

DEVELOPMENT OF TRANSFEROSONAL AND NIOSOMAL GEL OF CURCUMIN AND COMPARING THE ANTI-FUNGAL ACTIVITY OF NOVEL GELS WITH PURE DRUG

DETAILS OF THE MANUSCRIPT

DEVELOPMENT OF TRANSFEROSONAL AND NIOSOMAL GEL OF CURCUMIN AND COMPARING THE ANTI-FUNGAL ACTIVITY OF NOVEL GELS WITH PURE DRUG

A.Krishna sailaja¹ and Lakkavakula Sravanthi²

¹Professor, Department of Pharmaceutics, RBVRR Womens College of Pharmacy, Osmania University, Hyderabad, Telangana, India-500088.

²M-pharmacy student, Department of Pharmaceutics, RBVRR Women's College of Pharmacy, Osmania University, Hyderabad, Telangana, India-500088.

Corresponding author

Dr.A.Krishna sailaja, Head, Department of Pharmaceutics, RBVRR Women's college of pharmacy, Osmania University, Hyderabad
ORCID ID :- 0000-0002-1749-8998

ABSTRACT:

Aim:-The main aim of study was to prepare curcumin loaded transferosomal and niosomal gels and to determine the anti-fungal activity of prepared formulations.

Methodology:- Curcumin loaded transferosomes was prepared by using modified hand shaking method. Ten formulations were prepared by varying surfactant to lipid ratio (T1 to T5) and lipid to surfactant ratio (T6 to T10). Curcumin loaded niosomes was prepared by using thin film hydration technique. Nine formulations were prepared with different surfactants of varied ratios.

Results:-

Among all T6 formulation containing 100mg of lipid and 50mg of surfactant was considered as best formulation because of its particle size 441.0 nm, zeta potential of -36.9 mV, highest drug content of 95.4%, entrapment efficiency of 94.20% and in-vitro drug release of 95.19% in a

time period of 12hrs. Among all N5 formulation containing 1:1 ratio of cholesterol(100mg) to surfactant (100mg) was considered as best formulation because of its particle size of 412nm, zeta potential of -51.5mV, highest drug content of 96.80%, entrapment efficiency of 96.08% and in-vitro drug release of 97.78% in a time period of 12hrs. Among all the formulations, the best transferosomal (T6) and niosomal (N5) formulations was incorporated into gel and comparative studies was made with plain gel. Among the three gels (PG, T6G, N5G) niosomal gel (N5G) was exhibiting highest drug content of 88.19%, pH of 6.8, viscosity of 8796cP, spreadability 13.62 g cm/sec, in-vitro drug release of 91.54 and ex-vivo drug release of 95.05 in a time period of 12hrs with release rate of $31.45\text{microgram}/\text{cm}^2/\text{hr}^{-1/2}$, flux of $0.3865\mu\text{g}/\text{cm}^2/\text{hr}$. and permeation coefficient of $43.92\text{ cm}/\text{hr}$.

Conclusions:- Anti-fungal activity of pure drug, transferosomal & niosomal formulation was tested against *Candida auris*, *Aspergillus niger* and *Rhizopus sp*. The niosomal formulation was found to be more effective against *Aspergillus niger* and the transferosomal formulation was found to be more effective against *Candida auris* and *Aspergillus niger*.

Keywords: Curcumin, Transferosomes, Niosomes, Soya lecithin, Cholesterol, Span 60.

INTRODUCTION

Vesicles have emerged as the preferred vehicle for drug delivery in the vesicular drug delivery system. Liposomes, ethosomes, niosomes, transferosomes, pharmacosomes, and so on are examples[1,2].

TRANSFEROSOMES

Transferosomes are a special type of liposomes that contains phospholipid and an edge activator. These are a type of elastic or deformable vesicles. Because of their self-optimized and ultra-flexible membrane properties, they can deliver the drug reliably into or through the skin, depending on the mode of administration or application with high efficiency. Transferosomes

overcome the difficulty of skin penetration by squeezing themselves along stratum corneum's intracellular sealing lipid[3,4].

NIOSOMES

Niosomes are non-ionic surfactant-based vesicles that were developed as an alternative controlled drug delivery system to liposomes in order to overcome sterilization, large-scale production, and stability issues[5,6].

MATERIALS AND METHODS

Materials used for the preparation of transferosomes: Curcumin (drug), soya lecithin (phospholipid), Span60 (surfactant) and suitable solvents (ethanol, chloroform), phosphate buffer pH 7.4.

Method employed for the preparation of transferosomes: *Modified hand shaking method-* Drug, phospholipid, surfactant was dissolved in ethanol: chloroform and it is kept for rotary evaporator to form a thin film at 64°C then Saline phosphate buffer pH 7.4 is added with gentle shaking for 15 minutes, formation of transferosomes takes place[7,8].

Materials used for the preparation of niosomes: Curcumin (drug), cholesterol, non-ionic surfactant (span20, span60, span80), suitable solvents (ethanol, chloroform), phosphate buffer pH 7.4[9,10]

Method employed for the preparation of niosomes: *Thin film hydration technique-* Cholesterol and non-ionic surfactant are dissolved in Ethanol: Chloroform and it is kept for rotary evaporator to form a thin film at 64°C then drug is dissolved in Saline phosphate buffer pH 7.4 is added then kept for stirring for 1 hour, formation of Niosomes takes place[11,12].

PREPARATION OF TRANSFEROSOMAL GEL AND NIOSOMAL GEL

Required amount of Carbopol and guar gum dissolved separately in 10 ml of distilled water, soaked for 24hours. After 24 hours guar gum solution was added to Carbopol solution and subjected to mechanical stirring at 600rpm. The gel was neutralized by adding triethanolamine.

Then, the appropriate amount of propylene glycol, which acts as a penetration enhancer, was added to the gel, followed by the addition of curcumin-loaded transferosomes / niosomes. Finally, methyl paraben and propyl paraben was added to the gel and stirred continuously until the gel gets completely dispersed.

EVALUATION AND CHARACTERIZATION OF CURCUMIN LOADED TRANSFEROSOMES AND NIOSOMES:

Surface Morphology: Scanning electron microscopy was used to examine the surface morphology. One drop of transferosomal formulation/niosomal formulation was placed on a transparent glass slide and vesicles can be observed under projection microscope [13,14].

Mean vesicular diameter: The prepared transferosomes/niosomes was sonicated for 30 minutes after being dispersed in deionized water. The resulting dispersion was diluted and particle size was analysed using lite sizer 500[15, 16].

