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FORMULATION AND EVALUATION OF DIACEREIN EMULGEL FOR PSORIATIC ARTHRITIES

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Abstract: The aim of present work was to develop a emulgel for the topical delivery of the poorly water soluble drug diacerein (BCS Class II) which is useful the in the treatment of psoriatic arthrities. Different formula on emulgels were prepared and evaluated for their physical appearance, rheological behaviour and *in vitro* drug release. The influence of the concentration of gelling agent carbopol 940(0.75%,1%,1.25%), the concentration of both the emulsifying agent (2.5% and 1% w/w of mixture of span 20 and tween 20) and the oil phase (6%,7% and 8% w/w of liquid paraffin) were optimized by using 3^2 factorial design. Prepared emulgels was investigated for different parameters. All the prepared emulgels showed acceptable physical properties concerning colour, homogeneity, consistency, and pH value, spreadability, exdrudability. The results of *in vitro* drug release showed that carbopol 940 (1%) based emulgel gave better release. Also it was found that the emulsifying agent concentration had the most pronounced effect on the drug release from the emulgels, followed by the oil phase concentration, which has a retardation effect, and finally on the type of the gelling agent. It was suggested that the diacerein emulgel formulation prepared with carbopol 940 with 1% concentration, oil phase (8%w/w liquid paraffin) and optimum concentration of emulsifying agent(3.5%w/w), showed an optimum formula for highest drug release (91.55% after 4 hrs) and no skin irritation, which followed hixon crowell diffusion model with a diffusion controlled mechanism.

Keywords: Emulgel , carbopol , liquid paraffin , diacerein

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INTRODUCTION

Topical drug delivery (TDD), the delivery of drugs across the skin is gaining wide acceptance among patients. It is a viable administration route for potent, low molecular weight therapeutic agents susceptible to first pass metabolism. Advantages of TDD include non-invasiveness, prolonged drug levels in the blood stream, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug administration. In developing a transdermal delivery system, two criteria are considered: one is achieving adequate flux across the skin and the other is minimizing the lag time in skin permeation. One strategy of overcoming this constraint is the incorporation of various skin permeation enhancers into the vehicle. Another strategy is a choice of an appropriate vehicle that corresponds to the drug being used for the dermal route of administration.

When gel and emulsion are used in combined form the dosage forms are referred as emulgel. As the name suggest they are the combination of emulsion and gel. In recent years, there has been great interest 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 gels by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase.

EMULGEL [5-6]

Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles. Gel formulations provide faster drug release compared with ointments and creams. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation emulgels are prepared and with their use even a hydrophobic drug can enjoy the unique properties of gels. When gels and emulsions are used in combined form the dosage forms are referred as Emulgels. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Direct (oil-in-water) system is used to entrap lipophilic drugs where as hydrophilic drugs are encapsulated in the reverse (water-inoil) system.Emulsions possess a certain degree of elegance and are easily washed off whenever desired.

Advantages of Emulgel As Topical Drug Delivery:

- Bio-friendly
- Easily spreadable
- Easily removable

- Emollient
- Greaseless
- Longer shelf life
- Nonstaining
- Transparent & pleasing appearance
- Thixotropic
- Water-soluble

Psoriatic arthritis is estimated to occur in 27 to 30 % of the general psoriatic population and in most cases, psoriatic arthritis appears several years after psoriasis. Psoriasis may occur over any portion of the integument, such as the elbows, knees, scalp and nails. Diacerein (DCN) is a new anti-inflammatory analgesic and antipyretic drug developed specially for the treatment of osteoarthritis & psoratic arthrities. The present invention concerns the use of diacerein for the treatment of psoriasis and psoriatic arthritis. Another advantage of the diacerein is that it has been shown not to effect prostaglandin PGE2 production and therefore does not have gastrotoxic potential.

MATERIALS AND METHODS

Diacerein was obtained as a gift sample from Cadila Pharma(Ahmedabad).Carbopol 940,Carbopol 934,HPMC K4M,Span20,Tween20 was obtained as a gift sample from S. D. Fine Chemicals. All other chemicals used were of analytical grade.

EXPERIMENTAL METHODOLOGY

Drug Excipient Compatibility Study

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm-1 by KBr disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and polymers and physical mixture of drug with all polymers. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug and polymers.

Preparation of Diacerein Emulgel

The oil phase was prepared by dissolving certain amount of span 20 in liquid paraffin ,while the aqueous phase was prepared by dissolving the required amount of tween 20 in purified water .

