Formulation Development and Characterization of Novel Antipsoriatic Gel for Topical Drug Delivery System.

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***Abstract*—Compatibility between the drug and excipients was confirmed through Fourier Transform Infrared (FTIR) spectroscopy studies, indicating no significant interactions. The gel formulation was prepared using dimethyl sulfoxide (DMSO), Carbopol 10NF, propylene glycol, glycerol, methyl paraben, propyl paraben, and purified water.**

Among all the formulations developed, Formulation F3 was identified as the optimized formulation due to its superior performance. The prepared gel exhibited satisfactory physicochemical properties, including an assay value of 97% w/w and a pH of 4.99, indicating good drug content uniformity and suitability for topical application.

In vitro drug diffusion studies demonstrated that the optimized formulation released 98.2% of the drug within 12 hours, suggesting sustained and effective drug release. Furthermore, stability studies were conducted by storing the formulation under accelerated conditions of 40°C/75% RH and 30°C/65% RH for periods of one, two, and three months.

The results showed that the optimized formulation (F3) maintained its physical characteristics, drug content, and release profile throughout the study period, demonstrating good stability and satisfactory in vitro performance. These findings indicate that Formulation F3 is a promising gel formulation with potential for effective therapeutic application.

I. INTRODUCTION

SKIN

Structure of skin

The multilayered human skin is composed of many histological layers.The skin is the most accessible organ in the body. The skin, which has a surface area of around two square meters, receives about onethird of the blood that passes through an adult's body.The skin is a complex organ that allows various substances to pass through and enter. A few drugs that are systemically active are applied topically, where they are absorbed and then transported to the target tissues through the systemic circulation.The biggest organ in the body, it has a surface area of about 1.52 m2 in adults and contains glands, hair, and nails.

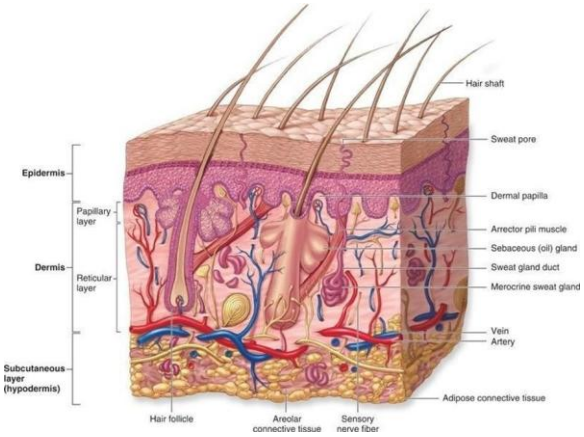

Figure 1: Structure of skin

Skin consists of two primary layers:

a) Epidermis

b) Dermis

a) Epidermis:

The epidermis, the skin's outermost layer, is a stratified squamous epithelium mostly composed of keratinocytes at different stages of development. The primary cells that comprise the epidermis are called keratinocytes, and they are in charge of making the protein keratin. The epidermis is completely dependent on the dermis underneath it for waste collection and nutrient delivery through the basement membrane because it lacks blood vessels.

The main function of the epidermis is to protect the body from allergens and irritants by acting as a physical and biological barrier. It also prevents water

loss and maintains internal homeostasis. While most bodily parts have four layers, some with the thickest skin have five.

1. The horny layer, or stratum corneum;
2. Stratum lucidum (found exclusively in thick skin, such as the fingers, palms, and soles of the feet);
3. Stratum granulosum (granular layer);
4. Stratum spinous (prickle cell layer); and
5. Stratum basales (germinative layer).

There are other cell structures in the epidermis. About 95% of epidermal cells are keratinocytes; the remaining cells are melanocytes, Merkel cells, and Langerhans cells.

b) Dermis:

The dermis is elastic and hard. Collagen and elastic fibers are intertwined in the matrix, which is composed of connective tissue.

The dermis contains the following structures:

1. Vessels of Blood
2. Vessels of lymph
3. Endings of Sensory Nerves
4. Sweat Glands
5. Hairs
6. The muscles of the rector pili and
7. Sebaceous glands.

