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FORMULATION AND CHARACTERIZATION OF PLURONIC MODIFIED CAPECITABINE LOADED NIOSOMES; FOR BREAST CANCER THERAPY

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ABSTRACT

Capecitabine is an anticancer drug which is widely used in the treatment of breast cancer. However, its clinical application for cancer treatment has been greatly limited due to its low bioavailability. To tackle this problem, pluronic conjugate micelles, which are amphiphilic copolymers, were designed and evaluated in this study. These highly stable micelles with capecitabine in the core were formulated by slurry method using span 60, mixed span60/pluronic F127, mixed span60/pluronic P85 and cholesterol. The prepared Capecitabine 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. F6 showed highest % drug content (99.51±0.36), % entrapment efficiency 85.03±0.54% and % of *in-vitro* release 98.82±0.47% 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 vesicles size, % drug retained and cumulative percentage of drug release.

KEYWORDS

Capecitabine, Non-ionic surfactants, Non-ionic copolymers surfactants, Slurry method, Evaluation parameters and *In-vitro* release.

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INTRODUCTON

The bioavailability of the drugs is influenced by a number of factors. The route of drug administration is the most important of all factors[1]. It is well known that oral administration of drugs is preferred over alternatives due to its convenience and lower costs. The oral administration of several drugs is hampered due to their unstable and water insoluble nature that leads to low bioavailability. Presystemic

metabolism, low intestinal permeability, and lack of drug release are some other factors that lower the oral bioavailability. In recent years, there has been an increasing interest on the usage of drug delivery systems to improve the oral bioavailability of active agents, and particularly, nanosized drug delivery systems (NDDSs) are emerging in this field[2]. The efficacy of NDDS for bioavailability enhancement is a challenge. The success of the NDDS is highly influenced by its ability to carry the drug through the biological membranes without degradation and specificity of its biodistribution[3]. Several transportation mechanisms have been proposed for NDDS passage through gastrointestinal barriers. Para cellular passage, endocytosis uptake, and lymphatic uptake via M cells in Peyer's patches are the main pathways.

Capecitabine, is an oral prod rug of fluorouracil (5-FU) and therefore a thymidylate synthase inhibitor (TS inhibitor). It is widely used in the treatment of patients with metastatic colorectal cancer and breast cancer. Since it is readily absorbed from the gastrointestinal tract. The recommended daily dose is large, i.e., 1250 mg/m2 and it have a short elimination half-life of 30 minutes which results in frequent administration of the dosage form and increased side effects. However, its short elimination half-life of Capecitabine is the major problem in formulation development step[4]. There are several approaches to improve the prolonged released time of Capecitabine including the formulation of NDDS[5,6].

This work was designed to developed Capecitabine loaded niosomes and characterize these carriers for oral Capecitabine administration. Capecitabine 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[7]. Three different Pluronic polymers Pluronic F127 (EO100-PO65-EO100) and Pluronic P85 (EO26-PO40-EO26) and Span 60 were used to prepare niosomes and mixed niosomes. Due to their colloidal properties, prepared formulations were characterized in terms of particle size, zeta potential, drug encapsulation efficiency and *in - vitro* drug release. The thermal analysis and microscopic visualization were further performed for characterization.

MATERIAL AND METHODS

Materials

Capecitabine was a gift sample from East West Pharma, Uttarakhand. Laboratories Pvt. Ltd., India. Pluronic F127and 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., LA, Mumbai, India. All other chemicals used were of analytical grade.

EXPERIMENTAL PROCEDURE

Drug- excipient 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[8].

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 Capecitabine, cholesterol, and non-ionic surfactants and Physical mixture of Capecitabine was recorded

using differential scanning calorimeter (Perkin Elmer STA 6000 Thermal Analyzer, USA)[9].

Preparation of niosomes by conventional thinfilm 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 (DCP)]. The mixture of surfactant, cholesterol, DCP and capecitabine was dissolved with chloroform in a rounded bottom flask at the molarities shown in Table No.1. Chloroform was removed by Rotavapor ((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[10].

ESTIMATION OF ENTRAPMENT EFFICIENCY

Entrapment efficiency of the capecitabine proniosomes derived niosomal dispersions were be done by separating the unentrapped drug by dialysis method and the drug remained entrapped in proniosomes 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:

$$EE\ \% = [(Ct - Cr/Ct)] \times 100\%$$

Where Ct is the concentration of total drug, Cr is the concentration of free drug[11,12].

