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Formulation and Evaluation of Lercanidipine HCL Loaded Nanomicelles

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Abstract

Among the strong calcium channel blockers, lercanidipine hydrochloride (LER) has been shown to be useful in reducing blood pressure by acting on L-type calcium channels. Nevertheless, the main drawback of lercanidipine is its low solubility and a 10% oral bioavailability because of the significant first pass metabolism. The aim of this study is to formulate nanomicelles by using the thin film hydration process utilizing Soluplus® in conjugation with other surfactants/polymers at different ratios in order to enhance the solubility and dissolution rate as a method to increase bioavailability of virtually insoluble LER. Six formulations were prepared and analyzed for their micelles size, polydispersity index (PDI), encapsulation efficiency (EE%), and in-vitro release. The optimum formula was determined to be the one prepared using Soluplus®, poloxamer188 and tween80 (50 mg). Micelle size was found to be (62.24 ± 6.63) nm, with PDI (0.233 ± 0.05) and EE (88.8 ± 1.3%). An in-vitro release study was conducted, and the results showed that the chosen formula (Solu/P188/Tween80 (7/2/5) released the entire dose of drug in 75 minutes with 94% release, compared to only 53% for pure drug. These findings indicate the strong potential of employing LER HCl micelles in dosage form formulation.
Keyword: Lercanidipine HCl, Encapsulation Efficiency (EE%), Nanomicelles, Soluplus®, Thin-film hydration.

Introduction

A scientific framework known as the biopharmaceutical classification system (BCS) is used to categorize medicinal substances according to their water solubility and permeability. It considers the two main variables that control the rate and degree of oral drug absorption: intestinal permeability, and solubility. When a pharmacological substance's absorption is greater than 90% and its maximal strength dissolves in 250 mL or less of an aqueous medium with a pH range of 1.0 – 7.5, it is classified as highly soluble and highly permeable; if not, it is classified as poorly soluble [1-3]. The improvement of solubility has been the subject of in-depth research over the past few decades, and a variety of strategies have been devised to address this problem with varying degrees of success. These methods can generally be divided into three categories: chemical modification, physical alteration, or miscellaneous modification [4,5].Micelles are amphiphilic colloidal structures with a particle width ranging from 5 to 100 nm. By solubilizing pharmaceuticals in their inner core, micellar structures have become viable carriers for poorly soluble medications; micelles are molecules with two distinct water-affinity regions [6-8]. However, their formation and stability can be influenced by several experimental challenges. There are specific concentrations and temperatures at which the amphiphilic molecules that form micelles associate. The critical micelle concentration is the concentration at which aggregation begins and the micelles are formed, the number of monomer molecules forming a micelle is known as the aggregation number of the micelle [9,10]. Controlling the size and polydispersity of micelles is crucial for their performance. Factors like surfactant concentration, temperature, and ionic strength can influence these parameters, making it difficult to achieve desired properties. The aggregation of the amphiphilic molecules leading to the formation of micelles occurs due to the removal of the hydrophobic fragments of the micelles from the aqueous environment and the formation of hydrogen bonds in water which leads to a decrease in free energy of the system. Nanomicelles have been used successfully to improve the solubility of poorly soluble drugs, increasing stability, reproducibility, and sterilization [11]. Nanomicelles are used with the main purpose is to solubilize hydrophobic compound [12] due to having lipophilic portion of monomer. Inner core of monomer prevent the compound from degradation [12]. Outer core of nanomicelles is hydrophilic that modulate the pharmacokinetic properties of drug compound due to increasing solubility [13]. Lercanidipine

