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DESIGNING AND EVALUATING FLUFENAMIC ACID EMULGELS

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ABSTRACT
The skin is indeed a widely explored route of administration, as it has no gastrointestinal side effects, avoids active ingredient metabolization through first pass effect. Semisolid treatments like lotions and ointments overcome some difficulties with additional constraints. An emulgel is a two-phase system in which an emulsion is entrapped within a matrix of an outer gel. The ability of novel polymers to gel allows for the preparation of stable emulsions and creams by reducing surface and interfacial tension while increasing overall the viscosity of the aqueous phase, which has sparked a lot of interest in their use as emulsifiers and thickeners in recent years.

Key words: Emulgel, Topical, Flufenamic acid, Sustained Release

INTRODUCTION

Pharmaceutical research must develop innovative technologies to overcome the therapeutic limits of standard dosage forms, including changeable release profiles, flexibility of usage, and the capacity to transport more than one active component. The skin is indeed a widely explored route of administration, as it has no gastrointestinal side effects, avoids active ingredient metabolization through first pass effect, and is easy to apply in those with swallowing difficulties, such as the elderly and young children [1].

Skin is a key channel for local and systemic medication delivery. The topical route offers a broad surface, self-administration, and an option to oral and hypodermic medication delivery. Percutaneous medication absorption takes place via stratum corneum. Permeation via skin relies on skin physiology, physicochemical qualities, and delivery mechanism. Patch, ointments, creams, etc., have numerous limitations. Patches can irritate skin. Semisolid treatments like lotions and ointments overcome some difficulties with additional constraints. These don't stay on the skin and can be wiped off by clothes [2].

Gels are a relatively newer class of dosage form that is created by entrapping large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles [11]. These particles can consist of inorganic substances such as aluminum salts or organic polymers of natural or synthetic origin. Gels are created by entrapping the liquid in the network. Compared to the ointment or cream basis, they feature a larger aqueous component that allows for more drug solubility as well as easier drug migration through a vehicle that is basically liquid. These are excellent both in terms of how well patients tolerate them and how simple they are to use. There are many different analgesic medications that can be purchased on the market as topical preparations. Flufenamic acid, a powerful non-steroidal anti-inflammatory drug (NSAID), has always been utilized as both an anti-inflammatory and analgesic medication. Tablets and suspensions are the traditional delivery methods for this substance [12]. There is no marketed topical formulation of Flufenamic acid available till date.

The majority of topical medicines are utilized for the localized effects at the place of their application. This was because drug penetration into the underlying layers of skin or mucous membranes allows for these effects to occur. The resulting dosage forms, when a gel and an emulsion are used together, are known as EMULGELS [13].

Emulgels

An emulgel is a two-phase system in which an emulsion is entrapped within a matrix of an outer gel. Emulgels are two-phase systems in which an emulsion is trapped in the matrix of an outer gel and is encapsulated

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within the matrix of an emulsion.

Hydrophilic drugs have been delivered with gels extensively as topical drug delivery systems. The advantages of gels over creams and ointments include greater dissolution of the drug, easier drug migration through the matrix, faster onset of action, and a better aesthetic appeal than oily formulations, but unless some solubility enhancers and/or agents to modify intermolecular interactions are used, they are not suitable vehicles for hydrophobic molecules.

Furthermore, emulgels are more stable, do not require intense sonification, and possess both emulsion and gel advantages [3].

PREFORMULATION OF FLUFENAMIC ACID

Determination of Flufenamic acid melting point

The melting point was determined by inserting a small quantity of the drug powder into a capillary tube. The tube was sealed from one side by flame, then put in Stuart electrical melting point [4].

Determination of Flufenamic acid- λ Max

10 mg of FFA was dissolved in 100ml of phosphate citrate buffer (pH 5.5), which is within the pH range of human skin. Until it is completely dissolve then diluted to reach 5µg/ml concentration and scanned with UV spectrophotometer from 200-400 nm and the result was recorded

Calibration Curve of Flufenamic acid

Calibration curves of FFA in phosphate citrate buffer (pH 5.5) were constructed by preparing a series of dilute solutions with different concentrations of FFA from stock solution containing 1mg/ml. The absorbance was then measured at the λ max of the drug. The measured absorbance were plotted against the respective concentrations [5].

