Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Research Article

Formulation and Evaluation of Venlafaxine Hydrochloride Niosomes.

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ABSTRACT

The aim of this study was to formulate and evaluate niosomes of venlafaxine HCl. It is a selective serotonin reuptake inhibitor type of drug used in the treatment of depression. It is practically soluble in water belongs to BCS class I with a bioavailability approximately 45%. Niosomes of venlafaxine HCl were prepared by using the cholesterol and span 80(1:1) by Ether Injection Method which is further used for targeted drug delivery. Nine batches were prepared by the Ether Injection Method and evaluated for *In vitro* drug release and drug release kinetics. Niosomes are acceptable and superior carriers and also have ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. Niosomes were characterized for entrapment efficiency, vesicle size, percentage yield, FTIR, DSC, and physical stability. Formulation F_9 niosomes batch was found to be optimized and followed zero-order release kinetic. Niosomes dispersion were found to be stable and preparation of niosomes using factorial design was found to be well suited and sound approach to be stable niosomal formulations.

KEYWORDS

Niosomes, non-ionic surfactants, targeted drug delivery.

1. INTRODUCTION

Venlafaxine HCl is potent serotonin reuptake inhibitor drug used for the treatment of major depression disorder (MDD) and panic disorder. Being a SSRI the most common adverse effects are gastrointestinal disturbances such as nausea, dry mouth, constipation, decreased appetite, vomiting, memory loss, vivid etc. It undergoes extensive first pass metabolism with a daily dose of 25-100mg[4]. Sustained release formulations of antidepressants for oral[1] and transdermal route[3,4] have been developed to improve the efficacy. Among the several enhancers, vesicular systems like niosomes and liposomes have been shown potential as penetration enhancer. These can act as a carrier for variety of drug molecules due to their structural properties. Successful delivery of therapeutic agents across the skin using niosomes has been stated in the literature[8-10]. This vesicular carrier can also be served as solubilizing matrix, as local depot for sustained release or as rate limiting membrane for the modulation of systemic absorption of drugs via the skin[11]. Hence, the present investigation involved the development of venlafaxine hydrochloride niosomes for targeted delivery. The niosomes were subjected to size and surface analysis; *in vitro* drug release and stability studies. Encapsulation of drug in vesicular structures like niosomes can be expressed to prolong the existence of the drug in the systemic circulation, enhance penetration into targeted tissue and reduce toxicity, if selective uptake can be achieved.

Niosomes are unilamellar or multilamellar vesicles that are made up of non-ionic surfactant it can entrap amphiphilic and hydrophobic solutes. Stability is a prime concern in the development of any formulation. Liposomes have shown advantage as drug carriers, but they are associated with problems related to physical stability such as fusion, aggregation, sedimentation and leakage on storage[13]. The niosome approach minimizes these problems and they are more stable during sterilization and storage. Ease of transfer and good drug carrier make niosomes a versatile delivery system[11]. The liposomes are very similar to conventional niosomes and more uniform in size. Reported methods for preparation of niosomes are the Reverse-Phase Evaporation technique, sonication method, multiple membrane extrusion method, hand shaking method and Ether Injection Method[8,17]. In the present study, Ether Injection method was used for the preparation and optimization of venlafaxine niosomes as this method is simple and easy to scale up[5,6]. The wide range of surfactant loading affects on encapsulation of an amphiphilic drug in niosomes. Many others formulation variables such as surfactant to cholesterol ratio and amount of drug, also affect the characteristic of niosomes. The niosomes are thus of interest form a technical view and allow a wider scope to be used to study the influence of various formulation variables, niosomes need to be optimized for desired response. Various experimental designs are useful in developing a formulation requiring less experimentation and providing estimates of the relative significance of different variables. In the work, 3^2 design was used to optimize niosomes containing venlafaxine. Independent variable selected was span 80 (X_1) and solvent (X_2) to evaluate their separate and combined effects on vesicle size and encapsulation expressed.

2. MATERIALS AND METHODS

2.1. Materials

Venlafaxine hydrochloride was received as a gift sample from Lupin Research Park (Lupin Ltd. Aurangabad, MS, India).

