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Research Article

Formulation and *In Vitro* Evaluation of Niosomal Gel for The Topical Administration of Losartan Potassium

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Abstract

This study aims to develop and test a topical drug delivery system for antihypertensive activity using Losartan potassium-loaded niosomes. The niosomes were created using the traditional ether injection approach, with four formulations made using cholesterol as the lipid and varying quantities of surfactants such as span 80 and span 60. The different formulations underwent testing for FTIR, particle size, zeta potential, drug content, entrapment efficiency, and *in vitro* release. FTIR analysis revealed that the medication was incompatible with excipients. The study concludes by highlighting current obstacles and future possibilities for the development of niosomes as effective vehicles. Overall, this analysis provides insight into the potential of niosomes in medication delivery and encourages further research in this field.

Keywords: Losartan potassium, Antihypertensive, Niosomes, Tween 80 and Span 20

INTRODUCTION

The force that blood is exerting against the inner walls of major blood vessels and arteries is known as blood pressure. When blood pressure surpasses the accepted range or becomes excessively high, it is recognized as hypertension. Hypertension risk factors fall into two categories: adaptable and non-adaptable. Adaptable risk factors encompass elements that can be modified through changes in dietary habits and life style such as consuming too much salt, eating a diet heavy in trans and saturated fats, and not getting enough fruits and vegetables, lack of physical activity, tobacco and alcohol use, and obesity. Non-adaptable risk factors include unalterable conditions like a family history of hypertension, age over 65, and co-existing illnesses like diabetes and kidney disease.

Losartan potassium is an angiotensin receptor blocker (ARB), belonging to a class of drugs that includes Olmesartan, valsartan, and telmisartan. It operates by blocking angiotensin II's effects, leading to blood vessel dilation and blood pressure reduction. This dual action helps manage hypertension and protect kidneys from diabetes-related damage. Losartan potassium has an oral systemic bioavailability of approximately 20-25%, and our choice of administration route aims to enhance its bioavailability by applying it topically.

Niosomes, also known as Microscopic lamellar structures known as non-ionic surfactant vesicles are created by mixing non-ionic surfactants belonging to the alkyl or di alkyl polyglycerol ether class with cholesterol, which are then hydrated in aqueous conditions. A unique vesicular drug delivery method called a noisome allows us to maintain a steady plasma drug concentration over an extended length of time. Niosomes are an alternative to liposomes for regulated drug administration to address the issues with sterilization, mass manufacturing, and stability. Surfactants are essential in the creation of such mixtures. Numerous non-ionic surfactants, including ester-linked surfactants, glucosyldialkyl ethers, polyglycerol alkyl ethers, and crown ethers, polyoxyethylene alkyl ether, Brij, and a variety of spans, have been utilized to create vesicles. For the creation of physically stable niosomes, most formulations typically contain a 1:1 molar ratio of cholesterol to surfactant. Niosomes may be made using several techniques, including reverse-phase evaporation, ether injection, and thin-film hydration approaches. [1, 2]

MATERIALS AND METHODS

Losartan Potassium obtained as gift sample from Suraksha pharmaceuticals, Hydereabad. Span 60, Span 80, Cholesterol, Diethyl ether, Methanol, Potassium dihydrogen Phosphate, Sodium hydroxide, Carbopol 934, Triethanolamine and Methyl paraben obtained from S.D Fine-Chem Ltd., Mumbai.

Spectroscopic Studies

Determination of λ_{max}

A suitable volume of pH 7.4 phosphate buffer saline was used to dissolve an accurately weighed quantity of Losartan potassium niosomes to produce the standard stock solution. Diluted solutions were prepared and scanned between 200 and 400 nm using distilled water as a reference. The drug's maximum absorption wavelength was identified.

Preparation of standard solutions and calibration curve of losartan potassium

2, 4, 6, 8, 10, 12, 14, 16 µg/ml solutions prepared by pH 7.4 phosphate buffer saline and the absorbance was measured at 213 nm using UV spectrophotometer against respective parent solvent as blank.

Optimization of process and formulation variables

Selection of method of preparation

Literature review witnessed the methods of preparation of niosomes like sonication, micro fluidization, reverse phase evaporation, thin-film hydration method and ether injection method. Among this thin film hydration method, ether injection method was selected because these methods showed maximum entrapment efficiency.

