Poly (Lactic Acid) Microspheres of Ketorolac Tromethamine for Parenteral Controlled Drug Delivery System

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Ketorolac tromethamine loaded poly (lactic acid) microspheres with different polymer composition were prepared by phase separation co-acervation induced by non-solvent addition method. The morphology of microspheres was analysed by scanning electron microscopy. The particle size distribution, studied by optical microscopy, showed that particles are of uniform size. *In vitro* drug release profiles of these microspheres were studied using pH 7.4 phosphate buffer. The release kinetics of ketorolac tromethamine from the microspheres was evaluated by fitting the release data to the zero order, first order, Higuchi and Korsemeyer-Peppas equations. All microspheres showed initial burst release, followed by ficklan diffusion of drug through microspheres. The stability of the formulations was found to be two years.

Controlled drug delivery systems have received tremendous attention over the last two to three decades and the significant research interest in the long term maintenance of therapeutic drug levels coincides with the increased medical and public acceptance of such systems[1,2]. Parenteral controlled release systems are of considerable value for drugs, which require daily administration with either high toxicity, or a very low oral bioavailability. Their therapeutic potential would be greatly increased if the dosage from can be injected to the patient. In addition, the use of biodegradable polymers in formulating systems eliminates the need for surgical removal of the polymer residue[3]. In case of microspheres as drug delivery system, various biodegradable materials and manufacturing methods using different kinds of biodegradable polymers encapsulating a variety of active pharmaceutical ingredients are available[4-7].

Poly (lactic acid) polymers are biocompatible and degrade to toxicologically acceptable products that are ultimately eliminated from the body[8]. All these characteristics make poly (lactic acid) ideal candidates for achieving the controlled drug delivery of drugs. Hence they are widely used as controlled release systems for a variety of drugs such as narcotic antagonists, local anaesthetics, immuno stimulants and steroid harmones[9].

Ketorolac tromethamine is an analgesic with moderate antiinflammatory activity. The biological half-life of ketorolac is 4-6 h. Therefore, frequent dosing is necessary to sustain the action of the drug to alleviate pain in post operative patients[10]. Various dosage form of ketorolac tromethamine such as gels[11], transdermal patchs[12] and matrices[13] have been prepared for obtaining sustained release effect. Thus in the present study poly (lactic acid) microspheres of ketorolac tromethamine were prepared for administering as controlled release parenteral dosage forms.

Ketorolac tromethamine was obtained as gift sample from Reddy's Laboratory, Hyderabad. Poly (lactic acid) with a molecular weight of about 4500 was obtained from Poly Sciences, USA. Methanol, sodium carboxy methyl cellulose and methylene chloride were purchased from M/s Loba Chemie, Mumbai. All other reagents and solvents used were of analytical grade.

Microspheres containing ketorolac tromethamine were prepared by non-solvent addition technique. Accurately weighed amount of the polymer was dissolved in 30 ml of methylene chloride and drug was dispersed in

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the polymer solution. This mixture was stirred at room temperature for 20-30 min using a sonicator (Telsonic, Switzerland). To this mixture, 20 ml of n-hexane was added drop wise with continuous stirring over a period of 15 min in order to avoid the formation of aggregate masses and then rigidified. The so obtained microspheres were washed three times with distilled water, filtered and dried at room temperature. Three formulations with drug:polymer ratios of 1:1, 1:2 and 1:3 were prepared and named L_1, L_2 and L_3, respectively. The quantity of drug used was 100 mg.

The amount of drug in microspheres was determined by directly recovering the drug from the microspheres. About 20 mg of microspheres was dissolved in 100 ml of methylene chloride and methanol in the volume ratio of 3:2 and it was agitated for 30 min. The solution was then centrifuged and 1 ml of the clear supernatant was diluted to 25 ml with 0.1 N hydrochloric acid and absorbance of the solution was measured at 313 nm against a reagent blank and the total drug content was calculated.

The surface morphology of microspheres was investigated with Scanning Electron Microscopy using a Jeol Japan Model JSM 840A Electron microscope. Mean particle size and diameter of microspheres was determined. The particle size and their distribution were measured by optical microscopy.

The dialysis tube diffusion technique was used to determine the rate of release of ketorolac. Five hundred millilitres of pH 7.4 phosphate buffer solution was used as the dissolution medium. Microspheres equivalent to 100 mg of ketorolac tromethamine were suspended in 5 ml of the dissolution medium and then the dispersion was placed in a dialysis bag. The bag was placed in a basket rotated at 100 rpm (rewarmed to 37 ± 2°). Samples of the dissolution medium were collected at an appropriate time interval and analysed. The volume was adjusted to 500 ml every time after collecting the sample. The experiment was conducted in triplicate. The *in vitro* drug release studies were conducted for 36 h.

Microspheres containing 100 mg of drug were stored for three months in amber coloured vials with rubber closures at different conditions namely, room temperature, 37°, 45°, and 82.5% relative humidity. The samples were with drawn weekly and analysed for the drug content. Rate constant (K) value was determined and shelf life was calculated.

To formulate parenteral controlled release system, 200 mg of microspheres (≡ 100 mg of ketorolac tromethamine) and 10 mg sodium carboxy methyl cellulose (5% as suspending agent) was taken in a 5 ml vial. This preparation was sterilised by dry heat sterilisation at 150° for 1 h. After sterilisation the microspheres were evaluated to detect any physico chemical changes by IR studies. Other tests carried out included test for sterility as per IP 1985, visual appearance, test for colour, odour and drug content and *in vitro* drug release.