Span 80 and cholesterol, diethyl ether, disodium hydrogen phosphate, potassium dihydrogen phosphate and potassium chloride were procured from chemical store at RDs College of pharmacy Bhor, Pune, (MS, India). All chemicals used in the study were of analytical grade and used without further purification.

2.2. Compatibility Study

The interaction between the drug and formulation excipients was analysed using Fourier transform infrared spectra (FTIR). The spectrum was recorded in Schimadzu FTIR (India) using potassium bromide pellets at a moderate scanning speed between 4000cm-^{1} - 400cm-^{1}.

2.3. Differential Scanning Calorimeter (DSC)

DSC thermogram of niosome formulation(Ad) was recorded (Mettler Toledo Instruments India Pvt. Ltd.) at a scanning rate of 10°C/min over a temperature range of 0 to 250°C, under an inert nitrogen atmosphere at a flow rate of 20ml/min.

2.4. Preparation of niosomes

Niosomes were prepared by the ether injection method. For ease of preparation, precisely weighed amounts of surfactant and cholesterol (1:1) and venlafaxine (10mg) were taken in a clean and dry wide mouth beaker of 100ml capacity and diethyl ether (5 ml) was added to it. The resulting solution was then taken in a syringe #14 and injected slowly into 30ml of aqueous phase (phosphate buffer pH 7.4) held in beaker maintained at 60oC to 65oC and agitated slowly. As the lipid solution was injected slowly into the aqueous phase, vaporization of ether resulting in the formulation of niosomes. The size and shape characteristics of niosomes were studied under a high power microscope[13].

2.5. Experimental design

The formula optimization was done by 3^2 factorial design using design expert (Version 11; Stat-Ease Inc., USA) for mathematical modeling and analysis of responses. The optimal level of variables was determined by 3^2 factorial design including center point. The significant factors selected were concentration of cholesterol and span 80 examining 9 runs.

Variables for experimental designs

Independent variable

X_1 = concentration of cholesterol

X_2 = non-ionic surfactant

Dependent variable

Y_1 = Particle size

2.6. Process yield[10]

Dried niosomes were accurately weighed, and considering the total amount of drug and polymers used for preparing the feed solution, the process yield was calculated, a using following formula

% yield =Estimated drug content / Theoretical drug content×100 ----------(1)

2.7. Particle size measurement[7]

The size of the prepared niosomes was measured by the optical microscopy method using a calibrated stage micrometer. Particle size was calculated using equation,

$Xg = 10 \times ([ni \times \log Xi]/N)$ ----------(2)

Where, Xg is geometric mean diameter, ni is number of particle in range, Xi is the midpoint of range and N is the total number of particles.

2.8. Drug entrapment efficiency[4]

Niosomes (50 mg) were powdered and suspended in 50 ml of 0.1 N HCL followed by 30 minutes sonication. The solution was kept undisturbed for 24 hrs; and filtered. The filtrate recovered was examined spectrphotometrically at 227 nm, and entrapment efficiency was calculated by the following formula.

2.9. In vitro venlafaxine HCl Release[8]

The release of venlafaxine HCl from the niosome was examined under sink condition. A quantity of drug equivalent to 1mg present in the niosomal preparation was placed in a dialysis bag and was suspended in 50ml of phosphate buffer (pH 7.4). The temperature was maintained at 37°C±0.5°C under constant magnetic stirring (500rpm) (Remi, India). At predetermined time intervals, 1ml of sample was withdrawn from the beaker and the drug content was determined by UV spectroscopy at 274nm.

2.10. Physical Stability

Physical stability analysis was carried out for one month for the niosomal formulation in order to assess any leaching of sertraline HCl from the niosome during storage at refrigerated temperature of 2 to 8°C. After storage, the vesicles were examined by UV spectroscopy for the encapsulation efficiency of venlafaxine HCl.

Table 1 Formulation composition of niosomes.