Zeta potential: Zeta potential can be analysed using lite sizer 500. One drop of transferosomal/niosomal formulation is diluted with doubled distilled water and measured for corresponding zeta potential[17,18].

Drug content: 1ml of transferosomal/niosomal suspension was taken in 10ml volumetric flask and makeup to with methanol to cause the vesicle to rupture and suitable dilutions were made then analyse under UV-visible spectrophotometer[19].

Entrapment efficiency: Entrapment efficiency can be performed by using ultracentrifugation apparatus. The amount of drug present in the clear supernatant after ultracentrifugation at 17640 rpm for 40 minutes was determined (w) by UV-Spectrophotometry to determine drug entrapment. The amount of drug in the supernatant was then deducted from the total amount of drug added during preparation (W). (W-w) effectively gives the amount of drug entrapped in the pellet [20].

$$(W - w)$$

$$\% \text{ entrapped} = \frac{\text{-----}}{W} \times 100$$

$$W$$

Invitro drug diffusion studies: Franz diffusion cell was used for determining drug diffusion studies. A known amount of transferosomal/niosomal suspension was pipette out and transferred to the donor compartment. The stirring speed was set to 400-700 rpm respectively. To maintain the sink conditions, aliquots of 1 ml of sample were withdrawn at predetermined time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 7, 8, 10, 11 hours and same volume of buffer was replaced. The samples were then examined using UV spectrophotometer set at 430nm [21].

EVALUATION AND CHARACTERIZATION OF CURCUMIN LOADED TRANSFEROSOMAL GEL AND NIOSOMAL GEL

Measurement of pH: The pH of various gel formulations was determined using a digital pH metre. The pH of each formulation was measured in triplicate, and the average value was calculated [22].

Viscosity: The measurement of viscosity of the prepared gel was done using Brookfield viscometer. The gels were rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading was noted. The viscosity of the gel was obtained by multiplication of the dial readings with factor given in the Brookfield viscometer catalogues.

Spreadability: It indicates that the area over which the gel spreads easily when applied to the skin or affected part. The therapeutic potency of the formulation is also determined by its spreadability. Spreadability is measured in terms of the time it takes two slides to slip off from gel placed in between the slides under a specific load. The less time it takes to separate two slides, the better the spreadability. $S = M \cdot L / T$

Where, S = Spreadability, W = Weight tide to upper slide, L = Length moved on the glass slide, T = Time taken to separate the slide completely from each other [23].

Drug content: 0.1g of prepared gel was mixed with 10ml of appropriate solvents (methanol). After filtering the stock solution and measuring absorbance at 430nm with appropriate dilutions, the percent drug content was calculated.

Invitro drug diffusion studies: The Franz diffusion cell is used in drug diffusion studies. A predetermined amount of transferosomal/niosomal suspension was pipetted out and transferred to the donor compartment. The stirring speed was varied between 400 and 700 rpm. To maintain the sink conditions, aliquots of 1 ml of sample were withdrawn at predetermined time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 7, 8, 10, 11 hours and replaced with the same volume of buffer. After that, the samples were analyzed under UV spectrophotometer set to 430nm [24].

RESULTS

EVALUATION AND CHARACTERIZATION OF CURCUMIN LOADED TRANSFEROSOMES

Surface Morphology: The prepared transferosomes was found to be spherical in shape

The prepared curcumin loaded transferosomes were found in small uni lamellar and large multilamellar vesicles.

Mean vesicle diameter: The mean vesicle size for transferosomes was recorded using lite sizer 500. The vesicle size ranged between 441.0-1821.3nm. It was found to be minimum for T6 (Fig 1)

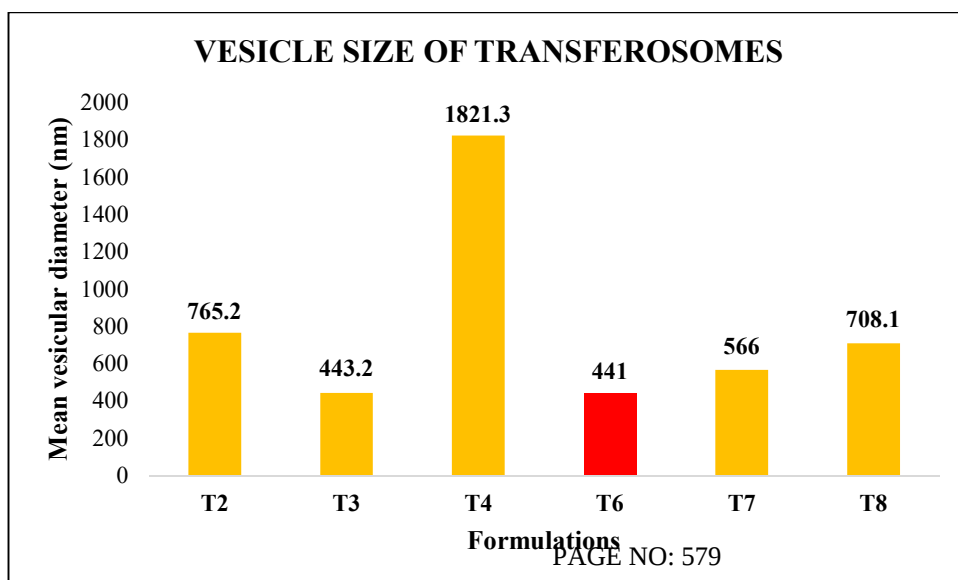


Fig 1: Comparison of vesicular diameter of six formulations for transferosomes

Among all the formulations T6 was exhibiting lesser particle size of 441nm.

Zeta potential: The zeta potential for transferosomes was measured using lite sizer 500. The zeta potential of T2, T3, T4, T6, T7, T8 formulations were found to be -35.6mV, -18mV, -25mV, -36.9mV, -21.9mV, -23.1mV (Fig 2).

