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FORMULATION DEVELOPMENT, EVALUATION AND ANTI-INFLAMMATORY EFFECTS OF KETOPROFEN CREAM ON RHEUMATOID ARTHRITIS PATIENTS

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A B S T R A C T

Purpose: Non-Steroidal Anti-Inflammatory Drugs have their historical origin as the derivatives of plants, which were observed to have their therapeutic effects in disease conditions. Topical delivery of NSAID is most widely used in the treatment of pain disorder. Ketoprofen is widely used NSAID but cream formulation is not available in Pakistan. To develop topical cream formulation of Ketoprofen to avoid all the potential adverse effects occur with the use of oral dosage forms NSAID and also remain stable for longer period of time.

Methods: Ketoprofen cream was prepared and its anti-Inflammatory effects were evaluated in human subjects to determine its efficacy in reduction of pain, swelling and redness. This cream formulation was checked on a group of thirty volunteers and it was found that ketoprofen cream is highly effective to lower the pain and to remove swelling and redness in Rheumatoid Arthritis patients.

Accelerated Stability Study of Ketoprofen cream was done at three different temperatures, room temperature, 40°C and 60°C for a time period of 6 months. The remaining percentage of drug was determined by an assay on UV- Visible Spectrophotometer. It was found that the highest percentage of remaining drug concentration was obtained by the cream sample stored at room temperature (22±5°C). Other physical parameters such as visual appearance, pH, and tube extrudability were also evaluated for a period of 6 months.

Results: The cream formulation stored at Room temperature (22±5°C) exhibited most satisfying results of all parameters as compared to storage at 40°C and 60°C. It is evident from the anti-inflammatory results that Ketoprofen cream is very effective to mimic the pain in Arthritis patients. This Study results reveals that Ketoprofen cream formulation causes a significant reduction in pain scales, removes the redness and swelling and improves the walking ability in Rheumatoid Arthritis patients.

Conclusion: By using Ketoprofen cream formulation can avoid all the potential adverse effects occur with use of oral dosage form NSAID in Rheumatoid Arthritis patients. The cream formulation of Ketoprofen has no direct contact of active drug with stomach wall. This can be a good reason to eliminate the chances of gastric mucosal damage to a reasonable level that is caused by the use solid dosage forms of Ketoprofen.

INTRODUCTION

Ketoprofen is a drug included in the group of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) that is used in management of Arthritis related inflammatory pains or severe Toothaches results in inflammation of gums [1] . The effects of NSAIDs have traditionally been described to their inhibitory action on Cycloxygenase enzymes. Multiple studies have shown that Ketoprofen can inhibit the formation of Thromboxanes and Prostaglandins, as both are the products of Cycloxygenase pathway [2]. Ketoprofen can cause a rebound effect on Cycloxygenase activity following withdrawal of agents. Ketoprofen also inhibit rabbit neutrophil and human lung Lipoxygenase activity [3]. Ketoprofen is generally indicated for symptomatic relief of Ankylosing Spondylitis, Psoriatic Arthritis [4], Rheumatoid Arthritis [5], Osteoarthritis [6], Tendinitis [7] and Gout [8]. Reduction of adverse drug reactions is being well considered to obtain high patient compliance and drug therapy efficacy in case of topical drug delivery system

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[9]. As oral preparations of NSAIDs are associated with large number of systemic adverse effects, so to solve this problem a Ketoprofen cream was prepared using different concentration of excipients and active ingredient.

MATERIALS AND METHODS

Chemicals

Ketoprofen 99.6% purity was received as a gift from (Martin Dow Pharmaceuticals (Pvt.) Ltd.), Ethyl alcohol Absolute reagent (RdHLaborchemiKalien GmbH & Co.), Sorbitol Liquid USP (Merck, Germany),Liquid Paraffin(Kukdong Oil and Chemicals,Korea), Cetostearyl Alcohol (BDH Labs, England), White Petrolatum (Kukdong Oil and Chemicals, Korea), Polyoxyethylene (80)Sorbitan monooleate (Tween 80) (Merck, Germany), Sodium Benzoate (BDH labs, England), Sodium Hydroxide (Merck, Germany), De-ionized Water (Medilines Diagnostic division), and Stearic Acid (BDH Labs, England).

