ORIGINAL ARTICLE

Design and Evaluation of Captopril-loaded Niosomes

Angilicam Avinash[1,2], P. Dwarakanadha Reddy[3], S. V. Satyanarayana[4]

[1]Research Scholar, Research and Development, JNTUA, Ananthapuramu, Andhra Pradesh, India, [2]Department of Pharmaceutics, Narayana Pharmacy College, Nellore, Andhra Pradesh, India, [3]Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [4]Department of Chemical Engineering, JNTUA College of Engineering, Ananthapuramu, Andhra Pradesh, India

Abstract

Aim: The goal of this study is to design a niosomal carrier system for captopril for the treatment of hypertension that is capable of delivering the encapsulated drug over a prolonged period of time by overcoming the limitations of conventional dosage forms. Captopril is a water-soluble drug but has low permeability. The main objective is to improve bioavailability and permeability. **Materials and Methods:** The niosomes are prepared by thin film hydration method, using materials like non-ionic surfactants (Span 20, Span 40, Span 60, and Span 80) and solvents such as chloroform and ethanol. **Results and Discussion:** The FTIR results revealed that there is no interaction between captopril and excipients. All the formulations showed better encapsulation efficacy. SEM analysis revealed the size reduction of captopril-loaded niosomes. The dissolution studies showed prolonged drug release. **Conclusion:** On comprising all formulations, F3 showed sustained release of 98.44% up to 12 h. This may be due to the longest saturated alkyl chain and shows the highest entrapment.

Key words: Bioavailability, Captopril, Niosomes, Prolonged drug release

INTRODUCTION

Niosomes are known as non-ionic surfactant vesicles which are microscopic lamellar structures formed on admixture of a non-ionic surfactant, cholesterol, and dicetyl phosphate with subsequent hydration with aqueous media.[1] Niosomes are capable of entrapping a variety of drugs and found as an alternative to liposomes. The niosomes have similar physical properties when compared to liposomes and are comparatively inexpensive delivery systems.[2]

In current years, transferring the drug molecules to the desired site in the biological systems has become a very precise and sophisticated area of pharmaceutical research. The role of the drug delivery system is not only limited to a drug package just meant for administration and convenience but also to bring a required improvement in pharmacological efficacy and safety by carrying the drug molecules to the required site in the most convenient manner.[3] Drug delivery system using colloidal particulate carriers like niosomes has distinct merits over conventional dosage form as the colloidal particulate can act as drug reservoirs.[4] Among different nanovesicular carriers, niosomes are selected as a carrier of choice because of its dominance over others carrier with regard to stability and cost effectiveness.[5] Conventional drug delivery systems face some significant challenges, such as unfavorable pharmacokinetics and distribution, which can lead to undesirable side effects. Drug degradation in blood circulation by the reticuloendothelial system and insufficient drug uptake at the specific site can reduce drug efficacy. Nanocarriers have been extensively investigated in the past decades to overcome the challenges associated with conventional drug delivery systems, due to the advantages such as (i) facilitate targeted drug delivery to the diseased site; (ii) enhance absorption as surface area increases and hence increase bioavailability; (iii) improve pharmacokinetics and biodistribution of active agents; and (iv) increase retention in biological systems and extend the efficacy of drugs.[6]

Address for correspondence:
Angilicam Avinash, Research Scholar, Research and Development, JNTUA, Ananthapuramu - 515 002, Andhra Pradesh, India.
E-mail: avinash.angilicam3@gmail.com

Received: 30-10-2021
Revised: 06-05-2022
Accepted: 25-06-2022

Cardiac diseases are leading cause of mortality and responsible for one-third of all deaths worldwide. The majority of cardiovascular disorders are not caused by single risk factor, it is a mixture of several factors such as high levels of blood lipids, obesity, lack of physical inactivity, smoking, glucose intolerance/diabetes, and age. High blood pressure (BP) certainly represents an amendable risk factor.[7] Captopril, an angiotensin-converting enzyme inhibitor (ACEi), lowers high blood pressure (BP) through its suppressive effect on the renin-angiotensin system at both peripheral and central sites. Captopril has significant benefits over other antihypertensive drugs on the outcomes of acute myocardial infarction (63% reduction), cardiovascular events (51% reduction), and mortality (62% reduction). Hence, I have chosen this drug over other antihypertensive drugs. ACE inhibitors are recommended as first-line therapy because they lower blood pressure and the risk of stroke and heart disease. Hence, captopril is recommended as the first-line therapy.