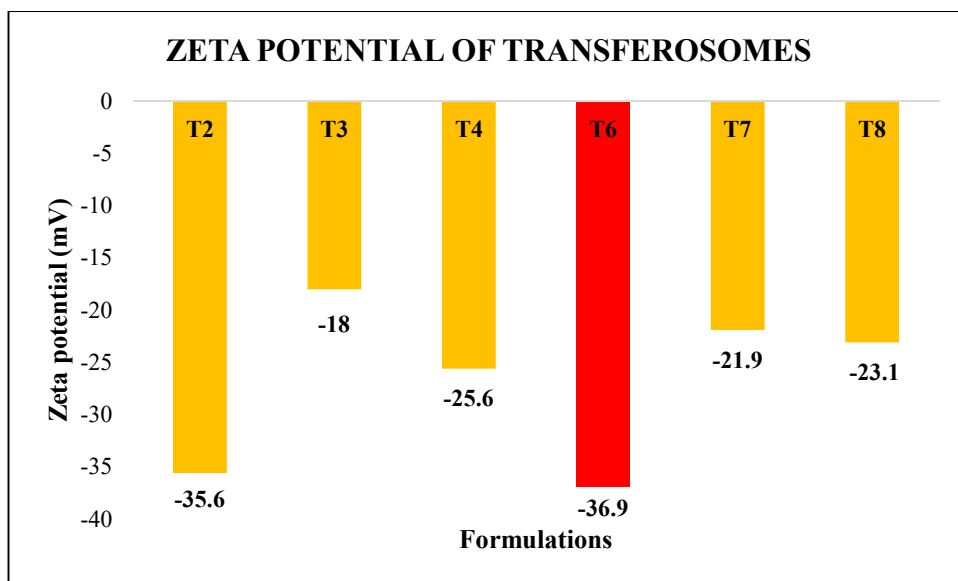


Fig 2: Zeta potential of six formulations for transferosomes

All the formulations were found to be stable. Among all T6 was showing highest stability i.e, -36.9mV.

Drug Content: The drug content of all ten formulations was evaluated and it varied between 70.00% to 95.40%.

The order for transferosomes: T6>T3>T8>T2>T4>T7>T1>T5>T10>T9

Among all the formulations T6 containing 1:0.5 ratio of phospholipid to surfactant was showing highest drug content of 95.40%

Entrapment efficiency: Out of ten formulations, two formulations were evaluated for entrapment efficiency using ultracentrifuge (Eltek model).

Entrapment efficiency of T2 and T6 was found to be 68.80% and 94.20% respectively. Out of two formulations the T6 formulation having 1:0.5 ratio of phospholipid: surfactant was considered to be best formulation because of its highest entrapment efficiency of 94.20%

Invitro drug diffusion studies: All transferosomal formulations were evaluated for in-vitro drug diffusion studies for a time period of 12hr. The drug release of all the formulations T1, T2,

T3, T4, T5, T6, T7, T8, T9, T10 was found to be 73.92%, 92.27%, 93.10%, 83.97%, 71.80%, 95.19%, 84.37%, 90.22%, 75.48%, 73.45% respectively (Refer figure 3).

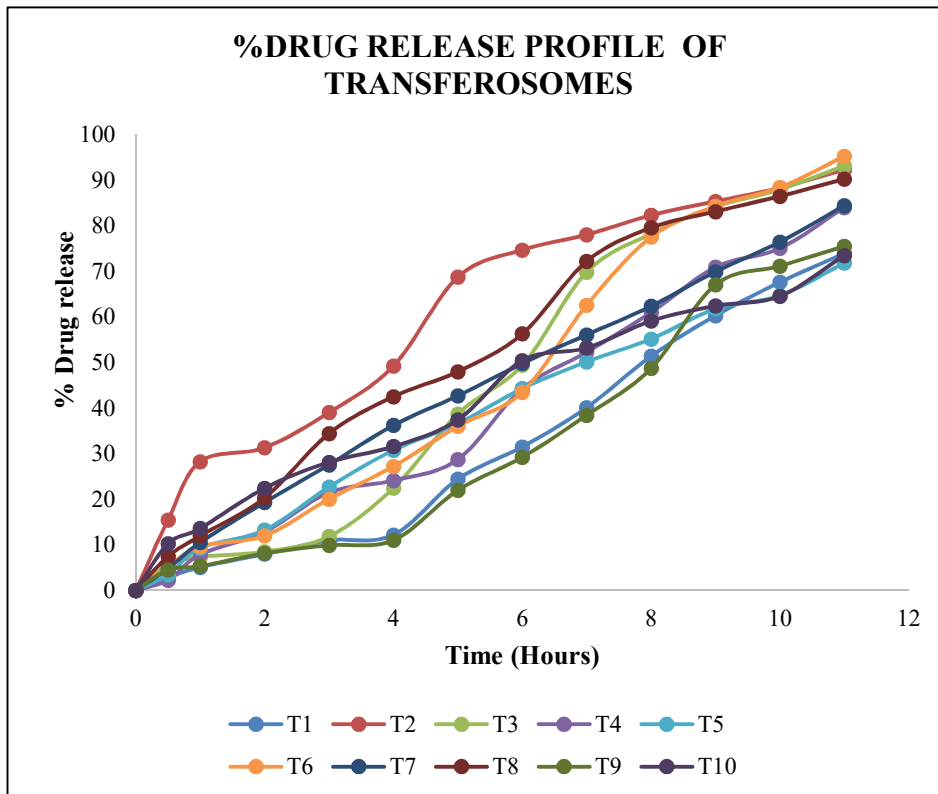


Fig 3: In-vitro drug release profile of all 10 formulations for transferosomes.

Among all T6 was showing highest drug release bearing the value of 95.19%.

Kinetics of drug release: Different plots (zero order, first order, Higuchi and Korsmeyer peppas plots) were drawn for the optimized formulation, in order to know kinetics of the drug. Based on the results, T6 was determined that the drug release followed zero order kinetics and with fickian diffusion mechanism as shown in table 1.

Table 1: Kinetic data of T6 formulation

Formulation	Zero order (R ²)	First order (R ²)	Higuchi plot (R ²)	Peppas plot (R ²)	Peppas plot(n)
T6	0.9906	0.8746	0.9172	0.9676	0.9896

EVALUATION AND CHARACTERIZATION OF CURCUMIN LOADED NIOSOMES

Surface Morphology: The prepared curcumin loaded niosomes was found to be spherical in shape.

The prepared curcumin niosomes were found in small and large uni lamellar vesicles.

