**RESEARCH PAPER**

# Nanostructured Liposomal Formulation of A-Arbutin for Improved Encapsulation and Sustained Drug Release

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**ABSTRACT**
The present study aimed to develop and characterize α-arbutin-loaded liposomal formulations for enhanced topical drug delivery. α-Arbutin-loaded liposomes were prepared using the reverse-phase evaporation technique and evaluated for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, surface morphology, FTIR, P-XRD, and in vitro drug release. The prepared liposomes exhibited nanometric particle sizes ranging from 446–460 nm with acceptable PDI values and negative zeta potential, indicating good colloidal stability. The formulation demonstrated high entrapment efficiency (90.45 ± 4.76%) and satisfactory drug loading (12.86 ± 0.98%). SEM analysis confirmed spherical vesicular morphology, while FTIR and P-XRD studies revealed successful encapsulation of α-arbutin without chemical degradation and conversion of crystalline arbutin into an amorphous form. In-vitro drug release studies showed significantly enhanced and sustained release from liposomes compared to free drug solution. Overall, the developed liposomal system represents a promising carrier for improved topical delivery of arbutin.

**Keywords:** α-Arbutin. Liposomes, Reverse-Phase Evaporation Techniques
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## INTRODUCTION

Topical delivery of bioactive substances is a powerful strategy to reduce systemic toxicity, and in recent years, several researchers have focused on the skin as a target site. (Zhao et al., 2024) The major problem with efficient drug delivery through the skin is its structure, as the stratum corneum primarily prevents the active compound from reaching deeper layers of the skin.(Esposito et al., 2024)

Among the several evaluated biomembrane models, liposomes have been widely studied for their properties as biomembrane models and as potential drug delivery systems. They have become valuable experimental and commercially important drug delivery systems due to their biodegradability, biocompatibility, low toxicity, and ability to entrap both lipophilic and hydrophilic drugs.(Beigi et al., 1998; Daniel et al., 2026; Selivanovitch et al., 2024) The application of liposomes has been reported to offer the advantages of enhancing drug efficacy and potency by reducing the toxicity of encapsulated drugs, targeting specific tissue sites, and controlling the timing and amount of drug release.(Pande, 2023)

Thus, liposomes are excellent formulations for drug and cosmetic carriers.(Wang et al., 2023) Liposomes can be used as slow-release drug delivery vehicles in extravascular regions, such as the skin, by direct application at the site of action. The potential use of liposomes as carriers via the transdermal route has been well documented.(Matharoo et al., 2024; Montanari et al., 2026; Xing et al., 2024; Xing et al., 2025) Despite reports that liposomes cannot carry drugs across the skin, the use of liposomes to enhance drug absorption has been extensively reviewed.(Y. Li et al., 2022)

α-Arbutin (hydroquinone-D-glucopyranoside, AR) is an *O*-glycosylated hydroquinone (Fig. 1) that has been found at high concentrations in the leaves of several plant species, such as Vaccinium spp. It is widely known as a skin-whitening agent and effectively inhibits tyrosinase activity and melanin formation in the skin.(Z. Li et al., 2025; Qiu et al., 2025; Shu et al., 2024) However, the formidable barrier property of the stratum corneum and the high hydrophilicity of α-Arbutin (log P value: -1.49) make it difficult to permeate the skin and reach its site of action (i.e., melanocytes). In many cases, traditional formulations, such as ointments and lotions, failed to

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achieve sufficient α-Arbutin deposition on the skin. Thus, the present study reports the development of liposomal formulations for α-Arbutin, prepared by the chloroform film method with sonication. The characteristics of the α-Arbutin liposomes and their in vitro skin permeation and skin deposition behavior were systematically observed and compared with those of aqueous solutions as a control.

