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DEVELOPMENT AND EVALUATION OF NIOSOMAL DRUG DELIVERY SYSTEM CONTAINING TRANEXAMIC ACID

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Abstract:

The present study aimed to optimize the drug delivery of tranexamic acid from the niosomes by using different grades of surfactants and cholesterol at different molar concentrations in order to achieve prolonged release time and sustained release. Tranexamic acid is one of the most effective antifibrinolytic drugs used in the treatment of fibrinolysis. Niosomes are the novel vesicular drug delivery system by which we can achieve the constant plasma drug concentration for the extended period of time. The vesicles are prepared from nonionic surfactants and cholesterol by thin film hydration technique. Niosomes have been investigated in recent years due to their potential applications in the drug delivery of hydrophobic and hydrophilic drugs. Niosomal drug delivery systems offer an advantage over conventional delivery systems by delivering the drugs in a sustained manner to overcome some problems associated with conventional drug delivery such as insolubility, instability and low bioavailability. The prepared Tranexamic acid niosomes were evaluated for size, shape and morphology, percent drug entrapment, and stability studies. In-vitro drug release studies were performed and drug release kinetics was evaluated. From this study it was observed that the formulation TNF 9 shows satisfactory particle size 861.9 nm, entrapment efficiency 92.70 % and in-vitro drug release 79.49 % for the period of 24 hours. Thus the niosomal formulation could be promising delivery system for tranexamic acid with better antifibrinolytic activity, stability and sustained drug release profile.

Keywords:- *Anti fibrinolytic, Tranexamic acid, Niosomes, Non ionic surfactants, Cholesterol.*

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INTRODUCTION:

Niosomes are formed by self assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, bilayered, multilamellar system and polyhedral structures depending on the method used to prepare and the inverse structure in case of non-aqueous solvent. The size of the niosomes ranges between 10 to 1000 nm [1]. In niosomes the vesicle forming amphiphile is non-ionic surfactant such as span 60 and span 80 which gives the rigidity to the bilayer and results in less leaky niosomes [2]. The unique structures of niosomes as vesicular systems make them capable of encapsulating both hydrophilic and lipophilic substances. Hydrophilic drugs are usually encapsulated in the inner aqueous core or adsorbed on the bilayer surfaces, while hydrophobic (lipophilic) substances are entrapped by their partitioning into the lipophilic domain of the bilayers [3]. Niosomes and liposomes are equally active potential of drug delivery and efficacy increases in both as compared with that of free drug. Niosomes are extremely preferred over Liposomes, due to the former exhibits a high chemical stability and an economic process [4].

Niosomes improve the therapeutic performance of encapsulated drug molecules by protecting the drug from harsh biological environments, resulting in their delayed clearance [5]. Niosomes are biodegradable, biocompatible and non-immunogenic [6].

Fibrinolysis is a physiologic component of hemostasis that functions to limit clot formation after major tissue damage that occurs during surgical and traumatic injury, inhibiting fibrinolysis may potentially inhibit other responses that contribute to bleeding. However excessive fibrinolysis may contribute to coagulopathy, bleeding, inflammatory responses and sometimes death also[7]. As a result, growing data have reported the efficacy of antifibrinolytic agents to reduce bleeding, allogeneic blood administration and adverse clinical outcomes.

Of all the pharmacologic agents, tranexamic acid is the agent most extensively studied in the literature and used in most countries due to its impressive safety records. And the half-life is 80 min and 34% [7].The objective of this study is to treat fibrinolysis with tranexamic acid niosomes, since it is a lysine analog that reversibly binds to the lysine-binding sites on plasminogen to inhibit its affinity to bind to multiple proteins including fibrin to treat the fibrinolysis [7].

The present study involves the preparation of tranexamic acid entrapped niosomes and evaluated for their optimum drug entrapment and prolongs release time with sustained drug release pattern.

MATERIALS AND METHODS:

Materials:-

Tranexamic acid was collected as a gift sample from Cipla Pvt. Ltd. Goa. Cholesterol and Spans were purchased from Loba chemie Pvt. Ltd. Mumbai. Di ethyl ether from Reachem laboratory chemicals Pvt. Ltd. Chennai. And chloroform from S D fine chem. Ltd. Mumbai.

