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Research Article

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Development and evaluation of novel Fluticasone Propionate Emulgel for topical drug delivery

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ABSTRACT

The studies were conducted with an object to develop even, harmless and efficient delivery system for Fluticasone Propionate. Topical drug delivery has gained a marvellous interest in today's pharmaceutical formulation and research is going on in achieving better product. Fluticasone Propionate is corticosteroids with anti-inflammatory medication that is generally used to treat eczema and dermatitis. Emulgel is a semi solid preparation which decreases the systemic side effects and to create a more pronounced effect with lower doses of the drug. Emulsion in gel have emerged as one of the most interesting topical drug delivery system as it has twofold release control system. Also the stability of emulsion is increased when it is incorporated into gel. The Emulgel was developed using polymers like Carbopol 934 and HPMC K-100 in various ratios of gel and emulsion. DSC and IR spectral studies were performed to confirm the compatibility of drug and polymers in the formulations. The prepared Emulgel was evaluated for their physical appearance, pH evaluation, spreadability, rheological study, and drug content and in-vitro permeation studies. All formulation was evaluated for their release patterns. The result indicates that Emulgels offers better release, controlled release, or a stable atmosphere for the incorporated drug (Fluticasone Propionate). From studies we can conclude that topical application would be effective by applying through novel delivery system like Emulgel of Fluticasone Propionate.

Keywords: Topical delivery, Achieving, Twofold release, Incorporated.

INTRODUCTION

In the past, the most commonly applied systems were topically applied lotions, creams & ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption of the drugs through the skin, which lead to the idea of TDDS [1]. Most of the 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 [2]. TDDS, the delivery of drugs across the skin is gaining wide acceptance among patients. On the other hand, topical delivery system increases the contact time and mean resident time of drug at the applied site leading to an increase in local drug concentration. While the pharmacological action of emulgel formulations may not change as rapidly as the solution form [3]. The main advantage of topical delivery system is to bypass first pass metabolism [4]. Avoidance of risk and inconveniences of intravenous therapy and of the varied condition of absorption like pH changes, presence of enzymes, gastric emptying time are other advantages of topical preparations [5, 6]. The topical drug delivery system is generally used where the other system of the drug administration fails.

Fluticasone Propionate, an effective topical corticosteroid has been used as an anti-inflammatory, antipruritic and corticosteroid agent.

The aim of this work was to develop an emulgel formulation of Fluticasone Propionate , a hydrophobic drug, using Carbopol 934, HPMC as gelling agent & penetration enhancer i.e. mentha oil. The influence of gelling agent and penetration enhancers was investigated.

Emulgel:
An emulgel is a gellified emulsion prepared by mixing an emulsion either water-in-oil (W/O) type or oil-in-water (O/W) type with a gelling agent. Due to solubility problems, most of lipophilic drugs cannot be formulated directly as hydrogel. For this reason; emulgel provide better stability and release of the lipophilic drug in comparison with simple hydrogel base. When gels and emulsions are used in combined form the dosage forms are referred as EMULGELS. In recent years, there has been great attention in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase[7,8,9,10].

EXPERIMENTAL SECTION

Materials
Fluticasone Propionate was procured from Tirupati Life sciences Pvt. Ltd., Himachal Pradesh. Carbopol 934 and HPMC K100M were procured from Maharishi Arvind Institute of Pharmacy, mansarovar, Jaipur. All other chemicals were used of analytical grade and without any further chemical modification.

Preparation of emulgel
Preparation of emulsion phases: The oily phase of emulsion was prepared by dissolving span-80 in light liquid paraffin with required quantity of Fluticasone Propionate in ethanol. Mentha oil was added to it as a permeation enhancer. Aqueous phase was prepared by dissolving tween-80 in purified water. Methyl paraben was dissolved in propylene glycol and mixed with aqueous phase.

