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Research Article

Formulation And Evaluation of Tacrolimus Gel

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ABSTRACT

Gel's are the preparations used to enhance the human appearance. The aim of the present research was to formulate the gel for the purpose of whitening, Moistening, Nourishing, lightening & Treatment of various diseases of the skin. Different gelling agent; HPMC, CMC, AEROSIL. Active pharmaceutical ingredients TACROLIMUS taken. Different types of formulations gel namely F1 to F6 were formulated by incorporating different concentrations of ingredients. The evaluations of all formulations (F1 to F6) were done on different parameters like, irritancy, and consistency were examined. Formulations showed good consistency, homogeneity, appearance, spread ability, no evidence of phase separation and ease of removal. F2 showing 99.81±0.044 drug content. Thus gel formulation is safe to use was proved and it can be used as the provision of a barrier to protect skin.

INTRODUCTION

Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use.

1.1 Advantages Of Topical Drug Delivery Systems:

1. Avoidance of primary pass metabolism.
2. Convenient to use and easy to apply.
3. Easily to terminate the medications.
4. Drug delivered selectively to a specific site.
5. The gastro-intestinal incompatibility will be avoided.
6. Provides drugs utilization with short biological half-life and narrow therapeutic window.

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7. Better patient compliance.
8. Self-medication.
9. It provides effectiveness in low doses and by continuous drug input.
10. Avoids fluctuation in drug levels and risks.
11. A large area of application compared to other route.

1.2 Disadvantages Of Topical Drug Delivery Systems:

1. Possibility of local skin irritation at the site of application.
2. Contact dermatitis due to some drug may occur.
3. Some drugs with poor permeability are difficult to penetrate via the skin.
4. Drugs with larger particle sizes are difficult to penetrate.
5. Possibility of allergenic reactions.
6. Drugs with a very small plasma concentration can be used for action the most popular derma products are semisolid dosage forms.

1.3 Gels As Pharmaceutical Dosage Forms:

The term 'Gel' was introduced in the late 1800 to name some semisolid material according to their physiological characteristics rather than molecular composition The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels are a substantially dilute cross-linked system, which exhibits no flow when in the steady-state. They consist of a two component semi-solid system rich in liquid. Their one characteristic feature is the presence of continuous structure providing solid like Properties .Gels have become a premier materials used for drug delivery formulations due to its biocompatibility, network structure, and molecular stability of the incorporated bioactive agent.

1.4 Characteristics Of Gels:

Gels should possess the following properties:

Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components.

- ✓ The gelling agent included in the preparation should produce a reasonable solid-like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application.
- ✓ It should possess suitable anti-microbial activity against microbial attack.
- ✓ The topical gel should not be tacky.
- ✓ The gels intended for ophthalmic use should be sterile.

Figure No: 1 Pharmaceutical Gels

1.5 Anatomy and Physiology Of Skin:

The human body has two systems that protect it from the harmful organisms existing in the environment. The internal defence system destroys microorganisms and bacteria that have already attacked the body. The external defence system prevents microbial microorganisms to enter the body. Skin is biggest external defence system. Skin covers the outside of the body but has other functions beside the defence mechanism. It serves as a mechanical barrier between the inner part of the body and the external world. Temperature of skin varies in a range of 30 to 40°C degree depending on the environmental conditions.

Epidermis: Consists of epithelial cells. Among these cells, both living cells and dead cells can be found. These new cells at the bottom of epidermis divide fast and push the older cells upward. The epidermis does not have any direct source of blood

veins to provide nutrition. It takes its nutrients from the diffusion of necessary molecules from a rich vascular network in the underlying dermis. Epidermal cells are connected very strongly by desmosomes. Desmosomes are in contact with the intracellular keratin film mates. Keratin film mates produce keratin. Keratin cells accumulate and crosslink with the other keratin cells in the cytosol during their maturation. Afterward when the older cells die, this network of keratin fibroses remains and provides a tough and hard protective layer in epidermis, called protective keratinized layer. This layer is water proof and airtight. It prevents most substances to enter the body or leave from the body. In diseased skin, particularly burns, epidermis is destroyed causing potential loss of body fluid and an increase in susceptibility to microbial infections, leading to fatal consequences untreated.

