Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

PLURONIC MODIFIED RALOXIFENE LOADED NIOSOMES AS A NEW DRUG DELIVERY

J. Gomathi*[1] and B. Jaykar[1]

[1*]Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamil Nadu, India.

ABSTRACT

Raloxifene, a second-generation selective estrogen receptor modulator uses to prevent breast cancer and osteoporosis in postmenopausal women is administered orally in the form of tablet. The absolute bioavailability of the drug is only 2% because of extensive hepatic first-pass metabolism. To tackle this problem, co-polymeric pluronic conjugate micelles, which are amphiphilic copolymers, were designed and evaluated in this study. These highly stable micelles with raloxifene the core were formulated by thin film hydration method using various types and combinations of non-ionic surfactant (span60), co-polymeric surfactants (pluronic L64 pluronic P85), and charge inducing agent (DCP). The prepared mixed raloxifene niosomes were characterized for particle size, PDI, zeta potential. FTIR and DSC studies revealed that there was no interaction between the drug and Excipients. SEM studies showed nearly spherical shaped vesicles. F5 showed highest % drug content more than 98% entrapment efficiency 94.64±0.48% and % of *in-vitro* release 99.32±0.06% was obtained at 24th hour. *In-vitro* kinetics release rate for the all formulations followed zero order mechanism. The Optimized F6 formulation was subjected to three months for stability studies at temperature 5°C ± 3°C showed that there is not much variation in the % drug release.

KEYWORDS

Raloxifene, Non-ionic surfactants, Co-polymeric surfactants, Thin film hydration technique, Evaluation parameters and *In-vitro* drug release.

Author for Correspondence:
Gomathi J,
Department of Pharmaceutics,
Vinayaka Mission's College of Pharmacy,
Yercaud Main Road, Kondappanaickenpatty,
Salem, Tamil Nadu, India.

Email: gomathidinesh1@gmail.com

INTRODUCTON

Raloxifene is an estrogen agonist/antagonist used to prevent breast cancer and osteoporosis in postmenopausal women. Raloxifene is poorly soluble drug as it belongs to class II category according to BCS classification. Raloxifene oral bioavailability of only 2% owing to extensive first pass metabolism, therefore, it is necessary to increase the solubility and dissolution rate of raloxifene which lead to improvement in oral

bioavailability[1,2]. Enhancement in oral bioavailability can be achieved by reducing the hepatic first pass metabolism. Such problem with conventional dosage form can be minimized by any suitable novel drug delivery system such as pro-drug concept or by the use of novel noisomal vesicular delivery[3].

This work was designed to developed Raloxifene loaded mixed niosomes and characterize these carriers for oral raloxifene administration. raloxifene was chosen as a model drug. niosomes are well-known NDDS formed from nonionic amphiphiles in vesicular form. A number of nonionic amphiphiles have been used to prepare niosomes. The idea of preparing mixed niosomes by using more than one amphiphiles in niosome formulation to improve the noisome properties such as stability and drug-loading capacity has not been adequately explored. Most of the studies focus on Span and Tween surfactants. One of the goals of this study was to evaluate the potential of Pluronics to form niosomes by themselves or combined with Span 60. Pluronics are widely used triblock copolymers consisting of hydrophilic poly (ethylene oxide) (PEO) and hydrophobic poly (propylene oxide) (PPO) groups. These polymers were chosen due to their excellent ability to interact with body membranes and hydrophobic surfaces, thus enhancing the drug transport across cellular barriers such as intestinal epithelial cells. Three different Pluronic polymers—Pluronic L64 (EO13-PO30-EO13) and Pluronic P85 (EO26-PO40-EO26),—and Span 60 were used to prepare niosomes and mixed niosomes[4]. Due to their colloidal properties, prepared formulations were characterized in terms of particle size, zeta potential, osmotic shock, drug encapsulation efficiency and *in -vitro* drug release. The thermal analysis and microscopic visualization were further performed for characterization.

MATERIAL AND METHODS

Materials

Raloxifene was gifted by Sanika Chemicals Pvt.Ltd, Mumbai, India. Pluronic L64 and Pluronic P85 were purchased from Pratham Chemical Company, Mumbai, Cholesterol and Span60 were purchased from Loba chemicals, India.. Dialysis membrane, 12,000-14,000 Da was purchased from Himedia Laboratories Pvt.Ltd, Mumbai, India. All other chemicals used were of analytical grade.

EXPERIMENTAL PROCEDURE

Drug- Excipients compatibility studies

FTIR study was done as a part of pre-formulation study for the selection of Excipients and to check the compatibility of drug with other Excipients. The discs were scanned over a wave number range of 400 to 4000 cm^{-1} in FTIR instrument (schimadzu FTIR – 8400S, Europe).

Differential scanning calorimetric (DSC) analysis is a fast and reliable method to understand the polymeric transitions, to screen drug excipients compatibility and provide maximum information about possible interactions. The DSC heating curves raloxifene, cholesterol, and non-ionic surfactants and Physical mixture of raloxifene was recorded using differential scanning calorimeter (DSC Q20V24.11 Build 124, USA)[5-7].

