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CHARACTERIZATION OF THE DERMAL TARGETING OF OPTIMIZED COMBINATORIAL LIPID-NANOSYSTEM

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Abstract

Dermal and transdermal medication delivery systems have benefited greatly from the development of nanotechnology and nanomedicine. This research looks at where we are now with (trans)dermal drug delivery using lipid-based nanotechnology and nanomedicine. In this article, we examine and contrast several types of (phospho)lipid-based drug delivery nanosystems, focusing on their capacity to provide regulated drug release to the skin and skin appendages, as well as drug targeting and safety. For both SLN and NLC, measurements and records were kept of the particles' sizes, polydispersity indices, entrapment efficiencies, X-ray powder diffraction patterns, thermal behaviors, and surface morphologies. For topical administration, hydrogels containing SLN and NLC loaded with LID were developed. The skin of guinea pigs was used to test the permeation characteristics of LID SLN gel, LID NLC gel, and a commercially available LID formulation (Xylocaine® gel) in a laboratory setting.

Keywords: lidocaine; local anesthetic effect; nanostructured lipid carriers (NLC); solid lipid nanoparticle (SLN).

INTRODUCTION

In the last two decades, nanotechnology has permeated almost every technological sector, including the pharmaceutical industry. Several unique and enhanced lipophilic drug delivery systems have been developed to address the solubility and formulation stability concerns that are believed to be responsible for the failure of around 40% of lipo-philic medication candidates (Mishra etal. 2010). When producing lipid nano-particles, physiological lipids with low acute and chronic toxicity are often employed.

Lidocaine (LID) is a local anesthetic that has a modest duration of action and a short half-life. LID hydrochloride (HCl) is the active ingredient in a variety of topical ointments, gels, and solutions marketed under the Xylocaine® brand name. Dosages range from 1% to 5% w/w. The eutectic combination of LID HCl and procaine HCl found in ELMA® is another effective medication (1). These preparations have an instantaneous effect but a brief half-life.

Long contact times post-percutaneous or dermal dosing are required for the uncharged, lipophilic drug to permeate the stratum corneum and desensitize the underlying pain receptors in the skin. Particulate carriers are one example of the new generation of topical drug delivery methods being developed to provide a steady release of a medication at the location of its pharmacological action. The use of particle carriers for topically administered medications has recently emerged as a key area of study in dermatology (2). Microemulsion, liposomes, and nanoparticles are only few of the carrier systems that have been studied for cutaneous medication delivery. Such systems have the potential to improve drug penetration in skin, lengthen the time that medications remain locally active, and inhibit systemic absorption of pharmaceuticals, all of which contribute to a decrease in drug-related adverse effects.

Solid lipid nanoparticles are an appealing alternative to liposomes because of their increased physical stability, lower cost relative to phospholipids, and simple scale-up and production requirements. It is also well documented that they have the potential to increase the photostability of active

pharmaceutical components and aid in epidermal targeting, follicular delivery, controlled drug administration, and topical application. As the medication is more mobile in this form, it remains relatively stable even if the solid lipid undergoes polymorphic changes. In addition, NLC has the potential to provide regulated medication delivery.

