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FORMULATION DESIGN, OPTIMIZATION AND ENHANCEMENT OF SKIN PERMEATION OF IBUPROFEN CREAM BY USING OLIVE OIL AS PERMEATION ENHANCER

Muhammad Razi Ullah Khan[1, 2]

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

[2]Faculty of Pharmacy, The Superior College Lahore, Pakistan

Abstract:

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. Ibuprofen is a better tolerated NSAID because its topical formulation has limited numbers of adverse effects. The present research was conducted with the aim to develop and evaluate a novel Ibuprofen cream formulation, which would attenuate the gastrointestinal related toxicities associated with oral administration. Olive oil was used as penetration enhancer and was added in formulation to see its enhancement effect on in-vitro dug release profile. In the present study, a fixed concentration of Ibuprofen cream (2%) was prepared alone and by using olive oil as penetration enhancer. The prepared cream formulations were evaluated for several physiochemical parameters to justify its suitability for topical use. The in-vitro drug release was carried out by using Franz cell diffusion apparatus across the synthetic membrane. The cream formulations were evaluated for anti-inflammatory and skin irritation study. The results obtained were encouraging; Ibuprofen (2%) cream with olive oil was successfully prepared and exhibited the most satisfying results of all the parameters including a better result of in-vitro drug release as compared to Ibuprofen cream formulation without a penetration enhancer.

Key Words: *Anti-inflammatory, Cream, Ibuprofen, In-vitro drug release, Olive oil, Permeation enhancer*

Corresponding Author:

Muhammad Razi Ullah Khan,

Faculty of Pharmacy,

University of Sargodha, Pakistan

Tel: +92-334-7524323

Email: raziullahpharmacist@gmail.com

QR code

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INTRODUCTION:

The delivery of medicinal agents via the topical route can be dated thousands of years back. In ancient times the Greeks used to apply a mixture of water, olive oil and lead oxide to the skin as a balm. Lead oxide is used as astringent and olive oil is used in combination with drug because it could act as a barrier and it also moisturizes the skin. It was thought up until the end of 19th century that the skin was impermeable for many elements to be penetrated to the systemic circulation even to the penetration of gases. But later on in 20th century it was suggested that skin is permeable but the outer layers of skin being acts as barrier and later epidermis was much debated to be responsible for the permeability barrier [1]. The topical route for drug delivery is often comprised by low bioavailability of the drug because of the skin barrier functions, but this route can provide constant drug release and avoiding the first past metabolism by GIT [2]. In topical therapies the amount of drug needed for therapeutic effect is less bio available as compared to oral route of administration, but the absorbed drug appears to be adequate for therapeutic uses [3]. Several diseases can be treated via topical route but are often limited by the poor penetration through the human skin. The fact that topical formulations like gels, ointments and creams can improve the delivery of NSAID's, could be of great importance in succeeding topical therapeutic approaches. The way to improve the penetration of certain drugs via topical route could be achieved by the use of penetration enhancers. Ibuprofen is a Non-Steroidal Anti-inflammatory drug that exhibits anti-inflammatory, analgesic and antipyretic activities [4]. Ibuprofen [2-(4-isobutylphenyl) Propionic acid], a potent non-steroidal anti-inflammatory (NSAID) drug that is often used for the treatment of acute and chronic arthritic conditions, has pH dependent solubility and permeability [5]. Although ibuprofen is highly permeable through the stomach, its poor water solubility (log P value 3.6) limits its entry into systemic circulation before gastric emptying (30 min to 2 hr) occurs [6]. During gastric empting, ibuprofen enters the small intestine, where it cannot permeate through the membrane despite being solubilized [7]. Since dissolution is the rate-limiting step during drug absorption, the poor water solubility in oral forms of ibuprofen results in low bioavailability due to erratic or incomplete absorption from the gastrointestinal tract [8]. In addition to absorption difficulties, oral formulations of ibuprofen can cause gastric mucosal damage, which may result in ulceration and bleeding [9]. Ibuprofen is indicated in the management of Osteoarthritis, Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, post operative pain, chronic low-back ache and Gout.