1 Blood vessels: The capillary branches of the arterioles form a thin network that supplies the dermis with sweat glands, sebaceous glands, and hair follicles. The epidermis, which lacks a blood supply, receives oxygen and nutrients from the interstitial fluid from the blood vessels in the dermal papillae.

2. Vascular lymph These comprise the network of the dermis. Three endings of sensory nerves: Numerous sense receptors, specialized nerve endings that are sensitive to pressure, temperature, touch, and pain—are found in the dermis. Depending on the input, different sensory receptors are activated.

4 Sweat glands:

Although they are present throughout the skin, sweat glands are more common in the groin, axilla, palms of the hands, and soles of the feet. They consist of cells known as epithelial cells. The subcutaneous tissues are wound with the bodies of the glands.

On the skin, a few ducts open. surface at hair follicles' tiny pores, indentations, and other openings.

5 Hairs: These are produced when hair follicles, which are epidermal cells, descend into the dermis, or subcutaneous tissue. At the base of the follicle is a group of cells called the bulb.

6. The arrector pili muscles: The arrector pili muscles are tiny bundles of smooth muscle fibers that are attached to the hair follicles. The hair stands straight up and the skin surrounding it rises when these muscles flex, producing "goose meat."

7. Sebaceous glands The same tissue that produces hair follicles also produces the secretary epithelial cells that comprise the sebaceous gland. They are present in all skin types and cause the hair follicles to produce sebum, an oily material.

1. Mechanisms of skin penetration

There are several methods that molecules can cross the stratum corneum, such as: The route between cells The transcellular and appendageal pathways (by a hair follicle or sweat gland) In normal circumstances The appendageal pathway is not very important because of the low surface that the appendages occupy. It is difficult to distinguish between the transcellular and intercellular routes. In vivo studies on methyl nicotinate skin absorption were evaluated using Fick's law of diffusion solutions. The best fit to the data was found to be a diffusional path length of 350 nm. Since the thickness of the skin is around 1/20 of this, it was assumed that the intercellular channel was important. According to developments in analytical methods, the intercellular gaps contain a mixture of ceramides, free fatty acids and their esters, cholesterol, and its sulfate. Skin Absorption & Barrier Drug absorption through tThe skin mostly happens through the intercellular pathway rather than through appendages (glands, hair follicles).

Skin acts as a strong barrier due to:

Tortuous pathway Structured lipid bilayers (ceramides, fatty acids, cholesterol)

Only a small percentage of drug reaches the target site when applied topically.

To improve delivery, systems like liposomes, niosomes, transfer some, ethosomes, nanoparticles, and hydrogels are used.

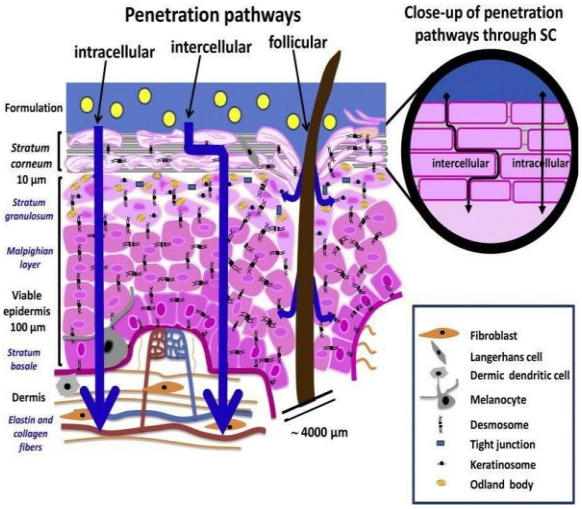

Figure 2: Skin Penetration Pathways

1. Topical Drug Delivery: -

Lowdose drug molecules that are restricted to a specific area of the body can be efficiently administered topically.

Topical Drug Delivery System Benefits Preventing first-pass metabolism Patient acceptance and compliance Continuous drug input allows for the achievement of efficacy with a reduced total daily dosage. Application simplicity and convenience comparatively broad field of applicability, Topical Drug Delivery System Drawbacks Drug and excipient-related skin irritation Drugs' poor skin penetration Potential for allergic reactions can only be applied to medications whose activity requires a low plasma concentration.