Determination of Solubility profile of Flufenamic acid

The solubility of FFA was estimated in phosphate citrate buffer (pH 5.5). An excess amount of the drug was putted in 50 ml volumetric flask. The flask shaken by sonicator for 30 min then kept for 24hrs at room temperature then filtered and diluted, the concentration of the filtrate was determined by analysing the sample spectrophotometrically at the λ max of the drug [6].

Preparation Of Flufenamic Acid Emulgel

Six emulgel formulas were prepared and each emulgel formula was prepared by mixing equal quantities of a gel and emulsion portions.

Preparation of the gel portion was done by dispersing and dissolving different amounts of polymers (SCMC, CMC, or Carbopol 940) within 50 ml of deionized water with constant stirring at a moderate speed and the system was heated until we have a homogenous gel base, then the gel was leaved to cool down and homogenization for 48 hrs. Triethanolamine was added as neutralizing agent to formulas containing CP 940 as gelling agent.

The oil phase of the emulsion was prepared by mixing certain quantity of Span 80 with certain amounts of light liquid paraffin or coconut oil. While the aqueous phase of the emulsion was prepared by dissolving estimated quantity of Tween 80, Propylene glycol in appropriate volume of deionized water.

Methyl paraben and propyl paraben as preservatives were added at 0.3% w/w and 0.1% w/w concentration in the final formulas respectively.

FFA was dissolved in ethanol, and then incorporated in this aqueous portion of the emulsion. Both the oily and aqueous portions of the emulsion were separately heated to 70º- 80º C; then the oily phase was added to the aqueous phase gradually with continuous stirring until getting homogenous emulsion and then cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio to obtain the final emulgel product.

EVALUATION OF FLUFENAMIC ACID EMULGEL

Physical evaluation

All the formulations were evaluated for colour, occulsiveness, washability, phase separation and odour

Determination of pH

The pH of the formulated gels was determined using digital pH meter. The electrode was immersed in the gel and readings were recorded from pH meter[96]

Spreadability

A sample of 0.1 g of each formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes where no more spreading was expected. Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability.

Homogeneity and grittiness

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. Also, the homogeneity can be detected when a small quantity of the gel is rubbed on the skin of the back of the hand. The grittiness of prepared gel is also observed in the same manner

Extrudability

The extrudability of gel formulations were determined by filling gel in the collapsible tubes. The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel [8].

Drug content determination

A specific quantity (100 mg) of developed gel was taken and dissolved in 100 ml of phosphate buffer of

pH 5.5. The volumetric flask containing gel solution was shaken for 2 hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 285 nm using phosphate buffer (pH 5.5) as blank [9].

Drug Content = (Concentration × Dilution Factor × Volume taken)

***In vitro* drug release**

The *in vitro* drug release studies were carried out using an egg membrane. The formulation was applied on membrane which was placed in the test tube and it was tied with the help of thread on the burette stand. Phosphate buffer pH 7.4 was used as a dissolution media. The temperature of the beaker containing phosphate buffer was maintained at 37°C. Sample (10 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analysed spectrophotometrically at 280 nm and the cumulative % drug release was calculated.

Stability study

The optimized formulation F4 was subjected to stability study for one month at 4°C (Refrigerator), room temperature and 45°C/75% RH. At the interval of 30 days, samples of nanogel formulation were taken and evaluated [10].

RESULTS AND DISCUSSION

Preformulation characteristics of Flufenamic acid

Determination of Flufenamic acid Melting point

The measured melting point of FFA was found to be 131.5^{o}C. This result is the same as reported in references, which indicates the purity of the drug powder used in the study

Determination of Flufenamic acid- λ Max

Scanning of FFA solution (5µg/ml) in phosphate citrate buffer (pH 5.5) by UV spectrophotometer at 200-400 nm gave the spectrum shown in figure 4. The maximum absorbance (λ max) found to be 280 nm, which is similar to standard references

Calibration Curve of Flufenamic acid

There are several dilutions that have been made using this method, including 2, 4, 6, 8, 10. The regression values were also calculated to be 0.9998, and the calibration values have been shown in table 2 as well as the image has been shown in figure 5.