hydrochloride belongs to the dihydropyridine class of calcium channel blockers. Its chemical formula is 2-[(3,3-diphenylpropyl) methylamine]. 1, 4 – dihydro -2,6 -dimethyl – 4 - (3-nitrophenyl)-1,1-dimethylethylmethyl Hydrochloride of pyridine carboxylic ester -3,5"Figure. 1". Because of LER's specificity and selectivity for smooth vascular cells, it is utilized to treat hypertension [14,15]. Lercanidipine HCl is classified as a BCS class II medication, and its limited solubility may restrict its bioavailability, thereby affecting its overall efficacy, which presents a significant challenge. Additionally, LER has been reported to undergo extensive first pass metabolism further reducing its bioavailability [16,17].It has been reported that approximately 50% of the oral dose undergoes first pass metabolism [18] . An attempt to alter LER solubility was through solid dispersion. PEG 6000 was successfully utilized to create a solid dispersion of LER HCl by the solvent evaporation technique. The absence of clear chemical interactions is revealed by FTIR analysis. DSC and X-ray diffraction spectroscopy have demonstrated that the medication in solid dispersions is present within the PEG 6000 matrix in an amorphous condition. The solubility and in-vitro drug release of the solid dispersions were improved. The enthalpy of drug melting in the solid dispersion was found to be lower than that of the pure drug, indicating that the molecule was amorphous in the solid dispersion [19]. Nonionic surfactants and cosurfactants were used with medium and short-chain glycerides in the formulation of Self-micro Emulsifying Drug Delivery Systems (SMEDDSs). There was no sign of precipitation and the self-micro emulsifying drug delivery systems (SMEDDS) were fully soluble. The findings contributed to the conclusion that LER HCl could not remain dissolved without the presence of a cosurfactant [20].

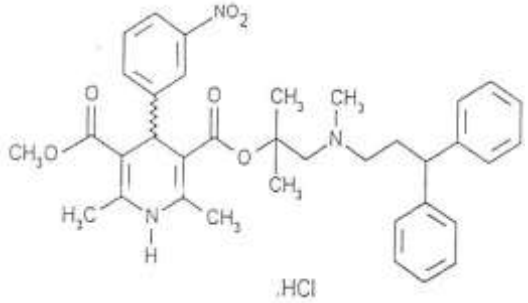

Figure 1. Chemical structure of lercanidipine HCl [16].

Another attempt at altering LER solubility was through its formulation as polymeric nanomicelles using Soluplus®, poloxamer 188, tween 80 and combinations thereof [21]. Soluplus® is an innovative pharmaceutical excipient characterized as a hydrophilic polymer that effectively solubilizes poorly water-soluble drugs and enhances the stability of nanomicelles. Its amphipathic structure comprises polyvinyl caprolactam and polyvinyl acetate, which contribute to the hydrophobic component, alongside polyethylene glycol (PEG), which serves as the hydrophilic component. This unique composition makes Soluplus a widely utilized amphiphilic copolymer in nanomicelle formulations, as it not only stabilizes the hydrophobic core but also significantly improves solubility and bioavailability [22] . Tween 80 is a non-ionic surfactant commonly used in nanomicelles to enhance the stability and delivery of various drugs. It acts as a surface coating on the micelles, improving their transport across biological barriers like the blood-brain barrier. Additionally, Tween 80 can help solubilize hydrophobic drugs, increasing their bioavailability and therapeutic efficacy [23] .TPGS, a synthetic derivative of alpha-tocopherol, is increasingly recognized for its potential in drug delivery systems. The fat-soluble alpha-tocopherol segment of the molecule contrasts with the water-soluble PEG component. This nonionic surfactant exhibits both biocompatibility and biodegradability. It is produced via an esterification reaction involving vitamin E and PEG. Its amphiphilic nature renders it effective as an emulsifier, solubilizer, and stabilizer in nanomedicine applications [24].

This study aimed to prepare lercanidipine hydrochloride loaded nanomicelles using Soluplus®, TPGS, poloxamer and combination thereof.

Materials and Methods

Materials

Lercandipine hydrochloride (LER HCl), Soluplus®, poloxamer 188, d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) were purchased from Hangzhou, Hyperchem (China). Tween 80 from Indiamart (India), ethanol from Alphachemica (India).

Methods

Preparation of nano-micelles loaded with lercanidipine HCl. Thin-film hydration method was used to prepare lercanidipine HCl nano-micelles. All components (LER HCl and the carrier polymers) were dissolved in 20 milliliters of ethanol in a round flask (100 ml). A thin layer then developed when the solvent was evaporated in a rotary evaporator for 30 minutes at 150 rpm and 50 °C under 7.4 Kpa of vacuum pressure. The film was then hydrated with 10 mL of deionized water, and the micelles solution was magnetically agitated for two hours at 500 rpm [25,26]. Full description of all formulation prepared in this study is presented in "Table 1". For some formulations and as needed, the formula was lyophilized to obtain a dry powder for subsequent analysis using Alpha 1-2 LDplus - Laboratory freeze-dryer (Christ/Sigma, Germany). A 2% w/v mannitol solution was utilized as a cryoprotectant.