Mean vesicle diameter: The mean vesicle size for niosomes were recorded using lite sizer 500. The vesicle size was ranged between 412-758.4nm (Fig 4)

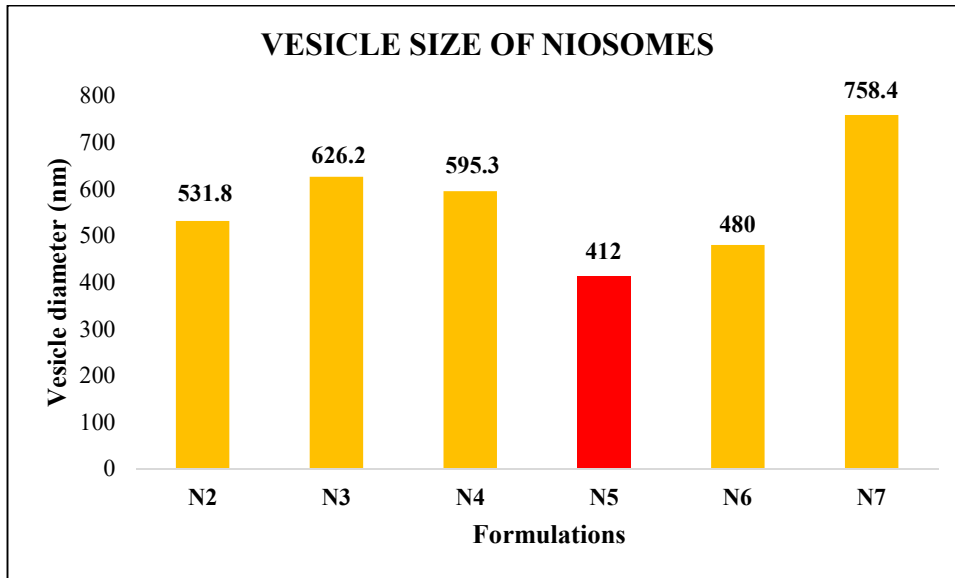


Fig 4: Mean vesicle diameter of six formulations for niosomes

Among all the formulations N5 was exhibiting lesser particle size of 412nm.

Zeta potential: The zeta potential for niosomes was measured using lite sizer 500. The zeta potential of N2, N3, N4, N5, N6, N7 formulations was found to be -50.8mV, -28mV, -10.6mV, -51.5mV, -37.9mV, -42.8mV (Fig 5).

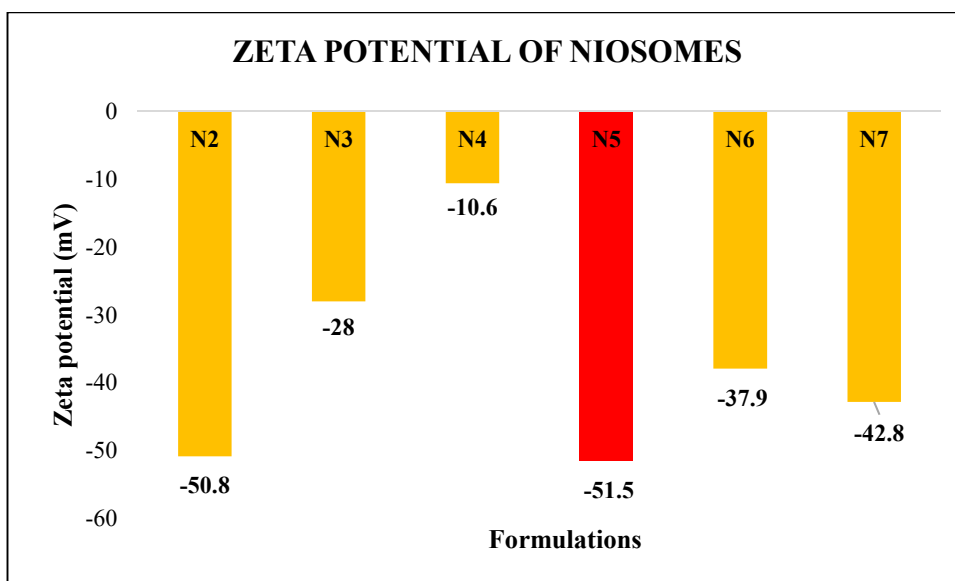


Fig 5: Zeta potential of six formulations for Niosomes.

Among all the formulations N5 was highly stable i.e., -51.5mV.

Drug Content: The drug content of all nine niosomal formulations was evaluated and it varied

between 76.86% to 96.80%

Among all N5 formulation having 1:1 ratio of cholesterol: surfactant (Span 60) was superior with highest drug content of 96.80%.

Entrapment efficiency: The optimized formulations were evaluated for entrapment efficiency using ultracentrifuge (Eltek model).

Entrapment efficiency of N2, N5 and N7 was found to be 91.70%, 96.08% and 88.78% respectively. Out of three formulations the N5 formulation having 1:1 ratio of cholesterol: surfactant (Span 60) was considered to be best formulation because of its highest entrapment efficiency of 96.08%.

Invitro drug diffusion studies: All the niosomal formulations were evaluated for invitro drug diffusion studies for a time period of 12hr. The drug release of all the formulations N1, N2, N3, N4, N5, N6, N7, N8, N9 was found to be 71.27%, 82.63%, 74.78%, 94.21%, 97.78%, 87.94%, 79.53%, 72.73%, 66.45% respectively. (Refer figure 6)

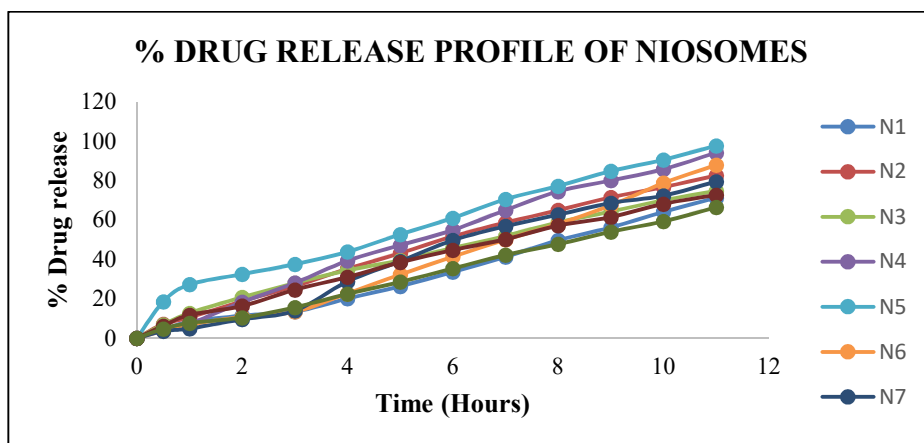


Fig 6: Invitro drug release profile of all nine formulations for niosomes

Among all N5 formulation having 1:1 ratio of cholesterol: surfactant (Span 60) was showing highest drug release of 97.78%.

