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Original Article

Development and evaluation of aceclofenac matrix tablets using polyethylene oxides as sustained release polymers

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ABSTRACT

Aim: The main aim of this study was to prepare and evaluate once daily sustained release tablets of aceclofenac by using polyethylene oxides (PEOs) of different molecular weights as matrix polymers.

Method: A direct compression method was used to prepare PEO matrices. Type and the amount of PEO in the matrices were varied to optimize *in vitro* aceclofenac release profiles.

Results: From the *in vitro* release studies, it was found that the matrix tablets containing 28% of PEO (80% PEO WSR 303 and 20% of PEO WSR N60K) showed similar release profiles, as estimated by similarity factor (f2), to a marketed product, Hifenac SR.

From the bioavailability study in human volunteers, it was found that there was no statistically significant difference in the pharmacokinetic parameters such as T_{max} and C_{max} between the optimized sustained release formulation containing 28% of PEO and Hifenac SR.

Conclusion: It can be concluded from this study, that the bioavailability of the sustained release formulation developed was similar to that of Hifenac SR and the hydrophilic PEO matrices are novel sustained release carriers for the delivery of aceclofenac.

1. Introduction

Aceclofenac, a phenyl acetic derivative related to diclofenac, is a widely used nonsteroidal anti-inflammatory drug (NSAID). The short biological half life (4 h) and dosing frequency of more than one per day, make aceclofenac an ideal candidate for sustained release. A once daily sustained release formulation for aceclofenac is useful to reduce the frequency of administration, to minimize the gastrointestinal disturbances such as peptic ulceration with bleeding and to improve patient compliance.[1]

Polyethylene oxide is a high molecular weight, nonionic homopolymer of ethylene oxide with good water solubility. It has been successfully used in different drug delivery systems.[2] Upon exposure to water or gastric juices, PEOs hydrate and swell rapidly to form hydrogels with properties ideally suited for a controlled drug delivery vehicle. In PEOs with molecular weight in the range of 0.6, 0.9 and 2.0 × 10^6, synchronization of the swelling and erosion processes was observed. In contrast, PEOs possessing a molecular weight of 4.0 × 10^6 and above did not present the balanced process of swelling and erosion; rather it was observed that the swollen

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gel layer kept increasing in volume until the entire polymer was hydrated, which was followed by a decrease in size because of the erosion of the swollen gel.[3] The objective of the present work was to prepare matrix tablets of aceclofenac with PEOs of molecular weights of 7×10^6 and 2×10^6 and to evaluate them for their *in vitro* and *in vivo* performance.

2. Materials and methods

2.1. Materials

Aceclofenac was kindly supplied by Ajantha Pharmaceuticals (Mumbai), and PEOs of different grades were supplied by Orchid chemicals, Chennai. Microcrystalline cellulose (Avicel PH 102), and poly vinyl pyrrolidone 30 (Kollidon 30) were obtained from Signet Chemicals (Mumbai). Acetonitrile was of HPLC grade (Qualigens). All other chemicals were of analytical or reagent grade and were used as received. A marketed sustained release aceclofenac tablet (Batch No. 35024; Hifenac SR) was obtained from Intas Pharmaceuticals Pvt. Ltd. (Ahmedabad) for comparative study of bioavailability with the formulation developed in the current study.

2.2. Preparation of matrices

Matrix tablets, each containing 200 mg of aceclofenac, were prepared employing (polyethylene oxides, Polyox 303 and Polyox N60K) in different proportions of drug and polymer as per the formulae shown in Table 1. The drug, polymer, binder and diluents were screened through sieve number #40 (size of aperture 390 μm) and were preblended manually. The glidant and lubricant were added and the blend was mixed again prior to compression. The formulation mixtures were directly compressed by using 8 station rotary tablet press (Cadmach, Ahmedabad). The tablets were round flat type, 12 mm diameter, 3.0 ± 0.5 mm thick, and had a hardness of 6–10 kg/cm.[2]

2.3. In *vitro* drug release study

Drug release from matrix tablets was studied using 8 station dissolution test apparatus (Lab India, Disso 8000) as per the method mentioned in Indian Pharmacopoeia.[4] The dissolution medium was phosphate buffer of pH 7.5 maintained at 37 ± 0.5 °C and the paddle speed was set at 50 rpm. Samples of 5 ml volume were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 275 nm for aceclofenac using an Elico BL 198 double beam UV-spectrophotometer. For comparison, aceclofenac release from Hifenac SR tablets was also studied. The drug release experiments were conducted in triplicate.

2.4. In *vivo bioavailability study in human subjects*

The bioavailability of the selected sustained release formulation of aceclofenac was compared with a commercial sustained release product (Hifenac SR) in healthy human volunteers. The study protocol was approved by the Institutional Ethics Committee for research on human volunteers, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam (Approval No. AUIEC-06/2010). Twelve healthy human subjects (63–80 kg) were randomly divided into two groups. After an overnight fast of 10 h, test group (Formulation F10) and reference group (Hifenac SR) received a single oral dose of tablet equivalent to 200 mg of aceclofenac. Two milliliters of blood was withdrawn from a cubital vein with a heparinized syringe at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 30 h post dose. After 4 h of dosing, the volunteers were given controlled diet. Sampling was continued for 30 h. The blood samples were centrifuged immediately at 5000 rpm and the separated plasma samples were stored at −70 °C until analysis. The study design used is a randomized, crossover, non-blinded, design.

2.5. HPLC assay of aceclofenac in plasma

A sensitive HPLC method[5] was used to analyze the aceclofenac in human plasma. The HPLC system (Make: M/s Shimadzu Corporation, Japan.) consisted of UV–Visible detector (Shimadzu, Model: SPD − 10AVP). To 500 μl of plasma, 400 μl of acetonitrile solution containing ibuprofen (10 μg/ml) as an internal standard was added and mixed for a minute. Diluent (100 μl) was added and centrifuged at 5000 rpm for 20 min. The supernatant layer was collected and analyzed using HPLC. The chromatographic conditions used: mobile phase: a mixture of phosphate buffer 6.8 (pH adjusted to 6.8 using phosphoric acid) and acetonitrile (30:70); Column: C-18 column (Phenomenex, DESC: Gemini 5 μ C18 110 A, Size: 250 × 4.6 mm, S/

Table 1 – Composition of Aceclofenac matrix tablets.

Ingredients (mg/tablet)	Formulation code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Aceclofenac	200	200	200	200	200	200	200	200	200	200	200
PEO WSR N60K	100	200	–	–	–	–	–	–	14	28	42
PEO WSR-303	–	–	100	200	120	140	160	180	126	112	98
AVICEL PH 102	185	85	185	85	165	145	125	105	145	145	145
PVPK-30 (Kollidon 30)	10	10	10	10	10	10	10	10	10	10	10
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight (mg)	500	500	500	500	500	500	500	500	500	500	500