Determination of Solubility profile of Flufenamic acid

Regarding the solubility of FFA, saturated solubility of FFA was calculated in phosphate citrate buffer (pH 5.5) at 37^{o}C; and the maximum solubility found to be **0.016 mg/ml.**

PREPARATION OF FLUFENAMIC ACID EMULGEL

Six emulgel formulations were prepared and each emulgel formula was prepared by mixing equal quantities of a gel and emulsion portions. The prepared formulation (F1-F6) has been undergoes to various evaluation test.

EVALUATION OF FLUFENAMIC ACID EMULGEL

Physical evaluation

The colour, occulsiveness, washability phase separation and odour of all formulation done and reported in table 3

All developed gel showed occulsiveness. No odour and phase separation were observed. All preparations were found to be washable.

Determination of pH

The pH of the formulated gels was determined using digital pH meter. The pH values of all developed gels were obtained in between **5.1-5.8.**

Spreadability

Table 5 values indicate the Spreadability of the gel which is easily spreadable by small amount of shear.

Homogenity and grittiness

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.

Also, the homogeneity can be detected when a small quantity of the gel is rubbed on the skin of the back of the hand. The grittiness of prepared gel is also observed in the same manner.

All developed gel showed good homogeneity with absence of lumps and no grittiness.

Extrudability

The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel. Extrusion of gel from the tube is important during application and for the patient compliance. The values of extrudability of different formulations were found good.

Drug content determination

All formulations were uniformly tested for content uniformity, and the results are shown in table 8. Spectrophotometric analysis was performed on each formulation to determine its drug content.

The drug content in Film Forming gel formulations is **81.21% - 96.36%,** indicating that the drug is distributed evenly in the formulation. F4 has the greater content of drug in it has 96.36%. It is suitable for the further studies hence it has a greater drug content.

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Figure 1: Schematic representation of an emulgel system

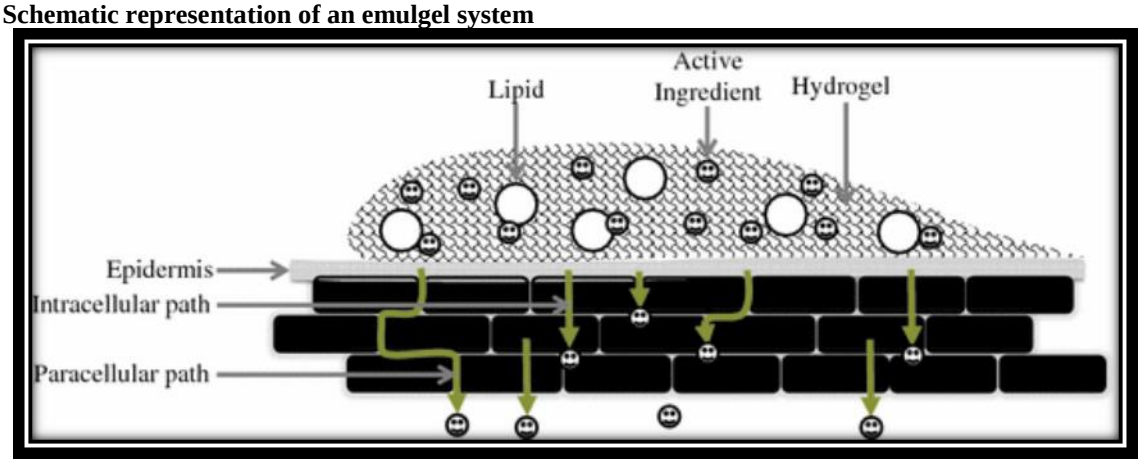

Figure 2: UV Spectrum of FFA in Phosphate citrate buffer (pH 5.5)

