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Formulation and evaluation of curcumin emulgel for topical delivery

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Abstract
Topical drug delivery system is the application of the formulation onto the skin directly treat skin diseases. The gel formulation has a disadvantage to delivery hydrophobic drugs. This can be overcome by formulating novel drug delivery known as Emulgel. Emulgel combines two formulation gel and emulsion. The Emulgel is used to treat skin infections like fungal infections, acne, and psoriasis. The emulgel was formulated and characterised for FTIR studies, pH analysis, spredability, swelling index, drug content, globules size, *in-vitro* drug release, comparative *in-vitro* drug release studies, SEM studies and *in-vitro* drug release kinetics using zero order, first order, highchair model and korsmeyer papas model. FTIR studies provided no evidence of chemical interaction between curcumene and excipients used. The pH of the formulations was within an appropriate range for skin. The swelling index and spredability were optimum for the better patient compliance.

Keywords: emulgel, hydrophobic, emulsion, gel, topical

Introduction
Topical drug delivery system can be defined as system in which API containing formulation is directly applied to skin to treat local cutaneous manifestations [1,2]. When other routes of administration like parenteral, sublingual and rectal fails or mainly to treat local skin infections like Tine capitals, Tine padi (fungal infections).
One of the major advantages of topical drug delivery system is to avoid presystolic metabolism, patient inconvenience, and risk by intravenous therapy and different conditions of absorption like presence of enzymes, change in PH [3-5]. Topical medicinal products are diverse in their formulation which are directly applied to the skin and available in liquid to powder consistency, but semisolid preparation is most popular among those formulations. When compare to creams and ointments, gels provide faster drug release but major limitation is unable to deliver hydrophobic drugs. So, to overcome this limitation emulgel is formulated. The routes for topical drug administration can be through ophthalmic, rectal, vaginal and skin as topical routes. Emulex possesses the properties such as thixotropic, greaseless, easily spreadable, and bio-friendly and increases patient acceptability. [6]
Turmeric (Curcuma longa) is widely used popular Indian medicinal plant and belongs to the family of Zingiberaceae. Cur cumin is polyphenolics compound and lipophilic in nature. This active constituent of turmeric is isolated from curcuma longa and it provides colour to turmeric. Traditionally curcumene is being used for its various medicinal properties and exhibits anti-inflammatory, anti-oxidant, anti-bacterial and anticancer activities. The yellow colour of the turmeric is due to the curcumene compound known as diferuloylmethane
The oral administration (up to 8 g per day), it is poorly absorbed, and only the traces of compound appear in blood. It undergoes extensive first-pass metabolism, and hence is a suitable candidate for topical gel formulation. [6-10]
II. Materials and methods
Chemicals – Cur cumin was obtained from Yucca Enterprises, Mumbai. HPMC, span 80, tween 80, liquid paraffin, Potassium Dihydrogen Phthalate and Sodium Hydroxide were procured from SD Fine Chemicals Ltd.

Methods
Standard Calibration Curve of Cur cumin
The stock solution (1 mg/ml) was prepared by weighed accurately 10 mg of curcumin emulgel and transferred to a 50 ml volumetric flask then makeup the final volume with methanol.

Different concentrations (2, 4, 6, 8, and10µg/ml) of solutions were prepared from the stock and measure the absorbance at 254 nm by using UV-Visible spectrophotometer and blank reagent. Graphs were plotted taking concentration on X-axis and absorption on Y-axis to give linear curve and the method obeyed Beer's law

