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FORMULATION DEVELOPMENT AND EVALUATION OF TOPICAL CURCUMIN EMULGEL

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ABSTRACT
The objective of the present study is to develop formulation for topical curcumin emulgel with targeted drug delivery for the treatment of inflammation of skin. All the excipients were cheked for their compatability with the drug by FTIR. The emulgel was prepared by making the emulsion and then gellifying this by mixing with the gel. The polymers carbpol 940, HPMC and sodium alginate were used as gelling agents here. The prepared emulgels were evaluated for physical examination, pH, consistency, drug entrapment, *ex vivo* diffusion, skin deposition, skin irritation. All the formulations showed acceptable physical properties, pH, consistency, drug entrapment, drug diffusion, drug deposition and no irritation on skin. Skin deposition values are much higher than the *Ex vivo* diffusion values which is a desired effect as anti-inflammatory action of curcumin requires drug deposition within the skin layers. Here, the effects of type of gelling agent, concentration of both the oil phase and emulsifying agent were investigated. All the formulations were free from skin irritation. From this work, it can be concluded that the emulgel formulation can be an innovative and promising approach for the topical drug delivery of curcumin for the treatment of skin disorders like inflammation.

KEYWORDS: Curcumin, Emulsion, gel, emulgel, consistency, diffusion, skin deposition, skin irritation.

1. INTRODUCTION
Gels are semisolid systems in which the movement of the dispersion medium is restricted by interlacing three dimensional network of particles or solvated macromolecules of dispersed phase. The increased viscosity caused by interlacing and consequently internal friction is responsible for the semisolid state. Also a gel may consist of twisted matted strands often tied together by stronger types of Vander Waals Forces to form crystalline and amorphous regions throughout the system.[1] Gel delivery systems have several advantages such as the ease of administration, non greasy, patient compliance, high residence time on the skin and better drug release. Curcumin a constituent of Curcuma longa chemically known as diferuloulmethane has been reported to possess antioxidant, anti-inflammatory ant carcinogenic and hypocholesterolemic properties. Curcumin has also been shown to counter inflammatory responses similarly to the action of steroids, but without side effects.[2] Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Percutaneous absorption of drugs from topical formulations involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed. In order to enhance drug release and skin permeation, methods such as the selection of a suitable vehicle, co-administration of a chemical enhancer have been studied.[3]

2. MATERIALS & METHODS
2.1 Materials
Curcumin obtained as gift sample from Nisarg Biosciences, hyderabad. Carbopol 934, HPMC k4M, Sodium alginate were purchased from S.D Fine Chem, pvt Ltd Mumbai. All other ingredients used throughout the study were of analytical grade and were used as received.

2.2 Methodology[5,6,7,8]
Emulgels are prepared by preparing the emulsion and its gellification by mixing with the gel solution. Preparation

of emulsion and gel solution. Mixing of both in 1:1 ratio with constant stirring. Oil phase was prepared by dissolving span 20 in liquid paraffin Aqueous phase was prepared Tween 20 was dissolved in distilled water. Drug was dissolved in ethanol. Propyl and methyl parabens were dissolved in propylene glycol. Later two solutions were added to the former solution and mixed well. Both the oil and aqueous phases are separately heated to 60-70^0 C and then oil phase is added to the aqueous phase with continuous stirring. Stirring is continued until it reached the room temperature. Gel was prepared by simply dispersing the corresponding gelling agent in distilled water. Finally, the emulsion and the gel were mixed in 1:1 ratio with gentle stirring and the emulgel was obtained. The gel for formulaions F1, F2, F3, F4, was prepared by dispersing carbopol 940 in with constant stirring at moderate speed and after the addition of emulsion, 1-2 drops of TEM (triethanolamine) was added and mixed thoroughly to get the final emulgel. The gel for the formulations F5, F6, F7, F8, was prepared by disoarsing HPMC K4M in purified water and for F9, F10, F11, F12, was prepared by dispersing Na. alginate in purified water.

Table 1: Composition of formulations of topical curcumin emulgel with gelling agent carbopol 940.

