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Formulation and Evaluation of Anti-Acne Film Forming Gel

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ABSTRACT

The objective of the present study was to develop film forming polymeric solution for the topical release of Salicylic Acid through the skin for the treatment of hyperkeratotic and scaling disorders. A film forming polymeric solution of Salicylic Acid was prepared by using hydroxypropyl methylcellulose, hydroxypropyl cellulose Eudragit RS100 and Polyvinyl Alcohol as a film forming polymer in different concentrations and PEG 400 used as plasticizer. The prepared solution was tested for pH, viscosity, drying time, folding endurance, drug content uniformity followed by *in vitro* diffusion study. All the formulations showed the results within acceptable range for various tests. Formulations exhibited pH within the range of 8.2 to 8.5. Drying time of all the formulation ranged between 320±0.6 to 455±0.6 second. The folding endurance of the films was found to be consistent. The F6 batch was found to be the most accurate and effective formulation. This formulation demonstrated desirable properties such as appropriate viscosity, pH, spreadability, and drug release. The film formed by this formulation exhibited good adhesion to the skin and provided sustained release of salicylic acid, potentially improving patient compliance and therapeutic efficacy. Hence this novel dosage form will improve the bioavailability and can be alternative to conventional topical application.[1]

Keywords: Anti-Acne, Film Forming Gel

1. INTRODUCTION

Pharmaceutical research faces the major challenge of developing new technologies to give formulations different characteristics that overcome the therapeutic limitations of traditional dosage forms, including adjustable release profiles, flexibility of use, ability to carry more than one active ingredient, improve patient availability and compliance Whether it is for topical application of dermatological dysfunctions or for transdermal application of systemic action, the skin is an increasingly explored route of administration, as it has no gastrointestinal side effects, avoids the metabolization of active ingredients by first pass effect, and is of easy application in individuals with swallowing difficulties, such as the elderly and children, for example[1]. However, the skin's main function is to be a barrier against external agents, so, even though it is a promising route of administration; it is not so easily passable Conventional topical dosage forms, such as cream, gels and ointments, are called semisolids. These usually have an unattractive sensory appearance and do not guarantee prolonged skin contact with the drug, requiring repeated applications throughout the day and may therefore cause less patient adherence to treatment. Therefore, the development of formulations that overcome this technological barrier may be crucial for improving the treatment of dermatological diseases. The film-forming system (FFS) is a novel approach that can be used as an alternative to conventional topical and transdermal formulations. It is defined as a non-solid dosage form that produces a film in situ, i.e., after application on the skin or any other body surface. These systems contain the drug and film-forming excipients in a vehicle that, upon contact with the skin, leaves behind a film of excipients along with the drug upon solvent evaporation. FFS rapidly creates supersaturated systems upon skin application, thereby overcoming the issue of instability.[2,3]

Salicylic acid is an organic compound with the formula HOC_6H_4COOH. A colorless (or, white), bitter-tasting solid, it is a precursor to and a metabolite of acetylsalicylic acid (aspirin). Salicylic acid topical is used to treat many skin disorders, such as acne, dandruff, psoriasis, seborrheic dermatitis of the skin and scalp, calluses, corns, common warts, and plantar warts, depending on the dosage form and strength of the preparation. The FFG containing Salicylic acid is designed to overcome the drawbacks of conventional topical SA formulations, such as poor adherence to the skin, limited residence time, and potential for easy wash-off.[4,5]

The Primary aim of this research is to develop and characterize a topical gel formulation containing salicylic acid (SA) as the active ingredient for the treatment of Acne Vulgaris.

