

Original Research Article

Formulation and characterization of lomustine-loaded solusomes nanovesicles

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Abstract

Purpose: To design and characterize Lomustine (LOM) nanoparticles encapsulated by solusomes to enhance the physicochemical properties.

Methods: Thin-film hydration technique was employed to prepare LOM-loaded solusomes. Sixteen formulations were produced and evaluated for entrapment efficiency, particle size, polydispersity index, and in vitro drug release. Then, the optimum formula was chosen for further evaluation using differential scanning calorimetry (DSC), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FTIR) and using a sheep nasal membrane to perform ex vivo drug permeation studies.

Results: Solusomes-loaded LOM F4 (lomustine 10 mg, cholesterol 10 mg, phosphatidylcholine 98 % 50 mg and Soluplus® 25 mg) was selected as an ideal formula since it has the optimum characteristics: high entrapment efficiency 99.76 ± 1.64 %, a small particle size 90.4 ± 9.98 nm, and a stable zeta potential - 32.16 mV. Additionally, it demonstrated significantly ($p < 0.05$) faster in vitro drug release 93 % after 120 minutes and a higher ex vivo permeation coefficient compared to the LOM suspension. Finally, encapsulating LOM in a more soluble and amorphous state facilitates rapid absorption for brain tumour treatment.

Conclusion: The LOM-solusomes could be considered a new approach to enhance the solubility and permeability of the drug and deliver optimum therapeutic benefit.

Keywords: Differential scanning calorimetry, Ex vivo drug permeation, Lomustine, Phosphatidylcholine, Solubility, Solusomes

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INTRODUCTION

Glioblastoma multiforme (GBM) is a brain tumour considered to be the most lethal and violent disease in adults because of its high rate of recurrence and rapid progression. The treatment of this disease is extremely challenging owing to the strong obstacle of the blood-brain barrier (BBB), in addition to the infiltrative nature of GBM. Besides, the BBB can restrict and sharply reduce the passage of most therapeutic

substance that leads to lessen the effectiveness of chemotherapies [1]. Alkylating agents are lipid-soluble nitrosoureas, approved by FDA to be applied for GBM therapy since they can successfully cross the BBB. One of the few orally administered drugs in this group is lomustine (LOM). It is a biopharmaceutics class II drug characterized by poor aqueous solubility and high permeability and works by damaging the DNA in tumour cells and preventing its replication to stop cell growth. Nevertheless, because of

LOM's strict dose-limiting toxicities like profound myelosuppression, fast chemical degradation and poor aqueous solubility, these lead to significant drawbacks in LOM clinical efficacy [2].

Novel drug delivery systems have been explored in the field of nanotechnology to overcome these obstacles by enhancing the stability and solubility of lipophilic drugs as well as the therapeutic index. Vesicular systems like niosomes, liposomes, or other lipid-based nanoparticles have been chosen as carriers for chemotherapy drugs [3]. Among them, the solosomes depict an engineered nano-carrier class that enhances the bioavailability of lipophilic pharmaceutical drugs, thereby increasing their solubility. This nanovesicle system, solosomes, includes mainly phospholipids, cholesterol and surfactants (Soluplus®, which is an amphiphilic graft copolymer). LOM would be encapsulated by the solosome vesicular system since the latter can retard drug degradation, improve its solubility, and consequently modulate its pharmacokinetic profile. Thus, this study aims to prepare and characterize novel formulation of LOM encapsulated by solosomes [4].

EXPERIMENTAL

Materials

Soya lecithin phosphatidylcholine 98 % (PC 98 %) and Lomustine (LOM) were provided by Baoji Guokang Bio-Technology Co., Ltd., China. Cholesterol was purchased from Wuhan Senwayer Century Chemical Co., Ltd., China. Soluplus® was purchased from BASF Pharmaceutical Co., Ltd., Germany. Methanol, chloroform, mannitol, Brij 35® (Polyoxyethylene lauryl ether), Sodium hydroxide and potassium

dihydrogen phosphate were bought from Yichang Tianrui Biopharma Co., LTD., China.

Saturated solubility of LOM

Solubility studies were conducted by adding excess LOM powder in a tightly sealed glass test tube containing 10 mL of selected media (methanol, phosphate buffer (pH 7.4), and distilled water (D.W)). The samples were incubated in a shaking water bath (Memmert® Shaker) at 37 ± 0.5 °C with an agitation speed of 100 strokes/ min for 48 hours. The collected samples were passed through 0.45 mm syringe filters and subsequently analysed using spectrophotometry at lambda max (λ_{max}) of 230 nm [5].

