The Pharma Innovation Journal 2015; 4(6): 104-106

www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 4(6): 104-106

www.thepharmajournal.com
Received: 26-06-2015
Accepted: 23-07-2015

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Formulation and evaluation of in situ gel of ketorolac tromethamine for Nasal delivery

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Abstract
The objective of this study was to develop an intranasal delivery system of ketorolac tromethamine using thermoreversible polymer Kolliphore® P407 and mucoadhesive polymer HPMC E4M. Due to increase in mucoadhesive polymer concentration there was increase in bioadhesion strength. An *in vitro* diffusion study revealed that the viscosity of the vehicle has an influence on drug release. The release of drug from gel matrix showed diffusion controlled.

Keywords: Ketorolac tromethamine, *In Situ* gel, intranasal delivery system, mucoadhesive polymer.

1. Introduction
Ketorolac tromethamine (KT), a pyrrolizine carboxylic acid derivative, is a potent anti-inflammatory drug. This non-steroidal and non-narcotic drug is administered systemically (*via* oral and parenteral routes) for the control of mild to moderate pain as well as some post-operative and cancer pain [1]. Administration of this non-selective COX inhibitor by the oral route causes many gastrointestinal side effects, e.g. nausea, vomiting, gastric irritation, peptic ulceration and bleeding.
Nasal delivery of KT with drug solution and powder forms has already been reported, but rapid nasal mucociliary clearance limits its absorption and thereby affects the bioavailability. Nasal drug delivery for systemic effects has been practiced since antiquity. However, over the past two decades, the nasal route has been used as an alternative to parenteral injections [2]. In fact, there are an increasing number of nasally administered dosage forms for systemic application currently on the market. The nasal route is advantageous because of the rapid absorption of drug molecules across the nasal membrane and the relative ease of administration [3].
However, this drug is not currently available as nasal formulation. With intranasal delivery, a drug is absorbed directly into the systemic circulation, bypassing the problems that occur with oral administration, including fast onset of therapeutic effect without the discomfort and inconvenience of an injection.

2. Materials and methods
Ketorolac Tromethamine were obtained as gift samples from Cipla Ltd. Mumbai, India. Kolliphor® grades were gifted by BASF, India. HPMC E4M, Sodium Metabisulphite were gifted by Dr. Reddys Lab, Hyderabad, India, Benzalkonium was purchased from Alpha chemicals Pvt. Ltd.

2.1 Preparation of gels
Nasal formulations consisting of aqueous gels of Kolliphore® P407 containing 17-19% of polymer were prepared using the method described by Schmolka [4]. Composition was given in Table 1.
The prepared nasal formulations were evaluated for clarity, pH, gelation temperature, gel strength, bioadhesive force, viscosity, drug content and *in vitro* diffusion study. Gelation temperature was measured by visual inspection. Viscosity study was performed using a Brookfield viscometer. The gel strength and bioadhesive force of each formulation was determined by measuring the weight required to detach the formulation from nasal mucosal tissue.

Table 1: Composition of all nasal formulation**.**

Sr. No	Ingredients	KT1	KT2	KT3	KT4	KT5	KT6	KT7	KT8	KT9
1	Ketorolac Tromethamine	0.1 %	0.1 %	0.1 %	0.1 %	0.1 %	0.1 %	0.1 %	0.1 %	0.1 %
2	Kolliphore® P 407	17 %	18 %	19 %	17 %	18 %	19 %	17 %	18 %	19 %
3	Hpmc E4m	0.1 %	0.1 %	0.1 %	0.2 %	0.2%	0.2%	0.3 %	0.3 %	0.3 %
4	Sodium Metabisulphite	0.02 %	0.02 %	0.02%	0.02 %	0.02 %	0.02%	0.02 %	0.02 %	0.02%
5	Benzalkonium Chloride	0.01 %	0.01 %	0.01 %	0.01 %	0.01 %	0.01 %	0.01 %	0.01 %	0.01 %
6	Purified Water	q.s to 100 ml	q.s to 100 ml	q.s to 100 ml	q.s to 100 ml	q.s to 100 ml	q.s to 100 ml	q.s to 100 ml	q.s to 100 ml	q.s to 100 ml

2.2 In Vitro Diffusion Study

A fresh sheep nasal mucosa (collected from local slaughterhouse) separated from sublayer bony tissues and blood was mounted onto donor chamber with Serosal surface towards receptor chamber.

Distilled water was used as a diffusion medium. The receptor chamber was filled with 60 ml distilled water and agitated continuously using a magnetic stirrer. The cell was equilibrated at 37±2 ºC, and 0.2 ml test formulation was placed on the dorsal mucosal surface and the position of the donor chamber tube was adjusted so that the Serosal surface just touches the diffusion medium. The temperature of the chamber was maintained at 37 ºC. The 1 ml sample was withdrawn from the receptor chamber at the predetermined time interval from 60 min to 480 min and immediately replaced with the fresh solvent (distilled water) maintained at 37 ºC. The sample withdrawn (1 ml) was diluted to 10 ml with distilled water and drug concentration was determined by UV method.

3. Result and Discussion

All the prepared sets of formulations were found to be clear. pH of all the formulations was found to be in the range of 4.5-6.5 which is considered as nasal physiological pH range. Lysozyme is formed in the nasal secretions, which is responsible for destroying certain microbes at acidic pH. Under alkaline pH, lysozyme is inactive and nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the pH of formulation in the range of 4.5 to 6.5.

In the preliminary studies, the minimum concentration of Kolliphore® P407 that formed gel below 34 ºC was formed to be 18% w/v.

