Research Article

Formulation and evaluation of Ketorolac hydrogel for effective management of dermatitis

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Abstract

Background: Topical delivery of drugs can be achieved by incorporating drug into the gel matrix for effective delivery of drugs, thus avoiding first pass metabolism and for increased local action in pain management and skin diseases. Transdermal delivery of Ketorolac has drawn much attention for the advantages of avoiding first-pass metabolism, reduced gastrointestinal side effects as bleeding, peptic ulcer, perforation, but the successful translation of reported transdermal drug delivery systems (TDDSs) is still limited by poor skin permeability and uncontrollable drug release. **Objective:** Present study was aimed to prepare hydrogel of ketorolac and overcome all the problems cause by oral administration of that drug. **Material and methods**: Herein, we designed hydrogel of ketorolac which are more stable in accelerated stability conditions at 40ºC ± 2ºC/ 75% RH ± 5%. **Results and conclusion:** Drug release profile study revealed that hydrogel preparation could be used for local or site-specific delivery of drug. Ketorolac Hydrogel could be better formulated and used commercially with various advantages over other dosage form. It could be used topically for site-specific drug delivery for any conditions of pruritus, insect bite induced urticarial, allergic conditions. Ketorolac hydrogel preparation was found to be acceptable, elegant and more patient compliance than other dosage form of this drug.

***Keywords*:** Ketorolac, hydrogel, drug delivery, carbopol, dermatitis

Introduction

In transdermal drug delivery (TDDS) system drug administered through skin as a site for nonstop penetration of drug into the systematic circulation. TDDS avoided first-pass metabolism and avoided the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time (Schoellhammer et al., 2014). Because of these advantage side effects of drug are lower. Now a days TDDS is a promising route of drug administration, especially for topical tissue damage and disease related to skin like acne, psoriasis (Prausnitz and Langer, 2008; Juluri and Murthy, 2014; Sintova and Hofmann, 2016).

In recent years, various TDDSs drugs are available such as hormones, analgesics, ant-inflammatory agents, and some transdermal formulations have been commercially available (Anselmo and Mitragotri, 2014; Zhiguo et al., 2021; Mastrangelo et al., 2021).

For the development of potent hydrogel various formulation aspects, various excipients, evaluation tests, challenges and drugs are explored in the field of topical drug delivery (Jianyu and Mooney, 2016).

TDDS basically includes two types of products: (a) External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area. (b) Internal topicals that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity.

Hydrogels are routinely used for biomedical and pharmaceutical applications, such as controlled drug release, artificial tendons, wound-healing bio-adhesives, artificial kidney membranes, artificial skin and contact lenses (Figure 1).

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) and is commercially available as an oral tablet, injectable, nasal spray and as an ophthalmic solution. It has been widely used as analgesic and in the treatment of postoperative pain, rheumatoid arthritis, osteoarthritis,

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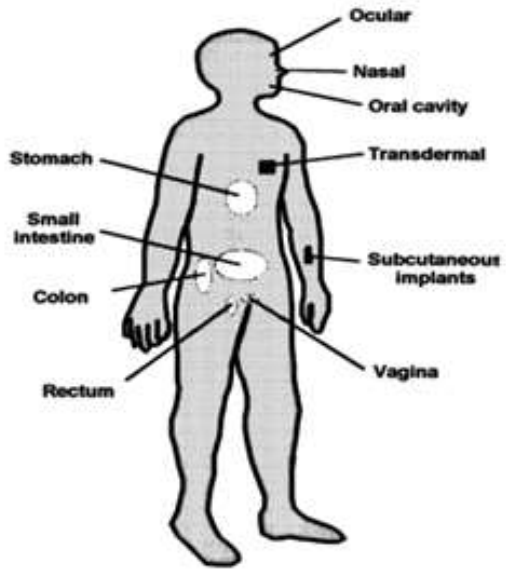

Figure 1. Application of hydrogel at various body sites

menstrual disorders, headaches, spinal and soft tissue pain, and ankylosing spondylitis. Impressively, ketorolac has a similar efficacy to standard doses of morphine and meperidine making it a useful opioid sparing agent. Since oral administration of ketorolac associate with three major problems such as poor bioavailability; second is gastrointestinal side effects such as bleeding, peptic ulcer, perforation; third it has short half-life (4hr) so require frequent administration. In this research work we are planning to make hydrogel of ketorolac and overcome all the problems cause by oral administration of drug.

