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RESEARCH ARTICLE

Formulation Development and Characterization of Topical Gel for Psoriasis

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ABSTRACT

The purpose of this research work was to develop and characterize a tacrolimus (TAC) gel using different polymers for the treatment of psoriasis. The physicochemical compatibility was confirmed between TAC and other excipients by Fourier transfer infrared. Formulated gels were characterized for drug content, viscosity, extrudability, skin irritation study, pH, *in vitro* diffusion study, and stability. Release of TAC from all formulations using dialysis membrane into a phosphate buffer pH 6.8 at 37°C was performed. Optimized batch was selected from this characterization study. Based on the data collected, it was revealed that TAC has proven to be a promising candidate for delivery through gel in the treatment of psoriasis.

Keywords: Carbopol 940, hydroxypropyl methylcellulose, psoriasis, tacrolimus, gel

INTRODUCTION

Psoriasis is an autoimmune disease that affects the skin. It occurs when the immune system mistakes the skin cells as a pathogen and sends out faulty signals that speed up the growth cycle of skin cells. It is a chronic inflammatory and proliferative skin disorder involving the interplay of both environmental and genetic factors.[1] This disease is chronic in nature with a tendency to relapse. Skin keeps scaling as flakes called psoriatic plaques due to rapid and excessive multiplication of epidermis cells which look like fishy skin and finally peels off as exfoliation.[2]

Psoriasis is not contagious. However, psoriasis has been linked to an increased risk of stroke. There are five types of psoriasis: Plaque, guttate, inverse, pustular, and erythrodermic. The most common form, plaque psoriasis, is commonly seen as red and white hues of scaly patches appearing on the top first layer of the epidermis (skin). Some patients, though, have no dermatological signs or symptoms. In plaque psoriasis, skin rapidly accumulates.

Plaques frequently occur on the skin of the elbows and knees but can affect any area, including the scalp, palms of hands, and soles of feet and genitals. In contrast to eczema, psoriasis is more likely to be found on the outer side of the joint.[2]

Tacrolimus (TAC) is an immunosuppressant drug that acts by the inhibition of calcineurin, a calcium-binding cytoplasmic protein involved in T-cell activation and proliferation. The initial binding of TAC with FK506 binding protein forms a complex that binds to calcineurin, thus inhibiting the calcineurin-mediated dephosphorylation of the nuclear factor of activated T-cells. This essentially involves the cascade of cytokine gene transcription such as interleukin (IL)-2, IL-4, interferon-ϒ, and tumor necrosis factor-alpha. Therefore, TAC has been widely explored in the treatment of psoriasis.[3]

MATERIALS AND METHODS

Materials

TAC was procured from Murli Krishna Pharma Ltd., India, as a gift sample. Gelling agents, hydroxypropyl methylcellulose (HPMC) and Carbopol 940, were obtained as gift sample from Colorcon Asia Pvt., Ltd., India. All other solvents and excipients used are of analytical reagent grade.

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Preparation of TAC gels

The composition of TAC gel formulae is designed in Table 1. TAC (0.1% w/w) was dissolved in a hot mixture containing propylene glycol (25% w/w) and glycerin (10% w/w) as moistening agent.[4] The gel formulations were prepared by dispersing weighed amount of polymers Carbopol 940 and HPMC in water with constant stirring using magnetic stirrer at a moderate speed. Then, mixture containing drug was added. The pH of Carbopol gel was adjusted using TEA. Finally, preservatives methyl and propylparaben were added slowly with continuous stirring. The prepared gels were packed in wide mouth glass containers covered with screw-capped plastic lid. The containers covered with an aluminum foil and were kept in dark and cool place.[5-10]

Table 1: Composition of tacrolimus gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Tacrolimus	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbopol 940	0.5	1	1.5	2	-	-	-	-
HPMC	-	-	-	-	0.5	1	1.5	2
Propylene glycol	25	25	25	25	25	25	25	25
Glycerin	10	10	10	10	10	10	10	10
Propylparaben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Methylparaben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Purified water	100	100	100	100	100	100	100	100

HPMC: Hydroxypropyl methylcellulose

Drug-polymer compatibility studies

Fourier transfer infrared (FTIR) spectrophotometer

The FTIR studies were carried for the pure drug and drug-polymer physical mixture separately with IR-grade KBr in the ratio of 100:1 and corresponding disks were prepared by applying 5.5 metric ton of pressure in a hydraulic press using FTIR spectrophotometer (Brooker Alpha T). The disks were scanned over a wavenumber range of 4000–400 cm [Figure 1-3].

Evaluation of TAC gel formulations[4,11-17]

Visual examinations

All prepared gel formulations were inspected for their color, syneresis, and presence of lumps by visual inspection after the gels have been kept in the containers.