Fig. 1: Ibuprofen structural formula

MATERIALS AND METHODS:

Chemicals

Ibuprofen was received as a gift from Stand Pharm Pakistan (Pvt) Ltd, Olive oil (Sigma Aldrich, Germany), Cetostearyl Alcohol (BDH Labs, England), White Petrolatum (Kukdong oils and chemicals, Korea), Methyl paraben and Propyl paraben (BDH labs, England), Liquid Paraffin (Kukdong oil and chemicals, Korea), Polyoxyethylene (80) Sorbitan monooleate (Tween 80) (Merck, Germany), Triethanolamine (Merck, Germany), Carbopol 980 NF polymer (Lubrizol, USA), Glycerin (Merck, Germany) and De-ionized water (Medilines Diagnostic division)

Apparatus

Glass beaker 50ml, 100ml (Pyrex, England), Conical flask 50ml, 100ml (Pyrex, Germany), Pipette 10ml (Preciclolor, Germany), White colored glass jar, Amber colored glass jar, Aluminum collapsible tubes and Aluminum foil

Instruments

UV-Visible Spectrophotomete (Shimdazu, Japan), Weighing balance (Analytical grade), Magnetic stirrer/ Hot plate (Made in Germany), pH meter (Model No: 3510, Germany), Homogenizer (Euro-Star, IKA D 230, Germany), Brookfield digital viscometer (model DV-III+, Brookfield Engineering Laboratory, INC. Franz diffusion cell Apparatus (Perm Gear, USA), Refrigerator (PEL, Pakistan), Soxhlet Apparatus, Incubator (Sanyo MIR-162, Japan), Oven (Schutzartdin 40050 IP-20, Germany).

Development of Ibuprofen Cream

2% by weight of Ibuprofen cream formulations along with and without penetration enhancer were developed by formulas given in Table 1.

Table 1: Development of Ibuprofen cream formulations

Serial No	Ingredients	Formulation 1 %age Composition	Formulation 2 %age Composition
1	Ibuprofen	2.0	2.0
2	Olive oil	---	1.0
3	Cetostearyl Alcohol	10.0	10.0
4	White Petrolatum	5.0	5.0
5	Methyl paraben	0.12	0.12
6	Propyl paraben	0.02	0.02
7	Liquid paraffin	5.0	5.0
8	Tween- 80	8.0	8.0
9	Triethanolamine	1.50	1.50
10	Carbopol 980	0.60	0.60
11	Glycerin	6.0	6.0
12	De-ionized water	61.76	60.76

Preparation of Cream

Ibuprofen topical cream was prepared in laboratory to investigate the penetration of Ibuprofen from cream and to investigate the effect of olive oil on penetration enhancement of Ibuprofen. The oil and aqueous phases were taken into bakers and heated to 75ºC over a water bath. In formulation 1 the oil phase was comprised of Ibuprofen, Liquid Paraffin, White Petrolatum, Cetostearyl Alcohol, Tween-80 and Carbopol 980 while in formulation 2 olive oil is also added in oil phase while the aqueous phase was composed of Methyl parabens, Propyl parabens, Glycerin and Triethanolamine and De-ionized water. 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 20 min. The homogenizer speed was then reduced to 1000 rpm and homogenization was continued for another 5-10 min. The speed was further reduced to 500 rpm and the homogenization extended for 5 min. The Ibuprofen cream was formulated.

Physiochemical Evaluation of Ibuprofen Cream

Homogeneity

The homogeneity of Ibuprofen cream was checked by visual inspection. In this regard the cream was filled into narrow transparent glass tubes and was checked in light for the presence of any particulate or lump.

pH

The pH of the Ibuprofen cream was found by immersing pH meter to a depth 0.5 cm in a beaker containing cream [10]. The determinations were carried out in triplicate and the average of three reading is recorded.

Spread ability

Spread ability was determined by the apparatus that consist of a wooden block, which was provided by a pulley at one end. By this method, spread ability was measured on the basis of 'Slip' and 'Drag' characteristics of creams [11]. A ground glass slide was fixed on this block. An excess of cream (about 2 gram) under study was placed on this ground slide. The cream was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. 1 Kg weight was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the cream between the slides. Excess of the cream was scrapped off from the edges. The top plate was then subjected to pull of 80 grams. 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. A shorter interval indicates better spread ability. Spread ability was then calculated using the following formula:

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

Where, **S** = is the spread ability, M = is the weight in the pan (tied to the upper slide), **L** = is the length moved by the glass slide and **T** = represents the time taken to separate the slide completely from each other.

