Microencapsulated Ketoprofen Loaded Suppositories For Rectal Administration

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ABSTRACT

The present work aimed to develop ketoprofen loaded microparticle based sustained release suppositories for rectal administration in order to enhance bioavailability of the drug as well as overcome first pass metabolism after effects associated with the active ingredient thereof. The microparticles were developed by ionic gelation technique while the final suppository system of the optimised microparticle formulation was developed by melting method. The optimised batch of the encapsulated system F3 showed high entrapment efficiency and better mucoadhesive strength. It also showed a good sustain ability of the drug release for approximately 12 hours; which can be significantly adopted for alternative route of administration of ketoprofen in order to overcome hepatic adverse effect associated with the drugs frequent administration.

KEYWORDS: ketoprofen, ionic gelation, mucoadhesion, suppositories, rectal administration, first pass metabolism.

INTRODUCTION

Alternative route of drug delivery and drug administration has drawn the attention of pharmaceutical researchers for past few decades. The sole aim of such approach is to either have a reduced side effects of the active principles or to mask its taste or achieving of other desired properties for patient benefit, out of all approaches one is delivery through rectal region which offers advantages over other routes and also is preferred area of drug delivery when most convenient oral route fails in certain cases [1,2]. Suppositories dosage system plays a major role in rectal administration but usage of fatty bases sometimes withdraws patient acceptance thus water soluble bases are more preferred. But use of water soluble bases restricts sustain ability of drug release thus promoting modification in formulation aspect of dosage form development. Designing of a sustained release rectal preparation is to achieve steady level of active principle in blood and also maintain such a concentration for desired period of time [3]. Strategically a sustained release suppository may be developed by modulating the viscosity of the base and incorporating the base with microparticulate loaded active principle in a rectal adhesive system. Microencapsulated systems are considered for quite a number of advantages with respect to delivery of drugs for example sustaining effect, protection against inactivation of the active principle, reduction of dosing frequency, etc.[4]. Coupling of mucoadhesive property with microparticles further enhances acceptability of the dosage form from pharmaceutical manufacturing point of view as well as sustaining and prolonging activity. Ketoprofen is a non steroidal anti inflammatory drug widely used against inflammation, pain and pyretic conditions. It is also used to manage rheumatic arthritis, osteoarthritis, dysmenorrhea etc [5]. Short biological half life and low oral bioavailability of ketoprofen [6] makes it an ideal candidate for being developed in to a sustained release formulation. Based on the above considerations modified rectal suppository loaded with ketoprofen muoadhesive miroparticles are to be developed.

MATERIALS AND METHODS

Ketoprofen was obtained as a gift sample from Ranbaxy Lab Ltd. India. Samples of Sodium alginate and calcium chloride were obtained from Loba Chem. (Mumbai, India). Freshly excised rectal cavity was obtained from the local butcher shop. Water used was HPLC grade. All other chemicals were of analytical grade.

Methods

The microparticles were developed by ionic gelation technique using calcium chloride as cross linking agent. Sodium alginate was dispersed in water to form a homogenous system to which ketoprofen was and stirred properly to give a uniform drug polymer dispersed system. Then by help of using a 24 gauge needle the above dispersion was added drop wise under stirring condition at 200 rpm in to calcium chloride solution (5% w/v). The process was continued for 30 minutes after that the formed particles were filtered out and dried at room temperature. The formulated dried microparticles were kept in a dessicator for further use. The formulation criteria is depicted in Table 1.

Evaluation Of Ketoprofen Microparticles

The formulated microparticles were evaluated for particle size analysis, entrapment efficiency, flow behaviour, mucoadhesive strength of microparticles and *in vitro* drug release study. The datas are highlighted in Table 2 and Figure 1 respectively

In-Vitro Release Studies of Ketoprofen Microparticles

In-vitro dissolution of the formulated encapsulated product of ketoprofen was carried out using USP dissolution rate testing apparatus II (DISSO 2000, LABINDIA, India). Accurately weighed quantity of microparticles (equivalent to 50mg of pure ketoprofen) was place in the dissolution flask containing 900ml of pH 6.8 phosphate buffer solution, 37 ºC ±0.5, 100 rpm. 5mL of aliquot was withdrawn at predetermined time interval and fresh amount of pre warmed dissolution medium was added back in equal amounts. The samples of fluid withdrawn were analyzed for ketoprofen content by using UV-Visible double beam spectrophotometer (UV-2450 Shimadzu, Japan) at 258nm. The release datas are conducted in triplicate and depicted in figure-1.

