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Research Article

Microneedles Assisted Enhancement of Transdermal Delivery of Curcumin through Organogel Formulation

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ABSTRACT

Curcumin is a natural compound found in turmeric and has been shown to have anti-inflammatory and antioxidant properties. Topical delivery of curcumin through an organic emulsion-based gel can effectively target inflammation at specific sites on the body. The current study aims to formulate Pluronic based organogel of curcumin, whose absorption is further assisted by microneedles technology. Nine organogel formulations were prepared and optimized by 3^2 full factorization model to fix the ratio of lecithin[A] and Pluronic[B] concentration in order to get optimum drug release after 2 hours (Q2) and maximum release of drug after 8 hours (Q8). The *in-vitro* study through the Franz diffusion cell indicated a significant impact of Pluronic F-127 concentration on the release of drug. As increased concentration of Pluronic increased the viscosity of formulations which ultimately retarded the release of drug. Based on Design of Experiment (DoE) study, optimized batch containing 6.5% lecithin and 20.6% Pluronic was further studied for microneedle assisted *ex-vivo* skin permeation through rat skin. Permeation without microneedle poration was around 70.26% after 8 hours, which was significantly increased (around 25%) after microneedle treatment of the skin. The results indicated promising application microneedle assisted skin permeation as a non-invasive and controlled delivery of curcumin through the transdermal route. Further, *in-vivo* studies are recommended to further establish this promising concept, targeting a variety of inflammatory conditions, including arthritis, psoriasis, and eczema, etc., through non-invasive transdermal drug delivery systems.

Introduction

Currently, topical drug delivery is most commonly used to reduce local inflammation in joints in conditions such as rheumatoid arthritis and osteoarthritis. However, they show various limitations such as less spreadability, low penetration through stratum corneum and stickiness. It is more challenging for the drugs such as curcumin which show very low systemic bioavailability (less than 1%) due to minimum absorption and rapid metabolism.[1] Curcumin has good potential as a topical anti-inflammatory agent as it prevents apoptosis of chondrocytes in the cartilage of joints and thus protects joint cartilage.[2-4] It can be used in long term delivery to treat chronic joint inflammation. Curcumin is derived from rhizomes of *curcuma longa*. It is the major curcuminoid, comprised of 77% of three curcuminoids present in it. Curcumin (Diferuloylmethane, 7bis (4hydroxy-3methoxyphenyl)-1,6-heptane-3,5-dione) is a polyphenolic compound (Fig. 1).[5.6] The anti-inflammatory action of curcumin is due to the suppression of the release of proteoglycans, metalloproteases, COX enzymes, and prostaglandins E2.[7,8] Since curcumin is poorly solubility in water(3 mg/liter) shows less absorption through the skin and less bioavailability by topical route. The main challenge in delivering curcumin effectively is that curcumin is a highly lipophilic compound. In microemulsion-based delivery emulsions stabilized by mixed surfactant systems, the surfactants' hydrophilic and hydrophobic parts might contribute to the solubilization of curcumin molecules inside the emulsions, leading to a high loading efficiency.[9] Isopropyl myristate

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can be used as an oily phase to facilitate the delivery of curcumin.

Organogels containing two surfactants Pluronic for polar phase and lecithin for nonpolar phase of microemulsion form reversible micelles and help to build a transparent gel with good adherence to skin.[10] Drug delivery can be assisted by using solid microneedles which will penetrate up to the epidermis, create micron-sized pores and help penetrate the drug by making a physical path through upper layers of the epidermis. It can be used to increase the permeability of skin; by bypassing the stratum corneum.[11] Currently, curcumin formulation as a nanocarrier system is much explored as liposomal and nanoparticulate systems of curcumin. These encapsulated drug deliveries depend on its drug loading and release through vesicles, are less stable and thus limited success.[12] Study on transdermal delivery of naltrexone along with diclofenac demonstrated week-long drug delivery after one microneedle application, which would increase patient compliance and allow delivery of therapies for chronic diseases.[13] Ketoprofen-loaded nanoparticles after applying silicon microneedle arrays enhanced ketoprofen flux and supplied the porcine skin with drug over a prolonged 24 hours.[14,15] This indicates that topical delivery through microneedles could be used for the development of effective and painless administration systems for sustained percutaneous delivery of curcumin.