Captopril exerts 75% bioavailability but in the presence of food the bioavailability reduces to 30-50% due to its relative short half-life.[8]

The main aim and objective of this study was to design a prolonged release captopril formulation which would benefit the patients by reducing dose frequency, increased patient compliance, effective treatment, reduction in plasma concentration fluctuations, and reduced side effects.[8]

MATERIALS AND METHODS

Materials

Captopril (Caplin Point Laboratories Limited, Chennai), Cholesterol (SD Fine Chemicals Ltd., Mumbai), Spans (SD Fine Chemicals Ltd., Mumbai), chloroform (Nice Chemicals Private Ltd., Kerala), and ethanol (Changshu Hongsheng Fine Chemical Co. Ltd., China) were used.

Preparation of captopril-loaded niosomes

The captopril-loaded niosomes were developed by thin film hydration method in a rotary evaporator. Accurately weighed amounts of non-ionic surfactants (Span 20, 40, 60, and 80) and cholesterol were transferred in a round bottom flask of the rotary evaporator. The chloroform and ethanol (4:1) solution was added to the flask and evaporated at 50°C for 15–20 min under vacuum. The formed film is then hydrated with phosphate buffer pH 7.4 containing drug and vortexed at room temperature for 20 min which forms milky white suspension. The resultant dispersion was then cooled in an ice bath and sonicated for 3–5 min.[9] Then, the resultant niosomes were stored at refrigerator (4–6°C). Various formulations were prepared, as shown in Table 1.

Evaluation of niosomes

% Practical yield

Percentage practical yield is calculated to know efficiency of any method, thus its help in selection of appropriate method of formulation. Niosomes were collected and weighed to determine practical yield (PY) from the following equation. The results are shown in Table 2.

$$\text{Percentage of practical yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

% Drug content

Niosomes equivalent to 50 mg of captopril was taken and dissolved in distilled water for the extraction of encapsulated drug with regularly shaking and kept undisturbed for 24 h for complete extraction. The extract was filtered and diluted serially with phosphate buffer pH 7.4 and the absorbance was measured at 206 nm and the drug content was calculated from the calibration curve.[10] The results are shown in Table 3.

$$\%\ \text{Drug content} = \frac{\text{Test absorbance}}{\text{Standard absorbance}} \times 100$$

In vitro drug release

The *in vitro* drug release was studied using USP dissolution apparatus. Niosomes equivalent to 50 mg of captopril were placed in the dialysis membrane tubes. The tubes were immersed in dissolution vessel containing phosphate buffer pH 7.4 maintained at 37 ± 0.5°C. Samples were withdrawn at periodic time intervals and replaced with equal amount of buffer to maintain sink condition. The samples were analyzed by UV/visible spectrophotometer.[11] The results are shown in Table 4.

Drug release kinetics

The release data obtained from various formulations were studied further for fitness of data in different kinetic models such as zero order, first order, Higuchi equation, Korsmeyer–Peppas, and Hixson–Crowell release models. The results are shown in Tables 5 and 6.

Scanning electron microscopy

Scanning electron microscopy of the niosomes was performed to examine the particle size and surface morphology. The niosomes were mounted on metal stubs and the stub was then coated with conductive gold with sputter coater attached to the equipment. The pictures were taken using a scanning electron microscope.[12]The results are shown in Figures 1 and 2.

Table 1: Composition of niosomes containing captopril

Quantities (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Captopril	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cholesterol	1	1	1	1	1	1	1	1	1	1
Span 20	1	__	__	__	0.5	0.5	0.5	__	__	__
Span 40	__	1	__	__	0.5	__	__	0.5	0.5	__
Span 60	__	__	1	__	__	0.5	__	0.5	__	0.5
Span 80	__	__	__	1	__	__	0.5	__	0.5	0.5
Ethanol (ml)	5	5	5	5	5	5	5	5	5	5
Chloroform (ml)	20	20	20	20	20	20	20	20	20	20
Phosphate buffer pH 7.4	25	25	25	25	25	25	25	25	25	25

Table 2: % Practical yield of niosomes

Formulation code	% yield
F1	77.6
F2	79.2
F3	94.4
F4	83.6
F5	84.4
F6	87.2
F7	85.2
F8	92.4
F9	86.8
F10	87.6

Table 3: % Drug content of niosomes (*n*=3)