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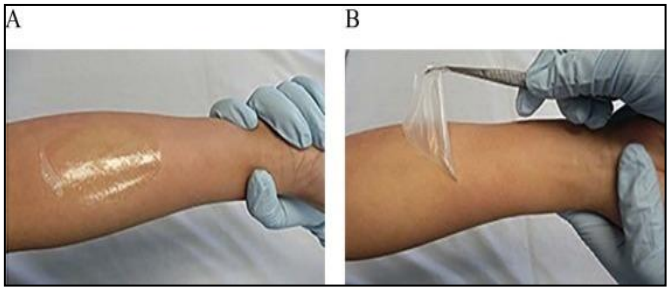

Fig.1 Film Forming Gel

2. MATERIAL FOR PREPARATION

Salicylic Acid (drug) from Cipla Pharmaceutical ltd; Eudragit RS100, Hydroxy Propyl Methyl Cellulose (HPMC) & Hydroxy Propyl Cellulose (HPC) from Yarrow Chem pvt Ltd; PolyVinyl Alcohol from Alpha Chemika pvt.Ltd; PEG 400 & Ethanol from Lobachemie Pharmaceutical pvt.Ltd; Methyl Paraben & Menthol from Pure LabChem Company.

3. METHOD OF PREPARATION

Transdermal films containing Salicylic Acid were prepared by the solvent evaporation technique. For the formulations Composition is shown in Table 1 given below. Solution of HPMC, HPC, Eudragit RS100 and PVA were prepared separately in ethanol and water (as per their solubility) in different concentrations as given in table. (Drug was added in solution containing ethanol). Above polymeric solutions was mixed to the other solvent on the magnetic Stirrer using continuous stirring. To this mixture, add PEG 400 as plasticizers, Menthol as a Soothing Agent, and Methyl paraben as a preservative. This drug-polymer solution was prepared in a Beaker and wrapped by aluminum foil, and preserved in desiccator for further studies.[5]

Table.1 Composition of different formulations containing Salicylic Acid

INGEDIENTS	F1	F2	F3	F4	F5	F6
Salicylic Acid	100mg	100mg	100mg	100mg	100mg	100mg
HPMC	100mg	150mg	200mg	-	-	-
HPC	-	-	-	100mg	150mg	200mg
Eudragit RS100	5%	5%	5%	5%	5%	5%
PVA	5%	5%	5%	5%	5%	5%
PEG 400	5%	5%	5%	5%	5%	5%
Menthol	q.s	q.s	q.s	q.s	q.s	q.s
Methyl Paraben	q.s	q.s	q.s	q.s	q.s	q.s
Ethanol (ml)	5	5	5	5	5	5
Water(ml)	5	5	5	5	5	5

4. PREFORMULATION STUDY

Before formulating a product, the physical and chemical properties of a drug substance have undergone some preformulation testing. It is the first step in rational development of dosage form[6].

a) Organoleptic properties: The color, odor and taste of the drug were recorded using descriptive terminology.[7]

b) Identification by UV: The absorption maximum of the standard solution was scanned between 200-400 nm regions on UV-Visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum[8].

c) Melting point determination: Melting point of the drug was determined by taking small amount of drug a capillary tube closed at one end. The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and average value was noted[9].

d) Solubility study: It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminologies.[10]

e) Standard calibration curve study:

From the stock solution (100µg/ml), aliquots of 0.5, 1.0, 1.5, 2.0 and 2.5 ml were transferred into 10 ml volumetric flasks and final volume was made upto 10 ml with pH 6.8. Absorbance values of these solutions were measured against blank (pH 6.8) at 365 nm using UV-Visible spectrophotometer and calibration curve was plotted against concentration *vs.* absorbance[11].

5. EVALUATION PARAMETERS

a) Physical appearance of Film: This parameter was checked simply with visual inspection of Films and evaluation of texture by feel or touch.

