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Preparation and standardizations of structural nano- lipid loaded lidocaine and conventional lidocaine

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***Abstract*---**The main of reformulated conventional lidocaine to structural nano lidocaine was to avoid the side effect of lidocaine with decrease the dose and toxic effect and the structural Nano lipid loaded lidocaine ($SNL_{lidocaine}$) reach deeply to the nerve which made animals always anaesthetic and reduce the pain. Success of creation loaded lidocaine in Nano- lipid with maintain the categorized chemical function and promise the new generation of safeness lidocaine and Nano behaver.

***Keywords*---**Structural Nano-Lipid Loaded Lidocaine $SNL_{Lidocaine}$, conventional lidocaine, anaesthetic.

Introduction

Lidocaine has serious jeopardrical disadvantages in several systematic function and tissue ranged allergic to cardiac arrest. The lidocaine was combined from Lidocaine (Lido) is a kind of amide local anesthetic that can block the sodium ion transport pathway that is involved in neuronal initiation and conduction. Since the middle of the 20th century, lidocaine has been used clinically as a local nerve block and for epidural anesthesia. Compared with other local anesthetics (ropivacaine, bupivacaine, etc.), lidocaine has lower anesthetic efficacy and less toxicity when used at clinical doses (Xia.*et.al.*2020).Nanostructured lipid carriers (NLCs) was the second generation of lipid nanoparticles, with SLNs being the first. The solid lipid matrix immobilizes the drug and keeps the particles from coalescing, while the liquid oil droplet within the solid matrix improves the particle's drug loading capacity. As a result, the lipid mixture allows for the formation of poorly structured lipid crystals within the particles, allowing for more pharmaceuticals to be encapsulated uniformly and inhibiting rapid drug diffusion

from the particles' surface (Zheng *et.al.*2019).Several methodological maneuverers for admitted the functional group of composition was affiliated to endowed with nano chemical structure of lidocaine amide group and distinguish their proprieties after the reformed.

Materials & Methods

Table 1: Solutions, instruments, and types of equipment

Apparatus and equipment's	Company	Origin
Stearic acid	HIMEDIA	India
Microsurgical scissor	Citoglas	China
Eppendorf tube	AFCODISPO	Jordan
Dimethylformamide	Panreac	Spain
Light Microscope	Olympus	Japan
Micropipette	Winlab	Germany
Normal saline	Pioneer	Iraq
Phosphate buffer	JOURILABS	France
Phosphatidylcholine	ChemCruz	USA
Slides	Citoglas	China
Spectrophotometer	MPW	Germany
Syringe(1,3,5)	Medco	USA
Vortex	Human Twiset	USA
Germany Formalin 37 %	EDUTECH	India
Lidocaine	Al-Hayat factory	Iraq
Glycerin	Now	USA
Castor oil	Now	USA
Phosphatic acid	HIMEDIA	India
Water bath	Hana	Romania
Tetracaine Hydrochloride/cooper	Konep A.E	Greece
Fluorescein indicator	TOOS NEGAH	Iran
Lidocaine injection	LONDON	UK
Sensitivity balance	MEDICALS	USA
Micropipette	Sartorius	Germany
Acetic acid	Winla	England
Carbopol	BHD	England
	Silverson	

Groundwork of preparation and standardization of structural nano-lipid loaded lidocaine ($SNL_{Lidocaine}$)

The formulations of $SNL_{lidocaine}$ was protocolled according to (Ulery et al., 2011) and standardized actual formation Nanoscale and quantify the loaded amount of lidocaine, the turnover of the complex structure of lidocaine-SNL in the gel formed shape.

Preparation protocol of structural nano-lipid loaded lidocaine ($SNL_{Lidocaine}$).

The preparation of structural nano-lipid Lidocaine ($SNL_{Lidocaine}$) via two phases; the lipid phase of SNL forming and the gel phase for the base vehicle figure 1.

Lipid form: The primer lipidic forming $SNL_{Lidocaine}$ was done according to solvent diffusion method, which comprises; stearic acid 100mg and glycerin monostearate 100mg dissolved and dispersed in castor oil 2ml to form lipid dispersion at 1500 rpm for 30 minutes (Shikanov *et al.*, 2007 and Sokolsky *et al.*, 2009).