Homogeneity

All prepared gels were tested for homogeneity after the gels have been set in the container. They were tested for their appearance and presence of any aggregates and results for the same were noted in Table 2.

Grittiness

The formulations were evaluated microscopically for the presence of particles if any. No appreciable particulate matter was seen under light microscope.

Table 2: Physical properties of tacrolimus topical gels

Formulation code	Color	Homogeneity	Grittiness
F1	Shiny transparent	++	−
F2	Shiny transparent	++	−
F3	Shiny transparent	+++	−
F4	Shiny transparent	+++	−
F5	Transparent	++	−
F6	Transparent	++	−
F7	Transparent	+++	−
F8	Transparent	+++	−

++ = Good, +++ = Excellent, −=Normal

Spreadability test

A sample of 0.5 g of each formulation was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 min where no more spreading was expected. Diameters of spreaded circles formed due to press were measured in cm and were taken as comparative values for spreadability.

pH determination

The pH of the formulated TAC gels was determined using digital pH meter (Systonic). Readings noted in Table 3.

Extrudability

The prepared gel formulations were filled in standard capped collapsible aluminum tubes and sealed by crimping to the end. The weights of the tubes were recorded. The tubes were placed between two glass slides and were clamped. 500 g was placed over the slides and then the cap was removed. The amount of the extruded gel was collected and weighed. The amount of gel extruded was calculated (>90% extrudability: Excellent, >80% extrudability: Good, and >70% extrudability: Fair). The graded results are shown in Table 3.

Rheological studies

The measurement of viscosity of the prepared gels was done using Brookfield viscometer. The gel was evaluated using spindle no. 64. Results are shown in Table 4.

Drug content determination

A specific quantity of prepared gel was taken and dissolved in 100 ml of phosphate buffer of pH 5.5. The flask containing gel solution was shaken for 2 h on mechanical shaker to get complete solubility of drug. This solution was filtered using Millipore filter (0.45 μm). After suitable dilution, drug absorbance was recorded using ultraviolet-visible spectrophotometer at λ_{max} 294 nm using phosphate buffer (pH 5.5) as blank.

Skin irritation studies

Guinea pigs (400–500 g) of each sex were used for testing of skin irritation study. The animals were maintained on standard animal feed and had free across to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4 cm^2 was marked on both the sides, one side served as control while the other side was test. Formulated gel was applied (500 mg/ guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any.

Table 3: Evaluation of tacrolimus gels

Formulation code	pH	Spreadability	Extrudability
F1	6.1	4.4	++
F2	5.99	4	++
F3	5.60	4	++ +
F4	5.62	3.6	++ +
F5	6.1	4.5	++
F6	6.13	4.5	++ +
F7	6.22	3.8	++ +
F8	6.65	3.8	++

++ = Good, ++ + = Excellent

Table 4: Rheological, % drug content, and skin irritation studies

Formulation code	Viscosity (cps)	% drug content	Skin irritation
F1	3120	92.34	A
F2	3278	95.44	A
F3	3305	98.91	A
F4	3655	97.32	A
F5	4226	87.55	A
F6	4548	88.00	A
F7	5674	91.22	A
F8	5209	90.17	A

A - No reaction, B - Slight erythema, C - Moderate erythema

In vitro diffusion studies

Diffusion studies were performed by applying 1 g of the TAC gel uniformly to the dialysis membrane. The membrane was mounted between the compartments of Franz diffusion cell. Reservoir compartment was filled with 15 ml of 6.8 pH phosphate buffer. The study was carried out at 37±2°C and was carried out for 24 h. The sample (1 ml) was withdrawn from reservoir compartment in consecutive intervals. Each time reservoir compartment was replenished with 1 ml of 6.8 pH phosphate buffer solution to maintain sink condition. Graph of the same is shown in [Figure 4].

Stability studies

Stability study was performed. The most satisfactory gel formulation was kept at 37 ± 2°C and 60 ± 2°C. At the end of 1 month, the samples were analyzed for the physical properties, drug content, and *in vitro* diffusion study. Graph of % drug release after stability study shown in [Figure 5].

RESULTS AND DISCUSSION

Drug-polymer compatibility studies

FTIR spectra were examined and checked for any shifting in functional peaks and non-involvement of functional group. From the spectra, it is clear that there is no interaction between the selected polymers, drug, and mixtures.

Physical properties study reveals that appearance formulated gel formulation was shiny transparent to transparent for Carbopol and HPMC. Hence, it was concluded that the gel preparations fulfill the requirement of freedom from particular matter and from grittiness as desired for topical preparation.

The values of spreadability indicate that the tacrolimus gel formulations easily spreadable. Spreadability of all formulations was fund to be good.