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 240nm 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[13],

%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 5mW 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^{o}C at an angle of 90^{o}. 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[14].

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[15].

***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. Initially the treatment of dialysis

membrane (mw-12,000-14,000Da, Hi media, LA 387, Mumbai.) Then niosomes was placed inside the pretreated dialysis membrane 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 240nm using UV-Visible Spectrophotometer. The *in vitro* release studies were also carried out for the control drug by the same method[16].

In vitro release kinetics

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.

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, 30, 60 and 90 days), after being hydrated to form niosomes and analyzed by spectrophotometer[17].

RESULTS AND DISCUSSION

Drug- excipient compatibility studies

The drug Capecitabine showed the sharp peak at 3519cm^{-1} N-H stretching, a board peak at 3222cm^{-1} of O-H stretching, 2931cm^{-1} C-H stretching, 1718cm^{-1} C=O stretching, 1614cm^{-1} C=C stretching and 1116cm^{-1} C-O bending vibrations and the sharp characteristics peaks. The FTIR spectra of the pure drug and other formulations indicated that no interactions between the drug and other components of the formulation. Shown in Figure No.1

In DSC measurements, Capecitabine pure drug showed the melting endotherm at 115.67ºC it was compared with the thermo gram 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

The entrapment efficiency (%EE) of capecitabine niosomes in F1-F5formulation varied between 61.90±0.82% and 85.03±0.54% (Table no 2). As the hydrophilic-lipophilic balance (HLB) of Pluronics increased, the entrapment efficiency of Cacpecitabine also increased in the niosomes prepared from plain Pluronics (F2 and F4). The highest encapsulation was obtained for Pluronic P85 niosomes. 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 F127, Pluronic P85, Span 60, and Capecitabine are 12,600, 4600, 430.62, and 359.36 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. Furthermore, the high interactions between water soluble polymers and amphiphile molecules have been reported. Span 60 is a hydrophobic amphiphile with a HLB value of 4.7, Therefore, when Pluronic F127 which has the highest HLB and longest PPO chain length is combined with Span 60, the entrapment site inside the bilayer has to be shared between Capecitabine and the hydrophobic amphiphile. This can explain the decrease of entrapment efficiency from 74.90 to61.98%. On the other hand, combination of Span 60 with Pluronic

P85, which have lower molecular weight and own longer hydrophilic PEO chain than PPO chain, increases the hydrophobicity level, thus contributing to entrapment efficiency from75.52 to85.03%.

Estimation of percentage of drug content

The Capecitabine loaded niosomes drug content was found to be in the range of 97.27±0.43% to 99.08 ±0.64%. 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 TEM micrographs of niosomes are given in Figure No.3. The TEM images confirmed the formation of niosomes. The shapes of the vesicles were spherical, and they were similar with the typical niosome micrographs obtained in prior studies. The size of the niosomes was around the average particle size (440 nm) measured by Zetasizer. The particle size distribution histogram revealed the bimodal size distribution of F5 formulation.

***In-vitro* release studies**

The Capecitabine release profiles from marketed formulation and F1–F5 in phosphate saline pH7.4, are given in Figure No.4. The *in vitro* drug release profiles demonstrated that the release rate of marketed formulation is significantly lower than capecitabine released from niosomes ($p>0.05$). This demonstrated the solubilizing effect of niosomes leading to enhanced drug release.

In Figure No.4 the cumulative release of Capecitabine was significantly highest in the F2 and F4 niosomes with 99.74±2.11 and 98.51±0.88% at the end of the 18th hour ($p>0.05$). The release rate was ordered as F2>F4 in niosomes prepared with plain Pluronics, in which the PEO chain length was also increased. 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 from F2 niosomes prepared from Pluronic F127. Higher density of PEO chains on the surface layer might have caused increased water loading on the surface thus enhancing the drug release as it was stated in previous researches. The drug release rate and drug loading were increased when Span 60 was combined with Pluronic P85 (F6 niosomes) it was shows 99.88±0.45% of drug release at end of the 24th hour. This comparative release data indicate that, by encapsulation of drug into niosomes (F5), it is possible to control the release of drug for longer duration.

***In-vitro* kinetic studies**

The *in-vitro* drug release of niosomes was best explained by zero order kinetics as the plots showed the highest linearity. R^2 was in the range of 0.9829 to 0.9944 for various formulations. All the formulations showed best fitted to Korsmeyer–Peppas model (r2: 0.9070 to 0.9965) with slope (n) values ranging from 0.6128 to 0.9080, 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.3.