So, the present work was carried out to develop pluronic lecithin organogel of curcumin for topical drug delivery assisted by microneedles non-invasive technique to maintain optimum therapeutic levels of the drug and avoid frequent applications, thus improving patient compliance. In the development of organogels, an important issue is to design an optimized formulation with an appropriate viscosity and drug release. The present study was aimed to prepare stable microemulsion based gel with 2% curcumin by decreasing interfacial tension and at the same time increasing the viscosity of the aqueous phase. A 3^2 full factorial design was to study the effect of pluronic (A), Lecithin (B) on viscosity, %cumulative drug release at 2 hours and %cumulative drug release at 8 hours.

Materials and Methods

Materials

Curcumin was a gift sample from Nuvagen Bioscience Pvt Ltd, Mumbai, Pluronic F-127 was purchased from Sigma Aldrich (St. Louis, MO, USA). Soya lecithin powder-Lecilite SP-97 was a benevolent gift from LECILITE, Nagpur, Isopropyl Myristate was purchased from Oxford lab fine chem Palghar, potassium sorbate and sorbic acid Water and chloroform HPLC grade were purchased from Avantor Ranchem Thane, acetonitrile and trifluoroacetic acid were purchased Loba Chemie Boisar, Strat M membrane

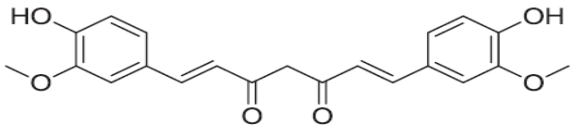

Fig. 1: Structure of curcumin

filters of 0.45-micron size were purchased from Priyanka Corporation Mumbai, Derma pen Ultima 2C was purchased from My M.

Drug Excipient Compatibility Study

Drug-excipient interaction plays a vital role in achieving stability of drugs in dosage form. Fourier transform infrared spectroscopy (FTIR) was used to study the physical and chemical interactions between drug and excipients. FTIR spectra of curcumin and physical mixture of curcumin: Pluronic F127 was recorded using KBr mixing method on FTIR instrument FTIR JASCO -4100 type A.

STD Curve of Curcumin by HPLC[16]

Concentrations of curcumin from 100 to 600 ng/mL in methanol were prepared for HPLC analysis. Reversed-phase high-performance liquid chromatographic (RP-HPLC) method using RP-C18 column was performed on HPLC model Jasco lc net II ADC. The mixture of acetonitrile: 0.1% trifluoroacetic acid (50:50) was used as mobile phase with a flow rate was 1.5 mL/min and elution was monitored at 420 nm (λ max of curcumin). The total area of the drug peak was used to quantify curcumin.

Development of Curcumin Organogel

As a solvent, the oil phase was prepared by taking a measured amount of completely dissolved lecithin and sorbic acid in isopropyl myristate. The aqueous phase was prepared by completely dissolving weighed quantity of Pluronic F-127 and potassium sorbate in water at 4° C. The next day, gel was prepared by slowly adding oil phase to the aqueous phase at various speeds of 200, 400, 600 and 800 rpm using a magnetic stirrer. The mixing was finally done at speed of 200 rpm for two minutes to get a uniformly dispersed microemulsion. The oil and aqueous phase ratio was kept at 50:50 since curcumin solubility is less in the aqueous phase. 2% curcumin was incorporated in isopropyl myristate before mixing with Pluronic phase.[17] Initially, trial batches were prepared to screen the optimum range of pluronic and lecithin. On the basis of trial batches, it was found that lecithin in the range of 4 to 8 % and pluronic in the range of 16 to 24% may be considered for further optimization. The process is depicted in Fig. 2 and Table 1.

