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Formulation and Development of Rutin and Gallic Acid Loaded Herbal Gel for The Treatment of Psoriasis and Skin Disease

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Abstract: *Psoriasis is a chronic, non-contagious, autoimmune genetic disorder characterized by keratinocyte differentiation and dermo-epidermal inflammatory infiltration affecting upper back sacral region, scalp, nails and joints and may cause psoriatic arthritis, myopathy, enteropathy, spondylitic heart disease, malignancy or the AIDS. It appears first in 15 and 30 years age group. Histopathology of disease involves acanthosis, elongation and oedema of dermal papillae, absence of granular cell layer suprapapillary thining of stratum malpighii and prominent parakeratosis. Many drugs have been introduced in the market like clobetasol propionate, acitretin, methotrexate etc. but no single entity has proved to be beneficial to the patients. Though advancements have taken place in modern therapy it suffers from few shortcomings like no cure, treatment dissatisfaction and unavoidable drug interactions on long exposure.*

Keywords*: Psoriasis, Histopathology, Drug interactions*

I. Introduction

Psoriasis is a common, chronic, non-contagious, auto-immune disease that primarily affects the skin and seen in about 2-3% of population world-wide [1]. The word "psora" comes from Greek word which means "to itch". Psoriasis, a term which has been in use since 133 AD, was originally grouped with leprosy until the 19th century. It has been suggested that biblical leprosy was, in fact, the disorder known today as Psoriasis [2]. It is mostly an inheritant disease, characterized by scaly, red and itchy plaques. The most commonly affected areas are the entire scalp and can also spread to the forehead, back of neck or behind ears, chest, arms, elbows, in the armpits, under the breasts, around the genitals, knees, legs, toenails and fingernails [3].It affects males and females equally and also affects children, adult, older peoples and may occur at any age of life. It is more common in people between the ages of 15 and 35, According to National Psoriasis Foundation. Psoriasis is partly due to genetic and partly due to environmental factors [4]. Psoriasis can be categorized as mild, moderate and severe. Mild psoriasis leads to formation of rashes and when it becomes moderate the skin turns scaly. In severe conditions, the red patches may be present on skin surface and become itchy. This affects a person's professional and social life. The normal mechanism of body is to form new skin cells every month to replace the skin which is shed off. But, in psoriasis the new skin cells grow rapidly within days rather than weeks. This leads to accumulation of dead skin on the skin surface resulting in thick patches of red, dry and itchy skin [5].

Types of Psoriasis

Sr.No	Types	Characteristics	Affected Areas	Causes
1	**Plaque Psoriasis** The Most common form of psoriasis. About 80–85% of those who have psoriasis have this type.	Characterized by inflamed skin covered with silvery-white scaly skin. plaques itch or may be painful.	Elbows, knees, scalp and lower back.	Irritation of skin, contamination, medications, alcohol, stress, smoking, and sunlight.
2	**Guttate Psoriasis** It is usually triggered by a bacterial infection such as streptococcal throat infection and often starts in childhood or young adulthood and affects about 18% of all psoriasis patients.	Characterized by many small scaly, red or pink drop like lesions.	Chest, arms, legs.	Streptococcal infection, bacterial or viral infections, injury to skin, e.g., cuts, burns, and insect bites, medicines, stress, sunburn, and alcohol.
3	**Inverse Psoriasis** Also known as Flexural Psoriasis. About 18% of those who have psoriasis have this type.	Characterized by bright red scratches that are smooth and shiny.	In the armpits, groin, below the breasts, and in additional skin folds nearby the genitals and the buttocks.	Yeast overgrowth, high sensitivity to friction or sweating.
4	**Postural Psoriasis** : Less than 5% of patients who have psoriasis have this type.	Characterized by white swellings of non-infectious pus surrounded by red skin.	Smaller areas on the hands, fingertips, or feet.	Overexposure to UV light, pregnancy, systemic steroids, contaminations, stress, and sudden withdrawal of systemic medications or potent topical steroids.
5	**Erythrodermic Psoriasis**: It is a uncommon form of psoriasis and affecting 1-6% of psoriasis cases.	Characterized by widespread, fiery redness of the skin shedding of scales in sheets.	It affects most of the body surface.	Use of steroid, simple sun burn, emotional stress, alcoholism, infection, allergy.
6	**Nail Psoriasis** Almost 50–80% of those who have psoriasis have this type.	Modification in nail color, little pits in nails, lines across nails, white area on nail plate, thickening of skin under nail, loosening of nail.	Toenails and fingernails.	Combination of genetic, environmental, and immune causes