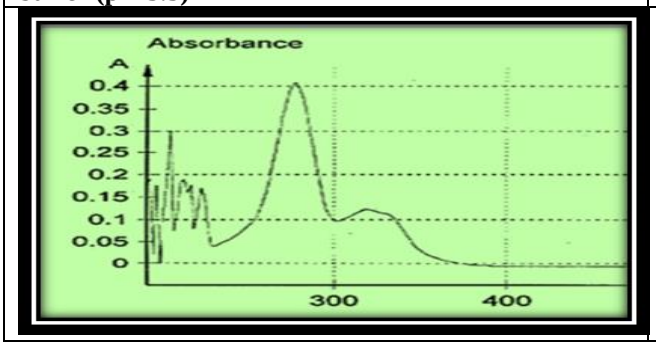

Figure 3: Calibration curve of FFA

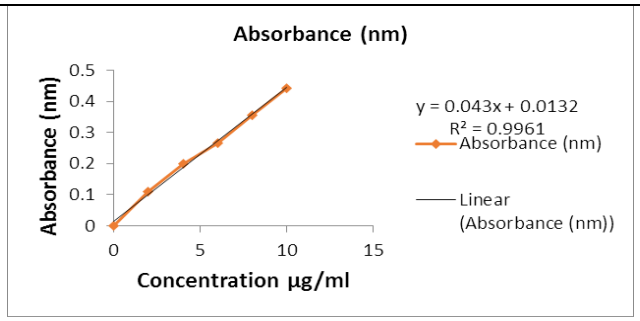

Figure 4: Drug content of FFA emulgel

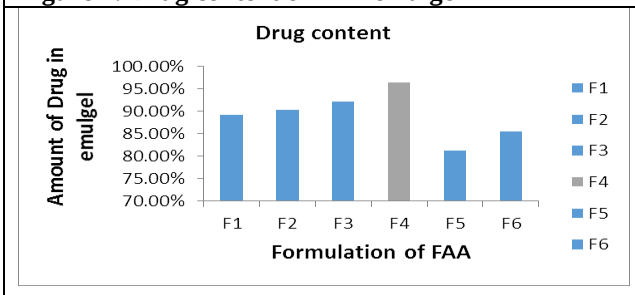

Figure 5: In vitro drug release data F1 formulation

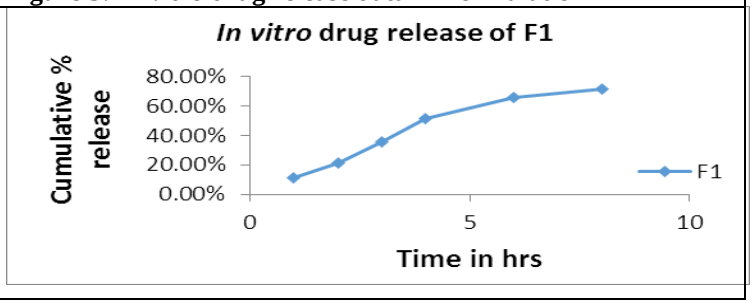

Figure 6: In vitro drug release data F2 formulation

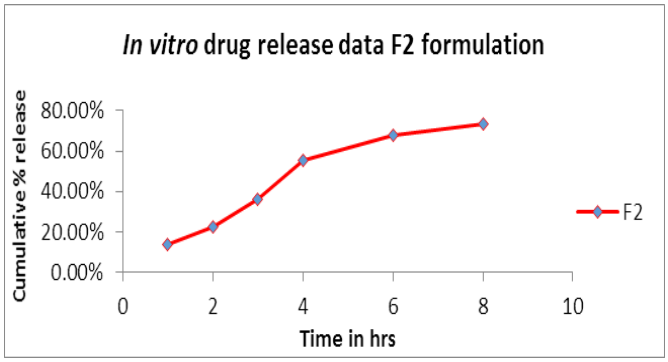

Figure 7: In vitro drug release data F3 formulation

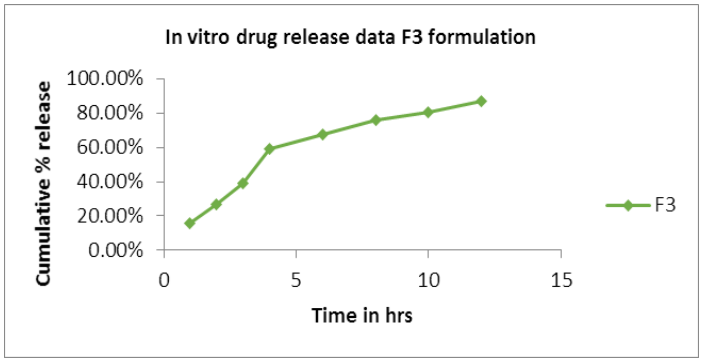

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Figure 8: In vitro drug release data F4 formulation