Method: -

Formulation of Tranexamic acid niosomes:-

Tranexamic acid niosomes were prepared by Thin Film Hydration Technique using Rotary flash Evaporator. Weighed quantity of cholesterol and surfactant were dissolved in chloroform and di ethyl ether mixture (1:1 v/v) taken in a round bottom flask. The flask was rotated in rotary flash evaporator at 100 rpm for 20 minutes in a thermostatically controlled water bath at 60 $^{\circ}$C± 2 $^{\circ}$C. The flask was rotated at 1.5 cm above the water bath under reduced pressure (10-15mm mercury) until all the organic phase evaporated and a slimy layer was deposited on the wall of a round bottom flask. To the thin dry lipid formed, tranexamic acid solution was added previously dissolved in 10 ml of phosphate buffer saline pH 7.4 and the flask was rotated again at the same speed and temperature as before but without vacuum for 30 minutes for lipid film removal and dispersion. The niosomal suspension so formed was then transferred to a suitable glass container and sonicated for 30 minutes using bath sonicator in an ice bath for heat dissipation. The sonicated dispersion was then allowed to stand for about 2 hours at room temperature to form niosomes. The formulation was sterilized by passing into 0.2 µm membrane filter. Each batch was prepared three times and stored in refrigerator [8,9].

Table No. 1: Formulation of tranexamic acid niosomes

COMPONENS	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9
Tranexamic acid (mg)	100	100	100	100	100	100	100	100	200
Cholesterol (molar conc.)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 60 (molar conc.)	0.5	1	1.5	2	-	-	-	-	1
Span 80(molar conc.)	-	-	-	-	0.5	1	1.5	2	1
Chloroform Di ethyl ether (1:1 v/v)	10	10	10	10	10	10	10	10	10
Buffer solution (ml)	10	10	10	10	10	10	10	10	10

Separation of Unentrapped Drug by Centrifugation: -
This technique was developed to achieve the removal of unentrapped solute from the vesicles.

Centrifugation.
The niosomal suspension was centrifuged, and the above phase was discarded. The pellet was resuspended to give a niosomal suspension free from unentrapped medication [10].

Evaluation of niosomes
Vesicle size and zeta potential determination: -
All the prepared batches of niosomes were evaluated for determination of vesicle size and Zeta potential distribution using Malvern particle size analyzer. The samples were prepared by applying suitable dilution [11].

Scanning electron microscopic study: -
Shape and surface morphology of niosomes was studied using scanning electron microscopy (SEM). The niosomes formed were mounted on an aluminum stub with double-sided adhesive carbon tape. The vesicles were then sputter-coated with gold/palladium using a vacuum evaporator and examined with the scanning electron microscope equipped with a digital camera at 25kV accelerating voltage [12].

Differential scanning calorimetric analysis: -
Differential Scanning Calorimetry (DSC) Measurements were carried out using differential scanning calorimeter (analytical technologies Pvt. Ltd.) for the sample's tranexamic acid, mixture of surfactant and cholesterol (dummy TNF 9) and tranexamic acid loaded niosomes (TNF9). For this purpose, 3mg of each sample were sealed thermatically in standard aluminum pans. Each sample was scanned between 30–300ºC using nitrogen as the purge gas. For calibrating enthalpy, indium was sealed in aluminum pan with sealed empty pan as a reference. Thermograms were obtained at a scanning rate of 10ºC/ min [13].

Fourier transform infrared spectroscopy analysis: -
The possibilities of drug-excipient (cholesterol, nonionic surfactants) interactions were investigated by FT-IR spectrum study. Fourier-transform infrared spectroscopy (FT-IR) measurements were performed using Bruker spectrophotometer. The samples were scanned over the range of 4000 to 400cm^{-1}. Infrared spectroscopic analysis was done for pure drug tranexamic acid, drug free niosomes (dummy TNF9) and drug loaded TNF9 formulation [13].

X-ray diffraction studies: -
The possibilities of drug-excipient interactions were further investigated by XRD analysis. The X-ray diffraction pattern (XRD) of pure tranexamic acid, drug free niosomes (dummy TNF9), and drug loaded TNF9 formulations were recorded using PANalyticalXpert pro X-ray diffractometer with Ni filtered Cu Kα radiation over the 2θ range of 10-90 and the peaks were indexed[14,15].