Dissolving form: The lidocaine loading in lipidic form was prepared via mixed phosphatic acid 100 mg with disbanded lidocaine base 100 mg in 1 ml of dimethylformamide then dispersed with the lipid forming phase with heat 70-75°C (Claudia *et al.*, 2017 and Cohen *et al.*, 2012). The loaded lidocaine in lipidic form was suspended in purified distilled water 10 ml and vortexed at 800rpm for 20 minutes to form structural Nano-lipid lidocaine, The structural Nano-lipid lidocaine suspension was filtered through a membrane with 0.45 µm pore size and stored at 8°C before use (Cohen *et al.*, 2012 and Hoare, *et al.*, 2008). The structural Nano Lipid $_{Lidocaine}$ was stored in the refrigerator overnight at 8°C, and the cold structural Nano Lipid $_{Lidocaine}$ stock solution was incubated in a water bath for 10 minutes while being vortexes for 30 minutes before use.

Gel phase preparation: The gel was prepared by dissolving carbopol 0.125 g and blending in purified distilled water 3ml to form the gel phase with equilibrize acidic feature in gel via adding 1ml of NaOH(0.1N) with mixed well until the suspension became thick and clear, then heated for 15 minutes for freed air bubbles (Sivakumaran *et al.*, 2011 and Jia *et al.*, 2004). Lidocaine loaded in the gel act as basic carrier, extender, wound dresser agent and set as diluent agents for lidocaine formulas SNL and conventional

Gel-Lidocaine stock: The concentrations of lidocaine formulations were prepared by mixing with gel depending on the lidocaine amounts as; 100 mg mixed with gel 100, 50, 25, and 20 g achieved 1, 2, 4, and 5 % respectively.

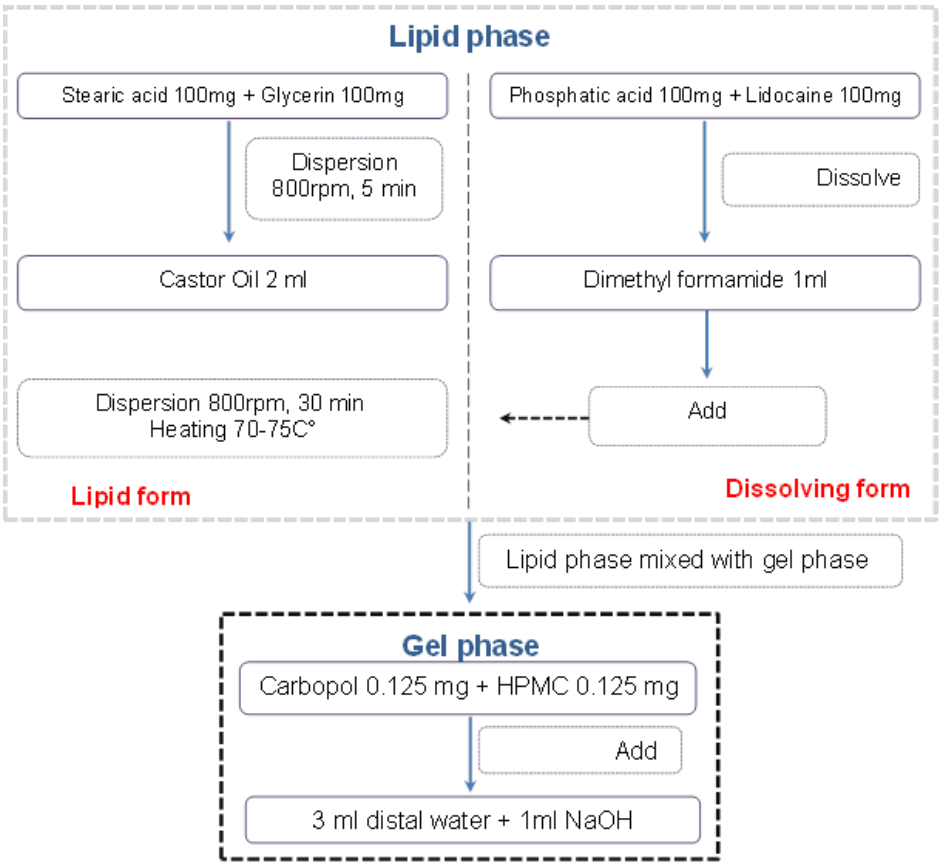

Figure 1. The Structural Nano-Lipid $_{Lidocaine}$(SNL$_{Lidocaine}$) preparation protocol

The Standardization of structural nano-lipid loaded lidocaine (SNL$_{Lidocaine}$): Identification, shape, and size of structural Nano-lipid lidocaine were investigated and standardized with parametric maneuvers (Mathur *et al.*, 2014).