The parenteral ketorolac tromethamine microsphere formulations were checked for syringeability using 23-gauge needle by pressuring vial with 1 ml of air using a syringe. The injection is syringeable if the plunger falls back to 1 ml mark as releasing the pressure.

Ketorolac tromethamine was encapsulated in poly (lactic acid) polymer. The microspheres prepared were spherical in shape and few being slightly elongated. The photomicrographs of microspheres revealed that they had relatively smooth surface (pictures not shown). The size distribution analysis of microspheres shows that the microspheres have a diameter of 16.67, 14.19, and 16.72 µm with maximum drug loading of 94.5%, 90% and 92% respectively.

In vitro release profiles are shown in fig. 1. The data obtained was fitted to zero order, first order, Higuchi and Korsemeyer-Peppas equations to understand the mechanism of ketorolac tromethamine release from the microspheres. All microspheres showed initial burst release, releasing about 20-30% of the drug in the first 5 h. Release of ketorolac tromethamine decreased with increase in polymer ratio. This may be due to low permeability of polymer to the drug. The slopes and the corresponding co-efficient of determination (r^2) for zero order, first order, square root of time and Korsmeyer-Pappas equation are listed in Table 1. The co-efficient of determination indicated that the release did not fit adequately to the zero order kinetics. Higuchi equation explains the diffusion controlled release rate.

Additional evidence for the diffusion controlled release mechanism was obtained by fitting the Korsmeyer-Peppas equation to the release data. The 'n' value was found to be less than 0.5 for different drug polymer composition, indicating Fickian diffusion of drug through microspheres. Thus all microspheres showed initial burst release followed by fickian diffusion. The drug release was found to be in a controlled manner, releasing up to 80% of the drug within 36 h.

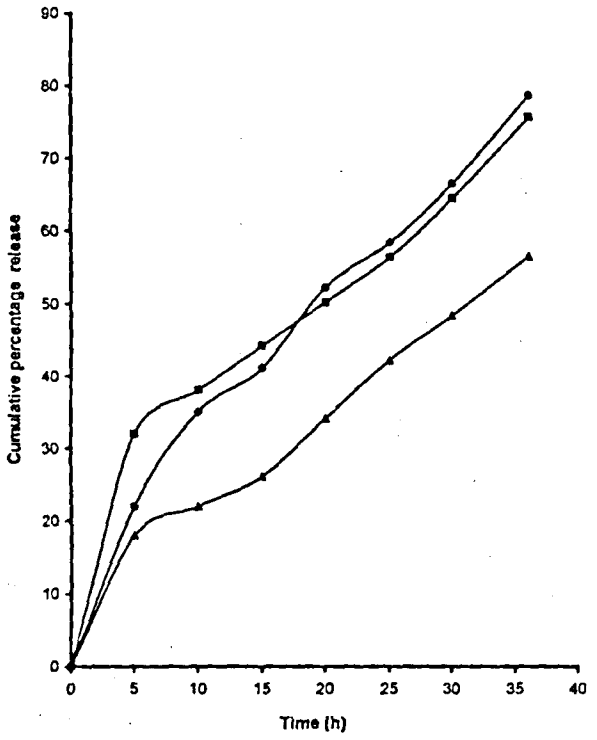

Fig. 1: *In vitro* release of ketorolac tromethamine form poly(lactic acid) microspheres

Release of ketorolac tromethamine was determined from microspheres formulated using drug, polymer ratios of 1:1 (L_1, -●-), 1:2 (L_2, -□-) and 1:3 (L_3, -▲-)

sterility using soyabean casein digest medium and fluid thio-glycolate culture media. There was no turbidity in the culture medium injected with the formulations, so the formulations are sterile. The sterilized microspheres were formulated into parenteral dosage form by suspending in water for injection with 5% sodium carboxy methylcellulose as the suspending agent and were subjected to syringeability test. All the formulations were found to be syringeable when 23-gauge needle was used.

The results presented in this investigation indicate that ketorolac tromethamine loaded poly (lactic acid) microspheres with controlled release characteristics can be successfully prepared. Thus these microspheres can be used as controlled release dosage from for post-operative conditions to improve patient compliance.

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TABLE 1: FIT WITH DIFFERENT RELEASE KINETIC MODELS

Microsphere Batch	Kinetic Model (r^2)			Korsemeyer-Peppas Equation ('n' value)
	Zero order equation	First order equation	Higuchi equation	
L_1	0.9841	0.9893	0.9102	0.3836
L_2	0.9814	0.9881	0.9452	0.4024
L_3	0.9822	0.9896	0.9272	0.4774

L_1, L_2, L_3 are microspheres formulated using drug, polymer ratios of 1:1, 1:2 and 1:3

The shelf life was calculated and found to be about two years. The microspheres are highly stable at all temperature conditions. All the formulations were subjected to dry heat sterilization at 150° for 1 h. So that, the polymers and drug will not undergo degradation due to heat as the melting point is higher than 150°. TLC and drug content analysis proved the intactness of drug in the polymer even after sterilization.

After sterilization, microspheres were evaluated for

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