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RESEARCH ARTICLE

FORMULATION DEVELOPMENT AND EVALUATION OF CREAM USING RICE BRAN WAX FOR TOPICAL APPLICATION

Rajeev Malviya*, Dr. M.D. Khirsagar, Dr. A.V. Chandewar

Sant Gadge Baba Amravati University, Amravati

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***Correspondence for Author**

Rajeev Malviya

Sant Gadge Baba Amravati University, Amravati, Maharashtra.

Email: rajeevmalviya33@gmail.com

ABSTRACT:

In the treatment skin disease, the vehicle (cream, ointment or lotion) may be as important as the active agent. Semisolid preparations are appropriate for patients with sensitive or dry skin who require a nonirritating, nondrying formulation. Patient with dry skin may complain of a “dry” feel with gels. So the people are performing deal with semisolid preparation (ointment, cream and lotion). Patients who have dry skin may be more comfortable with semisolid preparation like cream ointment and lotion, because they have an oily effect. Semisolid preparation work best in patients for the treatment of topical infections. The aim of the present investigation is to formulate and evaluate the best and safe semisolid preparation (cream) in topical composition by using rice bran wax as a base composition for econazole for the treatment of skin disease**.**

Keywords: Cream, Rice bran wax, econazole

INTRODUCTION

Over the last decades the treatment of illness have been accomplished by administrating drugs to human body via various roots namely oral, sublingual, rectal, parental, topical ,inhalation etc. [1]

Creams are semisolid emulsion systems with opaque appearances as contrasted with translucent ointments. Their consistency and rheologic character depend on whether the emulsion is water in oil or oil-in-water type and/or the nature of the solids in the internal phase.[2] Oil-in-water emulsions are most useful as water-washable bases where as water-in-oil emulsions are emollient and cleansing. Patients often prefer water in oil cream to an ointment because the cream spreads more readily, less greasy and the evaporating water soothes the inflamed tissue. Oil in water creams (vanishing creams) rub into the skin; the continuous phase evaporates and increases the concentration of a water soluble drug in the adhering film. The concentration gradient for a drug across the stratum corneum therefore increases, promoting percutaneous absorption. To minimize drug precipitation, a formulator may include a nonvolatile, water miscible co-solvent such as propylene glycol. An o/w cream is non-occlusive because it does not deposit a continuous film of water-impervious liquid. However such a cream can deposit lipids and other moisturizers on the stratum corneum and so restore the tissue's hydration ability, i.e. the preparation has emollient properties.[3]

Econazole (Eco), an anti-fungal imidazole compound, has been used in the treatment of vulvovaginal candidiasis [4,5] and superficial fungal infection.[6-8] Econazole has been shown to inhibit lipopolysaccharide-inducible nitric oxide synthase (iNOS) activity in rat aortic rings and cultured murine macrophage cells suggesting that it exerted a potential anti-inflammatory effect.[9]

MATERIAL AND METHOD

Material

Econazole of pharmaceutical grade were obtained as gift sample from Euphoria Healthcare Pvt. Ltd. Mumbai, Rice bran wax was procured from Bajaj Rice Mill, Warangal (Andhra-Pradesh, India), Lanolin & Lanolin Alcohols, Stearic acid purchased from Merck, Liquid paraffin purchased from Qualigens. All other reagents and chemicals used were of analytical reagent grade.

Formulation development of cream

Cream preparation

Preparation of aqueous phase

For the water phase all water soluble material (Triethenolamine, Glycerin, drug and Sorbitol) were mixed in a beaker and this solution heated till it attained a temperature of about 70^0 C.

Preparation of oil phase

For the oil phase rice brane wax, glycerol monostearate, cetostearyl alcohol, stearic acid, lanolin and liquid paraffin were added in a beaker and temperature was increase about 70^0C.

Preparation of cream

The aqueous phase was then transferred to the oil phase maintained at 70°C. The mixture was stirred manually with a glass stirring rod until the phases were homogeneous. The temperature of the mixture was allowed to cool to 50°C while stirring manually, and a separate solution of Methyl and Propyl Paraben in Propylene Glycol was added. The creams were then stirred until a smooth consistency was obtained, after which they were packed into 25 g ointment jars and stored at room temperature (25°C) until required for further analysis.

Table 1: Preparation of Cream

Ingredients (Gms)	Oil Phase								
	CE1	CE2	CE3	CE4	CE5	CE6	CE7	CE8	CE9
Econazole	1	1	1	1	1	1	1	1	
Rice Bran Wax	2.5	5	7.5	10	12.5	15	17.5	20	22.5
Stearic Acid	1.5	2.0	2.5	1.5	2.0	2.5	1.5	2.0	2.5
Lanolin	2	2	2	2	2	2	2	2	2
Liquid Paraffin	5	5	5	5	5	5	5	5	5
Cetostearyl Alcohol	2	2	2	2	2	2	2	2	2
Glyceryl Monostearate	3	3	3	3	3	3	3	3	3

				Aqueous Phase					
Triethanolamine	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Glycerin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Sorbitol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Propylene glycol	5	5	5	5	5	5	5	5	5
Methyl paraben	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water (qs to)	100	100	100	100	100	100	100	100	100

Characterization of developed formulation

Cream was 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.

Psychorheological Characteristic

The Psychorheological Characteristic was checked for topical cream formulations (colour, clogging, homogeneity and texture) and observations were shown in Table no.1 & 2

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually and observations were shown in Table No.