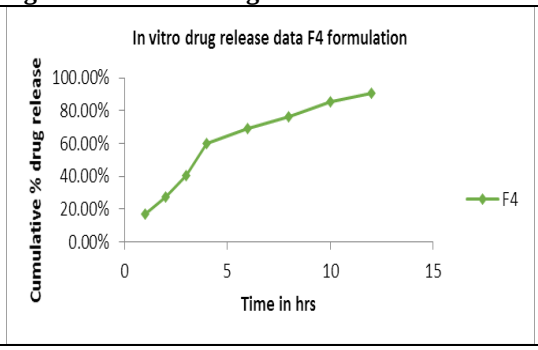

Figure 9: In vitro drug release data F5 formulation

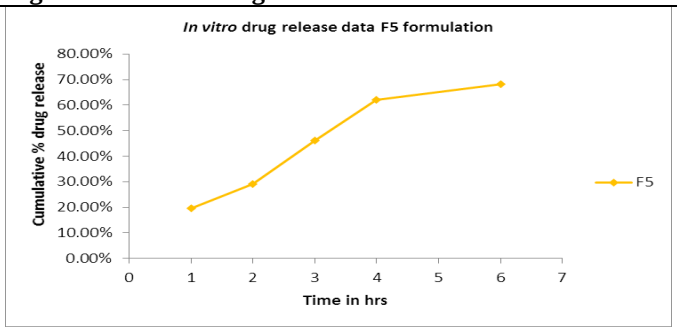

Figure 10: In vitro drug release data F6 formulation

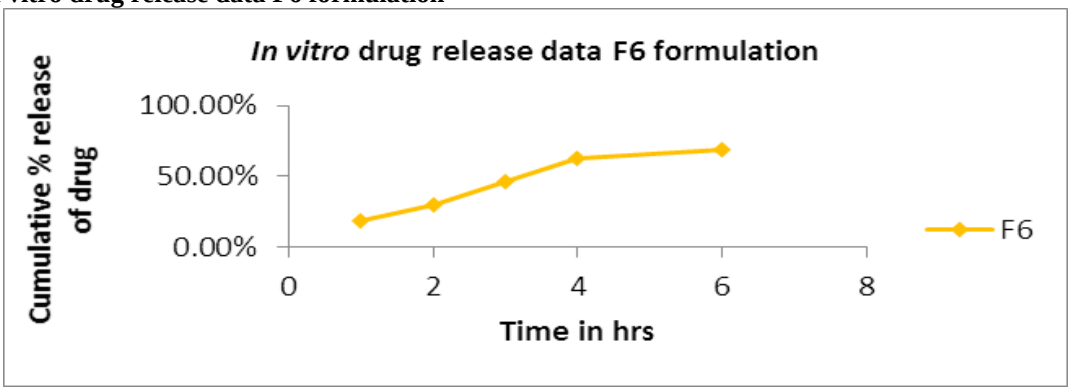

Figure 11: Stability Study release data for Formulation F4 at 4oC

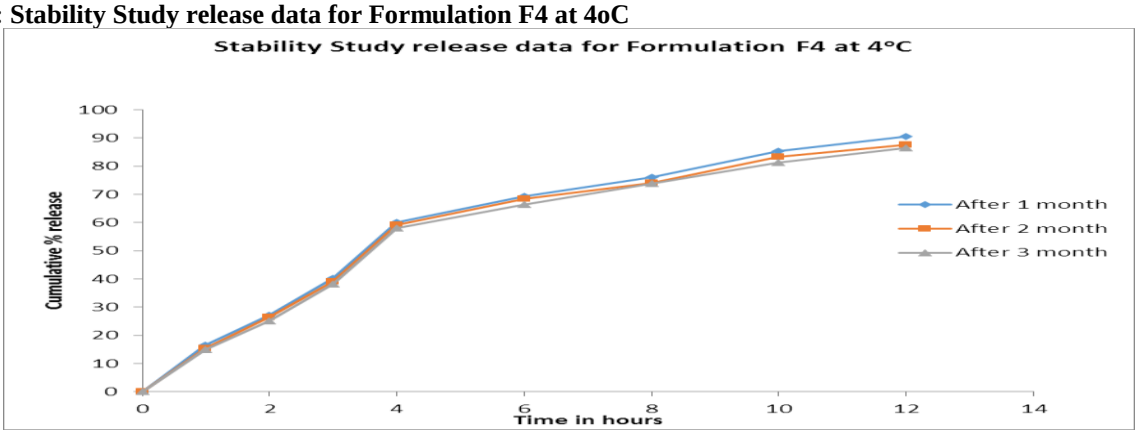

Figure 12: Stability Study release data for Formulation F4 37°C % /65% RH.

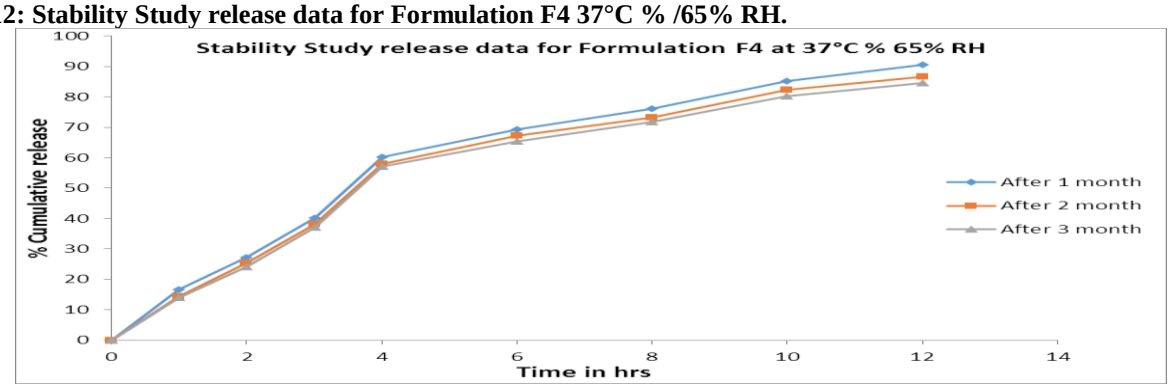

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Figure 13: Stability Study release data for Formulation F4 45°C % /75% RH