Formulation code	% Drug content±SD
F1	86.84±0.14
F2	88.62±0.24
F3	97.18±0.37
F4	89.99±0.28
F5	91.93±0.37
F6	92.25±0.48
F7	95.96±0.14
F8	96.37±0.24
F9	93.46±0.24
F10	94.59±0.14

FTIR studies

The chance of drug-excipients (cholesterol and non-ionic surfactants) interactions was investigated by FTIR spectrum studies. The FTIR spectrum of pure drug (captopril) and combination of drug with excipients were recorded using FTIR spectrophotometer.[13] The spectrum was scanned in the wavelength region of 4000-400 cm^{-1}. The results are shown in Table 7.

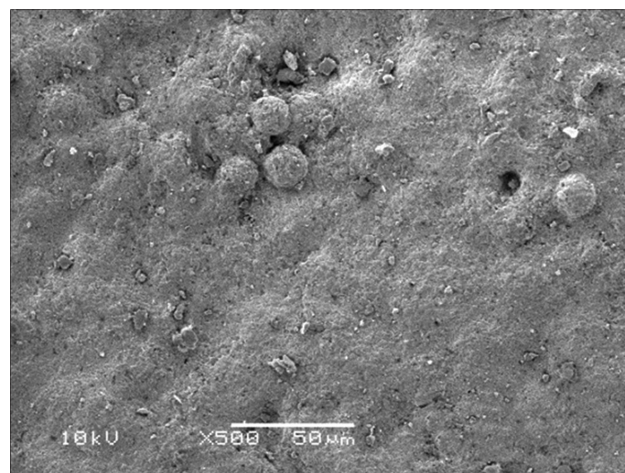

Figure 1: SEM image of captopril

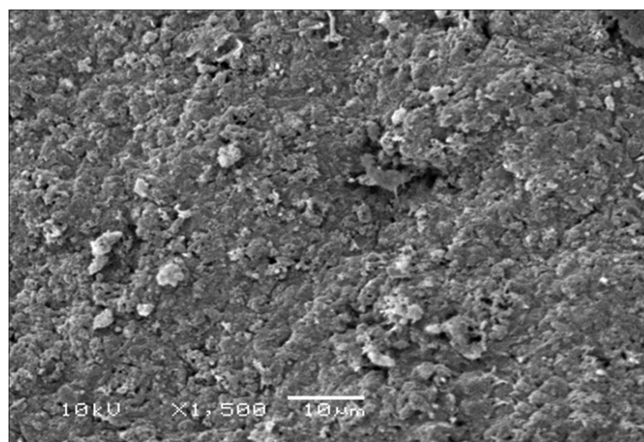

Figure 2: SEM image of optimized formulation

Stability studies

Stability studies for the optimized formulation were carried out at elevated temperature (45 ± 2°C) RH 75% for a period of 3 months as per ICH. At definite time periods, the samples from each batch were taken and evaluated for drug release.[14] The results are shown in Table 8.

Table 4: Comparative dissolution data of niosomes containing captopril (*n*=3)

Time (h)	% cumulative drug release (mean±SD)										
	Captopril (pure dug)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.5	27.97±0.14	16.13±0.09	15.16±0.06	10.47±0.05	14.16±0.10	17.03±0.05	17.41±0.05	10.53±0.05	10.63±0.22	12.75±0.09	13.16±0.05
1	48.72±0.14	27.97±0.05	26.22±0.05	20.72±0.09	25.34±0.05	27.91±0.06	28.84±0.05	21.06±0.14	20.81±0.25	23.06±0.10	24.88±0.11
2	70.88±0.16	47.75±0.05	44.31±0.05	37.16±0.05	41.78±0.05	47.59±0.05	48.53±0.05	37.16±0.05	37.34±0.30	39.63±0.05	41.75±0.05
3	97.41±0.94	72.91±0.05	57.16±0.06	44.72±0.09	54.97±0.11	60.72±0.05	62.69±0.11	45.81±0.11	51.13±0.05	47.69±0.11	49.87±0.19
4		90.06±0.05	70.72±0.05	55.34±0.05	72.72±0.05	70.94±0.14	73.81±0.05	55.91±0.11	61.53±0.05	57.69±0.05	60.69±0.11
5		96.49±0.03	89.41±0.11	64.06±0.22	82.66±0.05	85.09±0.05	89.88±0.11	66.06±0.05	72.72±0.20	69.69±0.05	72.75±0.19
6			97.50±0.16	73.63±0.05	89.66±0.05	97.56±0.27	98.31±0.19	76.16±0.05	82.91±0.05	80.50±0.11	86.84±0.54
8				82.81±0.06	94.78±0.10			94.69±0.16	91.75±0.11	96.75±0.49	97.32±0.82
10				91.81±0.05					97.53±0.05		
12				98.44±0.10							

RESULTS AND DISCUSSION

% Practical yield

From the results, it was observed that there was no significant loss of the drug and excipients during the preparation of niosomes by thin film hydration method.