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Curcumin	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbopol 940	1	1	1	1	2.5	2.5	2.5	2.5	3	3	3	3
Liquid paraffin	5	7.5	5	7.5	5	7.5	5	7.5	5	7.5	5	7.5
Tween 20	0.6	0.6	1	1	0.6	0.6	1	1	0.6	0.6	1	1
Span 20	1	1	1.5	1.5	1	1	1.5	1.5	1	1	1.5	1.5
Propylene glycol	5	5	5	5	5	5	5	5	5	5	5	5
Ethyl alcohol	10	10	10	10	10	10	10	10	10	10	10	10
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0/01	0.01	0.01	0.01	0/01	0.01	0.01	0.01	0/01	0.01	0.01
Water (upto)	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation of the Prepared Topical Curcumin Emulgel[9-15]

Physical appearance: The prepared curcumin emulgel formulations were inspected visually for their color, homogeneity, texture.

pH determination: 1% aqueous solutions of the emulgels were prepared and the pH was checked with a digital pH meter.

Consistency

This is done by using the consistency tester. One of the criteria for an emulgel to meet the ideal quantities is that it should possess good spreadability which depends upon the consistency. It is term expressed to denote the extent of area to which gel readily spread on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by the slide to move from A to B from 1gm of emulgel placed beneath the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula.

$$S = M. L / T$$

Where M = weght tied to upper slide
L = Distance between A and B
T = time taken to separate the slides

Drug Content Determination

Drug concentration in emulgel was measured by UV spectrophotometer. Curcumin content in emulgel was measured by dissolving 5ml quantity of emulgel in 100ml acetae buffer. Absorbance was measured after suitable dilution at 426 nm in UV/VIS spectrophotometer.

***Ex vivo* diffusion study[16-19]**

Superficial skin was taken from the back of pig ear and using a depilatory preparation, hair was removed. Then fat layer was removed from the skin.

Then the cleared area was washed with pH 5.5 acetate buffer. Then 2 gms of emulgel was applied on the pig skin and was tied on the donor compartment. Here, the donor compartment contains emulgel on stratum corneum side of skin and dermis side was facing receptor compartment. Receptor compartment contains 100ml of pH 5.5 acetate buffer. After diffusion starts, at specific time intervals, 1ml of sample was taken and replaced the same with receptor fluid. After 7 hours sampling absorbance taken at 426nm against blank of pH 5.5 acetate buffer by UV spectrophotometer. After diffusion starts, at specific time intervals, 1ml of sample was taken and replaced the same with receptor fluid. After 7 hours sampling absorbance taken at 426nm against blank of pH 5.5 acetate buffer by UV spectrophotometer.

Model fitting for drug release[20]

Drug release kinetics can be analyzed by various mathematical models, which are applied considering the amounts of drug released from 0 to 24 hour.

Zero order kinetic[21]

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium

conditions. are obtained) can be represented by the following equation

$$Q1 = Q0 + K0t$$

Where Q is the amount of drug dissolved in time t, Q is the initial amount of drug in the solution (most times, Q 50) and K is the zero order release constant.

First order kinetics[22]

This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in a theoretical basis. The following relation can also express this model:

$$\ln Qt = \ln Q0 - k1t$$

Where Qt is the amount of drug released in time t, Q0 is the initial amount of drug in the solution and K is the first order release constant.

Higuchi model[23]

Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. In a general way it is possible to resume the Higuchi model to the following expression

$$Qt = KH\ t1/2$$

Where Qt is amount of drug released in time t and KH is release rate constants. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent.

Korsmeyer–Peppas model[24,25]

An equation that can be described in the following manner

$$Mt / M\infty = atn$$

where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is M /M (fractional release of drug).

Skin deposition study[26]

At the end of the permeation experiments (after 7hr), the skin surface was washed five times with ethanol: Buffer pH 5.5 (1:1), then with water to remove excess drug from surface. The skin was then cut into small pieces. The tissue was further homogenized with ethanol: buffer solution pH 5.5 (1:1) and left for 6hr at room temperature. After shaking for 5 minutes and centrifuging for 5 minutes at 5000rpm, the curcumin content was analyzed by UVvisible spectrophotometric method after appropriate dilutions with Acetate buffer solution (pH5.54) at 426nm.

Skin irritation test[27]

A 0.5 gm sample of the prepared emulgel wsa applied to each site (two sites per rabbit) to an area of ear skin approximately 1 x 1cm2 and the rabbits were kept in their cages. They were checked for erythema and edema at specific time intervals.

3. RESULTS AND DISCUSSION

Physical Examination

The prepared Curcumin emulgel formulations were yellow viscous creamy preparations with a smooth and homogeneous appearance.

pH testing

The pH values of all the prepared formulations ranged from 5.5 to 6.5.

Table 2: pH data for prepared emulgels.