2. Gels: -

The term "gel" was introduced in the late 1800s to describe semisolid materials based on their physical properties rather than molecular composition. According to the United States Pharmacopeia (USP), gels are semisolid systems consisting of dispersions of small inorganic particles or large organic molecules within a liquid medium. They are dilute, cross-linked systems that exhibit solid-like behavior and do not flow under steady-state conditions. Due to their biocompatibility, network structure, and ability to maintain the stability of incorporated bioactive agents, gels are widely used in drug delivery formulations.

STRUCTURE OF GELS: -

A gel is a three-dimensional polymer network dispersed in a hydrophilic liquid. Upon application, the liquid evaporates, leaving a thin film that entraps the drug on the skin. The rigidity and properties of a gel are determined by the interconnected network of gelling agent particles and the nature of the linkages forming the gel structure.

CLASSIFICATION OF GELS: -

Topically applied gels are classified in two ways:

1. By gel system type:

Inorganic gels: Usually two-phase systems, such as aluminum hydroxide gel and bentonite magma.

Organic gels: Typically single-phase systems containing gelling agents like carbomer, tragacanth, or organic liquids such as Plastibase.

2. By dispersion medium:

Hydrogels: Water-based gels containing natural or synthetic polymers, including silica, bentonite, pectin, sodium alginate, methylcellulose, and sodium CMC.

Organogels: Gels containing organic solvents or oils, including hydrocarbons, fats, greases, and hydrophilic organogels.

Hydrogels are widely used as ointment bases due to their stability and suitable viscosity characteristics.

CHARACTERISTICS OF GELS

Gels should possess the following properties

A.Swelling:

When a gelling agent is kept in contact with a liquid that solvates it, the agent absorbs a significant portion of the liquid, increasing the volume. We call this process edema.

B. Syneresis Many gels frequently release a fluid medium and spontaneously constrict when standing.We call this phenomenon syneresis.

C. Growing older Slow spontaneous aggregation is typically seen in colloidal systems. We call this process "aging."

D. Organization: The presence of a network created by the interconnection of the gelling agent's particles gives a gel its stiffness.The structure of the network and the characteristics of gel are determined by the nature of the particles and the kind of force that creates the connections.

F. Rheology:

Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic i.e. exhibiting

Non-Newtonian flow behavior, characterized by a decrease in viscosity with increase in shear rate.

3. Psoriasis:

Psoriasis is a chronic inflammatory disease predominantly affecting the skin and is estimated to occur in 2 - 3% of the population.

Pathophysiology of psoriasis and dermatologic inflammation

Psoriasis and psoriatic arthritis are chronic inflammatory disorders caused by an imbalance in the immune system. Dendritic cells initiate abnormal immune responses by activating T cells, which differentiate into Th1 and Th17 cells and release pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-17, IL-22, IL-12, and IL-23. These cytokines promote inflammation, keratinocyte proliferation, and tissue damage.

Various immune cells, including dendritic cells, T cells, mast cells, neutrophils, and keratinocytes, contribute to the inflammatory process by producing inflammatory mediators. Persistent inflammation leads to skin thickening, increased blood vessel formation, and redness characteristic of psoriatic lesions. In psoriatic arthritis, chronic inflammation also affects bone remodeling and joint structure, resulting in joint erosion and damage. Overall, complex interactions among immune cells and cytokines drive the development and progression of both psoriasis and psoriatic arthritis.

II. MATERIAL AND METHODS

Materials

Sr. No.	Name of Material	Source
1	APA07 (Drug)	Grail Pharma Pvt Ltd.
2	Dimethyl Sulphoxide	Grail Pharma Pvt Ltd.
3	Propylene Glycol	Grail Pharma Pvt Ltd.
4	Glycerol	Grail Pharma Pvt Ltd.
5	Ethanol	Grail Pharma Pvt Ltd.
6	Carbopol	Grail Pharma Pvt Ltd.
7	Methyl Paraben	Grail Pharma Pvt Ltd.
8	Propyl Paraben	Grail Pharma Pvt Ltd.
9	Pottasium dihydrogen phosphate	Grail Pharma Pvt Ltd.
10	Sodium hydroxide	Grail Pharma Pvt Ltd.

