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DEVELOPMENT AND EVALUATION OF TENOXICAM LOADED EMULGEL FOR ENHANCED TRANSDERMAL DELIVERY

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ABSTRACT

The present study is to increase the transport of tenoxicam through transdermal route, and also to present it as a possible replacement for the oral NSAID therapy. The present investigation was to develop a tenoxicam emulgel with reduced particle size in order to improve the bioavailability of the anti-inflammatory drug, Tenoxicam. Emulgel is helpful in enhancing spreadability, viscosity and extrusion, this novel drug delivery become popular. Moreover, they will become a solution for loading hydrophobic drugs in water soluble gel bases for the long term stability. Similarly in the study, topical emulgels of Tenoxicam were formulated and subjected to physicochemical studies i.e. rheological studies, spreading coefficient studies and in vitro release studies. In vitro release of the tests formulations were performed to determine drug release from emulgel rate and duration of drug release. From the in vitro studies, formulation F3 showed maximum release of 99.41% in 6 hrs.

Key words: Tenoxicam, Emulgel, Formulation, Evaluation.

INTRODUCTION:

Emulgel are also called as gellified emulsions. Emulsion in gel have emerged as one of the most interesting topical drug delivery system as it has dual release system i.e. emulsion and gel. Emulgel are emulsion, either oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent (Panwar et al., 2011). Most pharmaceutical drugs are lipophilic compounds, which are practically insoluble in water. So, to overcome this limitation, an emulsion based approach is being used so that hydrophobic drug can be easily administered to the skin. An emulsion may be defined as a dispersion of two or more mutually insoluble liquids, one in other. The

liquid are typically water and oil. A gel is apparently solid, jelly like material formed from a colloidal solution. Being wet, gels are mainly liquid, yet they behave like solid due to the addition of gelling agent. The presence of gelling agent in water phase coverts a classical emulsion into an Emulgel. Emulsion possesses a certain degree of elegance. Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, longer shelf-life, water soluble, bio-friendly, transparent and having pleasing appearance.

As the name suggest they are the combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsion are used as vehicle to deliver various drugs to the skin. They also have a high ability to penetrate the skin. The presence of gelling agent in water phase converts a classical emulsion into an emulgel. Emulgel for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water soluble, longer shelf life, bio friendly, transparent and pleasing appearance (Kumar et al., 2016).

Numbers of medicated products are applied to the skin or mucous membrane that either enhances or restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products (Shen et al., 2015). Many widely used topical agents like ointments, creams lotions have many disadvantages. They are sticky in nature causing uneasiness to the patient when applied, have lesser spreading coefficient so applied by rubbing and they also exhibit the problem of stability. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So, to overcome this limitation, an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels.

Tenoxicam is an analogue of a piroxicam and is used to relieve inflammation, swelling, stiffness and pain associated with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, backache etc. It is commercially available in several dosage forms such as tablets, suppositories and injectables with each dosage form having its own limitation pertaining to patient compliance.

Emulgel have emerged as one of the most interesting topical delivery system as it has dual release control system i.e. gel and emulsion. The

topical applications of the drug offers the potential advantages of delivering the drug directly to the site of action and delivering the drug for extended period of time at the effected site that mainly acts at the related regions.

Tenoxicam (TNX) is a non-steroidal anti-inflammatory drug (NSAID) used for the treatment of rheumatoid arthritis, osteoarthritis, spondylitis, backache and pain. However, prolonged oral use of this drug is associated with gastrointestinal adverse events like peptic ulceration, thus necessitating its development as topical formulation that could obviate the adverse effects and improve patient compliance. The present study was aimed at development of emulgel based formulations of Tenoxicam for topical delivery at the affected site.

MATERIAL AND METHODS

Formulation development of emulsion

The general method was employed for preparation of an emulsion was as follows: The oil phase was prepared by dissolving Span 20 in liquid paraffin in the different ration given in table 1 while the aqueous phase was prepared by dissolving Tween 20 in purified water (Vats et al., 2014). 1 gram of Tenoxicam was dissolved in 5 ml of ethanol, while 0.15 g of methylparaben and 0.05 g of propylparaben were dissolved in 5 gm of propylene glycol and both were mixed with aqueous phase. Both the oily and aqueous phases were separately heated to 70-80°C. Then, the oil phase was added to the aqueous phase with continuous stirring at 500 rpm until cooled to room temperature.