Sr. No.	Formulation Batch	Cholesterol	Span80	Drug	Diethyl ether
1.	F_1	10	10	10	5
2.	F_2	20	20	10	5
3.	F_3	30	30	10	5
4.	F_4	40	40	10	5
5.	F_5	50	50	10	5
6.	F_6	60	60	10	5
7.	F_7	70	70	10	5

8.	F_8	80	80	10	5
9.	F_9	90	90	10	5

3. RESULTS AND DISCUSSION

3.1. Compatibility Study

FTIR spectral data were used to confirm the chemical stability of venlafaxine hydrochloride in niosome formulation. The FTIR spectra of pure venlafaxine hydrochloride, mixture of drug with span 80 and cholesterol and venlafaxine niosomes are shown in Fig. 1, 2, 3 respectively.

The spectra of pure venlafaxine hydrochloride showed peaks at 3479cm−1 (O-H stretching), 1577cm-1 (aromatic ring stretching) and at 1463cm−1 (CH2 vibration). The bands at 1137cm−1 and 1020cm−1 were due to aromatic ring stretching. The peak at 955cm−1 implies C-H twisting. The finger print characteristic vibration bands of drug appears in the FTIR spectra of drug, span 80 and cholesterol mixture. The aromatic ring association occurred at lower wave number in case of span 80. The band at 2999cm−1 corresponds to the C-H stretching of the methyl group (CH3) and at 1739cm−1 was due to C-H bending of ether carbonyl group present in venlafaxine HCl.

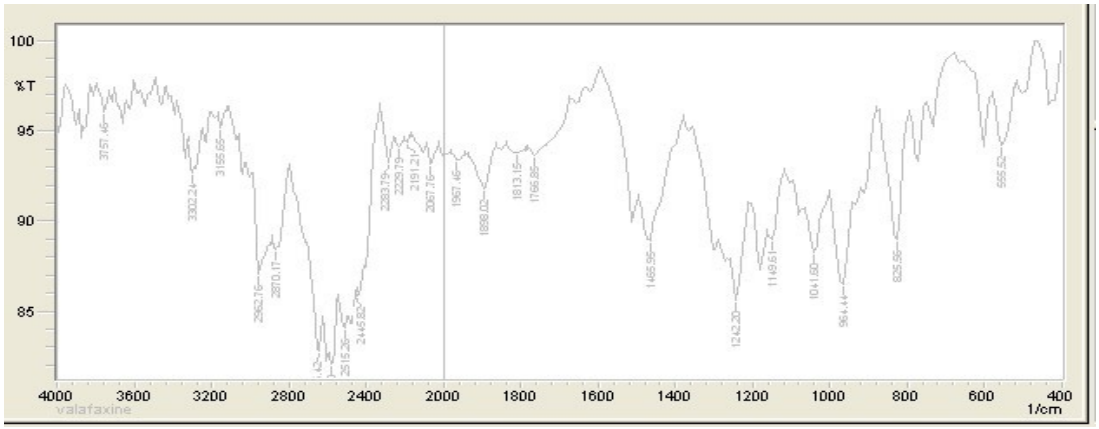

Fig.1. FTIR spectra of Venlafaxine HCl.