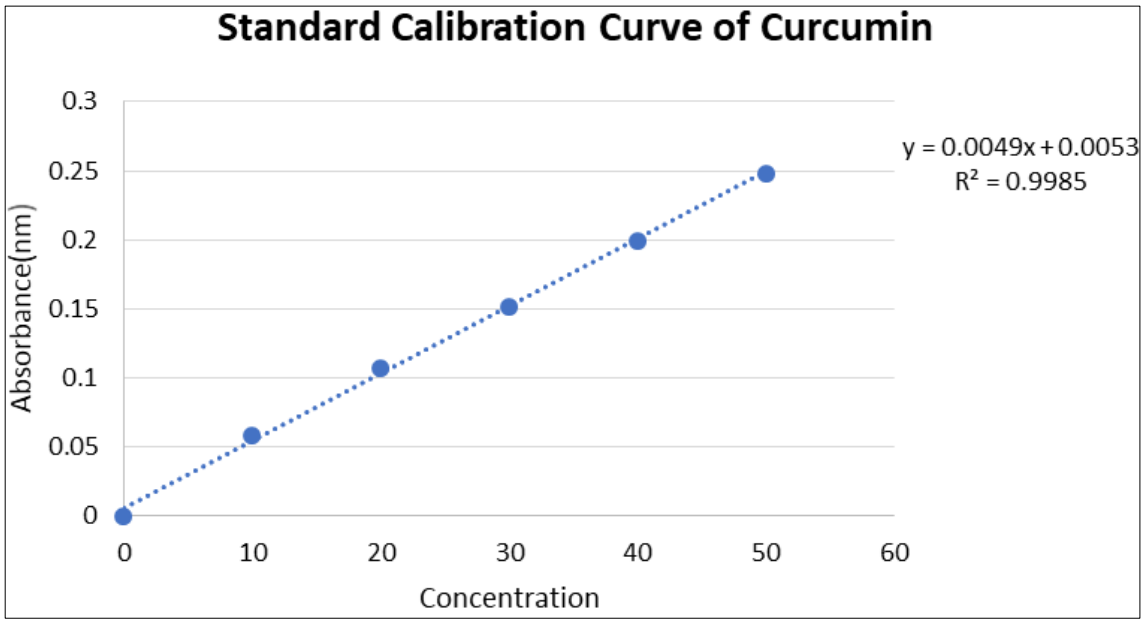


Fig 1: Standard calibration curve of curcumin

Preparation of curcumin emulgel:
The aqueous phase of emulsion was prepared by dissolving tween 80 in distilled water and the oil phase was prepared by mixing span80 in liquid paraffin. Both the oil phase and aqueous phases are heated separately at 70 ºC. The drug curcumin was dispersed in oil phase. Then, the oil phase was added to aqueous phase with continuous stirring and was allowed to cool down until the formulation reached to the room temperature. Gel base was formulated using 1g of the Carpool with a required quantity of water and kept for overnight soaking, Mix the prepared emulsion into gel base with continues stirring until the homogenous emulgel is formed. Different formulation was prepared using different concentrations of polymers. They were assigned with formulation codes (F1, F2, F3, F4, F5, and F6).

Table 1: Formulation trials (composition) of curcumin emulgel

Ingredients	F1	F2	F3	F4	F5	F6
1.Curcumin (0.1gm)	0.05	0.05	0.05	0.05	0.05	0.05
2.HPMC (gm)	0.2	0.15	0.1	-	-	-
3.Carbopol (gm)	-	-	-	0.3	0.2	0.15
4.Tween-80(ml)	0.15	0.15	0.15	0.15	0.15	0.15
5.Span-80(ml)	0.18	0.18	0.18	0.18	0.18	0.18
6.Liquid paraffin(ml)	5	5	5	5	5	5
7. Water	qs	qs	qs	qs	qs	qs

Evaluation parameters
Pre-formulation evaluation tests
1) FTIR analysis- The FTIR studies were conducted to check the drug excipient compatibility. Small amount of sample of drug, excipient was placed on the crystal of alpha Bruker FTIR instrument and the spectra were obtained by opus software, which were later interpreted for compatibility.11

Post-formulation evaluation tests
Physical examination the prepared formulations were inspected visually for their colour, homogeneity and consistency [12].

Determination of pH
For pH determination, take 1gram of product and dissolve in 10ml of distilled water and pH measured with digital pH meter value should be in the range of 5-6 similar to skin pH [13].

3. Spreadability
It can be determined by using the slip and drag method, for this take the emulgel on the glass slide and cover it with another glass slide. Now the weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Time to cover 5cmdistance for the upper slide was recorded and used to calculate Spreadability by using the following formula [14]:
Spredability(S) =M*L/T
Where M=Weight tied to the upper slide
L=Length of glass slides
T=Time taken to cover the distance

Swelling index
1gm of prepared emulgel is taken on a porous aluminium foil. It was then placed in a 50ml beaker containing 10ml of 0.1N NaOH. Then, samples were removed from beakers at different time intervals kept in a dry place for some time and reweighed. The swelling index is calculated as follows [15]:

Swelling index (SW)%=(Wt.-Wo)/Wo *100

(SW)%=Equilibrium per cent swelling
Wt.=Weight of swollen emulgel after time t
WO =Original weight of emulgel at zero time

5 Drug content determination
100mg of prepared emulgel is mixed with 50ml of methanol. This resultant solution is sonicated for 30 min. The absorbance was determined [16].

Microbial assay

Ditch plate technique was used to evaluate the antimicrobial activity. Agar media was prepared and placed in Petri-plates to solidify. A sterile cup borer was used to make a ditch into which emulgel was added and kept for incubation for 18-24hrs. The microbial growth was observed far from the emulgel. This states that the emulgel has bacteriostatic activity [17].

Globule size and its distribution in emulgel

1gm of emulgel was dissolved in purified water and agitated to get homogeneous dispersion. Calibration of eye piece micrometer was done using stage micrometer. Take emulgel on a slide and add 1-2 drops of amaranth dye to stain the oil globules and oil globules size is noted. 18

***In-vitro* release study- Franz diffusion cell method** Franz diffusion cell was used for the *in-vitro* drug release studies. Curcumin emulgel 100mg was applied onto the surface of the egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of the diffusion cell. The receptor chamber was filled with a pH 6.8 phosphate buffer. A magnetic stirrer was placed in the receptor chamber The samples were collected at regular time interval of 1hr. UV visible spectrophotometer was used to determine the drug content after appropriated dilutions. The amount of released across the egg membrane was determined as a function of time.19

Comparative *in-vitro* diffusion study

Franz diffusion cell was used for the drug release studies. Cur cumin emulgel 100mg and 100mg of pure curcumene was applied onto the surface of the egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of the diffusion cell. The receptor chamber was filled with a pH 6.8 phosphate buffer solution to solubilize the drug. The samples of F4 and pure drug were collected at regular time interval of 1hr. Samples were analysed by using UV spectrophotometer. The amount of drug released across the egg membrane was calculated with respect to time.

