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DEVELOPMENT AND EVALUATION OF TRANSDERMAL GEL OF KETOROLAC TROMETHAMINE

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ABSTRACT

Transdermal drug delivery systems are defined as self-contained dosage forms which when applied to the skin, deliver the drug through the skin at controlled rate to the systemic circulation. It maintains the blood concentration of the drug within the therapeutic system window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. The objective of the present work was to formulate transdermal gel of Ketorolac tromethamine. It is potent non-steroidal anti-inflammatory drug acting by inhibiting the synthesis of prostaglandins and is used in the management of moderate to severe pain. Due to its short biological half life (4-6 h), frequent dosing is required. To avoid invasive drug therapy such as injections and to eliminate frequent dosing regimen with oral administration, a transdermal drug delivery system has been studied as an alternative dosage form.

Keywords: *Ketorolac tromethamine, transdermal gel, in-vitro release, stability studies.*

INTRODUCTION

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to first pass hepatic metabolism and the tendency to produce rapid blood level spikes (both high and low) leading to a need for high and/or frequent dosing which can be both cost prohibitive and inconvenient [1].

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery systems are also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e. peptides, proteins) to their site of action without incurring significant immunogenecity or biological inactivation [2].

Apart from these advantages the pharmaceutical companies recognize the possibility of repattening successful drugs by applying the concepts and techniques of controlled drug delivery system coupled with the increased expense in bringing new drug moiety to the market. One of the methods most often utilized has been transdermal delivery-meaning transport of therapeutic substances through the skin for systemic effect. Closely related to it is percutaneous delivery, which is the transport into target tissues with an attempt to avoid systemic effects [3].

The term 'gel' was introduced in the later 1800 to name some semisolid material according to pharmacological, rather than molecular criteria [4].

Skin is one of the most readily accessible organs on human body for topical administration and is the main route of topical drug delivery system. Transdermal application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compared to creams and ointments · A gel is colloid that is typically 99% weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from small amount of a gelating substances present [5].

Ketorolac tromethamine is a potent non-steroidal anti-inflammatory drug acting by inhibiting the synthesis of prostaglandins and is used in the management of moderate to severe pain [6]. Oral bioavailability of the drug is reported to be 90 %, with a very low first pass metabolism. Due to its short biological half life (4-6 h), frequent dosing is required [7].

Ketorolac tromethamine was selected as a candidate for the drug delivery because

a. It has a low molecular weight 255.27 g/mol
b. It has melting point i.e. 165ºC that is suitable to develop a transdermal drug delivery system
c. It has short half life (4-6 hrs).
d. It has log P (lipophilic character) value of 2.72.
e. After oral administration it has many adverse effects, such as upper abdominal pain and gastrointestinal ulceration.
f. The frequent dosing, which results in unacceptable patient compliance.

To avoid invasive drug therapy such as injections and to eliminate frequent dosing regimen with oral administration, a transdermal drug delivery system has been studied as an alternative dosage form.

MATERIALS AND METHODS

Ketorolac tromethamine was received as gift sample from Torrent research, Gandhinagar, Gujrat, HPMC K100 (Cipla, Mumbai), Methyl cellulose (Asia private ltd.Goa), Triethanolamine, Propylene glycol, Glycerine (Central Drug House, Delhi). All other chemicals were of analytical grade.

Formulation development:

Different Ketorolac tromethamine transdermal gel formulations were prepared by adding different ingredients as shown in table 1 by means of a magnetic stirrer with continuous mixing until a homogenous gel was formed. The solution was then neutralized and made viscous by addition of triethanolamine. Final weight was made up to 100 g with distilled water. The gel was set aside for few minutes until the bubbles disappeared. All the samples were allowed to equilibrate for at least 24 hours at room temperature prior to performing rheological measurements. The gels were kept in plastic well-closed containers and stored at room temperature until the time of analysis.

Evaluation of formulations:

a) Physical appearance and homogeneity: [8]

The physical appearance and homogeneity of the prepared Ketorolac tromethamine transdermal gels were tested by visual observations after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

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b. Drug content: [9]

A specific quantity (100mg) of Ketorolac tromethamine transdermal gel of different formulations was taken and dissolved in 100ml of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 322 nm using phosphate buffer (pH 7.4) as blank.

c) Clarity: [10]

The clarity of various formulations was determined by visual inspection under black and white background and it was graded as follows; turbid: +, clear: ++, very clear (glassy): +++ .

d) Measurement of pH: [11]

The pH of various gel formulations was determined by using digital pH meter. One gram of Ketorolac tromethamine transdermal gel formulation was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated.

e) Viscosity study: [12]

The viscosity of the Ketorolac tromethamine transdermal gel formulation was determined using a Ostwald viscometer. The gel formulations were placed in the sample holder of the viscometer and allowed to settle for 5 min and the viscosity measured at a rotating speed of 50 rpm at room temperature (25 - 27^{o}C).

f) Extrudability: [13]

The extrusion of the gel from the tube is an important during its application and in patient acceptance. This study is useful in explaining whether the gel is removing from the collapsible tube during application in proper manner or not. Gels with high consistency may not extrude from the tube whereas, low viscous gels may flow quickly, and hence suitable consistency is required in order to extrude the gel from the tube. The formulations were filled into collapsible aluminum tubes. The tubes were pressed to extrude the 0.5 cm ribbon of the gel in 10 second and the extrudability of formulations was checked.