Preparation of gel: Accurately weighed quantity of carbopol-934 and HPMC K100M was taken in a previously dried beaker and 10 ml of distilled water was added to it. It was mixed well using mechanical shaker with constant stirring. More distilled water was added to it to maintain the consistency of the gel. The pH of the formulation was adjusted to 6.0 to 7.0 using triethanolamine.

Formulation of emulgel: Both the oily and aqueous phases were separately heated to 70^0C to 80^0C, than mixed with the continuous stirring and allowed to cool to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the Fluticasone propionate emulgel formulation [11, 12].

Table 1 Composition of Fluticasone propionate Emulgel Formulation (%w/w)

Ingredients (%w/w)	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	Emulsion									
Fluticasone propionate	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Light liquid paraffin	7	7	7	7	7	7	7	7	7	7
Tween 80	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 80	1	1	1	1	1	1	1	1	1	1
Propylene glycol	5	5	5	5	5	5	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methyl Paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Mentha Oil	3	4	3	4	3	4	3	4	3	4
Purified Water	q.s.									
Gel										
Carbopol 934	0.5	0.75	1	1.25	1.5					
HPMC K100M						1	2	3	4	5
Purified water	q.s.									
Emulsion : Gel	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
Triethanolamine was added to adjust the pH of all formulations from 5.5 to 6.5										

EVALUATION OF EMULGEL
Fourier transforms infra red spectroscopy (FTIR):
The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for formulation. The FTIR spectra of Fluticasone propionate was done and given in Fig.1 [13]

Differential scanning calorimetry (DSC):
DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a reference and sample are measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the study. Mainly, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The DSC analysis of Fluticasone propionate was given in Fig. 2[14]

Physical Examination:
The Prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency and phase separation. [15]

Determination of pH:
pH of the formulation was determined by using digital pH meter. pH meter electrode was washed by distilled water and then dipped into formulation to measure pH and this process was repeated 3 times.[16]

Measurement of viscosity:
The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25±1ºC) before the measurement was taken. Spindle was lowered perpendicular in to the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted. [17,18]

Spreadability:
To determine spreadability of the gel formulations, two glass slides of standard dimensions were selected. Formulation whose spreadability was to be determined was placed over one slide and the other slide was placed over its top such that the gel is sandwiched between the two slides. The slides were pressed upon each other so as to displace any air present and the adhering gel was wiped off. The two slides were placed onto a stand such that only the lower slide is held firm by the opposite fangs of the clamp allowing the upper slide to slip off freely by the force of weight tied to it. 20 gm weight was tied to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted [19]. The spreadability was calculated by using the following formula.

$$S = M \, . \, L/T$$

Where, M = weight tied to upper slide
L = length of glass slides
T = time taken to separate the slides

Extrudability:
The prepared emulgel formulations were filled in clean, lacquered aluminum collapsible tubes with a 5 mm opening nasal tip. Extrudability was then determined by measuring the amount of gel extruded through the tip when a constant load of 1 kg. was placed over the pan[20]. The extrudability of prepared emulgel formulations was calculated by using following formula.

$$\text{Extrudability} = \frac{\text{Amount of gel extruaded from the tube} \times 100}{\text{Total amount of gel filled in the tube}}$$

Drug content study:
Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Took 1 g of the formulation into 10 ml volumetric flask added 1 ml methanol in it and shake well and make up the volume with PBS pH 7.4. The Volumetric flask was kept for 2 hr and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered the mixer then measured absorbance by using spectrophotometer at 237.4 nm. [21]

Drug Content = (Conc. × Dilution Factor × Vol. taken) × Conversion Factor

***In-vitro* Drug release study:**
The *in vitro* drug release studies of the Emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was applied on to the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution

to solubilise the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable time interval sample were analyzed for drug content by UV visible spectrophotometer at 237.4nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time. The cumulative % drug release was calculated using standard calibration curve.[22,23]

Details of dissolution testing:

- Dissolution media: Phosphate buffer saline pH 7.4
- Speed: 50 rpm
- Aliquots taken at each time interval: 1 ml
- Temperature: 37 ± 2^0C
- Wavelength: 237.4 nm