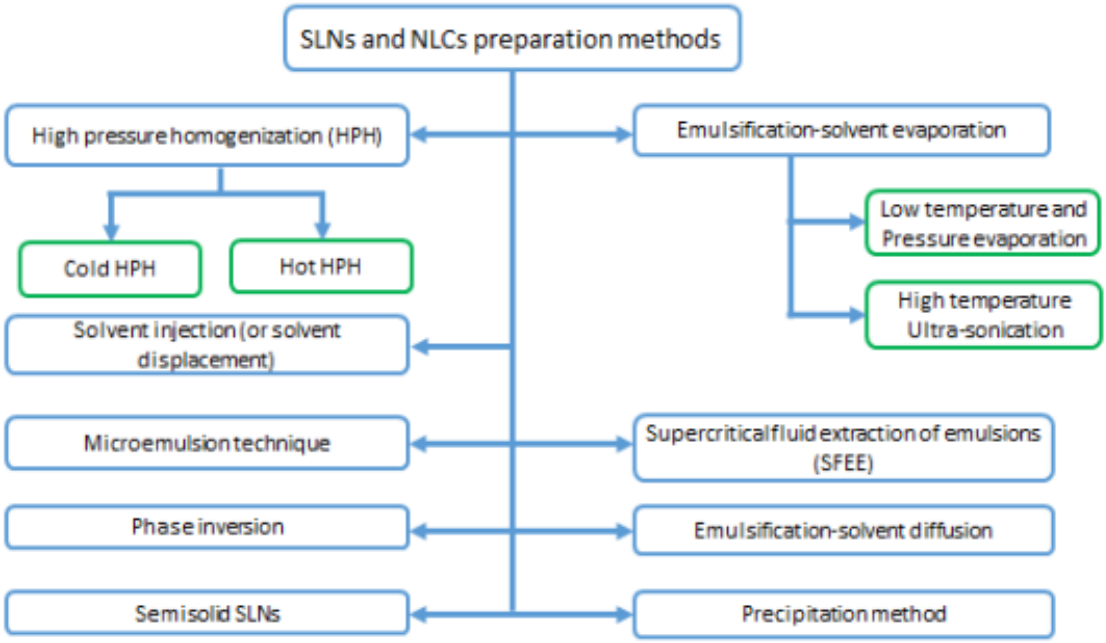

Figure 1. Solid lipid nanoparticles and Nanostructured lipid Carriers preparation methods

LITERATURE REVIEW

Hallan, S.S.; Sguizzato, M.; Esposito, E.; Cortesi, R. 2019, The use of nanoscale drug transporters has emerged as a cost-effective strategy with significant market potential. Applications of nanomedicine include not only medication delivery by intravenous, oral, transdermal, nasal, pulmonary, and other modes of administration, but also vaccination, antibacterial, diagnostic, and imaging technologies, and gene transfer. The composition, characteristics, and physical parameters of lipid nanosystems with diverse applications will be discussed in this study. Yet, there is still disagreement on how to best create a procedure for the physical assessment of nanoparticles. The fundamental problem is doubts about the selected method's sensitivity, repeatability, and dependability. This study compares and contrasts many significant methods. To further probe antioxidant activity and nanomaterial reaction to the epidermal membrane, an amperometric method has been introduced.

Researchers Piyush Jaiswal, Bina Gidwani, and Amber Vyas (2016), The intriguing evolution of nanoscale drug delivery devices over the last several decades is only one example of the many new drug-delivery technologies that have arisen in recent years. Drug kinetics, tissue distribution, and release profile may all be altered by using a colloidal drug-delivery method like nanoparticles (NPs). This work provides an overview of the various NLCs, their mechanisms of skin penetration and stability, their manufacturing methods, their characterization, and their applications in targeted drug administration. The use of nanoscale materials in diagnostic devices or for the controlled delivery of medicinal chemicals to specific targeted locations is a relatively young but quickly expanding topic of research. Long-term therapy of chronic human diseases offers significant potential because to nanotechnology's capacity to deliver drugs precisely to specified areas and targets.

Piyush Jaiswal, Bina Gidwani, Amber Vyas (2016),One exciting aspect of the emergence of new drug-delivery technology over the last several decades is the advent of nanoscale drug delivery devices.

Drug kinetics, tissue distribution, and release profile may all be altered by using a colloidal drug-delivery method like nanoparticles (NPs). This study provides a general overview of the several kinds of NLCs, the process by which they penetrate the skin, stability-related difficulties, and the methods by which they are produced, characterized, and used for targeted drug administration.

Colloidal nanoparticles containing a lipid combination of solid and liquid lipids (Khan Sh, Sharma A, Jain V., 2019; Nanostructured Lipid Carriers, NLC). In contrast to polymeric or metallic nanoparticles, this Lipid-Based Nanosystem is safe, non-toxic, and biocompatible. Researchers' attention was drawn to NLC because it is relatively risk-free, stable, and has a large drug loading capacity compared to other lipid-based nanocarriers. They are a perfect carrier for drug distribution through challenging routes because they can improve drug solubility and permeability while encasing the molecule in a lipidic shell. To improve drug targeting and residence time, the NLC surface is modified using a variety of compounds. Cancer, infections, neurological disorders, high blood pressure, diabetes, chronic pain, and other conditions may all be treated with NLCs thanks to their beneficial properties. Recent advances in using these nanocarriers to transport medications and genetic material are the subject of this article. In this article, we also go over the context, structure, and kinds of NLC, as well as the most prevalent methods used for producing lipid-based nanocarriers.