More quantity extruded better was extrudability. The extrudability was then calculated by using the following formula:

$$\text{Extrudability} = \frac{\text{Applied weight to extrude gel from tube (in gr)}}{\text{Area (in cm}^2\text{)}}$$

g) In-vitro drug release: [14]

The in vitro drug release from different Ketorolac tromethamine transdermal gel formulations was studied across cellophane membranes using modified Keshery Chien diffusion cell. The receptor compartment was filled with the mixture of phosphate buffer of pH 7.4 and polyethylene glycol 400 and maintained at 37±0.5^{o}C with constant magnetic stirring. Accurately weighed quantity of gel was placed on the donor compartment. The samples (1ml) was collected from the receptor compartment at predetermined time interval and replaced by equal volume of fresh receptor solution to maintain constant volume allowing sink condition throughout the experiment. The amounts of drug in the sample were assayed spectrometrically at 322 nm against appropriate blank.

h. Stability study: [14]

Stability studies carried out by storing the prepared transdermal gel of batch TG12 at various temperature conditions like refrigeration on (2-8^{0}C) room temperature (25±0.5^{0}C) and elevated temperature (45±0.5^{0}C) for a period of 12 weeks. Drug content and variation in the average vesicle diameter were periodically monitored. ICH (International Conference on Harmonisation) guidelines were followed.

RESULTS AND DISCUSSION

Four transdermal gel formulations of Ketorolac tromethamine was prepared by using different polymers i.e. HPMC, chitosan, PVP K30, and PEG 400 in different ratio.

Stability of the transdermal gel is crucial both during storage and *in-vivo* application. The amount of drug retained within the vesicles under defined conditions ultimately governs the shelf life of the drug. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions.

Accelerated stability studies for 12 weeks revealed that the transdermal gel formulation were stable at up to 45^{0}C. The results showed that transdermal gel formulation was quite stable at refrigeration and room temperatures as not much leakage of drug was found at these temperatures. Therefore, the selected transdermal gel formulations can be stored at either refrigeration or room temperature. The pure drug shows sensitivity to light and moisture. The physical appearance and homogeneity of the prepared Ketorolac tromethamine transdermal gels were tested by visual observations after the gels have been set in the container. The drug content of the gel formulations shows content uniformity in all formulations. All transdermal gel formulations were found to be transparent and were free from presence of particles. There was good homogeneity in all formulations and no lumps were present. The pH of the gel formulations was in the range of 6.57 to 7.05, which lies in the normal pH range of the skin and would not produce any skin irritation. Viscosity of various formulated gels was found in the range of 2186.5 to 3462.8 centipoises. The extrudability of formulations was found to be satisfactory and good. The in-vitro permeation of Ketorolac tromethamine transdermal gels formulation was studied using locally fabricated Franz diffusion cell. The cumulative percent drug release after 10 hrs in between 51.4 to 84.114 %. Rapid drug leakage was observed during the initial phase. However, after that a slow release occurred. It was also observed that the drug release generally decreased as the polymer ratio increased. The release of the drug was retarded due to the hydrophobic and insoluble nature of the polymers used.

Table No. 1: Compositions of the Ketorolac Tromethamine transdermal gel formulations

S. No.	Ingredients	TG9	TG10	TG11	TG12
1	Drug (gms)	0.05	0.05	0.05	0.05
2	Chitosan	0.2	-	-	-
3	PVP K30	-	0.1	0.15	0.2
4	Methyl Paraben (gms)	0.75	0.75	0.75	0.75
5	Triethanolamine (ml)	0.3	0.3	0.3	0.3
6	Glycerine	10	10	10	10
7	Propylene glycol (gms)	20	20	20	20
8	Distilled water (q.s.) gms	100	100	100	100

