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RESEARCH PAPER

Preparation and study of the inhibitory effect of nano-niosomes containing essential oil from artemisia absinthium on amyloid fibril formation

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ABSTRACT

Objective(s): Artemisia absinthium is an aromatic, perennial small shrub that shows multiple medical benefits, including anticancerous, neuroprotective, antifungal, hepatoprotective, antidepressant and antioxidant properties. One of the effective approaches to treat Alzheimer's disease is targeting amyloid aggregation by antiamyloid drugs. In the current research study, an excellent grouping of niosomal, lipid nano-carriers drugs containing artemisia absinthium is advanced and characterized to inhibit amyloid aggregation.

Materials and Methods: Niosomal vesicles were made employing phosphatidylcholine, span 60, cholesterol and DSPE-PEG2000 by the thin-film method. Then artemisia absinthium was loaded into the niosomes. Their physico-chemical attributes were analyzed utilizing Zeta-Sizer, FTIR, and SEM, and the amount of drug release was measured at 37° C. Finally, the inhibitory effect of artemisia absinthium that loaded niosomal vesicles on the aggregation of amyloid-β peptides was investigated using Thioflavin T fluorescence measurements and atomic force microscopy.

Results: Niosomes containing artemisia absinthium have a size of 174±2.56nm, the encapsulation efficiency of 66.73%, zeta potential of -26.5±1/42 mV and polydispersity index (PDI) of 0.373±0/02. The release of the drug is controlled in this nano-carrier and FTIR and SEM investigations showed that the drug and nano-carrier did not interact and their particles had a spherical structure. In the end, the inhibitory effect of artemisia absinthium that loaded niosomal vesicles on the aggregation of amyloid-β peptides was examined and confirmed through Thioflavin T fluorescence measurements and atomic force microscopy.

Conclusion: Meanwhile, the findings of the current study, confirm the appropriate physicochemical features of the system, a slow-release system, show that this nano-carrier inhibits amyloid aggregation, thus, the nano-niosomes containing essential oil from artemisia absinthium has the capability to preclude amyloid development.

Keywords: *Alzheimer's disease, Amyloid-β aggregation, Niosome, Artemisia absinthium, Drug delivery*

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INTRODUCTION

Accumulation of proteins and peptides into toxic amyloid formations is a crucial biological occurrence that gives rise to the onset of different destructive pathologies, comprising plenty of neurodegenerative diseases [1]. More than 50 amyloidogenic proteins and peptides by Amyloid aggregate formation have been realized to induce a couple of a diseases, including Parkinson's disease, Huntington's disease, and Alzheimer's disease [1-5].

Most proteins are chiefly alpha-helix. Amyloid fibers, by contrast, characteristically undergo the transition from the typically soluble form into amyloid fibrils classified mostly into cross-beta-sheet, which pile up in the extracellular space of numerous tissues [6]. Amyloid-beta is a constituent of cerebrospinal fluid and plasma of robust individuals in the soluble form and is secreted by normal cells [7]. In Alzheimer's disease, this Aβ (Amyloid-beta (1-42)) peptides can self-assemble to constitute neurological toxic aggregates with numerous morphologies, such as soluble oligomers and insoluble protofibrils and fibrils [8,9]. Consequently, it is significant to preclude amyloid aggregation-associated pathologies, and one

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of the efficient methods would be the elimination of original occurrence that commences amyloid collection [10]. Similarly, another substantial plan would be the disassembly of amyloid formats. [11-13]. Over the last few years, a lucrative form of inhibitors has happened being able to prevent amyloid creation of peptides and proteins which comprise using natural compounds, aminoasids, nanoparticles, protein, and peptides [14, 15].

Some research outcomes have confirmed that nanoparticles can influence the aggregation of Aβ [16-20]. In the previous research studies, it had been shown that PEGylated phospholipid nanomicelles, Sulfonated and sulfated polystyrenes, Fullerene, Fluorinated nanoparticles, Copolymeric NiPAM: BAM nanoparticles, CdTe quantum dots, and β-Cyclodextrin functionalized magnetic nanoparticles could interact with Aβ and clearly cut down its aggregation potential and nerve toxicity [12, 21-25].