Evaluation of Organogel

All formulations were inspected visually for their color, homogeneity, consistency, grittiness, smoothness, stiffness and phase separation. The pH of 1% organogel solution in

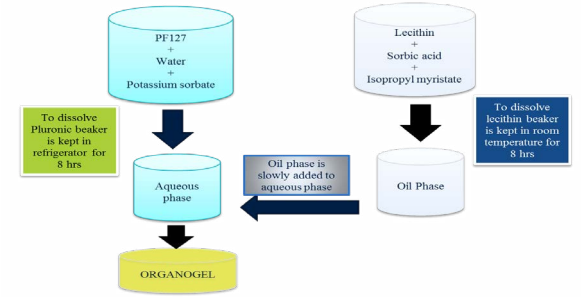

Fig. 2: Schematic diagram preparation of organogel

distilled water was determined using digital pH meter and viscosity was determined using a Brookfield viscometer (LVDV II model) using the LV61 spindle at speed 10 rpm. A thin gel film was spread on a glass slide and observed under a microscope on a 10 X lens.

Drug Content

To evaluate curcumin content in formulation gel containing 1-mg of curcumin was weighed accurately and dissolved in methanol. The absorbance was measured after suitable dilution was recorded at wavelength 420 nm using the HPLC method as mentioned above. The drug content was determined by using a standard curve of absorbance versus concentration in triplicate.

In-vitro Drug Release

Selection of Dissolution Media

Due to the very less solubility of curcumin in the buffer, there was a need of a huge amount of dissolution media in the receptor compartment of the Franz diffusion cell. In order to fulfill it, a modified Franz diffusion cell was designed for dissolution study. The partition coefficient study was performed using chloroform as the organic phase and saline phosphate buffer, pH 7.4, as the aqueous phase. The concentration of the drug in the buffer phase and chloroform was analyzed by HPLC at 420 nm using the same mobile phase composition and other parameters discussed in HPLC study of curcumin. The partition coefficient (P) of drug K chloroform/Buffer was calculated using the following formula.

(P) Ko/w = Concentration in chloroform/ Concentration in phosphate buffer pH 7.4.

Log *p-value* was 2.99.

Further the dissolution media was again quickly saturated shortly in the new setup, which again raised a need to establish sink conditions. Curcumin shows very low solubility in water and is found to be easily soluble in chloroform. As curcumin shows pH-dependent decomposition at neutral-basic conditions.[18] For the same, we made an alternate arrangement with a chloroform layer that settled at the bottom of the media and could absorb the majority of released curcumin immediately due to partitioning, creating a good sink condition.

In-vitro Permeation Study through Artificial Membranes

In-vitro drug release study was performed by using modified dissolution test apparatus. Dissolution apparatus make Veego VDA 8D was used. Dissolution media was taken as 800 mL phosphate buffer pH 7.4 equilibrated at 32 ± 0.5°C and chloroform 100 mL was used as a medium. The donor compartment of the Franz diffusion cell was covered with Strat M membrane (Cellulose acetate membrane). Membrane was soaked in buffer pH 7.4 overnight and held in the dissolution vessel so that about 1-cm of the bottom remains submerged in dissolution media. The speed of the paddle was kept at 50 rpm. Organogel equivalent to 3 mg of the drug was placed on the disk to ensure the release surface was flat on a membrane. Aliquots 5.0 mL from chloroform layer were withdrawn at the one-hour interval and equivalent amount of chloroform was replaced in order to achieve sink conditions. The amount of curcumin released in the chloroform layer was quantified by HPLC analysis. Assembly set up is shown in Fig. 3.

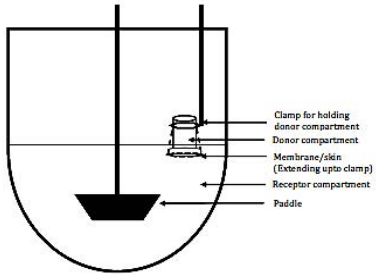

Fig. 3: Schematic diagram of assembly set up for *in-vitro* drug permeation study

Table 1: Formulation of Organogels

Type of phase	*Ingredients (All quantities in %)*	*B1*	*B2*	*B3*	*B4*	*B5*	*B6*	*B7*	*B8*	*B9*
Oil Phase	Curcumin	2	2	2	2	2	2	2	2	2
	Lecithin	4	6	8	4	6	8	4	6	8
	Sorbic acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Isopropyl Myristate(IPM)(upto)	100	100	100	100	100	100	100	100	100
Aqueous phase	Pluronic F127	16	16	16	20	20	20	24	24	24
	Potassium sorbate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Distilled water(upto)	100	100	100	100	100	100	100	100	100