Release kinetics of selected formulation:

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (cumulative % drug release v/s. time), First order (log cumulative % drug retained v/s. time), Higuchi model (cumulative % drug retained v/s. Square root of time) and Peppas model (log cumulative % drug release v/s. log time).[24,25]

RESULTS AND DISCUSSION

Fourier transforms infra red spectroscopy (FTIR):

Figure 1: IR spectra of Fluticasone propionate

Differential scanning calorimetry (DSC):

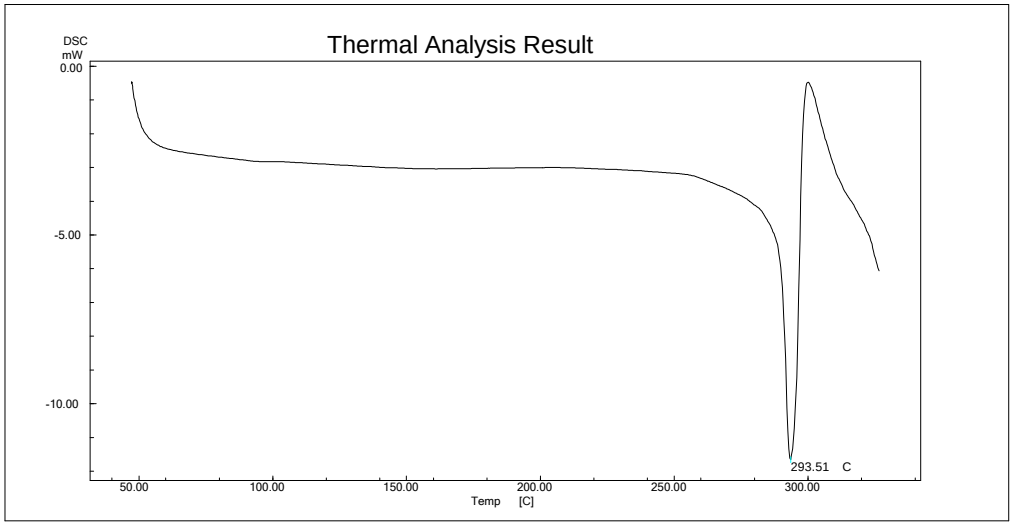

Fig 2: DSC analysis of Fluticasone Propionate

Physical Appearance:
Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table 2

Table 2.: Physical Appearance

S. No.	Formulation Code	Colour	Phase Separation	Homogeneity	Consistency
1	F1	White	None	Fair	+
2	F2	White	None	Excellent	+++
3	F3	White	None	Excellent	+++
4	F4	White	None	Excellent	+++
5	F5	White	None	Excellent	+++
6	F6	White	None	Good	++
7	F7	White	None	Excellent	+++
8	F8	White	None	Excellent	+++
9	F9	White	None	Excellent	+++
10	F10	White	None	Fair	+

Determination of pH:
The pH of the emulgel formulations was in the range of 6.8 ± 0.1 to 6.0 ± 0.3, which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations. The data is shown below in Fig 3.

