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A SCHEMATIC APPROACH OF EMULSIFYING AGENT AND PERMEATION ENHANCER IN CREAM.

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Abstract:
Topical route of application has a great potential as an effective and safe way to administer drug for its antifungal in effect. The concentration of surfactant and permeation enhancer significantly affects the critical parameters of cream formulation like flux, cumulative amount released at 12 hours and Enhancement ratio. In vitro permeation study across rat epidermal membrane showed that menthol enhanced the transdermal absorption of drug from cream formulation. The topical cream formulation developed in this study holds the promise for the further in vivo studies.
The aim of the present work under investigation is to check the effects of emulsifying agents(Cremophore RH40, Tween 60) and permeation enhancers (l-Menthol) on cream. Developing a formulation that is safe and can deliver the drug locally in an effective concentration for its effect . The development of topical antifungal drug delivery systems designed to have localised effects appears to be very advisable and beneficial over conventional routes of drug administration. However, due to the relative impermeability of the stratum corneum, which} provides the principal resistance to percutaneous absorption, extensive studies are generally necessary in order to optimize both the release of the drug from the topical vehicle and skin permeation Further, A topical formulation must be aesthetically pleasing, in addition to being} both physically and chemically stable, this require numerous excipients. Emulsifying agents and permeation enhancers have major influence on these} properties, hence they play an important role.

Key words: *of emulsifying agents, Permeation enhancers, stratum corneum, Antifungal , Topical cream*

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INTRODUCTION:

Creams are widely used in the cosmetic and pharmaceutical fields for the topical administration of hydrophilic and lipophilic active ingredients. There exist different types of emulsions, e.g. water-in-oil, oil-in-water, water-in-oil-in-water and oil-in-water-in-oil. Furthermore, emulsions are thermodynamically unstable and necessitate an emulsifier for the formation and stabilisation. Both, the type of emulsion and emulsifier could affect dermal and transdermal delivery, which has been reviewed in this chapter. Due to the complexity of topical emulsions and consequently the difficulty to investigate the exclusive effect of emulsifiers and emulsion type on skin absorption, as other emulsion ingredients may also contribute to interactions with the active ingredient and the skin, this chapter aimed at focusing mainly on studies with a systematic approach. For example, studies were included that investigated emulsions with the same composition and only differed in the emulsifier component or emulsion type. The review demonstrated that the type of emulsion significantly affected the dermal and transdermal delivery. In general, skin penetration of hydrophilic active ingredients was enhanced when the active was incorporated into the continuous phase of the emulsion. Furthermore, multiple o/w/o emulsions, in comparison to simple w/o emulsions, reduced the transdermal delivery of lipophilic active ingredients, whereas the dermal delivery was increased. Therefore, multiple emulsions could be useful for prolonged topical delivery. It was also demonstrated that the effect of the emulsifiers on dermal and transdermal delivery could vary, depending on the structure and physicochemical properties of the emulsifier/emulsifier system, such as the hydrophilic chain length, hydrophilic-lipophilic balance (HLB) value, emulsifier charge or solid particles vs. surfactant.

Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base. This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oilin-water emulsions. However, more recently the term has been restricted to products consisting of oil-inwater emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable Creams consist of medicaments dissolved or suspended in water removable or emollient bases. Creams are classified as water-in-oil or oil- in water therefore, combining immiscible compounds is possible by mechanical agitation or heat. The wet gum, dry gum, bottle, ad beaker methods are employed. More recently, the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable Types: Most commonly available creams classified on the basis of their function. • Cleansing & cold cream or lotion • Vanishing & Foundation cream • Night & massage cream. Hand & body cream • All purpose cream • Moisturizing cream

Physiology of the skin: The skin has several layers. The over laying outer layer is called epidermis; the layer bellow epidermis is called dermis. The dermis contains a network of blood vessels, hair follicle, sweat gland &sebaceous gland. Beneath the dermis is subcutaneous fatty tissues .Bulbs of hair project into these fatty tissues.