Material and Methods

Evaluation of Formulated Hydrogel

Formulation of hydrogel HG3 was evaluated for following parameters simultaneously and shown in Table 1.

Determination of Homogeneity

Homogeneity was tested by visually and by elegance effect. The + sign indicates the good homogeneity i.e. hydrogel is free from lumps; while – sign indicates the non-homogeneity of hydrogel (Kaur et al., 2010; Kumar and Kaur, 2013) (Table 1).

Table 1. Evaluation of formulated gel

Parameters	Formulation HG3
Viscosity (cps)	18274±675.62
Spreadability (gm.cm/sec)	20.33±0.41
pH	6.79±0.1
Homogeneity	+++
Grittiness	Not found
Extrudability	+++
Drug Content	98.65%±0.54

Grittiness

Hydrogel was evaluated microscopically for the presence of particles. Our hydrogel contains no particular matter and free from grittiness as desired for any topical preparation (Table 1).

Determination of pH

The pH of hydrogels was determined using a digital pH meter by dipping the glass electrode

completely into the gel system. pH of hydrogel was found to be 6.79 (Kumar and Verma, 2010) (Table 1).

Viscosity Determination

Brookfield Viscometer was used to measure the viscosity of formulated hydrogel. We used

spindle number-06; viscometer and set at 10 RPM (Table 1).

Spreadibility Determination

Spreadibility of hydrogel was determined by using wooden block. Spreadibility was measured on the basis of slip and drag characteristics of gels. An excess amount of gel (about 1g) was placed on the ground slide and covered with another glass slide. Gel was sandwiched between two slides having the fixed dimension, both slides attached with the hook. 1 kg weighed was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 60 gm. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted[12-13]. A shorter interval indicates better spreadibility. Spreadibility was calculated using the following formula:

$$S = M \times L / T$$

Where, S = Spreadibility, M = Weight in the pan (tied to the upper slide), L = Length moved by the glass slide and T = Time (in sec.) taken to separate the slide completely each other.

Drug Content

1 gm of hydrogel was taken in volumetric flask and dissolved it in 100 ml of phosphate buffer (6.8 pH). Shake the flasks and mix the content properly. This mixture was filtered, diluted and then measured the absorbance at 250 nm and the determine the drug content in hydrogel by making calibration curve.

Drug Diffusion Studies

The drug diffusion studies of formulated hydrogel were carried out in Franz diffusion cell using an egg membrane.

Phosphate buffer 6.8 was used as bathing solution in the receptor compartment. The membrane was mounted between the donor and receiver compartments of the diffusion cell. The donor cell was filled with 1 g of gel. The receiver medium is continuously agitated with a magnetic stirrer at a temperature of 370˚C ± 20˚C maintained thermostatically. Samples 1 ml in each case was withdrawn at regular intervals and fresh receptor fluid was added to maintain a constant volume of receptor fluid. The samples withdrawn from the receptor compartment were diluted and then analyzed spectrophotometrically at 360 nm and the drug content was determined from the calibration curve.

Determination of Extrudability

A good hydrogel extrudes optimally from the gel with slight pressure applied. The extrudability

of formulations from collapsible tubes was determined using manual operation. The collapsible tubes were filled with 10g gels were held between two clamps. The tubes were compressed by 500 g weight and then caps were opened[14]. The amount of gel extruded were collected and weighed. The % of gel extruded was calculated; and grades were allotted (+++ Excellent, ++ Good, + Poor) (Table 1).

Determination of Stability Study

The stability study was performed as per WHO-ICH guidelines. Formulations were subjected for accelerated stability studies in packed conditions in stability chamber at 40ºC ± 2ºC/ 75% RH± 5% for a period of 60 days and studied for appearance, pH, viscosity and drug content.

Analysis of Drug Release Mechanism of Optimized Hydrogel

To analyse the *in-vitro* release data various kinetic models were used to describe the release kinetics. The release mechanism of drug sample from the prepared topical hydrogel system of the optimized formulation (HG3) was based on the results of diffusion study that is % cumulative drug release which was examined in accordance to the kinetic models such as zero order, first order, Higuchi equation, Hixson – Crowell equation and Korsmeyer – Peppas model (Mithal and Saha, 2002; Mortazavi and Aboofazeli, 2003).