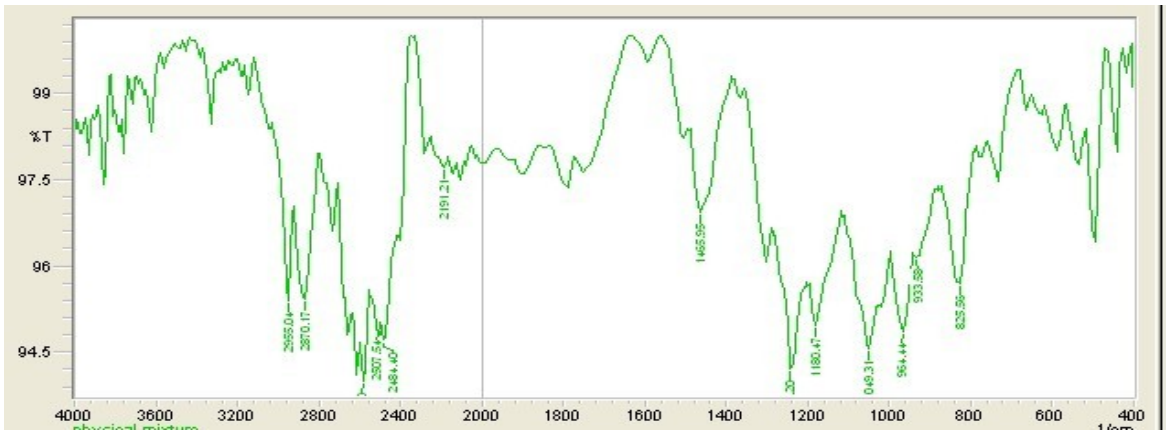

Fig.2. FTIR spectra of physical mixture of drug, cholesterol & span 80.

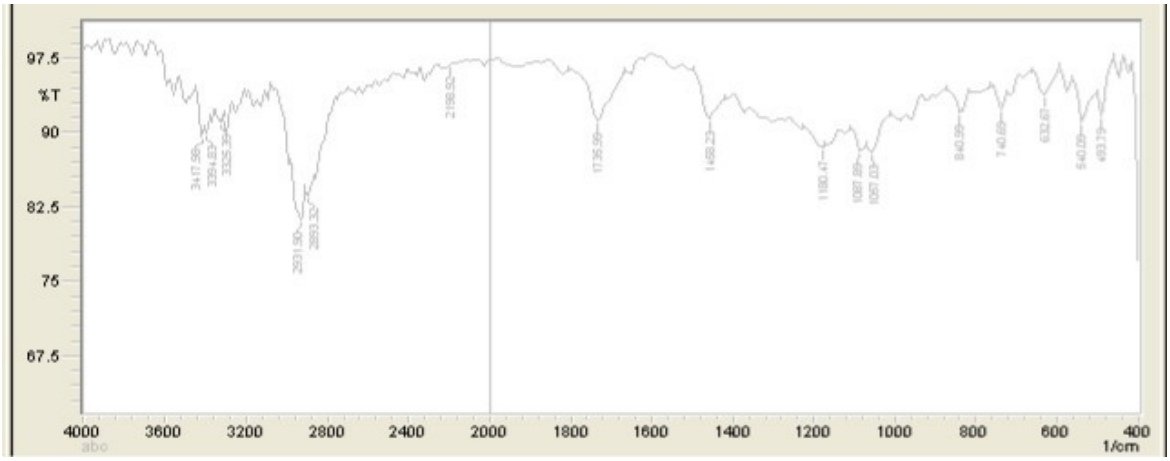

Fig.3. FTIR spectra of optimized niosomes formulation F_9.

The band at 882cm−1 was due to C-C-C stretching of cholesterol molecule. Hence, it has been confirmed that there is no significant chemical interaction had occurred between the drug and excipients except few association between them.

DSC thermogram of drug, physical mixture and niosome formulation is shown in Figure 4, 5, 6 respectively. The thermogram of the drug showed a sharp melting peak at 192.88°C.

The melting peak of cholesterol appeared at 199.03°C and melting peak of span 80 was showed at 125.34°C. Physical parameter like melting point is an essential parameter to find out interaction between the excipient and active substance (drug). No additional melting point peak was observed in niosomal thermogram. The findings confirmed the formulation thermal stability and compatibility between drug and excipients since no modification with respect to melting point of drug, cholesterol and span 60 were observed.