To generate the dry powder for evaluation, 2 ml of the optimal formulation was prepared and subjected to freeze-drying [27]. A round-bottom flask containing the selected formulation was frozen in liquid nitrogen at -60°C for 30 minutes. The vacuum port of the apparatus was then connected to the frozen flask, and the lyophilizer was operated at -60°C and 0.021 mbar until the dry powder was obtained. The sublimation of water from the frozen samples typically required about 10 hours.

Table 1. Nanomicelles formulations prepared in this study

Formula code	Formula	LER(mg)	SOLU(mg)	P188(mg)	Tween80 (mg)	TPGS (mg)	Polymers Ratio
F1	Solu/Tween80(5/5)	10	50		50		1:5:5
F2	Solu/P188(3/2)	10	30	20			1:3:2
F3	Solu/P188(5/2)	10	50	20			1:5:2
F4	TPGS/Tween80(3/3)	10			30	30	1:3:3
F5	Solu/P188/Tween80(7/2/5)	10	70	20	50		1:7:2:5
F6	Solu/P188/Tween80(7/2/2)	10	70	20	20		1:7:2:2

Characterization of LER nano-micelles

Determining the micelles size distribution and zetapotential

Using a Zetasizer (Malvern Instruments Ltd, United Kingdom), the micelles size, polydispersity index (PDI), and zeta potential of the diluted formulation were measured. Nanomicelles suspension was appropriately diluted prior measurement. All measurements were done in triplicate. The chosen formula underwent lyophilization for subsequent analysis using FTIR and FESEM techniques.

Encapsulation Efficiency (EE%)

The concentration of free LER in nano-micelles suspension was used to indirectly calculate the encapsulation effectiveness (EE%) and the percentage of LER encapsulated. The lercanidipine hydrochloride solubility in water (37 °C ± 1 °C) is **(**0.015 ± 0.0023 mg/ml) [28] .To find out how much free drug was not caught, an ultrafiltration method was employed. Briefly, an Amicon® Ultra Centrifugal tube with a molecular cut off size (MWCO) of 10 KDa was filled with 1 ml of LER nano-micelles solution, various speeds and durations were tested using Amicon®.The optimal outcome was achieved with centrifugation for 30 minutes at 5,000 rpm. This specific condition yielded the best results [29]. A spectrophotometer set at 235 nm was used to determine the concentration of unentrapped LER in the ultrafiltration containing the free LER after sufficient dilution [30].

The (EE%) was then computed as follows:

%EE = weight of LER in nanomicelles/weight of LER used [29].

Field Emission Scanning Electron Microscope (FESEM)

Lercandipine nanomicelles were also analyzed by field emission scanning electron microscope (FESEM). It is apparatus that used for an image surface roughness analysis, used to explain the shape, size droplets within formulated nanomicelles of lercandipine [31].

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR -7600 spectrophotometer from Australia was used to record the FTIR spectra of both bulk LER and lyophilized LER nanomicelle. Potassium bromide was added to the powders, and they were then crushed into disks using a hydraulic press and scanned from 4000 to 400 cm^{-1} [19,32].

In vitro release study

LER nanomicelles equivalent to 10 mg LER were directly added into the release medium and the use of syringe filters with smaller pore size (0.1 μm) has been used as a simple yet efficient way for sample separation, to separate the dispersed nanomicelles from the continuous phase at different time intervals [33]. The release media for the chosen formula was phosphate buffer (pH 6.8) with 0.5% sodium lauryl sulfate added as a surfactant to maintain sink condition (200 ml). A USP dissolution type II test apparatus (Lab India DS-apparatus) was employed to agitate the systems at a speed of 100 rpm, maintaining a temperature of 37°C. Regularly, five milliliters of the external medium were withdrawn and substituted with fresh dissolving medium [34]. The concentration of the dissolved LER was determined using a Shimadzu UVmini-1240 spectrophotometer at a wavelength of 235 nm[35]. Pure LER samples were treated similarly in parallel. Collected samples were analyzed spectrophotometrically to measure LER concentration. Pure LER HCl was analyzed in parallel. LER release was calculated as percent

cumulative release compared to original amount of drug. Samples were analyzed in triplicate.