Diacerein was dissolved in liquid paraffin ,while 0.03 gm of methyl paraben were dissolved in 5 gm of propylene glycol and both were mixed with aqueous phase . Both the oily and aqueous phases were separately heated to 70-80° C. Then, the oil phase was added to the aqueous phase with continuous stirring at 50 rpm until cooled to room temperature.The emulsion was poured into gel with gentle stirring until homogenous emulgel was obtain.

Evaluation of Diacerein Emulgel [11-15]

pH of gel

The pH of the carbopol gels were determined by a digital pH meter (Toshcon industry). 1g of gel was dissolved in 25 mL of distilled water and the electrode was then dipped in to gel formulation and constant reading was noted. The measurements of pH of each formulation were performed in triplicate.

Viscosity measurement

A Brookfield digital viscometer (Brookfield eng. Labs inc., U.S.A .Model RVT) with a suitable sample adaptor was used to measure the viscosities of the Carbopol gel in cps. All the measurements were conducted using spindle no.6 using about 100 ml sample volume at 50rpm.Direct multiplication of the dial readings with factors given in the Brookfield viscometer catalogue gave the viscosity in centipoises.

Appearance of formulation

The appearance of the formulations was determined by visual examination of the formulations under light.

Where + average, ++ good, +++ excellent

Spreadability

Spreadability was measured using the spreadability apparatus. The apparatus consists of two slides in which one slide is firmly fixed in a wooden frame while the other slide can easily slide over the surface of the fixed one. An excess of gel (2 gm) was placed between the two slides of the apparatus. A weight of 1Kg was allowed to rest on the slide for 5 minutes so that a uniform film of gel was formed and the air between the slides was expelled. The excess gel was removed carefully from the edges of the slides. The bottom slide was properly anchored and the top slide was subjected to a pull of 80 gms weight. The time (in seconds) required by the top slide to cover a distance of 5 cm be noted. A shorter interval indicates better Spreadability.

Spreadability was then calculated using the following formula:

$S = M \times L / T$

Where, S = is the spreadability, M = is the weight in the pan (tied to the upper slide), L = is the length moved by the glass slide and T = represents the time in seconds taken to separate the slide completely.

Extrudability

The gels were filled into collapsible tubes after formulating them. The extrudability of the formulation has been checked.

Where + average, ++ good, +++ excellent

% Drug content

Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Concentration and drug content was determined by using the same standard plot by putting the value of absorbance in the standard plot equation.

***In vitro* drug diffusion study**

Egg membrane (0.45µm, obtained by keeping egg into concentrated HCl) was used for this study. A sample of 1g of the preparation was spreaded on a egg membrane. The gel loaded membrane was firmly stretched over the edge of a glass tube of 2 cm diameter (oped at both end); the membrane was tied up with a rubber/string to prevent leakage. Tube was then immersed in the dissolution vessel which contained 100 ml of the release medium, PBS pH 7.4, and maintained at 37ºC ± 0.5ºC. The solution was stirred at 50 rpm and aliquots each of 5 ml were withdrawn from the release medium at specified time intervals. The withdrawn samples were replaced by equal volumes of fresh release medium. The samples were assayed spectrophotometrically at λmax 256 nm and the concentration of the drug was determined from the previously constructed calibration curve. Each data point represented the average of three determinations. In vitro release studies were recorded for a 4 hour period.

***Ex vivo* bioadhesive strength**

The modified method is used for the measurement of bioadhesive strength.The fresh skin is cut into pieces and washed with 0.1N NaOH. Two pieces of skin were tied to the two glass slide separately from that one glass slide is fixed on the wooden piece and other piece is tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left-hand pan. 1 gm of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin and some pressure is applied to remove the presence of air. The balance is kept in this

position for 5 minutes. Weight is added slowly at 500 mg/ min to the left-hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The Bioadhesive strength is calculated by using following:

Bioadhesive Strength = Weight required (in gms) /Area (cm^2)

Skin Irritation Study[16]

The skin irritation study will be conducted using white rats (n= 8) as test and control animal approved from animal ethics committee and approval number is ASP&BRI/AH/2014/06. The emulgel (1 gm) applied to each site (two sites per rat) by introduction under a double gauze layer on one square inch of the shaven skin. After 24 h exposure, the formulation will be removed. The test sites will wiped with tap water to remove any residual gel. The development of erythema/edema will be monitored for 24 hrs by visual observation.

