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Formulation, Design And Evaluation Of Nanostructured Lipid Carrier Of Lacidipine

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Abstract: *Nanostructured Lipid Carriers (NLC) are nano-sized colloidal drug delivery system that contains a lipid mixture consisting of both solid and liquid lipids in their core. This Lipid-Based Nanosystem is introduced as a biocompatible, non-toxic, and safe nano-drug delivery system as compared to polymeric or metallic nanoparticles. Due to its safety, stability, and high drug loading capacity compared to other lipid-based nanocarriers, NLC gained the attention of researchers to formulate safe and effective drug carriers. The ability to increase drug solubility and permeability while encapsulating the drug in a lipidic shell makes them an ideal carrier for drug delivery through difficult-to-achieve routes. Surface modification of NLC and the use of various additives result in drug targeting and increased residence time. With such qualities, NLCs can be used to treat a variety of diseases such as cancer, infections, neurodegenerative diseases, hypertension, diabetes, and pain management. This review focuses on the recent developments being made to deliver the drugs and genes through different routes via these nanocarriers. Here, we also discuss about historical background, structure, types of NLC and commonly employed techniques for manufacturing lipid-based nanocarriers.*

Keywords: *Nanostructured Lipid Carriers, Solid lipid nanoparticles, lacidipine,*

INTRODUCTION:

Nanostructured lipid carriers (NLCs) are novel pharmaceutical formulations which are composed of physiological and biocompatible lipids, surfactants and co-surfactants. Over time, as a second-generation lipid nanocarrier NLC has emerged as an alternative to first generation nanoparticles [1]. NLCs hold an eminent potential in pharmaceuticals and cosmetics market because of extensive beneficial effects like skin hydration, occlusion, enhanced bioavailability, and skin targeting [2]. SLNs are colloidal particles prepared from solid lipids (solid at room temperature and body temperature), surfactants, active ingredient and water. Still, SLNs experience certain limitations like poor drug loading capacity, unpredictable gelation tendency, polymorphic transitions and drug leakage during storage [3]. Nanostructured lipid carriers (NLCs) spring up as second generation of lipid nanoparticles to overcome the shortcomings of first generation i.e. SLNs. Biodegradable and compatible lipids (solid and liquid) and emulsifiers are used for the preparation of NLCs. Liquid lipids (oil) incorporation causes structural imperfections of solid lipids leading to a less ordered crystalline arrangement which avert drug leakage and furnish a high drug load [4]. NLCs were broadly studied as delivery systems for a variety of therapeutic and cosmetic applications due to their well-established biocompatibility and safety profiles. NLCs showed an increasing potential as drug carriers, in particular, by significantly enhancing the encapsulation efficiency for labile hydrophilic and hydrophobic drugs, protecting them from degradation in the body, improving their bioavailability, and controlling their release [5]. Examples of NLCs-based formulae for parenteral, topical, oral, ophthalmic, and pulmonary administration for management of central nervous system diseases, inflammatory diseases, skin conditions, bacterial and fungal infection, as well as the administration of local anesthetics [6]. Nanostructured lipid carriers (NLCs) were also used to improve the poor pharmacokinetic behavior of the incorporated chemotherapeutic agent. Dacarbazine is used in the management of metastatic malignant melanoma, Hodgkin's disease, and soft tissue sarcomas. However, its highly lipophilic nature and short half-life hinder its application. The lipid nature and minute size of NLCs may also influence the pharmacokinetic properties of the drug as it can alter its distribution and its specific uptake [7]. NLCs can be considered as relatively safe colloidal drug carriers as most of the ingredients involved in their preparation are approved for use in pharmaceutical formulations, especially those intended for topical application. However, many lipid-based nanocarriers used for the delivery of chemotherapeutic agents are administered via the parenteral route and they may

contain cationic components and linkers for the attachment of ligands for targeting specific sites which can result in an immune response. Like all NPs, the assessment of NLCs toxicity is a multifactorial process that involves testing all the components that make up the backbone of the formulation for their biological compatibility, as well as the effect of the particle size, surface charge and other physicochemical properties on the product safety. In vitro cell viability studies revealed that most cell lines can tolerate up to 1 mg/mL of lipid doses of drug-free NLCs [8-9].

