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Research Article

Formulation and evaluation of Ketoprofen cream containing natural anti-inflammatory agent *curcuma longa* in treatment of rheumatoid arthritis

Muhammad Razi Ullah Khan[1,2]*, Umer Farooq[1], Shahid Masood Raza[1]

[1]School of Pharmacy, The University of Faisalabad, Faisalabad, Pakistan

[2]Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan

*E-mail of the corresponding author: razi_pharmacist@yahoo.com

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Non-Steroidal Anti-Inflammatory drugs have their origin as the derivatives of plants which were observed to have strong analgesic and anti-inflammatory effects in various disease states. Ketoprofen is a better tolerated NSAID because of its limited numbers of adverse effects and topical formulation has excellent permeation and absorption into the skin. The present investigation was to develop novel Ketoprofen cream formulation in combination of most effective and potent anti-inflammatory agent curcuma longa, which is reported to possess strong anti-inflammatory effects in Rheumatoid Arthritis and Osteoarthritis, according to the study by university of Arizona researchers. Combination of Ketoprofen and curcuma longa is good rational, where curcuma longa produces synergistic anti-inflammatory effects with ketoprofen. Formulation containing fixed concentrations (3%) of ketoprofen with curcuma longa was prepared. To access the efficacy of formulation stability studies, spread ability, tube extrudability, viscosity, pH, skin irritation test, in vitro drug diffusion study and anti- inflammatory effects were evaluated. The results obtained were encouraging and formulation containing Ketoprofen (3%) with curcuma longa was found better than alone Ketoprofen cream formulation.

Keywords: Ketoprofen, Curcuma longa, Cream, Rheumatoid arthritis.

1. INTRODUCTION

Plants are the oldest source of pharmacologically active compounds and have provided human kind with many medicinally useful compounds from centuries (Evans and Saunders, 2002). Today more than two thirds of the world's population relay on plant derived drugs (Simmonds and Grayer, 1999). The origin of many effective drugs is found in the traditional medicinal practices, and in view of this it is very important to undertake studies pertaining to screening of medicinal plants for their proclaimed biological activity (Bassam et al., 2006). The use of non-steroidal anti-inflammatory drug is well recognized for regional inflammatory disorders such as Rheumatoid Arthritis, Osteoarthritis and Muscle pain (Roberts and Cross, 1999; Hadraft et al., 2002). Ketoprofen a well-recognized drug, included in the class of Non-steroidal anti-inflammatory drugs (NSAIDs), blocks the inflammatory cascade and cyclooxygenases (COX) by inhibiting prostaglandin and thromboxane production and lead to reduction in pain, fever, platelet aggregation and inflammatory response

(Rao and Knaus, 2008). Besides inhibiting the prostaglandin and thromboxane production, Ketoprofen also inhibit rabbit neutrophil and human lung lipoxygenase activity (Towheed, 2006). Ketoprofen is generally indicated for symptomatic relief of Rheumatoid Arthritis, Osteoarthritis, Inflammatory arthropathies (Ankylosing spondylitis, Psoriatic arthritis), Gout (Massey et al., 2010), Metastatic bone pain, Post-operative pain, Dysmenorrhoea, Migraine and Headache. Curcuma longa (the Common name is Tumeric) is a perennial member of the Zingiberaceae family, derived from the rhizomes of the plant and has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions (Ammon and Wahl, 1991). The major pigment compound of Curcuma longa is Curcumin which has been shown to have potent anti-inflammatory activities with specific lipoxygenase and COX-2 inhibiting properties including cytokines (TNF alpha and IL-1 beta) (Satoskor et al., 1986). The present research has been undertaken with the aim to develop a topical cream formulation of Ketoprofen and Curcuma longa, which would attenuate the gastrointestinal related toxicities associated with oral administration. Ketoprofen having molecular weight of 254.29 and melting point in the range of 93-96°C can be considered ideal to permeate through the skin.

2. MATERIALS AND METHODS

2.1 Chemicals

Ketoprofen was received as a gift from (Martin Dow Pharmaceuticals (Pvt.) Ltd.), Ethyl alcohol Absolute reagent (RdHLaborchemiKalien GmbH & Co.), Stearic Acid (BDH labs, England), Cetostearyl Alcohol (BDH Labs, England), Polyoxyethylene (80) Sorbitan monooleate (Tween 80) (Merck, Germany), White Petrolatum (Kukdong oils and chemicals, Korea), Liquid Paraffin (Kukdong oil and chemicals, Korea), Sodium Hydroxide (Merck, Germany), Sodium Benzoate (BDH labs, England), Sorbitol liquid USP (Merck, Germany) and De-ionized water (Medilines Diagnostic division)

2.2 Plant Material

Plant material used for that study was collected from the surroundings of Kasur city of Pakistan in the month of February and identified by Department of Botony, Faculty of Biological Sciences, University of Sargodha, Sargodha Pakistan.