Selection of surfactant

Literature survey revealed the use of Span-20; Span-40; Span-60; Span-80; Tween-80 as a surfactant. The surfactant chosen for niosome preparation was Span 80. Selection of surfactant was done on the basis of HLB values. As the lipophilicity of the surfactant increased (HLB value decreased), so did the order of entrapment efficiency. The HLB values of the different surfactants are as follows., Span 40 – 6.7, Span 60 – 4.7 and Span 80 – 4.3. [3, 4]

Drug-excipient compatibility studies

Fourier transform infrared spectroscopic studies (FTIR)

Due to their close proximity, the drug and excipient may interact during the niosome formulation process, potentially causing the drug to become unstable. Therefore, choosing the right excipients depends heavily on pre-formulation research on the drug-excipient interaction. FT-IR spectroscopy was utilised to determine whether the drug and the chosen excipients were compatible. Drugs without an excipient and drugs with one were scanned independently. Liquid cell method was used for analysis. [5]

OPTIMIZED METHOD FOR PREPARATION OF NIOSOMES

Ether injection method

The drug, cholesterol, and surfactant were all weighed individually and then dissolved in a 1:1 mixture of diethyl ether and methanol. A sufficient volume of deionized water was transferred into a beaker, set over a magnetic stirrer, and maintained at a temperature of 55 to 65 °C. Using a 14-gauge needle, the organic phase was injected at a rate of 0.25 ml/min into the whirling aqueous phase. The rapid vaporisation of ether and methanol due to temperature differences between phases causes spontaneous vesiculation, which in turn forms niosomes. In Table 1 and Table 2 Composition of Niosomes containing span 80 and span 60 given respectively.[6]

Table 1: Composition of Niosomes containing Span 80

Formulation	Surfactant : Cholesterol	Surfactant weight (gm) SPAN 80	Cholesterol Weight (gm)	Drug taken(mg)
F1	1:1	0.428	0.386	50
F2	1:2	0.428	0.772	50
F3	2:1	0.856	0.386	50

Table 2: Composition of niosomes containing Span 60

Formulation	Surfactant: Cholesterol	Surfactant Weight span 60 (gm)	Cholesterol Weight (gm)	Drug Taken (mg)
F4	1:1	0.430	0.386	50
F5	1:2	0.430	0.772	50
F6	2:1	0.860	0.386	50

CHARACTERIZATION OF NIOSOMAL VESICLES [1,7]

Appearance, consistency and clarity

It was determined by visual inspection under black and white background and graded. Shown in figure 1. The microscopic view of F1 ,i.e., the 1:1 ratio of surfactant (Span 80): Cholesterol is as shown in fig 2.

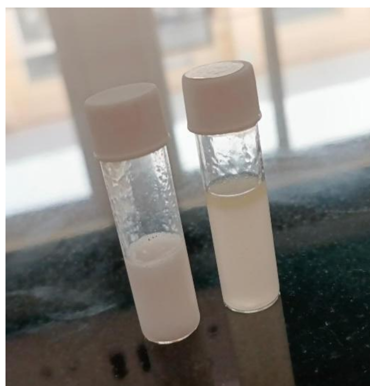


Figure 1: An illustration of F4 and F1 respectively

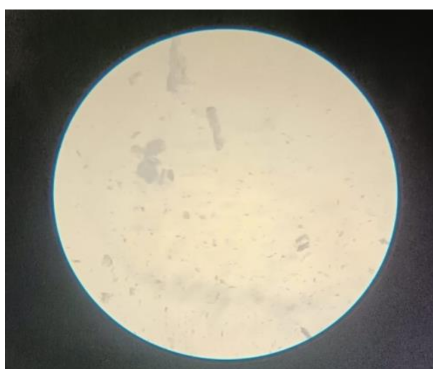


Figure 2: The microscopic view of F1

Examination under microscope

Percentage entrapment efficiency

It was found that the medication was entrapped within the niosomal vesicle. Centrifugation was used to separate the niosomes for 30 to 45 minutes at room temperature and 3500 rpm. Niosomes were distributed as pellets. The drug that was not entrapped in the supernatant was separated. carefully and analysed under UV- Visible Spectroscopy at 213nm. The entrapment efficiency was determined by using the formula. [7, 8]

Particle size and zeta potential determination

Vesicle properties such particle size and zeta potential were determined at room temperature by using Dynamic Light Scattering (DLS) method using a zeta sizer, Horiba SZ 100Z.

$$\% \text{ entrapment efficiency} = \frac{(\text{Total amount of drug} - \text{the amount of drug in supernatant}) \times 100}{\text{Total amount of drug}}$$

Preparation of Gel

Niosomal gel was prepared by carbopol 934 as the gelling agent. Methyl Paraben was dissolved in sufficient amount of water with the aid of heat at 37°C and allowed to cool. carbopol was hydrated by soaking in water for a period of 24 hours and was added to paraben. Triethanolamine was then added to the swollen polymer to form a gel. Niosomal was gelled by adding the aqueous portion (gelling agent) to the niosomal formulation with continuous mechanical stirring.