Drug encapsulation efficiency: -
After preparing niosomal dispersion, unentrapped drug was separated by centrifugation using pH 6.8 phosphate buffer for 45 min at 17,000 rpm. The resulting solution was analyzed by UV spectrophotometer at 204 nm for the total amount of entrapped drug [16].

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug taken} - \text{Amount of drug in supernatant}}{\text{Amount of drug}} \text{ X } 100$$

Drug content: -
1 ml of niosomal suspension was taken in a volumetric flask of 10 ml and volume was made up by phosphate buffer pH 6.8 and sonicated for 30 mins to obtain clear solution after that 1 ml of this mixture was diluted to 10 ml by phosphate buffer pH 6.8 and the percentage dug content was observed at 204 nm using UV spectrophotometer [17].

***In-Vitro* Diffusion Study: -**
The *in-vitro* drug diffusion studies can be carried out using Franz diffusion cells. A dialysis membrane (cellophane membrane) was washed and soaked in phosphate buffer solution which act as a donar compartment and 15 ml of 6.8 pH buffer was taken in the receptor compartment. The entire system was kept at 37 ± 05 ^{0}C with continuous stirring at 100 rpm. The samples were withdrawn at predetermined intervals and replaced by fresh medium simultaneously for time period of 24 hrs. The amount of drug diffused from each formulation at specific time interval was determined using UV-spectrophotometer at 204 nm [17].

Stability study:-
The purpose of stability testing is to provide evidence on how the quantity of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. Niosomal formulations were kept at two different temperature conditions, that is, refrigeration temperature (2-4^{0}C) and room temperature (RT) (27-30^{0}C) for 45 days (Short term stability study) as per ICH guidelines. Throughout the study, niosomal formulations were stored in screw capped HDPE bottles. Samples were withdrawn at different time intervals and examined for physical changes such as color, residual drug content and study drug release was examined spectrophotometrically [18]. The optimized formulation TNF 9 was selected for stability study.

RESULTS AND DISCUSSION:

Vesicle size and zeta potential determination: -
The particle size determination of the niosomal vesicles was carried out by using particle size analyzer (Malvern) and recorded in Table No.2. and Fig No.1. The average vesicle diameter of the niosomal vesicles was found to be in the range of 861.9 nm to 901.16 nm. It shows that particle size of the niosomal formulation was within the prescribed niosomal size range. From the result it was identified that particle size of niosomal formulation was increased on increasing the cholesterol content. Zeta potential determination was found to be -55.3^{0}C. It indicates that the drug was stable in the formulation. The result was shown in Fig No.2.

Table No.2: Average vesicle size of Tranexamic acid Niosomes.

Sl No	Niosomes code	Average size (nm)
1	TNF1	894.87
2	TNF2	888.38
3	TNF3	873.78
4	TNF4	865.40
5	TNF5	901.16
6	TNF6	890.32
7	TNF7	875.11
8	TNF8	868.05
9	TNF9	861.9

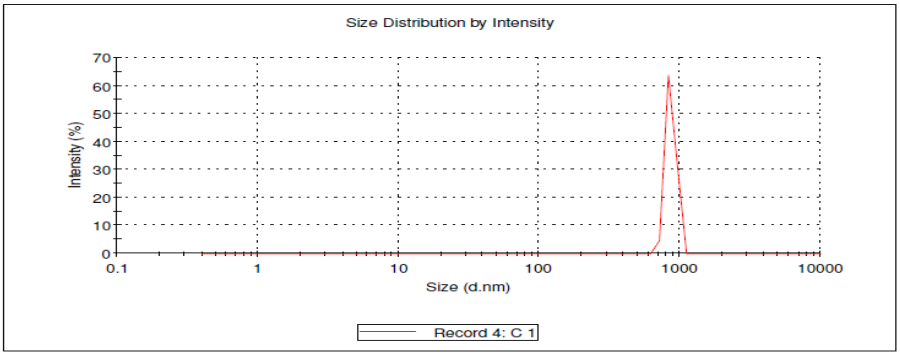


Fig No.1: Particle size distribution of Tranexamic acid Niosomes.