Extrudability study

The cream formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

Spreadability

Principle:

An important criterion for creams is that it must possess good spreadability. Spreadability is a term expressed to denote the extent of area to which the cream readily spreads on application to skin. The therapeutic efficacy of a formulation also depends on its spreading value.

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 off 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 cream 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 hair cream formulation between the two slides was traced uniformly to form a thin layer.

The weight was removed and the excess of the hair cream 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 50with 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 cream formulation.

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

Where, S=Spreadability (gcm/sec)

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

l= length of glass slide (6cms).

t = time taken is seconds.

Determination of pH

The pH of the skin creams were determined by digital pH meter. One gram of cream was dissolved in 25 ml of distilled water and the electrode was then dipped in to cream formulation for 30 min until constant reading obtained. And constant reading was noted. The measurements of pH of each formulation were replicated two times.

Viscosity

The measurement of viscosity of the prepared cream was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 6 at 10 rpm and 25^0C. The sufficient quantity of cream was filled in appropriate wide mouth container. The cream 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 creams were allowed to settle over 30 min at the constant temperature (25 $\pm/1^0$C) before the measurements.

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. 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 cream preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15mm internal diameter and 100mm height. The diffusion cell membrane was applied with one 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 phosphate buffer, freshly prepared (pH 7.4)as a receptor base and the system was maintained for 2 hrs at 37± 0.5^o C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of 15, 30, 45, 60, 90, 120 min 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 233.0nm for econazole and 264nm for 5-FU using phosphate buffer as blank.

Determination of stability conditions

Optimized formulation code C_{E3} was prepared and kept in humidity chamber at 25°C ± 2°C/60% RH ± 5% RH for 12 months and samples were withdrawn after every 3 months and evaluated for its physico-chemical properties such as pH, spreadability, and rheological measurement (as per ICH guidline).

Results and Discussion

Characterization of cream formulation

Table 2: Characterization of formulations C_{E1} to C_{E5}

Parameters	Formulation				
	C_{E1}	C_{E2}	C_{E3}	C_{E4}	C_{E5}
Physical Appearance	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application
pH	6.78±0.2	6.59±0.1	7.00±0.3	6.56±0.2	6.89±0.3
Viscosity (CP)	48840±3.5	52355±9.4	53147±5.0	54514± 4.56	55451± 2.5
Spreadability (gm.cm/sec)	32.36±0.7	31.56±0.58	31.56±1.2	32.54±3.56	30.45±2.15
% Drug content	98.1±0.50	98.3±0.12	99.7±0.12	98.16±0.	99.16±0.3
Extrudability	+++	+++	+++	+++	+++

+++ Excellent, ++ Good, + Satisfactory

Table 3: Characterization of formulations C_{E6} to C_{E9} and marketed formulation

Parameters	Formulation				
	C_{E6}	C_{E7}	C_{E8}	C_{E9}	Marketed Formulation
Physical Appearance	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application	Translucent, white, smooth on application
pH	6.36±0.3	6.27±0.1	7.09±0.6	6.76±0.4	6.53
Viscosity (CP)	48,440±7.3	48,584±2.8	51,323±4.3	52,456±2.2	53,426± 4.2
Spreadability (gm.cm/sec)	31.49±0.7	33.31±0.58	32.76±1.2	30.54±1.39	32.54±2.15
% Drug content	96.1±0.46	98.2±0.73	98.7±0.39	99.16±0.2	96.12±0.33
Extrudability	+++	+++	+++	+++	++

+++ Excellent, ++ Good, + Satisfactory

In-vitro Drug Release Studies of C_{E1} to C_{E9} and marketed formulation

Release of drug from cream base was significantly slower, which confirmed that slight prolonged drug release rate. Incorporation of rice bran wax affected the release rate of the drug. By increasing the amount of wax, the release rate of the drug decreased, which could be related to the increased rigidity of the formulation, followed by its de-creased permeability for the drug.

Table 4: In vitro drug release study of Econazole cream formulation

S. No.	Time (min)	% Cum. drug release									
		C_{E1}	C_{E2}	C_{E3}	C_{E4}	C_{E5}	C_{E6}	C_{E7}	C_{E8}	C_{E9}	Marketed
1	0	0	0	0	0	0	0	0	0	0	0
2	15	45.69	40.56	**38.89**	33.58	31.47	26.56	22.56	20.41	18.45	40.25
3	30	68.89	63.56	**58.74**	45.78	42.89	38.78	35.58	32.45	30.45	55.78
4	45	78.89	72.89	**69.78**	52.56	49.78	45.78	42.25	40.78	38.78	66.78
5	60	85.89	82.58	**78.41**	68.74	61.45	55.78	50.56	48.78	45.78	76.89
6	90	98.58	95.89	**93.69**	75.89	73.56	70.45	65.89	63.56	60.14	92.45
7	120	98.89	99.12	**99.78**	82.58	78.41	75.86	70.25	68.41	65.78	98.71

Discussion and conclusion

Different Semisolid preparation of econazole was prepared by fusion methods using rice bran wax as a semisolid base part. The semisolid preparations are able to giving local action for the treatment of skin cancer and had acceptable consistency and excludability. *In vitro* drug release from the semisolid preparation of rice bran wax shows significantly improved in drug release rate as compare to marketed preparation. It was concluded that in fusion method, C_{E3} formulation was the best formulation for deliver the drug for the treatment of skin disease. Hence it could be concluded that the rice bran wax based semisolid preparation would providing taste masking of drug and local onset of action without need of any device for their application on skin.

The preparation of rice bran wax based cream 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 targets by ointment, as both the groups found it difficult

to swallow conventional tablets and drug taste.

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