

Formulation and Evaluation of film forming spray containing Econazole Nitrate

Suchi S. Patel¹, Dr. V. M. Patel²

¹Student, A.P.M.C. College of pharmaceutical education and research, Himmatnagar

²Professor, M. Pharm, Ph.D., LLB,

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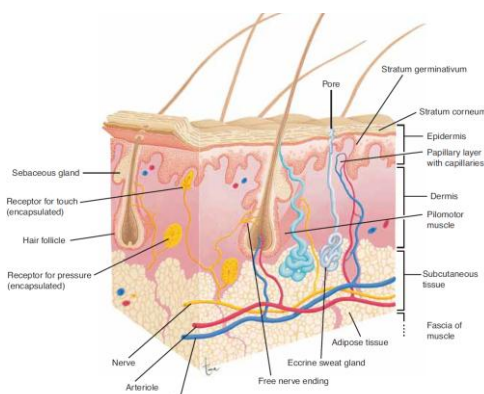
ABSTRACT: This research paper is about a film forming spray containing econazole nitrate which form a thin layer after evaporation of solvent and gives its effect on diseases. There are formulation for antifungal drug but yet econazole nitrate is not available in film forming spray form. Main purpose of this work was to prepare 1% W/V Econazole nitrate film forming spray for fungal infection. It was prepared using two polymer Eudragit RL 100 and HPMC E5 LV and other excipients. Ethanol and acetone were used as solvent in (60:40) ratio. Various parameters like viscosity, spray angle, volume of solution delivered on actuation, pH of the solution and ex-vivo parameters were performed.

KEYWORDS: Film forming spray, antifungal formulation, topical drug delivery, ex vivo evaluation, solvent evaporation.

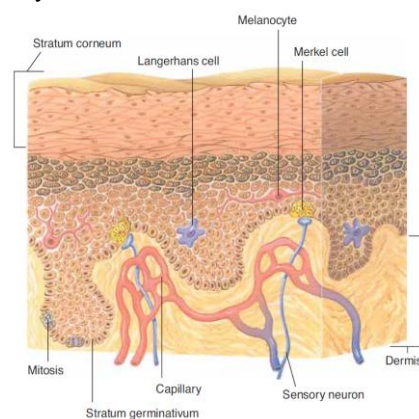
I. INTRODUCTION

In this paper formulation gives effect on skin a body organ which is readily available and prevents entry of micro and macromolecules into the body from environment because permeability of such substance is very low. Skin functions as a shield against the external molecules like micro and macromolecules. An average adult body has the skin of approximately 2m² surface area and it receives about 33% of the total blood circulating throughout the body.

There are major three layers of the skin (i) Outer Epidermis, (ii) Inner Dermis, (iii) Subcutaneous. Each of these layers is made of different tissues and they have very different functions.



A. Epidermis: The epidermis forms the outermost covering of the human skin. It consists of stratified squamous keratinized epithelial tissue and is particularly thick in areas such as the palms and soles. The epidermis is further divided into sublayers, including the **Stratum Germinativum** and the **Stratum Corneum**. The epidermis has several layers:



B. Dermis: The dermis's fibrous connective tissue is uneven, meaning that its fibers are not parallel but rather flow in all directions. Fibroblasts create collagen and elastin fibers. Collagen fibers are strong, yet elastin fibers can contract back after being stretched. The two characteristics of the dermis are strength and

flexibility. The skin becomes less elastic as we age due to the breakdown of the elastin fibers.

C. Subcutaneous Tissue: Another name for subcutaneous tissues is superficial fascia. Adipose tissue and areolar connective tissue make up this structure. Collagen and elastin fibers, as well as many white blood cells, are found in areolar connective tissue, also known as loose connective tissue, which circulates in the tissue fluid between muscles and skin. Pathogens that enter the body through the skin, also known as percutaneous absorption, is the term used to describe any molecules or substances that pass through several layers of skin and enter the systemic circulation. Drug transit into deeper dermal layers and systemic uptake occur very quickly and easily after the drug molecule crosses the stratum corneum barrier.