Stability studies of optimized proniosomes

Stability studies of optimized mixed niosome (F5) result shown in Table No.4. Indicated that there was no appreciable change in the formulation after 90 days months particularly at5°C ± 3°C. Hence, it may be concluded from the data obtained that the optimum storage condition for proniosome was 5°C ± 3°C.

Table No.1: Composition of Capecitabine loaded proniosomes

Formulation code	Cap (mg)	Convert mM to mg	Span 60	Pluronic F127	Pluronic P85	DCP	Cholesterol	Chloroform (ml)	Distilled water(ml)
F1	50	Mm	11.4	-	-	1.20	11.4	10	q.s.10
		mg	49.3	-	-	6.49	44.2	10	q.s.10
F2	50	mM	-	11.4	-	1.20	11.4	10	q.s.10
		mg	-	1436	-	6.49	44.2	10	q.s.10
F3	50	mM	5.70	5.70	-	1.20	11.4	10	q.s.10
		mg	24.6	165	-	6.49	44.2	10	q.s.10
F4	50	mM	-	-	11.4	1.20	11.4	10	q.s.10
		mg	-	-	524	6.49	44.2	10	q.s.10
F5	50	mM	5.70	-	5.70	1.20	11.4	10	q.s.10
		mg	24.6	-	262	6.49	44.2	10	q.s.10

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

Table No.2: Vesicle size, zeta potential analysis, % of entrapment efficiency and % of drug content of capecitabine loaded niosomes

Formulation code	Surfactant	HLB value	Vesicle Size (nm)	PI	Zeta Potential	% of Entrapment efficieny*	% of Drug Content*
F1	Span60	4.7	242.5	0.223	-39.2	80.90±0.37	97.99±0.68
F2	Pluronic F127	22	220	0.213	-27.6	74.90±0.82	98.53 ±0.32
F3	Span60, Pluronic F127	21.4	160.4	0.184	-26.5	61.98±0.54	99.37±0.13
F4	Pluronic P85	16	558.5	0.198	-24.8	75.52±0.63	98.67 ±0.41
F5	span60, Pluronic P85	15	440	0.209	-23.1	85.03±0.54	99.51±0.36

* indicates average of three values + SD.

Table No.3: *In-Vitro* Kinetic datas of capecitabine loaded niosomes

Formulation Code	Zero-order kinetics		First order kinetics		Higuchi model		Korsmeyer–Peppas model	
	KO(h-1)	R^2	K1(h-1)	R^2	KH h(-1/2)	R^2	n	R^2
F1	7.6382	0.9829	-0.14147	0.7161	28.0692	0.9631	0.6128	0.970
F2	5.8159	0.9866	-0.1072	0.755	26.3037	0.945	0.9080	0.9928
F3	4.7797	0.9944	-0.07188	0.6821	22.4376	0.9155	0.8121	0.9817
F4	5.5547	0.9915	-0.0833	0.8319	25.0160	0.9417	0.8121	0.9896
F5	3.9697	0.9903	-0.0746	0.6299	21.2559	0.9727	0.7035	0.9965

Table No.4: Stability studies of optimized capecitabine loaded niosomes (F5)

S.No	Temperature	Values obtained at zero day			Values obtained at 30th day		
		Vesicle size in nm	% of Drug retained*	% of *in-vitro* drug release*	Vesicle size in nm	% of Drug retained*	% of *in-vitro* drug release*
1	5°C ± 3°C	440	99.51±0.36.	99.88±0.45	429.4	99.08±0.71	98.94±0.05
2	25 ± 2°C/60% RH±5% RH	440	99.51±0.36	99.88±0.45	410.7	98.29±0.42	97.56±0.91

S.No	Temperature	Values obtained at 60th day			Values obtained at 90th day		
		Vesicle size in nm	% of Drug retained*	% of *in-vitro* drug release*	Vesicle size in nm	% of Drug retained*	% of *in-vitro* drug release*
1	5°C ± 3°C	424.8	98.91±0.09	97.89±0.84	420.2	98.06±0.81	97.01±0.10
2	25 ± 2°C/60% RH±5% RH	400	96.56±0.17	95.42±0.54	398.6	95.87±0.48	89.45±0.71