Characterization of drug entrapped noisome gel [2, 6]

pH Determination

Using a digital pH metre, the pH of the gel formulation containing potassium Losartan was determined. Distilled water was used to dilute the gel formulations. To calibrate the pH metre, standard buffer solutions with pH values of 7 and 10 were utilised. To stabilise the gel formulation, three separate tests were conducted to determine the mean pH values. The electrode was thoroughly washed between each sample (Nayak et al., 2020).

In vitro drug release study

The Franz diffusion cell was used for the in vitro release investigation. The top of the donor compartment was open, allowing the atmosphere to enter. The dialysis membrane with molecular weight about 855 (egg membrane) soaked for 24 h in buffer (phosphate buffered saline, pH 7.4). A clamp was used to keep the donor and receptor compartments together. Within the receptor compartment was 13 mL of Phosphate buffer (Phosphate buffered Saline, pH 7.4) and stirred with a magnetic stirrer and the receptor compartment contains 2 mg of the niosomal gel. A sampling port was included in the receptor compartment, and the temperature was kept at 37 ± 0.5ºC. Samples were taken every 30 minutes on average. Using a syringe, 3 mL of sample was taken out and replaced with new Phosphate buffer (phosphate buffered saline, pH 7.4) at each sampling interval. The drug's concentration was measured at 213 nm using a UV spectrophotometer. It was determined what the total percentage of drugs released were. [9, 10]

Preparation of egg membrane

An egg was purchased from the local market and all the content inside it was emptied. The outer shell of the egg immersed into concentrated HCl and continuously stirred. A thin membrane will be visible which is used for the diffusion studies. [11, 12]

RESULTS

Spectroscopic studies

Determination of λ_{max}

Diluted samples of concentration 10 ug/ml were prepared from standard solution of Losartan potassium in pH-7.4 phosphate buffer saline. The samples were scanned in a 1.0 cm cell against the buffer between 200 and 400 nm. λ_{max} of losartan potassium was shown in Fig. 3

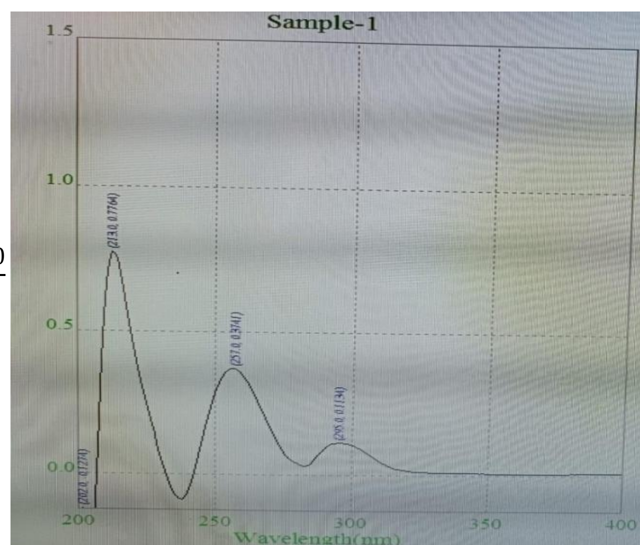


Figure 3: UV absorption spectrum of Losartan potassium.

Calibration curve of losartan potassium

Samples with concentrations ranging from 2 ug/ml to 16 ug/ml were prepared by diluting the standard stock solution of Losartan potassium. The samples were scanned in a 0.1 cm cell against buffer within the 200–400 nm range. Table 3 shows the absorbance at various concentrations of losartan potassium. The calibration curve of Losartan potassium was shown in Fig. 4. [13]

Table 3: The absorbance at various concentrations of losartan potassium

Concentration (µg/ml)	Absorbance
0	0
2	0.226
4	0.388
6	0.584
8	0.649
10	0.776
12	0.921
14	1.102
16	1.289

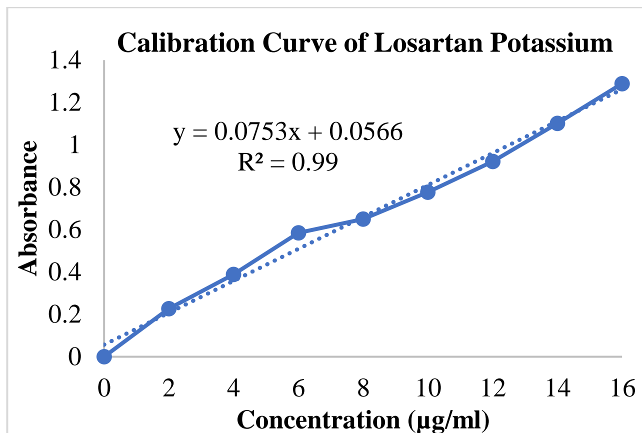


Figure 4: Calibration curve of Losartan Potassium

DRUG- EXCIPIENT COMPATIBILITY STUDIES

FTIR spectra of the pure drug, span 80, cholesterol, and physical mixture were given in Fig. 5, 6, 7, 8 respectively. Table 4 shows the FTIR spectrum wave numbers of different functional groups observed, which indicates that the drug and the excipients are compatible. [14]

