RESEARCH PAPER

Enhancing the Solubility of Carvedilol by an Optimised Nano-Liposomal Formulation: Characterisation and *In Vitro* Evaluation

Husain Saeed [1*], ***Sarmad Al-Edresi*** [2]

[1] *Najaf Health Directorate, Alzahraa Teaching Hospital, Najaf, Iraq*

[2] *Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, University of Kufa, Najaf-52001, Iraq*

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ABSTRACT

Carvedilol is a non-selective β-adrenergic blocker used in the management of cardiovascular disorders such as hypertension, heart failure, and post-myocardial infarction complications, with additional antioxidant and cytoprotective properties; however, its poor aqueous solubility and low oral bioavailability limit its therapeutic efficacy. This study aimed to enhance the solubility of carvedilol by developing an optimised liposomal formulation using the thin-film hydration method. The optimised composition, containing DPPC, HSPC, and cholesterol, was prepared and characterised for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency (EE), drug loading (DL), and morphological and structural attributes. The resulting liposomes exhibited a mean particle size of 90.8 nm, a PDI of 0.031, and a zeta potential of −15.2 mV, indicating a stable nanosized dispersion. The EE and DL were 86.5% and 10.61%, respectively, confirming efficient drug encapsulation. X-ray diffraction (XRD) revealed the conversion of carvedilol from a crystalline to an amorphous state, while FESEM images demonstrated spherical vesicles with smooth surfaces. In vitro release studies in phosphate buffer (pH 6.8) showed a biphasic pattern, with sustained release up to 83.1% after 14 hours. The solubility of carvedilol increased by approximately 22 % in the liposomal formulation compared with the pure drug, and stability studies confirmed minimal aggregation and acceptable retention of EE % after three months at 4 °C. Overall, the optimised liposomal system successfully improved the solubility and release behaviour of carvedilol, highlighting its potential as a promising delivery platform for poorly water-soluble drugs.

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INTRODUCTION

Carvedilol is a non-selective β-adrenergic blocker widely prescribed for the management of cardiovascular disorders such as hypertension, heart failure, and post-myocardial infarction complications. Beyond its classical β-blocking activity, it exhibits additional pharmacological benefits, particularly antioxidant, anti-inflammatory, and anti-apoptotic properties. These effects help preserve myocardial function,

* *Corresponding Author Email: husseins.alsarraf@student.uokufa.edu.iq*

attenuate oxidative stress, and protect against cellular damage, thereby enhancing its therapeutic value in the management of cardiovascular disease [1].

Despite its therapeutic importance, carvedilol exhibits very low aqueous solubility and consequently poor oral bioavailability, which limits its clinical effectiveness and often necessitates frequent dosing [2].

In our previous study, carvedilol-loaded liposomal formulations were systematically developed and optimised using a full factorial design with Design-Expert® software. Seventeen formulations were prepared and evaluated for particle size, polydispersity index (PDI), entrapment efficiency (EE), drug loading (DL), zeta potential, and *in vitro* release. Based on desirability criteria, an optimum formulation was identified that exhibited favourable physicochemical properties and encapsulation performance [3].

Building on these findings, the present work focuses exclusively on this optimised formulation to provide advanced physicochemical characterisation and to evaluate its potential to enhance carvedilol solubility. Specifically, the study investigates particle size, PDI, X-ray diffraction (XRD), field-emission scanning electron microscopy (FESEM), and *in vitro* release studies. Furthermore, the solubility of carvedilol in its optimised liposomal form is directly compared with that of the pure drug to assess the extent of solubility enhancement achieved through liposomal encapsulation.

This study aimed to enhance the solubility of carvedilol by developing an optimised liposomal formulation using the thin-film hydration method.

MATERIALS AND METHODS

Materials

Carvedilol was procured from Shanghai Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) was supplied by Shanghai CarbonBond Chemical Co., Ltd. (Shanghai, China). Hydrogenated soy phosphatidylcholine (HSPC) was obtained from JYOUKI Pharmaceutical Co., Ltd. (Fushun, China). Isopore™ polycarbonate membrane filters (100 nm pore size) were acquired from Merck Millipore Ltd. (Cork, Ireland).

Methods

The optimised liposomal formulation of carvedilol was prepared using the thin-film hydration technique with a Heidolph rotary evaporator [4]. For this composition, 45 mg of DPPC, 18.5 mg of HSPC, and 8 mg of cholesterol were dissolved together with the drug in a chloroform–methanol mixture (2:3 v/v) inside a round-bottom flask [5]. The organic solvents were subsequently removed under reduced pressure at a temperature maintained above the phospholipid phase transition, resulting in the formation of a thin lipid film [6].