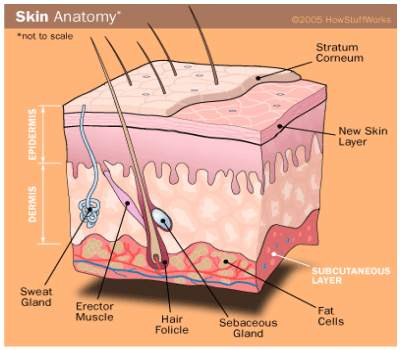

Fig.1.1: Cross section of Human skin The layers of epidermis are: 1. Stratum germinativum (growing layer) 2. Malpighion layer (pigment layer) 3. Stratum spimnosum (granular layer) 4. Stratum lucidum 5. Stratum corneum (horny layer). Epidermis The epidermis, the outermost part of the skin, is a continually renewing, stratified, squamous epithelium. It varies in thickness from around 0.06 mm on the eyelids to around 0.8 mm on the load-bearing areas of the skin.

Formulation Development:

Preparation of Cream :

Preparation of cream was done by emulsifying procedure in which at the same temperature of lipophilic phase and aqueous phase was thoroughly mixed. In the separate vessel lipophilic phase and aqueous phase was prepared. For the lipophilic phase, lipophilic ingredients, Cetyl alcohol, IPM, Cremophore RH40 was melted in a porcelain dish at 65-75oC. For the aqueous phase, hydrophilic ingredient, water, Tween 60 and drug was mixed and heat at temperature of 65-70oC. After melting the lipophilic ingredient, heating was stopped, aqueous phase added slowly and mixed properly. After completion of addition of all ingredients the homogeneous mixing for 10-15 minute with effective cooling was done to achieve better cream formulation.

Full Factorial Design:

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man hours and raw materials. Designing drug delivery formulations with the minimum number of trials is very crucial for pharmaceutical scientists (Hamed and Sakr, 2001). Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions (Li et al., 2005). The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Yi) is measured for each trial.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12}\ b_{22}X_{22}$$

Table 1: Full Factorial Design Layout

Batch No	**X_1 (concentration of Cremophore RH 40)**	**X_2 (concentration of Tween 60)**
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Table 2: Coded Values for % Concentration of Cremophore RH40 (X_1) and Tween 80 (X_2)

Coded value	% Concentration of Cremophore RH 40 (X_1)	% Concentration of Tween80 (X_2)
-1	2.5	1
0	5	2.5
1	7.5	5

Table 3: Formulations Using 3^2 Full Factorial Design (%w/w)

Batch no	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	1	1	1	1	1	1	1	1	1
Carbopol 940	1	1	1	1	1	1	1	1	1
IPM	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
Cetyl alcohol									
Tween 60	1	2.5	5	1	2.5	5	1	2.5	5

*** All the Quantity is in percentage**

Evaluation of Cream:

Table 4 Physical characterization of cream formulation F1 to F9.

Batch No	pH	Viscosity (cps× 10^3)	Spredability (gm.cm/sec)	Extrudability (%)	Drug content (%)
F1	5.22±0.1	683±4.24	13.23±1.13	92.33±0.45	99.05±0.20
F2	5.40±0.2	692±5.30	12.6±0.63	93.20±1.23	98.4±0.45
F3	5.48±0.3	714±3.45	13.64±1.02	93.31±0.89	99.6±0.24
F4	5.37±0.1	710±5.56	11.74±1.64	94.27±0.32	99.34±0.67
F5	5.41±0.2	725±7.30	12.59±0.80	91.61±0.80	98.23±0.30
F6	5.67±0.4	697±2.33	13.64±1.03	93.56±0.72	99.07±0.80
F7	5.89±0.2	707±1.77	11.6±0.85	93.31±1.12	100.6±0.34
F8	5.32±0.1	695±8.90	13.80±0.30	92.57±0.39	98.35±0.50
F9	5.45±0.2	715±3.40	13.50±0.45	91.90±1.10	100.2±0.98
Market Formulation	5.35±0.1	687±8.90	12.85±0.30	93.68±0.39	99.95±0.10

A.pH measurements:
The pH of the cream formulations was in the range of 5.22+0.1 to 5.89+ 0.2 (Table 1.3) which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations.