Statistical analysis

Samples were analyzed by one-way analysis of variance (ANOVA) followed by Tukey post-hoc test. Differences were considered significant at $p< 0.05$. Statistical analysis was conducted using GraphPad Prim V8.

Results and Discussion

Micelles size and poly-dispersibility index (PDI)

Micelles size and PDI was found to be polymer type dependent such that in the chosen formula Solu/P188/Tween80(7/2/5) Soluplus® generally resulted in smaller micelles compared to TPGS, "Figure. 2". Soluplus®, a novel pharmaceutical excipient, is a hydrophilic polymer that can solubilize drugs that are poorly soluble in water and stabilize nanomicelles more effectively because of its amphipathic nature. It is composed of polyethylene glycol (PEG), which represents the hydrophilic moiety, and polyvinyl caprolactam and polyvinyl acetate, which represent the hydrophobic moiety. Because of its capacity to stabilize the hydrophobic core of the nanomicelle and enhance its solubility and bioavailability, Soluplus® is a frequently utilized amphiphilic copolymer in the formulation of nanomicelles [36].Numerous parameters, such as the type of solvent employed, the preparation technique, and the copolymer concentration, affect the size of nanomicelles. In this study, reduction in the particle size of nanomicelles was observed when the quantity of Soluplus® was increased "Figure. 3". The enhanced stability of the hydrophobic core of the nanomicelle is assumed to be the mechanism underlying the decrease in particle size with increasing Soluplus® concentration, resulting in a more compact structure and lower particle size [37,38]. Additionally, it is apparent that tween80 has more stabilizing effect of the nanomicelles compared to poloxamer188 as evident by the smaller particle size and smaller PDI "Figure. 3" because of tween 80 is a non-ionic surfactant with a hydrophilic head and a hydrophobic tail and when combined with Soluplus® they can form mixed micelles with improved solubilization capacity for poorly soluble drugs [17].The study published in the research journal of pharmaceutical science investigated the effect of tween 80 on the stability and drug release profile of nanomicelles. The authors found that tween 80 could improve the stability of the nanomicelles. The statistical characteristics of nanomicelles seen in the "Table 2". Overall, these studies suggest that the use of tween 80 has a positive effect on the properties of nanomicelles, making them more effective for drug delivery and other applications [39,40] . Size report of the selected formula shown in the "Figure. 2"

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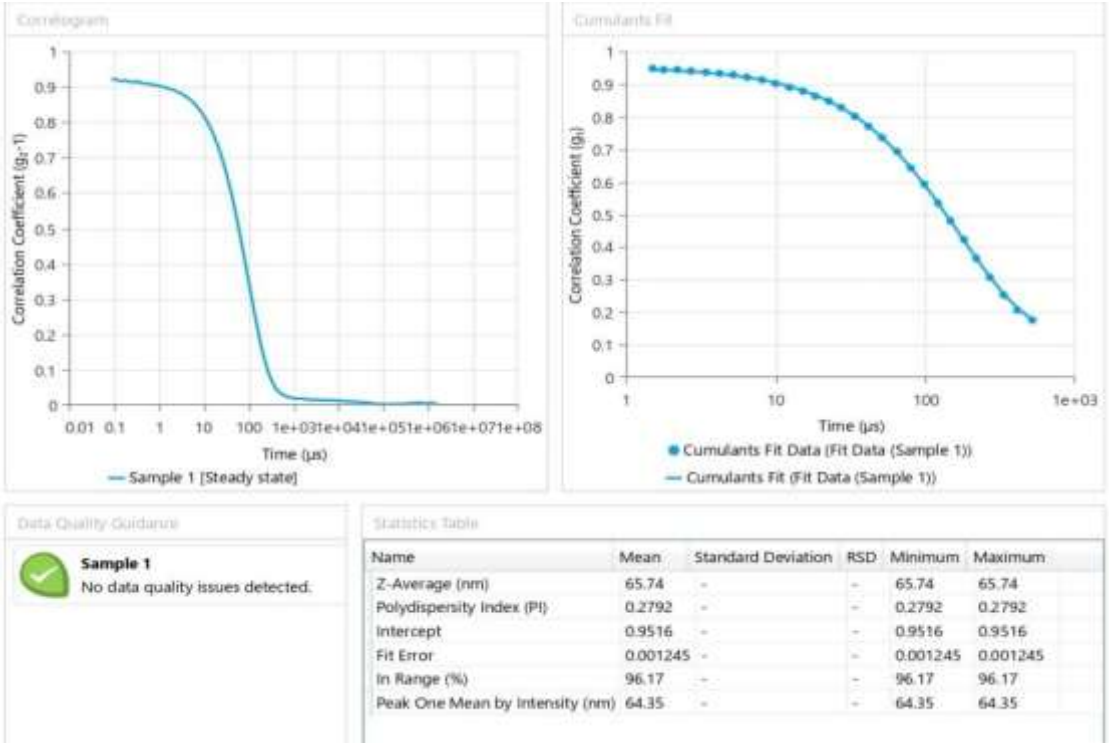