The obtained film was hydrated with 10 mL of phosphate buffer while maintaining the flask above the lipid transition temperature, leading to the development of a uniform milky suspension [7]. To reduce vesicle size, the dispersion was extruded 10 times through a polycarbonate membrane filter with a 100 nm pore diameter.

Characterisation of carvedilol liposomes

Measurement of particle size, polydispersity index

Particle size analysis was performed using the ABT-9000 Nano Laser Particle Size Analyser, operated at 25 °C with a scattering angle of 90°. A low polydispersity index (PDI) indicates a monodisperse system, whereas a high PDI value reflects a broad particle size distribution [8]. For lipid-based drug delivery systems, including liposomes and nanoliposomes, a polydispersity index (PDI) not exceeding 0.3 is typically regarded as optimal, as it signifies a uniform and well-dispersed population of phospholipid vesicles [9].

Measurement of zeta potential

The zeta potential of the liposomal formulation was determined using a Zetasizer (Malvern Panalytical, UK). Samples were appropriately diluted with distilled water before measurement, and the analysis was performed at 25 °C with a detection angle of 90° [10].

The charges that are present on the liposome surface are known as the zeta potential. All liposomes in the formulation must carry a surface charge to prevent particle coagulation [11]. This charge repels liposome particles, preventing coagulation. It is necessary to have a zeta potential value that falls between +30 and -30mV. These ranges stop liposomal particles from aggregating [12].

Entrapment Efficiency and Drug Loading

For the selected liposomal formulation, the

entrapment efficiency (EE) and drug loading (DL) were determined after separating the free (non-entrapped) carvedilol by centrifugation. A 2 ml aliquot of the selected formulation was centrifuged at 13,000 rpm for 30 minutes at 4 °C [7].

The supernatant was discarded, and the pellet was disrupted with methanol to release the encapsulated drug. The drug content was quantified using UV spectrophotometry at 285 nm [13]. The EE and DL values of the selected formula were then calculated according to Eqs. 1 and 2:

$$\text{Entrapment efficiency} = \frac{\text{Entrapped drug(mg)}}{\text{Total drug added(mg)}} \times 100$$

$$\text{Loading efficiency} = \frac{\text{Weight of entrapped drug(mg)}}{\text{Weight of liposome(mg)}} \times 100$$

In vitro drug release

The *in vitro* release profile of the selected carvedilol-loaded liposomal formulation was investigated using the dialysis bag diffusion method. A dialysis membrane with a molecular weight cutoff of 14,000 Da was pre-soaked in phosphate buffer (pH 6.8) for 24 h before use to ensure complete hydration and removal of any residual preservatives. The release experiment was conducted in phosphate buffer (pH 6.8) containing 0.1% Tween 80, maintained at 37 ± 0.5 °C under continuous magnetic stirring at 100 rpm [14]. A 2 mL portion of the selected formulation, equivalent to 2 mg of carvedilol, was transferred into the dialysis bag, which was securely sealed before immersion in the release medium. At predetermined time intervals (1, 2, 3, 4, 5, 6, 7, 8, and 14 h), 5 ml of the release medium was withdrawn and replaced with an equal volume of fresh buffer to maintain sink conditions [15]. The concentration of carvedilol released at each interval was quantified by UV–visible spectrophotometry.

X-ray diffraction study

The X-ray diffraction (XRD) patterns of pure carvedilol and the optimised liposomal formulation were obtained using an XRD instrument (Haoyuan, China). The measurements were carried out within an angular range of 2θ = 5°–80°, employing Cu Kα radiation with a wavelength of 1.5406 Å [16].

Field emission scanning electron microscopy

The surface morphology of the selected liposomal formulation was examined using field-emission scanning electron microscopy (FESEM; Inspect™ F50, Japan). Before imaging, the liposomal suspension was dried under a stream of warm air to obtain a sample suitable for analysis. The dried sample was then mounted onto an aluminium stub using conductive carbon tape to ensure firm adhesion and electrical conductivity. To prevent charging effects and improve image resolution, the specimen was sputter-coated with a thin gold layer under vacuum. Micrographs were captured at different magnifications to observe the surface characteristics and morphological features [17].

