ABSTRACT

The purpose of the present study was to develop and characterize an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropylmethylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9 hours in pH 6.8 phosphate buffer using United States Pharmacopeia (USP) type II dissolution apparatus. Along with usual physical properties, the dynamics of water uptake and erosion degree of tablet were also investigated. The in vitro drug release study revealed that HPMC K100CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor (f2) above 50. Water uptake and erosion study of tablets indicated that swelling followed by erosion could be the mechanism of drug release. The in vitro release data of CS and DS followed Korsmeyer-Peppas and zero-order kinetics, respectively. In conclusion, the in vitro release profile and the mathematical models indicate that release of CS and DS can be effectively controlled from a single tablet using HPMC matrix system.

KEYWORDS: Chondroitin sulphate, diclofenac sodium, hydroxypropylmethylcellulose, controlled release.

INTRODUCTION

Chondroitin sulfate (CS) belongs to a family of heteropolysaccharides called glycosaminoglycans or GAGs. Glycosaminoglycans were formerly known as mucopolysaccharides. GAGs in the form of proteoglycans comprise the ground substance in the extracellular matrix of connective tissue. CS is made up of linear repeating units containing D-galactosamine and D-glucuronic acid. CS is found in humans in cartilage, bone, cornea, skin, and the arterial wall. This type of CS is sometimes referred to as chondroitin sulfate A or galactosaminoglucuronoglycan sulfate. The molecular weight of CS ranges from 5000 to 50 000 d and contains ~15 to 150 basic units of D-galactosamine and D-glucuronic acid.

The mechanism of action and absorption of orally administered CS has not been clearly understood. Possible actions include promotion and maintenance of the structure and function of cartilage (referred to as chondroprotection), pain relief of osteoarthritic joints and anti-inflammatory activity.1-4 CS in combination with hyaluronic acid is available as a combination product in the United States. It is used as a viscoelastic agent in cataract surgery. CS is available generically from numerous manufacturers.

Diclofenac sodium (DS) is usually prescribed as once-a-day controlled release tablets for management of painful arthritis conditions to reduce the inflammation and thereby reduce pain. CS is coprescribed in many instances for its chondroprotective action and cartilage rebuilding. It was hypothesized that combining both drugs in a controlled release dosage form would reduce pill burden and increase patient compliance.

An effort was therefore made to develop simple and effective controlled release DS and CS tablets using a polymer matrix system with uniform in vitro release properties. Hydroxypropylmethylcellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems.5 The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly.6 The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution.7,8 As reported by Ford et al,9 as the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix. Narasimhan and Peppas10 showed that the dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and
dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC.\textsuperscript{11} The aim of this study was to develop a controlled release dosage form of DS and CS and to evaluate the drug release kinetics from the HPMC matrix.

**MATERIALS AND METHODS**

Diclofenac sodium United States Pharmacopeia (USP) was supplied by Lupin Ltd (Pune, India). HPMC (Methocel K100M CR) was procured from Colorcon (Dartford, UK). Chondroitin sulfate was procured from Biocon (Banglore, India) and polyvinylpyrrolidone (PVP) K90 USNF was purchased from BASF (Ludwigshafen, Germany). All other ingredients used throughout the study were of USP grade and were used as received.

**Preparation of Tablets**

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given in Table 1. DS, CS, and HPMC K100 were mixed in a polybag, and the mixture was passed through mesh (No. 40). Granulation was done using a solution of PVP K90 in sufficient isopropyl alcohol. The wet mass was passed through mesh No. 8. The wet granules were air dried for ~2 hours. The granules were then sized by mesh No. 16 and mixed with aerosil (Aerosil-200, Degussa Corp, Dusseldorf, Germany) and talc. Tablets were compressed at 900 mg weight on a 10-station mini rotary tableting machine (General Machinery Co, Mumbai, India) with 18-mm oval-shaped punches. Four different formulas, having different concentrations of HPMC K100 (15%, 20%, 30%, and 40%), were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

**Evaluation of Tablets**

As mentioned in the Preparation of Tablet section, to study the effect of polymer concentration on drug release, 4 different formulas, having different concentrations of HPMC K100, were developed. Because determination of CS is a complex process, the optimized formula was selected on the basis of DS release characteristics only. As shown in Figure 1, F4 formulation showed prolonged release and thus was chosen for further studies.

The prepared tablets were tested as per standard procedure for weight variation (n = 20), hardness (n = 6), drug content, thickness (n = 20), friability, water uptake, and erosion characteristics. Hardness of tablet was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test (n = 20) was conducted using Roche friabilator (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Thickness of the tablets was measured by digital Vernier caliper (Mitutoyo Corp, Kawasaki, Japan). Drug content of DS was analyzed by measuring the absorbance of standard and samples at $\lambda = 275$ nm using UV/Visible spectrophotometer (Jasco model V-530, Tokyo, Japan). Drug content of CS was analyzed by using method described by Zhang et al\textsuperscript{11} and measuring the absorbance of complex at $\lambda = 662.5$ nm and comparing the content from a standard calibration curve. Further the similarity factor ($f_2$) for the release of DS between the test product and that of marketed formulation, Voveran SR (Novartis, Basel, Switzerland), was performed.

**Quantification of the Water Uptake and Erosion Determination**

For conducting water uptake studies, the dissolution jars were marked with the time points of 0.5, 1, 2, up to 9 hours.