Preparation of niosomes by conventional thin film hydration method

Drug-loaded niosomes were formed by film hydration method combined with sonication. Niosome formulations were prepared by using various surfactant (Span 60, Pluronic P85, and Pluronic F127) combinations and charge inducing agent (dicetyl phosphate). The mixture of surfactant, cholesterol, DCP and raloxifene was dissolved with chloroform in a rounded bottom flask at the molarities shown in Table I. Chloroform was removed by Rotatory vapor ((Laborota 4000, Heidolph, Germany) at 55°C with a rotation speed of 60 rpm. In order to remove the traces of chloroform, vacuum was applied to the flask overnight. Subsequently, the thin film was hydrated with 10-mL ultrapure water at 60°C by 15-min vortexing and 15-min bath sonication. Further probe sonication was applied at 42 W for 15 min. The obtained noisome dispersions were stored in a refrigerator at 5±3°C. Formulations were characterized after a 2-day incubation period. Shown in Table No.1

Estimation of entrapment efficiency

Entrapment efficiency of the raloxifene niosomes derived niosomal dispersions were be done by separating the unentrapped drug by dialysis method and the drug remained entrapped in niosomes was determined by complete vesicle disruption using 0.1% Triton X-100 and analyzed UV spectro photometrically for the drug content after suitable dilution with pH7.4 phosphate buffer and filtered through what mann filter paper. The percentage of drug encapsulation (EE (%)) was calculated by the following equation:[8,9].

EE %=[(Ct-Cr/Ct)] ×100%

Where Ct is the concentration of total drug, Cr is the concentration of free drug

Estimation of percentage of drug content

The percentages of drug content of the formulations were determined by lysing method, using 50% n-propanol. 1ml of the niosomal preparations were pipetted out, sufficient quantity of 50% n-propanol was added and shaken well for the complete lysis of the vesicles. After suitable dilution with the phosphate buffered saline of pH 7.4, the absorbance of the solutions were measured at 290nm in the UV-Visible Spectrophotometer using plain niosomes as a blank and the percentage of drug content was calculated. The drug content is calculated following formula,[8,9].

%Drug content = Sample Absorbance/ Standard Absorbance× 100

Size and size distribution measurements and surface charge

The vesicle size and surface charge of the niosome is determined by measuring the electrophoretic mobility of the niosomes using a Malvern zeta sizer (Malvern Instruments ltd, UK) equipped with a 5 mW helium neon laser with a wavelength output of 633 nm. Glassware is cleaned of dust by washing with detergent and rinsing twice with water for injections. Measurements of size analysis are made at 25˚c at an angle of 90˚. Data are analyzed using the "CONTIN" method (Pecora, 2000). Polydispersity index was determined as measures of homogeneity. Values were obtained from the printed report of Malvern zeta sizer which includes the present intensity in terms of size distribution of noisome and their respective sizes. Small values of PI indicate a homogeneous population while high values indicate heterogeneity[10].

Effect of Osmotic Shock

The effect of osmotic shock on niosomal formulations was investigated by monitoring the change in vesicle diameter after incubation of niosomal suspension in media of different tonicity i.e., 1.6% NaCl (hypertonic), 0.9% NaCl (isotonic) and 0.5% NaCl (hypotonic). Suspensions were incubated in these media for 3 hours and the change in vesicle size was measured by optical microscopy with a calibrated eyepiece micrometer[11].

Transmission Electron Microscope observation of niosomes

The morphological appearance of niosomes was observed by transmission electron microscopy (TEM). In order to prepare the samples for the microscopy, niosome dispersion was dropped onto carbon-coated 200-mesh copper grids and held horizontally to allow the penetration. The excess sample was removed by filter paper, and one drop of 2% uranyl acetate was added to the grid for staining. The negatively stained samples were then imaged on a FEI Tecnai G2 Spirit Bio (TWIN) electron microscope (FEI, Eindhoven, Netherlands) at 120 kV[12].

***In-Vitro* release studies**

In vitro release rate of niosomes was carried out and the drug in pH 7.4 phosphate buffer saline was used as a control. Then niosomes was placed inside the pretreated dialysis membrane (mw-12,000-14,000Da, Hi media, LA 387, Mumbai.) with an effective length of 5 cm tied at both the ends. It was then transferred to a beaker containing 100ml of phosphate buffer saline pH 7.4. The temperature was maintained at 37±0.5ºC and the medium was agitated at a speed of 50 rpm using a magnetic stirrer. 5 ml of the samples were collected at a predetermined time and replenished immediately with the same volume of fresh buffer. The sink condition was maintained throughout the experiment. The collected samples were analyzed spectrophotometrically at 290 nm using UV-Visible Spectrophotometer. The *in- vitro* release studies

were also carried out for the control drug by the same method[13].

***In Vitro* release kinetic studies**

To predict the pharmacokinetics and mechanism of drug release, the results of *in vitro* drug release study of niosomes were fitted into various pharmacokinetic models viz. zero order (cumulative % release vs. time), first order (log % drug remaining vs. time), Higuchi's model (cumulative % drug release vs. square root of time), and the Korsemeyer- Peppas (log cumulative % drug release vs log time). The r^2 and K values were calculated for the linear curve obtained by regression analysis of the above plots[14].