Stability study

The prepared emulgels was packed in aluminium collapsible tubes (5 g) and subjected to stability studies at studies were carried out at 40° C ± 2°C and 75% ± 5% relative humidity (RH).Samples was withdrawn at 1 month time intervals and evaluated for physical appearance, pH, drug content, spreadability, Bioadhesive strength and %CDR.

RESULT AND DICCUSSION:

Drug Excipient Compatibility Study:

Infrared spectroscopy was used as means of studying drug-excipients interactions. It was found that there was no chemical interaction between Diacerein and excipients used because there were no changes in the characteristic peaks of Diacerein in the IR spectra of mixture of drug and excipients as compared to IR spectra of pure drug.(Figure 1,2)

EVALUATION OF FACTORIAL DESIGN FORMULATIONS (F1 TO F9)

pH

The pH measurements were done by using a digital type of pH meter by dipping the glass electrode into the emulgel. The measured values are presented in table 2. pH value indicate the suitability of emulgel for topical application.

Viscosity

The viscosity of the different emulgel formulations was determined at 25°C using a Brookfield viscometer with spindle no 6 at 20 rpm by Brookfield viscometer.Viscosity of the Emulgel from F1 to F9 was shown in table 2.

Appearance

All the batches from F1 to F9 were shown white viscous creamy preparation with homogeneous and glossy appearance.

Spreadability

Spredability was measured from F1 to F9 and results were shown in table 2. From all of spreadability it is observed that by increasing concentration of carbopol spreadability is decreased.

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 2.

Drug content

Drug content of emulgel was shown in table2. Amount of drug in the Emulgel indicates the suitability of the system for high entrapment in the internal phase.

Stability study

The promising formulation F5 was subjected at 40 ± 0.5 °C temperature and 75 ± 5 % RH for 1 month to check the stability. The results of physical appearance, drug content, folding endurance and other parameters after 1 month storage of prepared Emulgel are shown in (table 6 and 7)

CONCLUSION:

In the present investigation, factorial formulations F1-F9 were prepared using 0.75%, 1% and 1.25% of Carbopol 940 and 6%, 7% and 8% of liquid paraffin. Span20 and tween 20 was incorporated as emulsifying agent at concentration of 3.5%. The formulation F5 was selected as the promising formulation on the basis of spreadability, Extrudability,,Drug content% cumulative drug release. The cumulative % drug diffusion of F5 was found to be 91.55 ±1.47. From the results stability study it can be concluded that the Emulgel can be stored at 40 °C and 75% RH without any significant stability problems. The formulation satisfied all the

pharmaceutical parameters of Emulgel and appears to be promising, would be able to offer benefits such as sustained drug release, improving bioavailability, and thereby may help to improve patient compliance.

Table 1. Formulation of Emulgel of Diacerein

Ingredients	Formulation Code(%w/w)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diacerein	8	8	8	8	8	8	8	8	8
Carbopol 940	0.75	1	1.25	0.75	1	1.25	0.75	1	1.25
Liquid Paraffin	6	6	6	7	7	7	8	8	8
Span 20	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tween 20	1	1	1	1	1	1	1	1	1
Propylene glycol	5	5	5	5	5	5	5	5	5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Water(ml)	100	100	100	100	100	100	100	100	100

Table 2. Evaluation parameter of Emulgel of Diacerein

Batch code	Evaluation parameter				
	pH	Viscosity (cps)	Appearance	Spreadability (g.cm/sec)	Extrudability
F1	7.28±0.19	10520±0.03	++	30.56±1.92	++
F2	6.60±1.10	11200±0.07	+++	33.43±3.42	+++
F3	6.74±0.25	13400±0.02	+++	28.14±2.46	+++
F4	7.80±0.22	9900±0.09	++	29.56±1.80	+++
F5	7.40±1.07	12400±0.08	+++	34.22±1.45	+++
F6	7.65±1.20	9700±0.02	++	29.32±2.80	++
F7	6.94±1.08	11000±0.06	+++	28.69±3.94	++
F8	6.74±1.10	11200±0.03	++	31.47±2.20	++
F9	7.90±0.26	10450±0.07	+++	27.15±3.02	+++

Table 3. Evaluation parameter of Emulgel of Diacerein

Formulation batch Code	% Drug content	Bioadhesive strength(g/cm^2)
F1	93.45±0.42	3.04
F2	95.01±0.35	3.22
F3	92.25±0.28	3.35
F4	96.75±0.19	4.11
F5	97.65±0.36	4.75
F6	94.50±0.45	4.125
F7	97.95±0.62	4.00
F8	96.15±0.75	4.23
F9	92.65±0.94	4.25

*Values are mean±SD (n= 3)