Table No. 1: List Of Reagents and Chemicals

Manufacturing Formula:

Formulation	F1	F2	F3	F4
Ingredient	gm/100g	gm/100g	gm/100g	gm/100g
API	2.0	2.0	4.0	4.0
DMSO	10.0	15.0	15.0	10.0
Carbopol 10NF	1.2	1.2	1.2	1.2
Propylene glycol	27.3	24.3	24.3	24.3
Glycerine	28.3	26.3	24.3	29.3
Ethanol	6.0	6.0	6.0	6.0
Methyl paraben	0.1	0.1	0.1	0.1
Propyl paraben	0.1	0.1	0.1	0.1
Purified water	25.0	25.0	25.0	25.0

Table 2: Formulae of different formulations

(For 100 gm)

• Physical characteristics:

consistency, color, & lookMeasurement pH of the gels were measured using digital pH meter

• HPLC assay: retention period approximately 3.9 minutes

• Viscosity: Viscosities of the prepared gels were measured using cone and plate viscometer with spindle no. 1 at 25ºC±0.5ºC. • The percentage of drugs 1g of prepared gel formulation containing drug equivalent to 100 mg was taken. 100 ml of phosphate buffer of pH 7.4 was added to it and the solution was mixed properly. The solution was filtered. The absorbance of the resulting solution was measured at 229 nm using a UV spectrophotometer after suitable dilutions. The drug content of the formulation was determined using the following equation:

% Drug content = (Actual concentration of drug in the formulation)/ (Theoretical concentration of drug)×100

• Test for skin inflammation

Skin irritation test was performed for the gel formulations on human volunteers to find out any irritation problems which could make it unsuitable for topical use. About 1 g of final formulation to be tested was applied to the sensitive part of the skin (like wrist portion of the hand).

Spreadability test

1 g of the formulation was placed within a circle of 1cm diameter pre-marked on a ground glass slide. The gel formulation was sandwiched between this slide and the second slide having the same dimension. A

weight of 500 g was allowed to rest on the upper glass slide for 5 min. The increase in the diameter due to gel spreading was noted. The spreadability was then calculated from the following formula: Spreadability= M × L/T Where, M = mass in gram, L =distance traveled b

• Franz diffusion cell for in vitro diffusion • Stability studies: examined at various humidity and temperature levels

III. RESULT AND DISCUSSION

1. Calibration Curve

Concentration (µg/mL)	Absorbance
10	0.2216
20	0.3979
30	0.5593
40	0.736
50	0.9011
Intercept	0.0541
Slope	0.0849
Correlation coefficient (R^2)	0.9986

Table 3: Calibration curve for the estimation of APA07 (in pH 7.4 phosphate buffer)