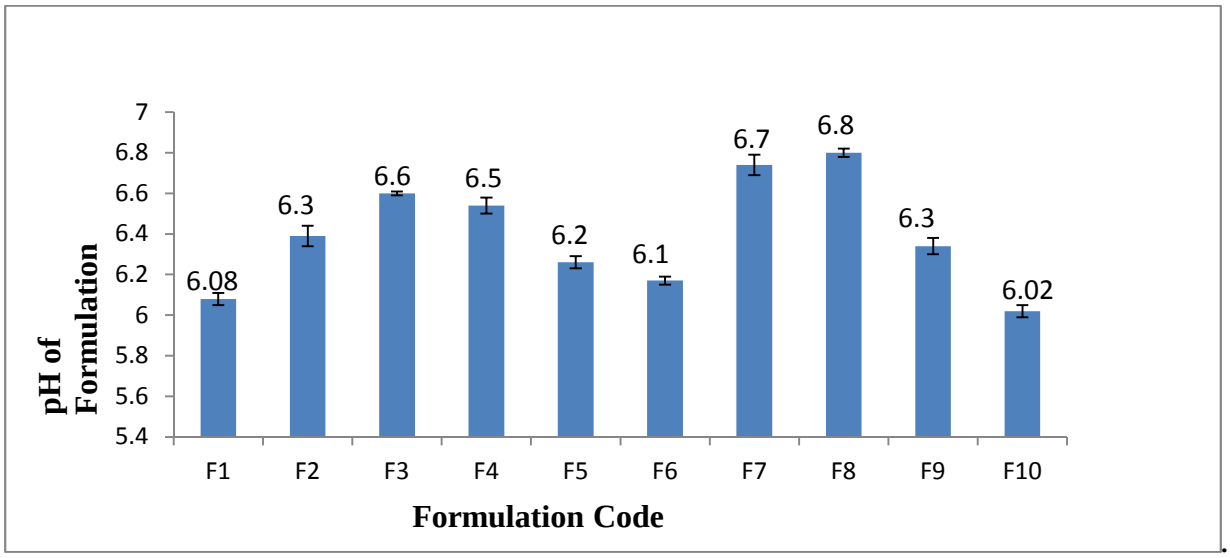

Fig.3: pH of Different Formulations F1-F10 (Mean±S.D.)

Rheological Study:
The emulgel was rotated at 50 rpm for 10 min with spindle 07. The corresponding reading was noted. The viscosity of the emulgel was obtained. The viscosity of the formulations increases as concentration of polymer increases. The data is shown below in Fig. 4

Spreadability:
Spreadability of the emulgel was decreases with the increases in the concentration of the polymer. The spreadability is very much important as show the behaviour of emulgel comes out from the tube. The data is shown below in Fig. 5