Formulation	pH
F_1	6.5
F_2	6.1
F_3	6.3
F_4	6.1
F_5	6.5
F_6	6.4
F_7	6.4
F_8	6.1
F_9	5.4
F_{10}	5.6
F_{11}	5.8
F_{12}	5.5

Consistency

Consistency values for the 12 formulations were represented as follows.

Table 3: Data of consistency of the prepared Emulgels.

Formulation code	Time taken for the movement from A to B (sec)
F1	5
F2	5
F3	3
F4	4
F5	4
F6	4
F7	2
F8	3
F9	2
F10	2
F11	2
F12	2

The Consistency and spreadability are interrelated. Lesser the consistency, better the spreadability. Here, the consistency was studied in terms of the time required for the movement of the slide from A to B. For all the formulations, the time was considerably less indicating optimum consistency. So the prepared emulgels were found to have good spreadability indicating better therapeutic efficienty.

Drug Content Determination

The drug content values for all the formulations are represented as following in term of percentages.

Table 4: Entrapment efficiency data for the prepared emulgels.

Formulation	Entrapment efficiency
F1	85%
F2	82%
F3	90%
F4	87%
F5	83%
F6	82%
F7	81%
F8	82%
F9	75%
F10	76%
F11	80%
F12	76%

***Ex Vivo* diffusion studies**

The release profiles of Curcumin through the pig skin from its various emulgel formulations are represented as following.

Table 5: Comparative drug release profiles of emulgels F1, F2, F3,F4.

Time(min)	F_1	F_2	F_3	F_4	F5	F6
0	0	0	0	0	0	0
5	0.46	0.48	0.75	0.37	0.516	0.35
10	0.92	0.95	1.53	0.72	1.1	0.716
15	1.36	1.44	2.31	0.996	1.67	1.2
20	4.6	3.4	8.1	4.8	5.566	3.53
30	4.8	3.83	8.13	5.6	6.2	4.5
45	5.53	5.2	9.533	6.76	7.43	5.6
60	7.566	4.7	11.5	8.433	9.26	5.5
90	9.16	6.43	14.4	10.86	12.46	7.133
120	12.63	8.5	17.2	13.63	14.5	9.73
180	15.26	10.8	20.7	16.43	17.6	11.76667
240	15.16	12.56	21.06	15.9	17.33	13.2
300	21.23	16.33	23.43	21.86	22.6	17.3
360	21.73	18.26	24.76	23.5	24.56	19.1
420	22.8	19.43	25.6	24.2	25.06	20.06

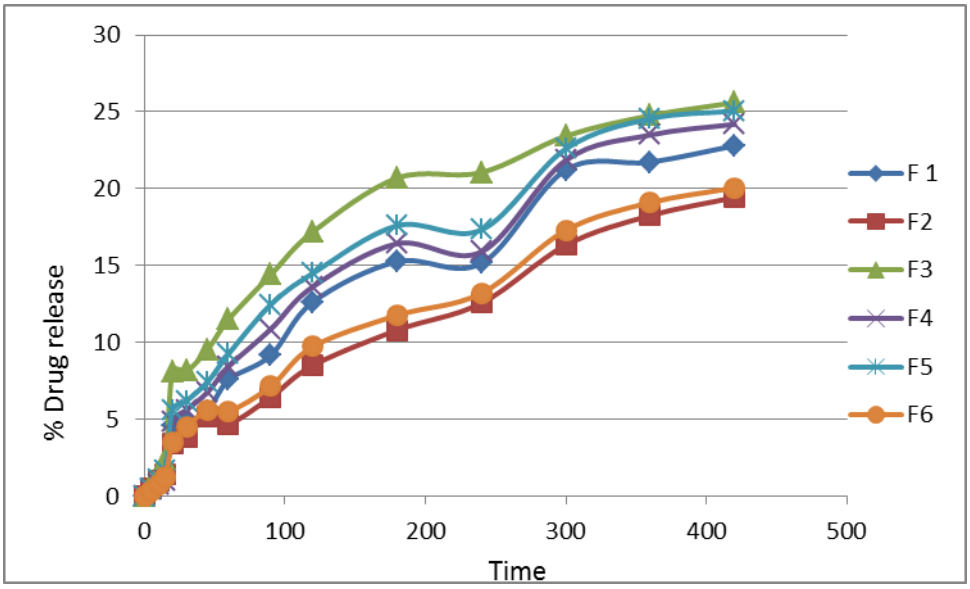

Figure 1: Comparative drug release profiles of emulgels F1, F2, F3,F4, F5, F6.