Optimization of Variables using Full Factorization Design

In 3^2 full factorial design study was used in the present study. In the design 2 independent factors-concentration of lecithin(A) and concentration of Pluronic F127(B) were evaluated each at 3 levels and experimental trials were performed for all possible combinations. The viscosity, drug release from the skin after 2 hours (Q2), and drug release from the skin after 8hrs(Q8) were taken as dependant variables. Multiple regression analysis and ANOVA was performed Design Expert Software (Version 7 Stat Ease Inc Minneapolis MN, USA) to generate a statistical relationship between indepandant variables and contour plots and 3D response surface plot.[16] The formulation layout for the factorial batches is shown in Table 2.

Ex-vivo Drug Permeation Study[19]

The permeation study of the drug was determined by using Franz diffusion cell in modified dissolution apparatus. The Sparge Dawley rat skin was mounted on receptor compartment with stratum corneum side facing upwards into donor compartment with a diffusion area of 2 cm^2 across excised rat skin was performed on an optimized batch in DOE as mentioned above. The Sprague-Dawley rat's skin was received from the animal facility of Principal Dr. K.M. Kundanani College of Pharmacy, Mumbai Insti-tute (Ref. Protocol no. IAEC/VIP/2021/June/P/03). The donor cell was suspended in dissolution media containing 800 mL phosphate buffer pH 7.4 and 100 mL of chloroform. The speed of the paddle was kept at 50 rpm. A gel equivalent to 3mg of the drug was spread on rat skin. Drug permeability studies were conducted for 8 hours. The temperature was maintained at 32 ± 0.05°C. The samples were withdrawn from the receptor cell at regular intervals of 1, 2, 3, 4, 5, 6, 7, and 8 hours and analyzed by HPLC.

Ex-vivo Skin Permeation Study with Microneedles

Drug permeation through intact rat skin was significantly less as compared to the artificial membrane. This may be because the artificial membrane has pores with no barriers like the actual skin membrane. There is a need to improve permeation through actual skin membrane. In this case, microneedle assisted poration of the rat skin was done through a microneedle array of Derma pen at a depth of 1-mm. This treated skin was further used for *ex-vivo* skin permeation study performed by the same procedure as mentioned above[20](Fig. 4).

Table 2: Layout of 3 x 2 factorial design

Factors (Independent variables)	*Levels*		
	Low	*Medium*	*High*
	-1	*0*	*+1*
A (Amount of soy lecithin in %)	4	6	8
B (Amount of Pluronic F127 in %)	16	20	24
Responses (Dependent variables)	Constraints		
Viscosity	5200 to 5600 cps		
Drug release after 2 hours (Q2)	25 to 35%		
Drug release after 8 hours (Q8)	90 to 100%		

Results and Discussion

Drug Excipients Compatibility Study

The FTIR spectrum of drug curcumin was comparable with that of STD curcumin found in literature. Curcumin exhibited characteristic bands at wave number 2,980–2,850 cm^{-1} due to the C–H stretching vibrations of methoxy (–OCH_3) group(s), which differentiates it from bisdemethoxycurcumin. Phenolic OH stretching region at 3503, benzene ring 1605, C=O and C=C at 1508, C-H bending vibration at 1427, aromatic C=O stretching vibration at 1273, C-O-C stretching vibration at 1026/826 cm^{-1} were also characteristic peaks observed in the spectra. (Fig. 5a and b).

HPLC Evaluation of Curcumin

Curcumin eluted well in the mobile phase and showed separation from the solvent front. The retention time of 5.5 minutes provided a faster determination. The STD curve of different concentrations vs peak area was obtained. The R^2 value was 0.9932 closer to 1.0. The std deviation was minimum**.** (Fig. 6).