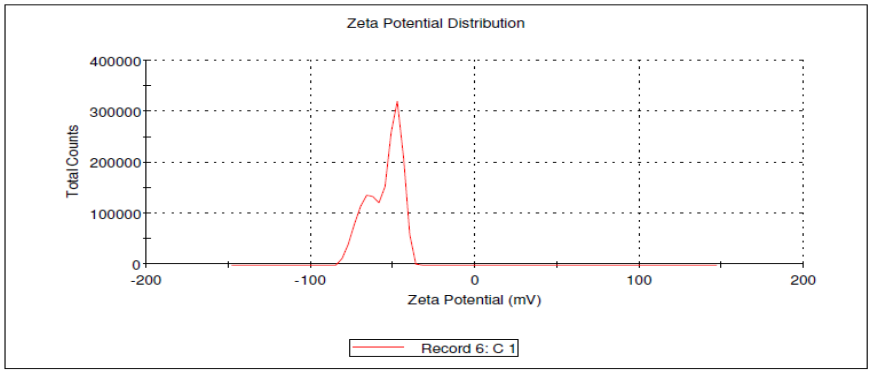
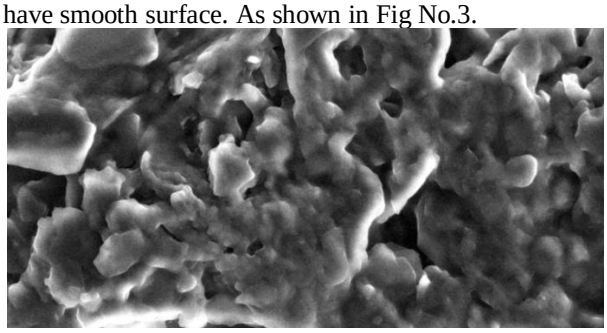
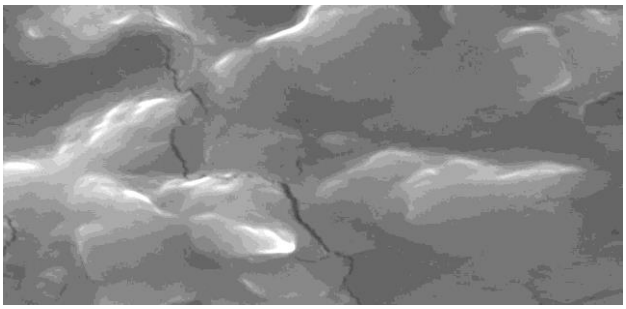


Fig No.2: Zeta potential distribution of Tranexamic acid Niosomes.

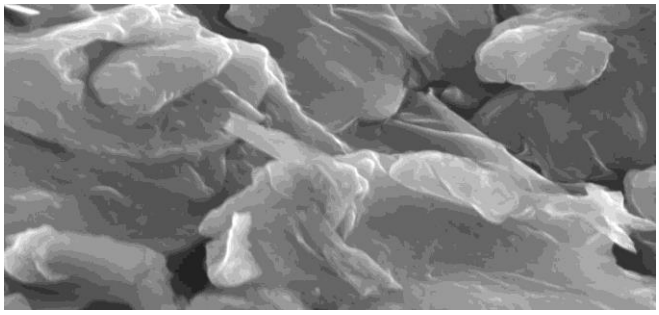
Scanning Electron Microscopic studies: -

The prepared vesicles were studied under scanning electron microscope to observe the formation of vesicles. Then the results showed that Tranexamic acid loaded niosomes have smooth surface. As shown in Fig No.3.





(a) **(b)**

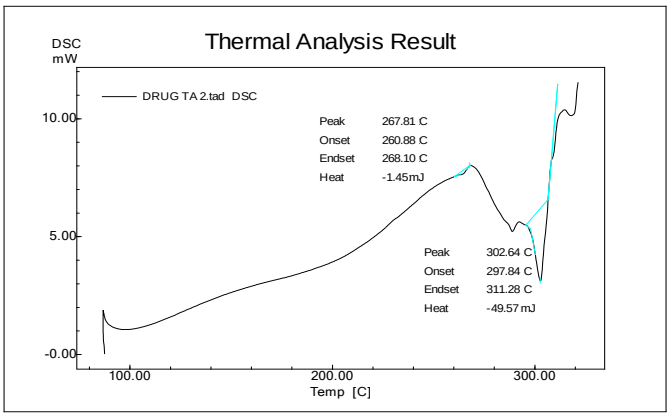


(c)