2.3 Apparatus

Beaker 50ml, 100ml (Pyrex, England), Conical flask 50ml, 100ml (Pyrex, Germany), Pipette 10ml (Preciclolor, Germany), Oven (Schutzartdin 40050 IP-20, Germany), Refrigerator (PEL, Pakistan), Aluminum foil, White colored jar, Amber colored glass jar, and Aluminum collapsible tube

2.4 Instruments

Spectrophotometer U.V1700 (Shimdazu, Japan), Weighing balance (Analytical grade), Magnetic stirrer/ Hot plate (Made in Germany), pH meter (Model No: 3510, England), Homogenizer (Euro-Star, IKA D 230, Germany), Franz Diffusion cell, Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA), Refrigerator (Dawlance Company, Pakistan), Incubator (Sanyo MIR-162, Japan)

2.5 Animal

Albino Rabbits

2.6 Methods

2.6.1 Preparation of Turmeric Extract

The rhizomes of *curcuma longa* were cleaned, washed with de-ionized water, sliced and dried in the sun for one week. Dried rhizomes were cut in small pieces and powered by electronic

mill. 200 gm of sample was taken into thimble and placed in a Soxhlet apparatus. The apparatus was setup with various solvents ranging from non polar to polar. 1 lit of solvent was added and extracted according to their boiling point for seven hours. The solvents used were chloroform (B.P. =61˚C), ethyl acetate (B.P. =77˚C), methanol (B.P. =65˚C) and acetone (B.P. =56.53˚C). After completion of extraction the dark brown extract was then cooled, concentrated using rotary evaporator get a crude dried extract which was black orange in colour.

2.6.2 Formulation of Ketoprofen cream containing Curcuma longa

3% by weight of Ketoprofen cream containing *curcuma longa* was made according to the formulation given in Table 1.

Table 1: Formulation of Ketoprofen cream containing *Curcuma longa*

Sr. No	Ingredients	%age Composition
1	Ketoprofen (99.6%)	3.0
2	*Curcuma longa*	5.0
3	Liquid Paraffin	5.0
4	Stearic Acid	0.30
5	White Petrolatum	5.0
6	Cetostearyl Alcohol	10.0
7	Tween 80	8.0
8	Sodium Benzoate	0.12
9	Sorbitol Solution	6.0
10	Sodium Hydroxide	1.50
11	De-ionized Water	56.08

2.6.3 Preparation of cream

Ketoprofen cream with extract of Curcuma longa was formulated by the method of Nazir et al (Nazir et al., 2013). The aqueous and oil phases were taken into bakers and heated to 75ºC over a water bath. The oil phase was comprised of Ketoprofen, Liquid Paraffin, White Petrolatum, Cetostearyl Alcohol, Tween-80 and Stearic Acid while the aqueous phase was composed of Extract of Curcuma longa, Sodium Benzoate, Sorbitol Solution and Sodium Hydroxide. Drop wise addition of the aqueous phase to the oil phase was done with constant stirring at 2000 rpm in a homogenizer for a period of 15 min. The homogenizer speed was then reduced to 1000 rpm and homogenization was continued for another 5 min. The speed was further reduced to 500 rpm and the homogenization extended for 5 min. Ketoprofen cream containing the turmeric extract was formulated.

2.6.4 Organoleptic Evaluation

Changes in organoleptic properties of the cream were evaluated by visual inspection and the properties evaluated included the color of the cream, liquefaction and phase separation. These were evaluated over a period of three months at specific time intervals.

2.6.5 Physical Evaluation of Cream

Physical tests including pH, Spreadability, Tube extrudability and viscosity were carried out on the cream over a period of three months at specific time intervals.

2.6.6 Determination of pH

pH of the cream was determined by using the digital pH meter. Prior to this, the pH meter was calibrated by using buffer solution of pH 3.99, 7.0 and 9.2 and then electrode was washed with de- mineralized water (Bates and Roger, 2006). pH was checked at the time of preparation of cream (zero time) and thereafter every month until the 3 months period.