MATERIALS AND METHODS

Coloron Asia, based out of Mumbai, India, has provided us with free samples of both their Compritol 888 ATO (COM) and Precirol ATO 5 (PRE) products. S. Zaveri and Sons, of Mumbai, India, generously provided us with a sample of their Miglyol 810 (MIG 810). Exim Pharm International and Heer Pharma of Mumbai, India, generously provided free samples of LID to the researchers. Noveon, located in Mumbai, India, generously sent a sample of their product Noveon AA1® (Polycarbophil). Sodium benzoate, glycerol, triethanolamine, and Tween 80 were all acquired from S.D. Fines in Bombay, India.

DATA ANALYSIS

We employed ultrasonic dispersion to create LID SLN, NLC, and NE. In a nutshell, we melted COM and PRE lipid mixes at 85-90oC, at the proportions shown in Table 1. The aforementioned molten lipids were treated with LID. In addition, the lipid phase was mixed with Tween 80 solutions at temperatures of 85-90oC to create a coarse emulsion. Sonication of the coarse emulsion was performed at 30 W for 1 to 4 minutes, using a Sonifier® Model 250 probe sonicator. After the nanosuspension formed, it was refrigerated to 4 C in order to extract SLN.

The identical methods used to make LID SLN were used to making LID NLC. Several concentrations of COM and MIG 810 were used to create the lipid combination (Table 2). A 20 mM Tween 80 solution was utilized, and the sonication process took place over the course of four minutes. The solid lipid in LID NE was replaced with MIG 810 and the process was otherwise identical to that used to make LID SLN. The quantity of Tween 80 employed was 20 mM, and the sonication period was 4 minutes.

In the optimization and in vitro permeation investigation, SLN, NLC, and NE formulations all had a lipid load (the total quantity of fat contained in the formulation) of 2.5% w/w. In addition, 2% w/w LID formulations were created using 5% w/w lipid load, and NE, NLC, and SLN formulations were added to the mixture at a ratio of 1:2.5 with regard to the quantity of lipid utilized for an in vivo effectiveness test.

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Table 1. Formulation Parameters and Characterization of LID SLN (n=3)

Formula no.	Lipid composition COM/PRE	Surfactant concentration (mM)	Sonication time (min)	Entrapment efficiency ± SD (%)	Mean particle size ± SD (nm)	Polydispersity index ± SD
BI	1:9	10	1	73.05±0.982	124.25±4.737	0.481±0.0197
BII	1:1	20	4	92.15±0.495	74.25±5.161	0.684±0.0919
BIII	9:1	10	1	78.52±0.134	247.85±2.333	0.685±0.0063
BIV	9:1	20	4	97.37±1.414	78.1±2.687	0.556±0.0862
BV	9:1	10	4	89.43±1.414	120.1±1.414	0.344±0.0516

Table 2. Composition and Characterization of LID NLC (n=3)

Formula no.	Compritol/total lipid (% *w/w*)	Miglyol 810/total lipid (% *w/w*)	Entrapment efficiency (%)	Mean particle size (nm)	Polydispersity index
N1	95	5	91.25±0.561	74.3±3.654	0.487±0.0121
N2	90	10	95.96±0.985	72.8±2.135	0.463±0.0421
N3	85	15	92.15±1.234	76.1±1.654	0.456±0.0712
N4	80	20	89.89±0.265	83.7±3.012	0.571±0.0257
N5	60	40	53.95±2.365	78.2±4.251	0.601±0.0719

Dispersions of SLN and NLC were diluted with distilled water and centrifuged at 13,200 rpm for 25 minutes using a Minispin. Using a V-530 UV-visible spectrophotometer, we compared the absorbance at 262 nm of the LID extract to that of a blank formulation that had undergone identical processing conditions. The following formula was used to get the entrapment efficiency as a percentage:

$$\%EE = (A/B) \times 100$$

where A is the total quantity of LID in the formulation and B is the amount of LID that was entrapped in the lipid.

All measurements were collected at room temperature (25 degrees C) at a right angle (90 degrees). To maintain the light-scattering intensity within the instrument's sensitivity range, dispersions were diluted using double-distilled water. Double-distilled water is filtered with 0.45 m membrane filters,

particle size was measured.

Uranyl acetate was utilized to generate a negative stain for the particle carriers. After the colored grid dried in the air, it was analyzed using a Jel-1010 electron microscope. These electron micrographs were taken between 2,500 and 120,000 times their original size. Freeze-dried SLN was made both with and without LID. Chromatopac R6A thermal analyzer acquired thermograms of both individual components and SLN. After carefully transferring 5 mg of each component into their own aluminum pans, the samples and the empty pan were heated from 30 to 110 degrees Celsius at a rate of 5 degrees Celsius per minute. X-ray diffraction (XRD) patterns were recorded to evaluate the stability of the formulations. Freeze drying was used to preserve the powdered form of both drug-free SLN and LID-loaded SLN. Using a Philips Analytical X'Pert PRO Powder X-ray diffractometer, XRD patterns were acquired in the range of 10° to 50° 2 at a scanning rate of 1°min1.