II. Material And Methods

Rutin obtained from Research Lab, Mumbai. Gallic Acid , Propylene Glycol and Triethanolamine obtained from Analab Fine chemical , Mumbai. Carbopol 940 from Research Lab Fine Lab Mumbai. DMSO from Merck Pvt.Ltd. All other chemicals used are of analytical grade.

- ***Preparation of formulation***

Sr. No	Ingredients	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	Rutin	1%	1%	1%	1%	1%	1%	1%	1%	1%
2	Gallic Acid	1%	1%	1%	1%	1%	1%	1%	1%	1%
3	Carbopol 940	1.25	1.25	1.25	0.15	0.5	2.0	2.3	0.5	2.0
4	Propylene glycol	6.5	4.3	6.2	6.5	8.0	5.0	6.5	5.0	8.0
5	Distill Water	q.s 100ml	q.s 100ml	q.s 100ml	q.s 100ml	q.s 100ml	q.s 100ml	q.s 100ml	q.s 100ml	q.s 100ml

- ***Evaluation of Gel***

1. pH
2. Viscosity
3. Spredability
4. Drug Content Test
5. In vitro drug Diffusion study studies.
6. Microbial Study
7. Antioxidant Activity
8. Animal Study

- ***Evaluation***

Methods for Evaluation Studies for Gel

1) Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicates and average values were calculated.

2) *Rheological Studies*

a) Viscosity Study

Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to measure the viscosity (in poise) of the prepared gel formulations. The spindle (T-D) was rotated at 10 rpm. The viscosity of formulations were more correct which was near to 100% torque. Samples were measured at 30 ± 1° C. Reading was detected 30 sec after measurement was made, when the level was stabilized.

b) Spreadability

The Spreadability of the BG5 was measured by spreading of 0.5 g of the gel on a circle of 2 cm diameter premarked on a glass plate and then a second glass plate was employed. Half kilogram of weight was permitted to rest on the upper glass plate for 5 min. The diameter of the circle after spreading of the gel was determined

3) In Vitro Diffusion Studies

Phosphate buffer of pH 6.8 was used for in vitro release as a receptor medium. The Cellophane membrane was used in franz- diffusion cell. The 1g of gel sample was applied on the membrane and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer of pH 6.8. The

temperature of diffusion medium was thermostatically controlled at 37±1ºC and the medium was stirred by magnetic stirrer at 100 rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically.

4) Antimicrobial Study

The crude drug and optimized formulation was screened for antimicrobial action on selected microbes i.e. Candida Albicans, and staphylococcus aureus which are normal flora of skin and also Pseudomonas Aeruginosa using cup plate method .Previous two microbes are opportunistic pathogens. They are involved in many secondary skin infections usually occurring in psoriatic lesions. Internal standards used were Beclamethasone for bacteria and fungi respectively.

5) Antioxidant Activity

(a) In Vitro Antioxidant Activity Of Drug By DPPH Method

The aliquots of drug and standard, Ascorbic acid was prepared in the range of 50,100,150,200 and 250 mcg/ml. Test samples and standards were taken 1 ml each and mixed with 5ml DPPH solution. The mixture was incubated at 37°C for 30 minutes and absorbance was taken at 517 nm. % radical scavenging activity was calculated using following formula,

$$\%\text{Free Radical Scavenging activity} = \frac{\text{Abs .of Sample} - \text{Abs. of Control}}{\text{Abs.of Sample}} \times 100$$

6) Stability Study

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, retest periods and shelf life to be established. FDA and ICH specifies, the guidelines for stability testing of a new drug products as a technical requirement for registration of pharmaceuticals for human use. The main objective of stability study is to evaluate stability of optimized formulation at different temperature and humidity conditions.