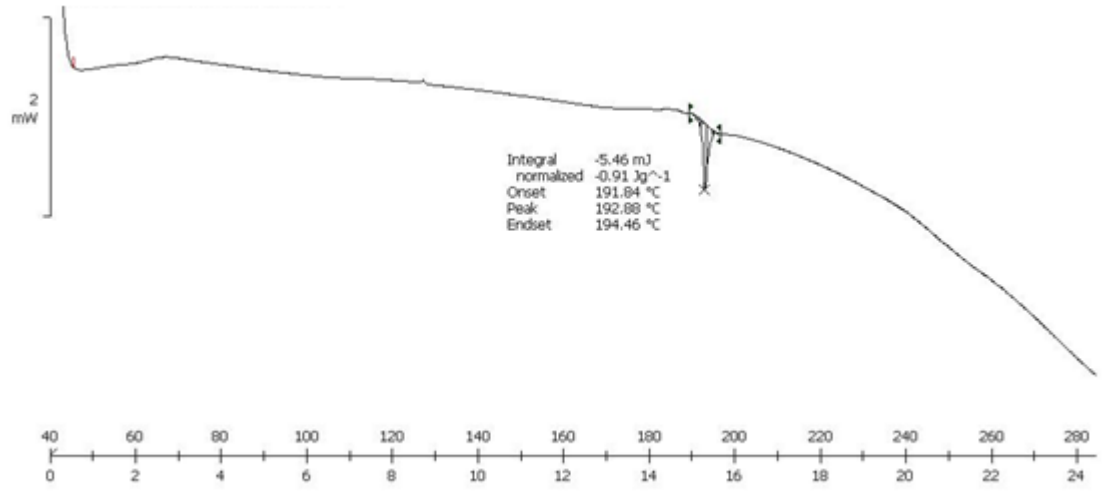

Fig. 4. DSC analysis of venlafaxine HCl.

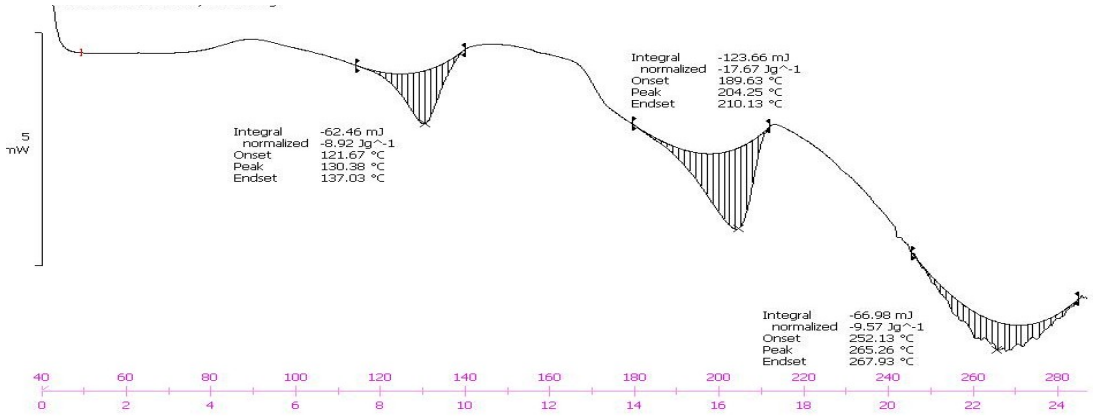

Fig.5. DSC analysis of physical mixture.

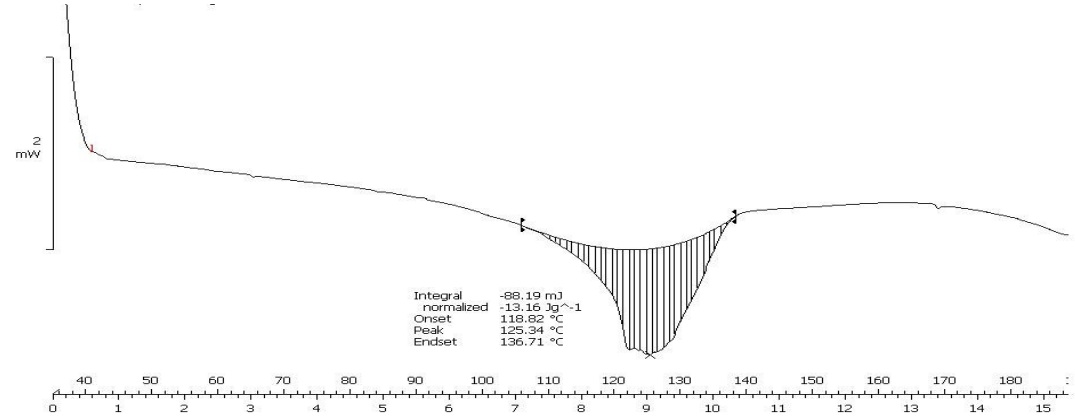

Fig. 6. DSC analysis of niosomes (F_9).