Furthermore, earlier studies have also indicated prohibition the influence of chosen natural combinations and their nanoformulations, as well [13, 26-29]. Metallic nanoparticles coated with capsaicin and piperine have displayed robust restriction amyloid aggregation [30]. Eugenol, a significant herb product with various medical profits, has been demonstrated to prevent amyloid aggregation [31]. Studies have exhibited that gold nanoparticles coated with hydrophobic debris (i.e., Tyrosine, Tryptophan) can effectively restrain amyloid aggregation probably because of their direct meddling with the intermolecular hydrophobic interaction within accumulating amyloid molecules [30]. Moreover, it has been indicated that tyrosine-coated nanoparticle can additionally cause the disassembly of amyloid fibrils [30].

Some natural combinations have been recognized to be able to conserve cells from amyloid-induced toxicity [32-34]. Although the prevention process against amyloid aggregation could be distinctive from the inhibition mechanism of amyloid-induced cytotoxicity, it is significant to consider that innate combinations maintaining these two assets could aid in arranging of anti-amyloid nominees [35]. Recognizing the antiamyloid activity of potential natural commodity could be useful, since most natural combinations are biocompatible and are distinguished to have less aftereffects as constructed with the chemically synthesized compounds [36]. The natural compounds that have a closeness for the amyloid prone stretches of the proteins are anticipated to exhibit powerful prevention efficiency versus protein amyloid composition [37]. Therefore, if the molecular structure of the compound permits it to tie the critical aggregation prone areas of the proteins, it may likely intrude with the amyloid fibrillation of proteins and its accumulation [38].

This study has selected Artemisia absinthium loaded nano-niosomes as an innate compound which has various health profits to explore whether it can target amyloid aggregation. Artemisia absinthium loaded nano-niosomes have been prepared and then characterized. Finally, the inhibitory effect of Artemisia absinthium loaded nano-niosomes on amyloid aggregation has been studied in vitro and confirmed. The capability to crack down amyloid aggregation and such an instinctive asset may aid in antiamyloid drugs.

MATERIALS AND METHODS

Materials

Phosphatidylcholine and sorbitan monostearate (Span 60) were obtained from Lipoid GmbH (Germany). Cholesterol and thioflavin T (ThT) were shopped from Merck Company (Germany). DSPE-PEG2000 and amyloid-β were obtained from Northern Lipid Inc. and Sigma-Aldrich, respectively. All of the organic solutions were analytical grade and the deionized water was utilized during the experiment.

Preparation of essential oils

The leaves, stems, and flowers of dried artemisia absinthium were chopped into small pieces and exposed to hydrodistillation type Clevenger for 90 min. The essential oil was extracted and dried over anhydrous sodium sulfate and stored in a refrigerator for future use.

Draw a standard diagram of artemisia absinthium essential oil in the PBS (Phosphate Buffered Saline) buffer

At this stage, a series of different dilutions of artemisia absinthium essential oil in the PBS was prepared. Then with the aid of the Spectrophotometer device, the absorption rate of each sample was measured. The experiment was repeated three times at this stage and then using the obtained absorption wavelengths, λ_{max}= 293 nm, standard diagram of artemisia absinthium essential oil in PBS was obtained.

Preparation of niosomes containing artemisia absinthium essential oil

Nano-niosomes were formulated using thin-film hydration technique with a slight modification. Phosphatidylcholine, span60, cholesterol, and DSPE-PEG2000 were mixed in 5ml chloroform as solvent [39]. Then essential oil was dissolved in methanol and was added to the mixture in a round flask. Organic solvents were vaporized under increased pressure by a spinning evaporator at 35°C until a thin film was built on the walls. The residual solvent was removed by nitrogen stream at 25°C. Then, 5 ml of distilled water was added to the flask and the lipid film was hydrated in a rotary evaporator (without vacuum) for 45 minutes at 37°C. In order to decrease the size, niosomal solution gained by the mentioned method was sonicated by a probe sonicator (Misonix, USA) in an ice bath. In order to separate the larger particles from smaller particles and homogenize the resulting suspension, 0.45 micrometer filter was employed and finally for sterile filtration, the solution was passed through 0.22 micrometers filter.