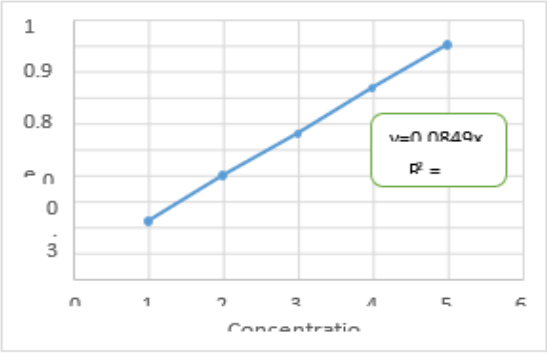

Figure 3: Calibration curve of APA07 2 IR Analysis

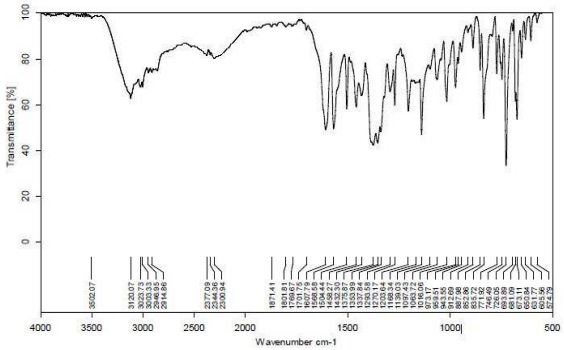

Figure4: FT-IR of Drug

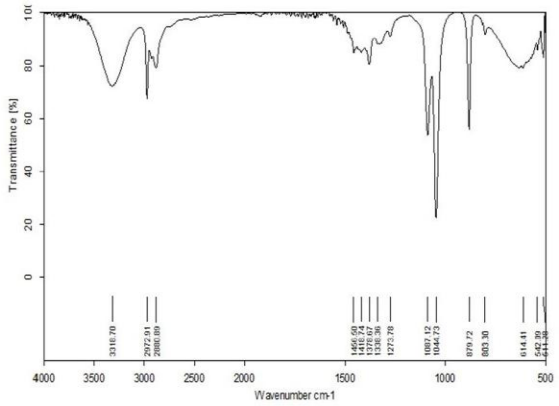

Figure 5: FTIR of APA07 and Ethanol

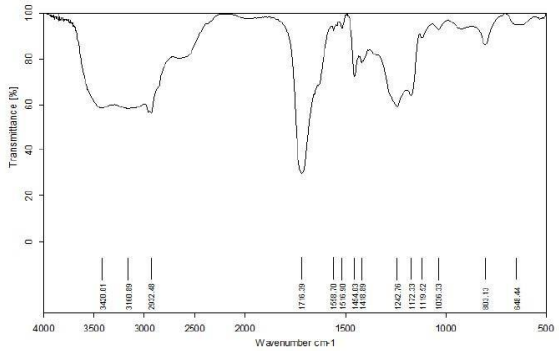

Figure 6: FT-IR of APA07 and Carbopol

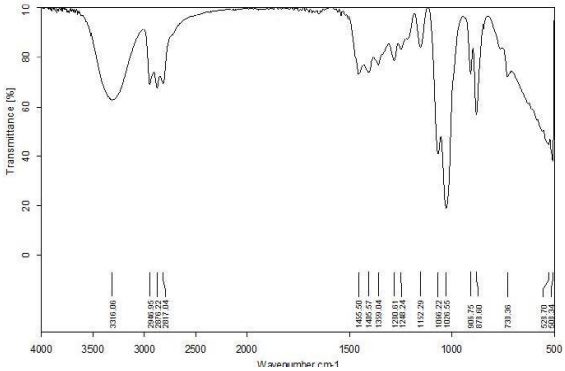

Figure 7: FT-IR of APA07 and Dimethyl Sulphoxide

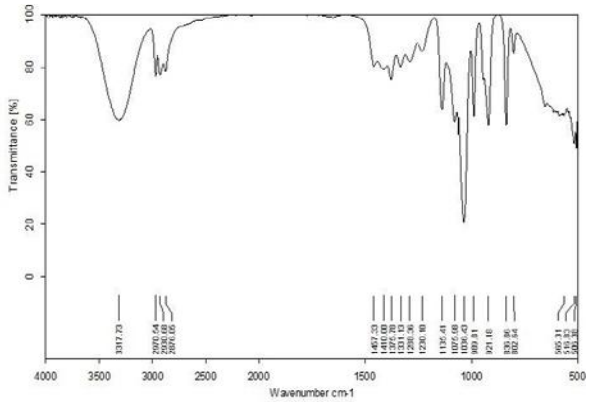

Figure 8: FT-IR of APA07 and Propylene Glycol

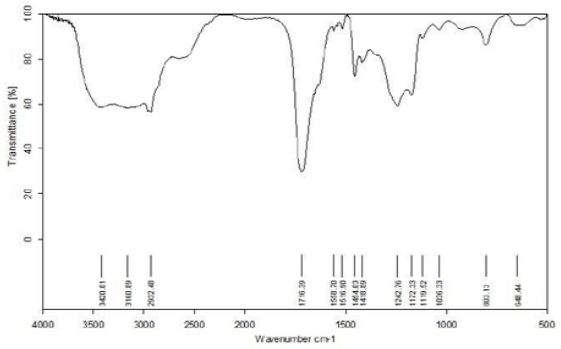

Figure 9: FT-IR of APA07 and Glycerol

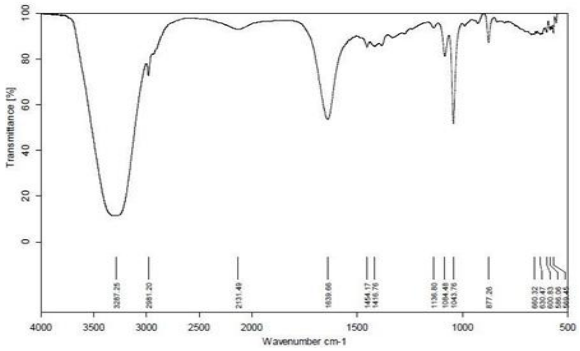

Figure 10: FT-IR of physical mixture

2.Evaluation of Formulated APA07 Topical Gels

Formulations→ Test parameters↓	F1	F2	F3	F4
Description	White to off white viscous gel	White to off white viscous gel	White to off white viscous gel	White to off white viscous gel