Micrograph: Structural Nano-Lipid $_{Lidocaine}$ size: Light micrograph: The Structural Nano Lipid $_{Lidocaine}$ smear was created and analyzed under a microscope with an optical filter at oil immersion magnifine scale and screening the created Nano-lipid structure of lidocaine distribution had been inspected (Oliveira *et al.*, 2005).

Electron micrograph: The stored structural Nano lipid $_{lidocaine}$ 0.2% was exams sample for scan and transmission electron microscope. Applied Research Foundation (AL-KAK) conducted scanning and transmission techniques, for micrographs in submitted to Kashan University in Iran (Szebeni *et al.*,1984). Nano-lipid Size**;** The scan electron microscopy was used to quantify the structure of Nano-lipid lidocaine based on the programmed picture and the Metric scale, and the average size percentage was estimated based on available information of Yokoyama *et al.* (2007)**.**

X-ray diffraction (XRD): XRD analysis of crystallization status of conventional and SNL lidocaine were performed using an X-ray diffractometer (2 to 40 C°) to

assess the structural Nano-lipid lidocaine and conventional lidocaine final structural form homogeneously (Soraya *et al.*, 2015).

FTIR spectroscopy: was used to assess the physical and chemical interaction of structural Nano-lipid lidocaine (Yaping *et al.*, 2019).

Zeta potential: Zeta potential of structural Nano-lipid lidocaine was assayed for the stability of a dispersion of Nanoparticles (Wang *et al.*, 2014).

Results

The micrography of structural Nano–lipid lidocaine and conventional lidocaine

The light micrograph was presented the particles formation in phasic technique of nano-lipid formation and exhibited the basic structure in loaded lidocaine without aggregation of particles.

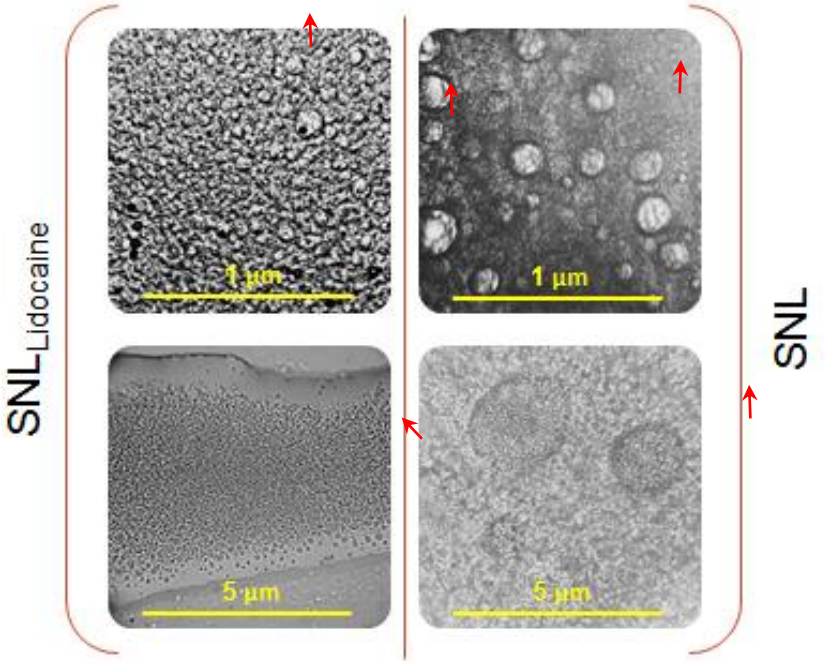

Figure 2. The light micrograph of $SNL_{Lidocaine}$

Electron micrograph

The transmission micrography of SNL- lidocaine represented in regular formation with different distribution of scale size distribution, (figure 4.2: A, B, C, D, E and F) with represented the globular formation of SNLlidocaine in G.