For any molecules applied to the skin, two main routes of skin permeation can be defined: (1) Transepidermal route, (2) Transfollicular route

1. Transepidermal route: Molecules travel an undamaged horny layer during transepidermal transfer. There are two possible micro-routes of entry: the intercellular pathway and the transcellular (or inner) pathway.

Both polar and non-polar chemicals can diffuse through intercellular and transcellular channels via various methods. While the non-polar dipoles dissolve and permeate the non-aqueous lipid matrix of the stratum corneum, the polar route is mainly

through the skin are eliminated by these migratory white blood cells. Adipose tissues are specifically designed to store fat. In addition to providing some insulation from the cold, this layer cushions the body's bony parts.

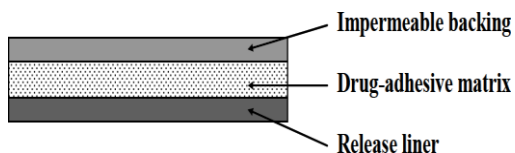
➤ **Absorption of drug through Skin:** The skin serves as a barrier that keeps harmful substances and bacteria out of the body and water within. For a topically applied medication to have a local or systemic effect, it must pass through the stratum corneum composed of 'bound water' that hydrates the stratum corneum. Therefore, a penetrates concentration ratio (log K) largely dictates its principal path. Lipophilic chemicals (octanol/water log K > 2) go through the stratum corneum via the intercellular channel, whereas hydrophilic substances partition more easily into the intracellular domains. The majority of molecules choose to pass through the stratum corneum via both routes.

2. Transfollicular route (Shunt pathway):

The sebaceous glands, which are connected to the sweat and hair follicles, are part of this pathway. Despite having a high permeability, these channels are usually regarded as less important because to their small surface area, which makes up only 0.1% of the skin's total area. This channel appears to be crucial for large polar molecules and ions that struggle to cross the stratum corneum.

II. INTRODUCTION TO DRUG DELIVERY SYSTEM

Research on topically applied drug delivery does have been going on for over a century, but only in last 40 years active development of product lines started to pick up steam. A new method for treating skin conditions that provides both topical and transdermal treatment is the topical film forming system. FFS is described as a non-solid dosage form that creates film in situ, meaning that the excipients in the formulations create film on the skin as the



vehicle evaporates. In addition to improving patient compliance, formed film serves as a matrix for the drug's prolonged release. It can perform better than traditional pharmaceutical dosage formulations in a number of ways, including being easier to apply, improving drug distribution, lowering the frequency of doses, and eliminating the first pass impact.

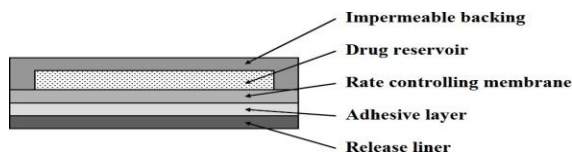
➤ **Transdermal Patch:**

The transdermal patch group is divided into two subgroups: reservoir-type patches and matrix-type patches. In matrix-type patches, the medication is either dissolved or delayed in a water-soluble or lipid-soluble polymeric matrix. This matrix either has good adhesive properties on its own (drug-in-adhesive type) or is completely or partially covered with an additional adhesive layer to guarantee a reliable attachment to the skin. To protect the delivery system and prevent drug diffusion to the patch's outer surface, an impermeable, often occlusive backing layer covers the outside of the drug-containing matrix. The outer edge of the

surface that will come into touch with skin is covered by a thin, inert release liner shown in figure.

In reservoir-style patches, drugs are integrated into a **Matrix type transdermal patch** reservoirs (such

as hydrogels) behind impermeable backing layers. The medication release from this reservoir is controlled by a microporous or non-porous membrane. In situations where the membrane is not sticky, an additional layer of adhesive ensures a tight fit between the skin and the patch system.