Stability studies

The optimized batch was stored in airtight sealed glass vials at different temperatures 5 °C± 3°C and at 25 ± 2°C/60% RH±5% RH (Modified ICH Guidelines) for 90days in an environmental chamber [Inlab equipments (Madras) Pvt. Ltd]. Surface characteristics, %drug retained and *in-vitro* drug release parameters evaluated at regular intervals of time (0, 30days and 90days) analyzed by spectrophotometer[15].

RESULTS AND DISCUSSION

Drug- Excipient compatibility studies

The drug raloxifene showed the sharp peak at 3643.10 cm-1 (O-H Stretching), 1234.67 cm-1 (C-O Phenolic), 1519.82 cm-1 (C=C Aromatic), 1730.36 cm-1 (C=O Keto), 1051.39 cm-1 (C-O Ether), 1234.67 cm-1, (C-N amine). All these peaks have appeared in physical mixture was indicated no chemical interaction between raloxifene, cholesterol, and non-ionic surfactants (span 60, pluronicL64 and pluronicP85). FT-IR study results revealed that all characteristic peaks of raloxifene were appeared in the niosomal formulation spectra, which indicated there was no phenomenal change in the position of peaks after successful method of preparation and also the drug is compatible with the components excipients. It also confirmed that the stability of drug during formulation Shown in FigureNo.1A and 1B.

In DSC measurements, raloxifene pure drug showed the melting endotherm at 144.67ºC it was compared with the thermogram obtained from the physical mixture. An endothermic peak revealed clearly that there was no interaction between the pure drug and the physical mixtures were shown in the Figure No.2A and 2B along with its corresponding melting point.

Estimation of entrapment efficiency of raloxifene niosomes

The entrapment efficiency (%EE) of raloxifene niosomes in F1-F6 formulation varied between 36.28±0.93% and 94.64±0.48% were shown in the Table No.2

The highest encapsulation was obtained for Pluronic P85 niosomes followed by Pluronic L64. This result could be attributed to the increased capacity of the lipophilic environment in the niosome bilayer resulting from the increasing PPO chain length and the increasing molecular weight. This relationship weakened upon combined usage of Pluronics with Span 60 in mixed niosomes. The molecular weights of Pluronic P85, Pluronic L64, Span 60, and raloxifene are 4600, 2900, 430.62, and 473.58 g/mol respectively. It is reported that combination of a low molecular weight amphiphile to Pluronics significantly affects the association or disassociation of these polymers to form micelles. Span 60 is a hydrophobic amphiphile with a HLB value of 4.7 raloxifene also hydrophobic. The combination of Span 60 with Pluronic P85, which has lower molecular weight and own longer hydrophilic PEO chain than PPO chain, increases the hydrophobicity level, thus contributing to entrapment efficiency from formulation (F4) 80.54±0.61 to formulation (F5) 94.64±0.48%.

The encapsulation efficiency percentage showed a tendency to decrease when amount of DCP was increased from formulation (F5) 94.64±0.48% to formulation (F6) 89.60±0.50%. This decrease may be due to decrease noisome stability aroused from enhanced repulsion within the bilayers of niosomes.

Estimation of percentage of drug content

The raloxifenee loaded niosomes drug content was found to be in the range of 98.02±0.53% to 99.71±0.24%. The results were indicated that the uniform distribution of drug in prepared niosomal

formulations. The observed results were shown in Table No.2.

Size and size distribution measurements and surface charge

The vesicle size of niosomes plays an important role in release character of the drug from microspheres. The vesicles size of niosomes varied somewhat, due to variation in the composition of span 60 and pluronic coploymeric surfactants. The vesicle size and surface charge of the niosome was done by using a Malvern zeta sizer. The average raloxifene niosomes size was varied between 112.5±1.14nm and 385.2±2.46nm and increased as the HLB value of surfactants increased. As expected, an increase in the length of PEO and PPO moieties in the structure of Pluronics, thus the molecular weight of the polymers, leads to the formation of larger niosomes. The higher hydrophilic chain lengths lead to the formation of less rigid and looser bilayers.

The average size of niosomes prepared with Pluronic P85 (F4) was found to be 225.0±1.04 nm whereas after addition of Span 60 formulation (F5) the size increased to 268.6±1.30 nm. The addition of an amphiphile, which has a dominant hydrophobic character, to this formulation leads to the formation of a more elastic and flexible lipid layer resulting in increased particle size.

The charge inducing agent DCP is known to stabilize niosomes against aggregation and precipitation by increasing their zeta potential. Furthermore, these agents enhance the permeability of the noisome membrane to water and lead to the formation of large niosomes. This relation was observed in F6 formulation in which noisome size increased from 268.6±1.30nm (F5) to 385.2±2.46 nm (F6) as DCP concentration was increased. Amomg all six formulations of niosomes, formulation F5 and F6 constantly increased in size. Formulation F5 produced optimum size of niosomes 268.6±1.30nm.

The quality and uniformity of the dispersed systems is expressed with the polydispersity index values. The values less than 0.7 are considered as suitable measurements. In the niosome formulations, PDI values ranged between 0.19±0.02 and 0.30±0.05. The low PDI values demonstrated the narrow size distribution and uniformity of the niosomal formulation. The observed results were shown in Table No.3.