Evaluation of Factorial Batches of Curcumin organogel

All batches of organogel were yellow in color, with smooth homogenous texture.[Figs 7 and 8] pH of all prepared microemulsion was found in the range of 5.585.82 which is an acceptable range for topical preparations. The viscosity of all factorial batches was found in the range of 5100 to 6162 cps. Drug content in all formulations ranged from 96.12 to 97.67%.

Correlation Between Viscosity and Drug Release

In *in-vitro* release study release of the drug after 2 hours was in the range of 24.19 to 37.2%.and at the end of 8 hours was in the range of 87.07 to 96.14%. The significant drug release was observed at the end of 8 hours and it followed zero order kinetics suggesting that the entire amount of drug in the gel would be available for partitioning into the stratum corneum (Table 3)**.**

In batch B1, B2 and B3 the viscosity was found to be less than or closer to lower limit of viscosity (i.e., 5200 cps). In these batches, the pluronic concentration was less (16%). Hence the 2 hours release of the drug was more than the predicted release. Due to low viscosity, there will be less contact of the drug with skin. In batches B7, B8 and B9 viscosity was found to be higher than the limit of 5600 cps. This may be due to a higher concentration of pwluronic. The formulations became more viscous and 2

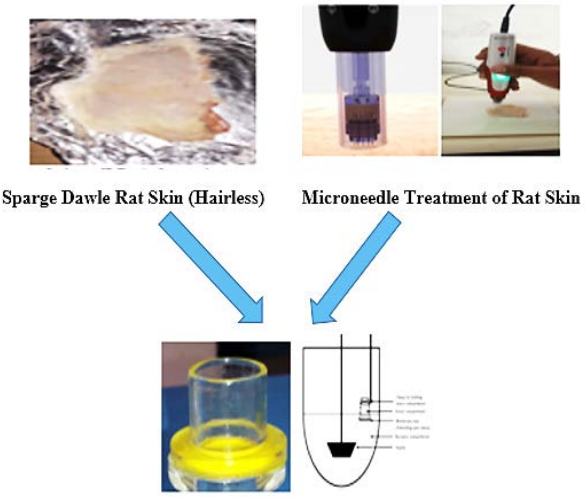

Fig. 4: Schematic Diagram of *ex-vivo* skin permeation study (With or without microneedle treatment)