The formulation KT1 with 17% polymer with 0.1% mucoadhesive polymer has minimum bioadhesion 310 dyne/cm^2. From all formulations, the formulation KT8 with 18% w/v Kolliphore® P407 with 0.3% mucoadhesive polymer showed maximum mucoadhesive force.

The decrease in the gelation temperature with increase in Kolliphore® P407 concentration may be due to the higher number and volume occupied by micelles at low temperature. As the concentration of Kolliphore® P407 increases, the gel structure becomes more closely packed with the arrangement in the lattice pattern and gelling occurs rapidly at low temperature. Incorporation of drug into in situ nasal gels increases the gelation temperature.

The mechanism of mucoadhesion may be related to hydrogen bonding between gel formulation and mucosal membrane [5]. Mucoadhesive strength depends on mechanism of mucoadhesion and strength of bonding of polymer with membrane which varies polymer to polymer; therefore, difference in mucoadhesive strength of different polymers was observed.

As concentration of mucoadhsive polymer (HPMC E4M) increased, there was a significant decrease in gelation temperature and increase in mucoadhesive force of formulations. Lowering effect on gelation temperature of mucoadhesive polymer could be explained by their ability to bind to PEO chains present in the Kolliphore® P407 molecules promoting dehydration and causing an increase in entanglement of adjacent molecules with more extensive intermolecular hydrogen bonding [6].

The results obtained with *in vitro* permeability study clearly indicated the permeation of drug through nasal mucosa. It was observed that the formulation of gel retards the extent of permeability. As the concentration of polymer in the formulation increases, the rate of permeation decreases. It was observed that the formulation KT8 and KT9 have shown maximum permeability in 8 hours as compared to the remaining formulations. This extended time release profile was observed may be due to the more amount of gelling agent.

It is clear that as the temperature increases, the viscosity of the formulations increases. At the gelation temperature there is a sudden increases in the viscosity indicating the conversion of sol to gel. It was found that the rheological parameters was directly dependent on the polymer concentration of the formulations.

Table 2: Characteristics of all formulations.

Batch Code	Clarity	pH	Gelation Temperature (ºC)	Drug Content (%)	Bioadhesive force (Dyne/cm^2)	Gel Strength (Sec.)
KT1	+++	5.49	41.7	99.22	310	19
KT2	+++	5.47	41.1	97.91	548.2	25
KT3	+++	5.60	40.0	100.05	1092.2	27
KT4	+++	5.52	38.4	99.89	450.9	23
KT5	+++	5.49	37.9	96.42	723.6	27
KT6	+++	5.42	36.3	97.71	1211.2	29
KT7	+++	5.43	35.4	98.37	609.4	24
KT8	+++	5.40	34.5	99.17	824.6	27
KT9	+++	5.41	31.9	99.01	1456.3	31

Table 3: Drug Release Profiles of Ketorolac Tromethamine from In Situ Nasal Gels.

Time (hrs)	KT1	KT2	KT3	KT4	KT5	KT6	KT7	KT8	KT9
1	41.46	37.21	32.65	30.41	26.25	23.75	20.91	18.24	16.75
2	59.90	51.16	47.78	53.06	46.13	43.53	41.96	43.29	40.12
3	87.24	82.12	76.21	69.16	65.12	58.41	64.87	58.96	57.12
4	98.52	100.03	98.45	79.41	77.38	74.10	81.38	73.15	76.37
5				90.17	87.79	86.56	93.78	81.19	86.41
6				99.78	101.03	91.45	100.21	92.58	89.30
7						99.62		98.14	96.15
8								101.16	99.17

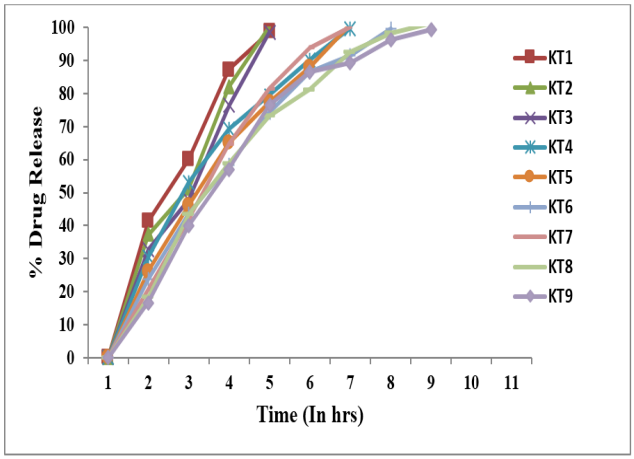

Fig 1: Drug release of Ketorolac tromethamine from in situ nasal gels.

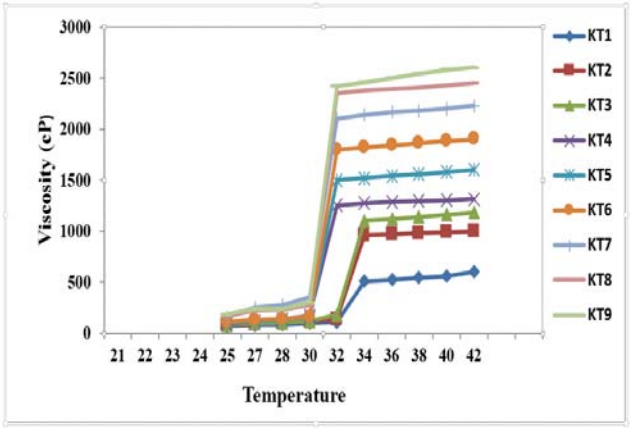

Fig 2: Viscosity of Gels Containing Various Concentration of Kolliphore® P407 and HPMC E4M.

4. Conclusions

In the present study, HPMCE4M and Kolliphore(R) P407 was used for the nasal drug delivery system of the drug ketorolac tromethamine.

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