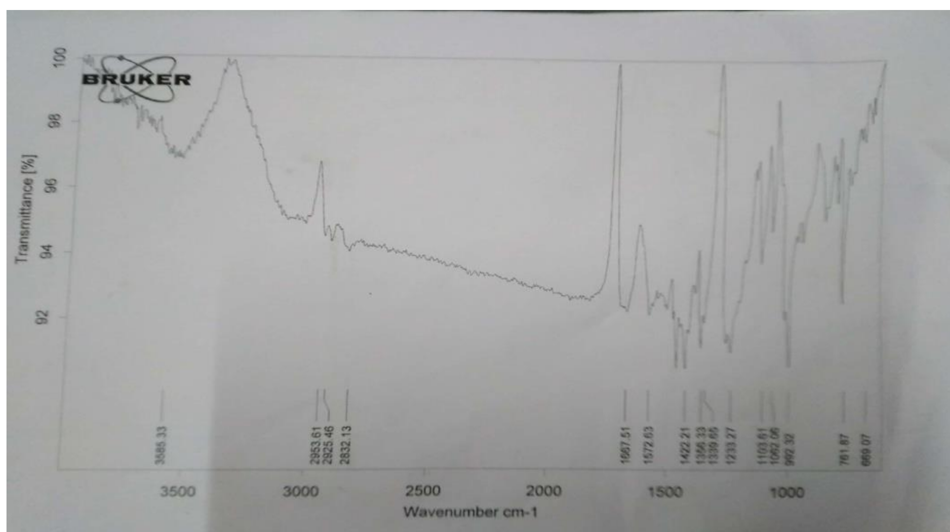


Figure 5: FTIR spectrum of pure drug Losartan Potassium

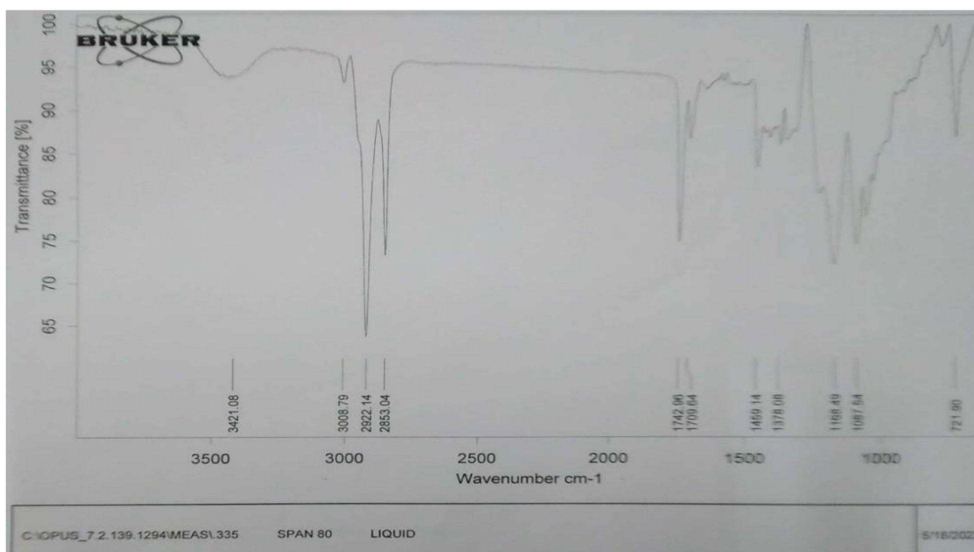


Figure 6: FTIR spectrum of Span 80

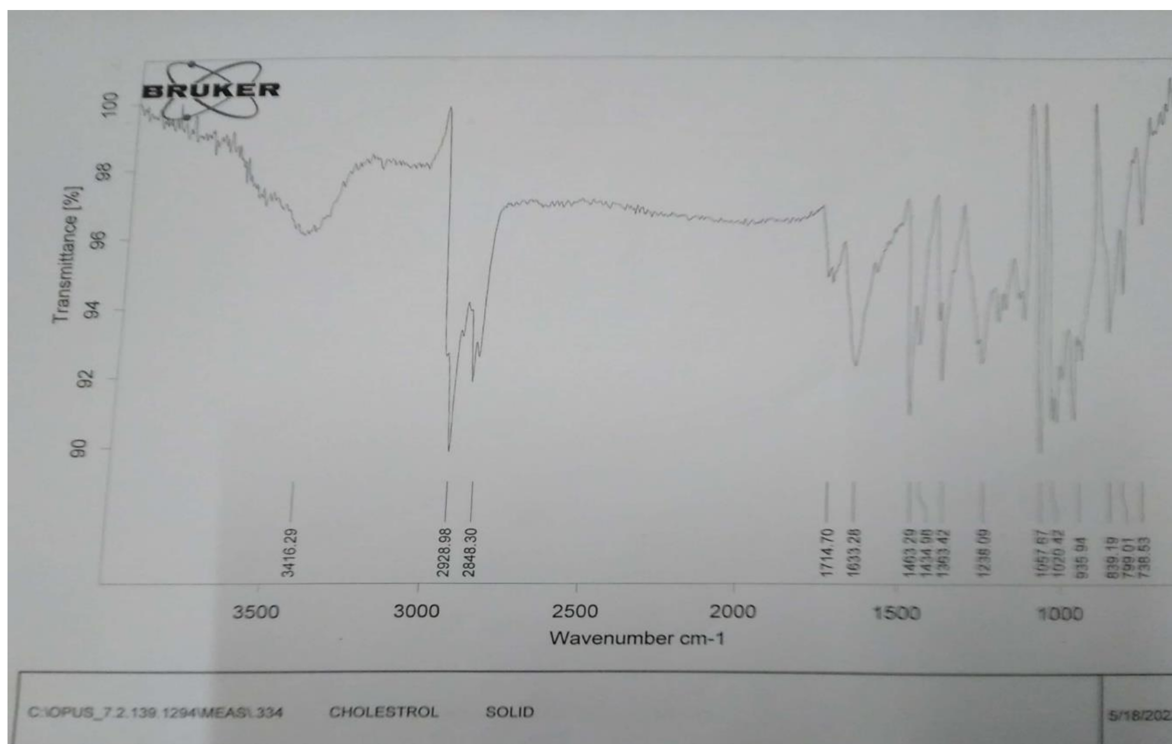


Figure 7: FTIR spectrum of Cholesterol

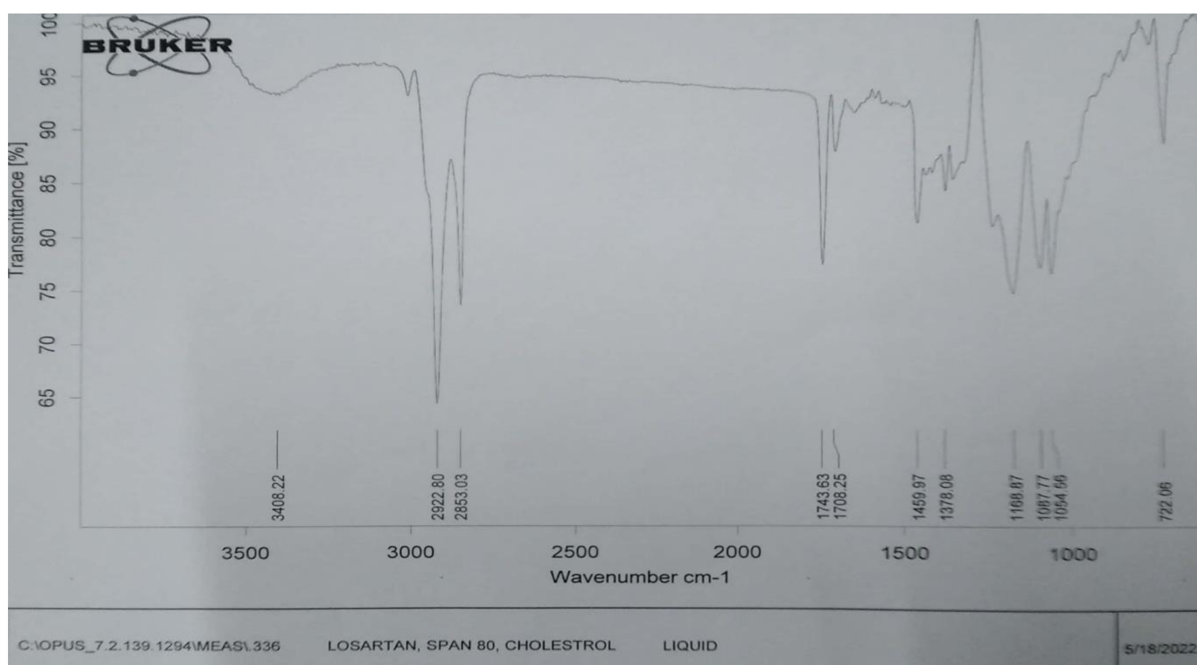


Figure 8: FTIR spectrum of the Drug, Surfactant and Cholesterol mixture

Table 4: The FTIR spectrum of losartan potassium was observed values

Functional group	Wave number of drug (cm$^{-}{}_{1}$)	Wave number of mixture(cm-1)
O-H	933.5	1054.56
C-O	1072.4	1087.77
N-H	2954	2922.80
C=N	1423.47	1378.08
Imidazole ring	1458.18	1459.57