Kinetics of drug release: Different plots (Zero order, first order, Higuchi and Korsmeyer peppas plots) were drawn for the optimized formulation N5, in order to know the release kinetics of the drug as shown in table 2.

Table 2: Kinetic data of N5 formulation

Formulation	Zero order (R ²)	First order (R ²)	Higuchi plot (R ²)	Peppas plot (R ²)	Peppas plot (n)
N5	0.9808	0.8224	0.9629	0.9671	0.5363

Based on the results, N5 was determined that the drug release followed zero order kinetics and with fickian diffusion mechanism.

ANTI FUNGAL ACTIVITY

Anti-fungal activity of pure drug, transferosomal & niosomal formulation against *Candida auris*, *Aspergillus niger* and *Rhizopus sp.* was tested. The results were shown in table 3

Table 3: Anti-fungal activity of Pure drug (Curcumin) and Curcumin loaded Transferosomes and niosomes.

Samples	<i>Candida auris</i>	<i>Aspergillus niger</i>	<i>Rhizopus sp.</i>
Standard (Clotrimazole)	25.83mm	17.25mm	8mm
Pure drug (Curcumin)	12.2mm	1mm	0
Transferosomal formulation	18.6mm	11mm	0
Niosomal formulation	0	8mm	0

The pure drug was found to be effective against *Candida auris* and *Aspergillus niger* with a zone of inhibition of 12.2mm and 1mm respectively.

The prepared niosomal formulation was found to be more effective against *Aspergillus niger* with a zone of inhibition of 8mm. On comparison, niosomal formulation was more effective than pure drug against *Aspergillus niger*.

The prepared transferosomal formulation was found to be more effective against *Candida auris* and *Aspergillus niger* with a zone of inhibition of 18.6mm and 11 mm respectively. On comparison, transferosomal formulation was more effective than pure drug against *Candida auris* and *Aspergillus niger*.

EVALUATION OF PLAIN GEL, TRANSFEROSOMAL GEL AND NIOSOMAL GEL

Measurement of pH: The formulated plain gel (PG), Transferosomal gel (T6G) and Niosomal gel (N5G) were determined for pH.

The pH of PG, T6G and N5G was found to be 6.5, 6.6 and 6.8 respectively.

Viscosity: The measurement of the viscosity of the prepared gels was done with Brookfield viscometer using spindle type-63. The gels were rotated at 30 rpm and the corresponding dial reading was noted^{25,26}.

Viscosity of PG, T6G & N5G formulations was found to be 2060cP, 3096cP & 8796cP respectively.

Spreadability: The formulated plain gel (PG), Transfersomal gel (T6G) and Niosomal gel (N5G) were evaluated for spreadability.

Spreadability of PG, T6G & N5G formulations was found to be 9.75 g cm/sec, 10.04g cm/sec & 13.62g cm/sec. N5G was exhibiting highest spreadability of 13.62 g cm/sec.

Drug content: PG, T6G and N5G formulations were evaluated for drug content.

The drug content of PG, T6G and N5G was found to be 81.20%, 85.06%, 88.19% respectively. N5G was showing highest drug content of 88.19%

In-vitro diffusion studies: PG, T6G and N5G formulations were evaluated for In-vitro drug diffusion studies. (Refer figure7)

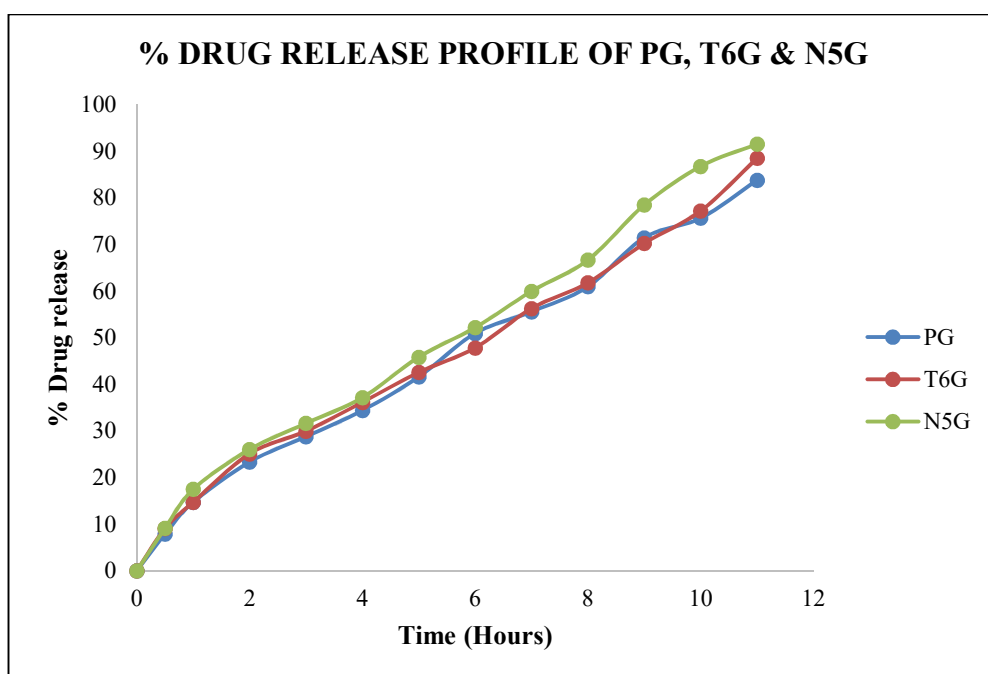


Fig 7: Comparison of invitro drug release of PG, T6G and N5G formulations

The invitro drug release of PG, T6G and N5G formulations were found to be 83.79%, 88.50% and 91.54% respectively. N5G formulation was showing better release.