2.6.7 Determination of Spreadability

Spreadability was determined by modified wooden block and glass slide apparatus. The apparatus consisted of a wooden block with fixed glass slide and a pulley. A pan was attached to another glass slide (movable) with the help of a string. For the determination of spreadability

measured amount of cream was placed in the fixed glass slide, the movable glass slide with a pan attached to it, was placed over the fixed glass slide, such that the cream was sandwiched between the two slides for 5 min. The weight was continuously removed. Now about 50 g of weight was added to the pan (Prasad and Dorle, 2006). Time taken for the slides to separate was noted. Spreadability was determined using the following formula:

$$S = M/T$$

Where S is the spreadability in g/s, M is the mass in grams and T is the time in seconds.

2.6.8 Determination of Tube Extrudability

Tube extrudability was determined by filling the cream in clean, lacquered aluminum collapsible tube and pressed firmly at the crimped end. When the cap was removed, cream extruded until pressure dissipated. Weight in grams required to extrude 0.5 cm ribbon of cream in 10 seconds was determined (Shinde et al., 2005).

2.6.9 Determination of Viscosity

The viscosity of cream formulation was determined by using Brookfield digital Viscometer. In a clean and dry 250ml beaker, take the test sample. Determine the viscosity of the test sample as per standard operating procedure of viscometer and the spindle T-D (Spindle code S 94) was used.The spindle was rotated at speeds of 2.5, 4, 5 and 10 rpm. The reading near to 100% torque was noted (Wood et al., 1963).

2.6.10 In Vitro Diffusion Studies

Cellophane membrane obtained from was used for this study. In Kiescary Chien (KC) diffusion cell, 1.0 gm of cream was kept in donor compartment. The entire surface of membrane was in contact with the receptor compartment containing 85 ml of 0.1 N sodium hydroxide. The receptor compartment was continuously stirred (100 rpm) using a magnetic stirrer. The temperature maintained was 37 ± 1°C. The study was carried out for 24 hrs with the interval of 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hrs. The sample was withdrawn at predetermined period of time and same volume was replaced with fresh 0.1 N sodium hydroxide. The absorbance of withdrawn sample was measured spectrophotometrically against appropriate blank (Subrahmanyam, 2009).

2.6.11 Skin Irritation Study

In skin irritation study three albino rabbits were selected for the study (Kulkarni and Jain, 2001). 24 hours prior to the test, the test sites were depilated on both sides of the spine and demarcated for the application of the formulation. The measured quantity of cream was applied over the respective test sites. The test sites were observed for erythema and edema for 24, 48 and 72 hours respectively after the application.

2.6.12 Stability Studies

Stability studies on the cream formulation were conducted over a period of three months at three different conditions: (a) At 4 ± 1 ºC in a refrigerator (b) at 25 ± 1 ºC in an incubator (c) at 40 ± 1 ºC in an incubator. The cream was analyzed by UV- Visible Spectrophotometer, immediately after preparation (at zero time) and after every month until three months period (Alexander and Thyangarajapuram, 2004).

The active contents in cream formulation were determined by measuring the absorbance of sample solution on UV Spectrophotometer at 255nm wavelength at above mentioned time intervals and by calculating the remaining %age of active content by following formula:

Remaining %age of active content in sample solution = (Absorbance of Sample / Absorbance

of Standard) × (Conc. of Standard / Conc. of Sample) × % age purity of Standard (USP, 2003).

2.6.13 Determination of Drug contents by Spectrophotometric Method

2.6.13.1 Preparation of Standard Solution

50 mg of Ketoprofen (99.66% pure) and Curcuma longa was carefully weighed on analytical balance and dissolved in ethanol (96%) and made the volume upto 100ml with ethanol. The solution was then filtered and 1ml was taken from that solution and made the volume of that solution up to 50ml with same solvent and it was taken to be the standard solution in UV Visible spectrophotometer.

2.6.13.2 Preparation of Sample Solution

5 g of the cream formulation was taken and dissolved in ethanol (96%) and made the volume up to 100ml with the same solvent. The solution was then filtered and 1 ml was taken made upto 50 ml with ethanol. The absorbance was measured at 255nm using ethanol as blank solution.

3. RESULTS AND DISCUSSION

The aim of the present study was to develop a Ketoprofen cream formulation along with a most effective and natural anti-inflammatory agent, curcuma longa, used for the management of Rheumatoid Arthritis and does not produce undesirable side effects.