Apparatus

Beaker 50ml, 100ml (Pyrex, England), Pipette 10ml (Precicolor, Germany), Conical Flask 50ml, 100ml (Pyrex, Germany), Refrigerator (Waves, Pakistan), Oven (Schutzartdin 40050 IP-20, Germany), Aluminum foil, Amber colored glass jar, White colored glass jar and Aluminum Collapsible tube

Instruments

Spectrophotometer U.V 1700 (Shimdazu, Japan), Weighing balance (Analytical Grade), Magnetic Stirrer / Hot Plate (Made in Germany) and pH Meter (Model No: 3510, England)

Human Volunteers

Age: 40-70 year
Gender: Both Male and Female

Methods

Formulation of Ketoprofen Cream

1% by weight of Ketoprofen cream was made according to the formulation given in Table I.

Preparation of Ketoprofen Cream

A mixture of Liquid Paraffin, White Petrolatum, Cetostearyl Alcohol,Tween-80 and Stearic Acid was mixed and mixture was melted by heating onto a hot plate at 75°C with continuous stirring. Separately, Sodium Benzoate, Sorbitol Solution and Sodium Hydroxide were dissolved into de-ionized water at temperature of 75°C.The solution was added to mixture previously prepared and mixture was emulsified. After cooling, the emulsion was allowed to congeal; a cream for topical use was obtained.

Chemical assay

Preparation of Standard Solution:

50 mg of Ketoprofen (99.66% pure) was carefully weighed on analytical balance and dissolved in ethanol (96%) and made the volume up to 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.

Preparation of Sample Solution

5 g of Ketoprofen cream (50 mg of standard Ketoprofen) 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 up to 50ml with ethanol. The absorbance was measured at 255nm using ethanol as blank solution.

In-Vitro Stability Study of Ketoprofen Cream

Stability study of Ketoprofen cream was conducted by putting the cream in nine white colored glass jars .These jars were divided into three sets, each set consisting of three jars. Each set was stored at Room temperature (22°C±5°C), 40°C and 60°C. The cream was analyzed by UV- Visible Spectrophotometer, immediately after preparation (at zero time), after 1 month, 2 month and thereafter every month until 6 months period [10]. The active content in cream formulation was 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 [11]

Physical Parameters of Ketoprofen Cream

Visual Appearance

The visual appearance (color and texture) of Ketoprofen cream was determined by taking 5g of cream from each set (stored at Room temperature, 40°C and 60°C) in three transparent glass jars and visual appearance was checked in light with in front of dark colored (black) background that was created with the help of black colored sheet. This process was done at the time of preparation of cream (at zero time) and there after at the end of everymonth until six months period.

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 9.2and then electrode was washed with de- mineralized water [12]. pH was checked at the time of preparation of cream (zero time) and thereafter every month until the 6 months. Randomly a cream jar from set of jars (stored at Room temperature, 40°C and 60°C) was selected to check the pH of the cream to ensure its stability at different temperatures.

Tube Extrudability

Tube extrudability was determined by filling 5g of the Ketoprofen cream in clean, lacquered aluminum collapsible tube with nasal tip of 5mm opening and applied pressure on tube with the help of finger press. Tube extrudability was determined by measuring the percentage of cream extruded through the tip when a pressure of finger was applied on tube.

Evaluation of Anti-Inflammatory Effects of Ketoprofen Cream Topically Applied on Human Volunteers in the Treatment of Rheumatoid Arthritis

Subjects and Method

The study was conducted in Bajwa Trauma center Sargodha. 30 patients of aged between 40-70 years who presented the hospital with acute Rheumatoid Arthritis during the study period (2 weeks) were invited to participate. Patients included 18 male volunteers and 12 female volunteers. The volunteers had the pathological signs of inflammation (Pain, Redness and Swelling) on knee and wrist joints. The volunteers were given written instructions to apply the cream regularly in a dose of 4 inches 3 times a day up to 14 days. The volunteers were given the diaries to keep the daily record of their symptoms and to keep the record of pain (observed at rest, during walking and standing), redness and swelling [13]. 24 volunteers (14 male and 10 female volunteers) returned their diaries and the results of three inflammatory parameters were collected from these subjects after 2 weeks.