Solubility studies in pH 6.8 phosphate buffer

The solubility of pure carvedilol and the freeze-dried selected liposomal formulation was evaluated using the shake-flask method in phosphate buffer (pH 6.8). In both cases, 10 mg of carvedilol was dispersed in 10 ml of the dissolution medium and stirred at 99 rpm in a shaking water bath at 37 °C for 48 h. A visual inspection confirmed the presence of undissolved solid drug, indicating that saturation had been achieved. Following equilibration, the suspensions were filtered, and the resulting filtrates were analysed using a UV–visible spectrophotometer to determine the solubility [18].

Stability study of liposomes

The selected carvedilol-loaded liposomal formulation was stored in a tightly closed glass vial at 4 °C for up to 3 months. Samples were withdrawn at predetermined time intervals (1 and 3 months) and analysed for particle size and entrapment efficiency [19].

RESULTS AND DISCUSSION

Particle size and PDI

Particle size analysis of the selected carvedilol-loaded liposomal formulation demonstrated a mean diameter of approximately 90.8 nm with a PDI of 0.031, indicating a highly uniform vesicle population, as shown in Fig. 1.

The nanoscale size of the prepared liposomes is mainly determined by the selected lipid composition and the extrusion through a 100 nm polycarbonate membrane. This process promotes size uniformity by breaking down larger vesicles and limiting the presence of multilamellar structures. The obtained PDI value further

supports this observation, as the extremely low PDI indicates a narrow particle size distribution and a well-dispersed liposomal population, in agreement with previous studies by Kuntsche *et al*., (2010) on membrane extrusion techniques [20].

These experimental findings are in close agreement with the Design-Expert® predictions for the optimised formulation, which estimated a particle size of 90.026 nm and a PDI of 0.03.

Measurement of zeta potential

The zeta potential of the selected carvedilol-loaded liposomal formulation was −15.2 mV, indicating a moderately negative surface charge. This negative charge mainly originates from the ionised phosphate head groups of the phospholipids forming the liposomal bilayer.

Although the magnitude of the zeta potential is relatively moderate, it is sufficient to generate electrostatic repulsion between vesicles, thereby reducing their tendency to aggregate. In addition, such zeta potential values are commonly reported for phosphatidylcholine-based liposomal systems prepared without the incorporation of charged stabilising agents. Under these conditions, vesicle size uniformity and low polydispersity can also help maintain colloidal stability.

Therefore, the observed zeta potential value further supports the successful formation of a stable nanosized liposomal dispersion.

Entrapment Efficiency and Drug Loading

The entrapment efficiency (EE%) and drug loading (DL%) of the selected carvedilol-loaded liposomal formulation were determined to evaluate the formulation's drug encapsulation capacity. The results showed an entrapment efficiency of 86.5% and a drug loading of 10.61%, indicating effective incorporation of carvedilol into the liposomal matrix.

The high EE and DL values can be explained by carvedilol's strong affinity for the lipid bilayer, which is mainly due to its lipophilic character and favourable interactions with phospholipids. Such interactions facilitate drug partitioning into the hydrophobic regions of the bilayer during liposome formation. Moreover, increasing the concentration of cholesterol also contributed positively, likely due to its role in enhancing bilayer stability and reducing membrane permeability, as reported by El-Nesr *et al*., (2010) for cholesterol-containing liposomal systems [21].

In addition, the experimental EE and DL values were in close agreement with those predicted by the Design-Expert® optimisation model (EE: 88.25%, DL: 10.89%), supporting the accuracy and reliability of the selected formulation and the