Surface charge of pluronic modified raloxifene niosomes

One of the parameters for interpreting the stability of colloidal systems is their zeta potential. As the zeta potential increases, the charged particles repel one another, and this stabilizes the system against agglomeration and prevents faster settling. Systems with the zeta potential value of >-30 mV or >+30mV are considered to be stable. The zeta potential of the niosomes was changed within a range of -23.20±0.8mV and-47.40±0.9 mV in this respect some of the formulations have adequate stability due to high electrostatic stabilization.

The zeta potential of the formulations F5 and F6 were found to -46.30±0.4 mV and --47.40±0.9mV this is due to higher repulsion, as a result of this precipitation retarded for F5 and F6 formulation. So evenly distributed suspension were obtained formulations F5 and F6 would yield better stable formulations. The observed results were shown in Table No.3.

Effect of Osmotic Shock

Formulations were treated with 1.6% NaCl (hypertonic), 0.9% NaCl (isotonic) and 0.5% NaCl (hypotonic) solutions. Vesicles size was not increased significantly in formulations with plain pluronic copolymeric surfactants. This shows that plain co-polymeric surfactants increase the rigidity of the vesicles. Increased vesicle size was observed in the formulations with span 60 and DCP. Inclusion of span 60, pluronic surfactants and DCP reduces the rigidity due to electrostatic repulsion thereby increasing the vesicle size. In hypertonic solution, all the formulations shrank uniformly. Formulation incubated with saline showed a slight increase in vesicle size when compared to other media. This demonstrates that raloxifene niosomes could be diluted with normal saline for parental use. The observed results were shown in Table No.4

***In-Vitro* release studies**

The Raloxifene release profiles from marketed formulation and F1–F8 in phosphate saline pH7.4, are given in Figure No.3. Thus a good sink

condition was observed in this study. It was found that more than 98% of control tablet was released within 6 hours. The in vitro drug release profiles demonstrated that the release rate of marketed formulation is lower than raloxifene released from niosomes ($p>0.05$).

The cumulative release of raloxifene niosomes was significantly lower in the F2 and F4 formulation with 82.27±0.94% and 88.56±0.65% at the end of the 24th hour ($p>0.05$). The release rate was ordered as F2>F4 in niosomes prepared with plain Pluronics in which the inner hydrophobic core of the micelles could retain raloxifene firmly, resulting in a slow drug release rate under sink conditions.

The drug release rate was higher when Span 60 was combined with co-polymeric pluronic surfactants (L64 and P85) it was shows 90.02±1.24% (F3) and 99.32±0.06% (F5) of drug release at end of the 24th hour in which the PEO chain length was increased and also increased release rate. This was attributed to the hydrophilic PEO chains surrounding the niosome surface and leading to a decrease in surface tension which provokes the drug release. Besides, as the length of the hydrophilic chain increases, this forms a looser bilayer in the niosomal structure and improves the drug release. This explains the high drug release rate F7 niosomes prepared from mixed span60, Pluronic P85 and DCP ratio at (0.5, 0.5:0.1). Higher density of PEO chains on the surface layer might have caused increased water loading on the surface thus enhancing the drug release. Increased DCP amount contributed to the drug release rate due to its hydrophilic nature. In this research, the maximum and minimum erosion effects were observed for F1 and F5 formulations, respectively.

This comparative release data indicate that, among various formulations, F7 was found to have a good release pattern and controlled release up to 24hrs it could be suggested that the developed micelle could act as controlled released niosomal carrier it was selected as the optimized formulation and used for the further studies.

***In-Vitro* kinetic studies**

The in-vitro drug release of raloxifene niosomes was best explained by zero order kinetics as the plots showed the highest linearity. R^2 was in the range of 0.9903 to 0.6702 for various formulations. All the formulations showed best fitted to Korsmeyer–Peppas model (r2: 0.9888 to 0.9903) with slope (n) values ranging from 0.5081 to 0.6702, indicating that non-Fickian diffusion (anomalous) was the predominant mechanism of drug release from all the formulations. It can be concluded that the release was dependent on both drug coupling diffusion, polymer relaxation and erosion mechanisms. The release kinetic parameters were shown in the following Table No.5.

Stability studies of optimized raloxifene niosomes

The Physical stability of optimized niosomal formulations (F5) were carried out by storing at 5°C ± 3°C, at 25°C ± 2°C/60% RH±5% RH and 40 ± 2°C/75% RH±5% RH for a period of three months. The vesicle size, remaining drug content and release study was estimated at the interval of one month over a period of three months. From the results it was monitored that there was not much variation in the colour and appearance and also the drug leakage from the vesicles and cumulative percentage drug release was less at 5±3°C when compared with 25±2°C and 40±2° C. Approximately more than 90% of raloxifene was retained in optimized niosomal formulations after the three-month period. Thus, Span 60 and pluronic P85 modified niosomes of raloxifene (F5) seemed to exhibit good stability at low temperature. At high temperature entrapment efficiency and release rate was reduced to a particular rate. This might be, upon storing leakage from vesicles occurred at high temperature due to phase transition of surfactant and lipid. The results of this study assumed that the stability of niosomes could be maintained at 5±3°C followed by 25±2°C.

