RESEARCH PAPER

Formulation and Evaluation of Curcumin Loaded Lipid Vesicles Based Cosmetic Preparation

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ABSTRACT

A Vesicular Drug Delivery System (VDDS) is that the system during which encapsulation of active moieties in vesicular structure, which bridges gap between ideal and available of novel drug delivery system. A variety of vesicular drug delivery systems like liposomes, niosomes, transferosomes, pharmacosomes, colloidosomes, herbosomes, sphinosomes, ethosomes etc. are developed. A completely unique drug delivery system is that delivers drug at predetermined rate decided as per the need, pharmacological aspects, drug profile, physiological conditions of the body etc. In current conditions, not one novel drug delivery system behaves ideally those high goals with fewer side effects. One promising methodology is that the utilization of lipid vesicles as they encourage drug conveyance across skin also as evade the disadvantages of ordinary skin details. Ethosomes are as of now the foremost contemplated lipid vesicles within the nanomedicine field. The significance on the advancement of those vesicles need to be coordinated to deciding the perfect creation, with low harmfulness, biocompatibility and which stays stable for extensive stretches.

Keywords: Liposomes, nanomedicine, ethosomes, Vesicular Drug Delivery System

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Introduction

Vesicles are basically colloidal compositions consisting of aqueous core bounded by amphiphilic molecules during a double-layered pattern, just in case of overindulgence of water these structures may cause to the formation of single layered (unilamellar) or multilayered (multi-lamellar) concentric vesicles. These biological vesicles origin was first reported in 1965 by Bingham [1]. There are different types of pharmaceutical carriers are present.They are particulate type carrier (lipid particles), microspheres, nanoparticles, polymeric micelles and vesicular systems (liposomes, transferosomes, pharmacosomes, ethosomes, niosomes etc) [2]. Vesicular systems might be potential delivery carriers for improving solubility and enhancing therapeutic concentration of drug at the target site [3].Among different vesicular systems, a completely unique vesicular system composed of phospholipids, ethanol and water might be effective in fulfilling the therapeutic requirements of drug [4].

Ethosomes: Ethosomes are soft and versatile multilayer vesicles composed of phospholipid phosphatidylcholine, water, and 20% - 50% ethanol. Ethosomes are non-invasive carriers that enable the component penetrate deeply into the skin layers or enter systemic circulation. High concentrations of ethanol make ethosomes unique. Since ethanol is understood to cause an imbalance within the arrangement of the skin's two-lipid layer, it can penetrate the attractive layer when mixed with a vesicle [5,6].

Ethosomes penetrate faster through the skin layers and possess considerably higher percutaneous flux as compared to classic liposomes [7].Ethosomes can not only improve the solubility of drug which can help attain superior drug loading but the highly deformable character of ethosomes could assist penetration in deeper skin layer surmounting the stratum corneum (SC)

barrier better than the normal liposomes. Ethosomes are reported to enhance the drug entrapment, skin penetration and deposition of varied drugs [8,9]

Curcumin

The herb selected for the study was Curcuma longa (Zingiberaceae), which contains curcumin, demethoxycurcumin, and bisdemetho- xycurcumin, three major pharmacologically important curcuminoids, has been shown to possess antioxidant property and also have wound healing effect [10].Curcumin has well established antioxidant property which supports its use as an antiwrinkle agent. The potential of ethosomes to deliver the antiwrinkle agent (curcumin) into the deeper layers of skin. Curcuma longa extract loaded ethosomes were incorporated into cream. The invivo studies revealed 10 to 50% improvement in skin viscoelasticity, total deformation, biological elasticity and sagginess. It was concluded that curcuma longa extract loaded ethosomal cream represents an efficient vehicle to deliver the antiwrinkle agent to the skin. Curcumin have shown its ability to significantly reduce the appearance of fine lines, wrinkles, and hyperpigmented macules [11,12].

MATERIALS AND METHODS:

Materials:

Curcumin was purchased from Central Drug House Ltd. (Vardhan House, Daryaganj, New Delhi). Soya Lecithin, Propylene glycol was purchased from CDH Fine chemicals, New Delhi. Ethanol was purchased from Changshu Hongsheng Fine Chemicals Co. Ltd.

Preformulation studies:

Preformulation studies are carried out in order to determine the physicochemical properties of drug which helps in the design of a safe, efficacious and stable dosage form. The Curcumin was underwent characterization for its organoleptic properties, such as color and odor, and was then compared with the standard outlined in the official monograph**.** Melting point of Curcumin was determined by using digital melting point apparatus.