Table No.2: Properties of Ketorolac tromethamine transdermal gel formulations

Formulation Code	Homogeneity	pH[a]	Viscosity [a] (Centipoise)	% Drug Content[a]	Extrudability
TG9	+	6.57±0.12	3190.5±0.08	98.26±0.37	+
TG10	+	7.05±0.14	2186.5±0.06	97.36±0.32	++
TG11	++	6.88±0.15	3451.7±0.07	97.22±0.26	++
TG12	+++	6.95±0.41	3462.8±0.04	99.72±0.41	++

a = Average ± SD of three determination has been reported

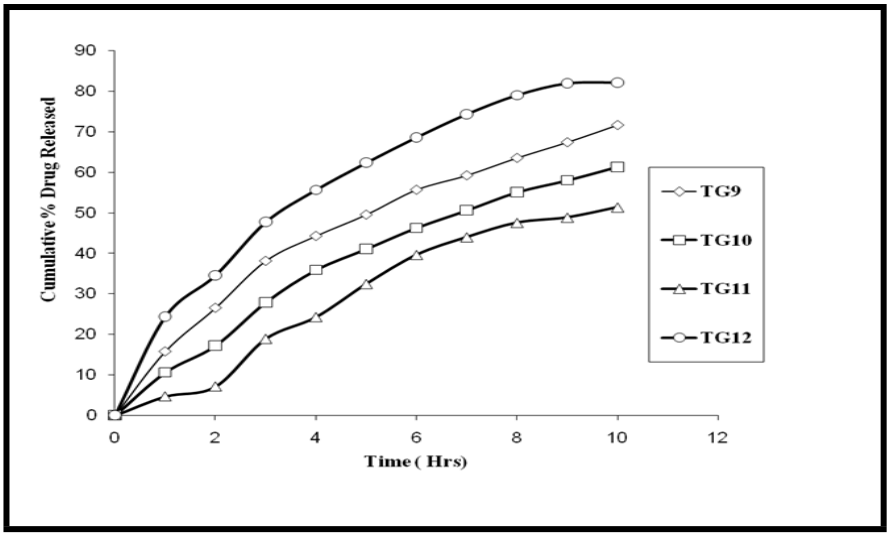

Fig. 1: Percentage of drug released from Ketorolac tromethamine transdermal gel of batch TG9 to TG12.

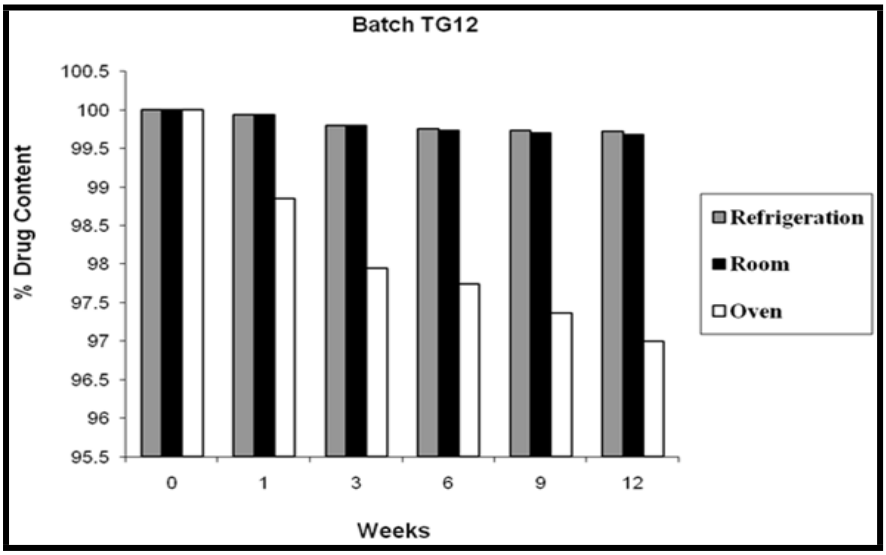

Fig. 2: Stability study of Ketorolac tromethamine transdermal gel of batch TG12 at different temperature

CONCLUSION

In all of the semisolid preparations, use of transdermal gels has expanded both in cosmetics and in pharmaceutical preparations. Transdermal application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compared to creams and ointments.

The present study has been a satisfactory attempt to formulate Ketorolac tromethamine transdermal gel formulations with a view of improving its oral bioavailability and giving a prolonged release of drug. Four Ketorolac tromethamine transdermal gel formulations were successfully developed by using different polymers i.e. HPMC, PVP K30, Chitosan, PEG. Accelerated stability studies for 12 weeks revealed that the transdermal gel formulations were stable at up to 45^0C. The stability study of the optimized formulation showed satisfactory characteristics without being drastically influenced.All transdermal gel formulations were found to be transparent and were free from presence of particles. On basis of drug content, particle size morphology, in-vitro release and stability studies, it can be concluded that formulation TG12 was an optimum formulation. However there is need in-vivo study to justify the development of transdermal gel of Ketorolac tromethamine.

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