Reservoir type Transdermal patch

➤ **Transdermal semisolids:** In the past, semisolid formulations were mostly used to treat skin diseases; instead of aiming for bloodstream absorption, they

directly targeted the skin. But with the creation of these semisolid formulations, an alternative has surfaced that has benefits above conventional polymeric patches. They are a good choice since they can transport sufficient amounts of drugs to the systemic circulation. In this field, alcoholic hydrogels in particular have become more well-known.

Depending on the type of formulations gels or creams different components are used. These substances include a wide variety of substances, such as glycols, alcohols, water, and emulsifiers. They also include fatty substances like paraffins, oils, and waxes, as well as hydrophilic or hydrophobic polymers like acrylates and cellulose derivatives.

III. EXPERIMENTATION

Materials: For the preparation of formulation Econazole nitrate (API), Eudragit RL 100 and HPMC E5 LV polymer were used, penetration enhancer (Menthol, camphor) and plasticizer (PEG 400) and solvent were used Ethanol:Acetone (60:40) in present investigation.

Method: At first, prepare (60:40) of Ethanol and Acetone solvent mixture. Then add film forming polymer of required quantity in 3/4 quantity of

solvent mixture (Ethanol:Acetone). Once the clear polymeric solution was obtained with constant stirring add other excipients such as plasticizer (PEG-400) and penetration enhancer (Menthol:Camphor - 1:1). After adding all the excipient, the drug (Econazole nitrate) of required quantity was added to solution. Stir solution till it become clear and make up the volume using solvent. Then prepared solution was filled into the spray bottle.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Econazole Nitrate (w/v)	1%	1%	1%	1%	1%	1%	1%	1%	1%
Eudragit RL (w/v)	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%
HPMC E5 LV (w/v)	1%	1%	1%	1.5%	1.5%	1.5%	2%	2%	2%
PEG 400 (w/v)	3%	3%	3%	3%	3%	3%	3%	3%	3%
Menthol:Camphor (1:1) (v/v)	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Ethanol: Acetone (60:40) (v/v)	upto 100%	upto 100%	upto 100%	upto 100%	upto 100%	upto 100%	upto 100%	upto 100%	upto 100%

TABLE 1: Formulation of Econazole Nitrate spray

IV. EVALUATION OF ECONAZOLE NITRATE SPRAY:

Preformulation study:

Melting point determination of drug: It is determined by capillary method in which sunbim instrument was used. The capillary was filled with

Econazole nitrate and it was tied with the thermometer. The thermometer with the capillary then place in sunbim instrument. The device was exposed to external heat and the point at which Econazole nitrate started to melt was recorded.

Determination of λ max: Wavelength maxima of Econazole nitrate were determined by using UV- Vis 1700 Spectroscopy by Shimadzu, Solution of Econazole nitrate in Methanol was scanned in 200-400 nm range.

Preparation of standard stock solution:

STANDARD STOCK SOLUTION 1 : 100 mg Econazole Nitrate drug sample was weighed accurately and transferred to 100 ml volumetric flask and diluted upto the mark with methanol (100 μ g/ml).

STANDARD STOCK SOLUTION 2 : From Stock solution 1 aliquot amount of 10 ml was taken and dissolved in 100 ml of Methanol in 100 ml volumetric flask.

Preparation of working solution:

This series consisted of different concentrations of

standard Econazole Nitrate solution ranging from 5-25 μ g/ml. The solutions were prepared by pipetting out 0.5, 1, 1.5, 2.0, and 2.5 from stock solution 2 of Econazole nitrate (100 μ g/ml) into series of 10 ml volumetric flasks and the volume was adjusted to mark with methanol to make 5, 10, 15, 20, and 25 μ g/ml solution of Econazole nitrate.