Preparation of LOM-loaded solosomes

Multi-lamellar solosomes containing varying ratios of LOM, PC, cholesterol, and Soluplus® (as seen in Table 1) were prepared via thin film hydration by dissolving the components in 10 mL of a 1:2 chloroform/methanol solvent system. The prepared solutions were transferred to the round-bottom flask of a rotary evaporator (Stuart rotary evaporator). The organic solvent was evaporated at 55 °C for 15 minutes at 80 rpm, resulting in the formation of a thin lipid film on the flask's inner surface. After drying overnight, the thin film was hydrated using 10 mL of phosphate-buffered saline (PBS, pH 7.4). This hydration process involved sonication for 10 minutes, followed by rotation at 100 rpm for 1 hour at 55 °C. Subsequently, the solosomes suspension was sonicated for 10 minutes at 55 °C to yield small unilamellar vesicles (SUVs). The LOM-loaded solosomes were stored at 4 °C [6].

Table 1: LOM-loaded solosomes formulations

Formula no.	Soluplus® (mg)	PC 98% (mg)	Cholesterol (mg)	Drug (LOM) (mg)
F1	10	80	10	10
F2	10	70	10	10
F3	10	75	10	10
F4	25	50	10	10
F5	25	30	10	10
F6	25	20	10	10
F7	50	30	-	10
F8	50	40	-	10
F9	50	50	-	10
F10	50	60	-	10
F11	50	100	-	10
F12	75	100	-	10
F13	100	50	-	10
F14	100	100	-	10
F15	100	150	-	10
F16	100	200	-	10

Characterization of LOM-loaded solusomes

Particle size (PS) and polydispersity index (PDI) estimations

The PS and PDI were determined using a Zetasizer Nano ZS after appropriate dilution of the dispersions. Data are expressed as the mean $\pm$ standard deviation (SD) of three independent replicates [7].

Determination of entrapment efficiency (EE%)

Entrapped LOM was separated via ultracentrifugation (Thermo Scientific ultracentrifuge) of 4 mL of each solusomes dispersion in an Amicon® Ultra Centrifugal Filter (10 kDa MWCO, sample volume 4 mL) at 6000 rpm for 30 minutes. The concentrations of LOM were estimated spectrophotometrically at λ_{max} 230 nm for LOM-free solusomes. The LOM EE% was calculated using Equation 1, with results expressed as the mean of three measurements $\pm$ SD.

$$\text{EE (\%)} = \{(\text{TD}-\text{FD})/\text{TD}\}100 \dots (1)$$

The terms 'total drug' (TD) and 'free drug' (FD) refer to the amount of drug in the LOM-loaded solusomes formulation and the ultrafiltrate, respectively [8].

In vitro release study

In vitro release studies were conducted using a USP Dissolution Apparatus Type II (Faithful® RC-6 Dissolution Tester, Huanghua Faithful Instrument Co., Ltd., China) to compare LOM-loaded solusomes (formulations F4, F5, F7, and F8 as seen in Table 1) against pure LOM powder.

Samples containing an equivalent of 10 mg LOM were enclosed in cellulose dialysis bags (MWCO 8,000 - 14,000 Da). These bags were immersed in 200 mL of phosphate buffer (pH 7.4) supplemented with 1 % Brij 35® (Polyoxyethylene lauryl ether), a non-ionic surfactant. The experiment was maintained at 37 ± 0.5 °C with a paddle speed of 100 rpm.

At predetermined time intervals (5, 10, 15, 30, 45, 60, and 120 min), 1 mL aliquots were removed from the release medium and immediately replaced with an equivalent volume of fresh medium to maintain constant volume. These samples were filtered through a 0.45 μm syringe filter and quantified spectrophotometrically at λ_{max} of 230 nm [9].

Selection and optimization of LOM-loaded solusomes

The selection of the optimum formula was predicated following the outcomes of PS, PDI, and *in vitro* release profile assessment. It underwent further evaluations regarding its zeta potential, *ex vivo* permeation study, morphological characterization and drug-polymer compatibility.