Determination of drug solubility:

The solubility of Curcumin was determined in water, methanol, ethanol, pH 6.8 phosphate buffer,acetone, Chloroform. In the known volume (10 ml) of solvent in different volumetric flasks, small increments of drugs were added with shaking until the saturation then drug solution was equilibrated at 32 ± 0.5ºC for 72 hours, solutions were filtered using whatmann filter paper. The absorbance of filtrate was measured at 425 nm for Curcumin, respectively using UV-Visible spectrophotometer [13].

EXPERIMENTAL WORK:

Determination of λ_{max} of Curcumin in Ethanol

A stock solution of curcumin was prepared by dissolving 10 mg of curcumin in 10 ml ethanol to give a stock solution of concentration 1000 µg/ml. From the stock solution, different aliquots were taken in series of 10ml volumetric flasks and volume made up with ethanol to get a series of working standard solutions of concentrations, 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml. The λmax of the drug was determined, and standard curve was plotted between concentration and absorbance [14].

FTIR (Fourier Transform Infrared Spectroscopy)

FT-IR spectrophotometer (Shimadzu FT-IR system) was used to observe possible interaction between drug and excipients [35]. FTIR spectroscopy was performed on the (FT-IR Shimadzu IRAffinity-1) instrument by KBr disc technique. The range of scans was 4000- 400 nm [15].

Preparation of Ethosomes:

Ethosomes were prepared by cold method using Phospholipid (3-5% w/v) were

dissolved in ethanol (10-30% v/v) at room temperature by vigorous stirring with the use of a mixer. Propylene glycol (5-10% v/v) was added during stirring and the temperature was maintained at 30℃ in a water bath. Distilled water (q.s to 100%), was added slowly in a fine stream of the above ethanolic lipid solution with continuous mixing using a magnetic stirrer at 900 rpm. Mixing was continued for another 5 minutes and finally, the vesicular dispersions resulted was left to cool at room temperature (25± 1°C) for 45 minutes [16].

Table 1: Composition of Ethosomes

Formulation Code	Curcumin (mg)	Phospholipid (mg)	Ethanol %	Propylene glycol %	Distilled water
F1	100	300	10	5	q.s
F2	100	300	10	7.5	q.s
F3	100	300	10	10	q.s
F4	100	400	20	5	q.s
F5	100	400	20	7.5	q.s
F6	100	400	20	10	q.s
F7	100	500	30	5	q.s
F8	100	500	30	7.5	q.s
F9	100	500	30	10	q.s

Evaluation of Curcumin Loaded Ethosomes:

Scanning Electron Microscopy(SEM):

Surface morphology of ethosome was observed by Scanning Electron Microscope (SEM). Ethosome was mounted on a glass stub, air-dried and coated with gold using a sputter coater (Carl Zeiss, India) and finally, visualized under a scanning electron microscope at an accelerating voltage of 10 kV from AIIMS, New Delhi [17].

Transmission Electron Microscopy(TEM):

The morphology of ethosomal formulations was assessed by transmission electron microscopy. A drop of nanovesicles' suspensions was placed onto a carbon-coated copper grid and allowed to dry at ambient temperature for 10 minutes. A solution of phosphotungstic acid (1% w/v) was used as a staining agent, placed onto the formulations, and after excess' removal, the samples were analyzed with a transmission electron microscope (Talos), equipped with a digital camera, at an accelerating voltage of 200 kV and proper magnification.

Vesicles size and zeta Potential :

Vesicle size (nm), polydispersity index (PDI) and zeta potential of ethosomal formulations were analyzed by Malvern Zetasizer Nano ZS90 (Malvern Instruments) that works on the Mie theory to determine at given temperature. Then dilution of formulation was done by deionized water and readings were recorded using a scattering angle of 90 at 25℃ using disposable polystyrene cells and disposable plain folded capillary zeta cells, respectively, after appropriate dilution [18].

Polydispersity Index:

PDI was measured using Malvern zeta sizer. PDI values range from 0.000 to 1.000 i.e. monodisperse to very broad particle size distribution. PDI values of all the

formulations indicate that particle size distribution was unimodal. Based on the results shows a least vesicle size, with a good zeta potential and PDI indicating the uniform distribution of the vesicles throughout formulation leading to maximum stability.