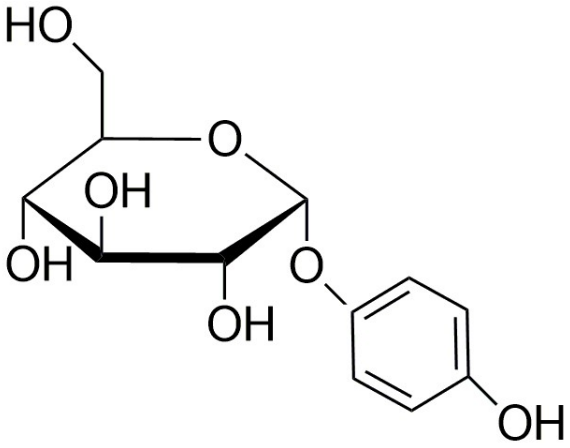



**Figure 1:** α-Arbutin structure

## MATERIAL AND METHODS

### 1. Materials

α-Arbutin, phospholipids, methanol, chloroform, diethyl ether, phosphate-buffered saline (PBS, pH 7.4), and all analytical solvents and reagents were used as provided in the formulations procured from Sigma Aldrich. Calibration for entrapment efficiency was performed using α-arbutin standards (20–100 µg/mL) with the vanillin–perchloric acid colorimetric method.

### 2. Preparation of α-Arbutin-Loaded Liposomes

Liposomes were prepared using the reverse-phase evaporation technique (REV). Phospholipids (200 mg) were dissolved in 10 mL of ethanol: chloroform (1:2, v/v). The lipid solution was rotary evaporated at 60°C and 150 rpm to form a thin, dry lipid film on the inner surface of the flask. The film was dissolved using 12 mL of diethyl ether. An aqueous phase containing 50 mg α-arbutin in 6 mL PBS (pH 7.4) was added to form a water-in-ether emulsion. The emulsion was subjected again to rotary evaporation under reduced pressure (150 rpm, 60°C) until the formation of liposomal vesicles. 4 mL of PBS (pH 7.4) was added, and the system was hydrated for 1 h at 60°C under rotation. The liposomal suspension was sonicated for 1 h at 40°C to reduce the vesicle particle size. Liposomes were stored in amber glass vials at 4°C prior to characterization.(Hatem et al., 2024)

### 3. Characterization of α-Arbutin-Loaded Liposomes

#### a) Particle size, PDI & Zeta-potential

Dynamic Light Scattering (DLS) was used to measure particle size, polydispersity index, and surface charge following liposomal characterization standards.(Large et al., 2021)

#### b) Entrapment Efficiency & Drug Loading

Liposome suspensions were centrifuged at 12,000 g for 1 hour at 4°C to separate the unencapsulated drug.(Gao et al., 2026) The supernatant was analysed using the vanillin–perchloric acid assay for α-arbutin quantification. EE% was calculated as:

EE% = (Encapsulated α-arbutin / Total α-arbutin added) × 100

Drug loading parameters followed standard liposomal calculations described for a similar system.(Yan et al., 2021)

#### c) SEM observation

The morphology of the freeze-dried liposomes was analysed by scanning electron microscopy (SEM). This will confirm the liposomes' surface morphology.

#### d) FTIR study

Fourier-transform infrared spectroscopy was used to assess lipid membrane composition and detect possible chemical interactions or lipid degradation, following established liposomal FTIR protocols.(Large et al., 2021)

#### e) P-XRD

Powder X-ray diffraction was used to examine the physical state of entrapped α-arbutin, with amorphization behavior comparable to α-arbutin vesicular systems.(Radmard et al., 2021)