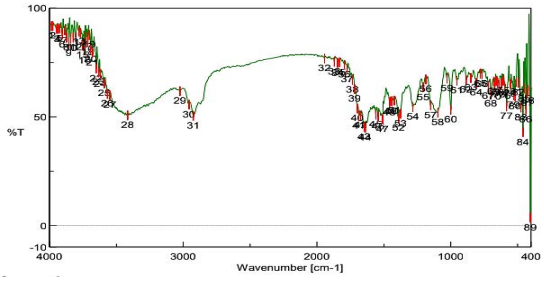

Fig. 5a: FTIR of curcumin

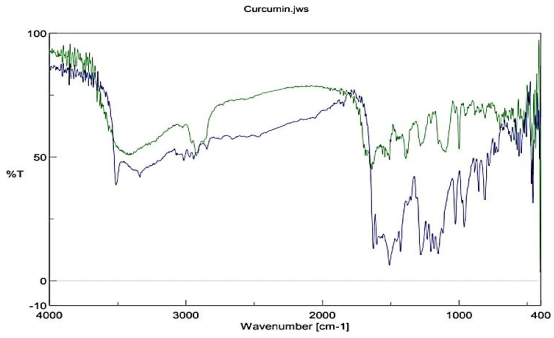

Fig. 5b: FTIR of curcumin with excipients

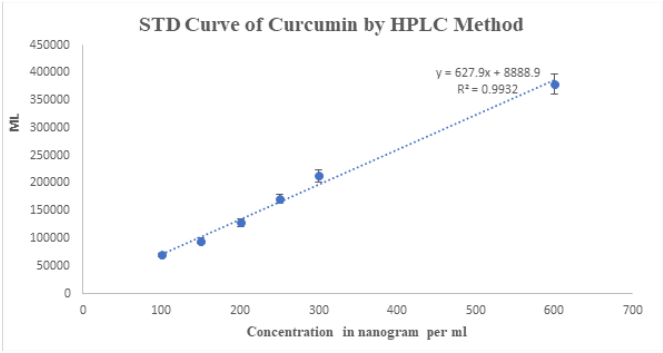

Fig. 6: STD Curve of curcumin by HPLC

Fig. 7: Organogel formulations batch B1-B9

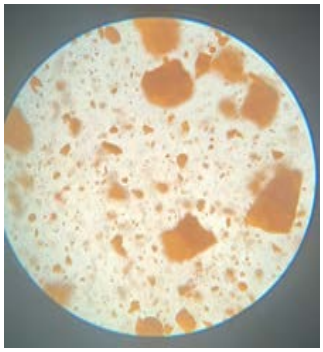

Fig. 8: Microscopy of an optimised batch of organogel

hours release was retarded and less than or closer to lower limits of drug release of 25%. For 8 hours drug release was also closer to lower limits of drug i.e. 90%. This may be due to an increase in resistance between layers. Thus, the percent cumulative amount of drug release was reduced, as the viscosity of the formulations increased and these results were in accordance with earlier study findings. The same trend was observed in case of lecithin concentration.

Table 3: Evaluation of organogels

Batch No.	*pH*	*Drug content %*	*Viscosity in centipoise*	*% Drug release in 2 hours*	*% Drug release in 8 hours*
B1	5.60	96.12	5100±167	37.20	97.10
B2	5.58	97.31	5188±154	34.80	96.14
B3	5.62	97.67	5280±123	33.00	95.87
B4	5.60	96.56	5315±234	32.70	95.80
B5	5.61	96.89	5398±251	31.00	95.61
B6	5.76	95.98	5517±189	30.24	94.27
B7	5.82	97.13	5602±196	28.17	91.85
B8	5.75	96.89	5740±203	26.65	91.69
B9	5.78	96.98	5862±156	24.19	87.07

In batch B4, B5 and B6 the viscosity and drug release were found to be well within the limit.

3^2 Full Factorial Design Model Evaluation[21]

After analyzing the polynomial equation depicting independent variables and responses. The formulation was optimized targeting the prescriptive criteria of viscosity in the range of 5200 to 5600, drug release in 2 hours 25 to 35% and drug release after 8 hours 90 to 100%.

Significant Factors for Viscosity

Viscosity was studied for all 9 batches. Quadratic vs 2FI model was suggested as it had Probability > F value was < 0. 0001. The model F-value of 108.92 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. *p-values* less than 0.05 indicate model terms are significant. The lack of fit test was insignificant. The "Pred R-Squared" of 0.9933 is in reasonable agreement with the "Adj R-Squared" of 0.9986. The resulting equation in terms of coded factors is as follows:

$$\text{Viscosity} = +5400.50 + 107.00 * A + 272.67 * B + 20.00 * A * B + 59.50 * B^2$$

The positive coefficient of the term A-lecithin indicates that increase in the concentration of lecithin increases viscosity due to matrix formation. The positive coefficient of the term, B-pluronic indicates that increase in pluronic concentration increases gel viscosity. From the contour and 3D response surface plot (Fig. 9a) and the regression coefficient values of factors, it was concluded the viscosity of microemulsion increases with an increase in the concentration of lecithin and pluronic. Interaction and nonlinearity were not observed. The results also indicated that the pluronic had a more significant effect on viscosity than lecithin. The coefficients of A and B were found to be 107 and 272.67, respectively.

Significant Factors for Percent Drug Release at 2 Hours (Q2)

The amount of drug released at 2 hours from the B1-B9 batches of PLO was in the range of 26.65 to 34.8%. Linear *vs* Mean model was suggested as it had Probability > F value was smallest (0.0065). The Model F-value of 6.35 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. *p-values* less than 0.05 indicate model terms are significant. The lack of fit test was insignificant. The "Pred R-Squared" of 0.4157 is in reasonable agreement with the "Adj R-Squared" of 0. 5953. The resulting equation in terms of coded factors is as follows:

$$\text{Release after 2 hours (Q2)} = +32.71 - 1.74 * A - 4.37 * B$$

The negative coefficient of both terms A-lecithin and B-pluronic indicate that a decrease in both concentration increases drug release. From the contour and 3D response surface plot (Fig. 9b) and the regression coefficient values of factors, it was concluded that a correspondence decrease as the drug-releasing of micro emulgel was observed with an increase in concentrations of lecithin and Pluronic. The drug release appeared to decrease more with an increase in the concentration of Pluronic compared to lecithin. Interaction and nonlinearity were not observed. For Q2, the coefficients lecithin and pluronic were found to be 1.74 and 4.37, respectively. Therefore, it was concluded that pluronic had a more significant effect on drug release than lecithin.