The long-term stability of the best SLN and NLC dispersions was investigated. Amber glass vials with rubber stoppers and metal lids were used to keep the samples. Aliquots were taken from the LID SLN formulations at 0, 15, 30-, 60-, 90-, and 180-day intervals while they were held at 4°C, 25°C/60 5% RH, and 40°C/755% RH for a total of 6 months. Aliquots of a LID NLC formulation were taken out at 0, 7-, 14-, 21-, and 30-day intervals after it was held for a month at 4°C, 25°C/605% RH, and 40°C/755% RH, respectively. Measurements of particle size, polydispersity index, and the percentage of LID retained were made for each nanoparticle dispersion. Ten grams were used of the LID topical gel. While waiting for the liquid to expand, it was agitated with a glass rod every so often. The pH was adjusted to 7-7.5 with the addition of triethanolamine drop by drop. One day before to the commencement of the tests, the topical gels containing LID were made.

RESULTS

Preparation of LID SLN and NLC using ultrasound dispersion was successful. The colloidal dispersions passed muster as far as visual inspection and sedimentation were concerned after 15 days. Both LID SLN and LID NLC have their own process parameters and characterisation tables, which may be found in Tables 1 and 2, respectively. From 70% to 97%, LID %EE in SLN was quite variable. The best entrapment efficiency was achieved using the BIV SLN formula with a 9:1 COM/PRE lipid combination, 20 mM surfactant concentration, and 4 minutes of sonication. (97%). Sonication was performed for 4 minutes, and the surfactant concentration was maintained at 20 mM. The entrapment effectiveness of this formula was measured at 95.96%.

Particle sizes in the LID SLN formulations were measured to range from 70 to 250 nm, indicating a tight size distribution (Table I). The mean particle size for formula BIV was 78 nm, whereas for formula BII it was 70 nm. Methods for preparing formula BII were similar to those used for formula BIV, with the exception of a 1:1 COM/PRE lipid ratio. The optimal LID NLC formula produced particles of 72.8 nm in size (Table 2). The polydispersity index is a ratio used to measure the consistency of a system's particle size distribution. Negative 0.3 is the sweet spot. When the polydispersity index is low, the system has a uniform distribution of sizes. The polydispersity indices for both LID SLN and NLC are in the range of 0.3–0.8. This suggests that there is a rather even distribution of sizes inside the LID SLN and NLC. For the BIV formula for LID SLN, the polydispersity index was 0.556, whereas that for LID NLC formula N2 was just 0.463.

Transmission electron microscopy analyses were performed to learn more about the nanoparticle systems' morphology. TEM micrographs of formula BIV (SLN) and formula N2 (NLC) reveal the roughly spherical shape of LID SLN and NLC with some flaws at the particle's periphery. (Figs. 2 and 3). The TEM particle size was consistent with the PCS particle size.

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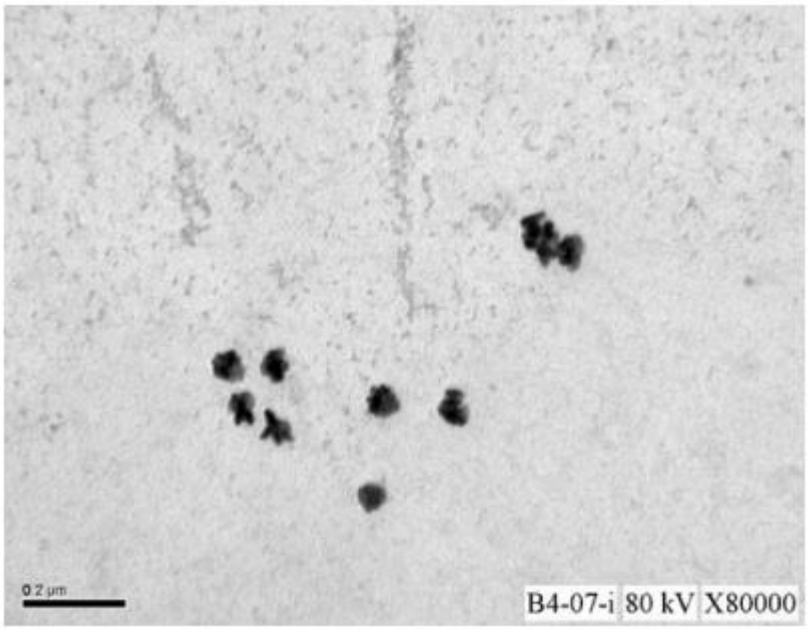