Ketoprofen cream along with potent anti-inflammatory agent Curcuma longa was prepared using different concentration of excipients and active ingredient. Accelerated stability study was done at 4 ± 1°C (in refrigerator), 25 ± 1°C (in incubator) and 40 ± 1°C (in incubator). Stability testing was done for the period of 3 months (90 days). It is evident from the results that cream formulation is best suitable at (4 ± 1°C) as % age of drug remaining is not decreased by more than 5% (Remington, 2000) as shown in Figure 1. It is also evident from the results of standard deviation at the end of three months that at 4 ± 1°C standard deviation was least and it fell into acceptable range, but at 25°C and 40°C the standard deviation is bit higher and away from normal and reasonable range. So it can be concluded, that at 4 ± 1°C, the cream formulation fulfils the criteria required for a pharmaceutical cream preparation to be acceptable concerning accelerated stability studies.

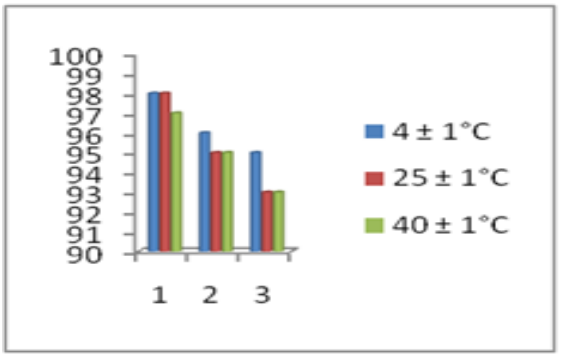

Figure 1: %age changes in drug content over time

Table 2: %age remaining of drug content at zero time

Absorption of Standard	Absorption of Sample	% age of active drug in the sample	Mean	Standard Deviation
0.625	0.623	99.28%	0.624	0.001414

Table 3: Evaluation data of Ketoprofen and Curcuma longa cream formulation

Parameters Evaluated	Study Period			
	At Zero time	**1 Month**	**2 Months**	**3 Months**
Visual appearance	White	No change	No change	No change
pH	6.79	6.81	6.78	6.80
Spread ability (g/sec)	4.95	5.53	6.12	6.47
Tube extrudability (g)	180	180	185	190

The visual appearance of cream formulation was checked at the time of preparation and at the end of every month until three months period. There was found no significant difference in visual appearance at the end of three months period from the time of preparation. The pH evaluation is also important to check the stability of cream formulation. The pH values were not found different for the period of three months. The result of spread ability varies from 4.95 to 6.47 g/sec whereas the extrudability of cream formulation from the collapsible tube varies from 180 to 190 g. The viscosity of cream formulation varies from 14410 cps to 15213 cps at 10 rpm as given in Table 3 and Table 5.

Figure 2: Rabbit Skin- on application with Ketoprofen and *Curcuma longa* cream

In Vitro Drug Diffusion study:

From the data we have found that the prepared topical cream formulation of Ketoprofen along with the extract of Curcuma longa releases 83.09% of drug over a period of 24 hours as given in Table 4. From the In – vitro drug diffusion study we have concluded that the cream formulation prepared, controls the release of drug for longer period of time which will be helpful to avoid the more fluctuation and also reduces the cost of therapy.

Table 4: In Vitro Drug Diffusion Study over period of 24 Hours

Time (Hours)	% age of drug release
0.0	0.0
0.5	7.68
1.0	13.77
2.0	23.57
4.0	31.98
6.0	43.03
8.0	52.17
10.0	64.82
12.0	73.45
24.0	83.09

Skin Irritation Test:

In skin irritation test, no signs of erythema and edema were found after 24, 48 and 72 hours of cream application in albino rabbits as shown in Figure 2.

Table 5: Viscosity of cream formulation (cps) at different rpm

Speed in rpm	At Zero time	1 Month	2 Months	3 Months
2.5	65187	65235	65235	65235
4.0	34470	34697	34846	35141
5.0	25953	26123	26547	26996
10	14110	14735	15174	15213

5. CONCLUSION

The present cream formulation was developed by taking into consideration that in cream formulations there is present no direct contact of active drug with stomach wall. This can be a reason to remove the chances of gastric mucosal damage to a reasonable level that is caused by the use of solid dosage forms of NSAIDs. The cream formulation contains Ketoprofen along with extract of *Curcuma longa*, a spice most often found in curry dishes may help prevent Rheumatoid Arthritis and Osteoporosis. Ketoprofen is an NSAID that is very effective to mimic the pain and inflammation in arthritis patients and Curcuma longa performs a synergistic anti-inflammatory effect.

Conflict of Interests

Authors declared no competitive interests for the presented work.

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