Table No.1: Composition of raloxifene loaded niosomes

Formulation code	Raloxifene (mg)	Span 60	Pluronic L64	Pluronic P85	DCP	Cholesterol	Chloroform (ml)	Distilled water(ml)
F1	60	11.4 mM	-	-	1.20	11.4	10	q.s.10
		49.3 mg	-	-	6.49	44.2	10	q.s.10
F2	60	-	11.4 mM	-	1.20	11.4	10	q.s.10
		-	330 mg	-	6.49	44.2	10	q.s.10
F3	60	5.70 mM	5.70 mM	-	1.20	11.4	10	q.s.10
		24.6 mg	165 mg	-	6.49	44.2	10	q.s.10
F4	60			11.4 mM	1.20	11.4	10	q.s.10
				524 mg	6.49	44.2	10	q.s.10
F5	60	5.70 mM		5.70 mM	1.20	11.4	10	q.s.10
		24.6 mg		262 mg	6.49	44.2	10	q.s.10
F6	60	5.70 mM		5.70 mM	6.00	11.4	10	q.s.10
		24.6 mg		262 mg	32.5	44.2	10	q.s.10

DCP-dicetyl phosphate, q.s.-quantity sufficient

Table No.2: % of entrapment efficiency and % of drug content of raloxifene loaded niosomal formulations F1 to F6

Formulation code	Surfactants	HLB value	% of Entrapment efficiency*	% of Drug Content*
F1	Span60	4.7	90.70±0.21	99.71±0.24
F2	Pluronic L64	15	36.28±0.93	98.02±0.53
F3	span60, Pluronic L64	13.7	73.63±0.41	99.15±0.62
F4	Pluronic P85	16	80.54±0.61	99.42±0.43
F5	span60,Pluronic P85	15	94.64±0.48	99.55±0.61
F6	span60,Pluronic P85	15	89.60±0.50	99.71±0.24

*Mean ± SD, (n=3)

Table No.3: Vesicle size, Zeta potential analysis of raloxifene loaded niosomal formulations F1 to F6

Formulation code	Vesicle Size (nm)*	PDI*	Zeta Potential (mV)*
F1	112.5±1.14	0.21±0.02	-30.45±0.6
F2	184.3±1.32	0.24±0.01	-27.61±0.2
F3	200.4±1.26	0.19±0.02	-35.80±1.4
F4	225.0±1.04	0.22±0.02	-24.62±0.4
F5	268.6±1.30	0.23±0.02	-46.30±0.4
F6	385.2±2.46	0.30±0.05	-47.40±0.9

*Mean ± SD, (n=3)

Table No.4: Effect of osmotic shock on raloxifene loaded niosomal formulations F1 to F6

	Average vesicle size (nm) after incubation with			
Formulation code	**PBS pH7.4***	**Hypertonic 0.5% Nacl***	**Normal 0.9%Nacl***	**Hypertonic 1.6%Nacl***
F1	112.5±1.14	115.1±0.56	113.2±1.32	shrunk
F1	184.3±1.32	187.5±0.18	185.5±1.14	shrunk
F3	200.4±1.26	203.8±0.72	201.0±0.56	shrunk
F4	285.2±1.60	288.8±1.80	286.4±1.21	shrunk
F5	372.5±2.22	376.3±1.57	374.0±1.34	shrunk
F6	225.0±1.04	228.7±0.41	226.4±0.90	shrunk
F7	268.6±1.30	271.0±0.65	269.0±2.32	shrunk
F8	385.2±2.46	388.6±0.98	386.7±1.15	shrunk

*Mean ± SD, (n=3)

Table No.5: Kinetics release data of formulation F1 to F6

Formulation Code	Zero-order kinetics		First order kinetics		Higuchi model		Hixsoncrowell		Korsmeyer–Peppas model	
	Slope	R^2	Slope	R^2	slope	R^2	slope	R^2	n	R^2
F1	7.8029	0.9918	-0.1372	0.7424	29.032	0.9617	-0.2642	0.9119	0.6702	0.9901
F2	3.0352	0.9944	-0.02741	0.9621	16.7710	0.9750	-0.7600	0.9852	0.5698	0.9900
F3	3.2846	0.9904	-0.0383	0.9409	18.2616	0.9827	-0.0960	0.9805	0.5081	0.9900
F4	3.3288	0.9909	-0.03582	0.9419	18.4633	0.9806	-0.0920	0.9811	0.5616	0.9903
F5	3.5503	0.9903	-0.0704	0.7915	19.7380	0.9819	-0.0730	0.9702	0.5081	0.9900
F6	3.2703	0.9903	-0.03653	0.9536	18.1967	0.9846	-0.0633	0.9723	0.5122	0.9888

Table No.6: Short term stability studies data of optimized raloxifene niosomal formulation (F5)

S.No	Temperature	% of *in-vitro* drug release		
		Values obtained at zero day	Values obtained at 30th day	Values obtained at 90th day
1	4 ± 1°C	99.32±0.06	98.99±0.05	98.05±1.26
2	25 ± 2°C/60% RH±5% RH	99.32±0.06	97.76±0.91	97.10±0.05
3	40 ± 2°C/75% RH±5% RH	99.32±0.06	94.01±1.48	90.48±0.92