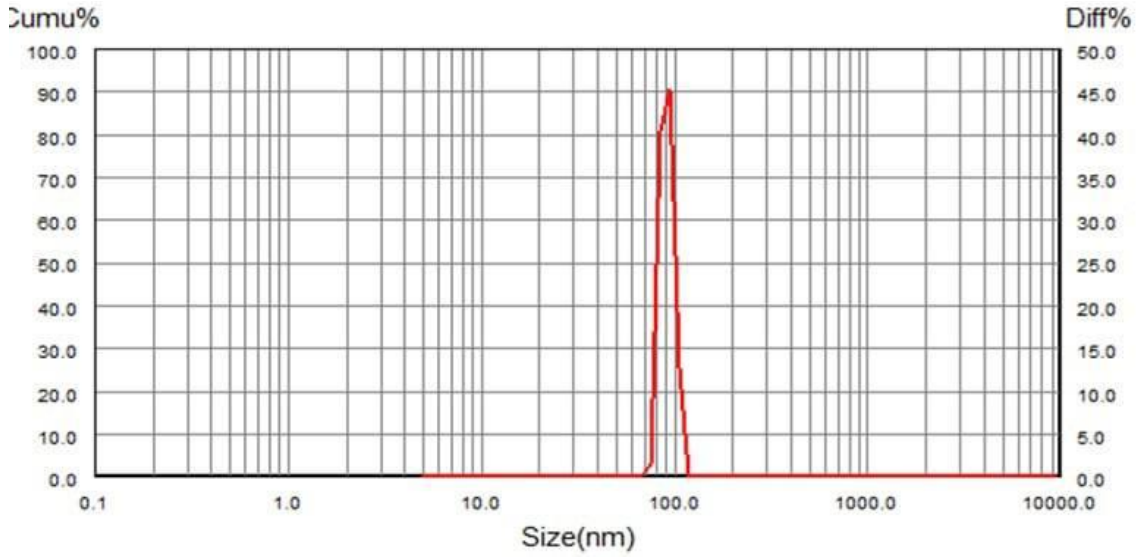

Fig. 1. Particle size distribution curve of the selected carvedilol-loaded liposomal formulation showing a narrow peak around ~91 nm.

applied optimisation approach.

In vitro drug release

The *in vitro* release profile of the selected carvedilol-loaded liposomal formulation (45 mg DPPC, 18.5 mg HSPC, and 8 mg cholesterol) exhibited a biphasic pattern, characterised by a sustained release period, with cumulative drug release of 83.1% achieved after 14 h.

This release extent was slightly lower than that reported for formulations F16-F17 (87.29% at 14 h) but higher than that of formulations F6-F7 (77.44% at 14 h), as previously reported for these formulations [3].

The relatively sustained release behaviour of the selected formula can be attributed to its high cholesterol content (8 mg), which enhances bilayer rigidity and retards drug diffusion, while the reduced HSPC proportion (18.5 mg) compared with formulations containing 45 mg HSPC improves membrane permeability and prevents excessive retardation. Consequently, the selected formulation achieved an intermediate release rate between the faster-releasing F16 = F17 and the more sustained F6 = F7 formulations, as illustrated in Fig. 2.

These findings confirm that both the ratio of saturated to unsaturated phospholipids and cholesterol concentration play crucial roles in modulating drug diffusion kinetics from liposomal vesicles. The selected formulation thus provides a balanced release profile, maintaining prolonged drug release while preventing overly slow diffusion that may limit bioavailability.

X-ray diffraction study

The XRD diffractogram of pure carvedilol showed multiple sharp, intense peaks in the 2θ range of 10–35°, indicating its crystalline nature. Distinct characteristic peaks were observed at 2θ angles of 11.97°, 13.85°, 17.42°, 19.38°, 23.38°, 25.36°, 28.41°, 33.18°. These diffraction features are in close agreement with previously reported XRD patterns of pure carvedilol, where Kar *et al.*, (2024) identified prominent peaks at11.66°, 12.94°, 17.52°, 19.24°, 23.53°, 25.27°, 28.04°, and 34.12°, further confirming the crystalline structure of the pure carvedilol [16].

In contrast, the selected liposomal formulation showed a significant reduction in both the intensity and sharpness of the diffraction peaks, suggesting that carvedilol transformed into an amorphous or partially amorphous form upon encapsulation (Fig. 3). This transformation not only verifies the successful incorporation of carvedilol into the liposomal matrix but also supports