#### f) In vitro drug release

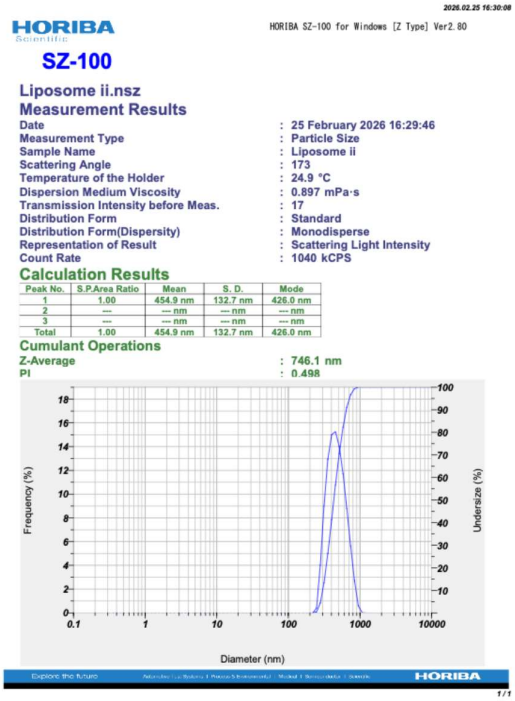
The in vitro drug release profiles of the liposomal formulation and the plain drug solution were investigated using the dialysis bag method in phosphate-buffered saline (PBS) media. Phosphate buffer saline (PBS) media and the dialysis bag method were used to examine the in vitro drug release characteristics of the liposomal formulation and the plain drug solution. A dialysis bag was filled with the samples (2 mL of liposomes or a drug solution

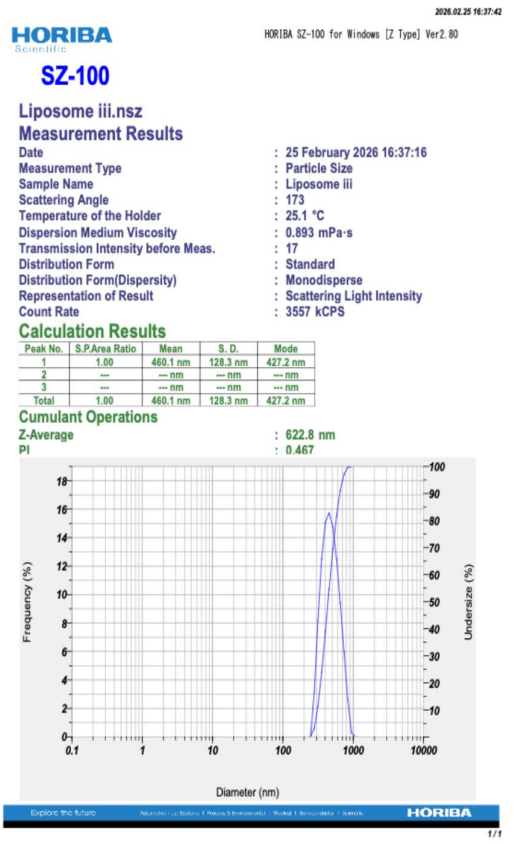
containing 5 mg of medication). After that, 50 mL of PBS was added to the bag. The containers were covered with aluminum foil to keep out light while the release research was conducted for 48 hours at 37°C with moderate stirring at 100 rpm. Two-milliliter aliquots were removed from the beaker and replaced with an equivalent volume of brand-new PBS at prearranged intervals. All buffered solutions outside the dialysis bag were replaced with new ones at 8, 24, and 48 hours. The drug release profile was evaluated by the same procedure.(Fazel et al., 2018)

## 3. RESULTS

### 3.1. Particle size, PDI & Zeta-potential

Dynamic light scattering analysis demonstrated that the α-arbutin-loaded liposomal formulations had particle sizes in the nanometric range and acceptable distribution profiles. Liposome I exhibited a mean particle size of 446.9 ± 138.1 nm with a Z-average diameter of 686.9 nm and a PDI of 0.433, whereas Liposome II showed a particle size of 454.9 ± 132.7 nm, Z-average of 746.1 nm and PDI of 0.498. Liposome III has a particle size of 460.1 ± 128.3 nm and PDI of 0.467. A PDI less than 0.5 indicates a moderate vesicle dispersity index (Fig 2).