Post formulation study:

Viscosity:

The viscosity of a solution determines its ability to spray through a spray bottle (atomizer), making it a crucial factor in the formulation of film-forming spray. It cannot be sprayed effectively if the viscosity is high, and it cannot be sprayed if the viscosity is excessively high. For proper spraying, the viscosity must be lower or comparable to that of water.

The viscosity of the 10ml solutions was measured at $26 \pm 1^\circ\text{C}$ using Brookfield viscometer (digital viscometer model DV-II+, Stoughton, MA, USA). The spindle number 61 was rotated at 20 rpm.

pH of the solution:

The formulation's pH was estimated using a digital pH meter. The buffer solutions for pH 4, 7, and 9 were ready. The pH meter was calibrated using those 4, 7, and 9 pH buffer solutions. The pH was instantly recorded from the meter after the rod was immersed in the formulation solution.

Volume of solution delivered upon actuation:

It was measured using weighing method i.e. the container is weighed before and after actuation. The volume of solution delivered upon each actuation was calculated using equation 1 as follows:

$$A_v = (W_0 - W_t)/D \dots \dots \dots \text{Equation 1}$$

Where,

A_v = Volume of solution delivered upon each actuation,

W_0 = Initial weight of the formulation before actuation,

W_t = Weight of formulation after actuation,

D = Density of the formulation

Spray angle: The spray angle, indicating the dispersion of the solution when sprayed through an atomizer, was evaluated in this study. The method entailed spraying the solution containing Sudan red (10 mg) onto a piece of paper for visualization. Sprays were discharged horizontally onto a white paper placed 10 cm away from the nozzle. The resulting circle's radius on the paper was measured from multiple directions in triplicate, and the spray angle (θ) was subsequently computed using Equation 2.

$$\text{Spray angle } (\theta) = \tan^{-1}(h/r) \dots \dots \dots \text{Equation 2}$$

Where,

h= Distance of nozzle from paper

r= Average radius of circle.

Drying time: Film can be dried by placing it on a volunteer's hand or forearm, or it can be placed on a glass slide for a predetermined amount of time while maintaining human body temperature. A proper FSS should have a brief drying time to prevent patients from having to wait a long time.

Drug content determination study: To prepare the film-forming solution, 1 ml of the solution, containing 10 mg of the active ingredient, was transferred into a 100 ml volumetric flask. The solution was filtered through whatmann filter paper. 1ml of the above solution was pipette out in 10ml volumetric flask and diluted to mark with methanol. From this 1.5ml of the solution was pipette out and transferred into 10ml volumetric flask and diluted upto the mark with methanol (15 μ g/ml). The absorbance of this solution was measured at 285 nm against the solvent mixture. The concentration of Econazole nitrate can be determined using Equation3.

$$y = mx+c \dots \dots \dots \text{Equation 3}$$

Where,

y = Absorbance,

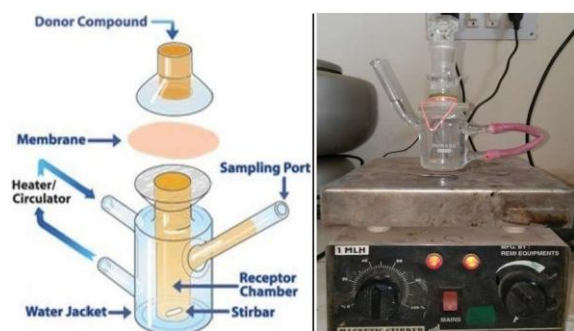
m = Slope of calibration curve,

x = Concentration of solution,

c = Constant

In-vitro drug release: In this Franz diffusion cell was used in the assessment of in-vitro drug release using membranes of mixed cellulose esters with pore size equal to 0.22 mm. Prior to the experiment, synthetic membranes was put in contact with phosphate buffer saline (PBS; pH 7.4) for 30 min. In donor compartment

1ml of the formulation and in receptor compartment 20 ml of PBS (pH 7.4) was filled. Throughout the Aliquots of 0.5ml samples were removed from the receptor compartment at different time intervals (10 min) for 60 min and diluted upto 25ml then, Econazole nitrate was spectrophotometrically measured at 285 nm. An equal amount of fresh dissolution medium was replaced after each withdrawal. UV spectrum of Econazole Nitrate was observed for Econazole nitrate transported through the membrane of different time interval.