Preparation of carbopol gel

Fifty (50) grams of the carbopol gel was prepared by dispersing 1 gram of carbopol powder in 50 ml purified water with aid of moderate speed stirrer (50 rpm), and then the pH was adjusted to 6.5-6.8 using 0.5 N of sodium hydroxide (Vats et al., 2014).

Formulation of Tenoxicam emulgel

Six formulations of Tenoxicam were prepared by dispersing the obtained emulsions with the gel in 1:1 ratio with gentle stirring until get homogenous emulgel.

Table 1: Different formulations of Tenoxicam emulgel (% w/w)

Formulation (%w/w)	Tenoxicam	Carbomer 941	Liquid paraffin	Span 20	Tween 20	Propylene glycol	water
F1	1	0.5	5	2	5	5	100
F2	1	0.5	5	2	10	5	100
F3	1	1.0	10	4	5	5	100
F4	1	1.0	10	4	10	5	100
F5	1	1.5	5	2	5	5	100
F6	1	1.5	5	2	10	5	100

Evaluation of emulgel

Physical Characteristic

The Physical Characteristic was checked for emulgel formulations (colour, clogging, homogeneity and texture) and observations were noted (Kute and Saudagar, 2013).

Determination of pH

The pH of the emulgel was determined by digital pH meter (Asija et al., 2015). One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained. And constant reading was noted. The measurements of pH of each formulation were replicated two times.

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually and observations were noted (Bhatt et al., 2013).

Extrudability study

The emulgel formulations were filled into collapsible metal tubes or aluminium collapsible tubes (Singla ety al., 2012). The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

Spreadability

An important criterion for emulgel gels is that it must possess good spreadability. Spreadability is a term expressed to denote the extent of area to which the gel readily spreads on application to skin. The therapeutic efficacy of a formulation also depends on its spreading value (Magdy, 2004). A special apparatus has been designed to study the spreadability of the formulations. Spreadability is expressed in terms of time in seconds taken by two slides to

slip of from formulation, placed between, under the application of a certain load. Lesser the time taken for the separation of two slides, better the spreadability.

Method:

Two glass slides of standard dimensions (6×2) were selected. The emulgel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the emulgel formulation between the two slides was traced uniformly to form a thin layer.

The weight was removed and the excess of the emulgel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied 50 with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each emulgel formulation (Kokane et al., 2013).

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)

m = weight tied to the upper slide (20 grams)

l= length of glass slide (6 cms).

t = time taken is seconds.

Viscosity

The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer (Ayub et al., 2007). The viscosity was measured using spindle no. 6 at 10 rpm and 25^0C. The sufficient quantity of gel was filled in appropriate wide mouth container. The gel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the Viscometer. Samples of the gels were allowed to settle over 30 min at the constant temperature (25 $\pm/1^0$C) before the measurements.

Drug content

1 gm. of the prepared gel was mixed with 100 ml. of ethanol. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 376 nm. Drug

content was calculated by linear regression analysis of the calibration curve.

***In-vitro* drug release studies using the prehydrated cellophane membrane**

Preparation of cellophane membrane for the diffusion studies:

The cellophane membrane approximately 25 cm x 2cm was taken and washed in the running water[63]. It was then soaked in distilled water for 24 hours, before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies.

Diffusion Studies:

The *in-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15 mm internal diameter and 100 mm height. The diffusion cell membrane was applied with 1 gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing neutralizing 7.4 pH phosphate buffer, freshly prepared as a receptor base and the system was maintained for 2 hrs at 37± 0.5º C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of upto 12 hrs and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 376.0 nm using neutralizing 7.4 pH phosphate buffer as blank (Ayub et al., 2007).

Data Analysis via Drug Release Kinetics study

The results of in-vitro release profile obtained for all the formulations were plotted in kinetic models as follows,

1. Cumulative of drug released versus time (zero order kinetic model).

2. Log cumulative percent drug remaining to be absorbed versus time (First order model)

3. Cumulative amount of drug release versus square root of time (Higuchi model)

4. Log cumulative drug released versus log time (Korsmeyer-Peppas model)

RESULTS AND DISCUSSION

Tenoxicam loaded enulgel were evaluated for their clarity, pH, viscosity, spreadability, skin irritation test, *in vitro* diffusion studies using standard procedure. All studies were carried out in triplicate and average values were reported.

The Psychorheological Characteristic was checked for emulgel formulations (colour, clogging, homogeneity and texture) Emulgel formulations were yellowish white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. The Spreadability was checked for emulgel formulations and observations were shown in Table 8.2. The Spreadability of formulation F1, F2, F3, F4, F5 and F6 was found to be 11.5, 10.3, 9.8, 12.3, 11.2 and 10.4 gcm/sec respectively.