* indicates average of three values + SD

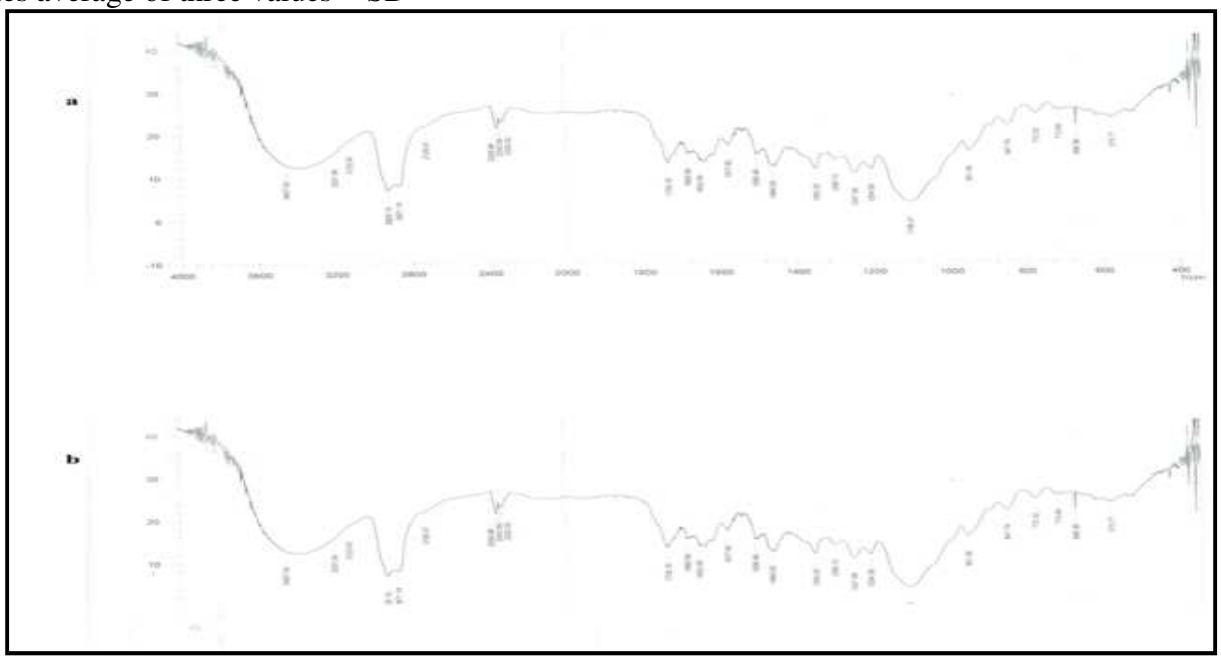

Figure No.1: A) FTIR graph of pure capecitabine drug B) FTIR graph of optimized mixed capecitabine loaded niosomal formulation F5

