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Development and Assessment of Novel in-Situ Ocular Gels of Ketorolac Tromethamine.

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Abstract: *The present study was aimed to prepare and characterise pH triggered in situ gel based ophthalmic drug delivery system of non steroidal anti-inflammatory drug (NSAID), ketorolac. Polyacrylic acid (carbopol 940) was used as a gelling agent in combination with hydroxy propyl methyl cellulose (HPMC- K15M, K4M) as a viscosity enhancer. Benzalkonium chlorides at suitable concentration were used as a preservative. The formulations were sterilized by moist heat sterilization as per I.P. The prepared formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, and in vitro diffusion study. Under rheological investigation both solution and gel was found to be in pseudo plastic behaviour. The selected formulations showed sustained release over a period of 8hrs with increased resident time. Eye irritation test using the Draize test protocol with cross over studies were preformed on selected formulations. All studies shown favourable results thus in-situ gelling system is a valuable alternative to counter the precorneal loss a major drawback in the ophthalmic preparation. In situ gel are viscous polymer-based liquid that exhibit sol-to-gel phase transition on the ocular surface due to change in specific physicochemical parameter like ionic strength, ph, or temperature. A major problem in ocular therapeutics is the attainment of optimal drug concentration at the site of action, which is compromised mainly due to pre-corneal loss resulting in only a small fraction of the drug being ocularly absorbed. The effective dose administered can be altered by prolonging the retention time of medication in to the eye by using in situ gel, thereby preventing the tear drainage. The object of the present study is to formulation and evaluation of the in situ ocular gelling system of ketorolac tromethamine. These gelling systems involve the use of gelrite as a polymer..*

Keywords: NSAID

I. INTRODUCTION

The eye is an interesting organ. The tear flow and blinking reflex maintains a good environment and removes foreign material from the eye. In ocular drug delivery, the physiological constraints imposed by protective mechanism of the eye lead to low absorption of drugs and sometimes short duration of therapeutics effect. One of the reasons for relatively low bioavailability of conventional eye drops is their short precorneal contact time. When drug solution is administered in the form of drops, effective tear drainage and blinking results in a 10-fold decrease in drug concentration in 4 to 20 min. The drug absorption is also dependent upon the chemical nature of the drugs since the corneal permeability depends upon molecular size and hydrophobicity of drugs.

The available drug delivery systems are fairly primitive and inefficient. Medication is applied to the surface of eye for two purposes, to treat the outside of eye for infection (conjunctivitis) or to provide intraocular treatment through the cornea for diseases (glaucoma). Most ocular diseases are treated with a topical application of solution into the lower cul-de-sac as eye drop.

Ketorolac is also a viable alternative to corticosteroids in treating ocular inflammation in the presence of pathogens[4]. Ophthalmic solutions of ketorolac (0.5%) are effective in the treatment of chronic aphakic and pseudoaphakic macular edema [5]. The topical ophthalmic dose of ketorolac is 1 drop qid in allergic conjunctivitis and in cystoids macular edema. The objective of the present work was to develop a pH-triggered in situ gelling system for sustained ophthalmic delivery of ketorolac and simultaneously determine the rheology behaviour, characterisation of gel.

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AIM

It is used to provide relief from various sorts of pain, such as sprains, strains and other injuries. It is also helpful in the treatment of different types of arthritis and gout. Along with that, it can be used to reduce pain and inflammation which follows after a surgery.

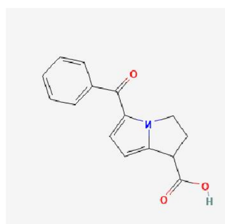
OBJECTIVE

Ketorol Gel is used for the short-term treatment of moderate to severe pain. It effectively alleviates pain, inflammation, and fever. It should not be used for mild or long-term painful conditions.
Ketorolac is used to relieve moderately severe pain, usually pain that occurs after an operation or other painful procedure. It belongs to the group of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs).

Material and Method

1. Ketorolac
2. Carbopol 940
3. HPMC
4. Benzalkonium chloride
5. Disodium hydrogen phosphate
6. Glycerin
7.Purified water

Ketorolac



Chemical constituent :
Ketorolac, sold under brand names like Toradol and Acular, is a nonsteroidal anti-inflammatory drug (NSAID) used to treat moderate to severe pain. It's typically used for short-term relief, and shouldn't be taken for more than five days.
Ketorolac is effective for pain after surgery or other procedures, and can also help with headaches, dental pain, menstrual pain, and pain from conditions like arthritis and gout.
Benefits:
Ketorolac is used to relieve moderately severe pain, usually pain that occurs after an operation or other painful procedure.
It belongs to the group of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). Ketorolac is not a narcotic and is not habit-forming.
Uses:
To lessen stomach upset, ketorolac tablets should be taken with food (a meal or a snack) or with an antacid.
Take this medicine with a full glass of water. Also, do not lie down for about 15 to 30 minutes after taking it. This helps to prevent irritation that may lead to trouble in swallowing.

