Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jopr

Original Article

Design and evaluation of sustained release pellets of aceclofenac

Venkat N. Ravella, Rama Rao Nadendla, Naga Chandrika Kesari*

Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, Lam, Guntur 522034, India

ARTICLE INFO

Article history:
Received 30 November 2012
Accepted 30 April 2013
Available online 29 May 2013

Keywords:
Aceclofenac
Ethyl cellulose N50
Hydroxy propyl methyl cellulose E5
Pelletization
Release kinetics

ABSTRACT

Aim: The aim of the present study was to prepare sustained release pellets of aceclofenac using pelletization technique.

Methods: The sustained release was ensured by coating the pellets with ethyl cellulose N50 and hydroxy propyl methyl cellulose E5. The influence of rate retarding polymer, ethyl cellulose in combination with film forming agent, HPMC in different weight ratios on drug release kinetics was studied.

Results: The *in vitro* dissolution studies of aceclofenac from the sustained release pellets were carried out in pH 6.8 phosphate buffer using USP type I apparatus. Statistically significant differences were found among the drug release profile from different formulations.

Conclusion: The kinetic study revealed that the release of drug from the optimized formulation was appeared to follow first order kinetics. The dissolution profile and *in vitro* release kinetics showed that aceclofenac pellets were promising for sustained delivery of the drug.

1. Introduction

Multi-particulate (MP) modified release drug delivery systems have several performance advantages over single unit dosage forms. MP formulations generally have a more reliable *in vivo* dissolution performance, resulting in more uniform bioavailability and clinical effect.[1] Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi spherical units, referred to as pellets.[2] Pellets offer a high degree of flexibility and can be divided into desired dose strengths without formulation or process changes.[3] Pellets are in a size range between 0.5 and 1.5 mm and are produced primarily for the purpose of oral controlled release dosage forms having gastro resistant or sustained release properties or the capability of site-specific drug delivery.[4] The pelletized products can improve the safety and efficacy of the active agent, showing a number of advantages over the single unit dosage system.[5] Extended release formulations are designed to allow at least twofold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance when compared to a conventional immediate release dosage form.[6] Sustained release pharmaceutical pellet is one of the most popular approaches among the various types of extended release dosage forms as it offers several manufacturing and biopharmaceutical advantages.[7] Pellets are also less affected by gastric emptying.[8] After administration, the coated pellets spread uniformly throughout the gastrointestinal tract resulting in a consistent drug release with reduced risk of local irritation and dose dumping of the drug can be avoided.

* *Corresponding author*. Tel.: +91 863 2524124.
E-mail address: chandrika.yht@gmail.com (R.R. Nadendla).

0974-6943/$ – see front matter
http://dx.doi.org/10.1016/j.jopr.2013.04.040

NSAIDs are a group of drugs of diverse chemical composition and different therapeutic potentials.[9] Most NSAIDs are weak acids, with a pK_a values in the range of 3.0–5.0 and contain hydrophilic groups and lipophilic ones.[10,11] Aceclofenac [(2, 6-dichlorophenylamino) phenyl] acetoxyacetic acid is a phenyl acetic acid derivative, and is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis. Aceclofenac (ACE) inhibits the cyclooxygenase enzyme and thus exerts its anti-inflammatory activity by inhibition of prostaglandin synthesis. Due to its short biological half-life (about 4 h) and dosing frequency (200 mg daily in 2 divided doses) of more than one per day, ACE is an ideal candidate for sustained release formulation.[12,13] The primary object of this study was to prepare and to characterize drug loaded aceclofenac pellets using solution layering technology and to give functional coating using ethyl cellulose in combination with hydroxy propyl methyl cellulose and to extend the drug release for more than 24 h. Here, ethyl cellulose acts as a release retarding polymer and hydroxy propyl methyl cellulose acts as a film-forming agent.

2. Materials and methods

Aceclofenac was obtained as a gift sample from Suyash Laboratories Ltd, Mumbai. Ethyl cellulose (EC) N50, Hydroxy propyl methyl cellulose (HPMC) E5 were obtained as gift samples from Zhejiang ZhongBao Imp& Exp. Corp Ltd, Mumbai. Nonpareil seeds (NPS) were procured from Nexus Drugs (Hyderabad, India). All other ingredients used throughout the study were of analytical grade and were used as received. Wistar rats (220–240 g) of either sex were used for biological screening. Animals were procured from Mahaveer Enterprises, Hyderabad. Animals were acclimatized to laboratory conditions for at least one week before commencement of the experiments and were kept under a 12 h light/12 h dark cycle. Animals were fasted overnight prior to treatment and received free access to water during the experiment.

2.1. Formulation of sustained release pellets

2.1.1. Preparation of drug layered pellets

Drug layered pellets were prepared by accurately weighing the non-pareil seeds of 22 mesh size and were charged into the coating pan which was pre-heated and the temperature of the inlet was maintained at 45 °C. Aceclofenac (ACE) was accurately weighed and dissolved in the solvent iso propyl alcohol by slow addition and continuous stirring. 1% PVP K30 (polyvinyl pyrrolidone) as a binder solution was added to the drug solution. This was sprayed with the help of spray gun (attached with compressor) till the bed become wet. Drying bed temperature and blowing air temperature were maintained properly to avoid overheating of drug loaded pellets. The formula for primary coating was given in Table 1 and the coating parameters were given in Table 2.

2.1.2. Preparation of coating dispersion

Iso propyl alcohol was used as a vehicle to prepare the coating dispersions. Five different coating dispersions were prepared having different ratios of HPMC E5 and ethyl cellulose N50.

Table 1 – Formula for primary coating.

Ingredients	Quantity
Aceclofenac	27 g
Polyvinyl pyrrolidone (PVP) K 30	1.3 g
Non-pareil seeds	70 g
Iso propyl alcohol	500 ml
Talc	0.3 g

Isopropyl alcohol was added slowly to the required amount of ethyl cellulose N50 containing TEC as a plasticizer with continuous stirring to prepare a homogenous dispersion. Another homogenous dispersion was prepared by mixing HPMC E5 with purified water. The above two dispersions were mixed with continuous stirring for approximately 15 min. Finally talc was added as an anti-sticking agent based on the solid dry weight of the polymers with continuous stirring for approximately 10 min. In this way all the coating dispersions were prepared and was sprayed onto the drug loaded pellets until the pellets achieved desired coating level. Compositions were given in Table 3.

2.2. Characterization and evaluation of pellets

The above pellets were evaluated for various parameters like particle size analysis, size distribution, shape and surface roughness, flow properties, drug content and *in vitro* dissolution profile. Particle size analysis was done by optical microscopy method. Drug content was carried out by UV method.[4,14,15]

2.2.1. Particle size analysis

The particle size of drug loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Weswox model having resolution of 45× was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to 30.07 μm.

2.2.2. Measurement of micromeritic properties

Angle of repose (θ) was assessed to know the flowability of pellets, by a fixed funnel method using the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Tap density and bulk density of the pellets were determined using tap density tester.

The percentage Carr's index (I, %) was calculated using the formula:

Table 2 – Primary coating parameters.

Parameters	Value
Inlet air temperature	60–65 °C
Bed temperature	45 °C
Exhaust air temperature	40 °C
Pan speed	5 rpm
Pump speed	1 rpm