Scanning electron microscopy

Scanning electron microscope is a test process that scans a sample with an electron beam to produce a magnified image for analysis.

The optimized formulation (F4) was visualized using SEM electron microscope with an accelerating voltage of 100 kV and magnification up to 20.00 sk. Samples were stained with a 1% aqueous solution of phosphotungstic acid (PTA) as a negative stain. Emulgel solution (10 mL) was dried on a microscopic carbon-coated grid for staining. The excess solution was removed by blotting. After drying, the stained samples were examined in the SEM electron microscope accelerated). 20

***In-vitro* Release kinetics**

The release data obtained was studied into various mathematical models. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient was determined by Kors meyer-peppas equation to understand the release mechanism.

Experiment and Result.

1) Drug-excipients compatibility by FTIR

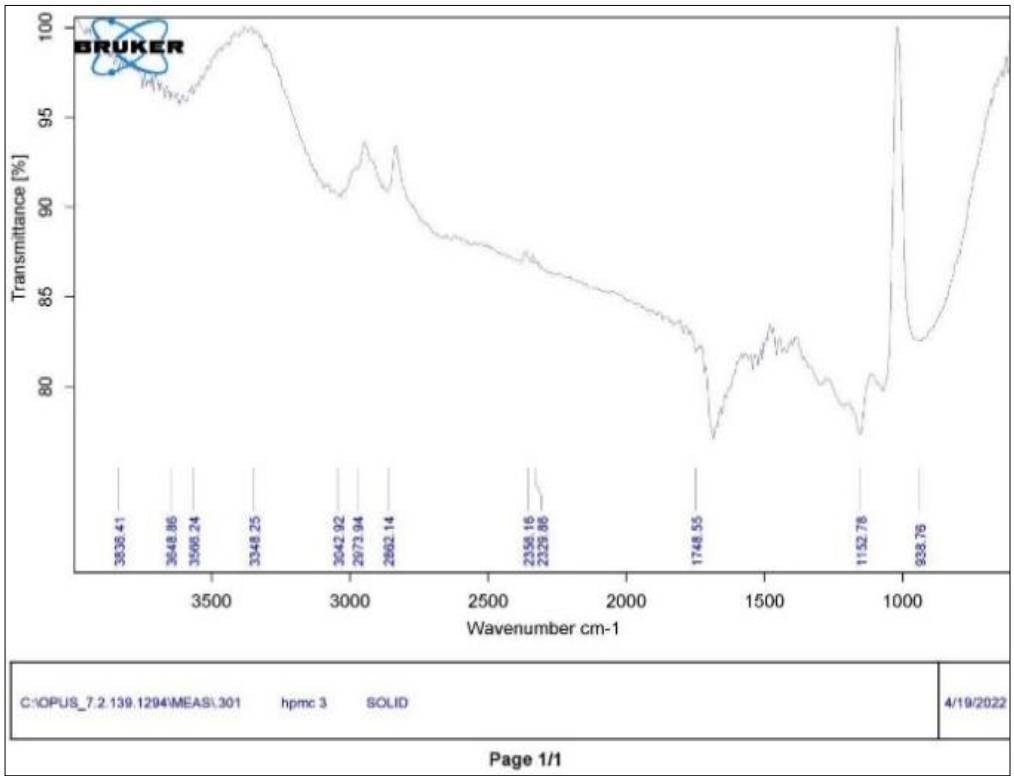


Fig 2: FTIR Graph of Cur cumin

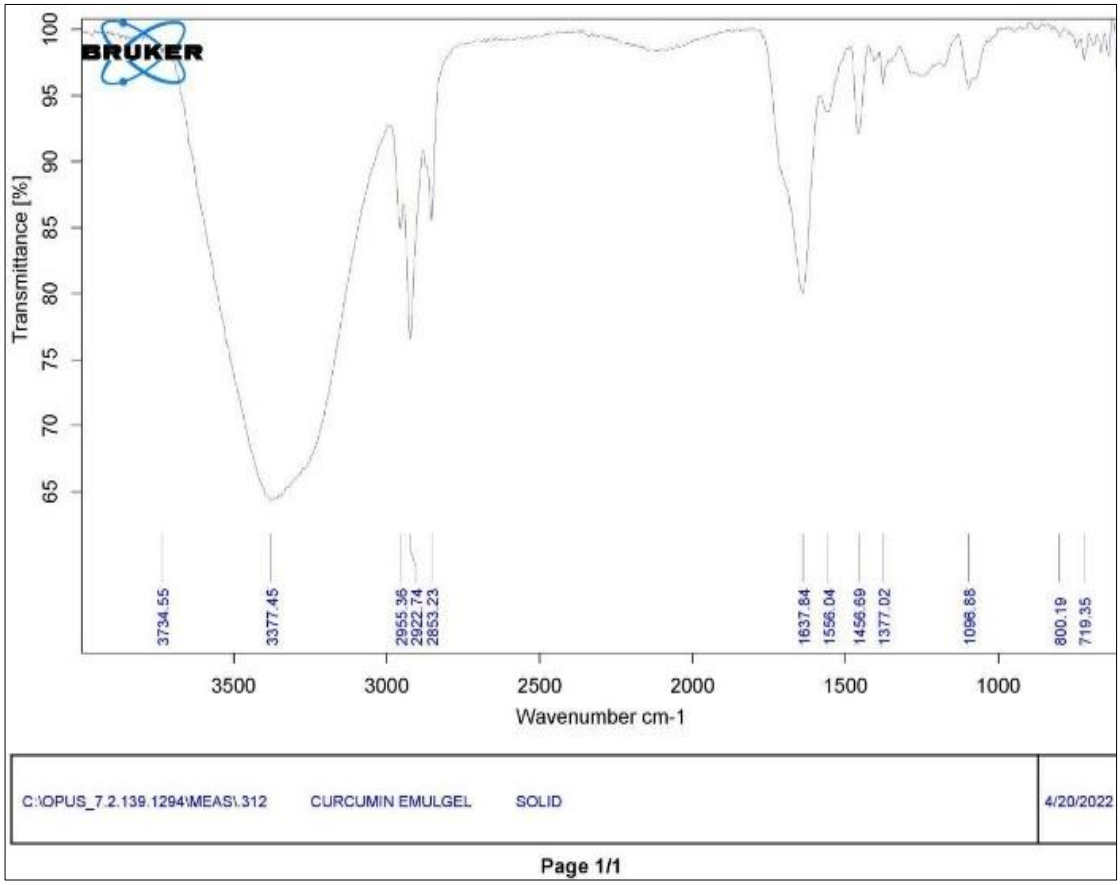


Fig 3: FTIR graph of HPMC

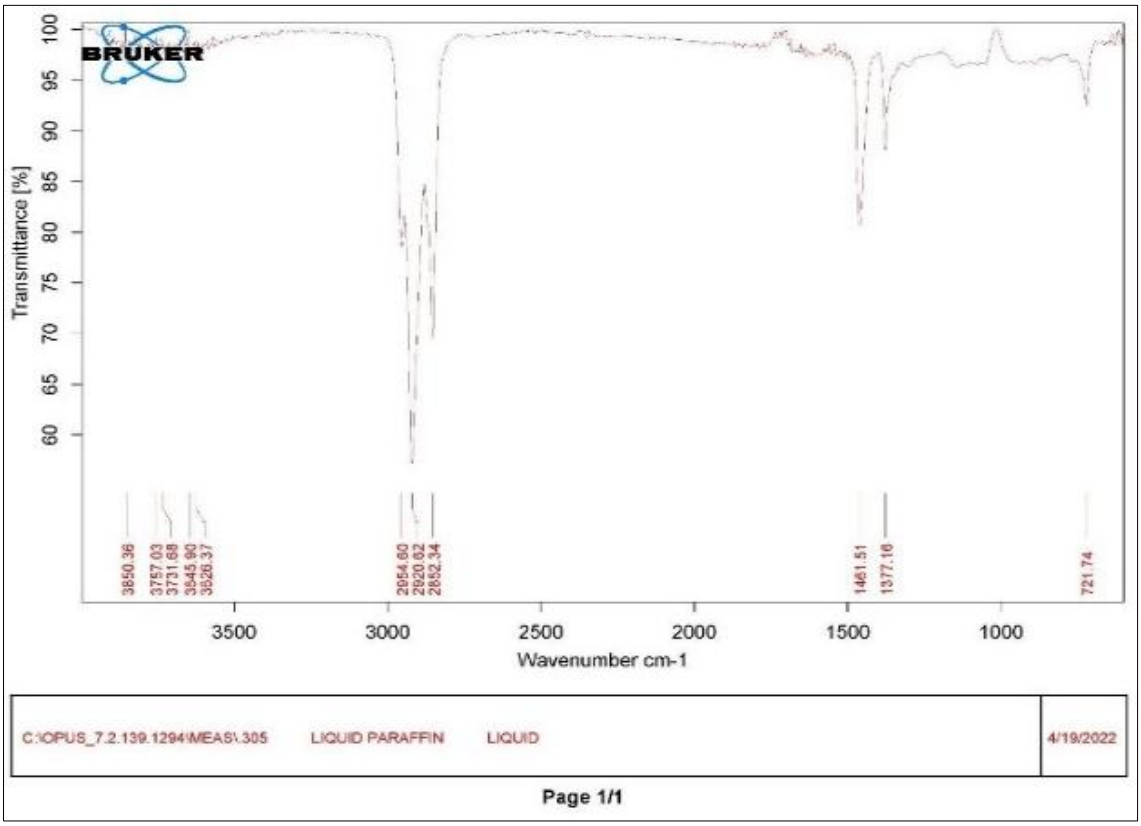


Fig 4: FTIR Graph of Liquid Paraffin

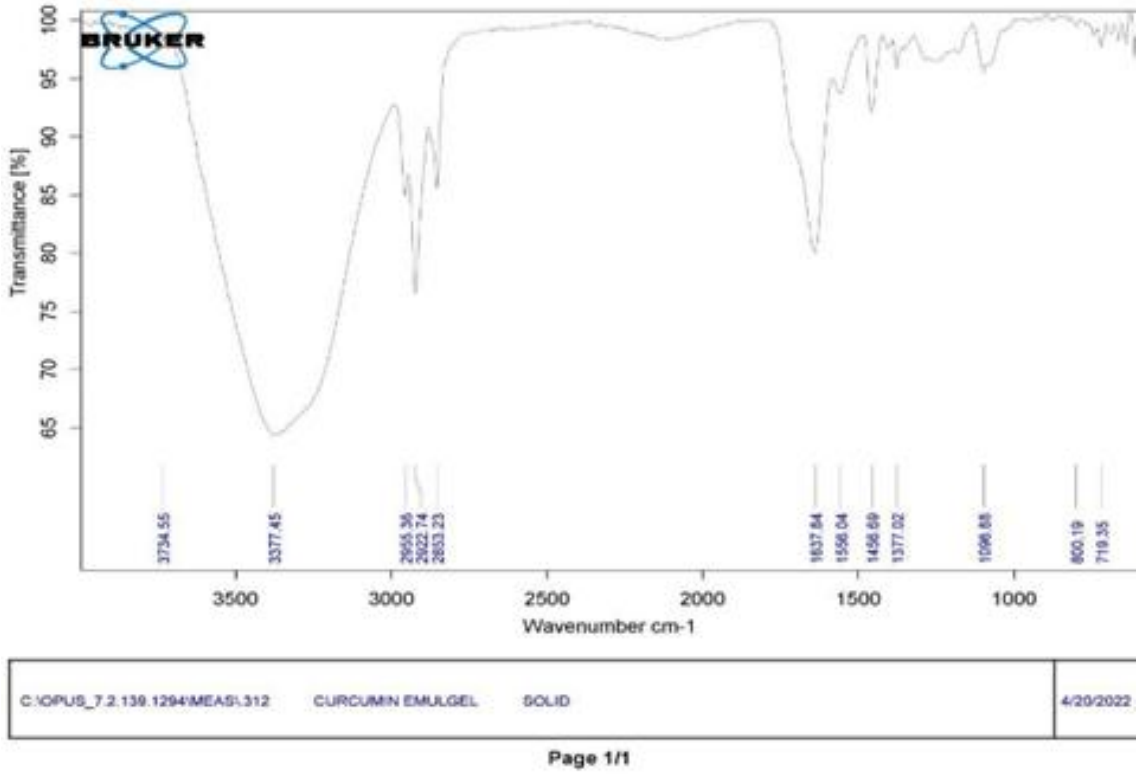


Fig 5: FTIR Graph of Curcumin Emulgel