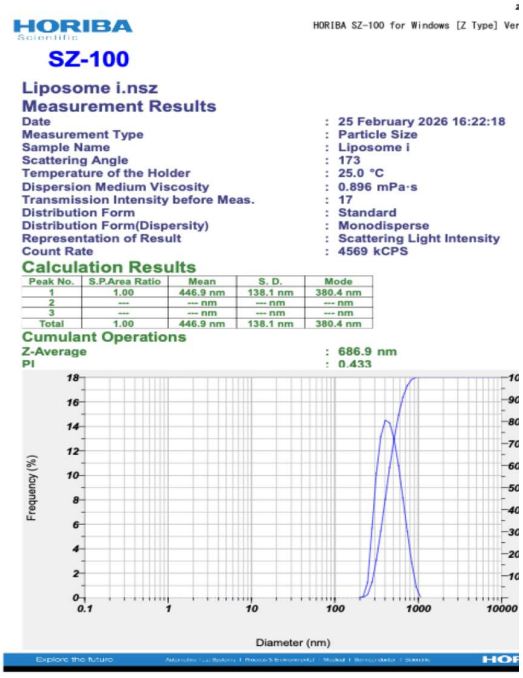
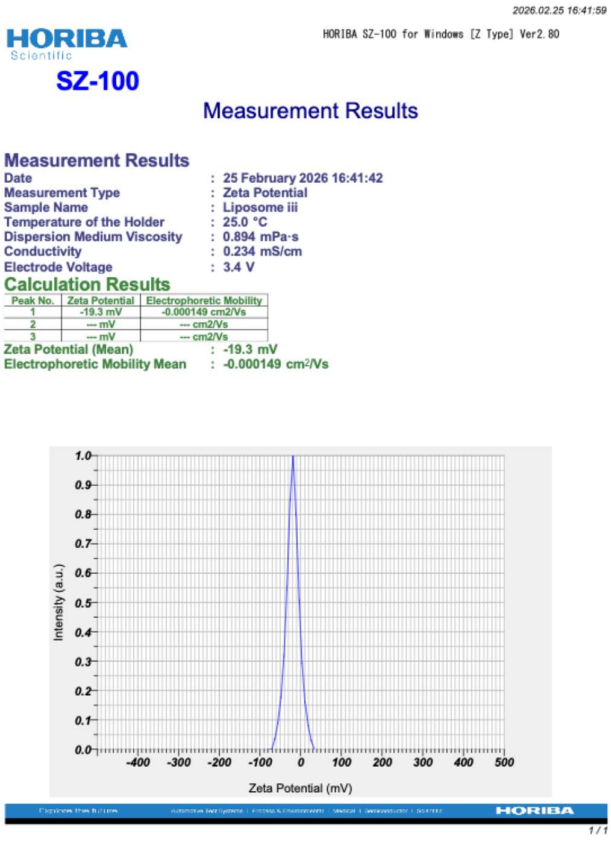