Ex vivo permeation studies of selected formulation

The efficacy of solusomes in enhancing nasal mucosal permeation and achieving brain targeting was evaluated through an *ex vivo* study utilizing fresh ovine nasal mucosa obtained from a slaughterhouse. The permeation of LOM from optimized LOM-loaded solusomes was evaluated against a control LOM suspension. Intact nasal membranes were isolated, thoroughly washed, and stored frozen. Prior to the experiment, the mucosal membranes were rehydrated in PBS (pH 7.4) and mounted in a Franz cell containing 11 mL of the same buffer to ensure stabilization.

Incubation of the cell (COPLEY Vertical Diffusion Cell HDT 1000) was carried out at 37 ± 0.5 °C for two hours. Using a stirring speed of 100 rpm, 0.5 mL of the selected formula (equivalent to 5 mg LOM) was tested. Complete medium replacement was performed at intervals ranging from 5 to 120 minutes to maintain sink conditions. The samples were analysed by UV spectrophotometer at λ_{max} of LOM. Three separate measurements were used to calculate the results, and their standard deviations were shown.

The results were expressed as the amount that reached the receptor chamber. The flux (J) was established by calculating the slope of the line that resulted from graphing the drug's permeation rate ($\mu\text{g}/\text{cm}^2$) against various time intervals (min). By dividing the resulting slope value (J) by the initial LOM concentration (C_0 or C_d) in the donor compartment, permeability coefficient (Kp) was calculated using Equations 2 and 3.

$$J = dM/S.dt \dots (2)$$

$$Kp = Jss/Cd \dots (3)$$

Where M is the amount of material that transfers through a unit section (S) of a barrier in unit time (t) [10].

Lyophilization of the selected LOM-loaded solusomes

Lyophilisation was done to convert the liquid dispersion to a solid state to prevent the particles from aggregating and to significantly extend the formulation's stability. A freeze-dryer (Martin Christ Alpha 1-2 LDplus, Germany), with a vacuum pump, was used. The lyophilised formulation of LOM-loaded solusomes with mannitol (5 % w/v) was chosen as cryoprotectant to maintain the integrity and vesicle structure. The specimens were frozen in liquid nitrogen bath at - 80 °C for 10 minutes. This was followed by drying for 10 hours at - 45 °C and 150 mT of pressure with a freeze dryer. The dried LOM-loaded solusomes obtained were analysed [11].

Evaluation of lyophilized LOM-loaded solusomes

Differential scanning calorimetry (DSC)

Thermal behaviour of LOM, Soluplus®, PC, physical mixture (LOM-Soluplus®-PC), and lyophilized solusomes was investigated using a Shimadzu differential scanning calorimeter calibrated with purified indium. Samples were placed in aluminium pans and heated from 30 to 300 °C at a scanning rate of 15 °C/ min under a nitrogen purge of 25 mL/ min [12].

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectra of LOM, Soluplus®, PC, the physical mixture of the selected LOM-loaded solusomes formula, and the selected formula were recorded at room temperature. Spectroscopy was employed to investigate potential physicochemical interactions between LOM and the formulation excipients. The spectra were recorded over a scanning range of 400-4000 cm⁻¹ [13].

Transmission electron microscopy (TEM)

Table 2: Characteristic FTIR bands of LOM

Functional groups and bonds	Experimental FTIR spectra (cm ⁻¹)	Reference FTIR spectra (cm ⁻¹) [15]
N-H stretching	3348.42	3348
CH stretching	2854.65	2857
C=O stretching	1703.14	1702
Nitroso group stretching	1533.41	1500
Cyclohexyl ring absorption (C-C stretching, ring vibrations)	1489.05	1450-148690

Saturated solubility of LOM

The solubility of the LOM in different media of methanol, phosphate buffer (pH 7.4), and D.W

This was utilized to evaluate the morphological features of both the freshly prepared solusomes dispersion and the lyophilized system following reconstitution with distilled water. The preparation involved placing a droplet of the diluted formulation onto a negatively stained copper grid, which was allowed to dry at room temperature before visualization [14].

Statistical analysis

Results are presented as the mean ± standard deviation (SD) with a sample size of n = 3. Two-way ANOVA (Analysis of variance) in the GraphPad Prism (version 8) software program was used to indicate the statistical significance ($p < 0.05$ is considered statistically significant) of varying PC 98 % and Soluplus® concentrations for in vitro drug release and ex vivo permeation studies.

RESULTS

Characterization of LOM

LOM melting point

The melting point of pure LOM powder was determined using the capillary tube technique, and it was recorded to be equal to 90 - 92 °C.

Differential scanning calorimetry of LOM

A sharp endothermic peak was observed at 92.04 °C, as shown in the thermogram in Figure 2.