Table no 7: ICH guidelines for stability study

Study	Storage condition	Duration
Long Term	$25^0C \pm 2^0C$, RH 60%±5%	12 months
Intermediate	$30^0C \pm 2^0C$, RH 65%±5%	6 months
Accelerated Temperature	$40^0C \pm 2^0C$, RH 75%±5%	3 months

III. Result and Discussion

- *Preformulation study*

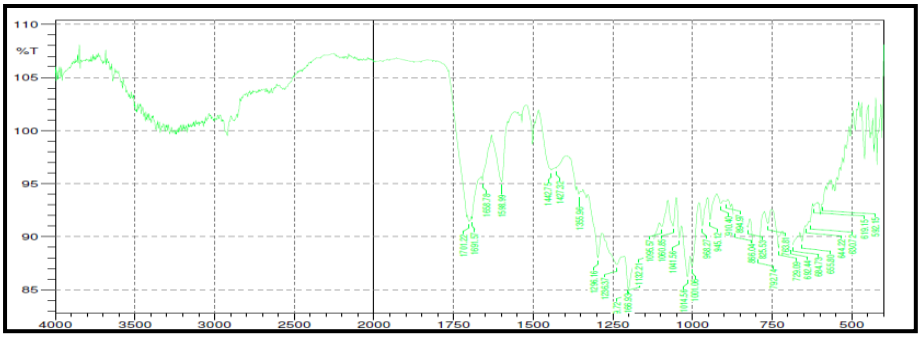
Properties	Rutin	Gallic Acid
Colour	Yellowish green	White
Odour	Odourless	Odourless
Nature	Powder	Powder

- *Solubility*

Solvents	Rutin	Gallic Acid
Methanol	Soluble	Soluble
Ethanol	Soluble	Soluble
DMSO	Soluble	Soluble
Dimethyl Formamide (DMF)	Soluble	Soluble
Water	Sparingly soluble	Sparingly soluble
Aq.Buffer	Sparingly soluble	Sparingly soluble

- *Identification*

- ***1. Melting Point***
  Melting Point of Rutin was observed as 241°C and Gallic Acid as 262°C.
- ***2. IR Spectrum of Drug***



FTIR Spectrum of Rutin and Gallic Acid with Carbopol 940

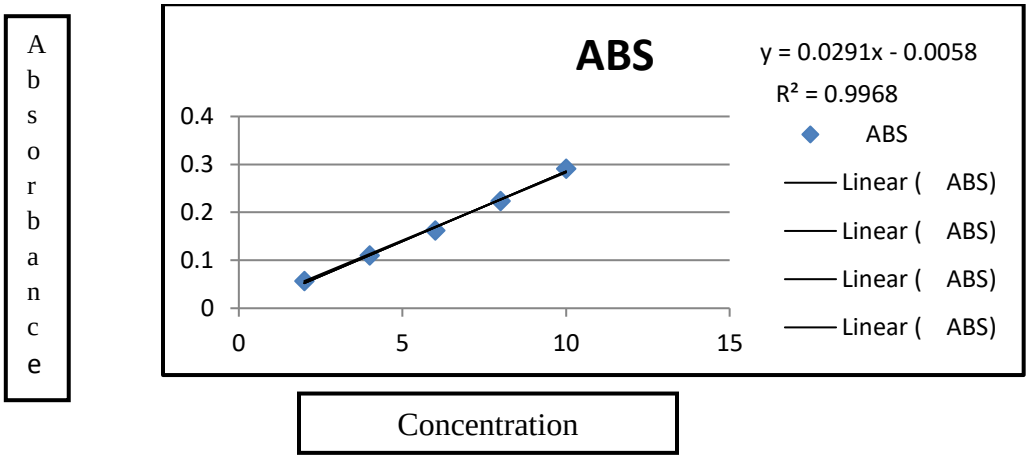
IR signal (cm^{-1})	Functional group
1701.22	C=O Stretching
1658.78	C=C Stretching
1427.32	O-H Bending
1296.16	C-O Stretching
692.44	C=C Bending