*Mean ± SD, (n=3)

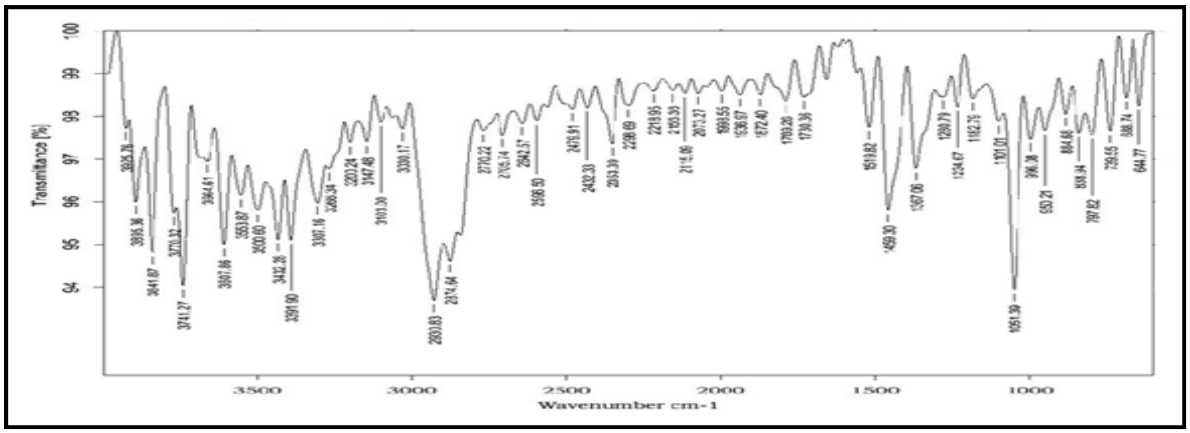

Figure No.1A: FTIR graph of pure raloxifene drug

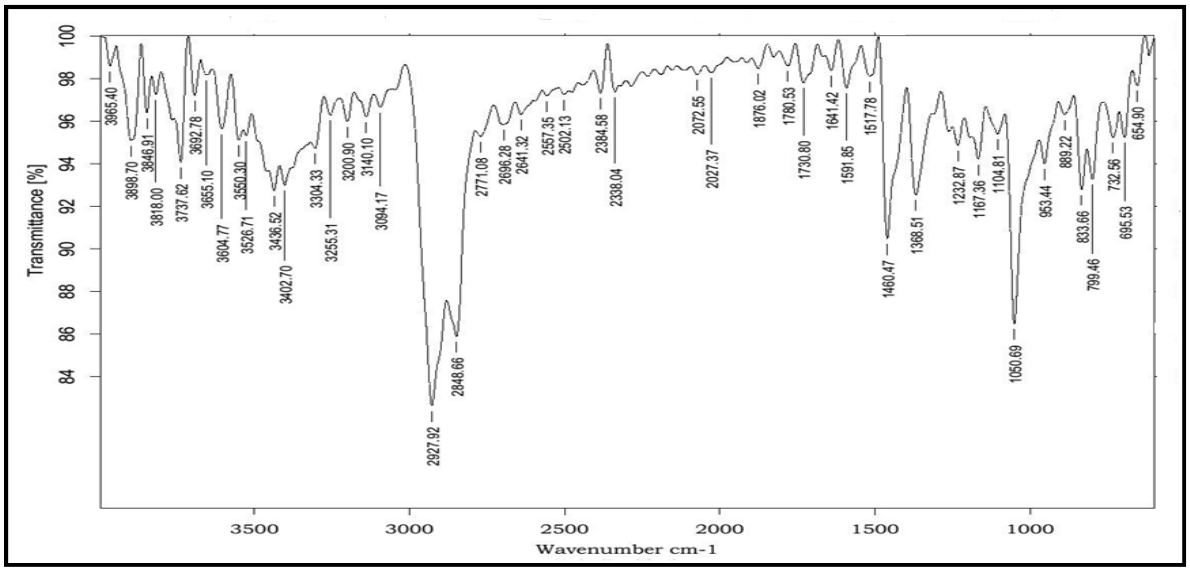

Figure No.1B: FTIR graph of optimized raloxifene niosome (F5)