Fourier transform infrared spectroscopy of LOM

Table 2 displays our experimental FTIR spectra of LOM (400–4000 cm⁻¹ range) in comparison with the cited FTIR spectra in Silverstein *et al* [15]. They were within the accepted range.

has been investigated and it was equal to 3 mg/mL (slightly soluble), 0.03 mg/ mL (practically insoluble) and 0.05 mg/ mL (practically insoluble), respectively.

Characterization of LOM-loaded solusomes

Table 3 depicts the results of PS, PDI, and EE % characterizations for the prepared formulations.

Particle size and polydispersity index of LOM-loaded solusomes

The PS, PDI and EE % ranged from solusomes from 90.4 ± 9.98 (F4) to 158.5 ± 8.34 (F1), from 0.172 ± 0.05 (F14) to 0.270 ± 0.08 (F12), and from 93.33 ± 1.65 (F12) to 99.76 ± 1.64 (F4), respectively, as seen in Table 3.

Entrapment efficiency of LOM-loaded solusomes

Regarding the relationship between the sixteen formulations and EE%, the composition of Soluplus® and PC has a significant positive effect on the EE of the drug. While all sixteen formulations show high EE % (above 93 %), certain combinations yield exceptionally high efficiency, nearing 100 %, as seen in Table 3.

In vitro release

Figure 1 presents the results of *in vitro* release of four solusomes nano-vesicle formulations (F4, F5, F7 and F8) and LOM suspension. All four Nano-vesicle formulations demonstrated significantly faster and higher percentages of drug release compared to standard LOM

suspension over 120-minute period. The suspension showed a much slower and lower release, reaching only 49 % after two hours, whereas all Nano-vesicle formulations released well over 60 % in the same timeframe. Among formulations, LOM suspension exhibited the slowest and lowest release rate. After the first 30 minutes, it had only released 23 % of the drug, and it plateaued at 49 % by 120 minutes. Formulation F7 showed the lowest release profile of solusomes Nano-vesicle formulations, reaching 60 % after 120 minutes. The F8 and F5 had very similar release profiles. F8 started slightly faster, releasing 25 % in the first 5 minutes compared to 22 % of F5. However, after 120 minutes, F5 slightly surpassed F8, reaching a total release of 71 % compared to 67 % of F8. Finally, F4 showed the most rapid and highest percentage of drug release at every time point. It achieved a 30 % release in just 5 minutes and reached 93 % release after 120 min.

Selection and optimization of LOM-loaded solusomes

From the sixteen LOM-loaded solusomes, F4 was the optimised formulation. It exhibited a significantly ($p < 0.05$) higher cumulative drug release (93 % at 120 minutes), the smallest mean PS (90.4 nm) and the highest encapsulation efficiency (99.76 %). Furthermore, it has an acceptable particle homogeneity (PDI 0.248). The zeta potential for formula F4 was -32.16 mV, which aids in nano-system stability.

Table 3: Represented PS, PDI and EE% of LOM-loaded solusomes formulations

Formula no.	Particle size (nm)	Polydispersity index	Entrapment efficiency (%)
F1	158.5±8.34	0.235±0.05	93.45±1.32
F2	111.6±8.75	0.231±0.02	95.88±0.77
F3	152.5±10.23	0.234±0.07	96.65±0.64
F4	90.4±9.98	0.248±0.03	99.76±1.64
F5	93.84±11.12	0.223±0.03	99.69±1.72
F6	112.9±12.61	0.199±0.06	95.62±1.16
F7	94.37±7.32	0.187±0.02	99.75±0.59
F8	103.2±10.50	0.231±0.08	99.74±1.78
F9	106.2±8.89	0.229±0.06	96.45±0.89
F10	118.9±6.18	0.243±0.04	95.34±1.12
F11	134.1±8.25	0.268±0.03	97.43±0.68
F12	124.6±13.43	0.270±0.08	93.33±1.65
F13	102.6±9.12	0.241±0.04	96.65±0.87
F14	151.3±15.65	0.172±0.05	95.56±0.75
F15	117.5±10.41	0.236±0.07	96.35±1.54
F16	151.9±9.21	0.267±0.06	95.66±1.24