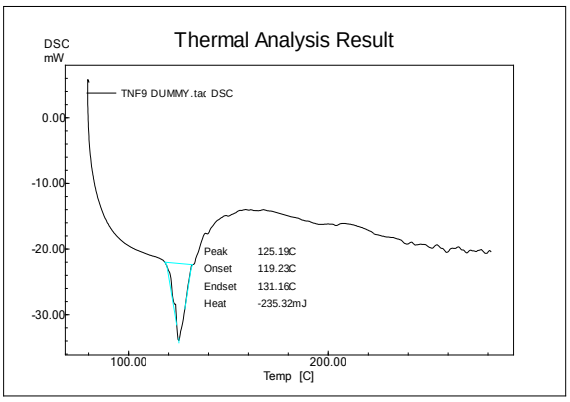
Fig No.3: Scanning Electron Microscopic photographs of TNF4 (a), TNF8 (b) and TNF9 (c) Niosomes

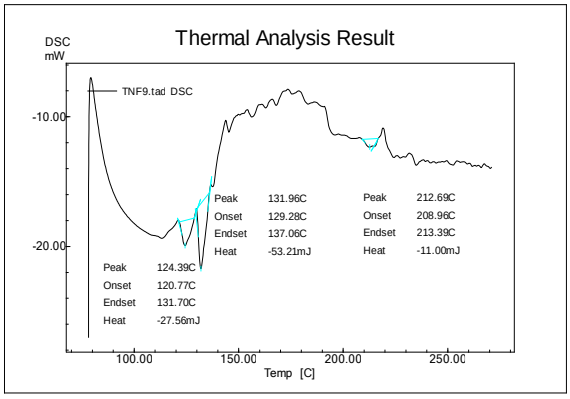
Differential scanning colorimetric analysis:-

DSC studies were carried out in order to investigate the possible interactions between drug and selected excipients. The DSC thermogram of tranexamic acid exhibited a single sharp endothermic peak at 310 ^{0}C due to its melting transition temperature. Finally the thermograms of drug free (dummy) TNF 9 shows peak at 130 ^{0}C and drug containing TNF 9 formulation showed peak at 130 ^{0}C in the DSC thermogram. The absence of endothermic peak of tranexamic acid in the entire spectrum of formulation pointed out complete entrapment and reduction of drug crystallinity in the formulation. The results are shown in the Fig No.4.



(a)





(b) **(c)**

Fig No.4: DSC Thermograms of Tranexamic acid (a), Dummy TNF9 (b) and drug loaded TNF9 Niosomes (c).

Fourier-transform infrared spectroscopy analysis:-

FT-IR spectroscopy studies were carried out in order to investigate the possible interactions between drug and selected excipients. IR spectrum for pure drug and physical mixture of drug-excipient were obtained and characterized. The broad peak at 3320cm^{-1} due to –OH group. And it shows peak at 3616 cm^{-1} due to amine stretching. Absorption peak at 1639 cm^{-1}is the peak of –C=O groups corresponding to ketone group. FTIR spectra of pure Tranexamic acid drug and physical mixture showed corresponding peaks which indicating no chemical interaction between tranexamic acid and excipients. The results are given in Fig No.5.