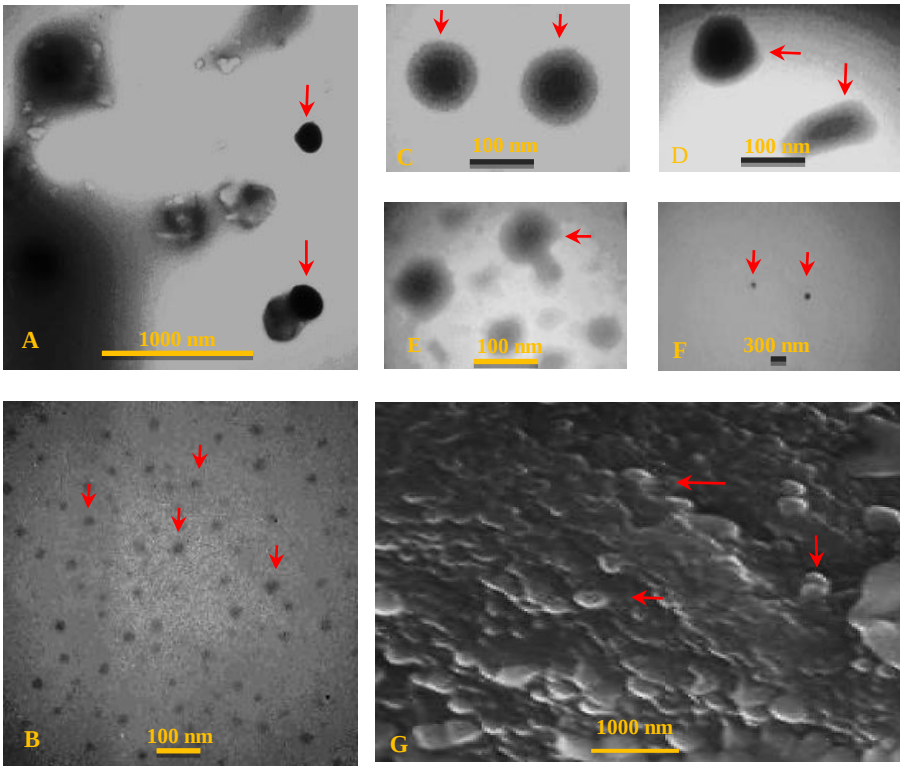

Figure 3. Micrograph of $SNL_{lidocaine}$ of electron microscope in of scan and transmission A, B, C, D, E and F transmission. The red arrow denoted to $SNL_{lidocaine}$ as globular formation in different size
G scan micrograph of lidocaine.

The Entrapment Amount

The standardization of lidocaine carrying by $SNL_{lidocaine}$ present entrapment percent and loading efficiency percent 86.51 ± 11.29 % and 77.75 ± 6.59 % respectively. The size of $SNL_{lidocaine}$ was showed the rang 93.95 – 147.35 mean 97.95 ± 8.57.

Table .1. The entrapment and loading efficiency percent of $SNL_{lidocaine}$ and size of Nano

Entrapment %	Loading efficiency %	Size range (nm)	Mean
86.51 ± 11.29	77.75 ± 6.59	93.95 – 147.35	97.95 ± 8.57

X-ray diffraction (XRD):

The status of crystalline of the Nano-Lipid structure lidocaine was compared with conventional lidocaine by the diffractograms method via X-ray diffraction

apparatus. The figure 4 display the $SNL_{Lidocaine}$ pattern of diffraction showed sharp peaks, representing the nature of lidocaine crystalline. The distinctive main peaks for lidocaine (2T 23.129, 40.938, 44.432, and 73.958) were mislaid from the diffractogram pattern of SNL form as compared with conventional lidocaine,

Fourier Transform Infrared (FTIR)

The spectrum of FTIR of the Lidocaine forms displayed a strong peak at 1676.23 cm^{-1} and 1671.56 cm^{-1} representing the carbonyl group stretching of the amide group. The FTIR spectrum of the lidocaine base exhibited dual sharp bands at the range 1473.46 - 1538.27 cm^{-1} may be due to C-N stretching, where the also have one higher energy group was refer to the bond with greater inductive effect O-C-N (Figure 5).