Tube Extrude ability

It is a usual empirical test to measure the force required to extrude the material from tube. The

method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow one such apparatus is described by wood et al., In the present study, the method adopted for evaluating Ibuprofen cream formulation for extrude ability was based upon the quantity in percentage of cream and cream extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of cream in 10 seconds. More quantity extruded better was extrude-ability. The measurement of extrude ability of each formulation was in triplicate and the average values are presented[12]. The extrude ability was than calculated by using the following formula [13]:

Extrude ability = Applied weight to extrude gel from tube (in gm) / Area (in cm^2)

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 [14]. The readings were taken as triplicate and average of readings was noted.

Drug Content

For the determination of drug content of Ibuprofen in respected cream, approximately 100 mg cream was dispensed in 100 ml hydroalcoholic solvent and was stirred with the help of a magnetic stirrer for 2-3 hrs until the complete dissolution of the cream. The solution was then filtered through a membrane filter (0.45µm) and was analyzed by using UV Visible spectrophotometer at 222 nm for drug concentration.

Skin Irritation Study

In skin irritation study three albino rabbits were selected for the study. 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[15]. 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.

In Vitro Drug Diffusion Protocol

Franz cell apparatus was used for in vitro diffusion studies of Ibuprofen across synthetic membrane. The excised albino rabbit skin was fixed in between donor and receptor compartments of Franz cell apparatus. The cell had a 25 ml receptor compartment. The dialysis membrane was mounted between the donor and receptor compartments. The cream formulations were applied uniformly on the dialysis membrane and the compartments were clamped together. The receptor compartment was filled with the phosphate buffer (pH 7.4) and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. The study was carried out for 24 hrs with the interval of 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hrs. 2ml of sample was withdrawn from the receptor compartment at pre-determined time intervals and an equal volume of buffer was replaced. The absorbance of withdrawn sample was measured spectrophotometrically at 222nm against appropriate blank [16].

Anti-Inflammatory activity of Ibuprofen Cream

Anti-inflammatory [17] study was conducted using 10 albino rabbits (approved by Institutional Animal Ethical Committee, University of Sargodha, Sargodha, Pakistan) of either sex and divided into 2 groups. In these rabbits, acute inflammation was induced by sub-planter injection of 0.1 ml of freshly prepared 1 % suspension of carrageenan in normal saline in left hind paw of the rats. The medicated formulation (0.25g) was applied topically with gentle rubbing to the paw of each rat of respective group one hour before and one hour after the carrageenan challenge. The paw edema volume was measured using plethysmometer at 1, 2, 3 and 4 hour after injection of carrageenan. The average paw edema volume of all rabbits was calculated.

RESULTS AND DISCUSSION:

Physiochemical Evaluation of Cream

The developed Ibuprofen cream was evaluated for physiochemical tests including Homogeneity, pH, Spread ability, Extrude ability, Viscosity, drug content and skin irritation study.

Table 2: Evaluation data of Ibuprofen cream formulation

Parameters evaluated	Study Period			
	1st Reading	2nd Reading	3rd Reading	Average
pH ± SD	6.65± 0.6	6.74± 0.46	6.81± 0.351	6.73± 0.44
Spread ability (g/sec)	4.75	5.53	6.25	5.51
Tube extrude ability (g)	185	190	195	190
Drug Contents	99.3%	99.2%	99.1%	99.2%

Table 3: Viscosity of Ibuprofen cream formulation (cps) at different rpm

Speed in rpm	1st Reading	2nd Reading	3rd Reading	Average
2.5	65187	65235	65235	65219
4.0	34470	34697	34846	34671
5.0	25953	26123	26547	26208
10	14110	14735	15174	14673