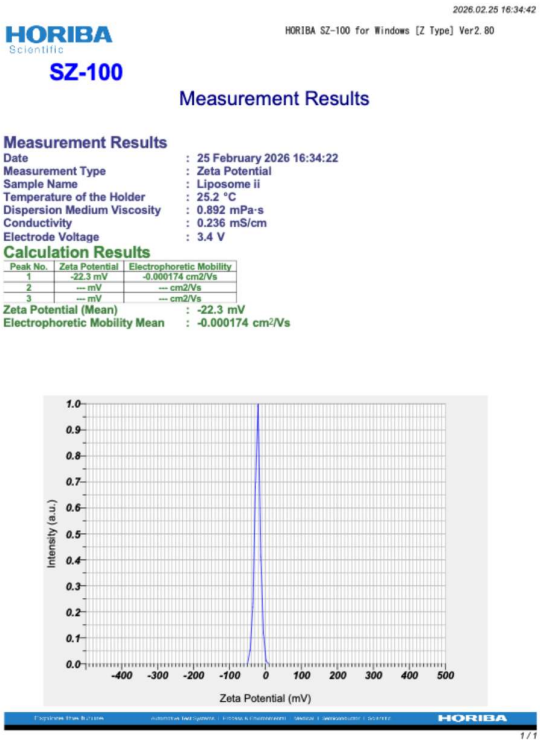

**Figure 2:** Particle size of liposome I, II and III

Zeta potential revealed negative charges for all the Liposomes I, II and III values of −26.4 mV, −22.3 mV, and −19.3 mV, respectively (Table 1; Fig 3). The negative charges indicate sufficient electrostatic repulsion between vesicles, leading to colloidal stability. Liposome I exhibits greater stability due to its higher negative charge and lower dispersity index.

**Table 1:** α-Arbutin loaded formulations

| Formulation | Particle Size (nm) (Mean ± SD) | Z-Average (nm) | PDI | Zeta Potential (mV) (Mean ± SD*) |
|---|---|---|---|---|
| Liposome I | **446.9 ± 138.1** | 686.9 | 0.433 | **−26.4 ± 0.0** |
| Liposome II | **454.9 ± 132.7** | 746.1 | 0.498 | **−22.3 ± 0.0** |
| Liposome III | **460.1 ± 128.3** | 622.8 | 0.467 | **−19.3 ± 0.0** |





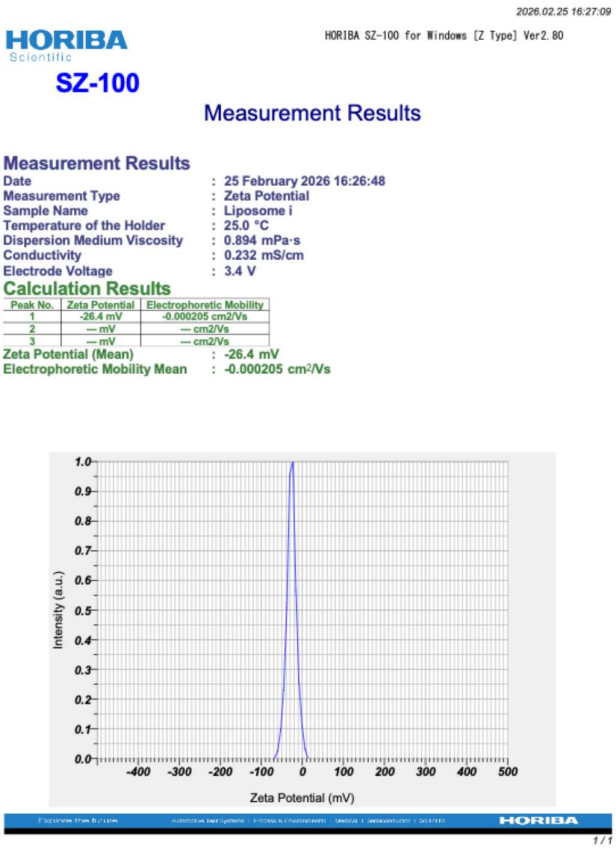




**Figure 3:** Zeta potential of liposomes I, II and III

### 3.2. Entrapment Efficiency% & Drug Loading%

The α-arbutin-loaded liposomal formulations demonstrated high drug incorporation efficiency, suggesting that arbutin was encapsulated within the lipid bilayer. The results showed that the DL was 12.86 ±0.98% and the EE was 90.45 ± 4.76% (Table 2). Greater drug retention and reduced loss during liposome production are suggested by the higher arbutin loading. Encapsulation efficiency has also been used to measure the increased interaction between the medication and the lipid matrix. In relation to the overall phospholipid content, the loading capacity shows good assimilation of the active arbutin molecule. These liposomes, produced for effective encapsulation and sufficient loading capacity, are beneficial for regulated and prolonged release and improved therapeutic efficacy.