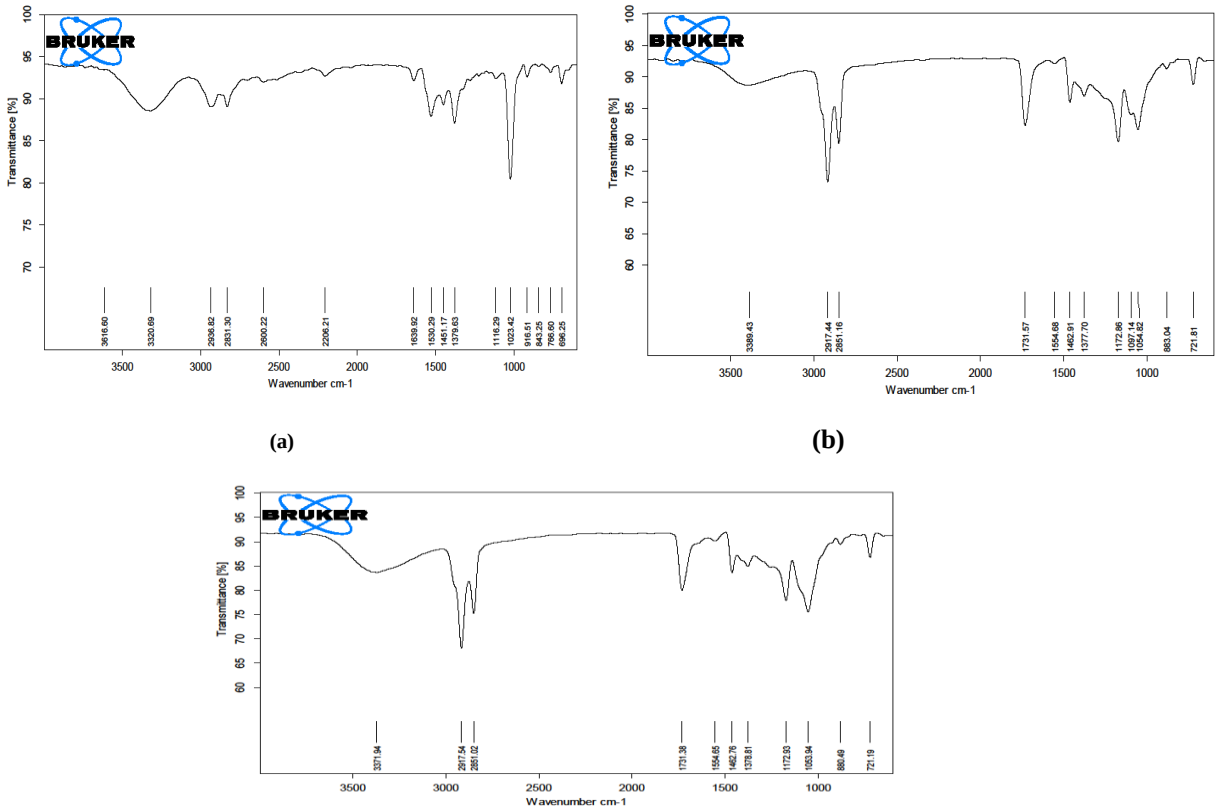


Fig No.5: FTIR spectra of Tranexamic acid (a), Dummy TNF9 (b) and drug loaded TNF9 Niosomes (c).

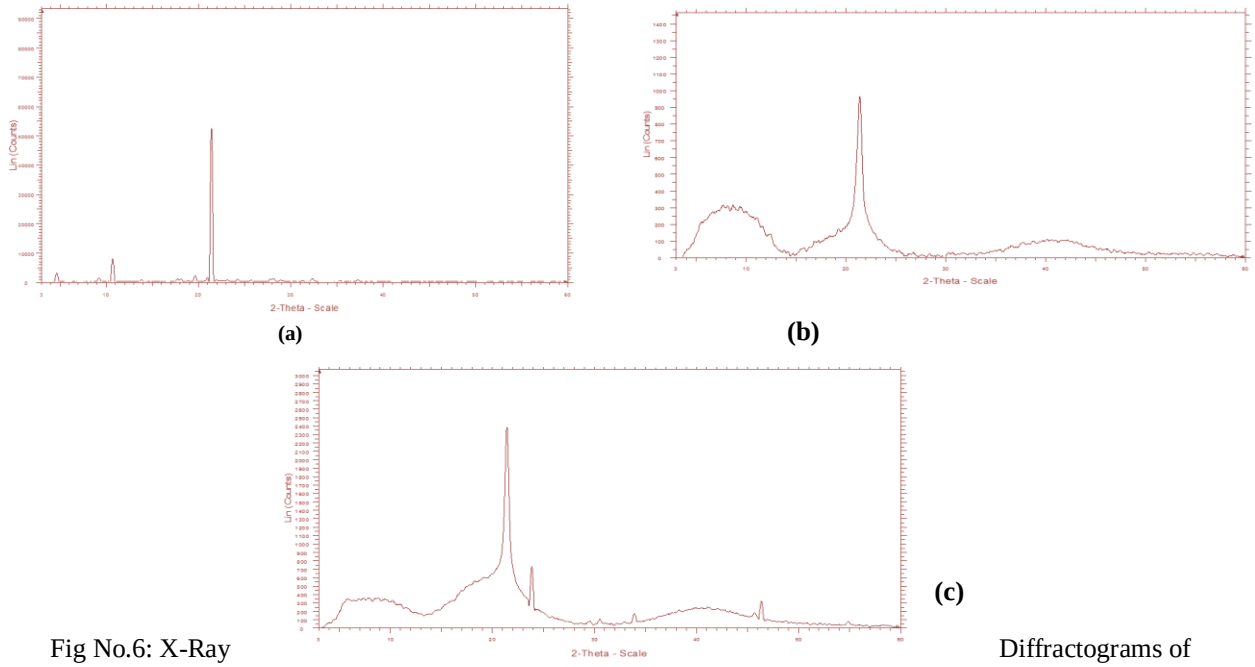


Fig No.6: X-Ray Diffractograms of Tranexamic acid (a), Dummy TNF9 (b) and drug loaded TNF9 Niosomes (c).