Table 6: Comparative drug release profiles of emulgels F7,F8, F11,F12.

Time(min)	F7	F8	F_9	F_{10}	F_{11}	F_{12}
0	0	0	0	0	0	0
5	0.84	0.63	0.35	0.336	0.746	0.66
10	1.613	1.24	0.74	0.63	1.46	1.353
15	2.26	1.8	1.2	1.3	2.033	1.96
20	8.2	6.1	3.5	3.1	7.3	4.03
30	8.93	7.6	4.6	3.36	7.53	4.56
45	10.33	8.1	5.53	5.033	8.96	5.6
60	11.3	9.7	6.4	4.133	10.46	7.1
90	15.7	13.3	7.53	5.333	13.63	9.7
120	18.2	15.5	10.866	7.133	15.7	11.7
180	22.5	18.53	12.4	9.166	18.9	13.63
240	24.1	18.33	13.4	11.133	20.92	14.53
300	25.5	23.56	18.23	14.13	21.8	19.2
360	26.3	25.566	20.267	16.067	22.1	21.3
420	28.1	26.1	20.8	18.16	22.62	21.53

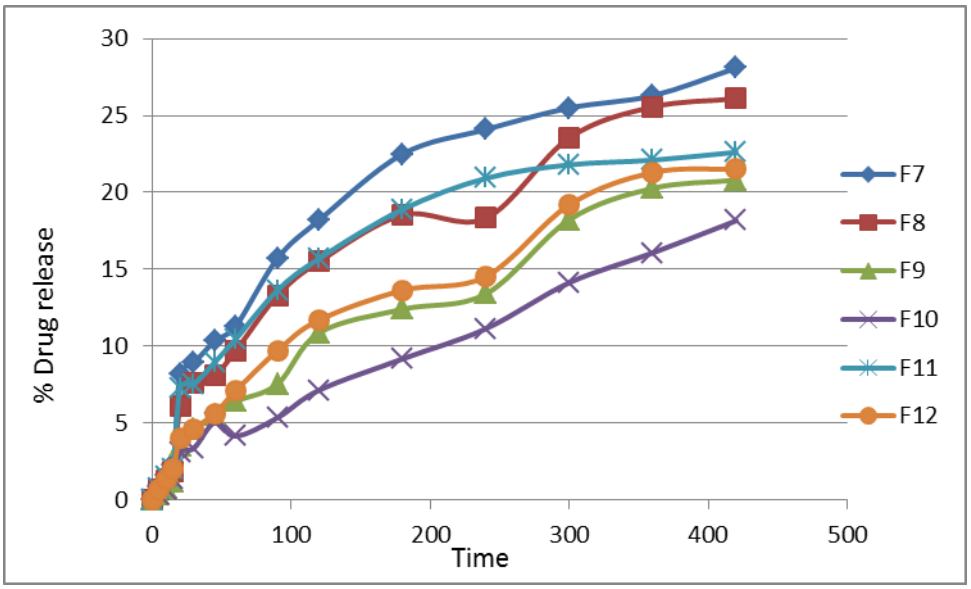

Figure 2: Comparative drug release profiles of emulgels F7,F8, F11,F12.

Model Fitting Data For Drug Release

This is the kinetic model fitting data for the all emulgel formulations.

Table 7: Kinetic model fitting data for all formulations.

Formulation code	Zero order	First order	Higuchi	Peppas	n
F1	0.93274	0.63266	0.80319	0.87244	0.68729
F2	0.97265	0.69948	0.85115	0.88552	0.63134
F3	0.84276	0.53963	0.73914	0.88851	0.66012
F4	0.91978	0.58552	0.75622	0.83417	0.72947
F5	0.9087	0.59046	0.77377	0.87753	0.69177
F6	0.95806	0.63911	0.79635	0.84741	0.67703
F7	0.84813	0.54889	0.74967	0.89694	0.67189
F8	0.89914	0.58242	0.77029	0.88627	0.68125
F9	0.95093	0.63398	0.79493	0.85079	0.68797
F10	0.97686	0.67641	0.81641	0.84023	0.6406
F11	0.82259	0.53991	0.74022	0.88577	0.64841
F12	0.94192	0.66967	0.84622	0.9221	0.63252