pH	4.84	4.92	4.99	4.88
Assay (% w/w)	96	96.40	97	96.60
Viscosity (cps)	3654	3701	4078	3800
Spread ability (gm.cm/sec)	6.578	6.530	6.529	6.552
Drug Content %	90	91	91.5	90.5

Table 4: Physical properties for APA07 topical gels (F1 – F4):

3.In vitro drug diffusion study for the formulations (F1 F4):

Time (Hrs)	Formulation codes and respective drug release profiles (%) of APA07 topical gel			
	F1	F2	F3	F4
0	0	0	0	0
2	14.7	18.7	19.1	15.2
4	19.8	21.0	24.0	23.5
6	75.2	59.2	69.9	60.4
8	81.5	85.2	96.4	85.2
12	89.5	91.2	98.2	94.2

Table 5: In vitro drug diffusion profiles of formulations (F1 – F4)

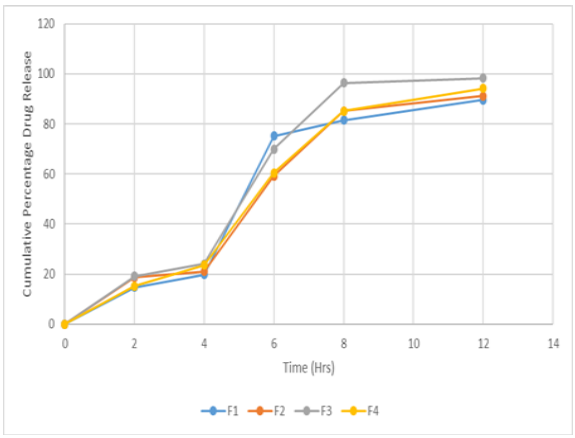

Figure 11: In-vitrodrug diffusion profiles for formulations (F1 – F4)

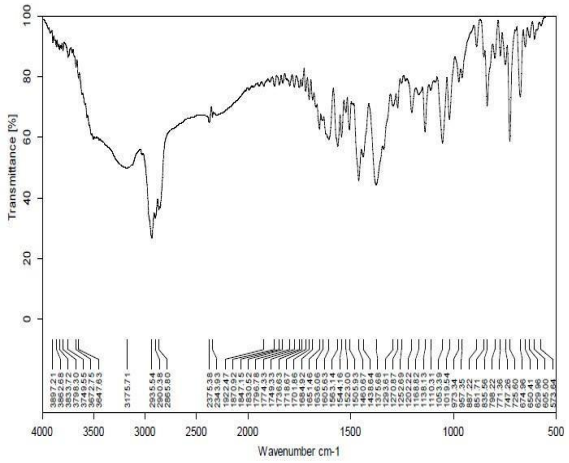

Figure 12: FT-IR of Optimized formulation (F3)

4.Stability studies for the formulation:

Condition→ Parameter↓	Initial/RT	1 Month	2 Month	3 Month
Description	White to off white viscous gel	White to off white viscous gel	White to off white viscous gel	White to off white viscous gel
pH	4.84	4.97	4.86	4.98
Assay (% w/w)	97	96.80	96.40	96
Viscosity (cps)	4078	3891	3765	3689
Spreadability gm.cm/sec	6.529	6.50	6.525	6.523

Table 6: Physical parameters for Stability loaded formulations at condition (40°C/75%RH) (F3)

Condition→ Parameter↓	Initial/RT	1 Month	2 Month	3 Month
Description	White to off white viscous gel	White to off white viscous gel	White to off white viscous gel	White to off white viscous gel
pH	4.84	4.92	4.95	4.98
Assay (% w/w)	97	96.70	96.50	96.20
Viscosity (cps)	4078	3910	3865	3690
Spreadability (gm.cm/sec)	6.529	6.501	6.4800	6.450

Table 7: Physical parameters for Stability loaded formulations at condition 30°C/65% (F3)

5.In Vitro Drug Diffusion study of Optimized formulation:

Condition→ Time point↓	40°C/75%RH			30°C/65%RH		
	1 month	2 month	3 month	1 month	2 month	3 month
0	0	0	0	0	0	0
2	17.2	17.1	16.8	18.2	18.5	17.8
4	22.9	23.2	22.9	25.4	24.6	23.8
6	65.8	65.1	63.8	71.2	69.5	69.7
8	92.5	93.5	94.5	94.2	93.7	93.2
12	98.2	98.0	96.2	97.2	97.4	96.7

Table 8: In vitro-drug diffusion data for stability loaded formulations (F3)

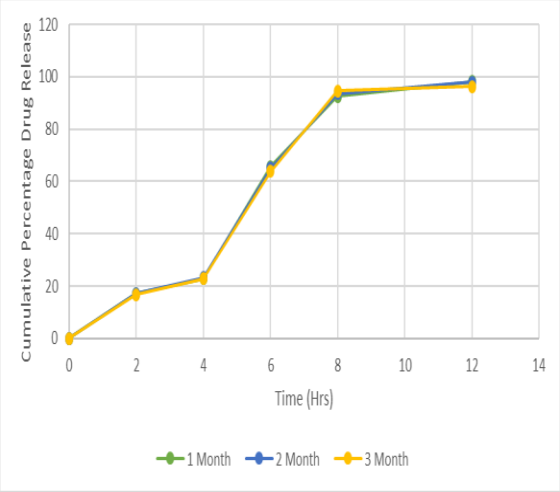

Figure 13: In vitro-drug diffusion profiles for stability loaded formulations (F3) at condition 40°C/75%RH

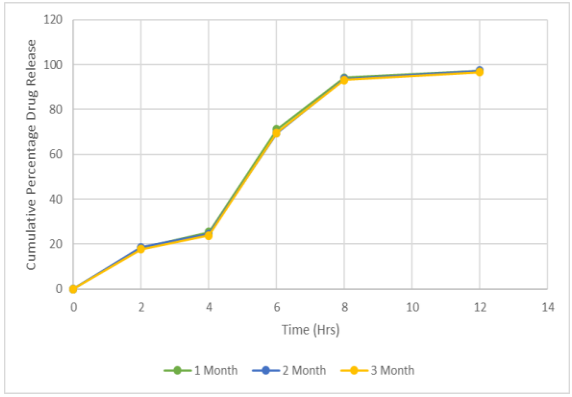

Figure 14: In vitro-drug diffusion profiles for stability loaded formulations (F3) at condition 30°C/65%RH

1.Preformulation Studies

Fourier Transfer Infrared Spectrophotometry (FT-IR): Infrared spectra for pure drug, excipients, physical mixture and Optimized topical gel of APA07 were determined to find the compatibility of the drug in the mixture using FTIR- Spectrophotometer by disc method. The FTIR were performed and the spectra obtained are represented from Figure 13 to Figure 19, Figure 21.