B. Viscosity measurements:
The data on viscosity study indicated that with constant concentration of the Cremophore RH40, increase in concentration of the Tween 60 viscosity of formulation was also increased. and with constant concentration of the Tween 60 increase in concentration of the Cremophore RH40 viscosity of formulation was also increased. So with both the emulsifying agents viscosity was found to be increased with increase in concentration. (Table 1.3)

C. Spreadability measurements:
Spreadability of cream was evaluated to test the ease of applicability of creams on skin The spreadability of the formulation was between 11.6±0.85 to 13.80±0.30 gm.cm/sec which showed good spredability(Table 1.3) and it was found to be comparable with the spredability of marketed product .

D. Determination of Extrudability:
Extrudability of cream was evaluated to measure the forces to extrude the material from a tube. Since the packing of creams have gained a considerable importance in delivery of desired quantity of cream from jar of extrusion of cream collapsible tube, therefore measurement of extrudability becomes an important criteria for creams. The exrtudability of the formulation was between 91.61±0.80 to 94.27±0.32 % (Table 7.3) which was found to be comparable with the marketed product .

E. Drug content:
The drug content of the cream preperation was found to be uniform among various formulations prepared and was found to range from 98.23±0.30% to 100.6±0.34 %. The drug content determination also showed that the all the formulations pass the acceptable drug content limit(Table 1.3)

F. Kinetic modelling and mechanism of drug release study:
Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism, and excretion (ADME), eventually becoming available for pharmacological action. Drug release is described in several ways. There are several models to represent the drug dissolution profiles where ft is a function of t (time) related to the amount of drug dissolved from the pharmaceutical dosage system. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in the function of some other parameters related with the pharmaceutical dosage forms. For this kinetic modeling and study of mechanism of drug release was done.The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R^2) was determined. The result of model fitting is shown in table1.4 given below:

Table 1.4: Result of model fitting(R^2)

Formulation	Zero order kinetics	First order kinetics	Higuchi model	Korsmeyer–Peppas model	n (release exponent)
F1	0.995	0.993	0.880	0.966	0.460
F2	0.995	0.991	0.883	0.977	0.471
F3	0.997	0.994	0.881	0.973	0.487
F4	0.999	0.996	0.897	0.977	0.498
F5	0.996	0.990	0.879	0.985	0.511
F6	0.984	0.972	0.878	0.999	0.516
F7	0.989	0.978	0.882	0.997	0.516
F8	0.993	0.983	0.882	0.995	0.534
F9	0.996	0.989	0.884	0.997	0.528

From the result shown in table 1.4, the in vitro drug release of batch F1, F2, F3,F4 & F5 were best explain by zero order kinetics as a plot showed highest linearity (R^2).The in vitro drug release of batch F6, F7, F8 & F9 were best explained by korsmeyer-peppas model. In case of F1 to F4, drug was released by Non-Fickian model (because n > 0.5) as shown in table 7.4. Among all batches from F1 to F9, F4 and F6 showed highest linearity (R^2 = 0.9990).

Accelerated Stability study:

Table1.5 Evaluation of accelerated stability study of optimized batch

Evaluation parameters	Time period for sampling		
	Initial	1 month	2 month
pH	5.40±0.1	5.39±0.1	5.37±0.2
Viscosity (cps*10^3)	698.23±0.12	697.12±0.23	695.78±0.62
Drug content (%)	99.34±0.21	99.01±0.12	99.00±0.55
% Drug released	80.21±0.12	79.95±0.15	78.20±0.24

Short-term stability study of optimized batch was carried out for 2 months at accelerated stability conditions. All the data are mentioned in table 1.5. Stability study revealed that no any major changes taken place throughout the stability study for 2 months so we can say that formulation F12 has good stability.

CONCLUSION:

Topical route of application has a great potential as an effective and safe way to administer drug for its antifungal in effect. The concentration of surfactant and permeation enhancer significantly affects the critical parameters of cream formulation like flux, cumulative amount released at 12 hours and Enhancement ratio. *In vitro* permeation study across rat epidermal membrane showed that menthol enhanced the transdermal absorption of drug from cream formulation. The topical cream formulation developed in this study holds the promise for the further *in vivo* studies and can be extrapolated for further development in treatment of fungal disease.

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