The X-ray diffractograms of pure drug Tranexamic acid, drug free Niosomes (dummy TNF9) and drug loaded Niosomes (TNF9) are presented in Fig No.6. Tranexamic acid had shown the characteristic intense peak at 2θ of 19^0-22^0 due to its crystalline nature. The drug free niosomes (TNF9 dummy) and drug loaded Niosomes (TNF9) shows characteristic peaks at 2θ of 2^0-26^0. However, the intense tranexamic acid peaks were not found in the formulation which shows that the drug is dispersed at the molecular level in the cholesterol and surfactant. As a result, no crystals are found individually in the formulation. So the drug was encapsulated by the cholesterol and surfactant.

Drug Entrapment Efficiency:-

The entrapment efficiency of the formulated niosomes was determined by separating the unentrapped drug using centrifugation method. And it was in the range of 77.40% -92.70%. The different molar ratios of surfactant and cholesterol may change the entrapment efficiency. From this study it was found that the entrapment efficiency of drug in TNF4 formulation containing span 60 and TNF8 formulation containing span 80 was found that 92.57% and 89.27% respectively. When compared with two formulations, niosomes formulated with span 60 were found to be optimum for loading maximum amount of tranexamic acid in niosomal formulation. And TNF9 formulation also shows highest entrapment efficiency (92.70%). The drug entrapment efficiency of niosomal formulation increased on increasing the concentration of surfactant. The results were shown in Table No.3.

Table No.3: Drug entrapment efficiency of the tranexamic acid Niosomes.

Niosomes code	DEE (%)
TNF1	82.89±1.90
TNF2	86.59±0.29
TNF3	89.78±0.38
TNF4	92.44±0.66
TNF5	77.48±0.20
TNF6	82.44±2.33
TNF7	85.63±0.42
TNF8	89.5±0.51
TNF9	92.70±0.48

In-Vitro Diffusion study:-

The *in-vitro* diffusion study of niosomal formulation was conducted by using Franz's diffusion cell in pH 6.8 phosphate buffer, cellophane membrane as barrier. The diffusion profiles of tranexamic acid niosomes are shown in Fig No.7. The cumulative percentage of drug diffusion from TNF1 to TNF9 formulations ranges from 90.13% to 73.11%.

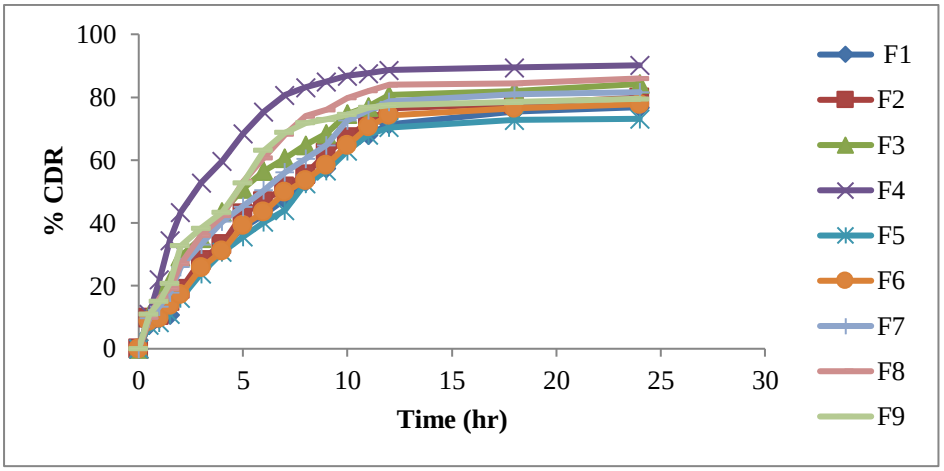


Fig No.7: In-vitro diffusion profile of Tranexamic acid from TNF1 to TNF9 Niosomes in Phosphate buffer pH 6.8