**Table 2:** Entrapment Efficiency & Drug Loading of α-Arbutin-loaded formulations

| Parameter | Value (Mean ± SD) |
|---|---|
| Entrapment Efficiency (%) | **90.45±4.76** |
| Drug Loading (%) | **12.86±0.98** |

### 3.3. SEM Observation

The suspension of drug-loaded liposomes was freeze-dried and examined by scanning electron microscopy to assess their surface morphology in the solid state. The microscopy images of liposomes show a spherical shape, as shown in the figure 4.

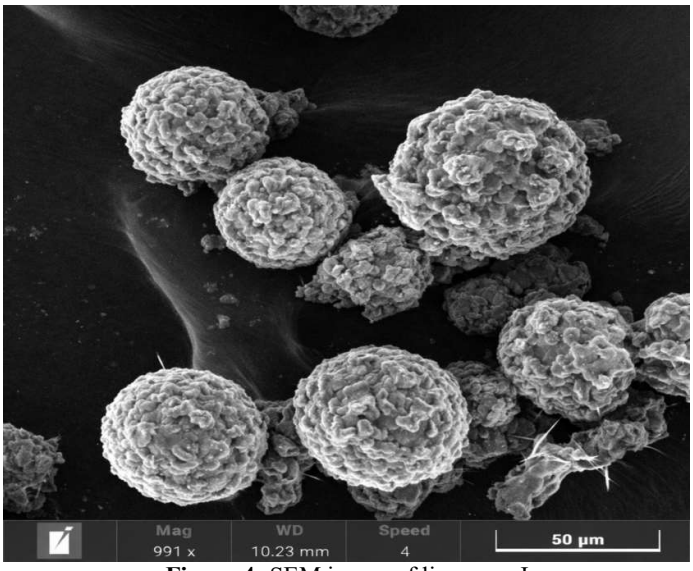



**Figure 4:** SEM image of liposome I

### 3.4. FTIR study

The FTIR spectrum was recorded to evaluate possible interactions between the drug and the liposomal excipients The spectrum of α-arbutin-loaded liposomes shows characteristic absorption peaks corresponding to functional groups in the drug and excipients (Fig 5).

The presence of hydroxyl groups in α-arbutin and the lipid matrix is indicated by a large peak between 3716 and 3440 $cm^{-1}$, corresponding to O–H stretching vibrations. The C–H stretching of aliphatic chains seen in the lipid bilayer matrix is responsible for the signal at 2934 $cm^{-1}$. The aromatic ring structure of arbutin is characterized by C=C or C=O stretching vibrations, which are represented by a prominent absorption band seen at 1658 $cm^{-1}$. C–H bending vibrations are linked to additional peaks at 1448 $cm^{-1}$ and 1369 $cm^{-1}$, whereas C–O stretching vibrations of phenolic groups are linked to peaks at 1294 $cm^{-1}$ and 1222 $cm^{-1}$. Additional peaks at 1085 $cm^{-1}$ and 1002 $cm^{-1}$ indicate C–O–C stretching vibrations, confirming the presence of a glycosidic linkage in arbutin. The peaks at 926 $cm^{-1}$, 824 $cm^{-1}$, and 705 $cm^{-1}$ are attributed to aromatic ring bending vibrations. Overall, the FTIR spectrum of α-arbutin-loaded liposomes showed the presence of all characteristic functional groups, without significant peak shifts or disappearance, indicating successful encapsulation of α-arbutin within the liposomal system and no chemical interaction or drug degradation.