Oral route is the most preferred route for the administration of the drugs. But the delivery of drug exhibiting low aqueous solubility and/or permeability (BCS class II or IV) is very challenging as bioavailability of these drugs is very low and pH of the GIT also varies from acidic in stomach to basic in the intestine. The pH of the GIT varies from 1 in stomach to 8 in the intestine. This wide difference in the pH can severely hamper the pharmacological activity of the drug by oxidation, deamidation, or hydrolysis of protein drugs. Lipid nanoparticles like SLN and NLC are transferred through intestinal barrier by clathrin-mediated transport. SLN is also transcytosed by caveolae-mediated endocytosis while NLC is transported by paracellular transport through tight junctions. Different nanoparticulate systems have been investigated to circumvent first-pass metabolism through lymphatic transport and includes nanoemulsion, liposome, SLN, and NLC. Size range of 100–500 nm has been proposed to be ideal in the lymphatic uptake but rate of absorption is faster when size is below 100 nm. Negatively charged nanoparticles show higher lymphatic uptake than positively charged and neutral nanoparticles. Lipophilicity acts as an add-on for lymphatic uptake of drug. NLC of hydrophilic drugs acts as a better approach for enhancing the uptake of such drugs. Furthermore, efflux transporter like P-glycoprotein present on the intestinal wall causes efflux of several antihypertensive leading to poor oral bioavailability [9]. Lacidipine is a lipophilic dihydropyridine calcium channel blocker with a slow onset of action used to treat hypertension. Lacidipine is a lipophilic dihydropyridine calcium antagonist with an intrinsically slow onset of activity. Its main action is to dilate predominantly peripheral and coronary arteries, reducing peripheral vascular resistance and lowering blood pressure. Nanoparticle drug delivery systems have gained significant attention due to their potential to improve the efficacy and safety of drugs. Lack of studies on the formulation and characterization of lacidipine-loaded oral micelles as NLC and investigated the use of oral micelles for delivering drugs, there is still a need for studies that focus specifically on lacidipine-loaded micelles. This would involve developing a suitable formulation for the drug and characterizing the physical and chemical properties of the micelles. Overall, more research is needed to fully explore the potential of NLC system for delivering lacidipine and to bridge the gap between preclinical and clinical studies.

MATERIAL AND METHODS

Determination of maximum wavelength by UV spectroscopy: A number of simulated gastric fluid (0.1 N HCl) pH 1.2 dispersing mediums are utilized for making determination of maximum wavelength of drug lacidipine. Initially one stock solution was prepared by dissolving 10 mg of drug in 10 mL of particular solvent and then dilutions were made in concentration from 10µg/ mL by adding simulated gastric fluid (0.1 N Hcl) pH 1.2. The dilutions made according to calibration standards and their absorbance was recorded at λmax.

Determination of calibration curve: The drug was solubilized in simulated gastric fluid (0.1 N HCl) pH 1.2 dispersing mediums for making calibration curves of drug lacidipine. Initially stock solution was prepared by dissolving 10 mg of drug in 10 mL of particular solvent. Now, various dilutions of different concentration starting from 1µg/ mL to 10µg/ mL by adding simulated gastric fluid (0.1 N HCl) pH 1.2. The dilutions made according to calibration standards [10].

Preformulation studies: Preformulation is a stage before the development of formulation where various physico-chemical properties relevant to the drug and excipients are examined. The results obtained of these studies are helpful for the investigator in the development of a safe, therapeutically effective and stable dosage form. Preformulation studies play a significant role in the selection of physical form of drug and conversion of drug into an appropriate dosage form. It involves the examination of different parameters including solubility studies of drug, melting point determination, drug-excipients interaction studies and stability studies of drug molecule along with the excipients selected for development of formulation. The study focus on getting the observations during the studies and their elucidation to predict the in-vitro and in-vivo pharmacokinetic behaviour of the drug development process. The evaluation of predicted incompatibilities contributes significantly in preformulation studies. Based on the

result of these studies, different additives are selected to blend with the drug to make an intended delivery system for the effective treatment of drug. The selection of substances to be added with the drug is crucial for achieving the best quality of formulation. Preformulation studies provide a guidance in appropriate selection of these supportive components [11].