CHARACTERIZATION OF NIOSOMAL VESICLES

Appearance, consistency and clarity

F1 is a clear suspension whereas F4 is a cloudy suspensi**on.** An illustration of F4 and F1 given in Fig. 1 respectively.

Examination under microscope

The microscopic view of F1, i.e., the 1:1 ratio of surfactant (Span 80): Cholesterol is as shown in Fig. 2 (In the microscopic view, Niosomes were not observed clearly because of their nano size).

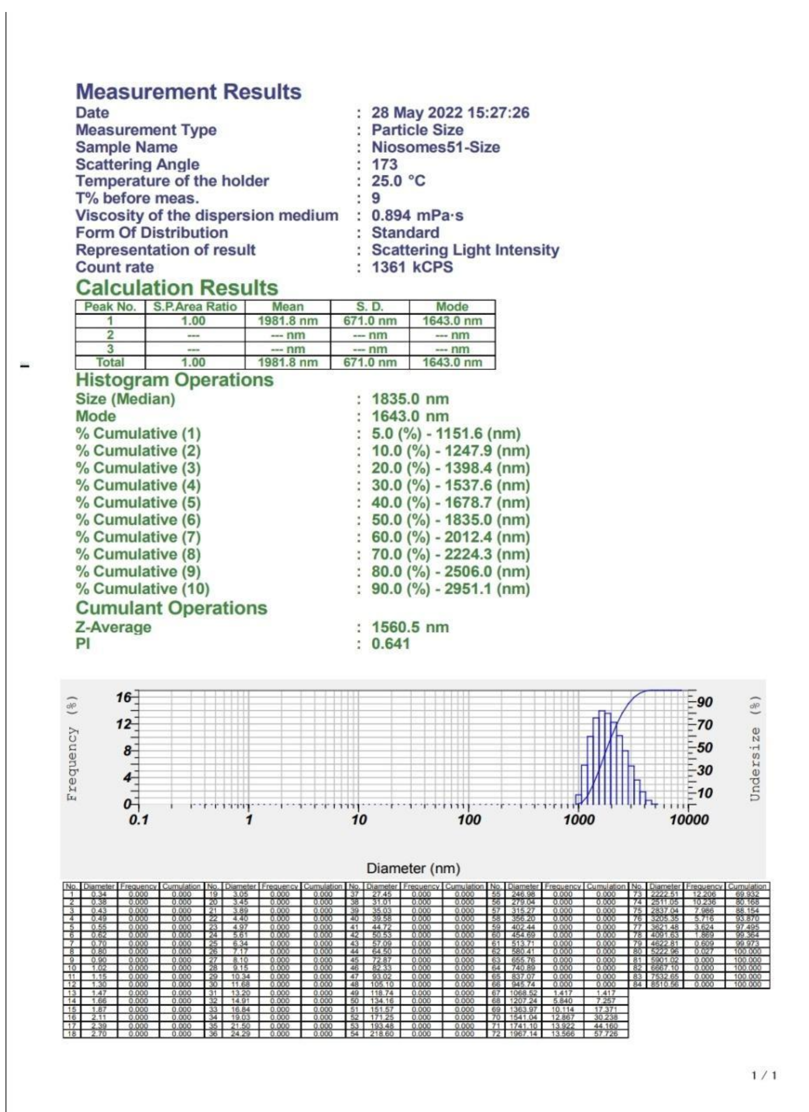
Particle size and Zeta potential

Vesicle properties such particle size and zeta potential were determined at room temperature using Dynamic light scattering (DLS) method using a zeta sizer, Horiba SZ 100 Z. Zeta potential and particle size results were given in the Table 5.

Table 5: Depicting the particle size and the zeta potential values

Formulation code	Particle size (nm)	Zeta potential	PI	Viscosity mPa.s
F1	1835.0	-3.7	0.641	0.895

The Polydispersity Index (PI) generally ranges from 0-1, when PI=0, the formed vesicles are said to be uniform, but if PI=1, the formed vesicles are not in uniformity. The PI obtained for our sample is less than 0.7. i.e., 0.641, which means the formed niosomal vesicles-uniform. Shown in Fig. 9 and 10.