Franz diffusion cell

% drug release = $\frac{\text{Cons. Of drug (in mg)} \times \text{Volume of receptor compartment}}{\text{Label (amount of drug in donor compartment)}} \times 100$

V. RESULT AND DISCUSSION:

Melting point determination:

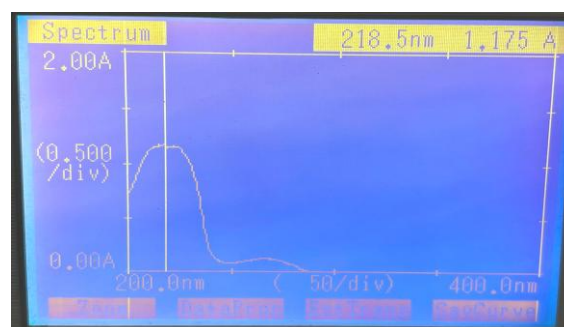
Sr. No.	Temperature (°C)
1.	161

2.	164
3.	162
Average (n=3)	162.33

Melting point of Econazole nitrate was found to be in range of 160-165 °C as reported in literature, thus indicating purity of the drug sample. If any impurity is present, it causes variation in the melting point of given drug.

Determination of λ max:

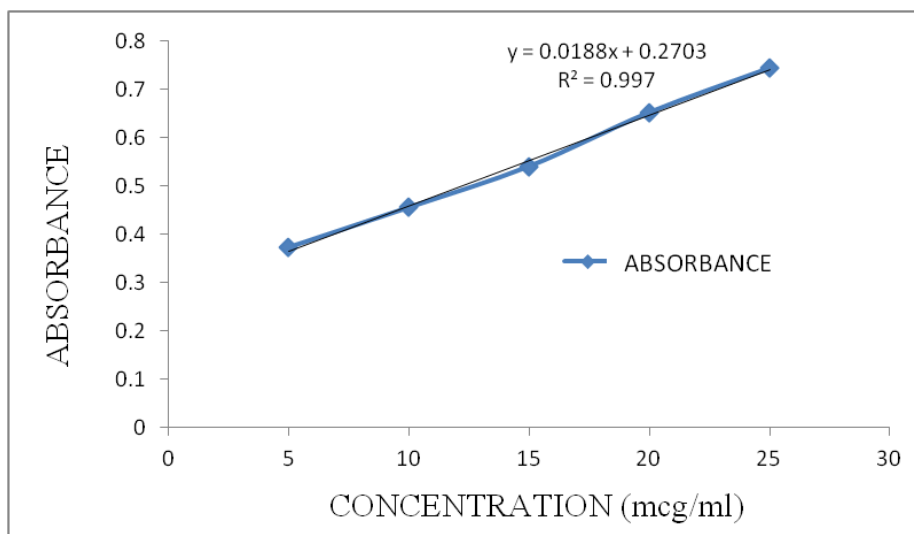
Drug (API)	Reported λ max	Experimental λ max
Econazole Nitrate	220 nm	218.5 nm



UV spectra of Econazole nitrate showing wavelength maxima

CONC (µg/ml)	Absorbance at 218.5 nm			Average Abs at 218.5 nm
	I	II	III	
5	0.373	0.375	0.369	0.372 ± 0.003
10	0.458	0.457	0.452	0.455 ± 0.003
15	0.534	0.535	0.551	0.54 ± 0.009
20	0.653	0.651	0.654	0.652 ± 0.001
25	0.746	0.743	0.745	0.744 ± 0.001