Zero Order Model: Describes the system where the drug release rate is independent of its concentration (Figure 2).

Q=K0t

Where, Q = Amount of drug release at time t; K0 = Release rate (constant). The graph was plotted between % cumulative drug release and time.

First Order Model

The first order model describes the release from system where release rate is concentration dependent. Most conventional

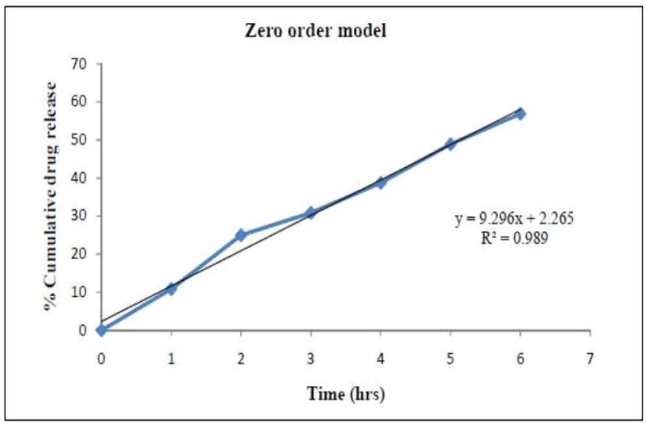

Figure 2. Zero Order Model for Hydrogel HG3

dosage forms exhibit this dissolution mechanism. Some modified release preparations, particularly prolonged release formulations, adhere to this type of dissolution pattern (Figure 3).

Log Q=Log Q0-Kt/2.303

Where, Q0 is the initial concentration of drug and K is the first constant. The graph was plotted between log cumulative of % drug remaining and time.

Higuchi Model

Higuchi described the release of drug from insoluble matrix as a square root of time. A large number of modified release dosage forms contain some sort of matrix system. In such instances, the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies (Figure 4).

$Q = Kt^{1/2}$

Where, Q is the percent of drug release at time t and K is diffusion rate constant. The graph was plotted between % cumulative drug release and square root of time.

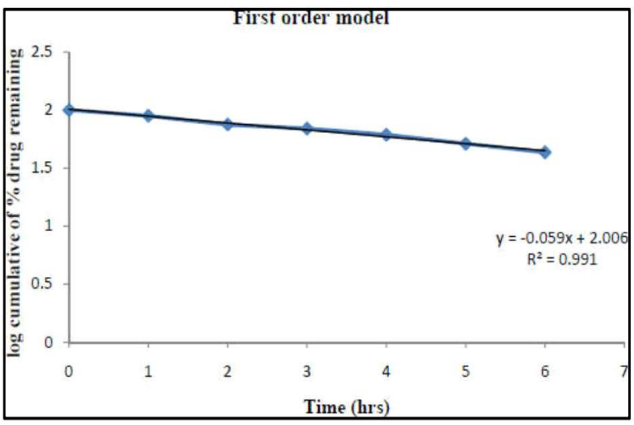

Figure 3. First order model for Hydrogel HG3

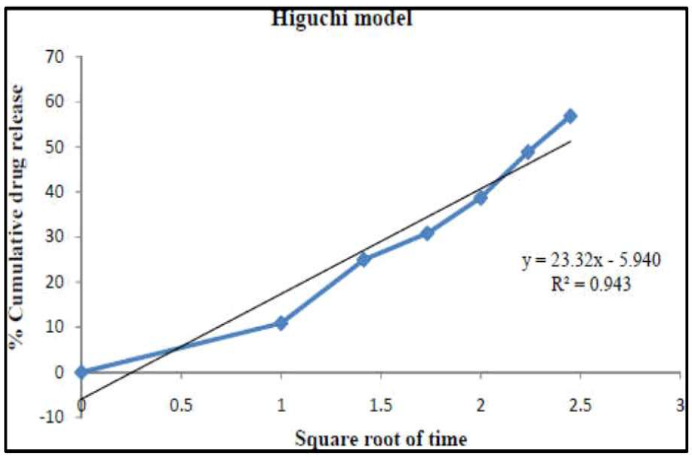

Figure 4. Higuchi model for Hydrogel HG3

Results and discussion

Preformulation Studies

Preformulation studies is the first step in the rational development of formulation of a drug substance. Physical characteristic of ketorolac was found to be as per specification like ketorolac shows white to off-white crystalline powder, tasteless and with characteristic odour. The drug was found to be freely soluble in ethanol and soluble in water, methanol, and chloroform and DMSO. The partition coefficient of drug was found to be 0.95 that indicated that the drug was portioning maximum in aqueous phase and hence it was found that drug was hydrophilic in nature. Partition coefficient was determined by using shake flask method. Quantitative estimation of drug was carried out by calibration curve in different solvents.