% Drug content

The solutions were analyzed for drug content spectrophotometrically at 206 nm. The drug content was calculated by estimating the amount of drug in niosomes. Results shown in Table 3 revealed that there was no significant loss of the drug during the preparation and all the formulations exhibited fairly uniform drug content.

In vitro drug release

The formulated niosomes were subjected to *in vitro* drug release studies using phosphate buffer pH 7.4 as a dissolution medium. The amount of captopril released was estimated spectrophotometrically at 206 nm. The free drug was released 97.41% within 3 h. F1 showed release of 96.49% within 5 h, F2 showed release of 97.50% within 6 h, F3 showed release of 98.44% within 12 h, F4 showed release of 94.78% within 8 h, F5 showed release of 97.56% within 6 h, F6 showed release of 98.31% within 6 h, F7 showed release of 94.69% within 8 h, F8 showed release of 97.53% within 10 h, F9 showed release of 96.75% within 8 h, and F10 showed release of 97.32% within 8 h. These results showed that captopril-loaded niosomes have shown sustained release when compared to pure drug. This is because the drug is released slowly for a prolonged period of time in niosomal formulation. The difference in the drug release was attributed to the structure of surfactant. As known, non-ionic surfactants such as Span 20, Span 40, and Span 60 have the same head group and different alkyl chain. Among these surfactants, only Span 80 has an unsaturated alkyl chain. The introduction of double bonds made the chains bend. This means that the adjacent molecular cannot be tight when they form the membrane of niosomes. These cause the membrane to be more permeable, which possibly made the lowest entrapment efficiency of the Span 80 formulation. However, of the other three kinds of non-ionic surfactants, Span 60 has the longest saturated alkyl chain and shows the highest entrapment. The encapsulation efficiency shows the trend C16 (Span 60) > C14 (Span40) >C12 (Span 20). It proposes that the length of alkyl chain is a crucial factor of permeability and high entrapment. Out of all 10 formulations, F3 consists of Span 60 was considered as optimized formulation.

Drug release kinetics

The time point to dissolve 50% of drug is T_{50} which was found to be 2.09 h for F1, 2.44 h for F2, 3.50 h for F3, 2.62 h

Table 5: Correlation coefficient (r) and release rate constant (k) values of captopril-loaded niosomes

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Zero order										
r	0.998	0.994	0.997	0.993	0.995	0.994	0.997	0.997	0.995	0.993
k	23.87	22.15	18.58	20.89	23.79	24.26	18.58	18.67	19.81	20.87
First order										
r	1	0.999	1	0.999	1	0.999	0.999	1	0.999	0.999
k	0.667	0.557	0.307	0.382	0.531	0.600	0.326	0.358	0.379	0.415
Higuchi										
r	0.990	0.991	0.995	0.993	0.993	0.993	0.991	0.990	0.994	0.995
k	45.39	40.52	30.50	38.06	39.68	40.86	33.32	34.57	34.35	35.40
Peppas										
r	0.998	0.999	0.996	0.999	0.998	0.998	0.998	0.999	0.997	0.996
k	0.857	0.740	0.711	0.745	0.710	0.707	0.715	0.816	0.680	0.668
Hixson–Crowell										
r	0.999	0.998	0.999	0.997	0.999	0.998	0.999	0.999	0.998	0.998
k	0.639	0.520	0.333	0.410	0.498	0.538	0.334	0.334	0.365	0.389
T_{50}	2.09	2.44	3.50	2.62	2.18	2.10	3.41	2.92	3.23	3.01
T_{90}	4.00	5.07	9.60	6.13	5.39	5.01	7.49	7.60	7.17	6.60

Table 6: Kinetic data for the optimized formulation (F3)