b) pH Determination: The pH value of film forming gels formulations were evaluated by using calibrated digital pH meter. 1 gm of gel was dissolved in 100 ml of distilled water and kept for 2 hours. The measurement of pH of each formulation was performed in 3 times and the mean values were calculated.[13]

c) Drying time: One gram of the gel was placed on a Petri dish which was spread uniformly on Petri dish and kept on a hot plate at 37˚C and time needed until gel dry.[14]

d) Irritancy: Small amount of gel was placed on the skin kept for few minute and it was non-irritant.[15]

e) Viscosity: The viscosity of prepared gel was determined by Brookfield Viscometer using spindle no. 06 at 100 RPM. The sample cup was filled with 16-20 ml of gel and allows the spindle to rotate for 1-2 minutes to stabilize. Viscosity reading was recorded.[16]

f) Spreadability: The spread ability of the prepared gel was determined by measuring the spreading diameter of 0.5 g of gel in between two horizontal smooth surface glass plates (20 cm × 20 cm). The initial diameter of the spreading of the gel in centimeter was formed by put the gel on the glass plate was noted.. The upper plate was gradually removed & diameter of the circle formed after spreading of the gel was measured in centimeters.[17]

g) Folding Endurance of Films: The flexibility of Films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the Films was determined by repeatedly folding a small strip of the Films (approximately 2x2 cm^2) at the same place till it broke. The number of times Films could be folded at the same place, without breaking gives the value of folding endurance.[18]

h) Content Uniformity: The films of known weight (dimension 2×2 cm^2) were dissolved in small quantity of Phosphate Buffer Solution. The solution was suitably diluted and absorbance was measured at 365 nm using UV-spectrophotometer.[18]

i) In Vitro drug diffusion studies: Franz diffusion cell were used to study the release profile of drug from film forming gel. The cell consists of two chambers it is the donor and the receptor compartment between in which a diffusion membrane was mounted. The donor compartment, of inner diameter is 24 mm. The diffusion medium used phosphate buffer solution pH was 5.8. 1 mL of the drug containing film forming gel was located in the donor compartment over the drug release membrane and was separated from the receptor compartment by the egg membrane. The egg membrane was previously soaked for 24 hours in phosphate buffer solution. The donor and receptor compartments were attached together using a clamp. Whole assembly was placed on a magnetic stirrer. The receptor compartment with 100 mL of phosphate buffer solution was placed on magnetic stirrer. It was maintained at 37 ± 0.50 C and stirred continuously at 50 rpm. Samples of 1 mL were collected at predetermined time intervals & analyzed for drug content by UV Spectrophotometer at λ max against blank. The receptor phase was replaced with an equal volume of phosphate buffer at each time of sample withdrawal.[20]

6. RESULTS AND DISCUSSION

- **Preformulation Study**

A. Organoleptic properties:

- Physical state: pastel yellow Semi Solid

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- Colour: Light Brown coloured
- Odour: Characteristic

Fig.2 Film Forming Gel Formulation

B. Determination of λ_{Max} of Salicylic Acid

The maximum absorption for Salicylic Acid was found at 301 nm. The λ_{Max} of salicylic acid was shown in the Fig no. 03.

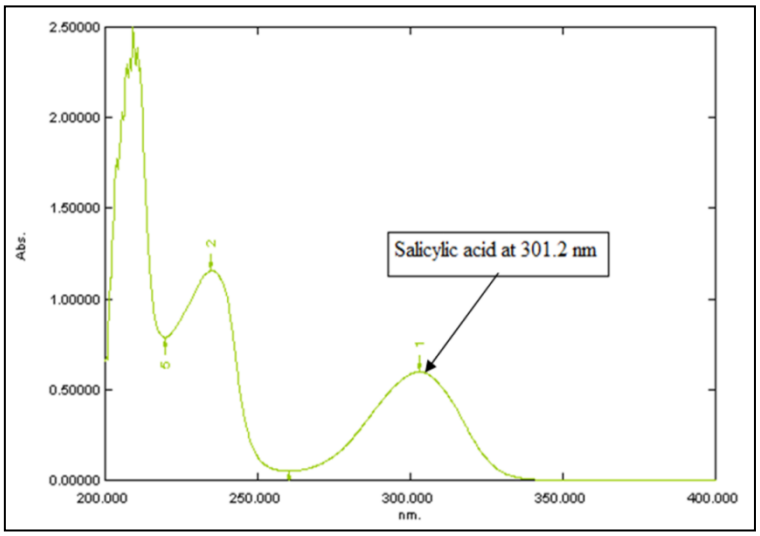

Fig.3 UV Spectrum of Salicylic Acid (ʎmax determination)

C. Melting point

Melting point values of Salicylic Acid sample was found to be in range of 157º C to 159ºC.The reported melting point for Salicylic Acid was 158- 159 º C. Hence, experimental values were same as official values. Melting of Film was given in the table no.2.