Preparation and optimization of nanoparticulate system (SLN): The solid lipid nanoparticles in the current research solvent –emulsification evaporation method for preparation. The drug (10 mg) was intended to be encapsulated in the lipid matrix combination with the help of variations in surfactant. The use of stabilizer in the formulation was for improvement in the stability of developed solid lipid nanoparticles. The method optimization for SLNs was on the quality and size of lipid nanoparticles, polydispersity index, entrapment efficiency and drug loading.

The solid lipid nanoparticles in the current research employed three techniques for the fabrication of solid lipid nanoparticles. The technique was optimized based on the particles size of the resultant nano lipid particles with poly dispersity index (PDI). The technique through which lower particle size with high entrapment efficiency derived was selected for further progress in formulation development [12].

Characterization of prepared nanoparticulate system (SLNs)

Particle size distribution: The particle analysis in solid lipid nanoparticles was investigated by photon correlation spectroscopy method. For this study, the dispersion of solid lipid nanoparticles was diluted with purified water in 1:2 ratios and final dispersion was filtered using membrane filter of 0.45µm. The angle for light scattering study was fixed at 90°C. The study was carried out at room temperature (25°C). Three reading were taken for calculating average mean to avoid any errors.

Determination of yield of SLNs: Yield of the formulation indicates the quantity of solid-lipid nanoparticles achieved after the preparation. The yield is derived from gravimetric analysis. In this process a 10 mL suspension of drug was dried until the weight was constant to express the ratio of lipid present after drying and used initially. The yield was calculated in percentage.

Zeta potential measurement: The zeta potential studies for prepared formulations were carried out utilizing Zeta sizer instrument. For the preparation of sample, the drug loaded solid lipid nanoparticles were diluted with purified water in the ratio of 1:2. The sample were analysed three times and average mean was taken into consideration.

Entrapment efficiency: Entrapment efficiency is the study of drug amount that is encapsulated in the lipid matrix and quantity of drug present in supernatant layer received after the process of centrifugation at very high speed of 16000 rpm for half an hour. The entrapment efficiency is the ratio of actual amount of drug loaded and theoretical amount of drug loaded in lipid nanoparticles. The loading of drug can be measured by subtracting the free drug amount from the total quantity of drug used in the formulation [13]. The entrapment efficiency and drug loading can be calculated using the formulas given below:

%EE = free drug amount / total weight of drug *100

% Drug loading= drug entrapped in SLNs/ weight of vehicle *100

Size and shape: The surface morphology is useful for study 3D structure of a particles. The study was performed using scanning electron microscopy. The sample was fixed and dehydrated with acetone [14]. After drying, the sample was coated with gold for imaging. The SEM was performed at 25°C.

In vitro Dissolution study: In vitro dissolution study was carried out using USP type II (basket type) apparatus with 0.1N HCl as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 1ml of aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analyzed for drug content at λ max 240 nm wavelength using UV-spectrophotometer [15]. The cumulative percentage drug release was calculated and reported.

RESULTS AND DISCUSSION

The absorption maxima (λ-max) of lacidipine (10 µg / ml) in 0.1 N HCl solution were found to be at 238 nm. The spectrum peak point graph of absorbance of drug vs. wavelength is shown in Figure 1. Lacidipine was estimated in-vitro by reported UV spectrophotometric methods. The reported UV spectrophotometric methods were slightly modified and optimized according to the existing laboratory conditions. The drugs were estimated in the dissolution medium (0.1 N HCl). The calibration curves in the various dissolution medium (0.1 N HCl) was prepared with drug solutions of known concentrations. The absorbance was measured and plotted against drug concentration (Figure 2). The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to

be greater than 0.99. The curves were found to be recti-linear in the concentration range 10 µg / ml to 50 µg / ml for the drug.