3.2. Percentage Yield

The percentage yield of niosomes was calculated by using the weight of final product after drying with respect to initial total weight.

The maximum percentage yield was found of F_9 batch and was noted to be 77.3 % among all the batches. The production yields of microspheres were found to be between 68.5 % and 77.3 % as shown in Table 2.

Table 2. Production yields of microspheres.

Formulation	% yield
F	68.5
F	70.1
F	71.4
F	73.2
F	74.1

F	74.8
F	75.7
F	77.3

3.3. Encapsulation Efficiency of Niosomes

The 1:1 ratio of surfactant and cholesterol was used in the niosome preparation, on the basis of the fact that this ratio is most beneficial for the efficient encapsulation of drugs [15]. The formulations F_7, F_8 and F_9 higher encapsulation efficiency of 51.18% ± 2.5%, 55.92% ± 2.7%, 53 and 71%±3.2% respectively. The lowest encapsulation efficiency of 19.35% ± 1.2% has been observed for F_1. The percentage encapsulation efficiency of niosomes increase with increase in concentration of surfactant and cholesterol was observed which might be due to the increased liphophilic and hydrophilic ambience that could accommodate more amount of the drug18.

3.4. In vitro venlafaxine HCl Release

Results of the *in vitro* release are shown in Figure 7. The study was performed for pure drug, formulations F_7, F_8, F_9 on the basis of their higher encapsulation of sertraline HCl. The study revealed that the entire pure drug has got released in a time span of 2.5h. Formulations showed a controlled and continuo us drug release with time and a maximum release of 75%±2.6% over a period of 12h was observed for F_9. With compared to F_7 .61% and F_8- 70%.

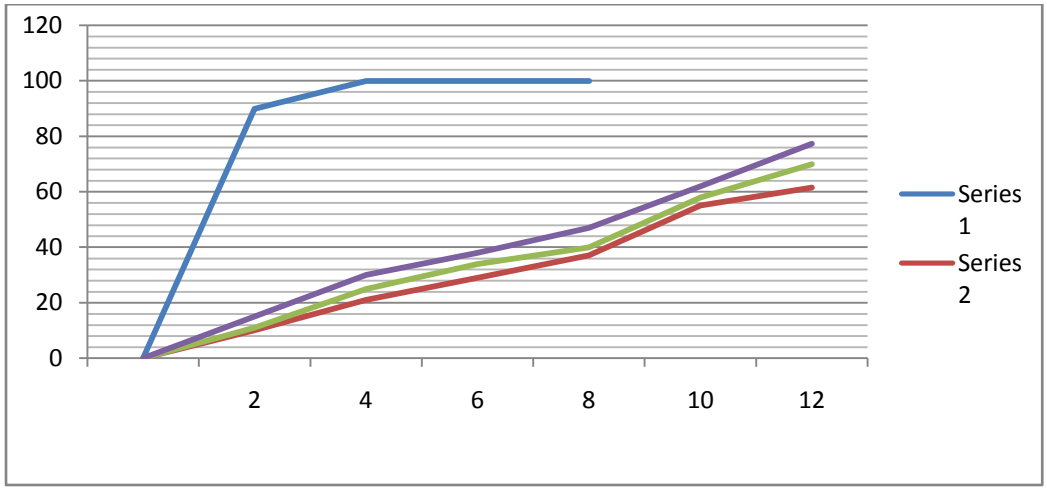

Chart 1. *In vitro* venlafaxine release (time in hr on X-axis and cumulative % drug release on Y-axis) Series 1- pure drug, Series 2- F_7, Series 3- F_8 and Series 4-F_9.