Table.2 Melting point of Salicylic Acid

Name of compound	Melting point (official)	Melting point (experimental)
Salicylic Acid	157 to 159 º C	158- 159 º C

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D. Solubility Study

Solubility of Solution was given in the table no.3.

Table.3 Solubility of Salicylic Acid in various solvents

Name of solvent	Solubility
Distilled water	Slightly Soluble
Ethanol	Freely Soluble
PEG 400	Freely Soluble
Phosphate buffer (6.8pH)	Sparingly soluble

E. Standard calibration curve

Preparation of standard graph of Salicylic Acid

Absorbance obtained for various concentrations of Salicylic Acid in pH 6.8 were represented in Table 4. The graph of absorbance vs. concentration for Salicylic Acid was found to bilinear in the concentration range of 5–25 µg/ml. The drug obeys Beer- Lambert's law in the range of 5–25µ/ml was shown in figure 4.

Table.4 Data of concentration and absorbance for Salicylic Acid

S.No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.248
3	10	0.481
4	15	0.755
5	20	0.988
6	25	1.223

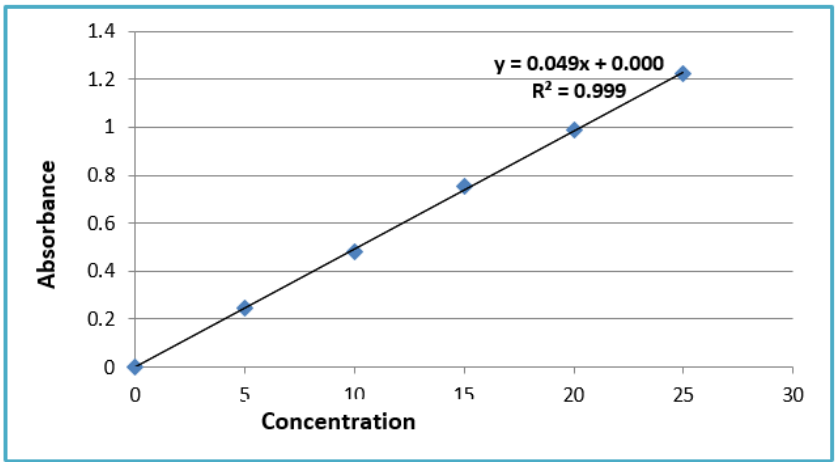

Fig.4 Standard Calibration curve for Salicylic Acid.

Table.5 Observed Data in calibration curve study

S.No.	Parameters	Values
1	Correlation coefficient(r)	0.999
2	Slope	0.000
3	Intercept	0.049

- **Physicochemical evaluation**

A. Spreadability: The spread ability tests were carried out between 5.4± 0.2 to 6.2 ± 0.2 cm. This indicates the spread ability increased with decrease in polymer concentration. Spreadability of film was given in the table no. 6.

Table.6 Spreadability

Formulation Code	Spreadability (cm)
F_1	6.0±0.2
F_2	5.4±0.2
F_3	6.1±0.2
F_4	5.8±0.2
F_5	6.2±0.2
F_6	6.1±0.2

B. Determination of pH

pH of all Formulation was shown in the table no.7.

Table.7 pH of gel

Formulation Code	pH
F_1	8.5±0.2
F_2	8.4±0.2
F_3	8.2±0.2
F_4	8.5±0.2
F_5	8.4±0.2
F_6	8.3±0.2

C. Determination of Drying Time

The Drying Time of all the formulations was found to be in 320 sec to 455 sec. The Drying Time of Formulations was given in the table no 8.