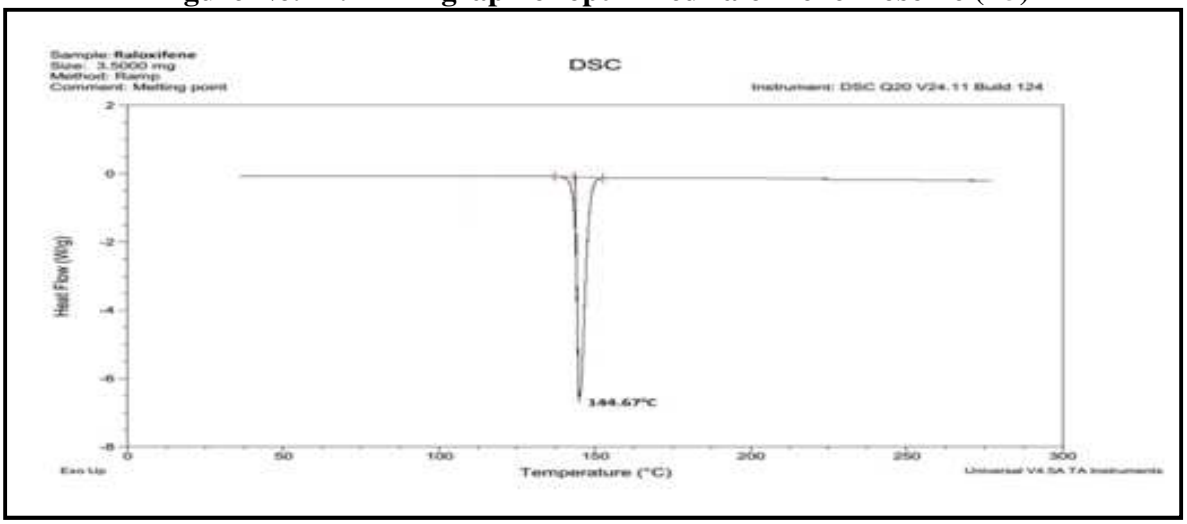

Figure No.2A: DSC thermogram of pure raloxifene drug

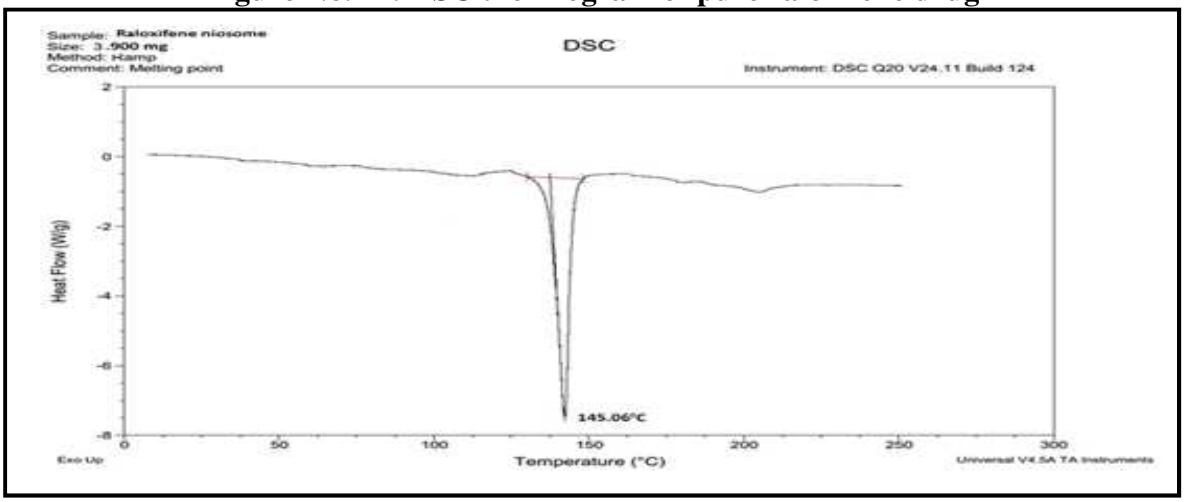

Figure No.2B: DSC thermogram of optimized raloxifene niosomes (F5)

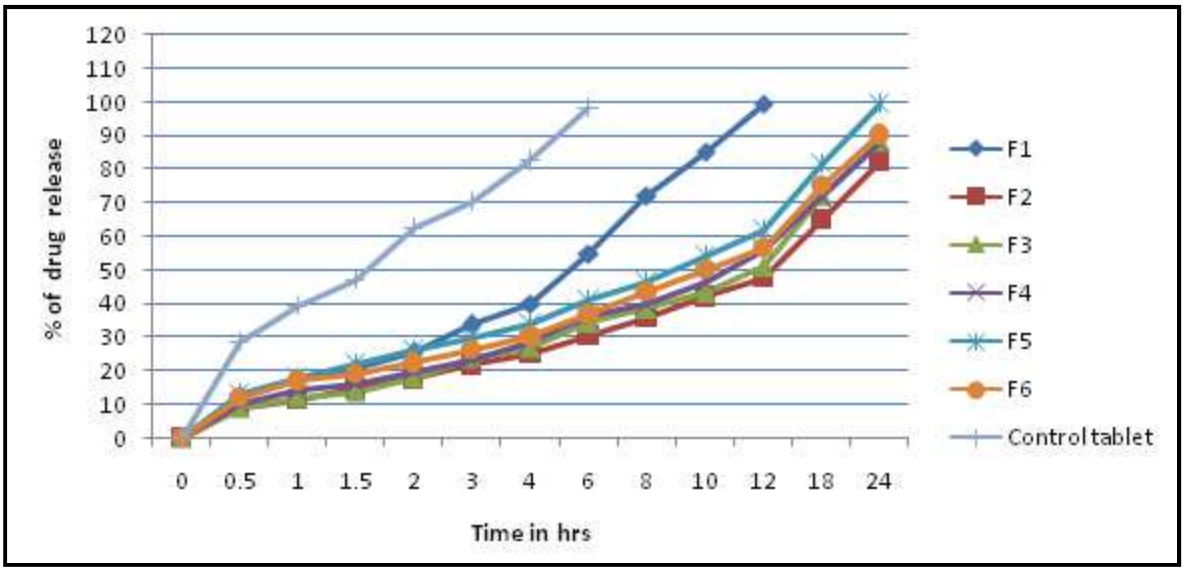

Figure No.3: Percentage drug release profile of formulation F1-F6 and control tablet