Fig. 2. TEM images of LID SLN

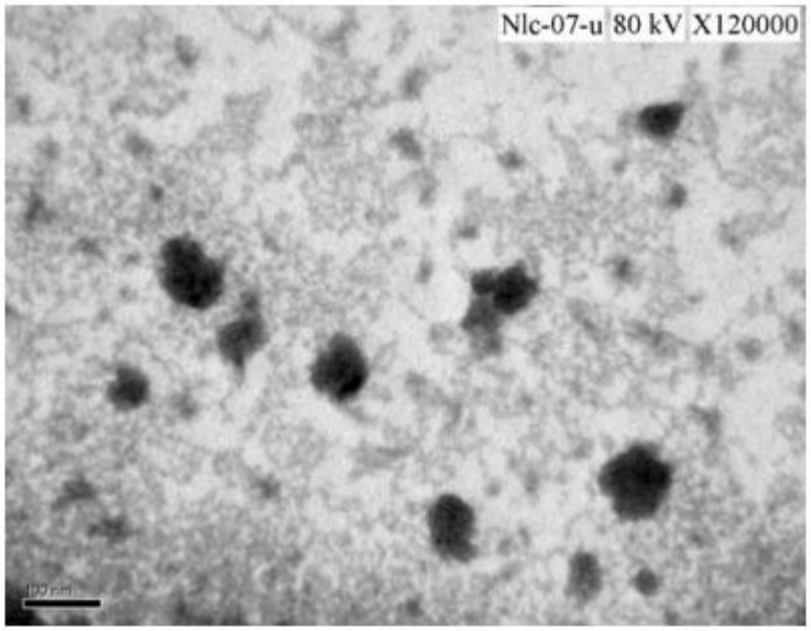

Fig. 3. TEM images of LID NLC

Thermogravimetric (thermogram) profiles of the LID SLN formulation and its constituent parts are shown in Figure 4. Freeze drying was used on both the SLN dispersions with and without LID to preserve the lipids' structural integrity. Cryoprotectant trehalose was utilized at a 1:10 concentration. The thermogram of LID SLN shows a lower endotherm compared to the physical combination.

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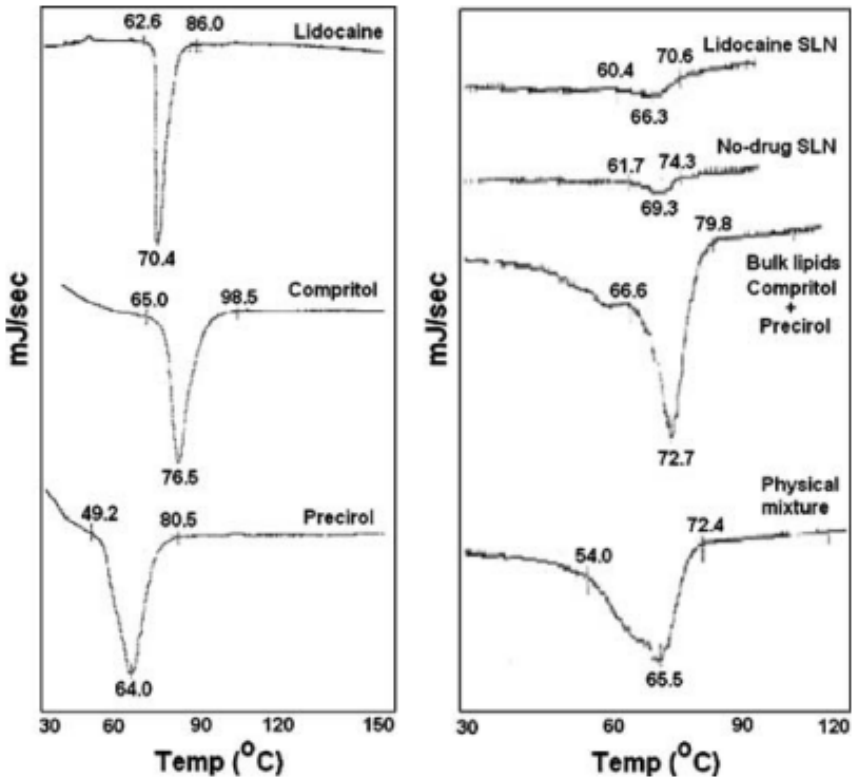

Fig. 4. DSC thermogram scans of LID SLN and its components

X-ray analyses of SLN showed that its constituent parts had lost their crystalline structure. The scan revealed that the LID powder was extremely crystalline, with distinct peaks. Freeze-dried SLN loses part of its crystalline form, as seen by the lack of a prominent peak in the XRD patterns. In an X-ray spectrum including SLN without LID, LID SLN, physical interaction with LID, and trehalose, the compound's distinctive peaks include a sharp increase in intensity at around 25°, where the 2 value lies.