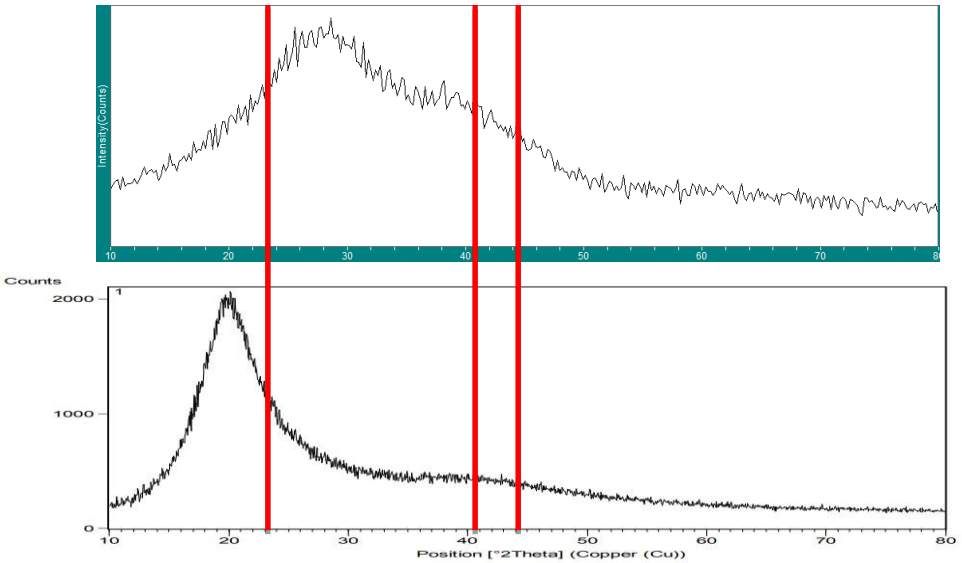

Figure.4. The X-ray diffraction for conventional lidocaine and $SNL_{Lidocaine}$

The red edor indicated the lidocaine peaks of groups structural Nano lipid lidocaine (2T 23.129, 40.938, 44.432, and 73.958)

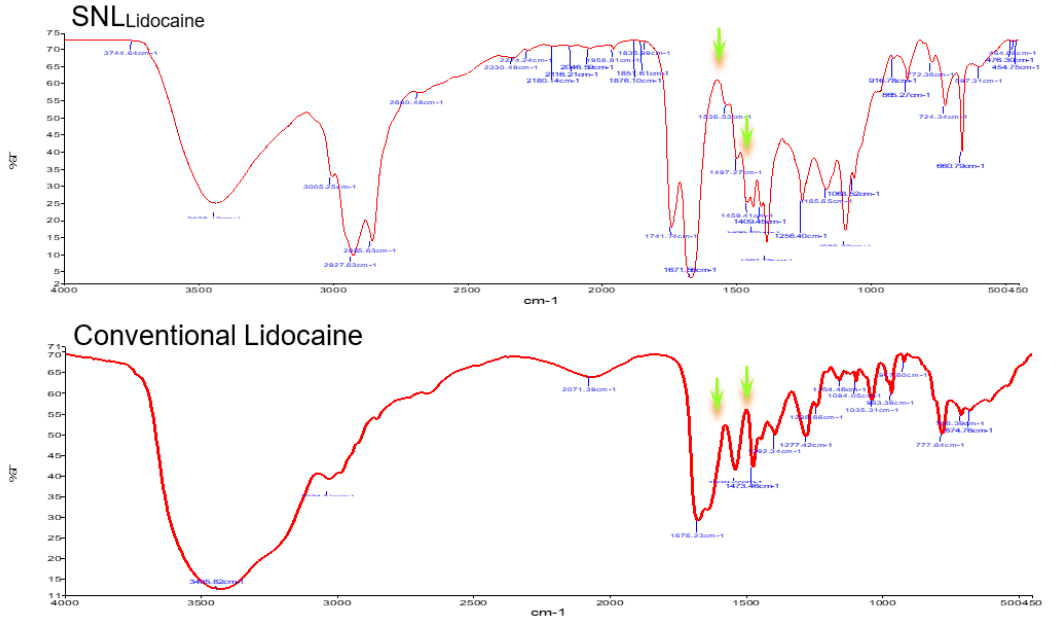

Figure 5. The spectra of FTIR for conventional lidocaine and $SNL_{Lidocaine}$

Zeta potential

The particle size, TSM-SEM micrograph, as well as zeta potential of the optimized new formulation are shown in the figure 6. The uniform distribution of NLC particles was clearly illustrated by SEM depiction. Zeta potential more negative in SNL loaded lidocaine than –58.4 mV as compared with conventional lidocaine 4.5 mV were generally considered to signify satisfactory reciprocal repulsion to promise the stability of a dispersion of Nanoparticles.