Table.8 Drying Time

Formulation Code	Drying Time
F_1	320
F_2	365
F_3	380
F_4	400
F_5	435
F_6	455

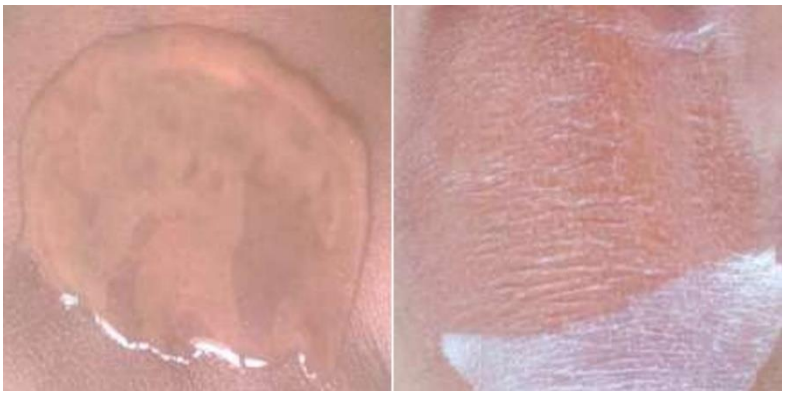

Fig.5 before and after drying Film

D. Viscosity Study:

Viscosity of gel was found to be between 1320 to 2263 cps. Viscosity of formulation was given in the table no. 9.

Table.9 Viscosity Reading

Formulation Code	Viscosity
F_1	**1320**
F_2	**1630**
F_3	**1849**
F_4	**1555**
F_5	**1974**
F_6	**2263**

E. Folding Endurance:

The folding endurance gives the idea of flexible nature of Films. The folding endurance was measured manually, Films were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the Films exhibited good physical and mechanical properties and the average folding endurance of all Films was given in Table 10. The drug loaded Films (2x2 cm^2) were tested for folding endurance of Films. The recorded folding endurance of the films was > 150 times. It means all formulations had good film properties.

Table.10 Folding Endurance data of F_1 to F_6 Film formulations

No.	**Formulation code**	**Folding Endurance Mean ± S. D.***
1	F_1	166.33 ± 4.50
2	F_2	189.00 ± 1.25
3	F_3	216.56 ± 2.36
4	F_4	150.33 ± 4.36
5	F_5	172.00 ± 1.25
6	F_6	194.0 ± 1.25

F. Drug Content Uniformity:

Salicylic Acid Films prepared with different polymers were subjected to the evaluation for uniform dispersion of drug throughout the Film. In each case three Films were used and the average drug content was calculated, the results were represented in Table 11. The drug was dispersed in the range of 92.31±0.345 to 97.40±0.425 %. Suggesting that drug was uniformly dispersed throughout all prepared Films. The standard deviation value calculated for such formulation is very less which suggest that the results are reproducible and accuracy in the method used to prepare the Films.

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Table.11 Drug content of F 1 to F6 formulations

S. NO	Formulation Code	Drug Content (%) Mean ± S.D.
1	F_1	97.40 ± 0. 425
2	F_2	95.27 ± 0. 380
3	F_3	93.29 ± 0. 281
4	F_4	92.31 ± 0. 345
5	F_5	94.39 ± 0. 488
6	F_6	93.29 ± 0. 281

G. In Vitro drug Release Study:

In vitro release studies data of Salicylic Acid are given in Tables 12, for Films F1 to F6. The percentage cumulative drug release over time for different formulations from F1 to F6 is depicted in Figure 6.

Regarding the in-vivo drug release study, the release of Salicylic Acid from the Film through membrane was investigated using a Franz diffusion cell with a 15 ml capacity. An observed trend indicated a decrease in drug release from F_1.to F_6 with an increase in polymer concentration in formulations from F1 to F3 and F4 to F6.