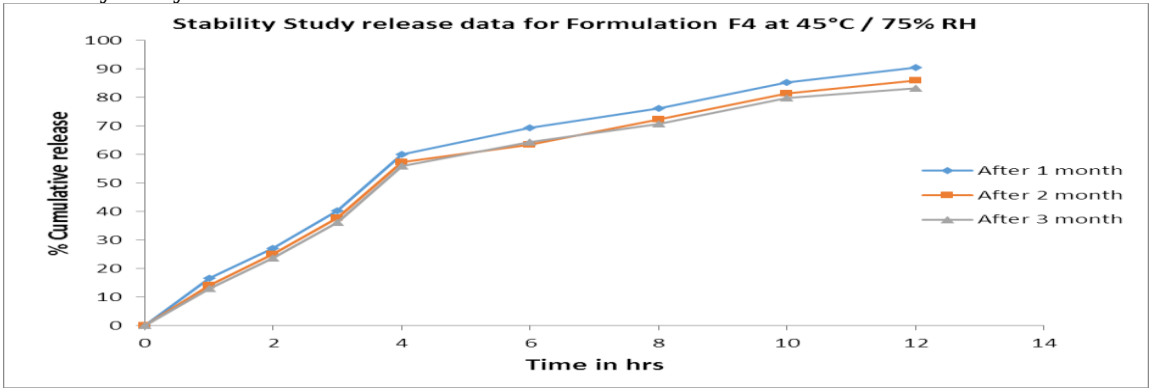

Table 1: Formula of FFA Emulgel

S.No	Formulation Code	FFA (gm)	SCMC (gm)	CMC (gm)	CP 940 (gm)	Liq Paraffin (gm)	Coconut oil (gm)	Span 80 (gm)	Tween 80 (gm)	Distilled water
1	**F1**	0.5	**0.75**	-	-	**6**	-	2.5	1.5	Q.S
2	**F2**	0.5	**1**	-	-	**6**	-	2.5	1.5	Q.S
3	**F3**	0.5	-	**0.75**	-	**6**	-	2.5	1.5	Q.S
4	**F4**	0.5	-	**1**	-	-	**6**	2.5	1.5	Q.S
5	**F5**	0.5	-	-	**0.75**	-	**6**	2.5	1.5	Q.S
6	**F6**	0.5	-	-	**1**	-	**6**	2.5	1.5	Q.S