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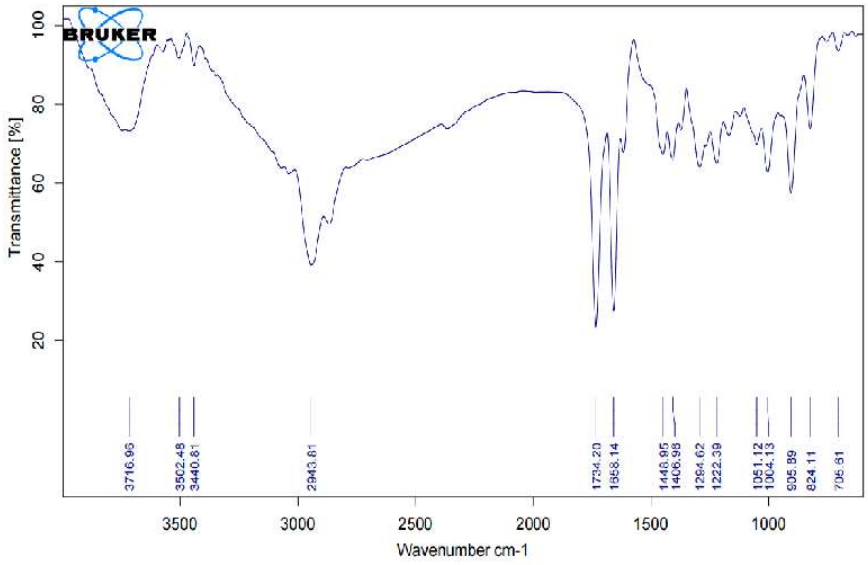


**Figure 5:** FTIR spectra of liposome I

### 3.5. P-XRD

The X-ray diffraction (XRD) pattern of the α-arbutin-loaded liposomal formulation was analysed to determine the physical state (crystalline or amorphous nature) of α-arbutin within the lipid matrix (fig 6). The diffractogram showed a diffraction peak centred at 2θ ≈ 20–25°, characteristic of an amorphous rather than a crystalline phase. The absence of sharp and intense crystalline peaks in the diffractogram indicates that arbutin is molecularly dispersed or encapsulated within the liposomal lipid bilayer. Pure α-arbutin generally exhibits distinct crystalline peaks; however, these peaks were not clearly observed in the liposomal formulation, suggesting that the drug has lost its crystalline nature during liposome preparation. The broad halo pattern observed in the diffractogram confirms the amorphous nature of the lipid matrix and successful incorporation of α-arbutin into the liposomal system. This transformation from crystalline to amorphous form may enhance the formulation's drug solubility and bioavailability. Overall, the XRD results support the successful encapsulation of α-arbutin drug in liposomes without the formation of separate crystalline drug particles.

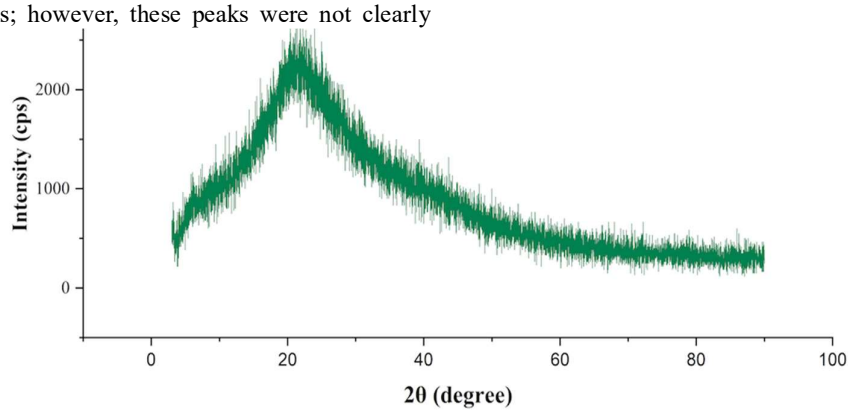


**Figure 6:** XRD pattern of α-arbutin loaded liposome formulation

### 3.6. In vitro drug release

The drug release profile of the liposome and plain drug solution has been performed by using the dialysis bag method using phosphate buffer saline for 48 hours. The results show a time-dependent increase in a cumulative drug release for both samples, but the highest drug release is shown by the liposomes formulation, i.e. 94.89 ± 9.45%, because the drug solution showed lower release, i.e. 29.67 ± 4.89%, as compared to the liposomal formulation at 48 hours (Fig 7). This improved behaviour in drug release of the liposomal system may be due to the efficient encapsulation and controlled drug diffusion from the bilayer of lipid matrix. Overall, the results indicate that the liposome provides good drug release properties compared to a free drug solution, suggesting its role in improved drug delivery and therapeutic efficacy.