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Carbopol

Chemical constituent :

Carbopol is a high molecular weight, cross-linked polyacrylic acid polymer. It's a type of carbomer, and its main chemical constituent is acrylic acid. These polymers are cross-linked with either ally sucrose or ally pentaerythritol.

Benefits :

Carbopol offers several benefits as a polymer, including thickening, suspending, and stabilizing formulations. It's particularly useful in cosmetic products, pharmaceuticals, and household cleaners, providing enhanced texture, stability, and overall performance.

Carbopol can also be used in topical drug delivery systems to improve mucoadhesion and drug permeation.

Uses :

Carbopol is a versatile polymer used as a thickener, stabilizer, and suspending agent in various industries.

It's commonly found in personal care products like gels, lotions, and creams, but also has applications in pharmaceuticals, home care products, and even some specialized applications like experimental tectonics.

Hydroxypropyl methylcellulose (HPMC)

Chemical constituent :

Hydroxypropyl methylcellulose (HPMC), also known as hypromellose, is a semi-synthetic polymer derived from cellulose.

Its chemical constituents include methoxyl and hydroxypropyl groups, which are attached to the cellulose backbone via ether bonds.

The specific percentages of these groups and the molecular weight determine the properties of the HPMC.

Benefits :

HPMC (Hydroxypropyl Methylcellulose) offers numerous benefits across various industries, including improved water retention, enhanced workability, thermal stability, and compatibility with other ingredients. It's also a biodegradable and non-toxic option, making it a "green" choice for many applications.

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Uses :

It is extensively used in the food industry as a stabilizer, as an emulsifier, as a protective colloid, and as a thickener. HPMC is used as a raw material for coatings with moderate strength, moderate moisture and oxygen barrier properties, elasticity, transparency, and resistance to oil and fat.

Benzalkonium chloride (BKC)

Chemical constituent :

Benzalkonium chloride (BKC) is a mixture of alkyl benzyl dimethyl ammonium chlorides, where the alkyl group has various even-numbered chain lengths. Specifically, it's composed of 24 structurally similar quaternary ammonium compounds (QACs). The core structure includes a benzyl group, a quaternary ammonium center, an alkyl chain, and a chloride ion. The alkyl chain typically ranges from C8 to C18.

Benefits :

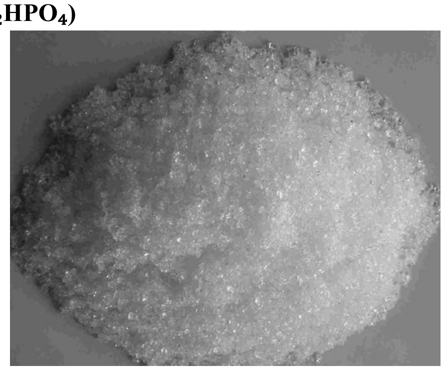
Benzalkonium chloride offers several benefits as a broad-spectrum antimicrobial agent. It effectively kills a wide range of bacteria, fungi, and viruses, making it useful in various applications.

Uses :

It is used prior to surgical procedures or for minor wound care to reduce risks of infection. It may be used for cold sore care.

antimicrobial agent, disinfectant, and preservative in various industries and applications. It's effective against bacteria, viruses, fungi, protozoa, and algae, making it useful in medical settings, personal care, and other areas.

Disodium hydrogen phosphate (Na_2HPO_4)



Chemical constituent :

Disodium hydrogen phosphate (Na_2HPO_4) is a versatile compound with applications in various industries, including food, water treatment, laboratory, and medical fields. It's commonly used as a buffering agent, pH adjuster, emulsifier, and nutrient source. In food, it helps control acidity, prevents coagulation in processed foods, and acts as a thickening or leavening agent. In water treatment, it functions as a water softener and pH regulator. Additionally, it's used in pharmaceuticals as a buffer, electrolyte replenisher, and laxative.

Benefits :

Disodium hydrogen phosphate (Na_2HPO_4), also known as disodium phosphate, offers several benefits across various industries. It acts as a buffering agent, emulsifier, stabilizer, and pH regulator in food, pharmaceuticals, and water treatment. In food, it helps control pH, acts as a sequestrant, and can be used as a thickening agent or leavening agent. In pharmaceuticals, it can be used as a source of phosphorus, in buffering solutions, and as a laxative. It also has applications in water treatment, where it can help soften water and prevent scale formation.

Uses :

It is a antiseptic and disinfectant.

It is used for prior to surgical procedure or for minor wound care to reduce risks of infection.

Glycerol

Chemical constituent :

Glycerol, also known as glycerin, is a clear, odorless, viscous, and colorless liquid with a sweet taste. It's a non-toxic, non-hazardous, and biodegradable compound found in all natural fats and oils. Glycerol has a variety of uses in the food, pharmaceutical, and personal care industries. Chemical properties: Glycerol is hygroscopic, meaning it absorbs moisture from the air.

Benefits :

Glycerin has a variety of uses in skincare, medicine, and food products. As a sugar alcohol, glycerin can sweeten foods, drinks, supplements, and medications. It can also help thicken and preserve some foods and cough syrups. Because glycerin is a humectant (a substance that attracts water), it is added to skincare, soap, eye drops, and cosmetics to help retain moisture. Glycerin can help lotion moisturize your skin, or eyedrops add moisture and lubrication to dry eyes. Glycerin's emollient (softening) properties also help create a layer on top of the skin to trap moisture and soften the skin.