Table 2: Calibration curve of FFA

S. No	Concentration (µg/ml)	Absorbance (nm)
1	2	0.109
2	4	0.199
3	6	0.265
4	8	0.356
5	10	0.441

Table 3: Physical evaluation of formulation

Formulation Code	Colour	Occulsiveness	Washability	Phase separation	Odour
F1	White	+ive	Washable	Absence	Odourless
F2	White	+ive	Washable	Absence	Odourless
F3	White	+ive	Washable	Absence	Odourless
F4	White	+ive	Washable	Absence	Odourless
F5	White	+ive	Washable	Absence	Odourless
F6	White	+ive	Washable	Absence	Odourless

Table 4: pH of FFA Emulgel

S. No	Formulation code	pH
1	F1	5.8
2	F2	5.7
3	F3	5.2
4	F4	5.2
5	F5	5.4
6	F6	5.1

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Table 5: Spreadability test of various formulations

S.no	Formulation code	Spreadability diameter (cm)
1	F1	3.4
2	F2	3.6
3	F3	3.8
4	F4	4.1
5	F5	3.5
6	F6	3.3

Table 6: Homogenity and grittiness of FFA emulgel

Formulation code	Homogenity	Grittiness
F1	**Good**	**Absence**
F2	**Good**	**Absence**
F3	**Good**	**Absence**
F4	**Good**	**Absence**
F5	**Good**	**Absence**
F6	**Good**	**Absence**

Table 7: Extrudability of FFA emulgel

Formulation code	Extrudability
F1	**Good**
F2	**Good**
F3	**Good**
F4	**Good**
F5	**Good**
F6	**Good**

Table 8: Drug content of FFA emulgel

S.no	Formulation code	Drug content
1	F1	89.23%
2	F2	90.23%
3	F3	92.23%
4	**F4**	**96.36%**
5	F5	81.21%
6	F6	85.45%

Table 9: In vitro drug release data F1 formulation

Time in hrs	Percentage of drug release	Cumulative percentage of drug release
1	**11.15%**	**11.20%**
2	**21.26%**	**21.31%**
3	**35.21%**	**35.40%**
4	**51.20%**	**51.29%**
6	**65.86%**	**65.91%**
8	**71.25%**	**71.56%**

Table 10: In vitro drug release data F2 formulation

Time in hrs	Percentage of drug release	Cumulative percentage of drug release
1	**13.51%**	**13.56%**
2	**22.60%**	**22.61%**
3	**36.15%**	**36.30%**
4	**55.10%**	**55.29%**
6	**67.81%**	**67.89%**
8	**73.15%**	**73.56%**

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Table 11: In vitro drug release data F3 formulation

Time in hrs	Percentage of drug release	Cumulative percentage of drug release
1	15.51%	15.56%
2	26.60%	26.61%
3	39.15%	39.19%
4	59.10%	59.14%
6	67.54%	67.61%
8	75.81%	75.92%
10	80.15%	80.25%
12	86.65%	86.78%

Table 12: In vitro drug release data F4 formulation

Time in hrs	Percentage of drug release	Cumulative percentage of drug release
1	16.65%	16.66%
2	27.10%	27.17%
3	40.13%	40.19%
4	60.11%	60.13%
6	69.34%	69.39%
8	76.17%	76.19%
10	85.14%	85.25%
12	90.60%	90.75%

Table 13: In vitro drug release data F5 formulation

Time in hrs	Percentage of drug release	Cumulative percentage of drug release
1	19.45%	19.49%
2	29.14%	29.18%
3	46.15%	46.21%
4	62.10%	62.19%
6	68.18%	68.24%