The melting point, IR spectroscopy, and UV spectroscopy were performed for the identification of drug. The melting point of drug was found in the range between 104-107 °C which meets as per specification. The IR spectra showed following peak: 3465 (O-H), 1474 (C-C), 1277 (C-H), 1628.09 (C=O) and 1136 (S-H) Bending. Ultraviolet spectroscopy absorption of drug was done at 200-400 nm. Drug absorption maximum λmax was found to be at 360 nm. Quantitative estimation of drug sample was done by different calibration curves which were prepared in methanol, phosphate buffer solution pH 6.8 in concentration range of 5-50 µg/ml and the R2 value was found to be 0.9979 and 0.9991 respectively which indicated the linearity of the graph.

DSC thermogram of drug showed endothermic and exothermic peaks. Drug and polymer displayed their characteristic individual melting trends without any appreciable deviation. From this it is observed that there is no interaction between drug and polymer. There is no incompatibility between drug and selected excipients. Hence, the excipients selected can be used with drug as they are compatible with each other. Solubility analysis was done in different projected solvents. On the basis of pre-formulation studies, it was concluded that the drug sample was found to be pure and authentic and there was no variation found in the drug sample and the drug was found to be suitable for the further formulation and optimization study.

Optimization of Hydrogel Formulation

Before making formulation of hydrogel, the hydrogel base without drug was prepared. The primary hydrogel base without drug was prepared with all the ranges of carbopol-934 polymer in which the physical appearance was visually examined like colour, clarity, homogeneity, and gelling (rigidity). Hydrogel was found to be clear, transparent, and homogeneous. After incorporation of drug in hydrogel formulations some changes in clarity, transparency and homogeneity of the formulations were observed. After all these studies the formulations were preceded for further studies.

The formulations of hydrogel were done based on change in polymer concentration in the ranges 0.5%, 0.7%, 1%, 1.2%, 1.5% and 1.8%. All these formulations were subjected to optimization based on appearance, gelling, viscosity, and drug release. The gelling of the hydrogel formulation HG1 was found to be very poor, in case of HG2 formulation the gelling produced was only good but not to be acceptable and both the formulations were translucent visually while the hydrogel formulations HG3, HG4, HG5, HG6 were good in their gelling nature and were clear. The viscosity range of all the hydrogel formulations shows a gradual increase in the viscosity as the concentration of polymer was increased. Viscosity of formulations was found to be 14230,17262,18143, 18327, 19523, 21636 all in cps unit. Based on viscosity, HG3, HG4, HG5 were found to be acceptable. The drug release study of the hydrogel formulations was compared based on % cumulative drug release up to 6 hrs which showed variations in drug release with the change in carbopol concentration. The drug release was found to be 65.48% with 0.5%carbopol, 61.89% with 0.7% carbopol, 61.19% with 1% carbopol, 58.59% with 1.2% carbopol,54.52% with 52.67% with 1.5% carbopol and 52.67% with 1.8% carbopol concentration. Based on combined data of appearance, gelling, elegancy, viscosity and% drug release HG3 formulation was selected as the optimized formulation and final formulation was prepared with respective concentrations for further evaluations.

Evaluation of Hydrogel

Various observations and calculations were done for optimized formulations on different evaluation parameters such as viscosity, spreadibility, pH, homogeneity, grittiness, and feel on application, extrudability, drug content, and

drug diffusion. Homogeneity was observed with the help of visual basis which showed good homogeneity in gel formulation HG3. The gel was found to be free from any lumps or any aggregates and was elegant.