Uses :

Glycerin can offer hydrating and moisturizing benefits to the skin and is often added to skincare products. Glycerin can also help prevent dry eyes and improve digestion, mainly due to its ability to help tissues retain water.

Ingredients :

Sr. NO.	Ingredient	Quantity
1	Ketorolac	7gm
2	Carbopol	4gm
3	HPMC	4gm

4	Benzalkonium chloride	1ml
5	Disodium hydrogen phosphate	10gm
6	Glycerol	8ml
7	Purified water	6ml

Method :

Differential scanning characterization calorimetry (DSC) Thermal characterization of pure drug and physical mixture was performed with Calorimeter. Samples were weighed (2.00 ± 0.5mg) and placed in sealed aluminium pans.

The equipment was calibrated with indium. The samples were scanned at 200C / min from 250C to 3000C.

Selection of vehicle:

The solubility of ketorolac was evaluated in various buffers, e.g., acetate buffer I.P. (pH 4.6, 4.8, 5.0, 5.5, and 6.0), citrophosphate buffer B.P. (pH 5.0. 6.0. 6.2 and 7.0) and phosphate buffer USP (pH 5.5, 6.0, 6.5, and 7.2) to select a suitable vehicle [7].

Solutions of ketorolac (0.5%, w/v) in the buffers in which it was soluble were prepared and tested for stability to light, temperature, and autoclaving.

Solubility of ketorolac was evaluated using a U.V. spectrophotometer at 321 nm [8]. Preparation of In-situ gelling system:

Aqueous solutions of varying concentrations of Carbopols 940 (CP) and HPMC of different grades (formulation codes K 1, K 2, K 3 ... K 28) were prepared and evaluated for gelling capacity and viscosity in order to identify the compositions suitable for use as in situ gelling systems (Table 1).

The gelling capacity was determined by placing 1 drop of the formulation in a vial containing 2ml of artificial tear fluid freshly prepared and equilibrated at 370C and visually assessing gel formation and noting the time for gelation and the time taken for the gel formed to dissolve.

The composition of artificial tear fluid used was NaCl 0.670 g, sodium bicarbonate 0.200 g, calcium chloride -2 H2O 0.008 g, purified water q.s. 100.0 g[9].

The viscosity at was measured using a Brookfield viscometer (DV- ULTRA model) in a small volume adapter used for purposes of comparative evaluation.

The detailed procedure for preparing the in situ gel-forming system of ketorolac is outlined below Table 2.

Buffer salts were dissolved in 75 ml of purified water, HPMC K15M, K4M was added and allowed to hydrate. Carbopols940 was sprinkled over this solution and allowed to hydrate overnight.

The solution was stirred with an overhead stirrer, Tween 80 was added while stirring. Ketorolac was dissolved in purified water, benzalkonium chloride(BKC) was then added and the solution was filtered through 0.2-µm cellulose acetate membrane filter.

The drug solution was added to the Carbopol - HPMC solution under constant stirring until a uniform solution was obtained. Purified water was then added to make up the volume to 100 ml.

The developed formulations were filled in 5-ml capacity amber glass vials, closed with gray butyl rubber closures and sealed with aluminium caps.

The formulations, in their final pack were subjected to terminal sterilization by autoclaving at 1210C and 15 psi for 20 min.

Evaluation :

Physical appearance:

The visual appearance of the film was conducted. The colour of the film as well as the texture was observed. Drug distribution within the film was also visualized.

Thickness:

The films were evaluated for the thickness of each film using a micrometre of sensitivity of 0.001 mm. The average of 10 readings was taken. The mean thickness of standard deviation was calculated.

Stability study:

A short-term stability study of the optimized formulation is carried out as per International Conference on Harmonization guideline at temperature 40°C and relative humidity (RH) at 75 % for in stability chamber. Physical appearance Surface pH The prepared formulation F1-F5 batch ocular inserts were translucent, colourless, smooth in texture, uniform in appearance, and show no visible crack or imperfection.

Surface pH:

It is a very important parameter to be evaluated to check the isotonic of ocular insert with tear fluid. The surface of formulations F1-F5 was measured using digital pH meter. The surface pH values were shown in. The surface pH of formulations F1-F5 ocular inserts were found to be in the range of 5.5 ± 0.10 to 7.0 ± 0.115, which were well within the pH of lachrymal secretion indicating no irritation.

II. CONCLUSION

Various batches of ketorolac tromethamine bio adhesive in-situ gelling ocular inserts were prepared using solvent casting method and evaluated. F4 was found to be better as it was smooth, translucent, and flexible. Physicochemical parameters like weight and thickness uniformity, folding endurance, tensile strength and percentage elongation was satisfactory and surface pH, swelling index, percentage flatness, percentage moisture absorption, percentage moisture loss, bio adhesive strength, force of adhesion showed optimum results and also better drug content uniformity in comparison with other formulations.

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