Preformulation studies: The drug sample was white in color, odorless and slightly bitter in taste. Bulk and tapped densities of lacidipine was to be 0.718 gm / cm3 and 0.776 gm / cm3. The particle size of lacidipine was found 92.7 µm. The flow properties of drug sample was excellent in nature. The solubility of drugat Water, 0.1 N HCl, Phosphate buffer pH 4.5, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 were 15.321 (mg / ml), 17.781 (mg / ml), 2.823 (mg / ml), 3.142 (mg / ml) and 2.011 (mg / ml) respectively**.** The melting point of drug sample is 251 °C. The partition coefficient of lacidipine was found to be -1.59. The interpretation of IR study spectrum is shown in Figure 3. The characteristic peaks of lacidipine were has some specifics wave numbers, namely at 3348.78, 2978.52 to 2808, 1702 to 1653.66, 1629.55 and 1292 cm^{-1}. The purpose of the method was completely accomplished as there seems no major interference by the excipients in present study.

Characterization of prepared nanoparticulate system (SLN): The optimization of lipid ratio over the solid lipid content on the result of dependent variables i.e. Particle size (Y_1), Zeta potential (Y_2), Poly dispersity index (Y_3), Drug percentage entrapment efficiency (Y_4) prepared various formulations from LSLN1 to LSLN6 according to 3^2 factorial designs. The content of solid lipid core phosphatidylcholine (PC) was coated with single layer of lipid content and double layer of combination of two layers of soyalecithine (SL), nutmeg oil (NO). The various combinations of lipid core materials optimize with constant concentration of surfactant as penetration enhancer of drug. The penetration enhancer affects the insertion of drug lopinavir amount inside the solid lipoid core (PC) through the single or double layer of lipid layers. The sonication time affect the multiilaminar vesicles to unilaminar vesicles and the process also useful for overcome the problem of agglomeration of vesicles. The result of all dependent variables were evaluated and among all the formulations LSLN4 having NO:PC:SL (1:1.5:2) was selected best formulation. The prepared solid lipid layers ratio varying from 0.5 to 1.5 in with solid lipid triglycerides (PC) provides a hydrophobic core. The result concluded that as the concentration of solid core varies and the amount of lipid content increase the particle size increase, thus increase the PDI and zetapotential action. The variations of result of all parameters also showed between the optimization of single or double layer. The optimization of sonication time was improving the particle size of LSLN1 and LSLN2, because of single layer of emulsomes and showed smaller size than the other formulations. Thus, the result of particle size distribution, PDI and zetapotential action of LSLN1 and LSLN2 was equivalent to the formulations LSLN4, because of amount of solid lipid core (SL) with addition of more amounts of PC and less amount of NO. The change of vesicles size and drug entrapment efficiency also correlated with each other, due to thickness of wall of lipid layers. The formulation LSLN4 has more than 90% drug entrapment with addition of Span 80 in 10% concentrations. All the result of dependent variables concluded that the formulation LSLN4 was selected for the optimize for the solubility enhancement by solid dispersion.

Summary and conclusion: Lacidipine is a antihypertensive drug having low solubility because of highly lipophilic nature. Hence lacidipine nanosphere preparation by using different polymers and surfactants. Finally, I am succeeded in increasing the solubility and bioavailability of the drug by the preparation of the lacidipine nanoparticles.

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Table 1: Variability in combination of oral micelle on the basis of lipid content (NO:PC:SL) Concentration of surfactant and sonication time

Formulation Code	Lipid content (X_1)			Amount of surfactant (X_2) (%) (Span 80)	Addition of sonication time (X_3) (Min.)
	Nutmeg oil (NO) (mg) X_a	Phosphatidylcholine (PC) (mg) X_b	Soyalecithin (LC) (mg) X_c		
LSLN1	20	10	15	10	10
LSLN2	10	20	15	10	10
LSLN3	20	15	10	10	10
LSLN4	10	15	20	10	10
LSLN5	15	20	10	10	10
LSLN6	15	10	20	10	10