Zero order		First order		Higuchi		Korsemeyer–Peppas		Hixson–Crowell	
Time	% cumulative drug release	Time	Log % drug remaining	Square root of time	% cumulative drug release	Log time	Log % cumulative drug release	Time	Cube root of % drug remaining
1	20.72	1	1.899	1	20.72	0	1.316	1	4.295
2	37.16	2	1.798	1.414	37.16	0.301	1.570	2	3.975
3	44.72	3	1.742	1.732	44.72	0.477	1.650	3	3.809
4	55.34	4	1.649	2	55.34	0.602	1.743	4	3.547
5	64.06	5	1.555	2.236	64.06	0.698	1.806	5	3.300
6	73.63	6	1.421	2.449	73.63	0.778	1.867	6	2.976
8	82.81	8	1.235	2.828	82.81	0.903	1.918	8	2.580
10	91.81	10	0.913	3.162	91.81	1	1.962	10	2.015
12	98.44	12	0.193	3.464	98.44	1.079	1.993	12	1.159

Table 7: FT-IR interpretations of pure drug and optimized formulation

Functional group	Characteristic peaks	Observed peaks	
		Captopril (CAP)	Optimized formulation
C-S (Stretching)	600–800 cm^{-1}	672.35 cm^{-1}	670.65 cm^{-1}
C-N (Stretching)	$1020^{-1}250$ cm^{-1}	1193.64 cm^{-1}	1193.33 cm^{-1}
C-H (Bending)	$1450^{-1}470$ cm^{-1}	1467.12 cm^{-1}	1467.45 cm^{-1}
N-H (Bending)	$1580^{-1}650$ cm^{-1}	1581.90 cm^{-1}	1582.41 cm^{-1}
C=O (Stretching)	$1690^{-1}760$ cm^{-1}	1740.90 cm^{-1}	1740.86 cm^{-1}
S-H (Stretching)	≈2550 cm^{-1}	2561.28 cm^{-1}	2561.61 cm^{-1}

for F4, 2.18 h for F5, 2.10 h for F6, 3.41 h for F7, 2.92 h for F8, 3.23 h for F9, and 3.01 h for F10 formulations. The time point to dissolve 90% of drug is T_{90} which was found to be 4.0 h for F1, 5.07 h for F2, 9.60 h for F3 and 6.13 h

Table 8: Dissolution data of optimized formulation

Time (h)	% cumulative drug release (mean±S.D.)			
	Initial	1st month	2nd month	3rd month
0.5	10.47±0.05	10.47±0.14	10.34±0.24	10.28±0.24
1	20.72±0.09	20.72±0.16	20.66±0.24	20.53±0.16
2	37.16±0.05	37.13±0.28	36.94±0.43	36.84±0.28
3	44.72±0.09	44.31±0.27	44.03±0.30	43.88±0.41
4	55.34±0.05	55.06±0.87	54.75±0.90	54.34±0.87
5	64.06±0.22	63.78±1.09	63.47±1.15	62.75±1.13
6	73.63±0.05	73.56±1.55	73.25±1.63	72.22±1.28
8	82.81±0.06	82.53±0.87	82.06±1.03	81.78±0.91
10	91.81±0.05	91.78±0.84	91.50±0.50	91.16±0.55
12	98.44±0.10	98.06±1.44	97.75±1.11	97.13±1.14

for F4, 5.39 h for F5, 5.01 h for F6, 7.49 h for F7, 7.60 h for F8, 7.17 h for F9, and 6.60 h for F10 formulations. The drug release data were fitted in different kinetic equations and "r" values are shown table. The drug release patterns from the niosomes have found to be followed the first-order kinetic model predominantly followed by Hixson–Crowell's cube root model as well. This release patterns are evident with the correlation coefficient "r" values.

Zero order, first order, Higuchi, Korsemeyer–Peppas, and Hixson–Crowell data were drawn for the optimized formulation to depict the release kinetics of the drug.

SEM analysis

Scanning electron microscopy was used to characterize the surface morphology. The particle size of captopril was found to be 50 µm whereas particle size of captopril-loaded niosomes was found to be 10 µm. The particle size of captopril was size reduced 5 times on niosomal formulation.

Pure captopril showed principal absorption peaks at 672.35 cm^{-1} (C-S stretching), 1193.64 cm^{-1} (C-N stretching), 1467.12 cm^{-1} (C-H bending), 1581.90 cm^{-1} (N-H bending), 1740.90 cm^{-1} (C=O stretching), and 2561.28 cm^{-1} (S-H stretching). The identical peaks of C-S stretching, C-N stretching, C-H bending, N-H bending, C=O stretching, and S-H stretching vibrations were also noticed in the spectra of drug-loaded niosomes. FT-IR spectra revealed that there was no interaction between the drug and the polymers used for niosome preparation.