Table 14: In vitro drug release data F6 formulation

Time in hrs	Percentage of drug release	Cumulative percentage of drug release
1	18.45%	18.49%
2	29.71%	29.76%
3	46.69%	46.75%
4	62.32%	62.35%
6	69.10%	69.14%

Table 15: Stability Study release data for Formulation F4 at 4Oc

Time in hours	Cumulative % release		
	After 1 month	After 2 month	After 3 month
1	16.61%	15.51%	14.89%
2	27.15%	26.50%	25.16%
3	40.17%	39.15%	38.11%
4	60.11%	59.06%	58.04%
6	69.36%	68.33%	66.30%
8	76.15%	74.11%	73.79%
10	85.23%	83.21%	81.18%
12	90.59%	87.56%	86.54%

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Table 16: Stability Study release data for Formulation F4 37°C % 65% RH

Time in hours	Cumulative % release		
	After 1 month	After 2 month	After 3 month
1	16.61%	14.31%	13.89%
2	27.15%	25.40%	24.16%
3	40.17%	38.11%	37.11%
4	60.11%	58.01%	57.04%
6	69.36%	67.32%	65.30%
8	76.15%	73.11%	71.79%
10	85.23%	82.21%	80.18%
12	90.59%	86.56%	84.54%

Table 17: Stability Study release data for Formulation F4 45°C % /75% RH

Time in hours	Cumulative % release		
	After 1 month	After 2 month	After 3 month
1	16.61%	14.01%	12.98%
2	27.15%	25.11%	23.61%
3	40.17%	37.79%	36.10%
4	60.11%	57.41%	56.04%
6	69.36%	63.42%	64.39%
8	76.15%	72.31%	70.65%
10	85.23%	81.51%	79.74%
12	90.59%	85.96%	83.34%

***In vitro* drug release**

In these studies, we found that the FAA Emulgel releases drug over a period of 12hrs. Tables 9-14 show the results of an *in vitro* drug release study of emulgel (F1-F6) that had been prepared.

The formulation F1& F2 made by using SCMC of 0.75 and 1 gm ratio show release of drugs up to 8hrs. Formulation F3 and F4 made by CMC of 0.75 & 1gm which shows 12hrs drug release and last two formulation F 5&6 has been made by Carbopol- 940 showing release of drugs up to 6 hrs.

In these 6 formulations F1-F3 composed of liquid paraffin as oil phase and F4-F6 formulation containing coconut oil as oil phase. Among all the formulation, F4 contains CMC (1%) and coconut oil as oil phase have shown 90.75% at 12 hours was helpful in release the drug in formulation.

Based on the drug release, the optimum formulation selected for further study was F4 (CMC (1%) % Coconut oil (6 gm)).

Stability study

The optimized formulation F4 was subjected to stability study for one month at 4°C (Refrigerator), 37°C / 65% RH and 45°C/75% RH. At the interval of 30 days, samples of emulgel formulation were taken and evaluated for the *in vitro* release of drug of optimized formulation F7 kept at 4°C shows a release rate of 86.54% after stability study.

The percentage release of formulation kept 37°C / 65% RH and at 45°C/75% were 84.54% and 83.34% respectively after period of stability study. The *in vitro* release of optimize formulation F4 shows that the emulgel formulation are more stable at 4°C (Refrigerator) when compared to and at 45°C/75%RH (stability chamber).

The emulgel formulation kept at 4°C showed a cumulative release of 86.54 % after 30 days of stability studies.

CONCLUSION

A gel formulation containing Flufenamic acid, a derivative of anthranilic acid, was successfully developed. Based on the preceding findings, we can conclude the following:

- Flufenamic acid was successfully incorporated into the different topical emulgel preparation
- Nearly all the developed 6 formulation showed acceptable physicochemical properties and the formula F4 which was CMC- based emulgel with coconut oil shows the finest bio-adhesion and optimum drug release properties.
- It was found that the pH of the emulgel was close to that of human skin, reducing the risk of irritation. Also stability up on storage for 3 month at room temperature, where no significant change was observed.

As a result, Flufenamic acid emulgel formula showed promise as a topical alternative for treating skin infections. It is necessary to conduct further preclinical and clinical studies.

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