Table 4. *In vitro* drug release data of factorial formulations F1 to F4

Time(min)	F1	F2	F3	F4
0	0	0	0	0
15	21.25 ±1.28	16.13±1.27	18.11±1.42	17.18±1.69
30	40.21±0.55	36.29±0.86	38.26±0.18	35.28±0.36
60	48.23±1.69	41.24±0.58	43.60±1.37	44.28±0.53
120	66.88±0.36	56.61±1.81	59.23±1.81	64.7±1.08
180	78.24±0.89	69.23±0.53	71.25±1.38	72.28±1.28
240	85.19±0.68	88.75±1.80	89.88±0.88	83.22±0.88

Table 5. *In vitro* drug release data of factorial formulations F5 to F9

F5	F6	F7	F8	F9
0	0	0	0	0
23.55±1.12	16.10±1.07	20.21±0.71	22.45±0.18	17.22±0.61
45.11±1.16	30.25±0.73	38.65±1.58	41.45±1.45	31.89±1.56
57.63±1.74	37.85±0.17	46.25±0.55	50.69±0.55	39.56±0.79
68.45±1.08	51.69±0.72	64.51±1.98	67.56±0.29	55.81±0.18
81.40±0.23	61.59±0.18	74.23±1.38	75.23±0.40	67.21±0.71
91.55±1.69	88.11±0.22	79.55±1.25	80.48±1.22	77.11±0.30

Table 6. Stability study of promising batch F5

Parameters	Before 30 days	After 30 days
pH	7.40±1.07	7.28±0.62
Viscosity(cps)	12400±0.08	11800±0.52
Spredability(g.cm/sec)	34.22±1.45	32.86±1.12
Bioadhesive strength(g/cm^2)	4.75	4.56
%Drug content	97.65±0.62	96.72±0.92

* Values are mean ± SD, (n=3)

Table 7. %Cumulative drug release study of F5 at 0 day and after 30 days

	Cumulative % drug release	
Time	**BEFORE 30 DAYS**	**AFTER 30 DAYS**
0	0	0
15	23.55±1.12	21.32±1.02
30	45.11±1.16	43.62±0.62
60	57.63±1.74	55.72±0.34
120	68.45±1.08	65.02±0.23
180	81.40±0.23	79.34±1.02
240	91.44±1.69	90.23±1.42

Table 8. Skin irritation studty

Group	Erythma		Edema	
	12 hr	**24 hr**	**12 hr**	**24 hr**
Control (n=4)	0	0	0	0
Test (n=4)	0	0	0	0

0 indicate no irritation.