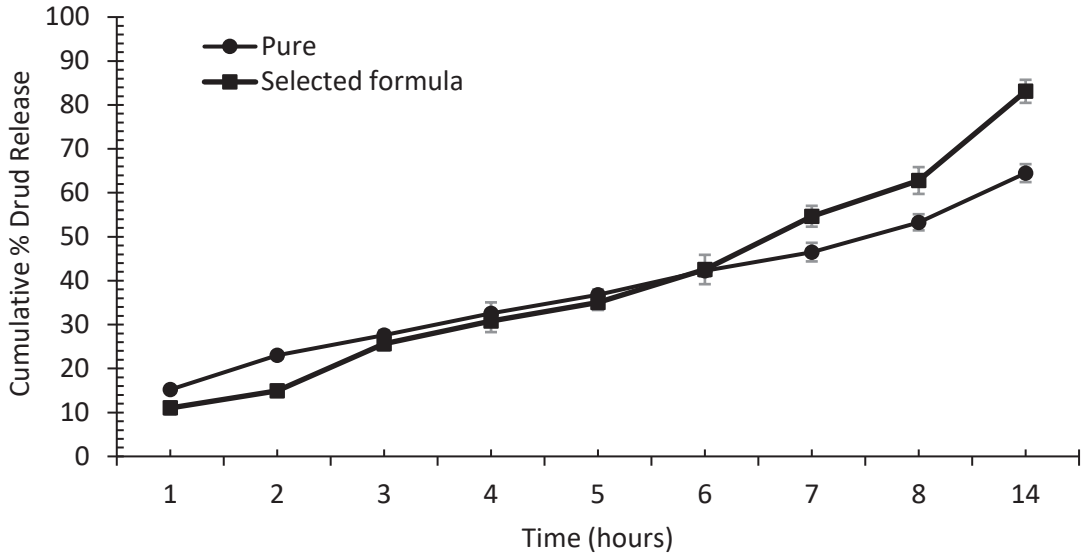

Fig. 2. *In vitro* release profile of carvedilol from the selected liposomal formulation and pure drug suspension in phosphate buffer pH 6.8.

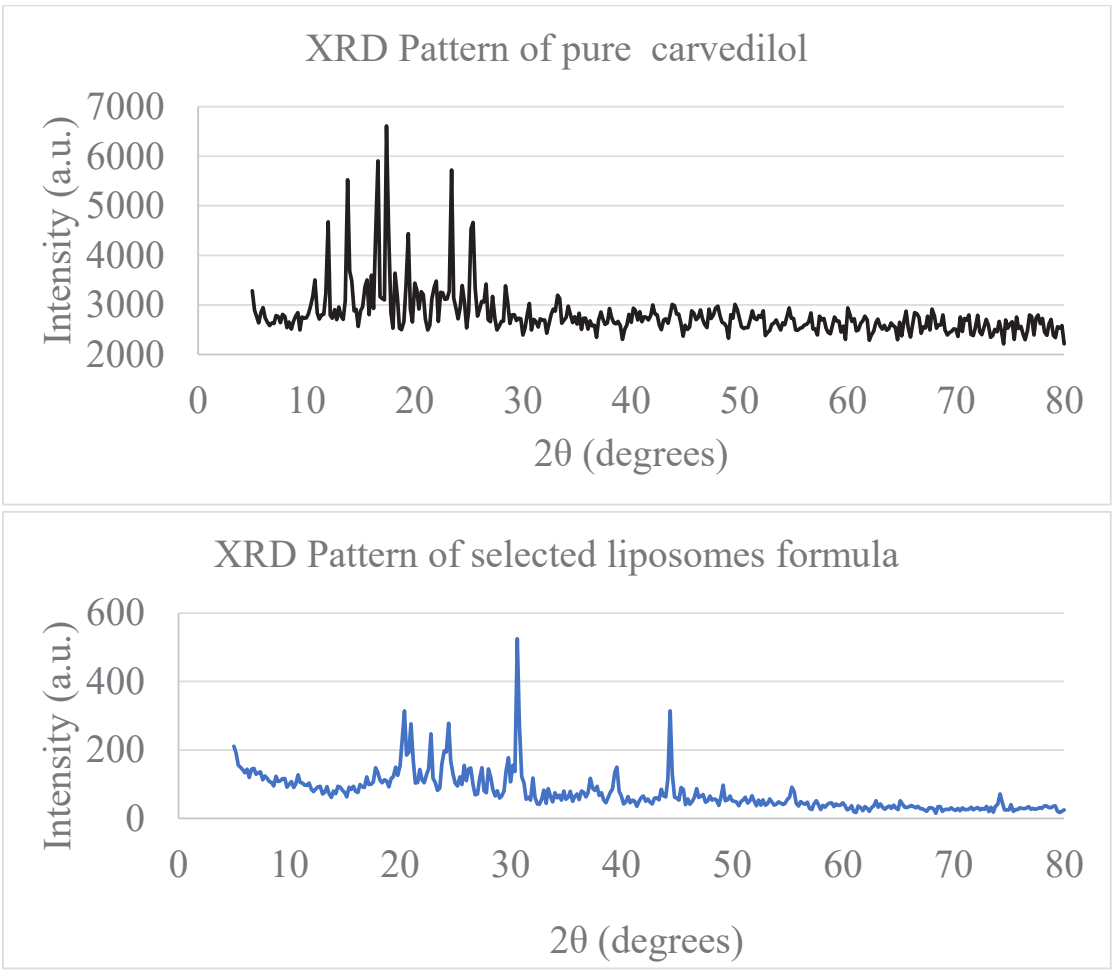

Fig. 3. XRD diffractograms of pure carvedilol (top) and selected liposomal formulation (bottom).