Formulation was evaluated microscopically and by feel on application. For the presence of particles if any, no appreciable particulate matter was seen under light microscope. No foreign particulate particles were observed and were smoothly applicable. Hence gel preparation the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

pH was determined by Digital pH meter. Hydrogel formulation (HG3) showed pH range of 6.79. These pH range was within the acceptable limit for topical formulation therefore the gel formulation was acceptable for pH values. The viscosity range of the gel formulation was determined; the viscosity of hydrogel formulation (HG3) was 18274 cps. Viscosity value was within acceptable range. The spreadibility was measured on the basis of slip and drag approach. The spreadibility of hydrogel formulation (HG3) was 20.33 gm.cm/sec. More the value of spreadibility more easily and quickly the gel can be applied. The drug content of the formulation that is hydrogel (HG3) was determined as 98.65%.

The drug content was within the limits. Drug diffusion studies were done by using an egg membrane for a period of 6 hrs which was calculated as cumulative percent drug release that showed 56.860% for hydrogel (HG3). The extrudability is a useful empirical test to measure the force required to extrude the material from a tube. Since the packing of gels have gained a considerable importance in delivery of desired quantity of gel from jar or extrusion of gel from collapsible tube, therefore measurement of extrudability becomes an important criterion for gels. More the quantity extruded better is the extrudability. The % gel extruded was calculated and the preparation HG3 showed acceptability extrudability. Stability studies was done to check the stability of dosage form for its drug potency, any changes at the physical and chemical basis. By following WHO-ICH guidelines both gel formulations were kept in accelerated stability conditions at 40ºC ± 2ºC/ 75% RH± 5% for a period of 60 days and studied for appearance, pH, viscosity, and drug content. In case of hydrogel formulations (HG3) the viscosity determined was 18542 cps, pH was 6.78, appearance was acceptable and good and the drug content was 97.89%. This result showed that the hydrogel formulation was stable at accelerated stability conditions as there were very slight changes in the observations. On the basis of evaluation parameters, in case of colour and appearance the hydrogel formulation was transparent with glossy appearance. The hydrogel was non-greasy. The viscosity of hydrogel was 18274 cps these ranges were within acceptable limit. Spreadibility was 20.33 gm.cm/sec for hydrogel and. These studies showed that hydrogel is acceptable and patient compliance, more elegant. The mean cumulative amount of drug diffused per unit surface area of the membrane was plotted versus time. The slope of the linear portion of the plot was calculated as flux Jss (µg/cm2/hr) which was 9.818 µg/cm2/hr in case of hydrogel by following WHO-ICH guidelines gel formulation was kept in accelerated stability conditions at 40ºC ± 2ºC/ 75% RH±5% for a period of 60 days and studied for appearance, pH, viscosity and drug content. In case of hydrogel formulations (HG3) the viscosity determined was 18542cps, pH was 6.78, appearance was acceptable and good and the drug content was 97.89%. This result showed that the hydrogel formulation was stable at accelerated stability conditions as there were very slight changes in the observations. At the end the release kinetics of the optimized hydrogel (HG3) was analysed on the basis of different models suggested for release kinetics such as zero-order model. First order model, higuchi model, Hixson-crowell model and korsmeyer-peppas model. The values were put into the equations and various graphs were plotted that resulted into the linear equations and regression values which were y=9.26x + 2.265; R2 = 0.989 for zero order model; y=-0.059x + 2.006; R2= 0.991 for first order model; y=23.32x -5.940; R2 = 0.943 for Higuchi model; y=- 0.185x + 4.641; R2 = 0.994 for Hixson-Crowell model; and y=0.891x + 1.068; R2 = 0.984 for Korsmeyer-peppas model. The regression value suggested that the release kinetic of drug follows Hixson-Crowell model for which R2 = 0.994, as Hixson – Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles. Some specialized dosage forms contain many drug particles of the same size and shape of their agglomerates that dissolve evenly. In such instances the cube – root law can express the release process. Here the release pattern of the drug in hydrogel is dictated by the actual dissolution of drug molecules.

Conclusion

On the basis of all these studies it can be concluded that topical hydrogel formulation of PMH can be successfully prepared with the help of polymer carbopol- 934. With the studies it could be concluded that hydrogel is more stable in accelerated stability conditions at 40ºC ± 2ºC/ 75% RH ± 5%. From the drug release profile, it is also concluded that hydrogel preparation could be used for local or site-specific delivery of drug. Thus, hydrogel of PMH could be better formulated and used commercially with various advantages over other dosage form. It could be used topically for site-specific drug delivery for any conditions of pruritus, insect bite induced urticarial or allergic conditions. PMH hydrogel

preparation was found to be acceptable, elegant and more patient compliance than other dosage form of this drug.

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