FTIR Interpretation: FTIR study of pure drug (fig. 2), carpool 934 (fig.3) and HPMC (k100) (fig. 4), span 80 (fig. 5), tween 80 (fig. 6), liquid paraffin (fig. 7), and with formulation (fig. 8) were performed.

The experimental result shows there was no significant deviation between drug and polymers which confirm the compatibility. So, these polymers and other excipients were selected for formulation.

Table 2: Interpretation of FTIR analysis

Chemical	Wave number	Functional groups
Drug	1427 cm^{-1}, 1512 cm^{-1}	(C=C stretching) (C=O stretching)
carpool	1703 cm^{-1} 2941 cm^{-1}	(C=O stretching bond), (OH stretching bond).
HPMC	2922.59 cm^{-1}, 3420.14 cm^{-1}	(C-H stretching vibration) N-H stretching bonds
Span 80	3359.78 cm^{-1} 1738.68 cm^{-1}	stretching vibration of the OH-group C=O stretching vibration
Tween 80	1092.46 cm^{-1} 1301.30 cm^{-1}	C=O stretching vibration C-O stretching vibration of ester group
Liquid paraffin	2920 $cm^{-1}$and 1461 cm^{-1},	C-H stretching and bending absorption bands
Formulation		

Post formulation studies

Physiochemical tests:

Table 3: Physicochemical observation of emulgel

S.no	Formulation code	Colour	homogeneity	Consistency	pH
1	F1	Yellow	excellent	excellent	6.70
2	F2	Yellow	excellent	better	6.75
3	F3	Yellow	excellent	excellent	6.6
4	F4	Yellow	Excellent	excellent	6.8