The FT-IR results showed that the prominent characteristic peaks of the drugs are maintained in the physical mixtures as well as in the final formulations which is an indication that there are no interactions affecting the activity of the drug. These excipients could be used for further study using these combinations.

Construction of calibration curve:

Calibration curve for APA07 using pH 7.4 phosphate buffer:

The calibration curve was constructed by preparing 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml and 50 µg/ml concentrations as the serial dilutions and then finding the corresponding absorbance values spectro - photometrically at 240nm. The data is represented in Table 03. The slope and intercept values were found to be 0.0849 and 0.0541 respectively and the correlation coefficient was 0.9986.

The calibration curve is represented in Figure 12. From the slope and intercept values it is observed that the curve is having a positive slope and positive intercept. The coefficient of correlation value of 0.9986 is satisfactory. From the data it is evident that the concentration range from 10 µg/mL to 50 µg/mL

is within the linearity range as per the Beer's Lamberts law.

2.Preparation of APA07 Topical Gel:

The APA07 Topical Gels were prepared as per the desired method. The formulae for the four formulations are tabulated in Table 2. And the manufacturing process are shown in Figure 11.

3.Evaluation studies of APA07 Topical Gel:

1.Description:

The formulated gels were physically examined for the colour, appearance and consistency, the results were found satisfactory for all the four formulations (F1-F4).

2.pH measurement:

pH for all the formulation were tested using pH meter, among the four formulations F3 showed pH 4.99.

3.Assay (% w/w):

The assay for formulations was checked, among all the four formulations, the assay value for F3 formulation was 97 %w/w.

4.Viscosity (cps):

The viscosity for the formulations were measured using cone and plate viscometer, for F3 formulation the viscosity was 4078 cps, which showed the best consistency among all the four formulations.

5.Drug Content % :

The % drug content of APA07 was carried out. Overall, the four formulations (F1- F4), the F3 showed the highest percentage of drug content i.e., 91.5%.

6.Skin irritation study:

The skin irritation study was carried out. All the four batches gave 100% result. The gel was very comfortable for sikn.

7.Spreadability:

Spreadability is an important factor to consider in the formulation of gel. The spreadability of prepared gel formulation was tested. Among all four formulations F3 batch showed spreadability of 6.529 gm.cm/sec.

8.In vitro-drug diffusion study:

The release of APA07 from the topical gels was carried out.

Overall, the four formulations (F1- F4), the F3 showed the highest percentage of drug release 98.2% for 12 hours.

IV. CONCLUSION

APA07 is classified as a Biopharmaceutics Classification System (BCS) Class IV drug, characterized by both low aqueous solubility and low permeability, which present significant challenges for effective drug delivery. Despite these limitations, APA07 has demonstrated promising anti-psoriatic activity, making it a potential candidate for topical psoriasis treatment. To overcome its poor permeability, formulation strategies involving the incorporation of co-solvents and skin permeation enhancers were employed. These excipients help improve drug solubilization and facilitate its transport across the stratum corneum, thereby enhancing dermal drug delivery.

In vitro evaluation of the developed formulations revealed favorable drug release and skin permeation characteristics. The performance of the formulations was assessed using the Franz diffusion cell technique, a widely accepted method for studying transdermal and topical drug transport. The results demonstrated sustained and efficient release of APA07 from the formulation, along with enhanced penetration through the skin membrane. These findings suggest that the selected formulation approach successfully addressed the inherent limitations associated with the drug's low solubility and permeability.

Furthermore, the enhanced permeation observed in vitro indicates the potential for improved therapeutic efficacy in the management of psoriasis. By increasing drug availability at the target site, the formulation may contribute to better control of inflammation, keratinocyte hyperproliferation, and other pathological features associated with psoriatic lesions. Future studies will focus on evaluating the anti-psoriatic efficacy and safety of APA07 in appropriate animal models. These investigations will provide valuable insights into the pharmacological activity, skin retention, therapeutic outcomes, and potential toxicity of the developed formulation under in vivo conditions. The results of these studies will be essential for determining the feasibility of advancing APA07 toward clinical development as a novel topical treatment for psoriasis.

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