Table 2: Physical properties of prepared lacidipine SLNs

Formulation Code	Layers	Particle size (nm)	PDI	Zeta potential (mV)
LSLN1	Single	122.01±1.02	0.216±0.08	-20.12±1.02
LSLN2	Single	123.03±1.04	0.215±0.02	-20.18±1.05
LSLN3	Double	129.03±0.08	0.221±0.27	-22.91±1.03
LSLN4	Double	127.21±1.11	0.216±0.05	-24.21±1.09
LSLN5	Double	130.12±1.06	0.224±0.07	-22.12±1.08
LSNL6	Double	128.21±1.02	0.219±0.05	-23.01±1.03

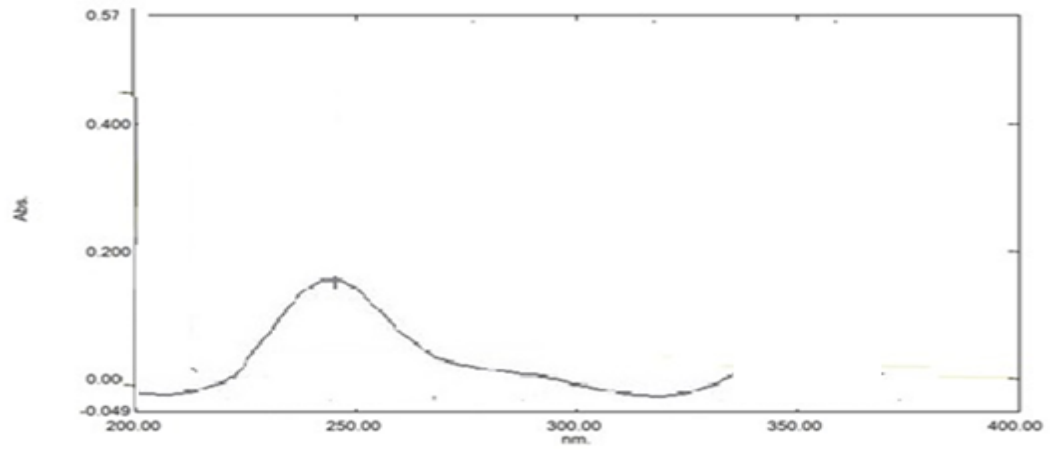

Figure 1: Absorption maxima (λ-max) of lacidipine in phosphate buffer 0.1 N HCl solution (10 µg/ml)

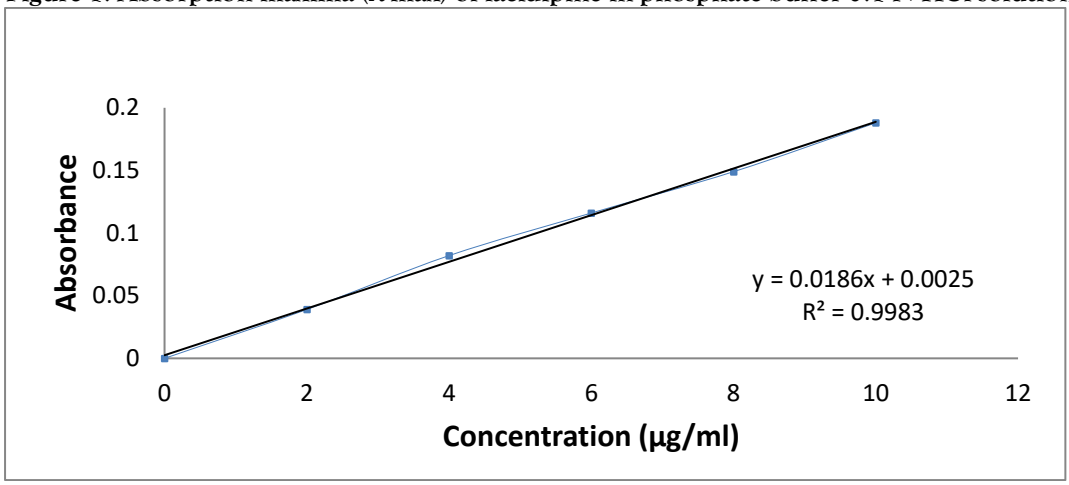

Figure 2: Standard curve of lacidipine in 0.1 N HCl solution (238 nm)