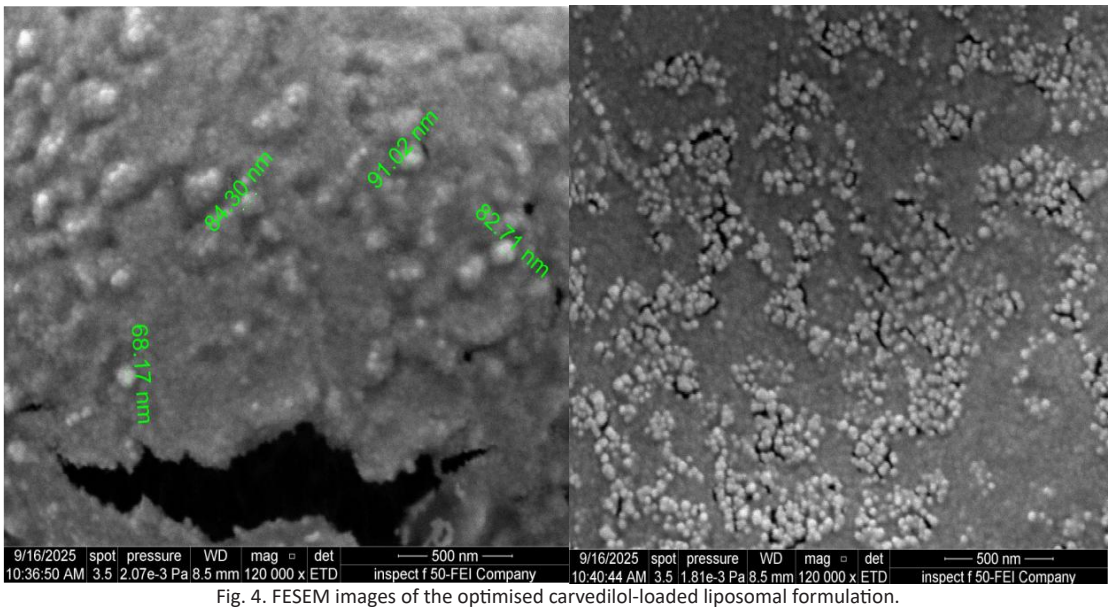

Fig. 4. FESEM images of the optimised carvedilol-loaded liposomal formulation.

the enhancement of its solubility potential, as the amorphous state is generally associated with improved dissolution and higher aqueous solubility compared to the crystalline state.

Field emission scanning electron microscopy

The FESEM images further confirmed the nanoscale dimensions of the optimised liposomal formulation, with spherical vesicles in the ~80–100 nm range, as shown in Fig. 4. The observed morphology indicates the successful formation of well-defined liposomal vesicles with smooth and relatively uniform surfaces.

These findings were in close agreement with the particle sizes measured by dynamic light scattering (DLS) and the values predicted by the Design-Expert® optimisation model (~91 nm). Minor variations between FESEM and DLS measurements can be attributed to differences in measurement principles, as FESEM provides dry-state particle images. In contrast, DLS reflects the hydrodynamic diameter of vesicles in dispersion.

Overall, the FESEM results corroborate the effectiveness of the optimisation strategy and further validate the structural integrity and nanoscale characteristics of the selected liposomal formulation.

Solubility studies in pH 6.8 phosphate buffer

The apparent solubility of carvedilol in phosphate buffer (pH 6.8, 37 °C) was found to be 0.0863 mg/ml. This value is comparable to that reported by Tushar *et al*. (2014), who found the solubility of pure carvedilol in pH 6.8 buffer to be 0.092 ± 0.010 mg/ml [22].

The apparent solubility of the selected carvedilol-loaded liposomal formulation in phosphate buffer (pH 6.8, 37 °C) was found to be 0.1053 mg/ml, which represents an improvement of approximately 22% compared to pure carvedilol (0.0863 mg/ml).

This enhancement can be attributed to the encapsulation of carvedilol within the liposomal bilayer, combined with the formulation's nanoscale particle size. The reduction in particle size increases the effective surface area available for interaction with the dissolution medium, in accordance with the Noyes–Whitney equation, thereby enhancing the drug–medium contact and reducing the diffusion layer thickness surrounding the particles. Consequently, these factors facilitate improved dissolution behaviour and maintain carvedilol in a more readily solubilised state, thereby increasing apparent solubility.