5	F5	Yellow	excellent	better	6.81
6	F6	Yellow	Better	good	6.7

Physical evaluation: The prepared curcumin emulgel formulations were examined for yellow viscous creamy characteristics with a smooth and homogeneous appearance. All of the samples showed positive results, however F4 formulation was subjected to have excellent homogeneity and consistency.

pH determination: According to literature, skin pH is said to be in the range 5.5-7. The pH was determined for all the 6 batches and the range was found to between 6.07-6.98. This analysis indicates that the compatibility of formulations matches with that of the skin pH and it can display good topical delivery.

Post-formulation evaluation tests

Table 4: Physical Evaluation Data of Emulgel formulation

Formulation no.	Drug content (%)	Swelling index (%)	spreadability (sec)	Zone of inhibition (cm)	Globule size and its distribution
F1	86.42	41.58	53.65	1.4	158.15
F2	89.49	52.45	46.66	3.2	135
F3	83.17	39.52	53.54	1.9	230.15
F4	90.24	93.56	67.47	3.4	72.5
F5	88.56	81.23	55.25	2.5	211.5
F6	83.36	42.89	46.45	1.8	104.75

Spreadability- Spreadability of emulgel is a significant parameter. With decrease in viscosity, spreadability increases. F4 showed highest spreadability 67.47 respectively. It was easily spreadable because of low viscosity.