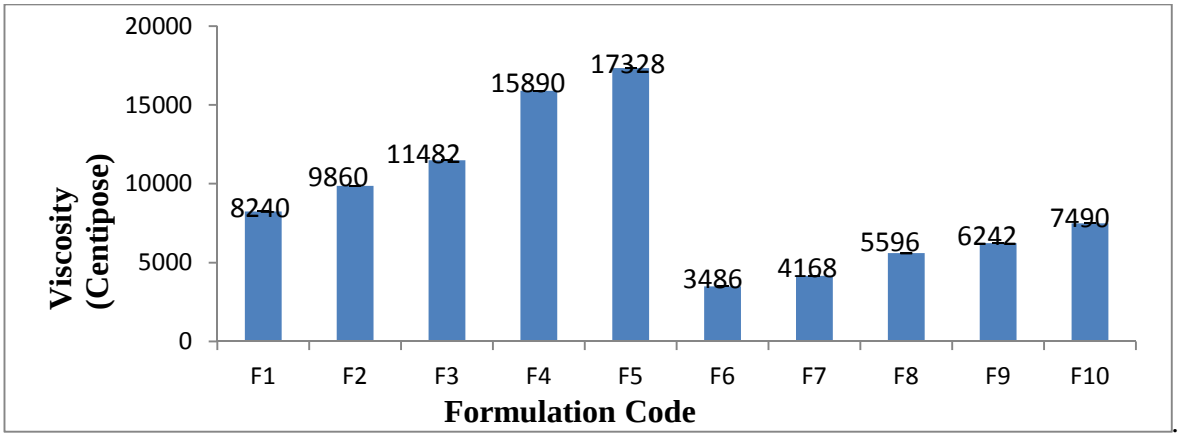

Fig. 4: Viscosities of Different Formulations F1-F10

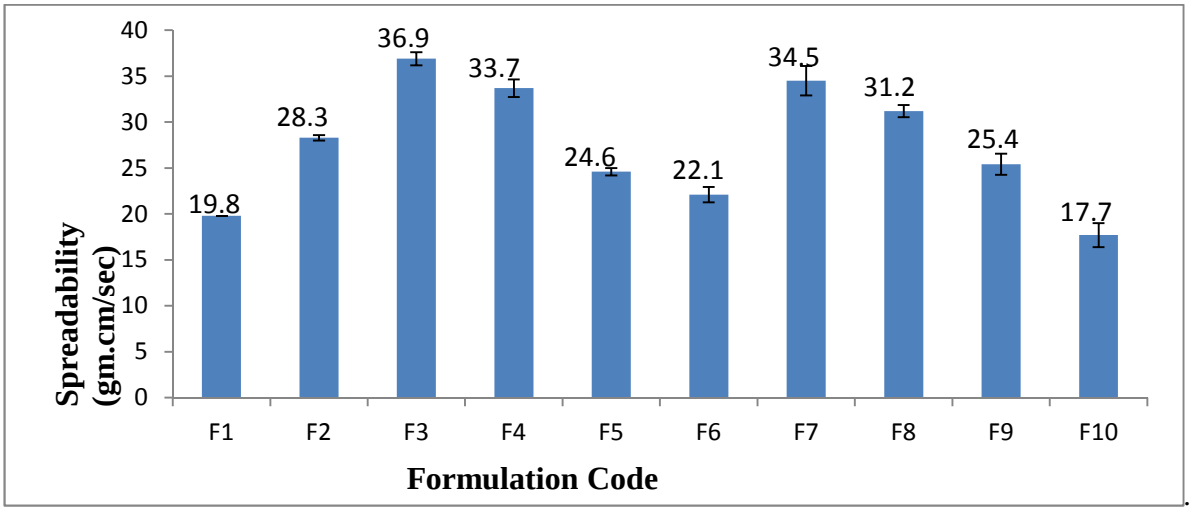

Fig. 5: Spreading Coefficient of Different Formulation F1-F10 (Mean±S.D.)

Extrudability:

The gels were filled into collapsible tubes after formulating them. The extrudability of the formulation has been checked and the results were tabulated Table 3

Table 3: Extrudability

S.no.	Formulation Code	Extrudability
1	F1	++
2	F2	+++
3	F3	+++
4	F4	+++
5	F5	++
6	F6	+
7	F7	++
8	F8	+++
9	F9	+++
10	F10	+++

Excellent +++, Good++, Satisfactory+

Drug content:

Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Formulated emulgel was estimated by spectrophotometrically at 237.4 nm. The data is shown below in Fig.6