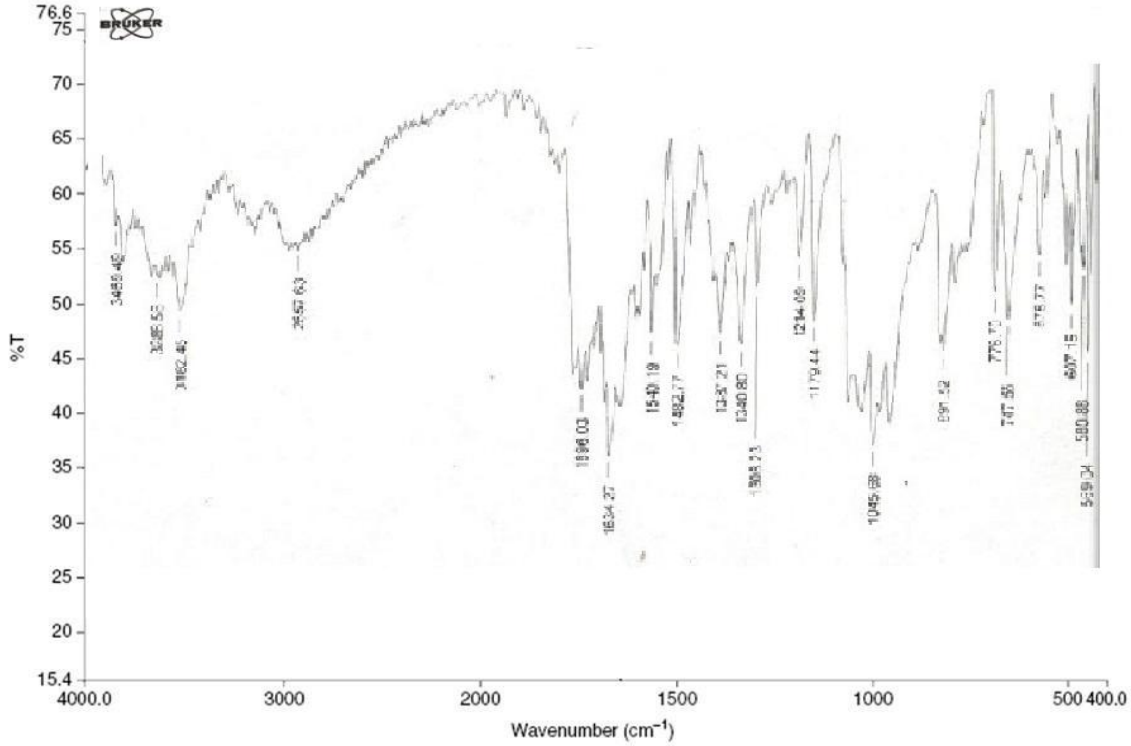

Figure 3: The I. R. Spectrum of lacidipine drug and all excipient

Results

		Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm): 127.21	Peak 1:	127	124.01	101
PdI: 0.216	Peak 2:	0.00	0.0	0.00
Intercept: 0.311	Peak 3:	0.00	0.0	0.00