Standard calibration curve of Econazole nitrate



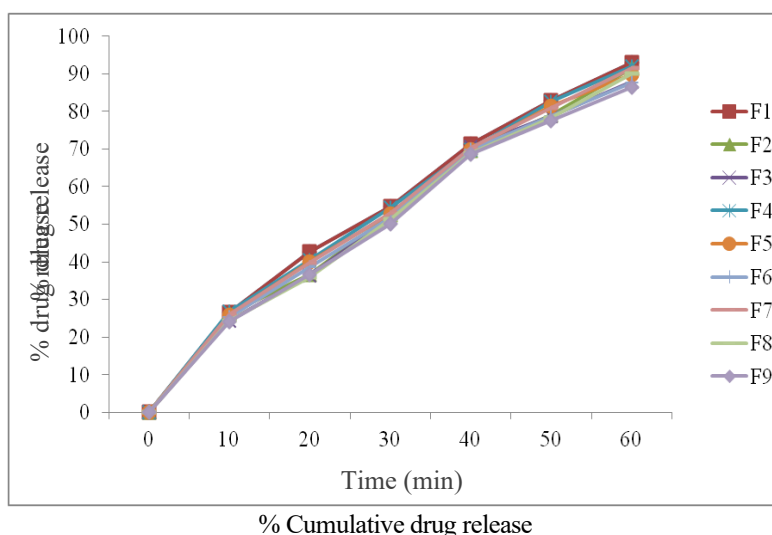
Standard calibration curve of Econazole nitrate

Post formulation study:

Formulation:	F1	F2	F3	F4	F5	F6	F7	F8	F9
Viscosity (cp)	5.68	6.92	8.84	7.12	8.65	10.94	9.35	11.84	14.72
pH of the solution	5.72	5.70	6.18	5.71	5.74	5.82	5.81	5.71	5.91
Volume of solution delivered on actuation (ml)	0.061	0.057	0.051	0.060	0.060	0.055	0.060	0.059	0.052
Spray angle	20.82	18.45	16.12	17.95	15.53	13.48	14.82	12.34	10.15
Ex-vivo physical evaluation									
Film formation time (sec)*	62	81	88	69	75	70	74	87	88
% Drug content	99.5	99.74	99.55	99.8	99.73	99.4	99.51	99.35	99.71
% drug release at 60 min	92.96	91.5	88.03	91.93	89.81	87.59	91.57	89.98	86.55

In vitro drug release: Drug diffusion study of Batch F1-F9 shows the drug diffuse through membrane in range of 92.96 – 86.55 at 60 min. (1 hr).

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	26.49	26.33	24.25	26.69	25.82	25.22	26.06	24.42	24.15
20	42.71	36.67	36.34	40.55	40.04	38.45	39.68	35.95	36.67
30	54.7	52.52	51.85	54.49	52.77	51.74	52.98	51.2	50.09
40	71.19	69.55	70.49	69.85	69.85	69.74	70.45	68.93	68.74
50	82.8	79.01	78.88	82.66	81.31	78.69	80.83	78.19	77.51
60	92.96	91.5	88.03	91.93	89.81	87.59	91.57	89.98	86.55



VI. CONCLUSION

Film forming spray of Econazole nitrate as antifungal drug, was successfully formulated using Eudragit-RL and HPMC E5 LV and using other excipients. Spray bottle was used to make spray of formulated formulation. When evaluation parameters such viscosity, pH, volume of solution supplied on actuation, spray angle, film formation time, film appearance, skin adherence, film flexibility, film washability, and in-vitro drug release were taken into account. Formulation F5 was determined to be the optimal formulation. The prepared formulation showed drug content within the acceptable limits, ensuring uniform dosing. The desired system will improve compliance of patients and reduce the limitation of current therapy. So,

Film forming spray can become an alternative to the current conventional dosage form.

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