Swelling index- The swelling index was compared. It was seen that the formulation containing Carpool showed maximum swelling index to xanthan gum. Among all the formulation, F4 emulgel with Carpool 934 (1.5%) showed the highest swelling index. The swelling index value may be dependent on the water uptake nature and chain strength of the polymer.

Drug content determination-The drug content of the formulations was determined by UV spectrophotometer at a wavelength of 254 nm. The drug content was between the limit of 95% to 102% and there is no major effect of change in polymers and its concentrations

Microbial assay – The evaluation test was carried to check the sterility as the emulgel formulation is more susceptible to a bacterial attack, commonly by E. coli. The F4 formulation was found to have less microbial growth when compared with other formulations.

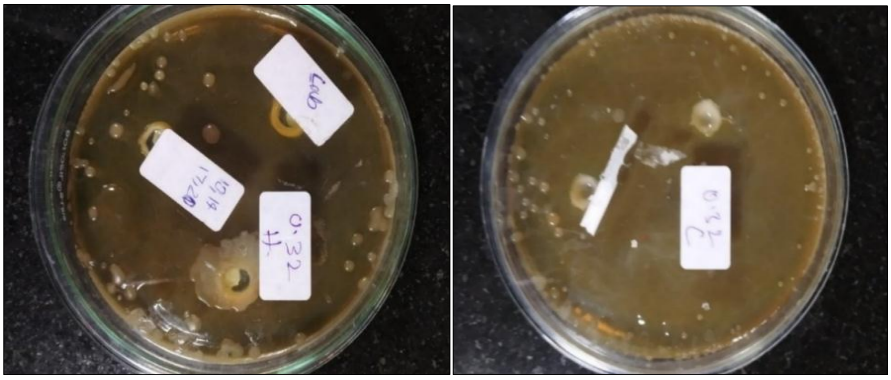


Fig 6: (a, b) microbial assay studies of optimized formulation (F4) a-before incubation, b-after incubation

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

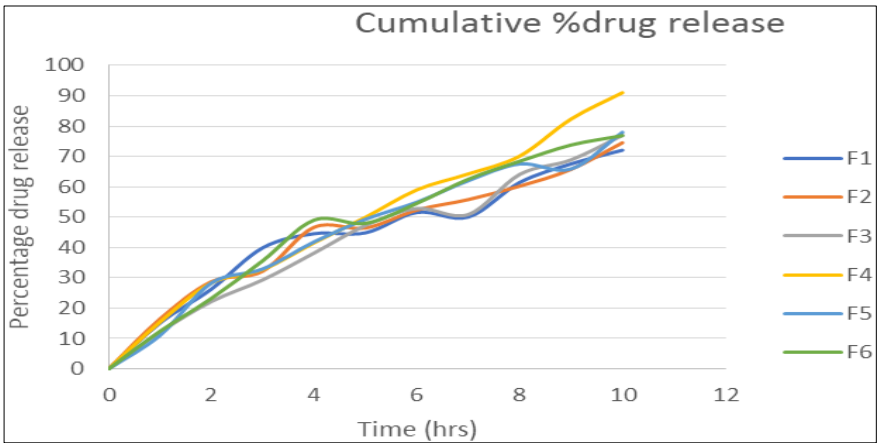


Fig 7: graphical representation of cumulative% *in-vitro* drug release

Release of drug from the formulation was depended to the nature and concentration of polymer. Formulations with Carpool 934 shows the drug release in descending order F3>F2>F1 where the amount of drug released after 10 h was 76.98%,74.54%,72.08% respectively, and for the formulations with HPMC (K100) the drug release was recorded in descending order F4>F5>F6 where the amount of drug released after 7 h was 90.04%, 77.98%, 76.89% respectively. It has been concluded that the HPMC (K100) emulgel with low concentration of polymer, F4 shows maximum release. It shows that HPMC (K100) is better polymer than carpool 934 for formulating emulgel. The cumulative% drug release profile of all the formulation batches has

Been shown in fig. 7

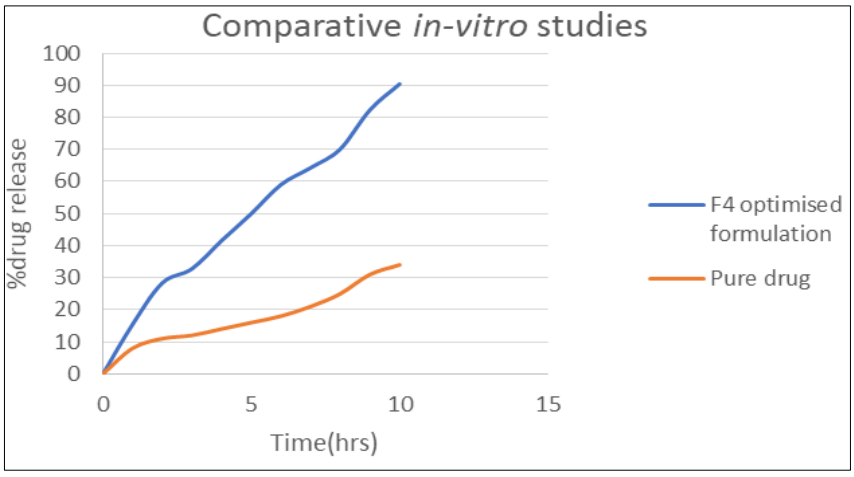


Fig 8: graphical representation of comparative *in-vitro* studies carried between optimised formulation (F4) and pure drug

This comparative *in-vitro* study was performed to compare the percentage drug release between the optimised formulation (F4) and that of the pure drug and it was found out that the drug release and diffusion rate of curcumin in emulgel was increased on comparison with pure drug.