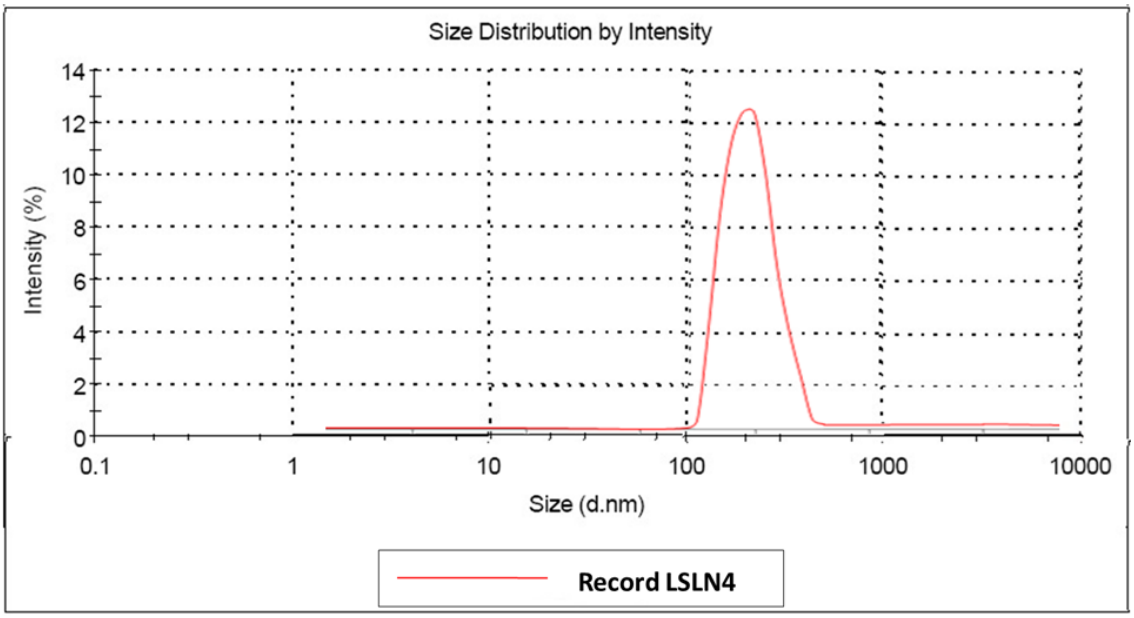

Figure 4: Particle size determination of prepared lacidipine SLNs (LSLN4)

Results

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):-24.21	Peak 1:	-24.21	99	3.19
Zeta Deviation (mV): 68.12	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 0.254	Peak 3:	0.00	0.0	0.00

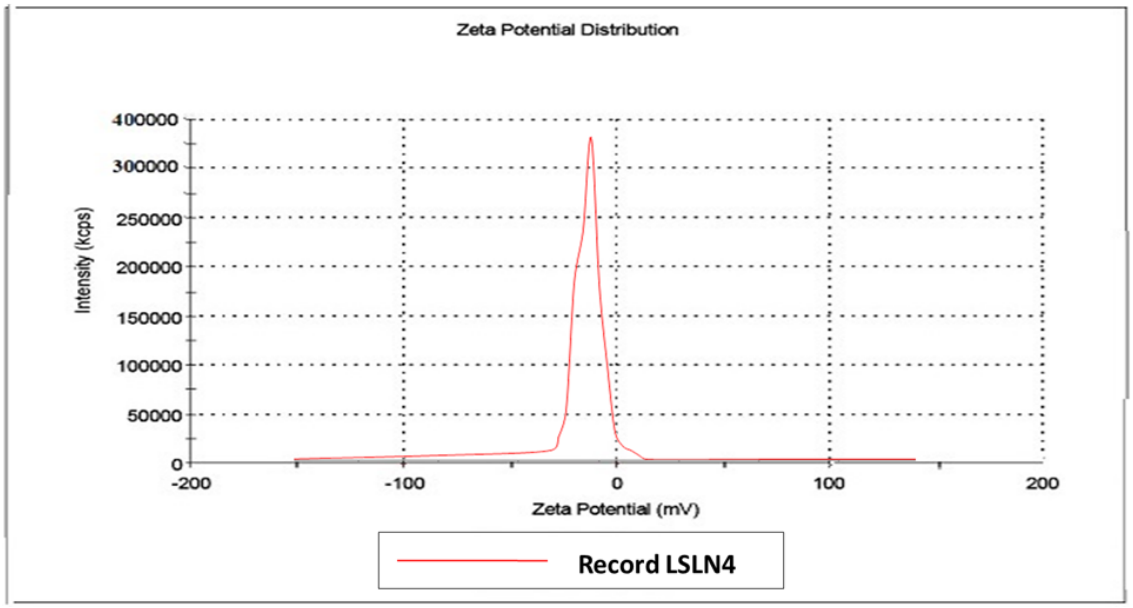

Figure 5: Zeta potential determination of prepared lacidipine SLNs (LSLN4)