The viscosity of all formulation was found 3345, 3265, 3566, 3545, 3895 and 3830 cps for formulation F1, F2, F3, F4, F5 and F6 respectively. The pH of formulation F1, F2, F3, F4, F5 and F6 was found 6.58, 6.72, 6.81, 6.74, 6.72 and 6.65. The pH of all formulation was found near to skin pH 6.8, which is no irritant to skin.

The result of drug content was found to be 96.65**,** 98.85, 99.45, 98.58, 98.12 and 99.05 for formulation F1, F2, F3, F4, F5 and F6 respectively. The maximum drug content was found in formulation F3, select as optimize formulation.

The study showed the release of the drugs from its emulsified gel formulation F3 formulation showed the amounts of the drug released after 0.5, 1, 1.5, 2, 4 and 6 hrs. were 22.23%, 36.65%, 49.95%, 65.65%, 76.42% and 99.41% respectively.

In vitro drug release from the semisolid preparation of Tenoxicam emulgel optimized formulation F3 shows significantly improved in drug release rate as compare to marketed preparation. It was concluded that developed formulations deliver the drug for the treatment of fungal disease. Hence it could be concluded that the carbomer based semisolid preparation would providing local onset of action without need of any device for their application on skin. The preparation of emulgel has potential advantages over marketed preparation as they improved patient compliance rapid local onset of action for longer period with cost effectiveness. The pediatric and geriatric populations are the primary ones whose problems are easily targeted.

Table 2: Psychorheological Characteristic

Formulation	Washability	Observation	Clogging	Homogeneity
F1	+++	white cream	Absent	Good
F2	+++	white cream	Absent	Good
F3	+++	white cream	Absent	Good
F4	+++	white cream	Absent	Good
F5	+++	white cream	Present	Average
F6	+++	white cream	Present	Average

Washability - Excellent: +++, Good: ++, Average: +, Poor: -

Table 3: Extrudability and Spreadability study

Formulation	Extrudability	Spreadability (gcm/sec)
F1	++	11.5
F2	++	10.3
F3	+++	9.8
F4	+++	12.3
F5	+	11.2
F6	+	10.4

Excellent: +++, Good: ++, Average: +, Poor: -

Table 4: Viscosity and pH

Formulation	Viscosity (cps)	pH
F1	3345	6.58
F2	3265	6.72
F3	3566	6.81
F4	3545	6.74
F5	3895	6.72
F6	3830	6.65

* Average of three determinations

Table 5: Results of drug content of emulgel

Formulation	% Drug content
F1	96.65
F2	98.85
F3	99.45
F4	98.58
F5	98.12
F6	99.05

Table 6: % Cumulative drug release of formulation F1-F6

S. No.	Time (Hrs.)	% Cumulative drug release						
		F1	F2	F3	F4	F5	F6	Pure Drug
0	0	0	0	0	0	0	0	0
1	0.5	42.23	33.35	22.23	18.85	15.65	14.52	45.65
2	1	55.65	46.65	36.65	29.91	25.41	23.32	65.58
3	1.5	73.32	68.85	49.95	36.65	33.12	31.45	98.45
4	2	89.98	85.65	65.65	55.83	45.65	43.32	-
5	4	98.45	98.23	76.42	68.85	63.32	61.78	-
6	6	99.45	99.65	99.41	79.98	68.85	65.45	-

Table 7: *In vitro* drug release data for optimized formulation F3

S. No.	Time (Hrs.)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.5	3.873	0.588	22.23	1.426	73.35	1.865
2	1	5.477	0.739	36.65	1.602	60.02	1.778
3	1.5	6.708	0.827	49.95	1.689	51.16	1.709
4	2	7.746	0.889	65.65	1.793	37.88	1.578
5	4	10.954	1.04	76.42	1.897	21.15	1.325
6	6	15.492	1.19	99.41	1.995	1.16	0.064

* Average of three determinations

CONCLUSION

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since emulgel is helpful in enhancing spreadability, viscosity and extrusion, this novel drug delivery become popular. Moreover, they will become a solution for loading hydrophobic drugs in water soluble gel bases for the long term stability. Similarly in the study, topical emulgels of Tenoxicam were

formulated and subjected to physicochemical studies i.e. rheological studies, spreading coefficient studies and in vitro release studies. In vitro release of the tests formulations were performed to determine drug release from emulgel rate and duration of drug release. From the in vitro studies, formulation F3 showed maximum release of 99.41% in 6 hrs.

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