Stability studies

A stability study for the optimized formulation was carried out at elevated temperature (45 ± 2°C) and RH-75% ± 5% for a period of 3 months as per ICH guidelines. Samples were withdrawn at definite time periods (1st month, 2nd month, and 3rd month) and dissolution studies were performed. The results from dissolution studies indicated that there was no significant difference of drug release. Stability studies indicated that optimized formulation F3 was stable.

CONCLUSION

The captopril-loaded niosomes were prepared by thin film hydration method. Cholesterol and non-ionic surfactants were used for the preparation of niosomes. Span 20, Span 40, Span 60, and Span 80 were used as non-ionic surfactants. The prepared captopril-loaded niosomes were evaluated for % yield, % drug content, FTIR, SEM analysis, and stability studies. The *in vitro* release studies were performed. Good results were obtained for % yield, % drug content, and *in vitro* studies. FT-IR spectra revealed that there was no interaction between the drug and the polymers used for niosome preparation. F3 formulation containing cholesterol and Span 60 exhibited the release of 98.44% up to 12 h. On comprising all formulations, F3 showed sustained release up to 12 h. This may be due to longest saturated alkyl chain of Span 60 and shows the highest entrapment. From this study, it is concluded that captopril-loaded niosomes have shown sustained release when compared to pure drug.

REFERENCES

1. Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D. Design and development of a proniosomal transdermal drug delivery system for captopril. Trop J Pharm Res 2007;6:687-93.
2. Ruckmani K, Sankar V. Formulation and optimization of zidovudine niosomes. AAPS PharmSciTech 2010;11:1119-27.
3. Jadon PS, Gajbhiye V, Jadon RS, Gajbhiye KR, Ganesh N. Enhanced oral bioavailability of griseofulvin via niosomes. AAPS PharmSciTech 2009;10:1186-92.
4. Bansal S, Aggarwal G, Chandel P, Harikumar SL. Design and development of cefdinir niosomes for oral delivery.

J Pharm Bioallied Sci 2013;5:318-25.
5. Patel KK, Kumar P, Thakkar HP. Formulation of niosomal gel for enhanced transdermal lopinavir delivery and its comparative evaluation with ethosomal gel. AAPS PharmSciTech 2012;13:1502-10.
6. Chen S, Hanning S, Falconer J, Locke M, Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. Eur J Pharm Biopharm 2019;144:18-39.
7. Qumbar M, Ameeduzzafar, Imam SS, Ali J, Ahmad J, Ali A. Formulation and optimization of lacidipine loaded niosomal gel for transdermal delivery: *In-vitro* characterization and *in-vivo* activity. Biomed Pharmacother 2017;93:255-66.
8. Stulzer HK, Silva MA, Fernandes D, Assreuy J. Development of controlled release captopril granules coated with ethylcellulose and methylcellulose by fluid bed dryer. Drug Deliv 2008;15:11-8.
9. Shalini M, Ali MM, Lakshmi PK. Formulation and evaluation of elastic niosomes of eletriptan hydrobromide. Int J Pharm Sci Res 2016;7:1679-85.
10. Srikanth Y, Kumar A, MallikarjunaSetty C. Preparation and evaluation of maltodextrin based proniosomes containing capecitabine. Int J Res Dev Pharm Life Sci 2017;6:2856-61.
11. Sankhyan A, Pawar PK. Metformin loaded non-ionic surfactant vesicles: Optimization of formulation, effect of process variables and characterization. Daru 2013;21:7.
12. Sunilkumar MR, Nesalin J, Mani TT. Development and evaluation of niosomes containing ketoconazole. World J Pharm Pharm Sci 2016;5:1318-27.
13. Meenakshi M, Elangoo K. Reparation and evaluation of lamivudine proniosomes for HIV infection. World J Pharm Pharm Sci 2016;5:1002-23.
14. Karthick K, Kumaran KS. Formulation and evaluation of niosomes co-loaded with 5-fluorouracil and leucovorin: Characterization and *in vitro* release study. Int J Res Pharm Nano Sci 2016;5:239-50.

Source of Support: Nil. **Conflicts of Interest:** None declared.