Dermis: Dermis is positioned under epidermis and is characterized by lots of elastin fibres that provide the stretching ability as well as lots of collagen that provides the strength to the skin. Blood vessels found in dermis provide nutrients for both dermis and epidermis. Dermis also plays a major role in temperature regulation. Nerves present there are responsible for pressure and pain sensation. Dermis has a thickness of 3-5 mm. In addition to elastin fibres, blood vessels and nerves, an inter fibrillar gel of glycosaminoglycan, salt, water, lymphatic cells and sweet glands are parts of dermis.

Hypodermis: Hypodermis is the inner layer of skin. It is the contact layer between skin and the underlying tissues in body such as muscles and bone. Sweat glands, sebaceous glands and hair follicles enfold in epidermis but they stem from dermis. Sweat glands release a dilute salt solution into the surface of skin. The evaporation of this solution makes skin cool and this is important for temperature regulation of both body and skin. Sweet glands are present all over the body. The amount of dilutions (sweet) that gets produced depends on environmental temperature, the amount of heat generating skeletal muscle activity and various emotional factors. The sebaceous glands produce sebum. Sebum is an oily liquid released into hair follicles and from there onto the skin surface. Sebum protects both hair and skin from drying out and provides waterproof layer.

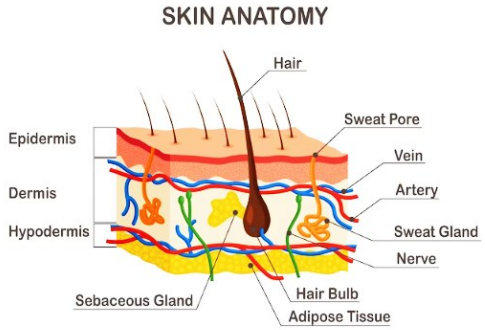


Figure No : 2 Human Skin

1.6 Application Of Gels:

Application of gels in Pharmaceutical and cosmetic industry:

- ✓ Gels are applied directly to the skin, mucus membrane or the eye to provide local action.
- ✓ They acts as long acting forms of drug injected intramuscularly or implanted into the body
- ✓ Gelling agents are useful binders in tablet granulation, protective colloids in suspensions,
- ✓ Thickeners in oral liquid, and suppository bases.
- ✓ Cosmetically gels have been employed in wide variety of products, including shampoos, fragrance products, dentifrices, skin and hair care preparations.
- ✓ Gel products containing anti-inflammatory steroids are used to treat inflammations of scalp because this is an area of the body where creams and ointments are too greasy for patient acceptance.
- ✓ Gels have better potential as a vehicle to administer drug topically in comparison to

ointment, because they are non-sticky, requires low energy during formulation, are stable and have aesthetic value.

2. DISEASE PROFILE

2.1 Vitiligo:

Vitiligo is a long-term skin condition characterized by patches of the skin losing their pigment. The patches of skin affected become white and usually have sharp margins. The hair from the skin may also become white. The inside of the mouth and nose may also be involved. Typically both sides of the body are affected. Often the patches begin on areas of skin that are exposed to the sun. It is more noticeable in people with dark skin. Vitiligo may result in psychological stress and those affected are sometimes stigmatized.