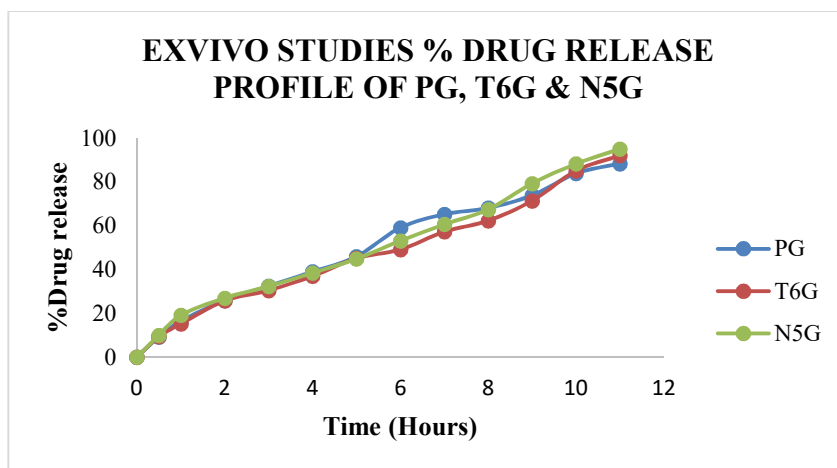
Kinetics of drug release for N5G formulation: Invitro drug release data of niosomal gel formulation (N5G) was fitted into zero order, first order, Higuchi and korsmeyer peppas plotsto know the drug release order and mechanism of drug release. The result was shown in table 4.

Table 4: In-vitro kinetic release data of N5G formulation

Formulation	Zero order (R ²)	First order (R ²)	Higuchi plot (R ²)	Peppas plot (R ²)	Peppas plot (n)
N5G	0.9937	0.8931	0.9630	0.9889	0.7196

According to the kinetic plots N5G formulation was following zero order kinetics with non-fickian diffusion mechanism.

Ex-vivo studies: Ex-vivo studies were performed for the formulated plain gel (PG), Transfersomal gel (T6G) and Niosomal gel (N5G). (Refer figure 8)

**Fig 8:** Comparison of ex-vivo drug release of PG, T6G and N5G formulations

The ex-vivo % drug release of PG, T6G and N5G formulations were found to be 88.32%, 92.11% and 95.05% respectively. N5G formulation was showing better drug release in a time period of 12 hrs.

Kinetics of drug release for N5G formulation: Ex-vivo drug release data of niosomal gel formulation (N5G) was fitted into zero order, first order, Higuchi and peppas plots to know the drug release order and mechanism of drug release. (Refer table 5)

Table 5: Ex-vivo kinetic release data of N5G formulations

Formulation	Zero order (R ²)	First order (R ²)	Higuchi plot (R ²)	Peppas plot (R ²)	Peppas plot (n)
N5G	0.9929	0.8383	0.9547	0.9848	0.6905

According to the kinetic plots N5G formulation was following zero order kinetics with non-fickian diffusion mechanism.

Release rate: Slope of the Higuchi plot gives the release rate. It is expressed in $\text{microgram}/\text{cm}^2/\text{hr}^{-1/2}$. The transferosomal and niosomal gel was showing the release rate of $30.176 \text{ microgram}/\text{cm}^2/\text{hr}^{-1/2}$ & $31.45 \text{ microgram}/\text{cm}^2/\text{hr}^{-1/2}$

Flux (J): A plot of time vs. cumulative percentage drug release/area will give the slope. The slope is called as flux and it is expressed in $\text{microgram}/\text{cm}^2/\text{hr}$.

The transferosomal and niosomal gel was showing the flux of $0.3522 \text{ } \mu\text{g}/\text{cm}^2/\text{hr}$ & $0.3865 \text{ } \mu\text{g}/\text{cm}^2/\text{hr}$.

Permeation coefficient: Flux/donor compartment will give the permeability coefficient. The permeability coefficient of the transferosomal and niosomal gel was obtained as $41.43 \text{ cm}/\text{hr}$ & $43.92 \text{ cm}/\text{hr}$.

DISCUSSION

Curcumin having several potential pharmacological effects mainly includes anti- inflammatory, antibacterial, antioxidant and anticancer activities. But main problem with curcumin is its poor oral bioavailability (3%). So, in order to increase its bioavailability, there is a need to develop vesicular system i.e., transferosomes and niosomes. These nanocarriers has the ability to reach the deeper layers of skin. Curcumin loaded Transferosomes and Niosomes were prepared by modified hand shaking method and thin film hydration technique. For transferosomes soya lecithin (phospholipid), span60 (surfactant) and solvents like ethanol & chloroform were used whereas for niosomes cholesterol, different non-ionic surfactants like span 20, span60, span80 and solvents like ethanol and chloroform were used.

TRANSFEROSOMES:

Curcumin loaded transferosomes were prepared by modified hand shaking method. Ten formulations were prepared by varying surfactant to lipid ratio (T1 to T6) and lipid to surfactant ratio (T6 to T10).

Surfactant to lipid: By increasing the concentration of lipid five formulations were prepared i.e., T1, T2, T3, T4, T5. All the five formulations were evaluated. The drug content of T1, T2, T3, T4, T5 was found to be 80.72%, 93.40%, 94.43%, 91.80%, 77.50%, invitro drug release was observed as 73.92%, 92.27%, 93.10%, 83.97%, 71.80%. Among all the five formulations T2 was considered as best formulation because of highest drug content of 93.40%, drug release of

92.27%, entrapment efficiency of 68.80%, particle size of 765.2nm and zeta potential of -37.6mV.

Lipid to surfactant: By increasing the concentration of surfactant five formulations were prepared i.e., T6, T7, T8, T9, T10. All the five formulations were evaluated. The drug content of T6, T7, T8, T9, T10 was found to be 95.4%, 90.6%, 93.73%, 70%, 72.60%, The in-vitro drug release was observed to be 95.19%, 84.37%, 90.22%, 75.48%, 73.45% respectively. Among all the five formulations T6 was considered as best formulation because of highest drug content of 95.40%, mean vesicle diameter 441.0nm, zeta potential value of -36.9mV, entrapment efficiency of 94.20% and in-vitro drug release data showed 95.19% in a time period of 12hrs. Among all the transferosomal formulations the best formulation (T6) was further incorporated into gel. The main factors affecting the size and shape of the vesicles are the concentration of phospholipid and surfactant.

Effect of surfactant (Span 60):

T1 to T5 transferosomal formulations were prepared by increasing lipid concentration from 50 to 300 mg. The concentration of surfactant up to 50mg it is showing good result i.e., lesser particle size, good stability, highest drug content, entrapment efficiency and drug release studies. Up on further increase in surfactant leads to increase in particle size, decrease in zeta potential, drug content, entrapment efficiency and drug release.

Effect of phospholipid (Soya lecithin):

T6 to T10 transferosomal formulations were prepared by increasing lipid concentration from 50 to 300 mg. Up to 100 mg the concentration of phospholipid is showing good result i.e., good stability, highest drug content and drug release. Up on further increase in phospholipid leads to increase in particle size, decrease in the zeta potential, drug content and drug release.