Encapsulation efficiency measurement

Encapsulation efficacy was specified by dialysis technique against distilled water at 4°C employing a cellulose membrane (with molecular weight cut-off of 10 kD) to separate the encapsulated essential oil from the residual material. Then, the dialyzed niosomes were disrupted with methanol and the amount of encapsulated essential oil was gauged utilizing a UV/VIS spectrophotometer (Beckman, DU 530, Switzerland) at λ_{max}= 293 nm. The essential oil concentration in nano-niosomes was calculated using the following equation.

EE%= C / Co×100

Where C is the amount of essential oil incorporated in nano-niosomes and Co is the amount of total essential oil.

Investigation of the release process

The in-vitro essential oil release pattern from nano-niosome was investigated using a dialysis bag method in PBS medium. In this procedure, 1 cc of niosomes containing artemisia absinthium essential oil was poured into the dialysis bag and then the bag was placed in 10 cc PBS buffer. The release study was performed for 24 h at 37 °C and pH = 7.4 with gentle shaking at 100 rpm and the vessels were protected from light. The spectrophotometer was used to measure the release amount of the essential oil from the niosome and then, the drug release profile was evaluated using the calibration equation in PBS.

Size analysis and zeta potential measurements

The size distribution of nano-niosomes and mean particle diameter were specified by Dynamic Light Scattering technique (DLS) (Brookhaven Instruments Ltd., Brookhaven, USA) at 25°C. Samples were dispersed at 25°C and at the angle of 90°. Prior to the size measurement, distilled water was added to the niosomal suspension for diluting. All the analysis was carried out in triplicate. Zeta potential of prepared samples was also assessed by the similar DLS-based tool at 25°C.

The morphology of nano-niosomes

Scanning Electron Microscopy (SEM) was utilized to determine the structure of prepared niosome containing artemisia absinthium essential oil.

Fourier Transform Infrared (FTIR) study

The empty niosome and niosome containing artemisia absinthium essential oil were assessed by FT-IR instrument. These compounds were mixed and pressed with KBr pellets to form a tablet and Fourier Transforms Infrared (FTIR) spectra of samples were recorded. The scans were conducted over a wavenumber range of 4000–400 cm^{-1}.

In vitro amyloid formation of Aβ

The peptide solution was obtained through dissolving 1 mg Aβ peptide in 10 mL phosphate buffer (20 mM Phosphate buffer, pH 7.4, and 100 mM NaCl). To make the blended solutions of Aβ with niosome containing artemisia absinthium essential oil, 1 mL newly obtained peptide solution was combined with 10 µL solution of niosome containing artemisia absinthium essential oil. All of the solutions were incubated at 37 ˚C.

Thioflavin T fluorescence assay

Thioflavin T (ThT), a dye binding to β-sheet structures, is utilized to distinguish and measure amyloid fibrils. A 1 mM aqueous stock solution of ThT was prepared and filtered through a 0.2 µm filter. Samples were attained through dissolving the 200µL Aβ (100 µM) solution and 50 µL ThT solution (1 mM) in 1 mL phosphate buffer (20 mM). The

control ThT sample was made by dissolving 50 µL ThT solution (1 mM) in 1.2 mL phosphate buffer (20 mM). The fluorescence intensity measurements were carried out promptly employing a Varian-Spectrofluorometer (Cary Eclipse). The excitation wavelength of 420 nm was utilized for the ThT fluorescence measurements.

AFM investigations

Atomic force microscopy (AFM) images were attained employing a PicoScan SPM microscope (Molecular Imaging, Phoenix, USA). Aliquots of samples were gathered at a prespecified incubation time, dropped onto the newly cleaved mica, and rinsed with deionized water and then dried with N_2.