CONCLUSION

In this study, niosomes and mixed niosomes encapsulating a poorly water soluble drug (Raloxifene) were successfully prepared by thin film hydration technique. Among the mixed niosome formulations prepared by combining Span 60 and Pluronic P85 (F5)-mixed niosomes containing low level of DCP as charge inducing agent represented highest drug entrapment and better stability in storage condition (5°C ± 3°C) compared to other formulation. *In-vitro* study revealed that formulation F5 showed maximum drug release at end of 24hrs. Further, the *in-vitro kinetics* models to explained the release mechanism by zero order release. So the prepared pluronic modified raloxifene niosomal vesicles could be the promising drug delivery system for controlled release of raloxifene and getting into the drug market.

ACKNOWLEDGEMENT

Sincere thanks to Prof. Dr. B. Jaykar, Registrar, Vinayaka Mission's Research Foundation, Salem for this unstinted support and constant encouragement and guidance. Sincere thanks to Principal, and faculties of Vinayaka Mission's College of Pharmacy, Salem for providing the facilities for carry out the work.

CONFLICT OF INTEREST

The author declares that there is no conflict of interests regarding the publication of this paper.

BIBLIOGRAPHY

1. Ettinger B, Black D M, Mitlak B H, Knickerbocker R K, Nickelsen T, Genant H K, *et al.* Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: result from a 3-years randomized clinical trial, *JAMA,* 6(1), 1999, 637-45.
2. Patil P H, Belamwar V S, Patil P R, Surana S J. Solubility enhancement of raloxifene using inclusion complexes and co grinding method, *J Pharm,* 1(1), 2013, 1-9.
3. Khoo H M, shackleford D M, Porter C J H, Edwards G A, Charman W N. Intestinal lymphatic transport of halofantrine occurs after oral administration of a unit dose lipid based formulation to fasted dogs, *Pharm Res,* 20(1), 2003, 160-75.
4. Tavano L, Vivacqua M, Carito V, Muzzalupo R, Caroleo M C, Nicoletta F. Doxorubicin loaded magneto-niosomes for targeted drug delivery, *Colloids Surf B: Biointerfaces,* 10(2), 2013, 803-17.

5. Vijay K N, Ramarao T, Jayaveera K N. Liquid compacts: a noval approach to enhance bioavailability of poorly soluble drugs, *Int.J.Pharm. Bio.Sci,* 1(2), 2011, 89-102.
6. Gomathi J, Palanisamy P. Formulation and Evaluation of Decitabine Loaded Niosomes, *American Journal of Pharm Tech Research,* 7(5), 2017, 73-86.
7. Bhama S, Sambathkumar R. Preparation and characterization of raloxifene proniosomes, *International journal of research in pharmaceutical science,* 1(7), 2016, 142-149.
8. Carafa M, Santucci E, Alhaique F, Coviello T, Murtas E, Riccieri F M, *et al.* Preparation and properties of new unilamellar non-ionic surfactant vesicles, *Int J Pharm,* 1(60), 1998, 51-79.
9. Liu T, Guo R. preparation of a highly stable noisome and its hydrotrope solubilization action to drugs, *Langmuir ACS J Surf colloids,* 1(10), 2005, 219-24.
10. Balakrishnan P, Shanmugam S, Leea W S, *et al.* Formulation and *in-vitro* assessment of minioxidil niosomes for enhances skin delivery, *International journal of pharmaceutics,* 37(7), 2009, 1-8.
11. Kandasamy Ruckmani, Venitramuthu Sankar. Formulation and Optimization of Zidovuine niosomes, *AAPS Pharm SciTech,* 3(1), 2010, 61-74.
12. Roser M, Fischer D, Kiser T. Surface modified biodegradable albumin nano and microspheres. II: effect of surface charges on *in vitro* phagocytes and bio-distribution in rats, *Eur J Pharm Biopharm,* 4(6), 1998, 255-63.
13. Cohen E. The permeability of liposomes to non-electrolytes. I. activation energies for permeation, *J.Member Biol,* 2(1), 2001, 205-34.
14. Das M K, Rama Rao K. Microencapsulation of Zidovudine by double emulsion solvent diffusion technique using ethyl cellulose, *Indian J Pharm Sci. 2ilani,* 6(9), 2007, 244-50.
15. Esmaeil Moazeni, Kambiz G, Farzaneh Sotoudegan, Abbas Pardakty, Rouhollah Ghalandari. Formulation and *in-vitro* evaluation of Ciprofloxacin containing niosomes for pulmonary delivery, *Journal of Microcapsulation,* 27(7), 2010, 618-627.

Please cite this article in press as: Gomathi J and Jaykar B. Pluronic modified Raloxifene loaded niosomes as a new drug delivery, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 7(2), 2019, 402-412.