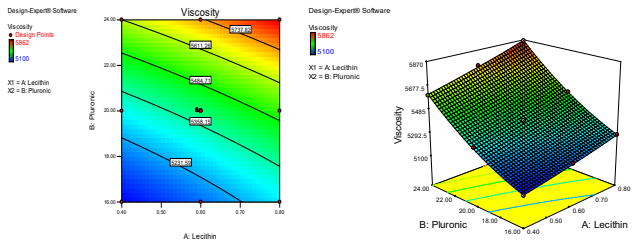

Fig. 9a: Contour graph and surface response graph showing The effect of lecithin and pluronic on viscosity

Significant Factors for Percent Drug Release at 8 Hours (Q8)

Quadratic vs 2FI model was suggested as it had probability > F value was smallest (0.0166).

The model F-value of 23.59 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. *p-values* less than 0.0500 indicate model terms are significant. The lack of fit test was insignificant. The "Pred R-Squared" of 0.8722 is in reasonable agreement with the "Adj R-Squared" of 0.9791. The resulting equation in terms of coded factors is as follows,

$$\text{Release after 8 hrs(Q8)} = +95.65 - 1.26 * A - 3.08 * B - 0.89 * A * B - 0.75 * A^2 - 1.87 * B^2$$

The amount of drug released at 8 hours from the B1-B9 batches of PLO varied from 87.07 to 97.1%. The negative coefficients of both the terms A–lecithin and B-pluronic indicate that a decrease in the concentration increases drug release. From the contour and 3D response surface plot (Fig. 9c) and the regression coefficient values of factors, it was concluded that a correspondence decrease as the drug-releasing of microemulsion was observed with increase in concentrations of lecithin and pluronic. Interaction and nonlinearity were not observed For Q8, the coefficients lecithin and pluronic were found to be 1.26 and 3.08, respectively. Therefore, it was concluded that pluronic had a more significant effect on drug release than lecithin.

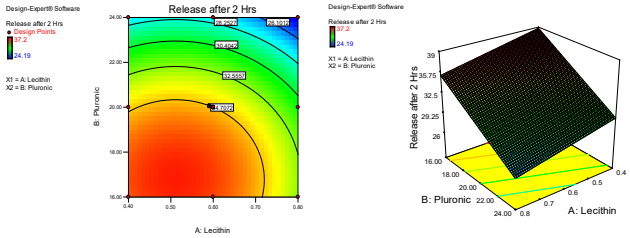

Fig. 9b: contour graph and surface response graph showing the effect of lecithin and pluronic on drug release after 2 hours

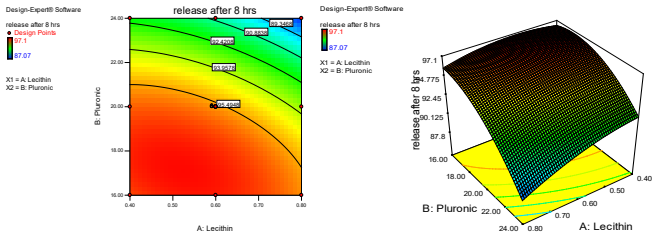

Fig. 9c: contour graph and surface response graph showing the effect of lecithin and pluronic on drug release after 8 hours

Formulation of Checkpoint Batch

To validate the evolved mathematical models (reduced models for viscosity, Q2 and Q8) one checkpoint batch was selected from overlay plot as shown in Fig. 10. The checkpoint batch was prepared and evaluated (Table 4). The observed and predicted values are as shown in Table 5. Good correlation was found between observed and predicted values. Hence it may be concluded that the evolved models may be used to theoretically predict responses within the factor space.