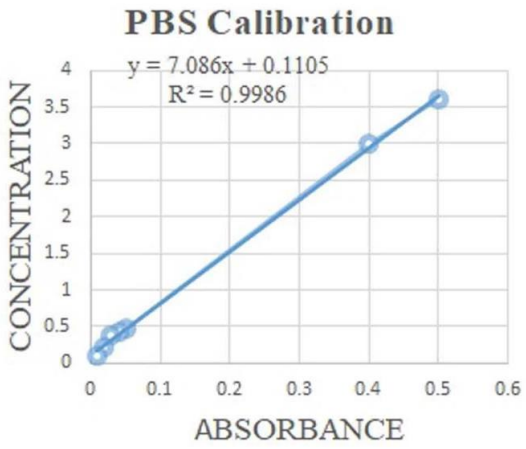

Fig 1. Standard calibration of Artemisia absinthium essential oil in PBS

RESULTS AND DISCUSSION

Fig 1 displays encapsulation efficiency of artemisia absinthium essential oil in noisome was calculated using a calibration chart (using UV-Visible Spectrophotometer) line equation which was 66.73 %.

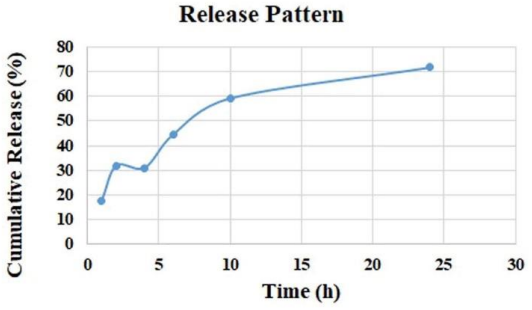

Fig 2. Graph of artemisia absinthium essential oil release from niosomal system

The release rate of the artemisia absinthium essential oil from noisome was calculated by dialysis bag over different time intervals using standard essential oil curves in PBS (Fig 1) and the pattern of release is shown in Fig 2. According to the diagram, the maximum amount of niosome released within 24 hours is 74%. Based on its release profile, it can be concluded that the release of the extract from the nano-carrier is controlled and slow.

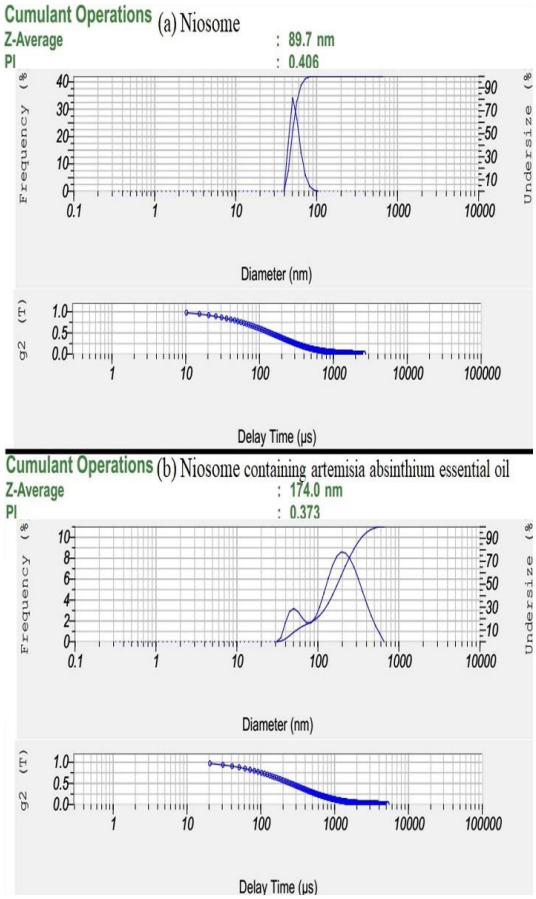

Fig 3. Particle size and particle scattering index for niosome (a) and noisome loaded artemisia absinthium essential oil system (b)

The size and zeta potential of the niosomes and niosomes containing artemisia absinthium essential oil were measured using a nanosizer (DLS). The average sizes of the niosomes nanoparticles and noisome loaded essential oil are 89.7 nm, 174 nm and the dispersion indexes of the nanoparticles are 0.406 and 0.373, respectively. This indicates that the particles are evenly dispersed (Fig 3). The mean zeta potentials of the nanoniosome and

nanoniosome surface containing essential oil is 0 and -26.5 mV, respectively.

Fig 4 indicates that the niosome loaded essential oil is an anionic system.