RESULTS AND DISCUSSION

Ketoprofen cream was prepared using different concentration of excipients and active ingredient. Accelerated stability study was done at Room temperature, 40°C and 60°C. Stability testing was done for the period of 6 months (180 days). It is evident from the results that Ketoprofen cream formulation is best suitable at Room temperature (22±5°C) as % age of drug remaining is not decreased by more than 10% [14]. It is also evident from the results of standard deviation at the end of 6 months that at Room temperature standard deviation was least and it fell into acceptable range, but at 40°C and 60°C the standard deviation is bit higher and away from normal and reasonable range.

Table I Formulation of Ketoprofen Cream

S.No.	Ingredients	% age Composition
1	Ketoprofen (99.6%)	1.0
2	Liquid Paraffin	5.0
3	Stearic Acid	0.30
4	White Petrolatum	5.0
5	Cetostearyl Alcohol	10.0
6	Tween-80	8.0
7	Sodium Benzoate	0.12
8	Sorbitol Solution	6.0
9	Sodium Hydroxide	1.50
10	De-ionized Water	63.08

So it can be concluded, that at room temperature, the cream formulation fulfills the criteria required for a pharmaceutical cream preparation to be acceptable concerning accelerated stability studies [15]. The visual appearance was also best at Room temperature. pH evaluation is also important to check the stability of a cream formulation [15]. pH values were not found different at all temperatures for a period of 6 months.

Table II %age remaining of Ketoprofen at zero time (At room temperature)

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

Tube extrudability was also checked and found no significant difference in tube extrudability values of 6 months period. The Anti-Inflammatory effects of Ketoprofen cream were evaluated in Rheumatoid Arthritis patients. It is evident from the anti-inflammatory results that Ketoprofen cream is very effective to mimic the pain in Arthritis patients. Study results reveals that Ketoprofen cream formulation causes a significant reduction in pain scales, removes the redness and swelling and improves the walking ability in Rheumatoid Arthritis patients.

In-Vitro Characteristics of Other Physical Parameters

Visual Appearance

The color of cream formulation at the time of preparation was observed to be**"**White**".**

pHof Cream Formulation

pH value at Zero time (At Room temperature) = 6.78

Tube Extrudability

Tube extrudability at zero time (At Room Temperature) = 97.08%

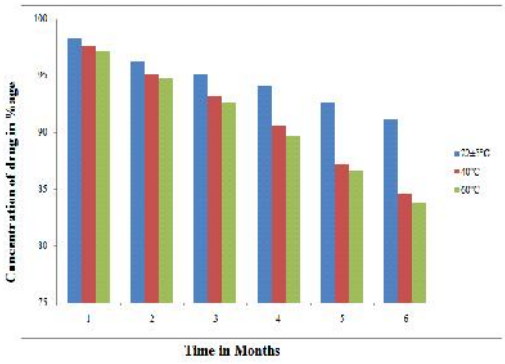

Fig. I An Overall representation of %age remaining of Drug until 6 Months

Table III %age remaining of Ketoprofen after 1 Month

	Absorption of samples	%age of active drug in sample	Mean	Standard deviation
At Room temperature	0.617	98.32%	0.621	0.005656
At 40 °C	0.612	97.52%	0.618	0.009192
At 60 °C	0.610	97.20%	0.6175	0.01060

Table IV %age remaining of Ketoprofen after 2 Months

	Absorption of samples	%age of active drug in sample	Mean	Standard deviation
At Room temperature	0.604	96.25%	0.6145	0.014849
At 40 °C	0.597	95.13%	0.611	0.019798
At 60 °C	0.595	94.81%	0.61	0.021213

Table V %age remaining of Ketoprofen after 3 Months

	Absorption of samples	%age of active drug in sample	Mean	Standard deviation
At Room temperature	0.597	95.04%	0.611	0.019798
At 40 °C	0.585	93.22%	0.605	0.028284
At 60 °C	0.581	92.58%	0.603	0.0311112

Table VI %age remaining of Ketoprofen after 4 Months

	Absorption of samples	%age of active drug in sample	Mean	Standard deviation
At Room temperature	0.590	94.02%	0.6075	0.024748
At 40 °C	0.568	90.51%	0.5965	0.040305
At 60 °C	0.563	89.71%	0.594	0.0438406

Table VII %age remaining of Ketoprofen after 5 Months

	Absorption of samples	%age of active drug in sample	Mean	Standard deviation
At Room temperature	0.581	92.58%	0.603	0.031112
At 40 °C	0.547	87.16%	0.586	0.055154
At 60 °C	0.543	86.53%	0.584	0.057982