2.2 Types Of Vitiligo:

There are three major types of vitiligo are as follows:

- ✓ Segmental Vitiligo
- ✓ Non-Segmental Vitiligo
- ✓ Mixed Vitiligo

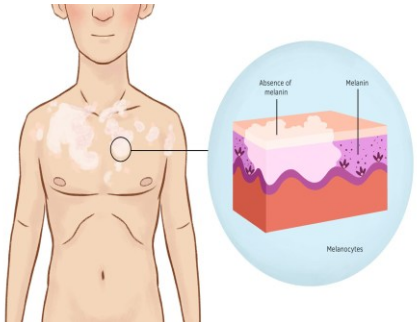


Figure No: 3 Vitiligo Disease

2.3 Factors:

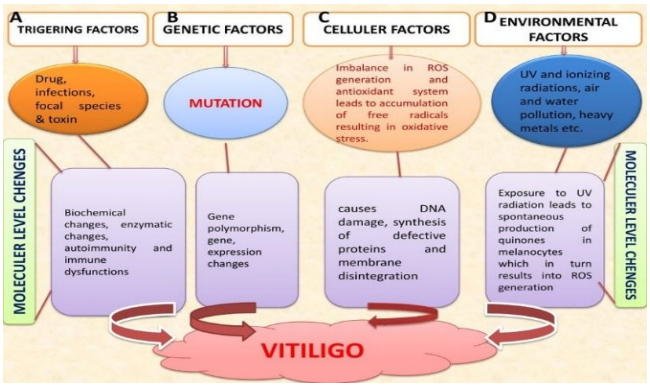


Figure No : 4 Factors Of Vitiligo Disease

2.4 Evaluation:

The evaluation of vitiligo is usually made on clinical features, through a wood light examination biopsy is sometimes helpful to differentiate vitiligo from other hypo pigmented or depigmented disorders. The histopathological examination of the skin reveals the absence of melanocytes and complete epidermal pigmentation loss. Superficial perifollicular and perivascular lymphocytic infiltrates may be present at the margin of the vitiligo lesions, due to the cell-mediated process that destroys the melanocytes.

3. DRUG PROFILE

3.1 Tacrolimus:

Tacrolimus, sold under the brand name Prograf among others, is an immunosuppressive drug. After allogeneic organ transplant, the risk of organ rejection is moderate. To lower the risk of organ rejection, tacrolimus is given. The drug can also be sold as a topical medication in the treatment of T-cell-mediated diseases such as eczema and psoriasis. For example, it is prescribed for severe refractory uveitis after a bone marrow transplant, exacerbations of minimal change disease, Kimura's disease, and vitiligo. It can be used to treat dry eye syndrome in cats and dogs.

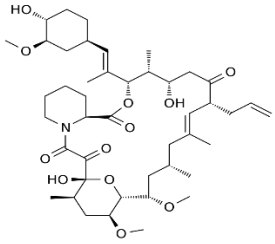


Figure No : 5 Structure Of Tacrolimus

3.2 Properties:

- ✓ **IUPAC** : (−)-(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,26aS)-8-allyl 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-{€-2-[(1R,3R,4R)-4-hydroxy-3-methyl cyclohexyl]-1-methylvinyl}-14,16-dimethoxy-4,10,12,18-

tetramethyl-15,19-epoxy-3H-pyrido [2,1-c][1,4]oxaazacyclotricosane-1,7,20,21(4H,23H)-tetrone

- ✓ **Molar mass:** 804.031gmol-1
- ✓ **Chemical formula:** $C_{44}H_{69}NO_{12}$
- ✓ **Bioavailability:** 24% (5–67%), less after eating food rich in fat
- ✓ **Protein Binding: ≥98.8%**
- ✓ **Elimination Half life:** 11.3 h for transplant patients (range 3.5–40.6 h)
- ✓ **Excretion:** Mostly fecal
- ✓ **Medical uses:** Tacrolimus ointment is used to treat the symptoms of eczema (atopic dermatitis; a skin disease that causes the skin to be dry and itchy and to sometimes develop red, scaly rashes) in patients who cannot use other medications for their condition or whose eczema has not responded to another medication.

4. MATERIALS AND METHODS

4.1 List Of Chemicals:

List of chemicals used in Tacrolimus, HPMC, CMC, Aerosil, Triethanolamine, Methyl paraben, Propyl paraben, Ethanol, PEG 400, Water.