Ex-vivo Skin Permeation Study

Ex-vivo skin permeation study was performed on an optimized batch in DoE as mentioned above. In the *ex-vivo* study drug release was observed 70.26% at the end of 8 hours. It was less compared to the *in-vitro* study. This may be due to less drug permeation through the rat skin's stratum corneum.

Ex-vivo Skin Permeation Study with Microneedles

The release of the drug was further improved when microneedles were applied. As solid microneedles penetrated up to 1 mm depth the temporary perforations increased the diffusion of the drug through the stratum corneum resulting in improved drug release by creating micron size pathways due to disruption of the skin layer, the drug could easily cross the skin at the required rate drug release was from 70.26 to 95.76% at the end of 8 hours (Fig. 11). Thus, the drug could easily move to the epidermis from where the necessary to act on inflammatory mediators for therapeutic action.

Therefore, it was concluded that microneedles drug delivery is a better carrier system for topical drug delivery of curcumin.

Table 4: Optimized batch formulation

Type of phase	*Ingredients (All quantities in %)*	*Optimised level%*
Oil Phase	Curcumin	2
	Lecithin	6.5
	Sorbic acid	0.2
	Isopropyl myristate(IPM) (Upto)	100
Aqueous phase	Pluronic F127	20.6
	Potassium sorbate	0.2
	Distilled water (Upto)	100

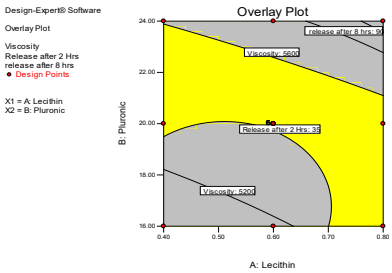

Fig. 10: Overlay plot of applied design

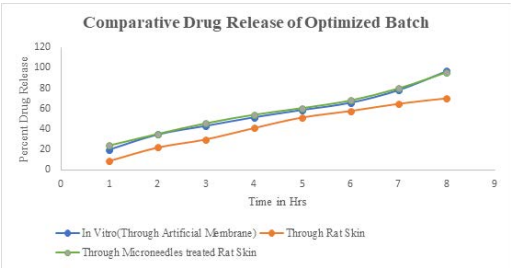

Fig. 11: Comparative drug permeation from the optimised batch after 8 hours under different conditions

Table 5: Experimental and predicted values for optimised organogel formula

Response	*Experimental ± SD (n=3)*	*Expected*	*% Relative Error*
Viscosity	5499.04 ± 192	5389.08	2.04
Drug release after 2 hours	34.80 ± 0.1	33.49	3.92
Drug release after 8 hours	96.83 ± 0.02	94.79	2.15

Conclusion

A curcumin organogel was prepared successfully using isopropyl myristate as an oil phase of the emulsion and pluronic lecithin as a surfactant system. From the factorial batch evaluations, batch B5 was selected as an optimized batch. The basic results showed that the viscosity and the drug release from the PLOs was the most critical factor for the release of drug from the gel formulation and the therapeutic efficacy of the formulation. It may be noted that an increase in lecithin and pluronic concentration showed retardation in a release. Due to the increase

in viscosity, the number and dimension of the aqueous regions available for the diffusion of the drug were reduced. At higher concentration density of spherical micelles might be increased, resulting in overlapping of PEO shells and thus forming stiff gel due to closed packing, significantly affecting the viscosity of the formulation.

The study effectively proved the enhancement of the permeation of the curcumin from PLOs through the skin. *An in-vitro* drug release study shows the control action of the formulation for up to 8 hours, which prolongs the active time for the drug in the topical treatment anti-inflammatory action. These results support the hypothesis that PLO is a promising candidate for the topical drug delivery system to overcome the limitation of enhancing skin permeability. Since delivery of curcumin was facilitated using trans epidermal microneedle approach, the combination approach can be an outbreak technology for getting desirable delivery of curcumin. This technology is a minimally invasive, cost-effective alternative to the conventional drug delivery system.

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