Name	Mean	Standard Deviation	RSD	Minimum	Maximum
Z-Average (nm)	65.74	-	-	65.74	65.74
Polydispersity Index (PI)	0.2792	-	-	0.2792	0.2792
Intercept	0.9516	-	-	0.9516	0.9516
Fit Error	0.001245	-	-	0.001245	0.001245
In Range (%)	96.17	-	-	96.17	96.17
Peak One Mean by Intensity (nm)	64.35	-	-	64.35	64.35

Figure 2. Size report of selected formula Solu/P188/Tween80(7/2/5) nanomicelle.

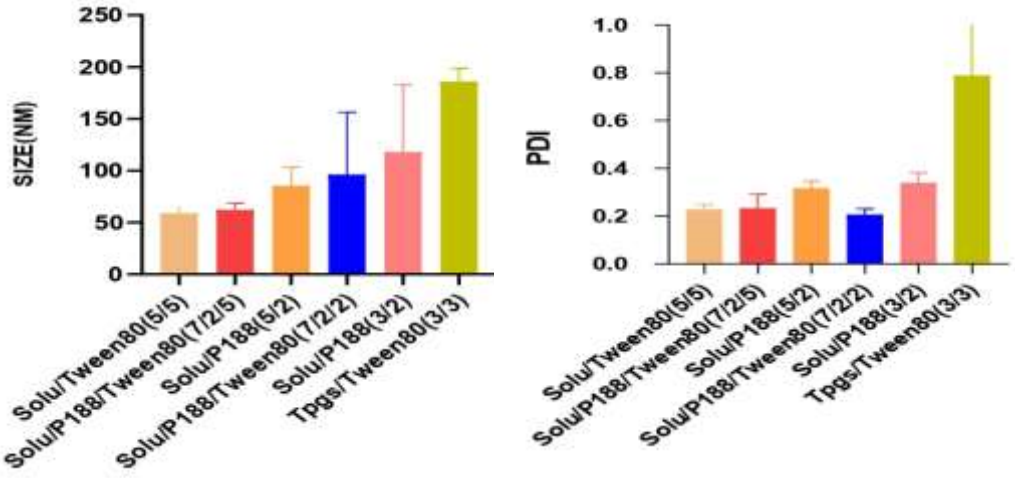

Figure 3. Effect of polymer type and ratio on (A) nanomicelles size and (B) size distribution, PDI. Data are presented as mean ± standard deviation, n=3.

Encapsulation Efficiency

The findings demonstrate that all nanomicells formulations had loading efficiency ranging from (71-88.8 %).However, nanomicelles prepared using Soluplus®, poloxamer188 and tween80(50mg) {Solu/P188/Tween80(7/2/5)} showed the highest encapsulation efficiency of 88.8 %, "Figure. 4". An increase in Soluplus® concentration was accompanied by an increase in entrapment efficiency in the presence of tween. This effect is caused by an increase in Soluplus® concentration, which raises the number of nanomicelles and, consequently, the number of drug molecules that are trapped in the hydrophobic core of the nanomicelles which finally lead to increasing the solubility of LER with increasing Soluplus® concentration [38].