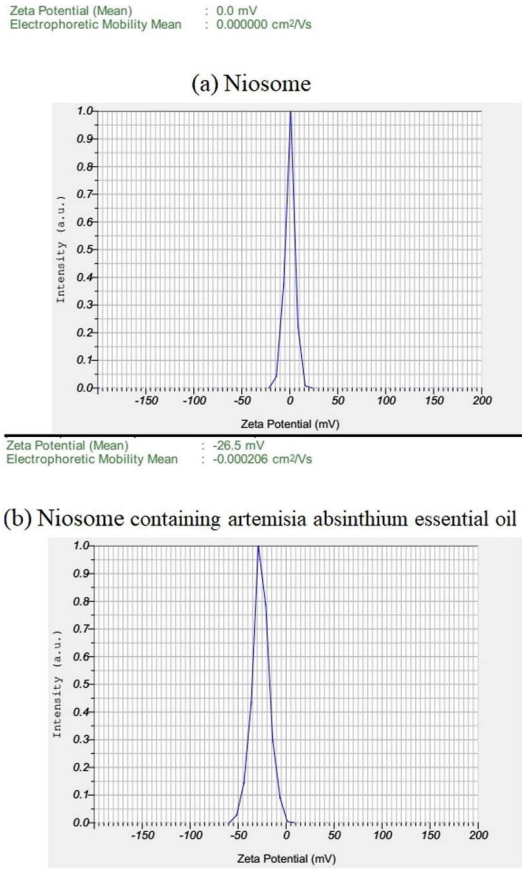

Fig 4. Zeta potential of niosome (a) and noisome loaded artemisia absinthium essential oil (b)

Infrared spectroscopy analysis was conducted to recognize the functional groups and the possible interactions between the compounds and to detect the encapsulation of the essential oil in niosomes. FTIR is one of the most essential investigates to define the stability of the formulation, presence of the drug, and drug release.

Fig 5 presents the FTIR spectrum of (a) empty niosome and (b) niosome containing artemisia absinthium essential oil.

Considering the FTIR spectrum of the empty niosome samples (Fig 5 a), a broad band at 3445.03 cm^{-1} is a representative of the hydroxyl (OH) bands vibrating group. $–CH_3$ asymmetric and symmetric stretching appeared at 2934. 6 cm^{-1} peak, and symmetric vibration of ethylene ($-CH_2$) group appeared at 2861.5 cm^{-1} peak. The peak at 1637.56 cm^{-1} proved the occurrence of C=O prolonging from the ester group, and $–CH_2$ bending in lipids and surfactant, respectively. The peak at 1070 cm^{-1} is assigned to C–O stretch in ether and ester groups.

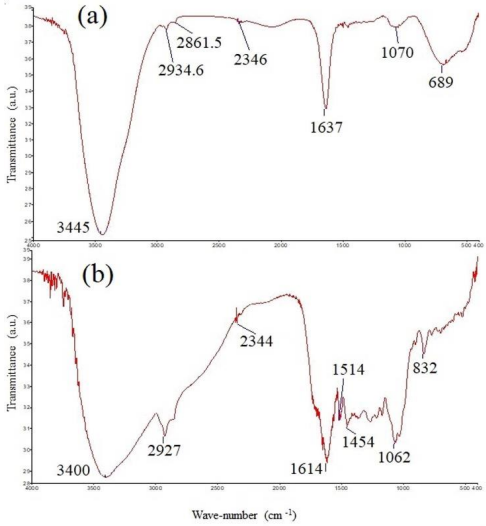

Fig 5. The FTIR spectrum of (a) empty niosome and (b) niosome containing artemisia absinthium essential oil

In Fig 5 b, niosome containing artemisia absinthium essential oil FTIR spectra, the broad peaks at 3400.04 cm^{-1}, 2927.80 cm^{-1} and 1614.53 cm^{-1}, show the existence of OH, CH_3 and C=O groups, respectively. The peak at 1514.14 cm^{-1} confirmed the presence of nitro groups. The peaks at 1454 8.8 cm^{-1}, 1062 $cm^{-1,}$ and 872.94 cm^{-1} are assigned for CH_3, CO and groups, respectively.