Ph of all gel formulation is measured and it is shown in Table 3, it found in between the range of 5.60 and 6.65.

All the gel formulations have satisfactory extrudability that good to excellent gradings of the same in Table 3.

The measurement of viscosity of the formulated topical gel was done with Brookfield viscometer. The highest viscosity was found in F7, it may

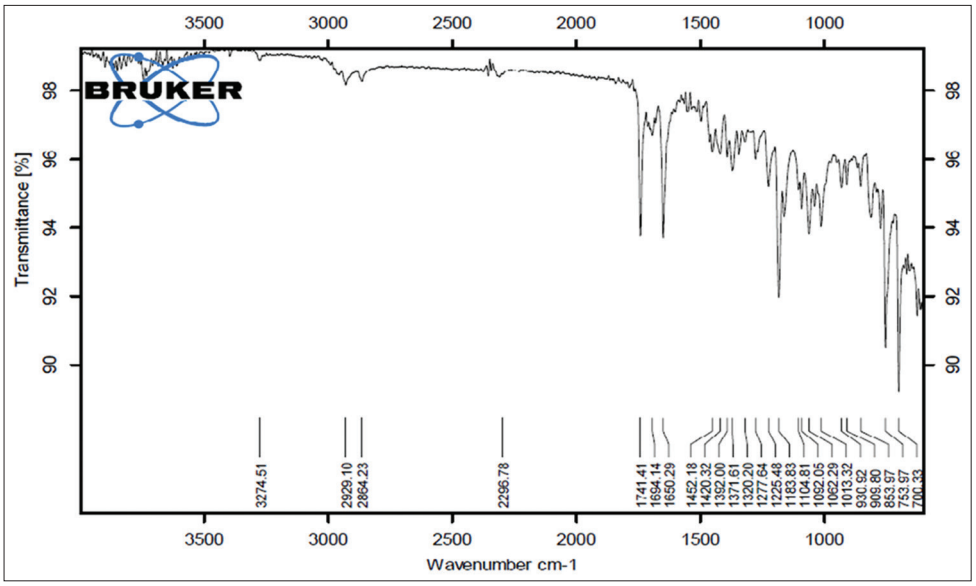

Figure 1: Infrared spectra of tacrolimus

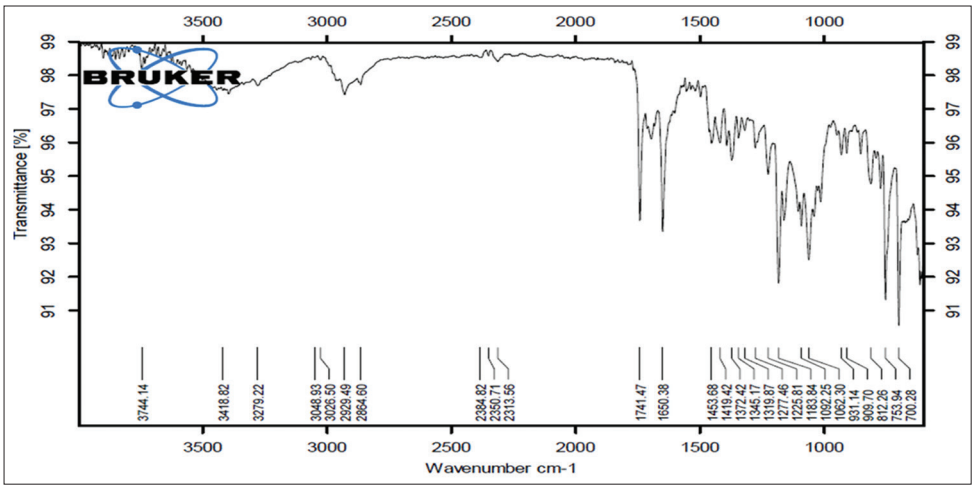

Figure 2: Infrared spectra of tacrolimus + Carbopol

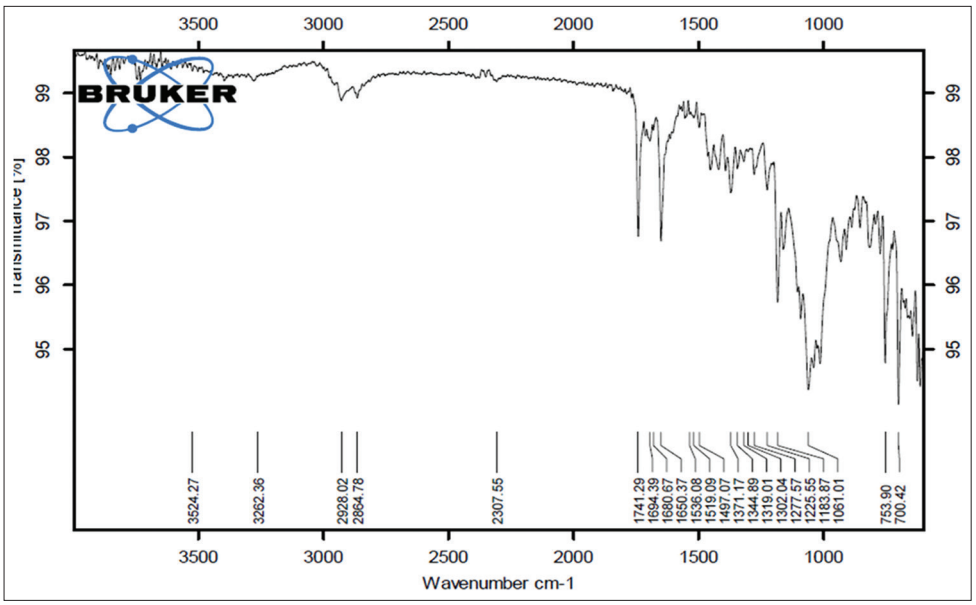

Figure 3: Infrared spectra of tacrolimus + hydroxypropyl methylcellulose

be due to concentration of gelling polymer. The lowest viscosity was found in formulation F1.

The drug content in TAC gel was found in the range of 88.00–98.91%. The highest drug content

Table 5: Results of stability studies F3 formulation

Parameters	Period of studies in months	
	0 month	3rd month
Drug content	98.91	98.01
pH	5.60	5.60
Homogeneity	+++ Homogeneous	+++ homogeneous
Physical appearance	Shiny transparent	Shiny transparent

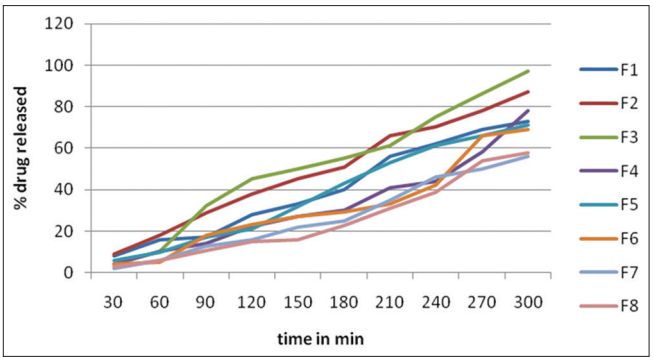

Figure 4: Graph of percentage drug release versus time in min

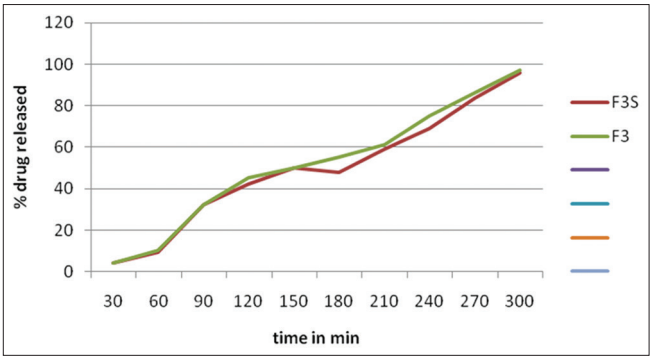

Figure 5: Graph of percentage drug release versus time in min of F3 and F3S (after stability studies)

found in batch F3. No irritation (erythema) was observed on the skin of the guinea pigs after test of 7 days.

The *in vitro* drug release of drug from the gel formulations was varied due changing the ratio of drug and polymer. It has been concluded that drug diffused from formulation F3 was the highest among all the formulations.

In vitro drug released study was performed for all formulations, it was found in between 56% and 97%. Batch F3 shows the highest drug release in all the prepared formulations.

Stability studies of optimized batch formulation F3 were performed as per ICH guidelines. It was observed that the F3 formulation showed no major change in relation to the pH, drug content, and *in vitro* drug release study. The formulation shows stability for a period of 3 months, results of this are shown in Table 5.

CONCLUSION

In this work, an attempt was made to formulate topical gel of TAC for the treatment of psoriasis as efficient delivery of drug across the skin. Topical gels were prepared using gelling agents such as Carbopol 940 and HPMC in different concentrations. All formulations were evaluated for physical appearance, pH, drug content, viscosity, extrudability, skin irritation study, and stability. From the *in vitro* studies, formulation F3 showed maximum release of 97.23% in 300 min. Optimized formulation F3 found stable for parameters such as pH, physical appearance, drug content, and *in vitro* drug release study after 3 months. In the upcoming years, topical drug delivery systems will be used extensively to impart better patient compliance.

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