Measurement Results

Date : 28 May 2022 15:27:26
Measurement Type : Particle Size
Sample Name : Niosomes51-Size
Scattering Angle : 173
Temperature of the holder : 25.0 °C
T% before meas. : 9
Viscosity of the dispersion medium : 0.894 mPa·s
Form Of Distribution : Standard
Representation of result : Scattering Light Intensity
Count rate : 1361 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	1981.8 nm	671.0 nm	1643.0 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	1981.8 nm	671.0 nm	1643.0 nm

Histogram Operations

Size (Median) : 1835.0 nm
Mode : 1643.0 nm
% Cumulative (1) : 5.0 (%) - 1151.6 (nm)
% Cumulative (2) : 10.0 (%) - 1247.9 (nm)
% Cumulative (3) : 20.0 (%) - 1398.4 (nm)
% Cumulative (4) : 30.0 (%) - 1537.6 (nm)
% Cumulative (5) : 40.0 (%) - 1678.7 (nm)
% Cumulative (6) : 50.0 (%) - 1835.0 (nm)
% Cumulative (7) : 60.0 (%) - 2012.4 (nm)
% Cumulative (8) : 70.0 (%) - 2224.3 (nm)
% Cumulative (9) : 80.0 (%) - 2506.0 (nm)
% Cumulative (10) : 90.0 (%) - 2951.1 (nm)

Cumulant Operations

Z-Average : 1560.5 nm
PI : 0.641

No.	Diameter	Frequency	Cumulation
1	0.34	0.000	0.000
2	0.38	0.000	0.000
3	0.43	0.000	0.000
4	0.49	0.000	0.000
5	0.55	0.000	0.000
6	0.62	0.000	0.000
7	0.70	0.000	0.000
8	0.80	0.000	0.000
9	0.90	0.000	0.000
10	1.02	0.000	0.000
11	1.15	0.000	0.000
12	1.30	0.000	0.000
13	1.47	0.000	0.000
14	1.66	0.000	0.000
15	1.87	0.000	0.000
16	2.11	0.000	0.000
17	2.39	0.000	0.000
18	2.70	0.000	0.000
19	3.05	0.000	0.000
20	3.45	0.000	0.000
21	3.89	0.000	0.000
22	4.40	0.000	0.000
23	4.97	0.000	0.000
24	5.61	0.000	0.000
25	6.34	0.000	0.000
26	7.17	0.000	0.000
27	8.10	0.000	0.000
28	9.15	0.000	0.000
29	10.34	0.000	0.000
30	11.68	0.000	0.000
31	13.20	0.000	0.000
32	14.91	0.000	0.000
33	16.84	0.000	0.000
34	19.03	0.000	0.000
35	21.50	0.000	0.000
36	24.29	0.000	0.000
37	27.45	0.000	0.000
38	31.01	0.000	0.000
39	35.03	0.000	0.000
40	39.58	0.000	0.000
41	44.72	0.000	0.000
42	50.53	0.000	0.000
43	57.09	0.000	0.000
44	64.50	0.000	0.000
45	72.87	0.000	0.000
46	82.33	0.000	0.000
47	93.02	0.000	0.000
48	105.10	0.000	0.000
49	118.74	0.000	0.000
50	134.16	0.000	0.000
51	151.57	0.000	0.000
52	171.25	0.000	0.000
53	193.48	0.000	0.000
54	218.60	0.000	0.000
55	246.98	0.000	0.000
56	279.04	0.000	0.000
57	315.27	0.000	0.000
58	356.20	0.000	0.000
59	402.44	0.000	0.000
60	454.69	0.000	0.000
61	513.71	0.000	0.000
62	580.41	0.000	0.000
63	655.76	0.000	0.000
64	740.89	0.000	0.000
65	837.07	0.000	0.000
66	945.74	0.000	0.000
67	1068.52	1.417	1.417
68	1207.24	5.840	7.257
69	1363.97	10.114	17.371
70	1541.04	12.867	30.238
71	1741.10	13.922	44.160
72	1967.14	13.566	57.726
73	2222.51	12.206	69.932
74	2511.05	10.236	80.168
75	2837.04	7.986	88.154
76	3205.35	5.716	93.870
77	3621.48	3.624	97.495
78	4091.63	1.869	99.364
79	4622.81	0.609	99.973
80	5222.96	0.027	100.000
81	5901.02	0.000	100.000
82	6667.10	0.000	100.000
83	7532.65	0.000	100.000
84	8510.56	0.000	100.000