NIOSOMES:

For the preparation of niosomes by thin film hydration technique nine formulations were prepared by different surfactants of varied ratios (span20, span60, span80).

Span 20: By increasing the concentration of span 20 from 50 to 200mg three formulations were prepared i.e., N1, N2, N3. All the three formulations were evaluated. The drug content of N1, N2, N3 was found to be 88%, 90.12%, 87.22%. The in-vitro drug release was observed to be 71.27%, 82.63%, 74.78% respectively. Among all N2 was considered as best formulation because of highest drug content of 90.12%, drug release of 82.63%, entrapment efficiency of 91.70%, particle size of 531.8nm and zeta potential of -50.8mV.

Span 60: By increasing the concentration of span 60 from 50 to 200mg three formulations were prepared i.e., N4, N5, N6. All the three formulations were evaluated. The drug content of N4, N5, N6 was found to be 93.60%, 96.80%, 94.93%. The in-vitro drug release was observed to be 94.21%, 97.78%, 87.94% respectively. The particle size was found to be 595.3nm, 412nm, 480nm for the prepared formulations. The zeta potential values were observed to be -10.6mV, -51.5mV, -37.9mV. Among all N5 was considered as best formulation because of its highest drug content of 96.80%, drug release of 97.78%, entrapment efficiency of 96.08%, particle size of 412nm and zeta potential of -51.5mV.

Span 80: By increasing the concentration of span 80 from 50 to 200mg three formulations were prepared i.e., N7, N8, N9. All the three formulations were evaluated. The drug content of N7, N8, N9 was found to be 92%, 76.86%, 81.68%. The in-vitro drug release was observed to be 79.53%, 72.73%, 66.45. Among all N7 was considered as best formulation because of its highest drug content of 92%, drug release of 79.53%, entrapment efficiency of 88.78%, particle size of 758.4nm and zeta potential of -42.8mV.

Up on comparison the best formulations of span 20, span 60 and span 80, Span 60 was considered to be best surfactant for the preparation of niosomes. At 100 mg concentration it is exhibiting highest drug content of 96.80%, drug release of 97.78%, entrapment efficiency of 96.08%, particle size of 412nm and zeta potential of - 51.5mV. Among all the niosomal formulations, the best formulation (N5) was further incorporated into gel.

Effect of Cholesterol:

Cholesterol is one of the common and essential additives used in niosomal formulation. Incorporation of cholesterol was known to influence vesicle stability and permeability. The effect of cholesterol on curcumin entrapment was varied according to the non-ionic surfactants used. Cholesterol was found to have little effect on drug entrapment. The prepared niosomal formulation using cholesterol: surfactant (span 60) 1:1 ratio has shown higher entrapment efficiency, drug content and drug release.

Effect of surfactants (Span20, span 60 and span 80)

The main factor affecting the size and shape of vesicles is the concentration and HLB values of surfactants. The entrapment efficiency of niosomes prepared by span 60 was superior when compared to other surfactants. The HLB value of span 20, 60, 80 was found to be 8.6, 4.7, 4.3 respectively. Even though span 80 is having the least HLB value but the entrapment efficiency was not found to be optimum. It may be mainly because of existence of unsaturated alkyl chain length.

The ratio of surfactant was optimized for all the three surfactants. It was considered that the drug release was decreased when the concentration of surfactant was more than or less than the cholesterol. Equal amount of cholesterol and surfactant was giving good result. It was found that span 60 was suitable for the preparation of curcumin loaded niosomes because span 60 having long alkyl chain length and saturated alkyl chain compared to other spans. Finally, 1:1 ratio of cholesterol: surfactant (span 60) was considered to be best formulation because of its good entrapment efficiency, lesser particle size, highest zeta potential, drug content and drug release in a time period of 12 hours.

TRANSFEROSOMAL AND NIOSOMAL GEL:

The best formulations of both vesicular delivery systems i.e., transferosomes (T6) and niosomes (N5) were incorporated in to gel. Comparative study was made among plain gel, transferosomal

gel and niosomal gel. Spreadability, viscosity, pH, drug content, invitro drug release studies and exvivo drug release studies were evaluated for all the three gels. pH of PG, T6G & N5G was found to be 6.5, 6.6 and 6.8 respectively. Viscosity of PG, T6G & N5G was found to be 2060cP, 3096cP and 8796cP. Spreadability of PG, T6G & N5G was found to be 9.75 g cm/sec, 10.04 g cm/sec and 13.62 g cm/sec. N5G was exhibiting highest spreadability of 13.62 g cm/sec. Drug content of PG, T6G, N5G was found to be 81.20%, 85.06% and 88.19%. N5G was showing highest drug content of 88.19%. Invitro drug release of PG, T6G & N5G was found to be 83.79%, 88.50% and 91.54%. N5G was showing highest drug release of 91.54% in a time period of 12 hours. Exvivo drug release studies of PG, T6G & N5G was found to be 88.32%, 92.11% and 95.05%. N5G was showing highest drug release of 95.5% in a time period of 12 hours with release rate of 31.45 microgram/cm²/hr^{-1/2}, flux of 0.7031 µg/cm²/hr. and permeation coefficient of 43.15 cm/hr. Among the three gels, niosomal gel was considered to be best gel because of its pH 6.8, Viscosity of 8796cP, spreadability of 13.62 g.cm/sec, drug content of 88.19%, invitro drug release of 91.54% and ex-vivo drug release of 95.05% in a time period of 12 hours with release rate of 31.45 microgram/cm²/hr^{-1/2}, flux of 0.3865 µg/cm²/hr. and permeation coefficient of 43.92 cm/hr.

CONCLUSION

Curcumin has several potential pharmacological effects mainly includes anti-inflammatory, antibacterial, antioxidant and anticancer activities. But main problem with curcumin is its poor oral bioavailability (3%). In order to improve its permeability and bioavailability there is a need to develop vesicular drug delivery system for curcumin.

Curcumin loaded transferosomes and niosomes were successfully prepared by modified hand shaking method and thin film hydration technique and evaluated for particle size, zeta potential, entrapment efficiency, drug content and invitro drug release studies.

T6 formulation of soya lecithin: span 60 (1:0.5 ratio) was considered to be best formulation

with highest drug content of 95.40%, mean vesicle diameter 441.0nm, zeta potential value of -36.9mV, entrapment efficiency of 94.20% and in-vitro drug release data showed 95.19% in a time period of 12hrs.