Preparation Of Sustained Release Suppositories Containing Ketoprofen Loaded Mucoadhesive Microparticles

Sustained release suppositories of ketoprofen were developed by melting method using PEG 6000. Homogenous dispersions of the optimised microparticles formulation and base was developed and then the system was moulded. The formulation details are represented in table-3.

Evaluation Parameters Of SR Suppositories

Melting Time Ketoprofen Content And In-Vitro Drug Release

The sustained release suppositories of ketoprofen microparticles were analyzed for their weight variation, melting time and in-vitro dissolution datas of which are represented Table 3. Melting time was determined by using disintegration apparatus USP at 37°C in a 900 ml pH 6.8 phosphate buffer, and time taken by suppository to disintegrate completely was observed. *In-vitro* dissolution tests of the formulated suppositories were carried out and the percentage of the drug dissolved was evaluated.

Table 1: Formulation details

Formulation code	Drug: polymer	Curing agent (% $CaCl_2$)	Curing time (min)	Stirring speed (rpm)	% Yield
F1	1:1	5	30	200	60.31 ± 0.02
F2	1:2	5	30	200	78.32±0.02
F3	1:4	5	30	200	90.56±0.09
F4	1:5	5	30	200	88.47±0.06

Table 2. Characterisation of prepared microparticles

Formulation code	Particle size (µm)	Entrapment efficiency (%)	Flow behaviour (sec)	Mucoadhesive strength (%)
F1	612±6.5	58.12±1.24	28	77.65
F2	689±6.9	79.36±3.10	32	81.24
F3	756±8.6	91.24±6.21	57	94.69
F4	899±8.9	86.34±3.21	-	90.12

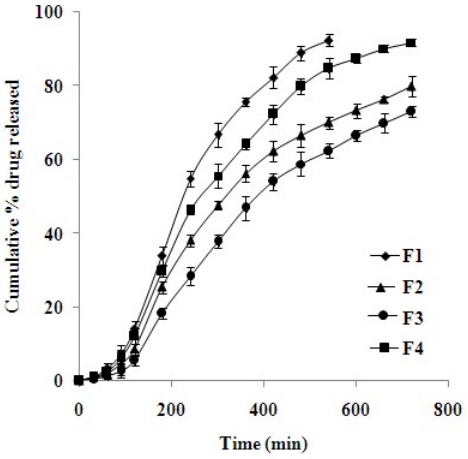

Figure 1: *In vitro* release of formulations

Table 3: Formulation of optimised microparticle (F3) into suppository and its characterisation

Ingredients	Formulation code
Ketoprofen optimised microparticles formulation (F3)	0.876 gm
PEG 6000	1.124 gm
Total weight	2 gm
Melting point (mins.)	11.24±0.56
Content uniformity	97.89±1.02
Weight variation	2.0±0.1
In-vitro dissolution sustained up to	12 hours

RESULTS AND DISCUSSION

The influence of drug: polymer ratio on particle size, entrapment efficiency and drug release rate is depicted in Table 2 and Figure1. A steady increment in polymer concentration markedly influenced particle size, % entrapment and *in-vitro* release of active constituent. There was increase in the values of % yield, entrapment efficiency as concentration of sodium alginate increased which may be attributed to the fact that as amount of alginate was enhanced there was more availability of space for networking by calcium ions. Thus, entrapping of ketoprofen was progressive with progression of polymeric concentration. The *ex-vivo* mucoadhesion test revealed that ketoprofen loaded microparticles adhered to the site of administration i.e. the lower rectal region thus enabling the formulation to stay in position avoiding upper intestinal haemorrhoidal veins that otherwise lead to entero hepatic circulation followed by first pass metabolism of the active principle [4]. The *in-vitro* drug release from the microparticles revealed a good sustaining effect in release behaviour of the active principle. It may be attributed to the fact that calcium (divalent) ion could form a networking mesh like structure that enabled hardening of the microparticles. The so formed network might have contributed to diminished exchange of calcium ion

with phosphate ion of the dissolution medium thus lowering release of active ingredient from the formulated particles (7). The in-vitro drug release of the optimised formulation from the PEG 6000 based suppositories formulation as depicted in table- 3 suggested that sequential dissolution of PEG 6000 in to the medium enabled release of microparticles to the rectal wall post administration and there by releasing the drug in sustained manner for 12 hours.

CONCLUSION

In this study the authors have tried to developed a PEG 6000 based suppository drug delivery system of ketoprofen for prolonging the drug release as well as avoid first pass metabolism which is otherwise difficult to achieve through conventional systems of oral dosage form. The formulation can also be considered as an alternative route for avoiding hepatic side effects associate with the drug.

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