1 / 1

Figure 9: The Polydispersity Index (PI) generally ranges from 0-1, when PI=0 , the formed vesicles are said to be uniform, but if PI=1, the formed vesicles are not in uniformity. The PI obtained for our sample is less than 0.7.i.e., **0.641, which means the formed niosomal vesicles-uniform.**

2022.05.28 15:35:30

Measurement Results

Measurement Results

Date	: 28 May 2022 15:32:16
Measurement Type	: Zeta Potential
Sample Name	: Niosomes51-Zeta
Temperature of the holder	: 25.0 °C
Viscosity of the dispersion medium	: 0.895 mPa·s
Conductivity	: 2.041 mS/cm
Electrode Voltage	: 2.8 V

Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-3.7 mV	-0.000028 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean)	: -3.7 mV
Electrophoretic Mobility mean	: -0.000028 cm2/Vs

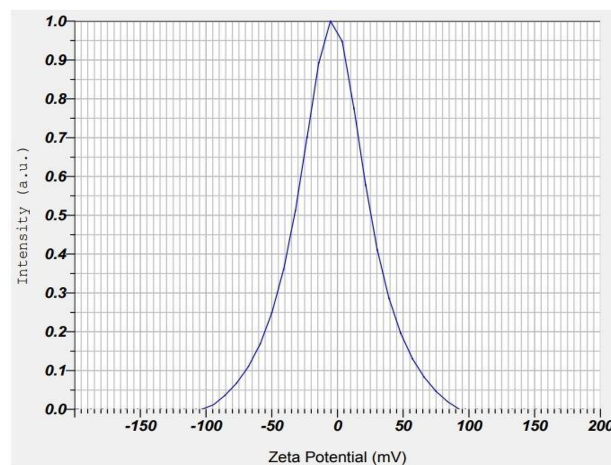


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Figure 10: In this figure, the viscosity and the Zeta potential measurements are shown, which are said to be 0.895 mPa.s and -3.7mV respectively.

Viscosity of the formulation

The measured viscosity of the dispersion medium is said to be 0.895 mPa.S.

Entrapment Efficiency

Table 6 Shown the percentage entrapment efficiency of the drug in different formulations, which were from 55 to 78%.

Table 6: The Percentage entrapment efficiency of the drug in different formulations

Formulation code	Percentage entrapment efficiency, %
F1	78
F2	58
F3	55

In vitro drug diffusion Studies

After 3 hours the cumulative percentage. Table 7 indicates the drug diffusion studies at various time intervals **Fig.11** showed the *In vitro* drug diffusion studies at various time intervals.

Table 7: *In vitro diffusion studies*

Time	% Drug diffused		
In min	F1	F2	F3
0	0	0	0
30	20	10	5
60	26	14	12
90	32	25	16
120	57	32	21
150	63	41	34
180	72	55	42

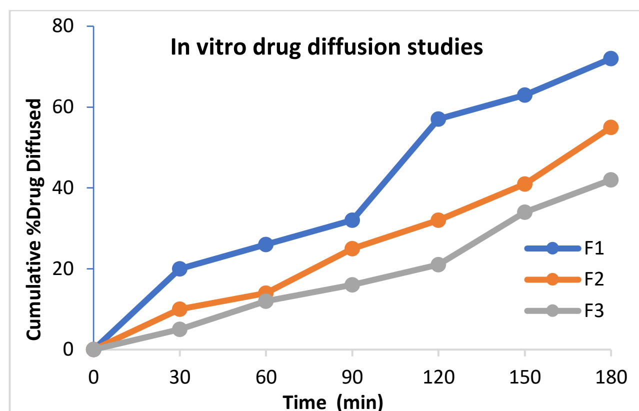

Figure 11: A plot showing the *In vitro* drug diffusion studies at various time intervals.

CONCLUSION

Niosomal formulation of Losartan Potassium was prepared and evaluated for transdermal delivery. Losartan Potassium niosomes was done by ether injection method using Span 80 as surfactant, cholesterol as entrapping agent, methanol and diethyl ether as solvent. The prepared niosomal formulations were evaluated for optical microscopy, drug content, pH, Particle size, in vitro release, entrapment efficiency, and zeta potential. Particle size of F1 formulation was 1835.0nm. F1, F2 and F3 niosomal formulation was found to be optimized as their entrapment efficiency were high i.e., 78%, 58% and 55% respectively. The pH was found to be in the limits which indicated less chances of irritancy on skin. The *in vitro* release study and drug content analysis was carried out for the optimized formulations F1, F2 and F3 formulation and was found that F1 formulation has good drug release. The zeta potential of the niosomal dispersion is also said within the limit range i.e., -3.7mV. The Polydispersity Index was also found out to be within the limits i.e., lesser than 0.7, the value was around 0.64 which indicates uniform niosomal vesicles.

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