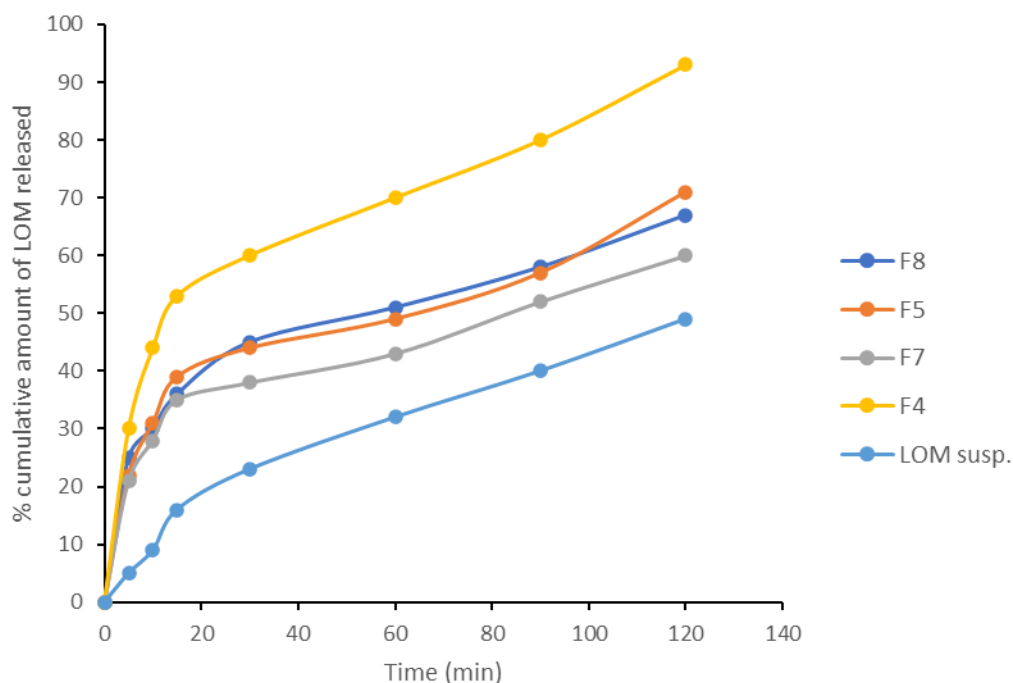


Figure 1: *In vitro* LOM release profiles

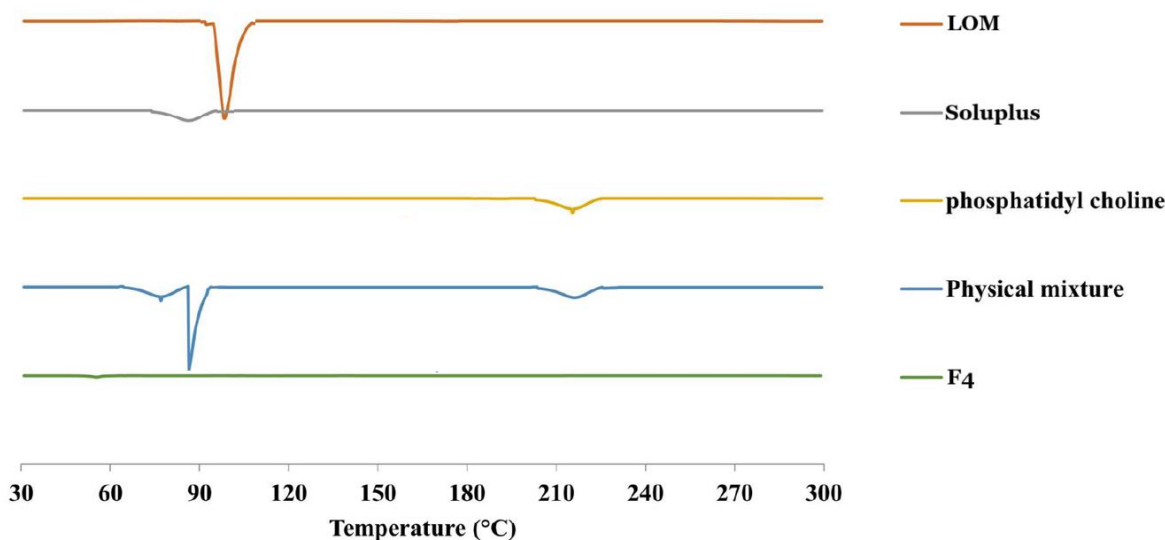


Figure 2: DSC Thermogram of LOM, Soluplus®, PC, physical mixture of LOM-Soluplus®-PC and lyophilized selected formula F4

Differential scanning calorimetry

The thermogram of LOM exhibited a distinct endothermic peak at 92.04 °C. This corresponds to the drug's melting point and is a definitive confirmation of its crystalline nature. In contrast, the excipients displayed broader thermal profiles, with Soluplus® showing a broad endotherm at 84.14 °C, characteristic of its amorphous polymeric nature, while PC exhibited a thermal event at 211.68 °C, as shown in Figure 2.