Venlafaxine HCl is soluble in water having only 45% oral bioavailability. Hence niosomes were developed to enhance the bioavailability and target the specific organ. Niosomes formulation of venlafaxine HCl was prepared by using Ether injection method. The significant factors selected were concentration of cholesterol and span 80. The dependant variables selected were particle size. Factor like cholesterol conc. and span 80 showed significant effect on micromeritic properties. The release of batch F9 was enhanced due to the presence of high quantity of cholesterol and span 80. The venlafaxine hydrochloride niosomes showed a slow and prolonged *in vitro* release.

4. ACKNOWLEDGEMENT

We would like to thank Lupin Research Park (Aurangabad, MS, India) for providing the gift sample of Venlafaxine HCl. The authors are thankful to Rajgad Dnyanpeeth's College of Pharmacy, Bhor, Pune- 412206, Maharashtra, India for their valuable support and permission to carry out the work.

5. REFERENCES

1. Arunothayanun P., Bernard MS., Craig DQM. Uchegbu IF., Florence A.T. The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from hexadecyl diglycerol ether. *Int J Pharm.*201 (2000) 7–14.
2. Ana melero., Garrigues TM., Almudever P., Martin villodre TM. Lehr CM., Shafer U. Nortriptyline hydrochloride skin absorption-Development of a transdermal patch. *Eur J Pharm Bio Pharm*. 69 (2008) 588-596.
3. Baillie AJ., Florence AT., Hume LR., Muirhead GT., Rogerson A., The preparation and properties of niosomes non-ionic surfactant vesicles. *J. Pharm. Pharmacol.* 37 (1985) 863- 868.
4. Blazek-Welsh, A.I., Rhodes, D.G., SEM imaging predicts quality of niosomes from maltodextrin- based proniosomes. *Pharm. Res.* 18 (2001b) 656–661
5. Choi MJ., Manibach HI. Liposomes and niosomes as topical drug delivery systems. *Journal of Pharmacological and Biophysiological Research* 18 (2005) 209-219.
6. De Gier J., Mandrsloot JG., Van Deenen LLM. Lipid composition and permeability of liposomes. *Biochim Biophys Acta*. 150 (1968) 666-675
7. Fang JY., Lin HH., Hsu LR., Tsai YH. Characterization and stability of various liposome-encapsulated enoxacin formulations. *Chem Pharm Bull.* 45 (1997) 1504–1509
8. Gannu R, Vishnu YV, Kishan V, Rao YM. Development of nitrendipine transdermal patches: *in vitro* and ex vivo characterization. *Current Drug Delivery*. 4 (2007) 69-76.
9. Jia-You Fang., Chi-Tzong Hong., Wen-Ta Chiu., Ying-Yue Wang. Effect of liposomes and niosomes on skin permeation of enoxacin. Int J Pharm. 219 (2001) 61-72.
10. Khandare JN., Madhavi G., Tamhankar BM., Niosomes Novel Drug Delivery System. *The Eastern Pharmacist*. 37 (1994) 61-64.
11. Malhotra M., Jain N.K., Niosomes as Drug Carriers. *Indian Drugs.* 31, 3 (1994) 81-866.
12. Madhav. N.V.S., saini. A., niosomes: a novel drug delivery system. *Int. J.rpc*. 1, 3 (2011) 498-511.
13. Mark chasin, Biodegradable polymers as drug delivery systems. (2008) 261-338pp.
14. Rogerson A. et al. The distribution of doxorubicin in mice following administration in niosomes. *J Pharm. Pharmacol.* 40 (1988) 337
15. Rogerson A. et al. Adriamycin-loaded niosomes –drug entrapment, stability and release. *J. Microencap*. 4 (1987) 321.
16. Shahiwala A and Misra A., Studies in topical application of niosomally entrapped nimesulide. *J. Pharma. Sci.* 5 (2002) 220.

17. Schreier H. Liposomes and niosomes as topical drug carriers: dermal and transdermal delivery. *J. Controlled Release*. 30 (1985) 863-868

18. Satturwar, P.M., Fulzele, S.V., Nande, V.S., Khandare, J.N., Formulation and evaluation of ketoconazole Niosomes. *Indian J. Pharm*., 64, 2 (2002) 155-158.