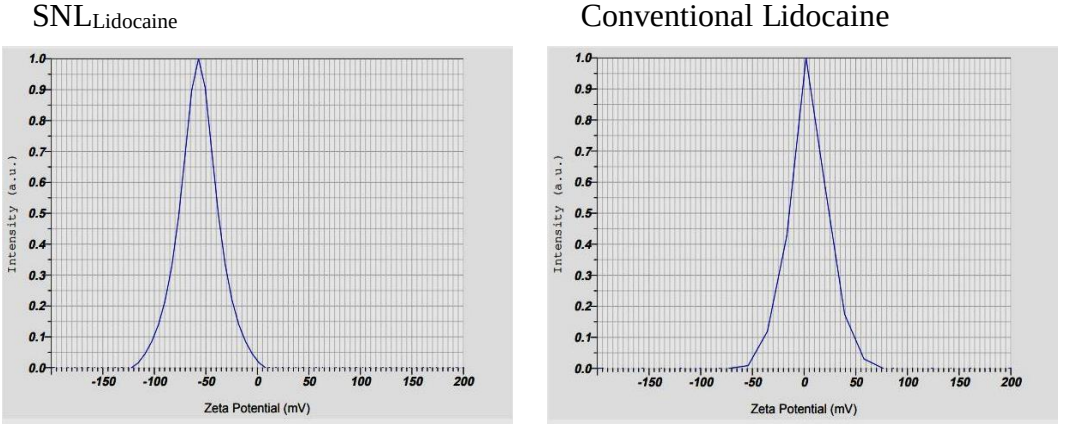

Figure 6. The Zeta potential for conventional lidocaine and $SNL_{Lidocaine}$

Discussion

Standardization

Factually, local anesthetic one of worldwide usage as various kind of pain management and progress as a primer actor of surgical theater, for instance the lidocaine on amide local anesthetic classical like conventional local anesthetic eventually dramatic feasible context turn off the voltage- gated sodium channels via the Na^+ channel which been formed of one alpha subunit and one or two beta subunits, which may be found in three distinct states: resting, open, and inactivated. The alpha subunit of the Na^+ channel is composed of one alpha subunit and one or two beta subunits. Local anesthetic attaches to sodium channels after crossing the plasma membrane and in doing so they bind to an internal part of the alpha subunit, preventing it from activating and causing depolarization of the plasma membrane. As a result, the impulse is not transmitted via the neurons, and the sensation of nociceptive pain is not experienced. That attributed to serpent in consequences promote loss of sensation and absence of response to pain induction trigger of blind needle at brachial plexus as induction of pain directly that provide due to their evidence own chemical structure categorized by lipophilic, Aromatic end and hydrophilic amine end, which appeared the characteristic of lack or poor water solubility and stability of gave sensation of absorption of maintain anesthesia.

Furthermore, the structural evidence of tertiary amine was turn on weak lidocaine bases and skin acidic media have been driven reduced absorption of lidocaine favors the reality of Hinri - Mechalis – maintain equation of ionization derived solubility penetration in skin for this reason the study was built recovery the parameters intensity anesthetic via moderated their solubility and penetrable into the skin via nano-gel maneuver for occupied residence time and increase penetration rate. The approval idea of endosed the Nano for increase the efficiency of lidocaine as a goal of experementable creation of SNL loaded lidocaine and demined their timing of releasing in vehicles gel.

Discussion X-ray diffraction

The result of XRD presumably that lidocaine was homogeneously as well as molecularly regular distributed in the lipid base matrix. The diffraction pattern of SNL was much weaker than that of lidocaine, which designates that lidocaine loaded in SNL was partially recrystallized and reformed less ordered crystals; this type of less-crystalline structures was attributed to a large amount of capacity of loading lidocaine.

Lidocaine base, the sharp peaks due to crystalline form lidocaine, and the absence of any crystalline appearance were presumably proposed there was no evidence on the interaction between the lipid base polymer and the lidocaine in the physical mixture; meanwhile, the lidocaine molecules existed in a dissolved status in the base of lipid and maybe as amorphous form or through molecular dispersion status (Repka *et al.*, 2005).

Discussion Fourier Transform Infrared (FTIR)

One broad peak ranges refer to the equivalent of the two C-N bonds in the lidocaine base. The spectrum of the electrostatic and physical combinations of SNL and lidocaine base was equivalent to the ratio of entrapment, where a broad peak appeared at the range 1538.27 - 1676.23 cm^{-1}lidocaine and 1536.53 - 1671.56 cm^{-1} $SNL_{Lidocaine}$ due to additive of these duel carbonyl groups stretching of the SNL (polymer chain) and the lidocaine. This may be indicated presumably there was not have an interaction between the lidocaine and the SNL when mixed physically.