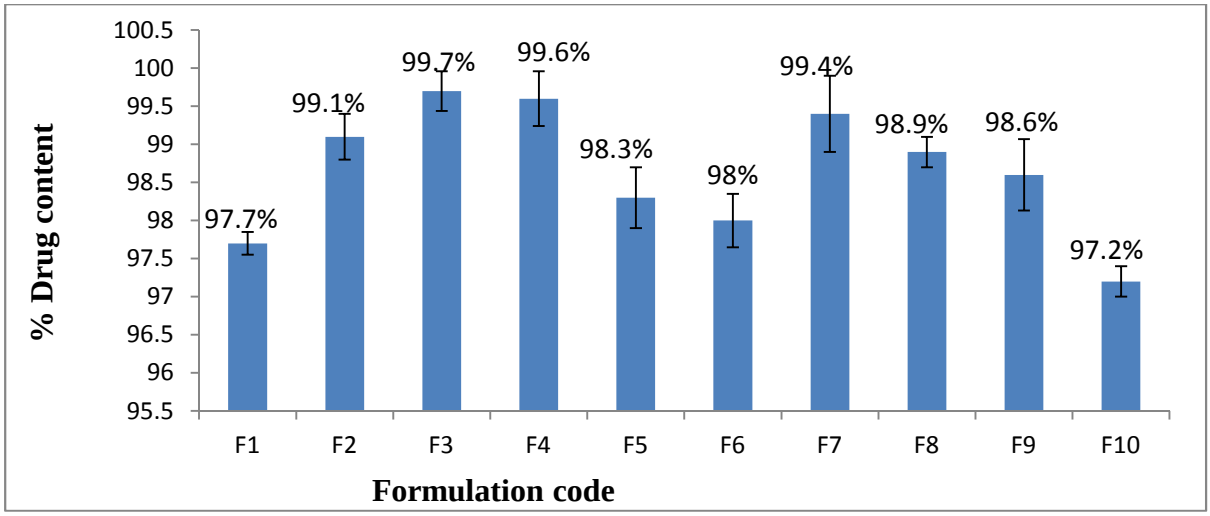

Fig. 6: Drug content of Different Formulation F1-F10 (Mean±S.D.)

***In-vitro* drug release study:**

The release of Fluticasone Propionate from the emulgel was varied according to concentration of polymer. The release of the drugs from its emulsified gel formulation can be ranked in the following descending order: F3 > F7 > F4> F8 > F2 >F9 > F5 > F6>F1>F10. The progressive increase in the amount of drug diffusion through membrane from formulation attributed to gradual decrease in the concentration of polymer. It has been over and done with that, if we raise the concentration of polymer, the diffusion of drug through the membrane also decreases. The drug content of the formulated emulgel was estimated by spectrophotometrically at 237.4 nm. The results were within the official limits and the cumulative % drug release profile of all the formulation batches has been shown in Table 4 and Fig. 7

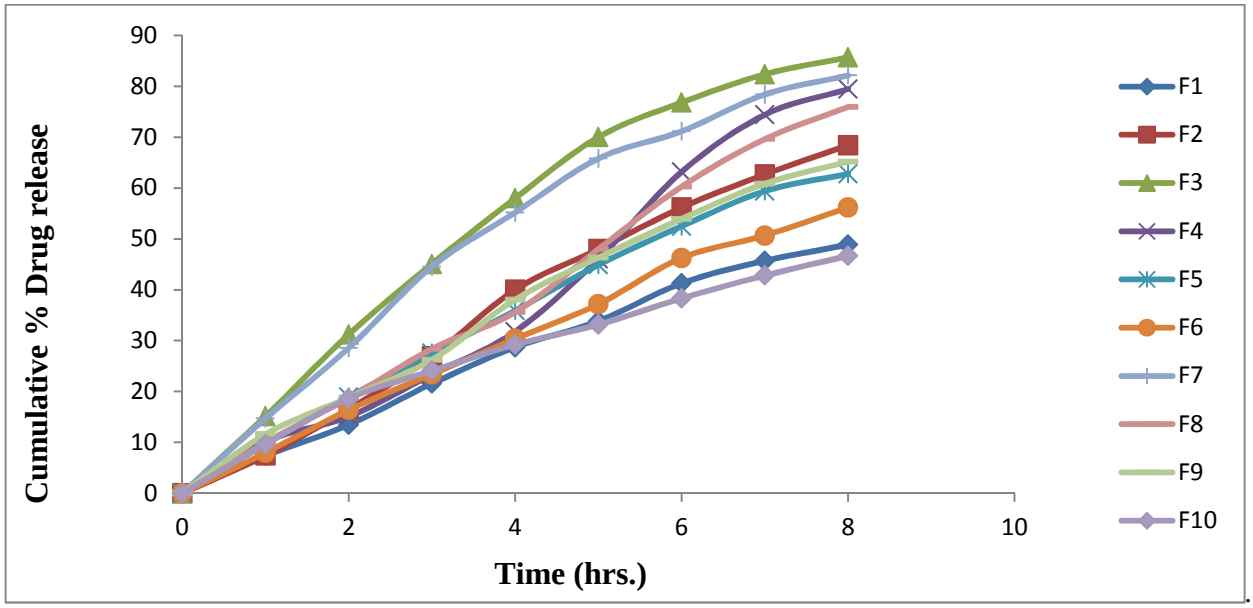

Fig. 7: *In Vitro* Cumulative % Drug Release Different Formulation F1-F10

Release kinetics of optimized formulation (F3)