Fourier transform infrared spectroscopy

FTIR spectra of the main constituents were displayed, including LOM, Soluplus®, PC, physical mixture of F4 (LOM-Soluplus®-PC) and lyophilized F4, as shown in Figure 3. LOM's FTIR spectra displayed obvious bands at 3348.42 cm^{-1} relating to N-H stretching and also the CH stretching at 2854.65 cm^{-1} . Furthermore, a sharp absorption peak was recognized at 1703.14 cm^{-1} , corresponding to the stretching vibration of C = O group. The stretching vibrations of the Nitroso

group appeared at 1533.41 cm^{-1} and the vibrations) at 1489.05 cm^{-1} .
cyclohexyl ring absorption (C-C stretching, ring

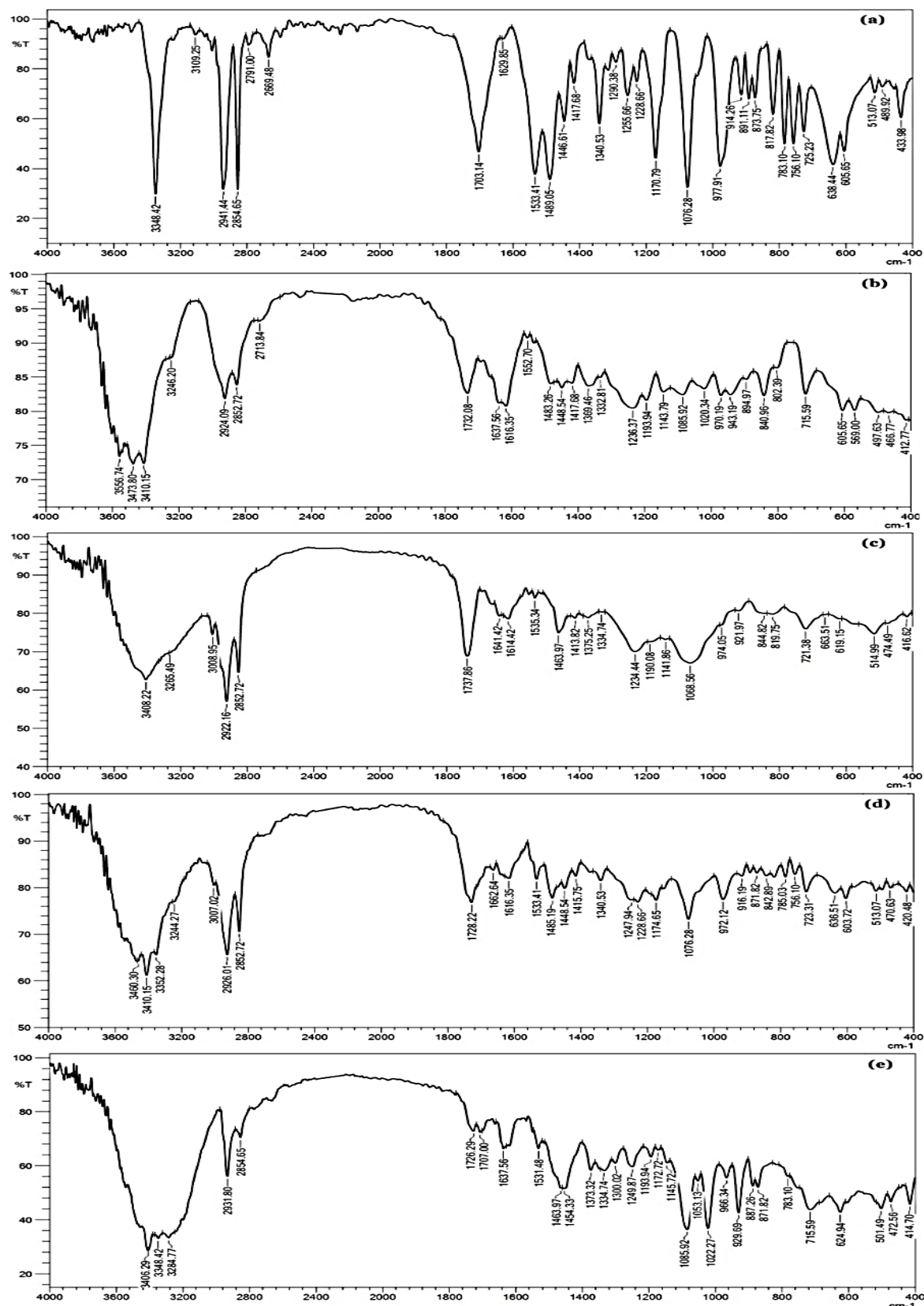


Figure 3: FTIR of (a) LOM, (b) Solupus®, (c) PC, (d) physical mixture of F4 (LOM-Soluplus®-PC) and (e) lyophilized F4

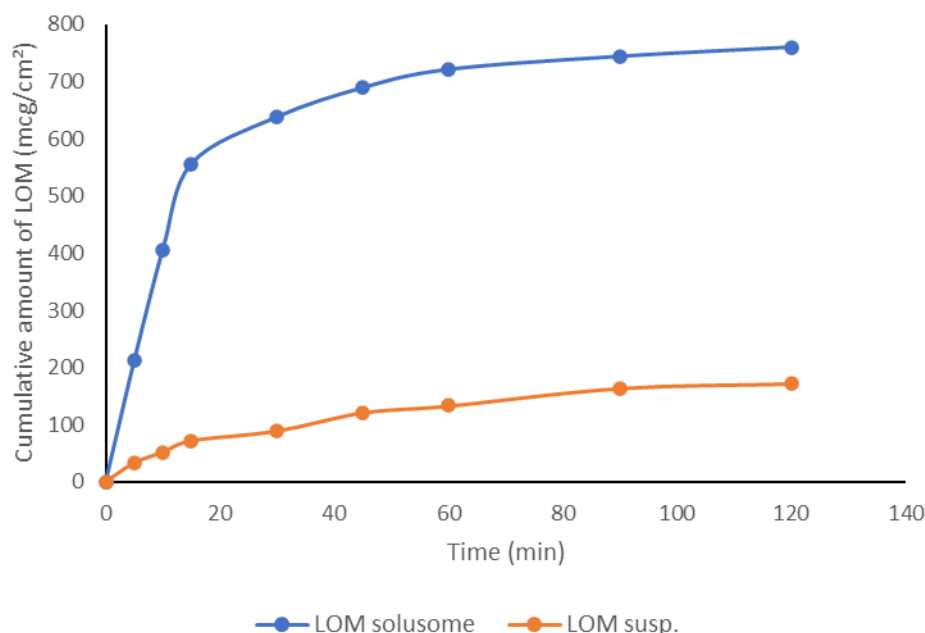


Figure 4: Ex-vivo permeation studies

Ex vivo permeation studies of selected formulation

As illustrated by Figure 4, the LOM solusomes formulation (F4) demonstrates a significantly ($p < 0.05$) higher and more rapid permeation rate across the sheep nasal membrane compared to the LOM suspension. Through calculation of the permeation coefficient (K_p), they found that the K_p of LOM solusomes F4 (0.038 cm/ h) is approximately 4.4 times higher than that of LOM suspension (0.0086 cm/ h).

Transmission electron microscopy (TEM)

Analysis of the freshly prepared F4 solusomes dispersion by TEM revealed spherical nano-vesicles. These vesicles were observed to be well-dispersed, indicating a non-aggregating nature, and possessed a homogeneous particle size distribution.

DISCUSSION

Data demonstrate a complicated but clear correlation between concentrations of Soluplus® and phosphatidylcholine (PC) with the resultant particle size (PS) of solusome nano-vesicles. Increasing concentrations of these components generally increase the particle size of the formula; however, this relation is non-linear and dependent on other factors, in particular the presence of cholesterol. PC is the main phospholipid building block of the primary structure of the vesicle bilayers, while cholesterol is added to modulate the membrane fluidity and

stability. Furthermore, Soluplus® acts as an effective polymeric stabilizer [16]. The subsequent analysis determines the impact of each of these individual components on the physical properties of the prepared formulations.