Whereas Nurkeeva *et al.* (2002) documented polymeric chain complexes of lidocaine with gel carbopol by using FTIR analyses, displayed the lidocaine binding of gel was occurred due to forces of electrostatic cast represented by hydrogen bond as well hydrophobic interface. Furthermore, Jimenez-Kairuz et al. (2002) proposed the interaction between gel and Lidocaine presumably due to salt fraction formation between the carboxyl group of carbopol and the quaternary nitrogen of lidocaine and provoked by loaded SNL. Furthermore, the presence of a weak band for the amino group suggested the formation of Lidocaine carbopol salt. That may be due to the Lidocaine base, which is a weak basic *pK*a 7.9. The decrease in solution pH < 7.9 increases its apparent solubility whereas, Carbopol gel in water has a pH of (2.5-3.0), (Pharmaceutical Excipients, 2006) which were lower than lidocaine *pKa* that govern lidocaine was neutralizes the acidic hydrogel is formed, that referred to an acid-base reaction it as salt-forming (Jimenez-Kairuz *et al.*, 2002; Elkheshen, 2001 and Burgalassi *et al.*, 1996). Recently, Ganesh S. Bommareddy *et al.* (2006) were suggested to be the motive reason for the slower and sustained release of the salts compound which presumably increased efficiency of Lidocaine duration of action and SNL was reduced time of onset of action. The increased salted formation was promotion the gel neutralized with NaOH during preparation.

Discussion Zeta potential

SNL may provide more stable lidocaine as a delivery system in negative values than positively. On the other hand, Zeta potential refers to the composition of SNLs as well as is a functional property of particles environment. The aggregation of SNLs can be created by small size, the large surface area was profiled in the Zeta potential of nanoparticles.

Low Zeta potential was implied lower charged particles that facilitated aggregation of the Nanoparticles due to less electric repulsion. In another word, the Zeta potential was small values the attraction overwhelms than repulsion. The ZP value of >−30 mV is considered optimal value for excellent stabilization of a Nano-dispersion. SNL-loaded lidocaine with high Zeta potential values, less than ~ 20 mV, admitted the system's stability and was reduced prone to aggregated form and increased their particle size. For this reason, the Nano-lipid form was loaded soluble crystalline form of lidocaine and represented decrease the size of features and increase stability in environmental factor of aggregation.

References

A. Shikanov; A.J. Domb; and C.F. Weiniger. (2007). Drug delivery system for prolonged duration local anesthesia. Journal of control Release, 117, 97–103.

B.D. Ulery; L.S. Nair; C.T. Laurencin; J. Polym. (2011). Drug delivery system for prolonged duration local anesthesia, *Journal of Polymer Science*, 49,832–864.

Babaei, S.; Ghanbarzadeh, S.; Adib, Z. M.; Kouhsoltani, M.; Davaran, S. and Hamishehkar, H. (2016). Enhanced skin penetration of lidocaine through encapsulation into nanoethosomes and nanostructured lipid carriers: a comparative study. Die Pharmazie-An International Journal of Pharmaceutical Sciences, 71(5), 247-251.

Bommareddy, G. S.; Paker-Leggs, S.; Saripella, K. K. and Neau, S. H. (2006). Extruded and spheronized beads containing Carbopol® 974P to deliver nonelectrolytes and salts of weakly basic drugs. International journal of pharmaceutics, 321(1-2), 62-71.

Claudia M. Santamaria; Alan Woodruff ; RongYang and Daniel S.Kohane. (2017). Drug delivery systems for prolonged duration local anesthesia. Journal of Materials Today

D. Sivakumaran; D. Maitland; T. Hoare. (2011). Drug delivery system for prolonged duration local anesthesia. Journal of Biomacromolecules 12, 4112–4120.

Del Barrio, M. A.; Hu, J. ; Zhou, P. and Cauchon, N. (2006). Simultaneous determination of formic acid and formaldehyde in pharmaceutical excipients using headspace GC/MS. Journal of pharmaceutical and biomedical analysis, 41(3), 738-743.

Jimenez-Kairuz; A., Allemandi; D. and Manzo, R. H. (2002). Mechanism of lidocaine release from carbomer–lidocaine hydrogels. Journal of pharmaceutical sciences, 91(1), 267-272.

Kumar, R. (2019). Lipid-based nanoparticles for drug-delivery systems. In Nanocarriers for Drug Delivery .Journal of Elsevier, 249-284.

M. Sokolsky-Papkov; Ludmila Golovanevski ;Abraham J. Domb and Carolyn F. Weiniger. (2009). Drug delivery system for prolonged duration local anesthesia. Journal of Pharmaceutical Research, 26, 32–39**.**

Mathur, V.; Satrawala, Y.; and Rajput, M. S. (2014). Physical and chemical penetration enhancers in transdermal drug delivery system. Asian Journal.

Nurkeeva, Z. S. ; Mun, G. A. ; Khutoryanskiy, V. V. ; Bitekenova, A. B. and Dzhusupbekova, A. B. (2002). Polymeric complexes of lidocaine hydrochloride with poly (acrylic acid) and poly (2-hydroxyethyl vinyl ether). Journal of Biomaterials Science, Polymer Edition, 13(7), 759-768.