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (cumulative % drug release v/s. time), First order (log cumulative % drug retained v/s. time), Higuchi model (cumulative % drug retained v/s. Square root of time) and Peppas model (log cumulative % drug release v/s. log time). The data is shown below in Table 5

Table 4: *In Vitro* Cumulative % Drug Release Data of Formulation F1-F10

Formulation	%CDR (8hr)*	Drug content*
F1	48.86±0.70	97.7±0.15
F2	68.41±1.07	99.1±0.3
F3	85.70±0.66	99.7±0.26
F4	79.45±1.65	99.6±0.36
F5	62.77±0.80	98.3±0.4
F6	56.16±1.74	98.0±0.35
F7	82.13±0.86	99.4±0.5
F8	75.93±0.96	98.9±0.20
F9	65.18±1.49	98.6±0.47
F10	46.65±0.55	97.2±0.2

** All the values are expressed as ±S.D.*

Table 5: Data of release kinetics

Formulation Code	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) M/L.S	R^2	K_H	R^2	n
F3	0.960	11.01	0.184	10.00	0.963	30.30	0.699	0.67

The data were treated according to zero order, first order, higuchi model and korsmeyer peppas pattern for kinetics of drug release during dissolution process. The regression equation of optimized formulation F3 were find out according to zero order equation 0.960, first order equation 0.184 and higuchi model 0.963, respectively. These values clearly indicate that the formulation showed to be best expressed by Higuchi model for release kinetics. This model is based on the hypotheses that

(i) Initial drug concentration in the matrix is much higher than drug solubility.
(ii) Drug diffusion takes place only in one dimension.
(iii) Drug particles are much smaller than system thickness.
(iv) Matrix swelling and dissolution are negligible.
(v) Drug diffusivity is constant
(vi) Perfect sink conditions are always attained in the release environment.

The dissolution data was also plotted to the well known exponential equation (Korsmeyer-peppas eq.), which is often used to describe the drug release behaviour from polymeric system. According to this model, a value of $n<0.45$ indicates fickian release, $n>0.45$ but $n<0.89$ for non-fickian (anomalous) release and $n>0.89$ indicate super case II type of release. Case II generally referred to the erosion of the polymeric chain and anomalous transport (non-fickian) refers to a combination of both diffusion and erosion control drug release. The n-value describe in table 1.5. On the basis of n-value the optimized formulation (F3) exhibit non-fickian type drug release.

CONCLUSION

Fluticasone propionate emulgel were successfully formulated using the gelling agent like Carbopol 934 & HPMCK100M with emulsifiers like span-80 & tween-80 with penetration enhancers in ten different concentrations. This study demonstrates that the different concentration of gelling agent with emulsifiers and penetration enhancers led to prolonged and pronounced local action. the formulated ten batches shows white in appearance. Optimized batch F3 shows white in appearance. pH of all ten batches was found between 6.0- 6.8. pH of optimized batch F3 was found 6.6 which lies in normal pH of skin.

Viscosity is important parameter for characterizing the emulgels as it affect spreadability, extrudability and release of the drug, all the formulated batches should increase viscosity as the concentration of gelling agent increased. Optimized batch F3 show model viscosity. Extrusion of the emulgel from the tube is an important during application and for the patient compliance. Emulgels with high consistency may not extrude from the tube easily, where as low viscous gel may show quickly extrudabilty of emulgels. Optimized batch F3 show superior extrudability than other ten batches. Formulation with less concentration of gelling agent was found to be good and with high concentration of gelling agent it was satisfactory. Optimized batch F3 show ideal gelling agent concentration. All the prepared emulgel formulations showed uniformity of emulgel content.

All the prepared batches show uniformity in drug content. Optimized batch F3shows 85.12% drug content which indicate uniform drug dispersion in emulgel. *In vitro* release studies were carried out by using phosphate buffer pH

7.4 release of Fluticasone propionate from all prepared emulgel formulations was found to be satisfactory and extended over longer period of time.

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