Stability study of liposomes

The stability of the selected carvedilol-loaded liposomal formulation was evaluated by monitoring particle size and entrapment efficiency (EE %) during storage at 4 °C for up to 3 months. Samples were withdrawn at predetermined time

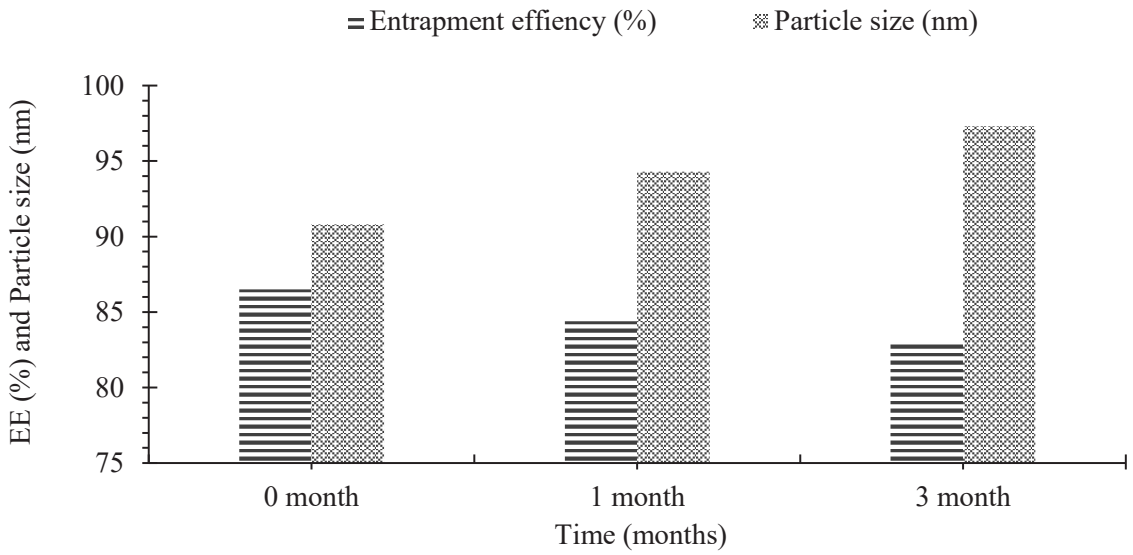

Fig. 5. Effect of storage on entrapment efficiency and particle size of carvedilol-loaded liposomes.

intervals (0, 1, and 3 months) and analysed to assess any variations that might indicate physical or chemical instability of the vesicles. The results are presented in Fig. 5.

A gradual decrease in EE% and a slight increase in particle size were observed during storage, indicating minor aggregation and drug leakage; however, the magnitude of these changes remained within acceptable limits, thereby maintaining overall formulation stability.