3. Calibration curve of Rutin

Analysis data for calibration curve of rutin

Concentration (µg/ml)	Absorbance (nm)
2	0.057
4	0.110
6	0.162
8	0.224
10	0.291

Absorbance of Rutin



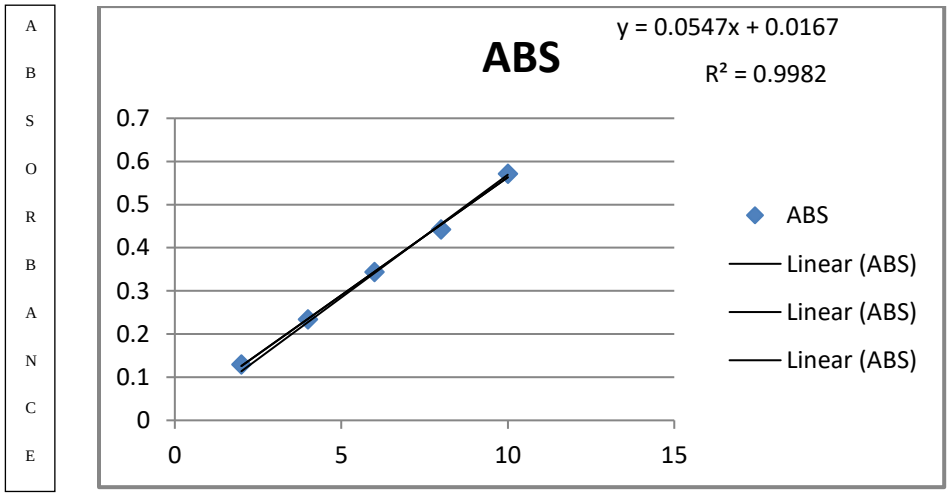
Calibration curve of Rutin

4. Calibration curve of Gallic Acid

Analysis data for Calibration curve of Gallic Acid

Concentration (µg/ml)	Absorbance (nm)
2	0.130
4	0.234
6	0.344
8	0.443
10	0.572

Absorbance of Gallic Acid



Calibration curve of Gallic Acid

- ***Evaluation of Gel***

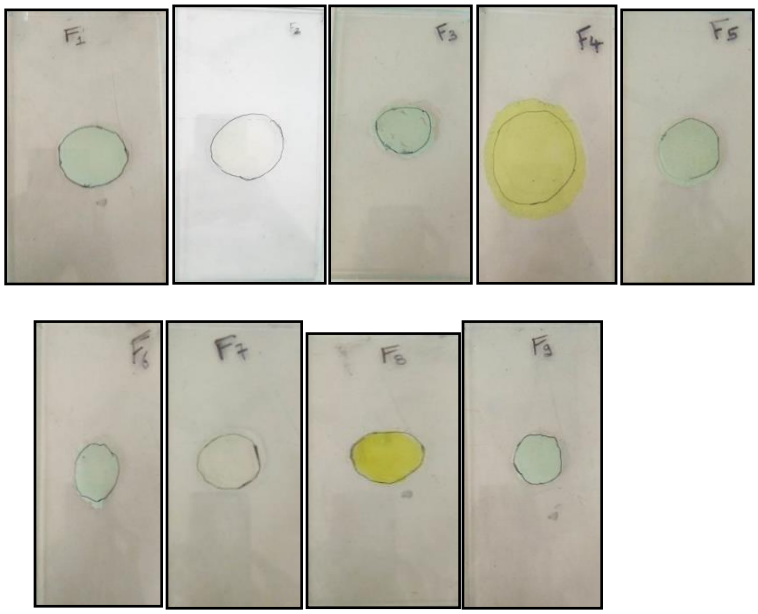
1. pH:

The pH of all formulations were observed in the range of 6.8 to 7.1 which indicated prepared formulation were compatible with skin pH

2. Spredability

It was observed that for each formulation the concentration of carbopol 934 was associated with a spredability.