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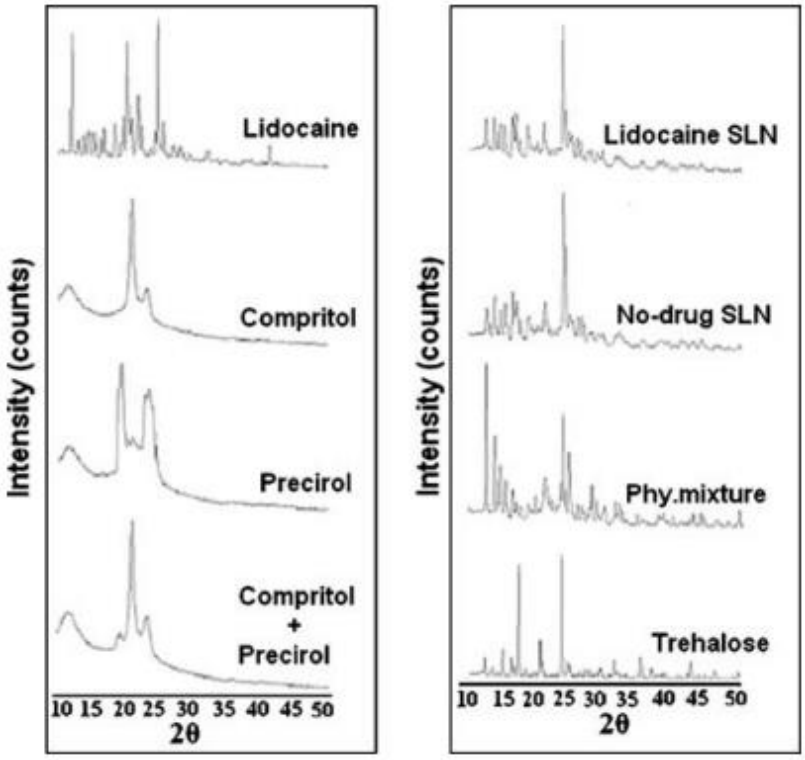

Fig. 5. XRD pattern of LID SLN and its components

DISCUSSION

It has been stated that COM and PRE were used to make SLN and NLC. Blends of the lipids were used to determine how composition affected entrapment efficiency. For the SLN formulation, it was shown that a higher COM ratio has the potential to improve entrapment efficiency. The entrapment efficiency of LID NLC is also sensitive to the amount of liquid lipid present in the given experimental conditions. When the lipid content in the liquid was more than 10%, the entrapment efficiency decreased. When the lipid content in the liquid was decreased to below 10%, the entrapment efficiency likewise decreased. The increased lipid content may have been too much for the solid lipid to handle, leading to its expulsion. Any decrease in liquid below 10% was insufficient to maintain LID.

Images captured by transmission electron microscopy (TEM) reveal that both formula BIV and NLC N2 formulations of LID SLN and NLC have a nearly spherical shape, with flaws only at the particle carriers' peripheries. The differences might be due to differences in the methods of preparation. In contrast to the apparently smoother and rounder surface provided by the solvent diffusion and solvent injection procedures, the probe sonicator's high frequency waves may generate defects on the particle surface.

Permeability, leakage rates, and SLN stability are all affected by the lipids' physical condition. It is widely established that triglycerides (, ′, and) undergo a phase change. This indicates that the lipids and LID have lost their crystalline structure after being incorporated into SLN. XRD investigations supported these results by demonstrating that freeze-dried SLN had lost at least portion of its crystalline structure, as seen by the lack of a prominent peak in the XRD patterns of the dried substance.

CONCLUSION

The ultrasonic dispersion approach may be used to combine LID into SLN and NLC, making for a

more robust system. Gel formulations of LID SLN and NLC exhibited delayed LID penetration in vitro and produced long-lasting, profound local anesthesia in guinea pigs when given topically.

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