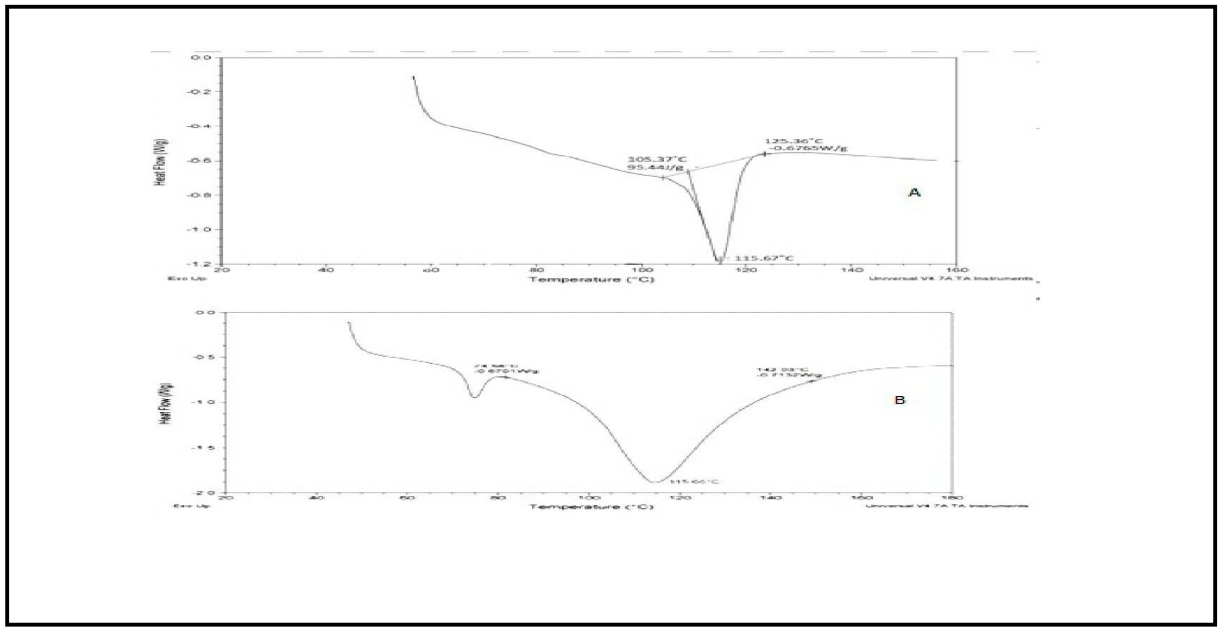

Figure No.2: A) DSC thermograms of capecitabine pure drug B) DSC thermogrms of optimized mixed capecitabine loaded niosomal formulation F5

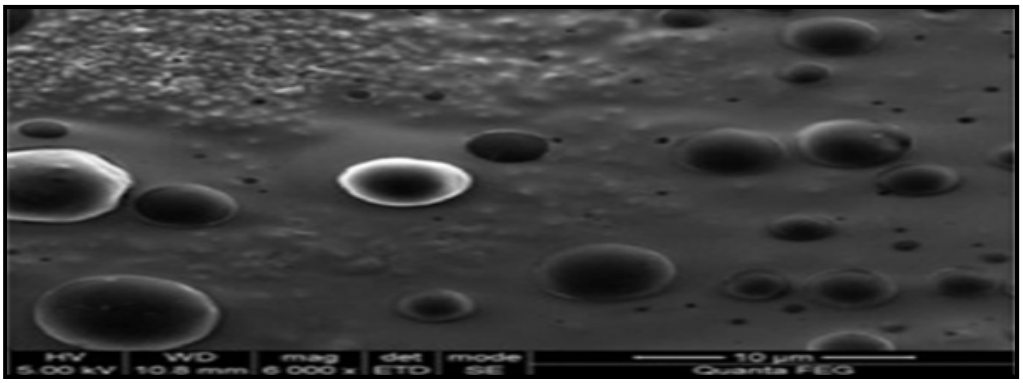

Figure No.3: Transmission electron microscopic image of optimized mixed capecitabine loaded niosomal formulation F5

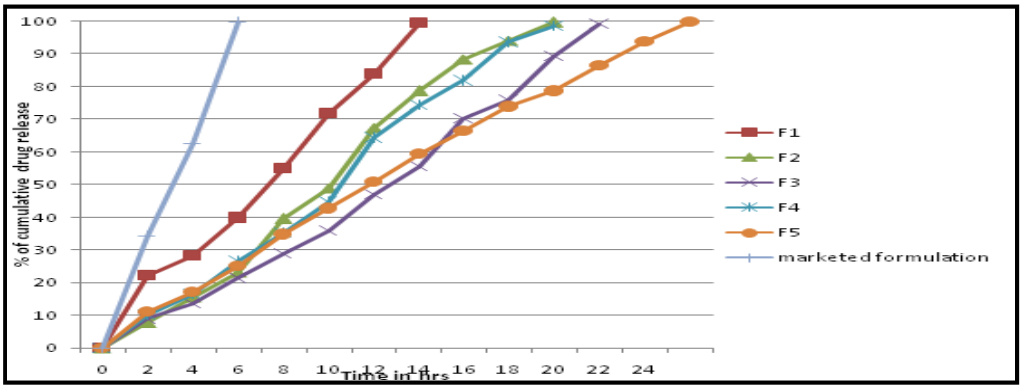

Figure No.4: *In-vitro* drug release of mixed capecitabine niosomal formulations with marketed formulation

CONCLUSION

In this study, niosomes and mixed niosomes encapsulating a poorly bioavilability drug (Capecitabine) were successfully prepared by using different compositions. Among the mixed niosome formulations prepared by combining Span 60 and Pluronic P85 (F5)-mixed niosomes as worthy of further exploration because they might have great potential in improving the oral bioavailability of drug and better stability in storage conditions and getting into the drug market.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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