The concentration PC is directly related to PS, especially in the prepared formulations without cholesterol. For instance, F7 – F11 contain 50 mg of Soluplus® in each formula; when PC quantity increased from 30 to 100 mg, a gradual increase was observed in PS from 94.37 to 134.1 nm because PC is the predominant building block of the vesicle membrane. Besides, Soluplus® is a polymeric stabilizer that coats the surface of vesicles mechanistically. The effect of Soluplus® on PS is more complex, but generally it leads to larger dimensions at higher concentrations. Higher concentrations of the polymer may either lead to a thicker stabilization layer or to the aggregation of smaller particles into larger ones, which in turn increases the measured hydrodynamic diameter [17]. Therefore, when PC was kept constant at 50 mg, the rise of Soluplus® from 25 mg (F4) to 50 mg (F9) resulted in an increase of the PS from 90.4 nm to 106.2 nm. However, the relation between the polymer and PS is not strictly linear since a further increase to 100 mg (F13) resulted in a small reduction in PS to 102.6 nm. Furthermore, the data provided suggests that there was no significant correlation between the different formulations and the polydispersity index (PDI), as all sixteen formulations resulted in successful formation of nanoparticles with an acceptable PDI value below 0.3. The entrapment efficiency

(EE %) showed that formulations of F4, F5, F7, and F8 had the highest values, all > 99.6 %. The most successful formulations contained intermediate Soluplus® concentrations (25 - 50 mg) with low-to-moderate PC levels (30 - 50 mg), suggesting that this particular ratio appears to be most effective for drug entrapment. This type of encapsulation is essentially controlled by the drug's solubility in the medium. LOM is a highly lipophilic drug; hence, it has a low solubility in aqueous solutions, which hinders its release. However, some nanotechnology approaches greatly enhance the solubility by reducing PS, increasing surface area, and inducing a critical phase transition from a crystalline to an amorphous phase [18]. Thus, F4 exhibited improved release profile with the fastest and highest percentage of drug release. F4 demonstrated a 30 % release in 5 min and a maximum of 93 % after 120 min, which was considerably more effective than other nano-vesicle formulations and far superior to the standard LOM suspension.

On the other hand, the analysis of DSC thermograms provided crucial information about the physical state of the mixtures that showed the persistence of the melting peak characteristic of LOM at 92 °C. It shows that the physical mixing did not modify the solid state of the LOM. Conversely, the complete disappearance of the melting peak in F4 is an encouraging indication of a successful crystalline-to-amorphous transition. Also, the rapid and critical drug-excipient compatibility assessment by FTIR spectroscopy provided essential compositional inputs to the optimal formula. FTIR is an instrumental method to gain insight into structural changes in the components of the formulation, especially when the drug is subjected to environmental effects or process-related changes [6]. The results of its spectra indicated that the feature bands of LOM were exactly within the original range positions without any significant shifting. This confirmed, especially in the lyophilized F4 formulation, that there was no detrimental interaction between the drug and selected excipients.

Penultimately, transmission electron microscopy (TEM) analysis showed that formula F4 contains uniform, discrete, and spherical nanovesicles. These physical properties are basic requirements to ensure stable pharmaceutical dispersion and directly contribute to efficient permeation and high bioavailability in further biological evaluation [19]. Finally, *ex vivo* permeation studies on sheep nasal mucosa confirmed that F4 had optimal permeation efficacy when compared to ordinary LOM suspension. Consequently, it is a

viable nasal delivery system. The 4.4-fold increase in permeation coefficient proves the successful conversion of LOM into a high-flux nasal formulation using solosome preparation method. These results collectively confirm the potential of F4 as a promising and non-invasive alternative for rapid systemic delivery of drugs.

CONCLUSION

Solosomes have been formulated as amorphous, stable, and homogeneous nano-vesicles through an encapsulation process. The potency of this dosage form is the effective delivery to the brain from the nose, since it could enhance the permeation in the nasal membrane (*ex vivo*). Therefore, the solosomes dosage form can be considered as an approach to enhance the solubility and permeability of lomustine and present optimum therapeutic benefit.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work

Use of Artificial Intelligence

The authors acknowledge that AI-based techniques were employed just for language editing and document polishing (e.g., grammar, phrasing, clarity). No AI technologies were utilised to generate content, analyse data, or impact study design, results, or conclusions. All the intellectual contributions, analyses and interpretations of the study contained in the publication are the unique work of the authors.

Contribution of authors

We declare that this work was done by Ihab Dahham Hammoodi and Nawal Ayash Rajab in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. In addition, Ihab Dahham Hammoodi: concept, practical work, data analysis, writing the article. While Nawal Ayash Rajab: proofreading and supervising the article, providing research supplies.

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