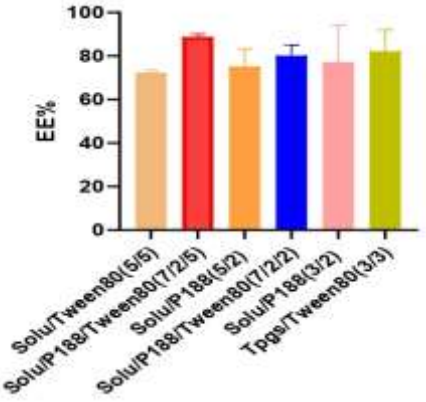

Figure 4. Encapsulation efficiency (EE%) of LER HCl nanomicelles. Data are presented as mean ± standard deviation, n=3.

Table 2.The statistical characteristics of nanomicelles, which included the Particle Size, PDI, and EE%.

Formula code	Particle Size ± SD	PDI ± SD	EE%± SD
F1	59 ± 6.81	0.22 ± 0.02	72.3 ± 1.15
F2	80.8 ± 7.4	0.316 ± 0.03	77.1 ± 16.8
F3	85.5 ± 17.7	0.338 ± 0.04	75.1 ± 8.09
F4	186 ± 12.7	0.565 ± 0.233	82.16 ±9.82
F5	62.2 ± 6.6	0.226 ± 0.05	88.8 ± 1.31
F6	62 ± 9.8	0.203 ± 0.02	80.23 ± 4.89

Field Emission Scanning Electron Microscopy (FESEM)

To ascertain proper formation of micelles, visual characterization of micelles morphology was conducted. FESEM imaging of the Solu/P188/Tween80(7/2/5) nano-micelles' confirmed properly formed spherical micelles. The micelles did not show evidences of aggregation and had particle size agreeing with the Zetasizer measurement results, "Figure. 5". These outcomes further support successful preparation of LER nanomicelles.

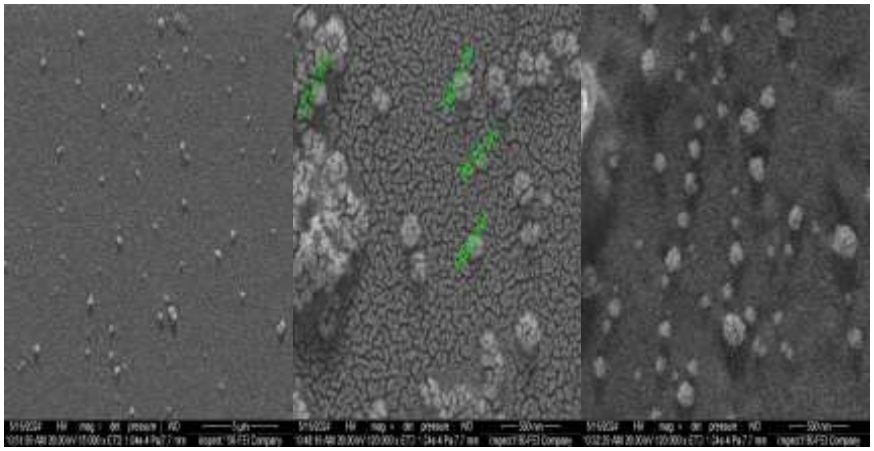

Figure 5. FESEM imaging of Solu/P188/Tween80(7/2/5) micelles at different magnification.

FTIR spectrum

FTIR analysis was conducted to investigate the possible drug carrier interaction. The spectrum of pure lercanidipine HCl presented characteristic peaks at 3182 cm-1 (NH stretching vibration), 3000-2900 cm-1 (alkyl and phenyl stretching), 2500 cm-1 N+ -H stretching, 1671 cm-1 c=o stretching, 1524 cm-1; 1348cm-1 (asymmetric and symmetric stretching of NO2 group), 1402 cm-1; 1348 cm-1 (bending of germinal methyl groups); 800 cm-1-500 cm-1 (out of place bending of 5 and 3 adjacent hydrogens on aromatic rings) "Figure. 6". These peaks were preserved in the LER nano-micelles Solu/P188/Tween80(7/2/5). FTIR, indicating drug compatibility with polymers. This states that the drug was in its stable state throughout the formulation process and that there was no noteworthy chemical interaction between the excipients and the drug [33,21].