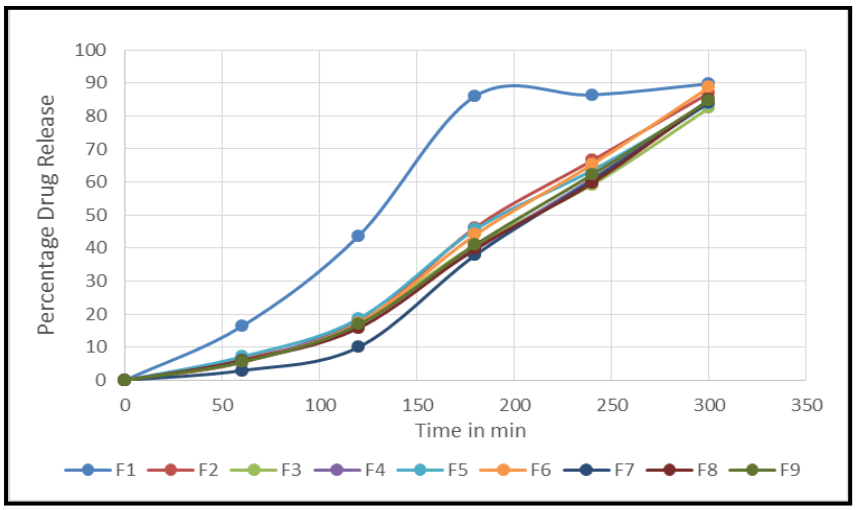
Formulation Code	Spredability (ɵ) in cm
F1,F5,F6,F9,F12	4.3
F2	5.01
F3	3.68
F4	4.5
F7	4.1
F8	4.9
F10	3.8
F11	4.1
F13	4.6



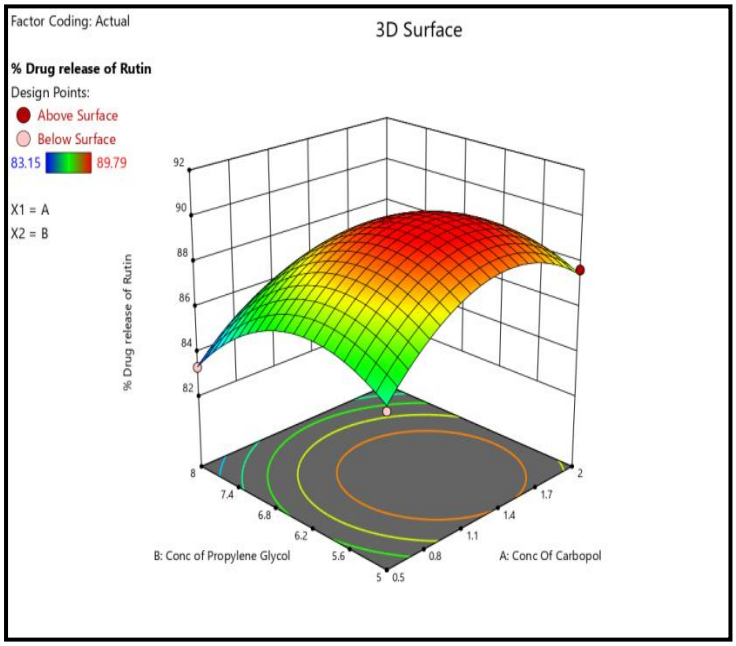
Spredability of formulation F1 to F9

3. In vitro Drug Diffusion of Rutin (Drug release)

In-vitro drug diffusion was carried out in franz diffusion cell using prehydrated cellophane membrane.Study performed for 5 hours using Phosphate buffer pH 6.8.Percent drug diffused after 5 hours. Across membrane and percent drug retained in membrane was determined.