Oliveira, M. F.; Kycia, S. W.; Gomez, A.; Kosar, A. J.; Bohle, D. S.; Hempelmann, E.; ... and Ferreira, S. T. (2005). Structural and morphological characterization of hemozoin produced by Schistosoma mansoni and Rhodnius prolixus. Journal of Febs letters, 579(27), 6010- 6016.

R.Cohen; HibaKanaan; Gilbert J.Grant ; YechezkelBarenholz. (2012). Drug delivery system for prolonged duration local anesthesia, Journal of Control Release, 160,346–352.

Repka, M. A.; Gutta, K.; Prodduturi, S.; Munjal, M. and Stodghill, S. P. (2005). Characterization of cellulosic hot-melt extruded films containing lidocaine. European Journal of Pharmaceutics and Biopharmaceutics, 59(1), 189-196.

Samimi, S. ; Maghsoudnia, N. ; Eftekhari, R. B., and Dorkoosh, F. (2019). Lipid-based nanoparticles for drug delivery systems. Characterization and biology of nanomaterials for drug delivery. Journal of Science Direct, 47-76.

Soraya Babaie; Saeed Ghanbarzadeh; Soodabeh Davaran ; Maryam Kouhsoltani, and Hamed Hamishehkar . (2015). Nanoethosomes for Dermal Delivery of Lidocaine. Journal of national library of medicine.

Szebeni, J.; Di Iorio, E. E.; Hauser, H.; and Winterhalter, K. H. (1985). Encapsulation of hemoglobin in phospholipid liposomes: characterization and stability. Journal of Biochemistry, 24(12), 2827-2832.

T.R. Hoare; D.S. Kohane; Polymer.Beloqui A; Solinis MA; Rodriguez-Gascon A ; Almeida AJ and Preat V. (2008). Nanostructured lipid carriers: Promising drug delivery systems for future clinics. Journal of Nanomedicine; 12(1):143-161.

T.Wang; JiajiangLin; ZuliangChen; Mallavarapu Megharaj and RavendraNaidu. (2014). Green synthesized iron nanoparticles by green tea and eucalyptus leaves extracts used for removal of nitrate in aqueous solution. Journal of Cleaner Production, Volume 83, Pages 413-419.

Vilches, A. P.; Jimenez-Kairuz, A.; Alovero, F.; Olivera, M. E.; Allemandi, D. A. and Manzo, R. H. (2002). Release kinetics and up-take studies of model fluoroquinolones from carbomer hydrogels. International journal of pharmaceutics, 246(1-2), 17-24.

Widana, I.K., Sumetri, N.W., Sutapa, I.K., Suryasa, W. (2021). Anthropometric measures for better cardiovascular and musculoskeletal health. *Computer Applications in Engineering Education*, *29*(3), 550–561. https://doi.org/10.1002/cae.22202

Wannaphatchaiyong, S.; Heng, P. W. S.; Suksaeree, J.; Boonme, P.; and Pichayakorn, W. (2019). Lidocaine loaded gelatin/gelatinized tapioca starch films for buccal delivery and the irritancy evaluation using chick chorioallantoic membrane. Saudi Pharmaceutical Journal, 27(8), 1085-1095.

X.Jia; GaiaColombo; RobertPadera; RobertLanger and. (2004). Drug delivery system for prolonged duration local anesthesia. Journal of Biomaterials, 25, 4797–4804.

Xia, J.; Lyons, R.J.; Lin, M.Y.; Khalifa, Y.M. and LaRock, C.N., (2020). Combination of lidocaine gel and povidone–iodine to decrease acquired infections in procedures performed using topical anesthesia.Journal of Cataract and Refractive Surgery, 46(7), pp.1047–1050.

Yaping Wang; Xihui Wang; Xiangyu Wang; Yilei Song; Xiaodan Wang and Jifu Hao. (2019). Design and Development of Lidocaine Microemulsions for Transdermal Delivery. Journal of Springer.

Yokoyama, T.; Fukui, T.; and Masuda, H. (2007). Chapter 1: Basic Properties and Measuring Methods of Nanoparticles. Journal of Nanoparticle Technology Handbook (edited by: Hosokawa, M.; Nogi, K.; Naito, M.; Yokoyama, T.).

Zheng Pang; Renee Raudonis; Bernard R. Glick; Tong-Jun Lin and Zhenyu Cheng. (2019). Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies, Journal of Biotechnology Advances, 37,177-192.