Table VIII %age remaining of Ketoprofen after 6 Months

	Absorption of samples	%age of active drug in sample	Mean	Standard deviation
At Room temperature	0.572	91.15%	0.5985	0.037476
At 40 °C	0.531	84.62%	0.578	0.066468
At 60 °C	0.526	83.82%	0.5755	0.070003

Reduction in Mild Arthritis Pain (Pain at Rest) over 14 Days Period:

Table XIII Pain scores of volunteers at rest over 14 days study period

Study Days	Reduction in Pain Scale
0	4.0
2	3.5
4	2.0
6	1.0
8	0.5
10	0.0
12	0.0
14	0.0

Table IX Visual appearance of Cream at different temperatures until 6 months period

	Color after 1st Month	Color after 2nd Month	Color after 3rd Month	Color after 4th Month	Color after 5th Month	Color after 6th Month
Room temperature	white	white	white	white	white	white
40°C	white	white	white	white	an off white tint	an off white tint
60°C	white	white	white	an off white tint	an off white tint	an off white tint

Table X pH of Cream at different temperatures until 6 months period

	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
Room temperature	6.81	6.79	6.80	6.78	6.81	6.79
40°C	6.79	6.77	6.78	6.82	6.81	6.79
60°C	6.80	6.79	6.81	6.78	6.83	6.80

Table XI Tube Extrudability Results until 6 months period

Months	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
Tube Extrudability	97.06%	97.03%	97.02%	96.94%	96.91%	96.84%

Table XII Characteristics of patients entered into study (n =30) and those eligible for analysis (n =24)

Sr. No	Characteristics		Patients Entered	Patients Analyzed
1	**Sex**	Male	18	14
		Female	12	10
2	**Occupation**	Sedentary	6	5
		Standing light	11	9
		Standing heavy	9	7
		Retired/Unemployed	4	3
3	**Pain Scale**	None	0	0
		Mild (1-3)	8	6
		Moderate (4-6)	15	12
		Severe (7-10)	7	6
4	**Swelling**	None	0	0
		Mild	11	8
		Moderate	12	10
		Severe	7	6
5	**Redness**	None	0	0
		Mild	10	7
		Moderate	14	9
		Severe	6	8
6	**Knee and Wrist joint Movement**	Full range	8	6
		Strictly restricted	14	11
		Markedly restricted	8	7
7	**Ability to bear the weight**	Walking normally	0	0
		Slightly limp	12	8
		Limp badly	9	8
		Unable to bear weight	9	8

Reduction in Moderate Arthritis Pain (Pain on Standing) over 14 Days Period:

Table XIV Pain scores of volunteers on standing over 14 days study period

Study Days	Reduction in Pain Scale
0	7.0
2	6.0
4	5.0
6	3.5
8	2.0
10	0.5
12	0.0
14	0.0

Reduction in Severe Arthritis Pain (Pain on Walking) over 14 Days Period:

Table XV Pain scores of volunteers on walking over 14 days study period

Study Days	Reduction in Pain Scale
0	10.0
2	9.0
4	8.0
6	6.5
8	5.0
10	3.5
12	2.0
14	0.5

Improvement in Walking Ability over 14 Days Period:

Table XVI %age improvement in walking ability of volunteers over 14 days study period

Study Days	%age improvement
0	0.0%
2	10.0%
4	20.0%
6	35.0%
8	50.0%
10	65.0%
12	80.0%
14	95.0%

Improvement in Mild Redness and Swelling over 14 Days Period:

Table XVII %age improvement in mild redness and swelling of volunteers over 14 days study period

Study Days	%age improvement
0	0.0%
2	20.0%
4	50.0%
6	75.0%
8	100.0%
10	
12	
14	

Improvement in Moderate Redness and Swelling over 14 Days Period:

Table XVIII %age improvement in moderate redness and swelling of volunteers over 14 days study period

Study Days	%age improvement
0	0.0%
2	15.0%
4	35.0%
6	55.0%
8	70.0%
10	90.0%
12	100.0%
14	

Improvement in Severe Redness and Swelling over 14 Days Period:

Table XIX %age improvement in severe redness and swelling of volunteers over 14 days study period

Study Days	%age improvement
0	0.0%
2	10.0%
4	25.0%
6	35.0%
8	50.0%
10	65.0%
12	80.0%
14	90.0%

CONCLUSION

Ketoprofen 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.

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