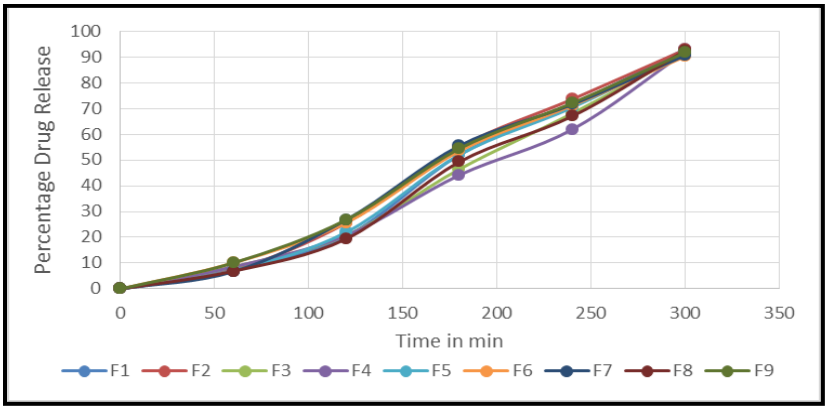
Graph for drug Release of Rutin



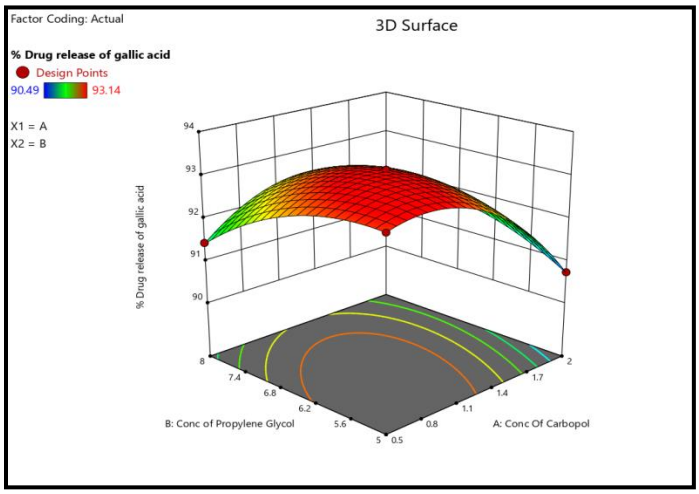
3D Plot Effect for Drug Release of Rutin

4. In vitro Drug Diffusion of Gallic Acid (Drug Release)

In-vitro drug diffusion was carried out in franz diffusion cell using prehydrated cellophane membrane.Study performed for 5 hours using Phosphate buffer pH 6.8.Percent drug diffused after 5 hours. Across membrane and percent drug retained in membrane was determined.



Graph for Drug release of Gallic Acid



3D Plot effect for Drug Release of Gallic acid

5. Anti-Microbial Study

- Antimicrobial study on the culture of Candida Albicans, Pseudomonas aeruginosa and staphylococcus aureus was done by cup plate method .
- Microbial study was done using marketed formulation of Beclamethasone and optimized formulation F1.
- The Cup plate assay of drug potency is based on the measurement of the diameter of zone inhibition of microbial growth surrounding cylinders.

Candida Albicans

Pseudomonas aeruginosa

Staphylococcus aureus

6.Antioxidant Study

- ***In-Vitro Antioxidant Activity Of Rutin And Gallic Acid By DPPH Method***
  - The anti oxidant activity of drug compared with standard ascorbic acid. Both drug comparable and acceptable activity by DPPH method.
  - Formula used to calculate the % inhibition or free scavenging activity is as follow-

$$\% \text{ inhibition} = \frac{(\text{Abs of Std} - \text{Abs of Control})}{(\text{Abs of Standard})} \times 100$$

  - Where, Standard used for sample and Control used for DPPH .Absorbance taken at 517 nm
  - The absorbance was of control sample that is DPPH solution alone was found to be 0.0988.This Finding was further used to calculate % free radical scavenging activity.

- The % inhibition or free radical scavenging activity of Rutin And Gallic Acid at concentration of 25mcg/ ml was found to be 89.34% and 89.45 % respectively.

IV. Conclusion

- The study exhibits that Rutin and Gallic Acid can be presented to human body in more effective manner when formulated in gel.
- Tannins and Flavonoids which are prime constituents of these drugs effectively treat different skin conditions.
- The topical use of these drugs can be combined with other systems of medicines to improve life standard of patients.
- To develop topical gel delivery system to treat psoriasis and skin infection disease using herbal drug
- To increase the effect of herbal drug for treatment of Psoriasis
- Unlike other marketed preparation like steroidal which are used for psoriasis and skin infections widely inspite of their other side effects these herbal drugs offers anti-oxidant activity as well as anti-inflammatory activity for psoriatic and skin infection

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