Hence the objective of improving solubility and diffusion of drug through the skin by formulating into emulgel formulation has been achieved.

Scanning Electron Microscopy Studies

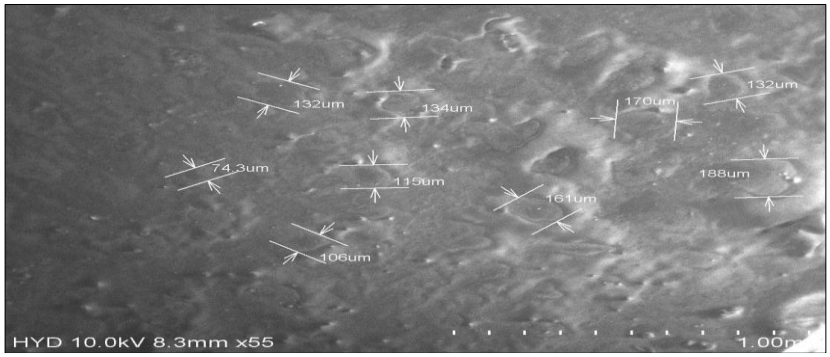
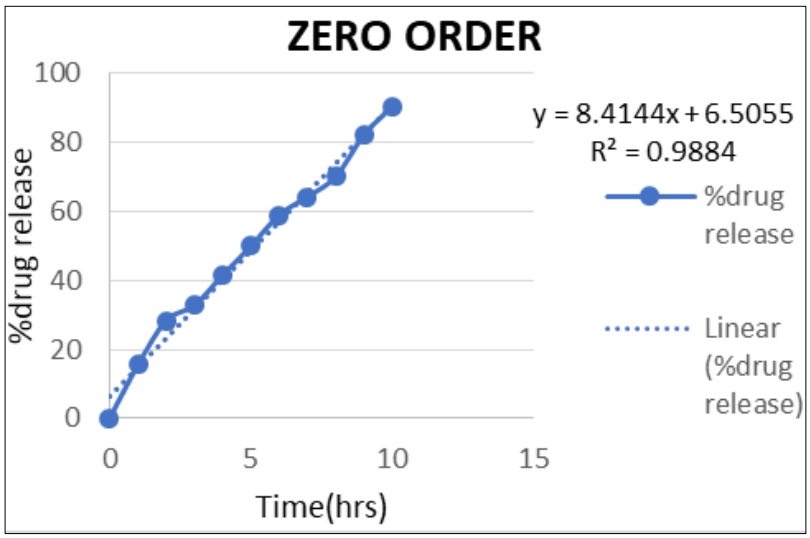


Fig 9: SEM photographs of optimised formulation (F4)

SEM studies Interpretation:

The surface morphology of the optimized emulgel formulation examined by SEM was illustrated in Fig 29, 30, 31 and 32. The emulgel formulation appeared as amorphous spherical particles with smooth surface morphology

***In-vitro* Drug Release Kinetics**



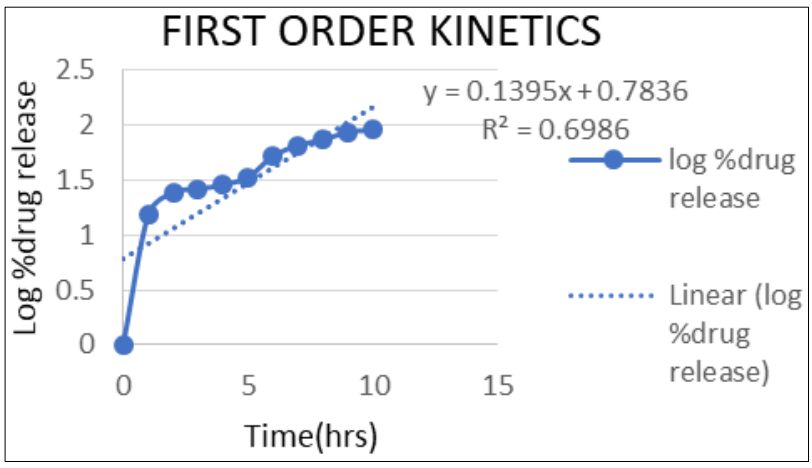
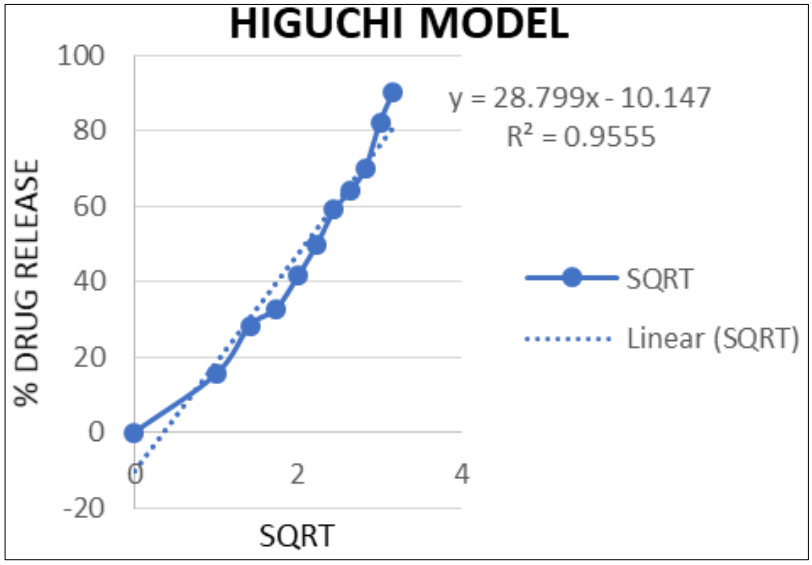