Entrapment Efficiency (EE):

Centrifugation method was used to determine the entrapment efficiency of drug. Drug loaded ethosomes were kept overnight at 4°C before centrifugation. Then they were subjected to centrifugation at 12000 rpm for 30 mins using centrifuge (Remi CM-8 Plus instrument). The supernatant liquid was collected and analysed for free Curcumin by UV-Visible spectrophotometer (UV-1800 series, Shimadzu) at 425 nm [19].

In vitro Drug Release Study:

Samples of ethosomes were put into dialysis bags, sealed, and submerged in a dissolution medium. The USP Dissolve Test Apparatus, Type II, was used to conduct a 2 hr drug release study at 37±0.5°C and 100 rpm. 5 mL of sample were taken at each interval and replaced with brand-new buffers. Following suitable dilutions, spectrophotometric evaluation was performed on the samples [20].

Result anf Discussion:

Development of Calibration Curve:

Curcumin was dissolved in little amount of ethanol and diluted with ethanol and scanned in a UVspectrophotometer have shown the maximum absorbance wavelength at 425 nm . It was concluded that the perfect linearity between the concentration and absorbance was observed when the concentration range was from 2 to 10 µg/ml. Regression coefficient (r^2) was thus found to be 0.999 .

Table 2: UV Spectra of Curcumin in ethanol (λmax = 425nm)

Concentration (µg/ml)	Absorbance
0	0
2	0.145
4	0.267
6	0.398
8	0.529
10	0.649

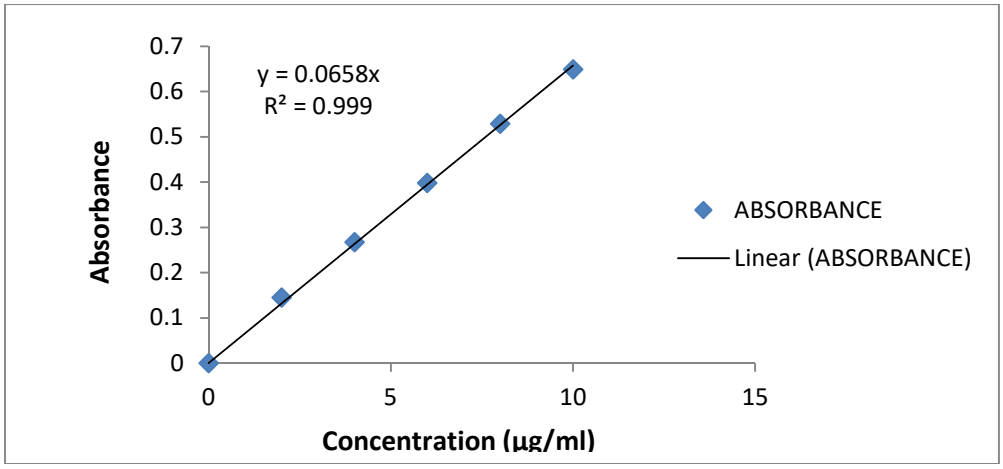

Figure 1: Calibration curve of Curcumin in ethanol (λmax = 425nm)

FTIR (Fourier Transform Infrared Spectroscopy): FT-IR spectrophotometer (Shimadzu FT-IR system) was used to observe possible interaction between drug and excipients. The result wasfound to be-