The release of the drug from its emulgel formulations can be ranked in the following descending order: F7 > F3> F11 > F8 > F5 > F4> F1>F12 > F9 > F6 > F2 > F10 where the amounts of the drug released after 7 hours

were 27.1%, 25.22%, 22.548%, 26.1%, 25.06%, 24.2%, 22.8%, 21.53%, 20.82%, 20.06%, 19.43%, 18.16% respectively. Thus, the greatest drug release was observed with formulations F7, F3 and F11. This finding may be due to the presence of liquid paraffin in its low level and the emulsifying agent in its high level in both such formulations. The lower drug release from formula F3, which is Carbopol-based, than the drug release from formula F7, which is HPMC-based, may be due to the higher viscosity of Carbopol emulgel formulations. It may also be due to the entrapment of the drug in the network structure of Carbopol 940. The lower drug release from F11 may be due to the improper entrapment of the drug in the structure of net work of the gelling agent sodium alginate. Contrary to the formulations F7, F3 and F11 among all the formulations, the formulations, F6, F2 and F10 have shown the lowest drug release. In these formulations F6, F2 and F10, liquid paraffin is present in its high level, while the emulsifying agent is in its low level. Formula F8, containing both liquid paraffin and the emulsifying agent in their high levels, has exhibited greater drug release than formula F5, containing both liquid paraffin and the emulsifying agent in their low levels. This finding indicated that the enhancing effect of the emulsifying agent on the drug release was more pronounced than the lowering effect of liquid paraffin on the drug release. The same observation was found in F4 and F1 formulations and also in F12 and F9. Although F3 is Carbopol based, it showed a greater drug release than F8, which is HPMC based. This finding is due to the lower liquid paraffin content in formula F3 than in formula F8. The same is true for F1 and F6. This finding proved that the effect of liquid paraffin in decreasing the drug release from the emulgel was more predominant than the enhancing effect of HPMC on the drug release. Thus the 3 studied factors can be arranged according to their effect on the drug release from the emulgel formulations as follows: the emulsifying agent concentration > liquid paraffin concentration > the gelling agent type.

Zero order is the best fit model for the diffusion of all the formulations because it is having the maximum r^2 value.

Drug deposition study

Table 8: Drug deposition data of Emulgels.

Formulation Code	% Drug deposited
1	55.6
2	48.86
3	66.66
4	58.4
5	60.12
6	50.12
7	71.5
8	62.2
9	51.6
10	46.32
11	63.8
12	53.06

The deposition values are higher values with maximum of 71% whereas diffused drug values are very less indicating that most of the drug is deposited within the layers of the skin. This may be because of the lipophilic nature of the stratum corneum which facilitates the permeation of the drug which is lipophilic in nature into the layers of the skin and hydrophilic nature of the dermis layer which resists the movement of the drug curcumin crossing the skin.

Skin irritation test

The Primary Irritation Index of the test article was calculated and found to be zero.

Table 9: Skin irritation test of Curcumin Emulgel on rabbit skin.

Rabbit group code	Erythema		Edema	
	1hr	6hr	1hr	6hr
A	0	0	0	0
B	0	0	0	0
C	0	0	0	0

Scores: 0-nill, 1-very low, 2-low, 3-average, 4-severe.

The rabbits were checked for redess, swelling, irritation at specific time intervels on the skin of rabbit after the test. There was no edema and erythema observed on the skin of the rabbits indicating all the excipients are compatable with the skin and do not cause any irritation.

CONCLUSION

The topical curcumin emulgels were prepared and evaluated. All the formulations showed acceptable physical properties, pH, consistency, drug diffusion, deposition and no irritation on skin. *Ex vivo* diffusion values are less whereas skin deposition values are high. The high skin deposition facilitates the anti inflammatory activity of the drug curcumin. In drug release studies, emulgels were compared with resect to concentrations of oil phase, emulsifier and type of gelling agent. The HPMC-based emulgel with the liquid paraffin in its low level and the emulsifying agent in its high level proved to be the formula of choice, since it showed the highest drug release and drug deposition. It undergoes extensive first pass metabolism and hence is a suitable candidate for topical gel formulation[3]. Among polymers used for formulation of gel base is combination of CRB and HPMC, combination of CRB and Sodium Alginate, alone CRB to describe physical properties, rheological behavior and to determine the amount of drug diffused better. These polymers have several attributes as a gelling agent like high viscosity at low concentration and give pleasant texture, do not support bacterial or fungal growth and are non irritating. A ideal penetration enhancer should have no pharmacological activity in body, should work rapidly, nontoxic, nonirritating, no allergic, should be suitable for formulation into topical formulation and should be compatible with drug and excipient.[4]

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