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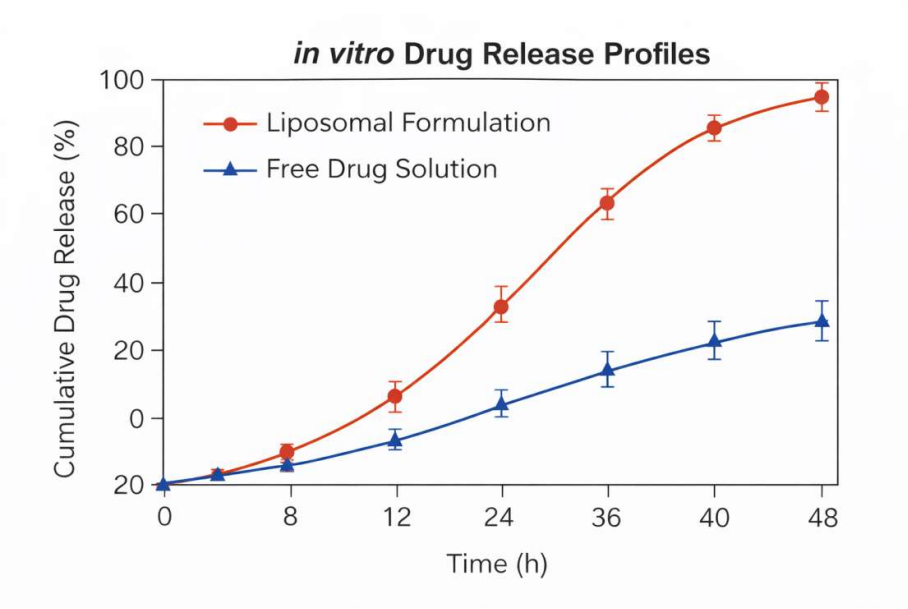


**Figure 7:** Drug release profile of the liposome and plain drug solution

## CONCLUSION

The present study successfully developed and characterized α-arbutin-loaded liposomal formulations using the reverse-phase evaporation technique for enhanced topical drug delivery. The prepared liposomes exhibited nanometric particle size with acceptable polydispersity and sufficient zeta potential, indicating good colloidal stability. High entrapment efficiency (90.45 ± 4.76%) and satisfactory drug loading (12.86 ± 0.98%) confirmed the effective incorporation of α-arbutin within the lipid vesicles. SEM analysis demonstrated spherical vesicular morphology, while FTIR studies revealed successful encapsulation of α-arbutin without any significant chemical interaction or degradation. P-XRD analysis indicated the transformation of crystalline α-arbutin into an amorphous form within the lipid matrix, which may contribute to enhanced solubility and bioavailability. Furthermore, the liposomal formulation exhibited significantly improved and sustained in vitro drug release compared to the free drug solution, demonstrating its potential as an efficient controlled-release topical delivery system. Overall, the developed α-arbutin-loaded liposomes may serve as a promising nanocarrier platform for improved skin delivery, enhanced therapeutic efficacy, and cosmetic applications in skin depigmentation therapy.

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**Declaration of Interest:** The authors declare no potential conflict of interest.

**Author Contribution:** Shalini Juglan, Peeush Singhal and Neha Sodiyal: Conceptualization, investigation, formulation development, characterization studies, data collection, analysis, and manuscript drafting; Pankaj Sharma and Shivanand Patil: Technical support, data analysis, and manuscript review; Kapil Kumar Goel: Research supervision, validation of results, data interpretation, critical review, and final approval of the manuscript.

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