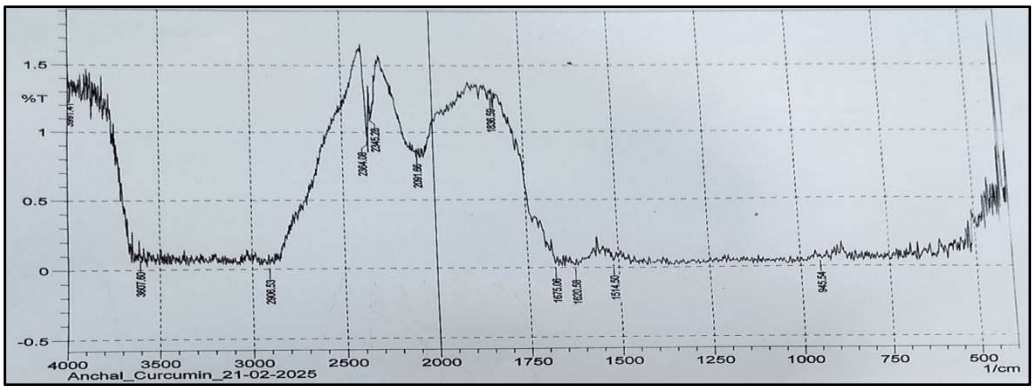

Figure 2 :FTIR Spectra of Curcumin

Table 3: FTIR Spectral Peaks of Curcumin

S.No.	Functional group	Observed peak (cm^{-1})	Standard Range (cm^{-1})	Inference
1	O-H Stretching	3607.6 cm^{-1}	3200-3600 cm^{-1}	Phenolic –OH
2	C=O Stretching	1620.5 cm^{-1}	1610-1630 cm^{-1}	Overlapping C=C and C=O
3	C=C Stretching	1514.5 cm^{-1}	1510-1520 cm^{-1}	Aromatic C=C bonds

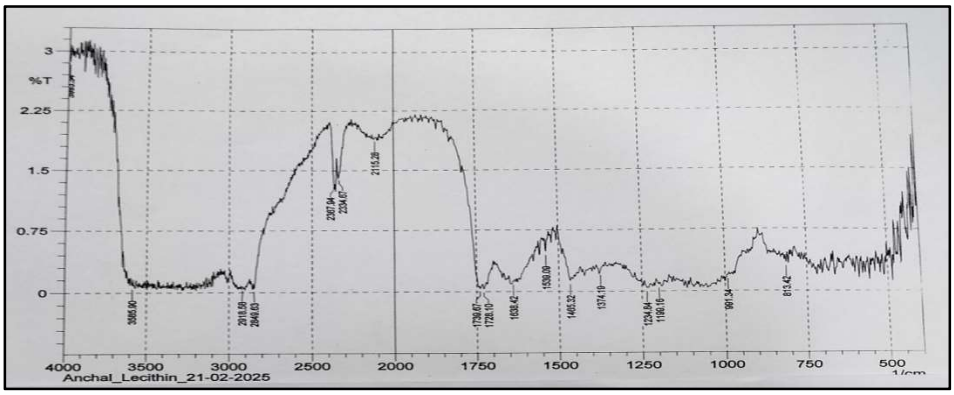

Figure 3 :FTIR Spectra of Lecithin

Table 4: FTIR Spectral peaks of Lecithin

S.No.	Functional group	Observed peak (cm^{-1})	Standard Range (cm^{-1})	Inference
1	O-H Stretching	3485.9 cm^{-1}	3300-3500 cm^{-1}	hydroxyl groups
2	CH_2 Stretching	2918.5 cm^{-1}	2921-2928 cm^{-1}	Asymmetric CH_2
3	CH_2 Stretching	2849.6 cm^{-1}	2850-2855 cm^{-1}	Symmetric CH_2
4	C=O stretching	1739.6 cm^{-1}	1736-1740 cm^{-1}	carbonyl groups in esters
5	CH_2 Bending	1465.3 cm^{-1}	1462 cm^{-1}	CH_2 Scissoring
6	C-O stretching	1374.1 cm^{-1}	1376 cm^{-1}	C-O stretching
7	P=O stretching	1234.8 cm^{-1}	1230-1240 cm^{-1}	phosphate group
8	P-O-C stretching	991.3 cm^{-1}	985-1050 cm^{-1}	P-O-C stretching

