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Research Article

FABRICATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF KETOROLAC TROMETHAMINE

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ABSTRACT

The aim of the present paper was to study preparation of methacrylate microparticles for delivery of ketorolac tromethamine via the oral route. Drug was encapsulated within polymethacrylate copolymer (Eudragit RS100 and Eudragit RL100), by solvent evaporation method. Magnesium stearate was used as droplet stabilizer in concentration of 0.3% (v/v). Selected formulations were characterized for their entrapment efficiency, particle size, surface morphology and release behavior. *In vitro* dissolution tests were performed by using dissolution media with two different pH. All the selected formulations exhibited a prolonged release for almost 24 hr. The mean particle size of microspheres ranged from 75 to 225 µm and encapsulation efficiency ranged from 72.72 to 95.88% (w/w). Scanning electron microscopy of microspheres revealed a spherical and uniform appearance with rough surface. Mechanism of release was found to be Higuchi type. *In vivo* study of microspheres in albino wistar rats demonstrated significant analgesic and anti-inflammatory activities of microspheres for longer period of time compared to the parent drug. This study indicated that eudragit microspheres containing ketorolac tromethamine could be prepared successfully by using an emulsion solvent evaporation technique, which would not only sustain the release of drug but also minimize the side effects of this drug.

Keywords: Ketorolac tromethamine; Microspheres; Eudragit; NSAID(S).

INTRODUCTION

Ketorolac tromethamine is non-steroidal anti-inflammatory drug (NSAID), which has potent analgesic and anti-inflammatory activity due to prostaglandin related inhibitory effect of drug[1]. This drug, like other NSAID(S), may produce gastrointestinal side effects. After oral administration it is rapidly eliminated from blood exhibiting a short biological half life of 4-6 hr.

Microspheres are one of the microparticulate delivery systems which are widely accepted to achieve oral controlled drug delivery. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects due to decrease in dosing frequency and improving patient compliance[2]. Among the various methods developed for the formulation of microspheres, oil in oil solvent evaporation gained much more attention due to its ease of fabrication without compromising the activity of drug.[3-5]

Eudragit polymers are series of acrylate and methacrylate polymers available in different ionic forms. Eudragit RS100 and Eudragit RL100 are referred to as aminomethacrylate copolymers with the former having 5% functional quarternary ammonium groups and later having 10% functional quarternary ammonium groups which are responsible for permeability of water in polymer matrix.[6-8]

The aim of this study was to prepare eudragit microspheres containing ketorolac tromethamine by solvent evaporation method to achieve a controlled drug release profile. Investigation of the effect of various processing and formulation factors such as drug to polymer ratio, stirring speed, phase ratio and surfactant concentration on the shape, mean particle size, yield of production, particle size distribution, encapsulation efficiency, surface properties and release rate of drug from the microspheres were performed. After examination of all the formulation variables on the microspheres properties, the optimized batch was selected and *in-vivo* study performed. By monitoring its analgesic and anti-inflammatory effects sustained release of drug from microsphere formulation was confirmed.

MATERIALS AND METHODS

Materials

Ketorolac tromethamine was obtained as a gift sample from Dr. Reddys Laboratories, India. Eudragit RS100 and RL100 were obtained from Rohm Pharma, GmbH, Darmstadt, Germany. All other reagents and solvent used were of pharmaceutical or analytical grade.

Methods

Preparation of microspheres

Ketorolac tromethamine microspheres were prepared by solvent evaporation method. In this method a combination of Eudragit RS100 and Eudragit RL100 (in different ratios) was dissolved in a mixture of solvents containing acetone (5.0ml) and methanol (3.0ml) in a 100 ml of beaker with the help of magnetic stirrer. After complete dissolution, this solution was added with drug (100 mg). Magnesium stearate, as dispersing agent, was dispersed in drug and polymer solution with the help of sonicator. Resulting dispersion was poured in another 250ml beaker, containing mixture of paraffin oil light (60ml) and n-hexane (6.8ml), with continued stirring at 500-1500 rpm. Stirring was continued for 2 h until acetone evaporated completely. After evaporation of acetone, formed microspheres were filtered and residue was washed 4-5 times in 50 ml petroleum ether, each. Microspheres were dried at room temperature for 24 h. All the microsphere formulations were prepared in triplicate.

Scanning electron microscopic analysis

The shape and surface characteristics of microspheres were analyzed by scanning electron microscopy (SEM). Sample was dusted on a double-sided adhesive tape applied previously to an aluminium stub. Excess sample was removed and stub coated (Polaron Sputter 7040) with 30 nm layer of gold-palladium observed with a scanning electron microscope (Leo 0430, Leica Cambridge Ltd., Cambridge, UK).

Particle size analysis

Prepared microspheres (10 mg) were dispersed in water and particle size and particle size distribution of microspheres were determined by laser light scattering method (Malvern Mastersizer, Malvern Instruments, UK).

Percentage yield

The percentage yield value of microspheres was determined from the ratio of amount of solidified total microspheres to total solid material used in the inner phase.