CONCLUSION

The present study has successfully demonstrated that liposomal encapsulation constitutes a practical method to enhance the solubility and release performance of carvedilol, a β-blocker characterised by poor water solubility. The optimised liposomal formulation, prepared via the thin-film hydration technique utilising DPPC, HSPC, and cholesterol, yielded nanosized spherical vesicles with a uniform distribution and satisfactory stability. These findings substantiate that liposomes can function as an effective carrier system for carvedilol, thereby augmenting its aqueous solubility and facilitating a more controlled drug-release profile. Consequently, this approach signifies a promising strategy for the delivery of poorly soluble drugs through liposomal encapsulation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Hafez MA, Mahmoud MF, Ibrahim IA. Carvedilol: New pharmacological approaches. Zagazig Journal of Pharmaceutical Sciences. 2024;33(2):1-21.
2. Jhaveri M, Nair AB, Shah J, Jacob S, Patel V, Mehta T. Improvement of oral bioavailability of carvedilol by liquisolid compact: optimization and pharmacokinetic study. Drug Delivery and Translational Research. 2020;10(4):975-985.
3. Zare-Zardini H, Saberian E, Jenča A, Jenča A, Petrášová A, Jenčová J, et al. Development and In Vivo evaluation of liposomal fentanyl nanocarriers using thin-film hydration and AI-based characterization for enhanced analgesic efficacy in anesthesia. Sci Rep. 2025;15(1).
4. Pattni BS, Chupin VV, Torchilin VP. New Developments in Liposomal Drug Delivery. Chem Rev. 2015;115(19):10938-10966.
5. Joshi H, Shelat P, Dave D. Development and Characterization of Liposomal formulation for ophthalmic delivery of Prednisolone Acetate. International Journal of Pharmaceutical Sciences and Drug Research. 2020:175-180.
6. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: structure, composition, types, and clinical applications. Heliyon. 2022;8(5):e09394.
7. Godbole MD, Mathur VB. Selection of Phospholipid and Method of Formulation for Optimum Entrapment and Release of Lamivudine from Liposome. Journal of Drug Delivery and Therapeutics. 2018;8(5-s):175-183.
8. Al-Edresi S, Albo Hamrah K, Al-Shaibani A. Figure 5 from: Al-Edresi S, Albo Hamrah K, Al-Shaibani A (2024) Formulation and validation of Candesartan cilexetil-loaded nanosuspension to enhance solubility. Pharmacia 71: 1-13. https://doi.org/10.3897/pharmacia.71.e114943. Pensoft Publishers; 2024.
9. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of Particle Size and Polydispersity Index on the Clinical Applications of Lipidic Nanocarrier Systems. Pharmaceutics. 2018;10(2):57.
10. Janga KY, Jukanti R, Velpula A, Sunkavalli S, Bandari S, Kandadi P, et al. Bioavailability enhancement of zaleplon via proliposomes: Role of surface charge. Eur J Pharm Biopharm. 2012;80(2):347-357.
11. Shawka Al-Asadi LJA, Al-Edresi S. Reduction of Time and Cost in Preparation of Nanofibers from Pva, Peo and Hpmc Using Design-Expert® Software. International Journal of Applied Pharmaceutics. 2024:257-266.
12. Umbarkar M, Thakare S, Surushe T, Giri A, Chopade V. Formulation and Evaluation of Liposome by Thin Film Hydration Method. Journal of Drug Delivery and Therapeutics. 2021;11(1):72-76.
13. Abdelwahab NS. Spectrophotometric methods for simultaneous determination of Carvedilol and Hydrochlorothiazide in combined dosage form. Arabian Journal of Chemistry. 2016;9:S355-S360.
14. Ghassemi S, Haeri A, Shahhosseini S, Dadashzadeh S. Labrasol-Enriched Nanoliposomal Formulation: Novel Approach to Improve Oral Absorption of Water-Insoluble Drug, Carvedilol. AAPS PharmSciTech. 2018;19(7):2961-2970.
15. R. Atiyah S, Al-Edresi S. Preparation and Justification of Nanofibres-Loaded Mafenide Using Electrospinning Technique to Control Release. International Journal of Applied Pharmaceutics. 2024:224-230.
16. Intranasal Delivery of Carvedilol- and Quercetin-Encapsulated Cationic Nanoliposomes for Cardiovascular Targeting: Formulation and In Vitro and Ex Vivo Studies. American Chemical Society (ACS). http://dx.doi.org/10.1021/acsabm.4c00102.s001
17. Hu Y, Zhang J, Dong L, Xu L, Chen E. DOX-loaded mesoporous hydroxyapatite modified by hyaluronic acid can achieve efficient targeted therapy for lung cancer. Journal of Drug Targeting. 2023;31(6):612-622.
18. Abed MR, Abood AN. Preparation and In vitro Evaluation of Cinnarizine Nanosuspension for Enhancement of Solubility and Dissolution Rate. Karbala Journal of Pharmaceutical Sciences. 2025;15(25):68-85.
19. Aboud HM, El komy MH, Ali AA, El Menshawe SF, Abd Elbary A. Development, Optimization, and Evaluation of Carvedilol-Loaded Solid Lipid Nanoparticles for Intranasal Drug Delivery. AAPS PharmSciTech. 2016;17(6):1353-1365.
20. Kuntsche J, Freisleben I, Steiniger F, Fahr A. Temoporfin-loaded liposomes: Physicochemical characterization. Eur J Pharm Sci. 2010;40(4):305-315.
21. El-Nesr OH, Yahiya SA, El-Gazayerly ON. Effect of formulation design and freeze-drying on properties of fluconazole multilamellar liposomes. Saudi Pharmaceutical Journal. 2010;18(4):217-224.
22. Durge N, Parida K. Formulation and Evaluation of Nimodipine Tablet by Liquisolid Technique. International Journal of Trend in Scientific Research and Development. 2019;Volume-3(Issue-4):739-745.