics and Biopharmaceutics 68 (2008) 701–714
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Solubilization of indomethacin using hydrotropes for aqueous injection

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Received 2 June 2006; accepted in revised form 15 June 2007
Available online 26 June 2007

Abstract

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, antipyretic and anti-inflammatory activities. It is practically insoluble in water. The effect of various hydrotropes such as urea, nicotinamide, resorcinol, sodium benzoate and sodium *p*-hydroxy benzoate on the solubility of indomethacin was investigated. The solubility enhancement of indomethacin by the hydrotropes was observed in decreasing order as sodium *p*-hydroxy benzoate > sodium benzoate > nicotinamide > resorcinol > urea. In order to elucidate the probable mechanism of solubilization, various solution properties of hydrotropes such as viscosity, specific gravity, surface tension, refractive index and specific conductance of hydrotropic solutions were studied at 25 ± 2 °C. Each solubilized product was characterized by ultraviolet, infrared, powder X-ray diffraction and differential scanning calorimetry techniques. The hydrotropic solubilization of indomethacin at lower hydrotrope concentration may be attributed to weak ionic interactions while that at higher hydrotrope concentration may be due to molecular aggregation. Aqueous injectable formulations using sodium *p*-hydroxy benzoate, sodium benzoate and nicotinamide as hydrotropes were developed and studied for physical and chemical stability.

Keywords: Hydrotropic solubilization; Indomethacin; Aqueous injection; Cyclo-oxygenase (COX)

1. Introduction

Indomethacin is an acidic non-steroidal anti-inflammatory agent. It is a non-selective inhibitor of cyclo-oxygenase (COX) 1 and 2 enzyme that participates in prostaglandin synthesis from arachidonic acid. Indomethacin for injection has great implications for patient care. It is labeled for closing hemodynamically significant patent ductus arteriosus (PDA) in premature infants weighing 500–750 g when medical management is ineffective after 48 h and there is clinical evidence of respiratory distress, continuous heart murmur, hyperactive precordium, cardiomegaly, or pulmonary plethora (by chest radiography) [1]. Although not a labeled use, indomethacin for injection has also been used prophylactically within the first 24 h of life to prevent the development of symptoms in premature infants with PDA [2] and to reduce the occurrence of intracranial or intraventricular hemorrhage in very-low-birth-weight neonates [3–5].

Indomethacin is practically insoluble in water (0.02 mg/ml), which precludes its use in injection formulations. Thus, indomethacin for injection had been on shortage due to manufacturing difficulties [6]. Hydrotropic solubilization of a wide variety of drugs has been demonstrated [7–15] in the literature and a number of mechanisms have been reported [16–27]. The present study was aimed to investigate the effect of hydrotropes on the solubility of indomethacin, and to attempt formulation in aqueous injection [28–30]. Formulations were also studied for physical and chemical stability [31,32]. The chemical structures of drug and various hydrotropes used in this study are shown in Fig. 1.

2. Materials and methods

2.1. Materials

The gift sample of indomethacin was provided by M/S Signa Pharma Pvt. Ltd., Kanpur, 208 012 UP, India. Urea,

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doi:10.1016/j.ejpb.2007.06.013

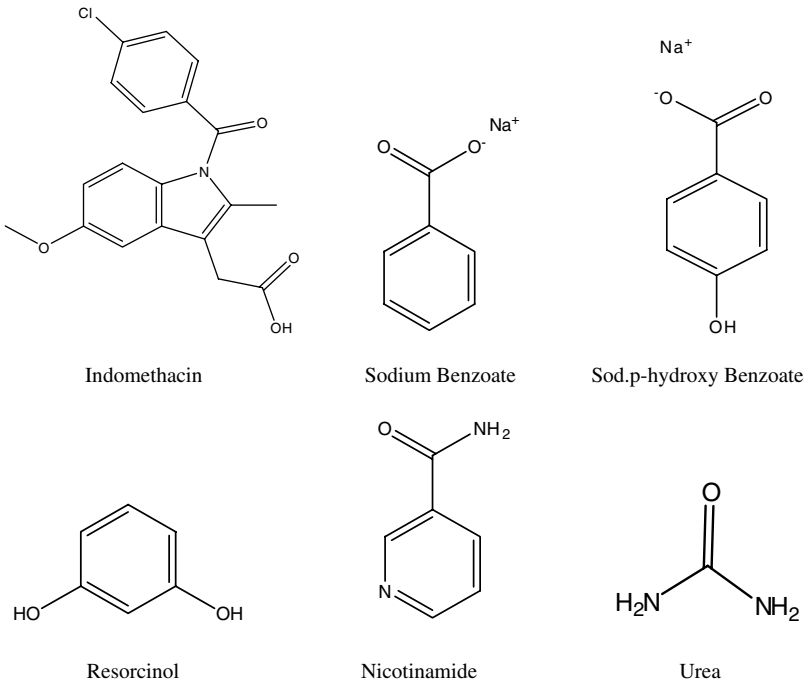

Fig. 1. Chemical structures of indomethacin and various hydrotropes.

nicotinamide, resorcinol, sodium benzoate and *p*-hydroxy benzoic acid all AR grade were purchased from CDH, Mumbai, India.

2.2. Estimation of indomethacin

In the present study, UV spectrophotometric method [33] was used for the estimation of indomethacin. The calibration curve of indomethacin was prepared in distilled water at 319.5 nm using double-beam spectrophotometer (UV-1701, Shimadzu, Japan).

2.3. Solubility study

An excess quantity of indomethacin was added to screw-capped 10 ml glass vials containing the different aqueous systems viz. distilled water, buffers of pH 2.5–8 (pH is maintained during vortexing) and hydrotropic solutions of different concentrations (0.2, 0.4, 0.6, 0.8, 1.0, 1.2 and 2.0 M) in water. The vials were shaken vigorously for 15 min on a touch type vortex mixer (Jyoti Scientific Industries, Gwalior 474 009, India) and then the solutions were allowed to equilibrate with mechanically shaking and intermittent vortexing for 72 h at 25 ± 2 and 37 ± 2 °C in a rotary flask shaker and shaker water bath (Jyoti Scientific Industries, Gwalior 474 009, India). After completion of 72 h each vial is centrifuged for 10 min at 2000 rpm. The supernatant of each vial was filtered through 0.45 μm membrane syringe filter (Sonar Axiva, Axiva Sichem Pvt. Ltd., Delhi, India), filtrate diluted suitably with distilled water and analyzed spectrophotometrically at 319.5 nm against respective hydrotrope solution diluted accordingly as blank. The solubility of indomethacin was determined in triplicate.

2.4. Properties of hydrotropic solutions

The various solution properties of hydrotropes such as pH, viscosity, specific gravity, surface tension, refractive index, conductance and diffusion rate were also studied in an attempt to reason out the increase in solubility of indomethacin with increase in hydrotrope concentration [34,35].

2.5. UV spectral studies

In order to interpret the probable mechanism of solubilization, UV spectral studies of indomethacin were performed in different hydrotropic solutions to study the possible spectroscopic changes in the structure of indomethacin in presence of different hydrotropes.

2.6. Fourier transform infrared (FTIR) spectral studies

FTIR spectra were obtained by means of a FTIR spectrophotometer (FTIR – 8400 s, Shimadzu, Japan). The samples were prepared by the potassium bromide disk method and measurements were attempted with the accumulation of 20 scans and a resolution of 4 cm^{-1} over the range of 400–4000 cm^{-1}.

2.7. Thermal analysis

Differential scanning calorimeter (DSC) curves were obtained with a Pyris-6 DSC (Pyris series, Perkin Elmer,