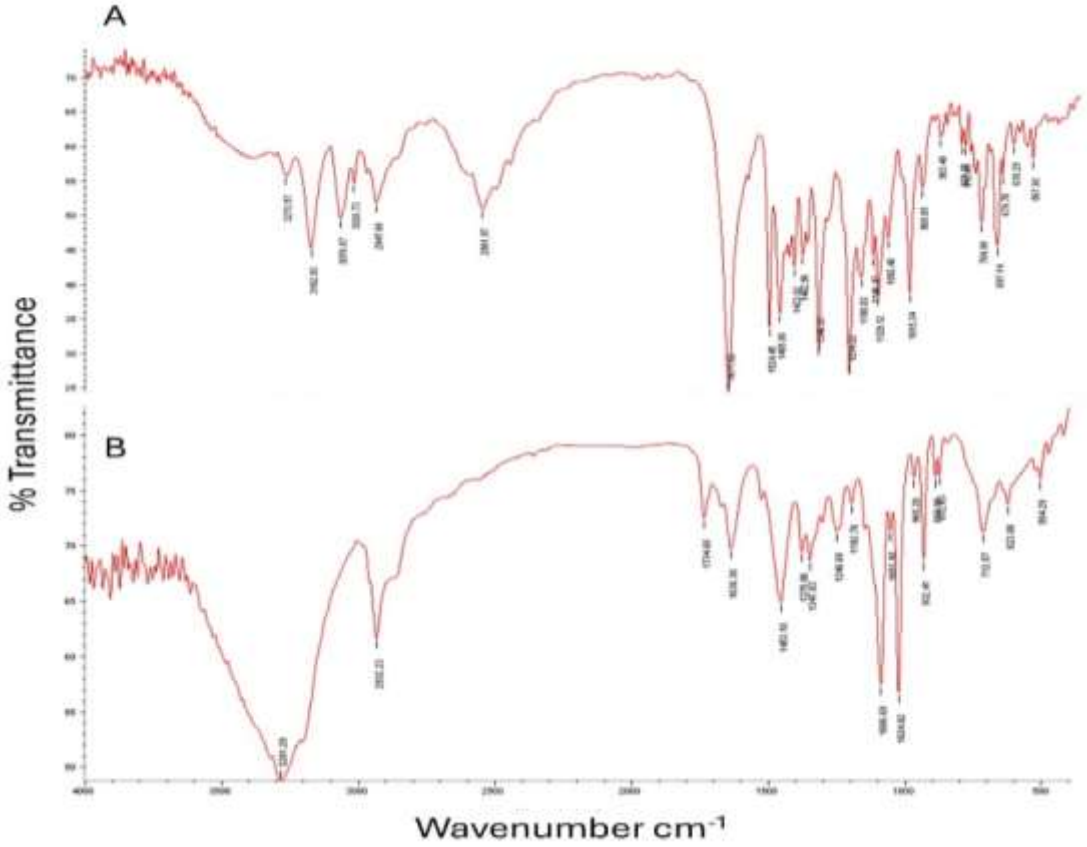

Figure 6. FTIR spectrum of (A) LER HCI and (B) LER HCl micelles.

In vitro release study

Based on the above results, solu/p188/tween80(7/2/5) and solu/p188(5/2) were further evaluated for the in vitro release of LER HCl. Solu/P188/Tween80(7/2/5) released 94% of its LER after 75 minutes, whereas the pure medication only released 53% after the same period, "Figure. 7" .Soluplus-poloxamer mixed micelles have been reported as a successful approach for solubility improvement [41]. Soluplus, being an amphiphilic polymer, has been shown to solubilize low solubility drugs through micellar effect [42, 43]. This is evident in the improved LER dissolution in both micellar formulations compared to pure LER. The presence of tween can explain the higher release obtained for the Solu/P188/Tween80(7/2/5) micelles compared to tween-free micelles. Additionally, smaller micelles might have a higher diffusion coefficient, which would enable a quicker rate of drug release. Drug release may be impacted by certain interactions between the surfactant molecules and the drug component. Tween 80's increased hydrophobicity may improve its interactions with hydrophobic medications, resulting in a faster release [44].