***In-vitro* release kinetics:-**

The release kinetics was evaluated by making use of zero order, first order, Higuchi's and korsmeyer-peppa's equations. The drug release from the tranexamic acid niosomes follows korsmeyer-peppa's release kinetics with sustained release mechanism and the 'n' values are in between 0.5743 to 0.7480. By fitting in the korsmeyer-peppa's equation the release kinetics follow non-Fickian kinetics. If the 'n' values below 0.5 which indicates Fickian kinetics. The prepared tranexamic acid niosomes release kinetics fitted in kosmeyer-peppa's equation. The 'n' values are in between 0.5 to 1, so the release is following non-Fickian sustained release mechanism. The 'n' values and R^2 values of all niosomal formulations are listed in Table No.7.

Table No.4: Regression co-efficient (R^2) values of tranexamic acid niosomes according to different kinetic models

Formulation	Zero order		First order		Higuchi	Peppa's	
	N	R^2	N	R^2	R^2	N	R^2
TNF1	4.7600	0.9124	0.089	0.9632	0.9670	0.7480	0.9754
TNF2	4.8971	0.9005	0.097	0.9515	0.9666	0.6935	0.9762
TNF3	4.8979	0.9845	0.109	0.9436	0.9732	0.6027	0.9845
TNF4	5.114	0.7310	0.148	0.8793	0.8904	0.5743	0.9187
TNF5	4.6885	0.9107	0.085	0.9480	0.9582	0.7598	0.9742
TNF6	4.8347	0.9120	0.093	0.9552	0.9648	0.7168	0.9783
TNF7	4.9475	0.8828	0.105	0.9510	0.9736	0.6547	0.9845
TNF8	5.3420	0.8328	0.127	0.9150	0.9520	0.6647	0.9757
TNF9	4.7957	0.7879	0.103	0.8717	0.9380	0.6189	0.9576

Stability study: -

The short term stability studies were carried out as per ICH guidelines on the most satisfactory formulation TNF 9 at two different temperature conditions, that is, refrigeration temperature (2-4^{0}C) and room temperature (RT) (27-30^{0}C) for a period of 45 days to assess short term stability as per ICH guidelines. At fixed time, the formulation was evaluated for drug content and *in-vitro* drug profile. Drug content study shows there was no significant changes in drug content. *In-vitro* drug release profile were found to super impossible with the initial results, the results are shown in Table No.5 and 6. Therefore the TNF9 formulation is stable.

Stability Study:-

Drug content:-

Drug content of optimized tranexamic acid niosomes was studied according to earlier procedure.

Table No.5: Drug content study

Formulation	Percentage CDR	
	Before stability test	After stability test
TNF 9	92.70±0.48	91.98±0.061

Diffusion study:-

Diffusion Study of optimized Niosomes was studied according to earlier procedure and determined drug release rate. The results are given in Table No.13.

Table No.6: Diffusion study

Formulation	Percentage CDR	
	Before stability test	After stability test
TNF 9	79.49±0.0707	79±0.0354

CONCLUSION:

Niosomes containing tranexamic acid were formulated using Cholesterol and different surfactants such as span 60 and span 80 and evaluated for various parameters. From the above studies, it can be concluded that tranexamic acid is encapsulated with span-60 and span- 80 mixed non-ionic surfactants in the formulation TNF 9 containing 1:4 cholesterol: surfactant ratio showed prolonged release and longer duration of action than individual surfactant, there by achieving sustained release. The optimized formulation TNF 9 was found to follow sustained release pattern with better stability. However by the pharmacokinetic studies, it indicates that *in-vitro* drug release pattern of the TNF9 follows Korsemeyer-Peppa's release kinetics and the mechanism followed non- Fickian diffusion. The formulation was found to be stable in short term stability study. So it can be suggested that there is further scope for *in-vivo* and pharmacokinetics study.

The Tranexamic acid drug is highly soluble and high permeable drug (BCS class I) and having less half life and bioavailability. So by formulating drug in niosomal formulation half life and bioavailability of the drug can be enhanced in the form of niosomes. Present work indicates that using biocompatible and cost effective surfactants, efficient niosomal form of Tranexamic acid with good percentage entrapment efficiency can be formulated. Thus the prepared niosome could be promising delivery system for tranexamic acid with sustained drug release.

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