Table 10: release kinetics of optimized formulation of r^2value



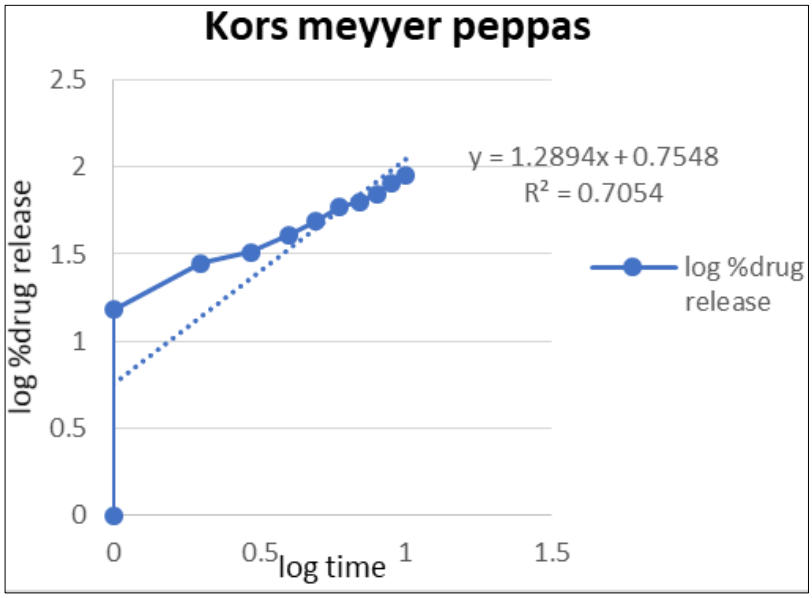


Table 5: Release Kinetics of Optimised Formulation of R^2 value

Formula code	Zero order	First order	Higuchi	Korsmeyer poppas	
	R^2	R^2	R^2	R^2	n
F4	0.9884	0.6986	0.9555	0.7054	0.8369

From the above coefficient of determination and release exponent values collected from zero order kinetics, first order kinetics, highchair model and korsmeyer poppa's model, the n value is less than 1, indicating that the optimized formulation follows non-fiction diffusion model [38, 39, 40, 41, 42]

Conclusion

Topical drug delivery system, being a novel drug delivery will be used broadly for its uprising advantageous factors. This research was undertaken with an aim to formulate curcumin emulgel. Loading curcumin drug into an emulgel base will increase its absorptive properties, bio-availability and enhanced target-drug delivery.

This study was started with drug-excipient studies by using FTIR, the results obtained from the FTIR analysis showed no possible chemical interactions between the drug (curcumin) and excipients (Carpool 934, HPMC, Span 80, Tween 80, Liquid paraffin and formulation). Therefore, these excipients were selected for formulating the emulgel.

Eventually, 6 batches of emulgel with formulation codes (F1, F2, F3, F4, F5, and F6) were prepared and evaluated for their physiochemical parameters, physical characteristics such as colour, homogeneity, pH, drug content, spreadability, swelling index, zone of inhibition and globule size along with *in-vitro* drug release studies.

The best formulation from the 6 batches (F1 to F6), F4 was found to be efficient with yellowish creamy consistency, pH (6.89), drug content (90.24% from UV analysis), swelling index of 93.56%, spreadability (67.47 sec), less microbial growth, globule size (72.5 µm) and *in-vitro* drug release was F4 with release of 90.45%.

The optimised formulation (F4) was now evaluated for comparative *in-vitro* studies, SEM studies and *in-vitro* release kinetics using zero-order, first-order, Higuchi and korsmeyer models.

Comparative *in-vitro* study was performed to compare the% drug release between the optimised formulation (F4) and that of the pure drug and it was found out that the drug release and diffusion rate of curcumin in emulgel was increased on comparison with pure drug.

From SEM studies, F4 was found to have smooth surface morphology with spherical oil globules evenly distributed. By *in-vitro* release kinetics, we can conclude that the optimised

formulation (F4) follows nonfiction diffusion as the n value is less than 1.

Therefore, findings of our study indicate that a hydrophobic drug, curcumin can be delivered topically as an emulgel with improved solubility and diffusion of drug through the skin for the local treatment of inflammation, wound healing with required physiochemical parameters and also can be made available to the young and old after technology transfer to pharmaceutical industries.

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