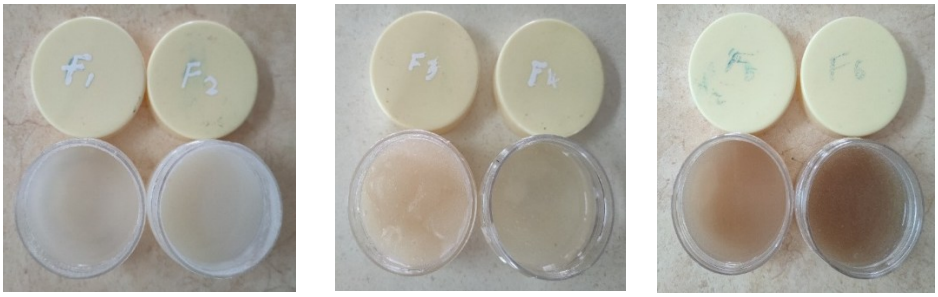
4.2 Methodology:

S.NO	COMPONENTS	F1	F2	F3	F4	F5	F6
1	Tacrolimus	1gm	1gm	1gm	1gm	1gm	1gm
2	HPMC	1.5 gm	2 gm	-	-	-	-
3	CMC	-	-	1.5 gm	2 gm	-	-
4	Aerosil	-	-	-	-	2 gm	2.5 gm
5	Triethanolamine	0.5 gm	0.5 gm	0.5 gm	0.5 gm	0.5 gm	0.5 gm
6	Methyl paraben	0.5 gm	0.5 gm	0.5 gm	0.5 gm	0.5 gm	0.5 gm
7	Propyl paraben	0.2 gm	0.2 gm	0.2 gm	0.2 gm	0.2 gm	0.2 gm
8	Ethanol	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
9	PEG 400	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml
10	Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table No: 1 Formulation Of Tacrolimus gel

4.3 Preparation Of Gel:

The appropriate amount of polymers was weighted and added slowly in a ethanol solution (under constant stirring by a paddle stirrer. After addition of solid material of drug, the gel was allowed to swell under moderate stirring for at least 1h. Or until fully swollen and transparent. Other ingredients, such as (PEG-400), preservative, water and triethanolamine were added to obtain a homogeneous dispersion of gel was added in the buffer used for gel preparation.



F1 and F2 (HPMC) F3 and F4 (CMC) F5 and F6 (AEROSIL)

Figure No: 6 F1 to F6 Gel Formulation

5 EVALUATION OF TACROLIMUS GEL

5.1 Physical Parameter:

The prepared topical gel were inspected visually for their color, homogeneity, consistency, spread ability and phase separation. The pH was measured in each gel, using a pH meter, which was calibrated before each use with standard buffer solutions at pH 4, 7, 9. The electrode was inserted in to the sample 10 min priors to taking the reading at room temperature.

5.2 Colors:

All the formulated gel were tested for color by visual inspection. They were checked against white background.

5.3 Determination Of PH:

Weighed 50 gm of each gel formulation were transferred in 10 ml of the beaker and measured it by using the digital pH meter. pH of the topical gel formulation should be between 3–9 to treat the skin infections.

5.4 Spreadability:

The spread ability of the gel formulation was determined, by measuring the diameter of 1 gm gel between horizontal plates (20×20 cm2) after 1 minute. The standardized weight tied on the upper plate was 125 gm.

5.5 Viscosity Measurement:

Viscometer can be used to measure the viscosity of prepared gel formulations. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading is noted. The viscosity of gel is obtained by multiplication of dial reading with factor given in the viscometer catalogues.

5.6 Homogeneity:

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

5.7 Irritancy Test:

Mark an area (1sq.cm) on the left hand dorsal surface. The gel was applied to the specified area and time was noted. Irritancy, erythema, edema, was checked if any for regular intervals up to 24 hrs and reported.