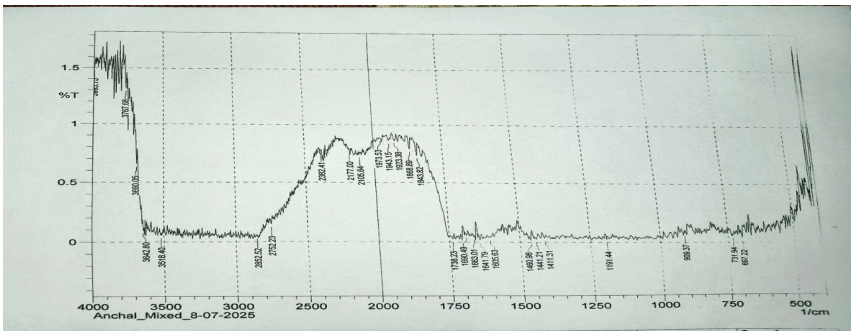

Figure 4 :FTIR Spectra of Physical Mixture

Table 5: FTIR Spectral peaks of Physical Mixture

S.No.	Functional group	Observed peak (cm^{-1})	Standard Range (cm^{-1})	Inference
1	O-H Stretching	3607.6 cm^{-1}	3200-3600 cm^{-1}	Phenolic –OH
2	C=O Stretching	1620.5 cm^{-1}	1610-1630 cm^{-1}	Overlapping C=C and C=O
3	C=C Stretching	1514.5 cm^{-1}	1510-1520 cm^{-1}	Aromatic C=C bonds
4	O-H Stretching	3485.9 cm^{-1}	3300-3500 cm^{-1}	hydroxyl groups
5	CH_2 Stretching	2918.5 cm^{-1}	2921-2928 cm^{-1}	Asymmetric CH_2
6	CH_2 Stretching	2849.6 cm^{-1}	2850-2855 cm^{-1}	Symmetric CH_2
7	C=O stretching	1739.6 cm^{-1}	1736-1740 cm^{-1}	carbonyl groups in esters
8	CH_2 Bending	1465.3 cm^{-1}	1462 cm^{-1}	CH_2 Scissoring
9	C-O stretching	1374.1 cm^{-1}	1376 cm^{-1}	C-O stretching
10	P=O stretching	1234.8 cm^{-1}	1230-1240 cm^{-1}	phosphate group
11	P-O-C stretching	991.3 cm^{-1}	985-1050 cm^{-1}	P-O-C stretching

Scanning Electron Microscopy:

Ethosome obtained were spherical shaped, which could have an impact on drug-release. According to SEM images, Size of SEM of ethosomes blank,F7 and optimized ethosomal cream was found to be 206.2,86.33 and 62.93 nm respectively are illustrated in Fig.5 a,b,c. An increase in ethanol concentration (from 36% to 40% ethanol) generally decreases the vesicle size of ethosome. The smooth surface of vesicles was confirmed by SEM.

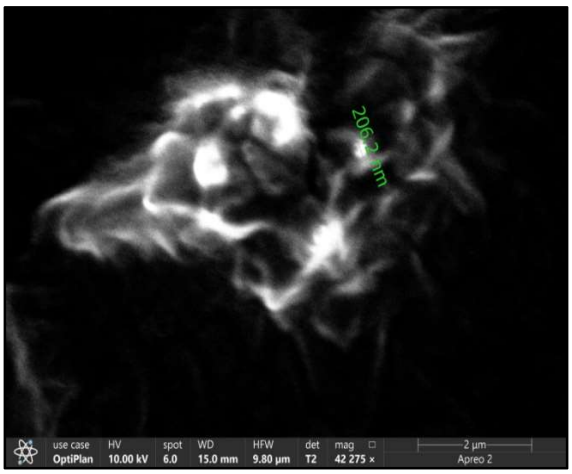

Figure 5 (a) : SEM of ethosomes of Blank

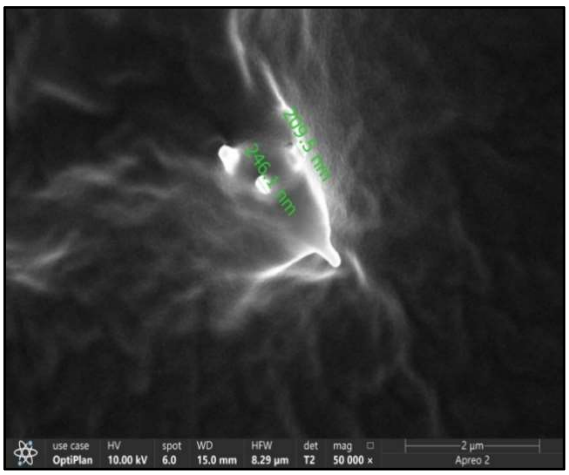

Figure 5 (b) : SEM of ethosomes of F7

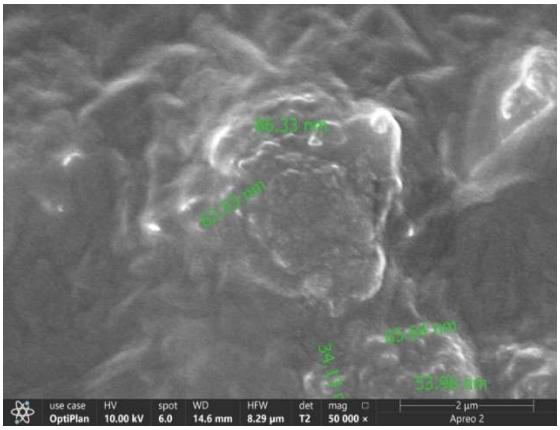

Figure 5 (c) : SEM of optimized Ethosomal cream

TEM: The morphology of ethosomal formulations was assessed by transmission electron microscopy. The resilts was found to be shown in figure 6 (a) and (b).