N5 formulation of Cholesterol: span60 (1:1 ratio) was found to be best formulation with drug content of 96.80%, particle size of 412nm, zeta potential of 51.5mV, entrapment efficiency of 96.08% and in-vitro drug release data showed 97.78% of drug release in a time period of 12hrs.

T6 and N5 were incorporated into gel and compared with pure gel (PG). On comparison with pure drug, curcumin loaded transferosomal and niosomal gel were showing greater permeability. Among the three gels, niosomal gel was considered to be best gel because of its pH 6.8, Viscosity of 8796cP, spreadability of 13.62 g.cm/sec, drug content of 88.19%, in-vitro drug release of 91.54% and ex-vivo drug release of 95.05% in a time period of 12 hours with release rate of 31.45 microgram/cm²/hr^{-1/2}, flux of 0.3865µg/cm²/hr. and permeation coefficient of 43.92cm/hr.

The Objectives has been fulfilled. The permeability of curcumin has been enhanced. The obtained results lead us to the conclusion that transferosomal and niosomal gel can be a promising carrier for curcumin.

DECLARATION

Ethics approval and consent for participation:-Not applicable

Consent for publication:-Not applicable

Availability of data and material:-Data is available

Competing Interest:- Not interested

Funding:-Not applicable

REFERENCES

- 1 Chaurasiya P., Ganju E., Upmanyu N Ray S.K., Jain P (2019)Transfersomes: A novel technique for transdermal drug delivery, *J. Drug Deliv. Ther* 9:279–285. doi: 10.22270/jddt.v9i1.2198
- 2 Jain A.K., Kumar F (2017)Transfersomes: Ultradeformable vesicles for transdermal drug delivery. *Asian J. Biomater Res* 3:1–13.

- 3 Yadav D., Sandeep K., Pandey D., Dutta R.K (2017) Liposomes for drug delivery. *J. Biotechnol. Biomater* 7:1–8.
- 4 Anoop KR et.al (2013) A review on surfactants as edge activators in ultra- deformable vesicles for enhanced skin delivery. *International Journal of Pharma and Bio Sciences* 4(3) 337-344.
- 5 Ms. Reshmy Rajan et.al (2011) Transferosomes - A vesicular transdermal delivery system forenhanced drug permeation. *J Adv Pharm Technol Res* 2(3): 138–143.
- 6 Priyanka Chaurasiya et.al (2019) Transferosomes: a novel technique fortransdermal drug delivery, *Journal of Drug Delivery & Therapeutics* 9(1): 279-285.
- 7 Akhlesh kumar jain et.al (2017)Transferosomes: Ultra deformablevesicles for transdermal drug delivery,*Asian Journal of Biometrical Research* 3(4): 1-13.
- 8 Reddy YD et.al (2015) Transferosomes: A Novel Vesicular Carrier for Transdermal Drug Delivery System. *J Innov Pharm Biol Sci* 2(2):193–208.
- 9 Jangme et.al (2013) A Review on Transferosome: Is a Boon to Human Life, *Int Res J Pharm Appl Sci* 3(2) : 174–179.
- 10 Satyanand tyagi et.al(2012) Novel drug delivery system (NDDS): Niosomes, *Journal of Biomedical and Pharmaceutical Research*. 1(3): 14-21.
- 11 Arora S Prashar et.al(2012) Niosomes: The unique vesicular drug carriers, *Journal of Drug Delivery and Therapeutics*.2(1): 96-101.
- 12 Usman, M.R.M et.al(2017) Niosomes: A novel trend of drug delivery. *Eur. J. Biomed. Pharm. Sci* 4: 436-442.
- 13 Rekharao et.al (2011) Preparation and characterization techniques in niosomal vesicular systems-A review, *Journal of Pharmacy and BiomedicalSciences* 5: 1-7.
- 14 Simran chaurasia et.al(2017) Transferosomes: Novel approach for intranasal delivery, *European Journal of Pharmaceutical Sciences* 4(3):192-203.
- 15 Benson HA. et.al (2006) Transferosomes for transdermal drug delivery, *Drug Deliv* 3(6): 727-37.

- 16 Ezzat H.M., Elnaggar Y.S.R., Abdallah O.Y.(2019) Improved oral bioavailability of the anticancer drug catechin using chitosomes: Design, in-vitro appraisal and in-vivo studies, *Int. J. Pharm* 565: 488–498. doi: 10.1016/j.ijpharm.2019.05.034.
- 17 Junyaprasert, V. et.al (2008) Effect of charged and non-ionic membrane additives on physicochemical properties and stability of niosomes. *AAPS Pharm SciTech* 9: 851-859.
- 18 Tejaswini et.al. Formulation and Evaluation of Fluconazole Loaded Transfersosomal Gel, *IJSRM*. 2016; 3(3) : 1-14.
- 19 Usman, M.R.M et.al (2017) Niosomes: A novel trend of drug delivery, *Eur. J. Biomed. Pharm. Sci.* 4: 436-442.
- 20 Verma P, Pathak K. et.al (2010) Therapeutic and cosmeceutical potential of ethosomes: An Overview, *Journal of Advanced Pharmaceutical Technology and Research* 1(3) : 274-282.
- 21 Leuva S, et.al(2009) Development and characterization of curcumin loaded transfersome for transdermal delivery, *J Pharm Sci Res* 1(4): 71-80.
- 22 Honary, S. et.al (2009) Formulation and characterization of doxorubicin nanovesicles, *J. Vac. Sci. Technol. B. Microelectron. Nanometre. Struct* 27:1573 -1577.
- 23 Sandeep kumar sharma et.al(2009) Formulation and evaluation of fluconazole niosomal oral suspension, *Journal of Pharmaceutical Research and health Care* 1(2) :142- 156.
- 24 Abitha MH et.al(2015) Recent advances in topical gel formulation, *World Journal of Clinical Pharmacology Microbiology and Toxicology* 1(13) : 1-13.

DECLARATION

Ethics approval and consent for participation:-Not applicable

Consent for publication:-Not applicable

Availability of data and material:-Data is available

Competing Interest:- Not interested

Funding:-Not applicable

Author's contribution:-All authors have read and approved the manuscript.

AKS developed the concept and reviewed the manuscript

LS executed the work

Acknowledgements:-Both authors thank the management, RBVRR Women's college of pharmacy for supporting the work.