Skin Irritation Test

Fig. 2: Rabbit Skin- on application of Ibuprofen cream

In Vitro Drug Diffusion study

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

Time (Hours)	% age of drug release (Formulation 1)	% age of drug release (Formulation 2)
0.0	0.0	0.0
0.5	7.56	10.73
1.0	12.55	18.77
2.0	21.95	30.85
4.0	29.66	41.12
6.0	38.98	51.33
8.0	57.13	72.41
10.0	65.42	85.62
12.0	71.56	89.22
24.0	76.46	91.51

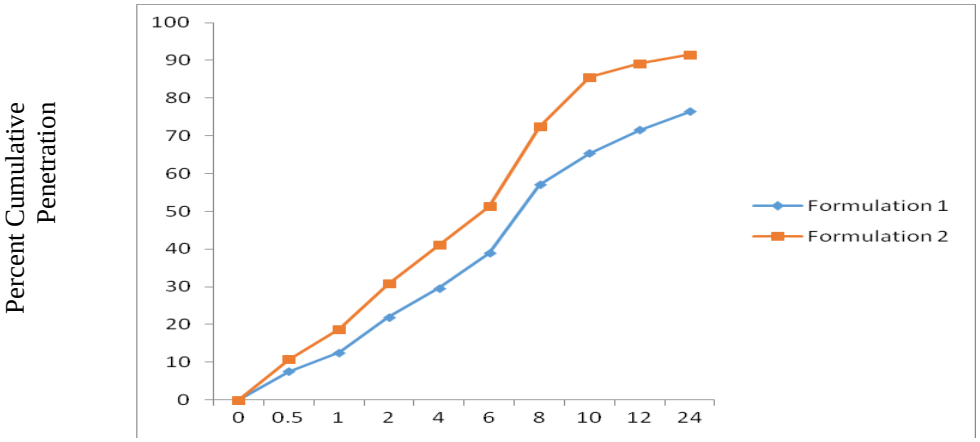

Fig. 3: Release curves of Ibuprofen cream across rabbit skin in phosphate buffer 7.4

Anti-Inflammatory effect of Ibuprofen Cream

Percentage increase in paw volume (inflammation) and percentage inhibition of inflammation in all the groups treated with test the product.

Table 5: Mean paw edema volume and %age inhibition of edema in albino rabbits

Time (Hours)	Mean paw edema volume	%age inhibition of edema
0	0.204	24.36
1	0.163	37.59
2	0.103	63.08
3	0.097	70.72
4	0.096	73.41
5	0.099	74.54
6	0.105	75.56

The developed Ibuprofen cream was evaluated for physiochemical tests including Homogeneity, pH, Spread ability, Extrude ability, Viscosity, drug content and skin irritation study. Good homogeneity was found in the cream formulation with no visual particles and lumps. pH evaluation is also important to check the stability of Ibuprofen cream formulation. Three reading of pH were taken at the time of preparation of cream and their average was determined. The pH of Ibuprofen cream was in the range of 6.6 ± 0.6 to 6.8 ± 0.351 and the average was found to be 6.73, which lies in the normal pH range of the skin and would not produce any skin irritation. The result of spread ability varies from 4.75 to 6.25

g/sec whereas the extrude ability of cream formulation from the collapsible tube varies from 185 to 195 g. The viscosity of cream formulation varies from 65219 cps to 14673 cps from 2.5 to 10 rpm. Three readings of the drug contents of Ibprofen cream were taken and the average was found to be 99.2%. In skin irritation test, no signs of erythema and edema were found after 24, 48 and 72 hours of Ibuprofen cream application in albino rabbits. From the data we have found that the prepared topical Ibuprofen cream formulation with olive oil released 91.51% of drug as compared to cream formulation without penetration enhancer that released 80.46% of drug over a period of 24 hours. 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.

CONCLUSION:

Ibuprofen topical cream was successfully prepared and was evaluated for physiochemical properties, In-vitro drug diffusion and anti-inflammatory studies. From the above results olive oil was found to be effective enhancer for the *in vitro* skin permeation of Ibuprofen. From the above results it can be concluded that the Ibuprofen cream formulation containing 2% Ibuprofen was suitable for topical application and it shows comparable results with that of marketed product.

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