Table.12 In vitro release of Salicylic Acid from film F1-F6 in phosphate buffer pH 6.8

S.no	% Drug Released with time	Time (Hrs.)	F_1	F_2	F_3	F_4	F_5	F_6
0		**0**	0	0	0	0	0	0
1		**1**	11.35	8.83	9.67	5.71	4.8	4.32
2		**2**	19.36	17.11	17.23	17.76	13.96	12.9
3		**3**	29.63	26.78	28.69	25.31	24.22	21.78
4		**4**	47.43	36.2	40.11	39.23	37.99	34.56
5		**5**	57.82	56.06	53.41	48.32	46.93	45.8
6		**6**	73.4	68.34	62.12	57.03	54.65	54.34
7		**7**	80.57	77.19	75.97	67.17	64.49	63.65
8		**8**	92.61	90.41	87.12	79.59	76.79	72.86

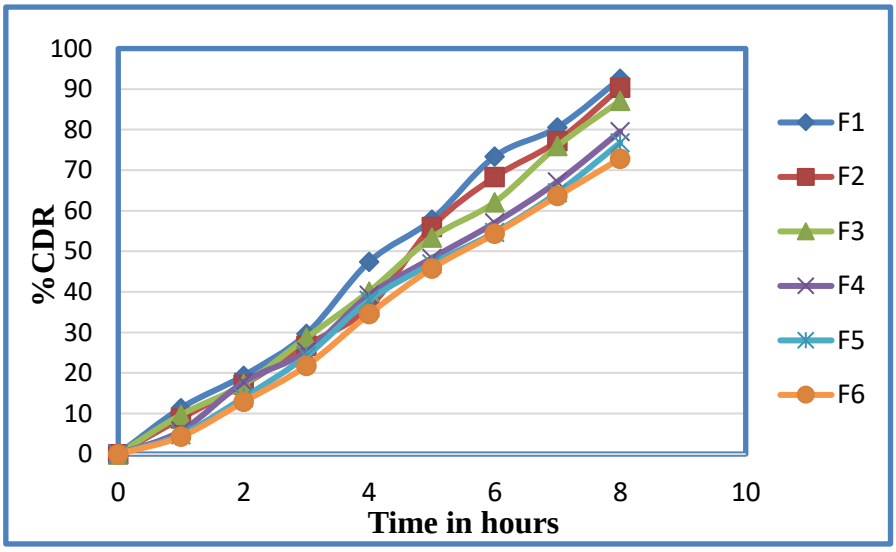

Fig.6: %Cumulative Drug release of different formulations F1-F6

Above observations proves the rate of drug release is contingent upon the type and concentration of the polymers employed. This observation can be attributed to the hydrophilic polymer's capacity to absorb water molecules, resulting in an escalation of the swelling percentage. No significant drug release was observed in any formulation until polymers start to swell. Presence of polymers in high concentrations results in increase in its viscosity as well as reducing the porous network causing reduction in hydration rate and/or entry of solvent molecules into the system. The hydrophilic polymers have polar groups in their structure that affect the amount of inter cross linking and bonding with water molecules. Consequently, this resulted in a decrease in the dissolution rate of the drug from the film matrices, thereby reducing the diffusion of the drug. The formulations can be arranged in order of release rate as: F1 > F2 > F3 > F4 > F5 > F6.

7. CONCLUSION

Six batches of salicylic acid Anti-acne film-forming gel were formulated and evaluated. The F6 batch was found to be the most accurate and effective formulation. This formulation demonstrated desirable properties such as appropriate viscosity, pH, spreadability, and drug release. The film formed by this formulation exhibited good adhesion to the skin and provided sustained release of salicylic acid, potentially improving patient compliance and therapeutic efficacy. Further optimization and stability studies are recommended to refine this formulation for clinical applications. It also proves that The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs as it provides controlled release of the drug, and produces, leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage forms and improves patient compliance.

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