The TEM images confirmed that the developed ethosomes were discrete and spherical in shape .The representative TEM micrographs of the elaborated nanocarriers (blank and curcumin-loaded) are illustrated in Fig. 9,10. As evident from the TEM images, both vesicles exhibit spherical shapes with well-preserved membranes. The obtained sizes on the micrographs are smaller compared to the data from DLS analysis, which may be related to the differences in sample preparation: in TEM analysis, the samples are dehydrated, which determines the shrink age of their dimensions, while in DLS they are in a hydrated state, which contributed towards larger sizes [21].

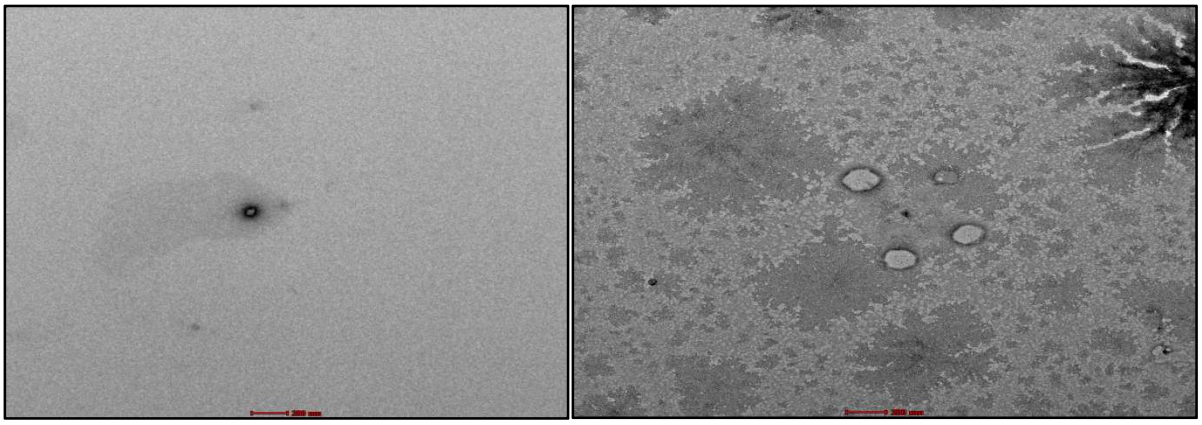

Figure 6(a):TEM of ethosomes of Blank and 6(b): TEM of optimized Ethosomal Cream

Particle Size and PDI:

Dynamic Light Scattering technique was used to measure the particle size and polydispersity index (PDI).The mean particle size of all formulations was ranged from 46.01 nm to 97.77 nm and PDI value was ranged between 0.376 to 0.994.Above all formulation, F7 exhibited the mean particle size of 68.69 nm and a PDI of 0.376.

Vesicle size play an important role in topical drug delivery systems as small size vesicles delivers their contents more efficiently across deeper layers of skin. The stability of dispersion can be assured on the basis of PDI result

Figure 7: Particle Size Distribution of Optimized Ethosomal Cream

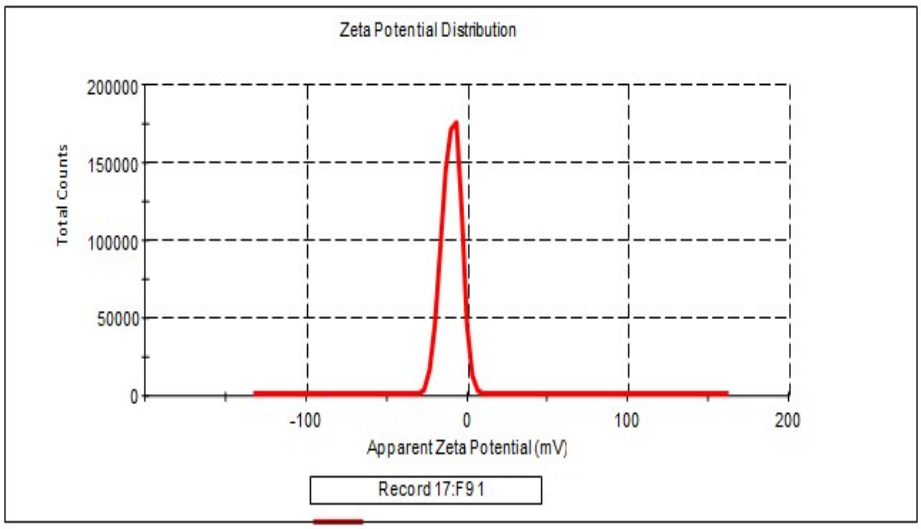

Figure 8: Zeta Potential of optimized Ethosomal cream

Zeta potential:

The Zeta potential of different ethosomal formulations from F1 to F9 showed value ranging from -10.3 mV to -36.1 mV.F7 showed the maximum (-36.1 mV) Zeta potential range .Increased anionic charge in formulation means resisted agglomeration. As the Zeta potential increases the charged particles repel one another and they become more stable against aggregation.

Table 3 : Vesicle Size, Zeta Potential, PDI, Entrapment Efficiency of Various Batches

Formulations	Vesicle size (nm)	Zeta Potential (-mV)	Poly dispersity Index (PDI)	Entrapment Efficiency
F1	46.01	-24	0.994	46.2
F2	63.82	-27.3	0.811	55.7
F3	71.70	-20.2	1.000	61.4
F4	64.21	-30.1	0.523	67.2
F5	97.77	-35.3	0.679	69.5
F6	85.04	-18.3	0.913	71.2
F7	68.69	-36.1	0.376	75.5
F8	81.68	-12.1	0.484	80.2
F9	83.87	-10.3	0.428	87.09

***In-vitro* Drug Release of Ethosomes**

F1 shows minimum In vitro Drug Release 5.20 and F8,F9 shows maximum In vitro Drug Release 85.6,89.5 respectively. As the concentration of Ethanol increases, In vitro Drug Release also increases. The In vitro release study suggested that the penetration enhancing effect might be of greater importance to enhance skin delivery of Curcumin by ethosomal vesicles under non occlusive condition, than intact vesicle permeation into the stratum corneum.

Table 4 : Invitro Drug Release of Ethosomes

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9

5	5.20	5.70	5.9	6.10	7.2	9.3	11.7	13.4	15.8
10	9.8	10.2	11.5	12.5	16.8	19.4	24.6	27.2	29.2
15	19.5	20.5	28.2	24.5	26.4	30.2	34.5	37.1	40.2
30	25.6	26.6	29.5	30.1	33.2	36.2	39.2	44.7	49.2
60	32.5	34.6	36.2	37.5	39.7	44.2	50.5	53.2	57.7
120	40.1	44.5	47.2	49.5	53.5	57.2	62.4	67.2	70.5
240	52.6	55.5	56.5	58.5	62.4	67.5	70.2	74.2	75.2
360	59.2	63.5	64.4	66.2	71.5	74.2	75.4	78.5	79.2
480	64.5	68.12	69.4	74.2	76.1	78.2	79.3	85.6	89.5

CONCLUSION:

The preformulation study provides a profile of drug and other excipients added to the formulation development, confirming their adherence to standard specifications. Consequently, these ingredients were utilized for the subsequent development of both cream base and ethosomes. The Curcumin loaded ethosomes was prepared using cold method. Different concentration of phosphatidylcholine as lipid, ethanol as penetration enhancer and solvent were selected on the basis of literature survey. Ethosomal formulations were evaluated for Uv, Fourier Transform Infrared Microscopy, Scanning electron microscopy, Transmission electron microscopy, Entrapment efficiency, Invitro Drug Release Study, pH, Viscosity. The optimized formulation on the basis of morphology, entrapment efficiency was further evaluated for particle size and zeta potential. On the basis of entrapment efficiency (%), SEM, TEM analysis in ethosomal suspension formulation F7,F8,F9 was selected for further investigation of particle size distribution and zeta potential. The formulation F7,F8,F9 was further selected for loading in the optimized cream base to obtain a topical cream containing ethosomes of Curcumin. Delivery of drug by ethosomes was significantly influenced by variations in lipid and ethanol concentrations in formulations.Thus, the overall study concluded that this ethosomal approach offers a new delivery system for targeted delivery for Curcumin.

The present study conclusively supported that ethosomal cream containing Curcumin to be an advantageous topical drug delivery system in treatment of inflammation of skin. However detail in- vivo study should be conducted in future to justify the in- vitro study.

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