Figure: 1 FTIR spectra of Test sample

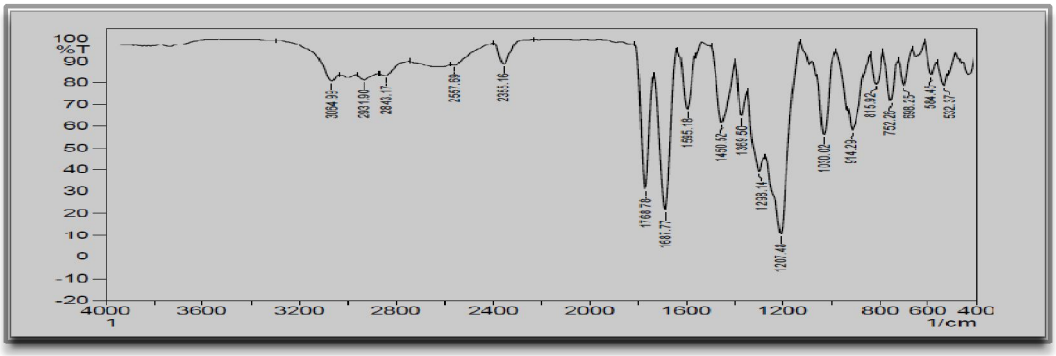


Figure: 2 FTIR spectra of Drug+Excipient

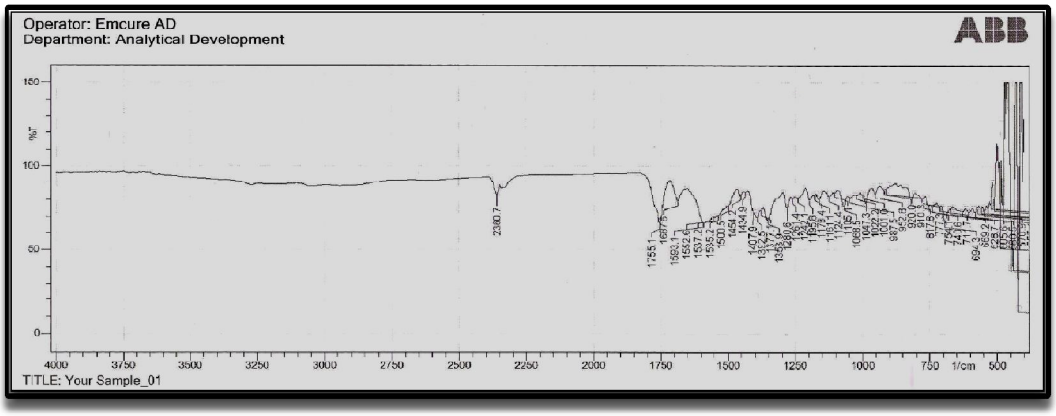


Figure: 3 *In vitro* Drug release of F1 to F9 batches

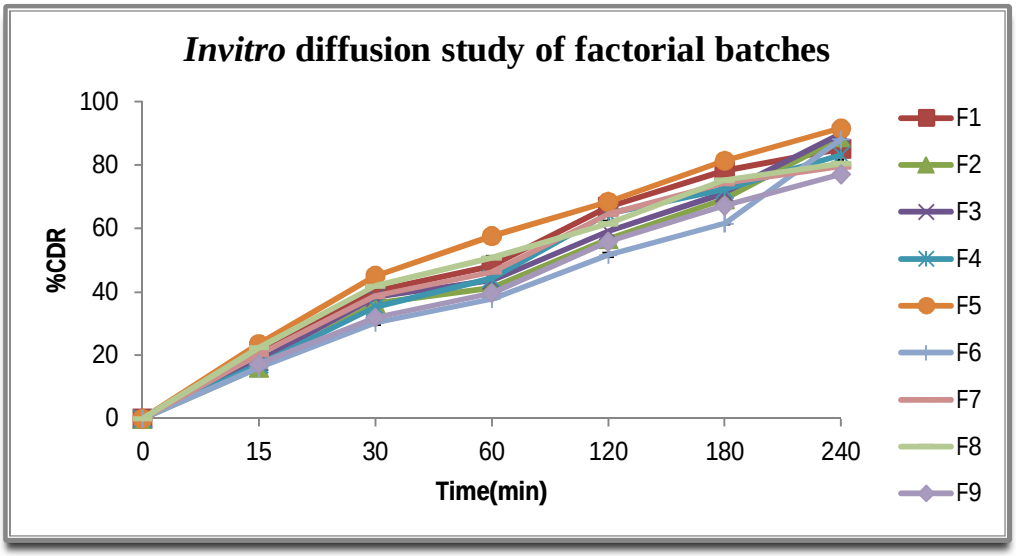
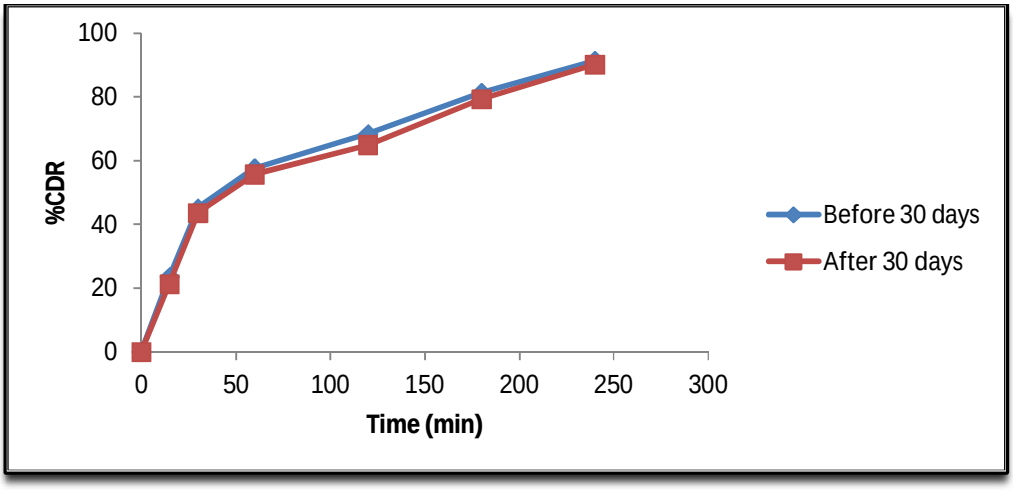


Figure: 4 *In vitro* Drug release of F1 to F9 batches after 30 days.



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