5.8 Drug Content:

Weighed 10 gm of each gel formulation were transferred in 250 ml of the volumetric flask containing 20 ml of alcohol and stirred for 30 min. The volume was made up to 100 ml and filtered. 1 ml of the above solution was further diluted to 10 ml with alcohol and again 1 ml of the above solution was further diluted to 10 ml with alcohol. The absorbance of the solution was measured spectrophotometer at 294 nm.

5.9 Percentage Yield:

The empty container was Weighed in which the gel formulation was stored then again the container was weighed with gel formulation. Then subtracted the empty container weighed with the container with gel formulation then it gives the practical yield.

5.10 Solubility:

The formulation of Tacrolimus gel was dissolved in various solvents to observe the solubility.

5. RESULTS AND DISCUSSION

5.1 Physical Parameters:

S.NO	Code	color	pH	Viscosity	Percentage yield
1	F1	White	7.35	8532	94.14 %
2	F2	White	7.78	8321	97.16 %
3	F3	Whitish brown	7.32	8712	91.35 %
4	F4	White	7.96	8418	89.23 %
5	F5	Light brown	8.11	4790	93.66 %
6	F6	Light brown	6.31	3953	90.31 %

Table No: 2 Physical Parameters

S.No	Code	Spreadability	Homogeneity	Consistency 60 Sec	Drug content
1	F1	5.6	Homogenous	5.7mm	98.98±0.023
2	F2	5.7	Homogenous	5.7mm	99.81±0.044
3	F3	5.5	Homogenous	5.5mm	97.31±0.113
4	F4	5.8	Homogenous	5.8mm	98.07±0.150
5	F5	5.3	Slightly Homogenous	5.3mm	81.63±0.067
6	F6	5.0	Slightly Homogenous	5.0mm	89.67±0.114

Table No: 3 Physical Parameters

5.2 Irritancy Test:

S.No	Code	Edema	Erythema	Irritation
1	F1	Nil	Nil	Nil
2	F2	Nil	Nil	Nil
3	F3	Nil	Nil	Nil
4	F4	Nil	Nil	Nil
5	F5	Nil	Nil	Nil
6	F6	Nil	Nil	Nil

Table No: 4 Irritancy Test

5.3 Solubility:

Table No: 12 Solubility

S.NO	Code	Water	Acetone	Methanol
1	F1	+++	+++	+++
2	F2	+++	+++	+++
3	F3	+++	++	+++
4	F4	+++	++	+++
5	F5	+++	++	+++
6	F6	+++	++	+++

+++ = Good washable

++ = Washable

+ = Non-washable

DISCUSSION:

The main objective of the present work was to prepare and assess dermal delivery of tacrolimus. Topical applications of drugs have advantages of delivering the drug directly to the site of action and acting for a longer period of time. Six formulations were developed with varying concentrations of polymers like CMC, HPMC and Aerosil. The gels were tested for Homogeneity, Spreadability, Viscosity, pH, drug Content uniformity, skin irritation. F2 showing 99.81±0.044 drug content. Thus gel formulation is safe to use was proved and it can be used as the provision of a barrier to protect skin.

6. CONCLUSION:

The clinical evidence indicates that topical gel is a safe and most effective treatment option for use in the management of skin related disease and used for local action to reduce the side effects associated with other conventional dosage form. Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery of gels. Topical gel formulation provides a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Gel formulation provides better application property and stability in comparison to cream and ointments.

Vitiligo, a common depigmenting skin disorder, has an estimated prevalence of 0.5–2% of the population worldwide. The disease is characterized by the selective loss of melanocytes which results in typical nonscaly, chalky-white macules. In recent years, considerable progress has been made in our understanding of the pathogenesis of vitiligo which is now clearly classified as an autoimmune disease.

Tacrolimus (Tac) is an immunosuppressive drug that is used in preventing organ and tissue rejection in patients after transplantation. TAC is used most frequently in comparison to other immunosuppressants because it offers better safety profile with increased long-term survival in patients especially in children and adolescents.

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