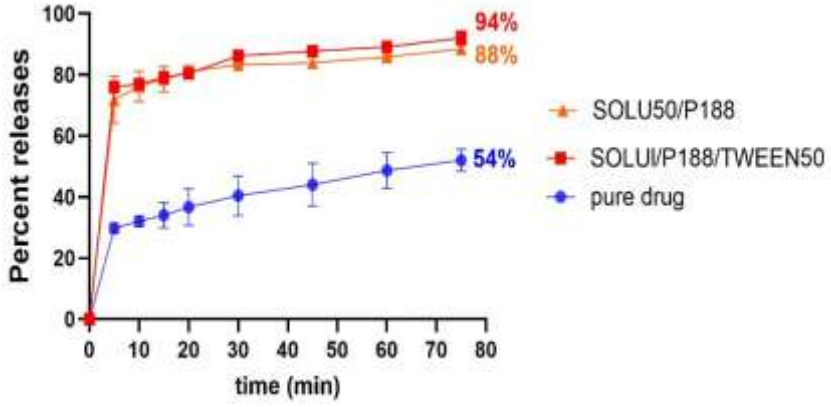

Figure 7. In vitro release of Solu /P188 / Tween 80 (7/2/5), Solu/P188(5/2) and pure LER HCl in phosphate buffer pH 6.8. Data are presented as mean ± standard deviation, n=3.

These findings further assert successful LER HCl nanomicelle formulation with excellent loading, and superior dissolution profile compared to naked LER. These improved dissolution LER nanomicelles enables LER delivery within a sublingual dosage. Such approach allows the bypass of the first pass effect which is a main contributor to reduced LER bioavailability.

Conclusion

Based on the results demonstrated in this study, it could be concluded that LER HCl was successfully loaded into nanomicelles. When compared to pure LER HCL, the Solu/P188/Tween80(7/2/5) had excellent release profile. Particle form was virtually spherical and there was no particle aggregation and of high (EE%). The formulated nanomicelles would serve as a potential component for a drug delivery system of LER HCL that can contribute to improved drug bioavailability.

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Conflicts of Interest

Authors declare no conflict of interest.

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Ethics Statements

In vitro study, no ethical statements are required.

Author Contribution

Study design and conceptualization: HM Fatih and KK Ahmed, Experimental procedure: HM Fatih , data analysis: HM Fatih and KK Ahmed, writing and reviewing the manuscript: HM Fatih and KK Ahmed.

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تحضير وتقييم المذيلات النانويه المحملة بالدواء الليركاندبين هايدروكلورايد

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الخلاصة

من بين حاصرات قنوات الكالسيوم القوية، تبين أن ليركانيديبين هيدروكلوريد (LER) مفيد في خفض ضغط الدم من خلال العمل على قنوات الكالسيوم من النوع L .ومع ذلك، فإن العيب الرئيسي لليركانيديبين هو ذوبانه المنخفض وتوافره البيلوجي عن طريق الفم بنسبة ١٠٪ بسبب استقلابه الاول.الهدف من هذه الدراسة هو تكوين جزيئات نانويه باستخدام عملية ترطيب الأغشية الرقيقة باستخدام ®Soluplus بالاقتران مع المواد الخافضة للتوتر السطحي/البوليمرات الأخرى بنسب مختلفة من أجل تعزيز معدل الذوبان والذوبان كوسيلة لزيادة التوافر الحيوي ل LER الغير القابلة للذوبان تقريبًا. تم إعداد ستة تركيبات وتحليلها من حيث حجم المذيلات، ومؤشر التشتت المتعدد (PDI)، وكفاءة التحميل (EE%)، والإطلاق في المختبر. تم تحديد الصيغة المثلى لتكون الصيغة المختارة هي تلك المحضرة باستخدام ®Soluplus و poloxamer188 و tween80(50mg). اظهرت الصيغة المختارة حجما مقبولا حيث كان حجم المذيلة (62.24 ± 6.63) نانومتر، مع PDI (0.233 ± 0.05) و EE (88.8 ± 1.3%) ٪ .تم إجراء دراسة التحرر في المختبر، وأظهرت النتائج أن الصيغة المختارة (Solu/P188/Tween80(7/2/5 تطلق الجرعة الكاملة من الدواء خلال ٧٥ دقيقة بنسبة تحرر ٩٤٪، مقارنة بـ ٥٣٪ فقط للدواء النقي. وتشير هذه النتائج إلى الإمكانات القوية لاستخدام مذيلات LER HCl في صياغة أشكال الجرعات

الكلمات المفتاحية: هايدروكلورايد الليركانديبين ، كفاءة التحميل ، المذيلات النانويه, ، سولوبلوس ، ترطيب الاغشية الرقيقه