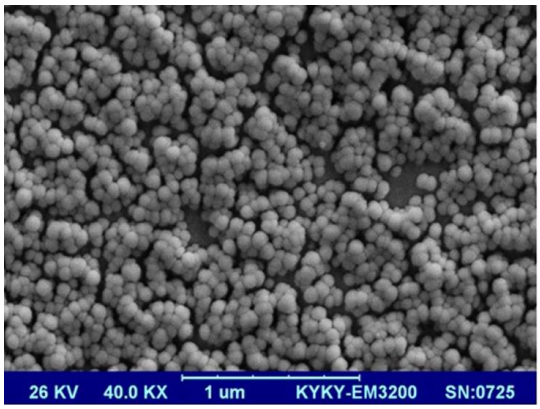

Fig 6. Scanning electron microscope image of niosomal system containing artemisia absinthium essential oil

The FTIR spectra of the niosome containing the essential oil (Fig 5 b) have been shifted slightly, which confirms the encapsulation of the essential oil into the niosome. In comparison to the FTIR

spectra of niosome, no additional peak in essential oil containing niosomal system has been created which confirms the lack of chemical interaction between the niosomal system and the essential oil.

Fig 6 shows the morphology of the nano-niosome containing the artemisia absinthium essential oil using scanning electron microscopy. As shown in Fig 6, niosome nanocarriers containing essential oil have homogeneous morphology and spherical structure and are well-sized and uniformly distributed.

Effect of niosomal system containing artemisia absinthium essential oil on Aβ aggregation has been investigated using ThT fluorescence and AFM.

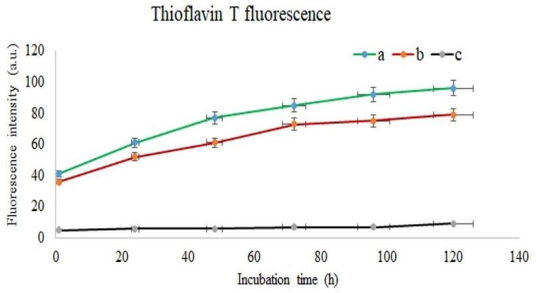

Fig 7. The fluorescence intensities of ThT bound to Aβ (a), Aβ with niosomal system containing artemisia absinthium essential oil (b) and niosomal system containing artemisia absinthium essential oil, without the presence of Aβ(c), as a function of incubation time

Fig 7 presents the ThT fluorescence measurement of Aβ without and with niosomal system containing artemisia absinthium essential oil as a function of incubation time in solution to demonstrate the alteration of Aβ arrangement in lack and existence of nano-carriers. The ThT fluorescence spectra of the newly obatined Aβ solutions without nano-carriers are presented in Fig 7 (a). It is evident that the fluorescence severity of Aβ without nano-carriers is larger than that of Aβ with nano-carriers (Fig 7 (b)). It is noteworthy the ThT fluorescence severity corresponds to the scale of the amyloid accumulation. The obtained result displays that the existence of niosomal system containing artemisia absinthium essential oil would inhibit the amyloid aggregation, Aβ oligomers to form β-sheet formations, even at the initial stage.

Moreover, the prevention influence on amyloid generation was furthermore explored through AFM (Fig8). In the event of the Aβ solvent, in the lack of nano-carriers (Fig 8(b)), entangled fibrils with microsized lengths were noticed after 120 h of the fibrillation process. In the existence of nano-carriers, niosomal system containing artemisia absinthium essential oil and its release inhibit Aβ aggregates after 120 h of the fibrillation process (Fig 8(a)).

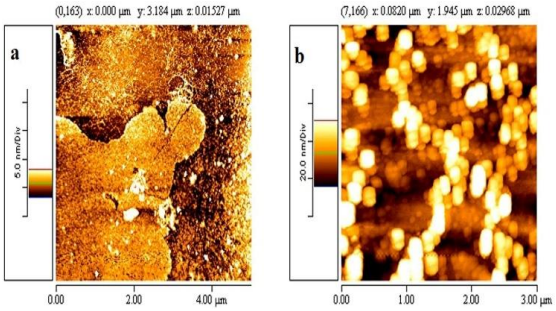

Fig 8. Atomic force microscopy (AFM) image of Aβ fibrillation in the presence (a) and absence (b) of the niosomal system containing artemisia absinthium essential oil after 120 h of incubation time

These observations suggest these nano-carriers containing artemisia absinthium essential oil, give rise prohibition of aggregation and intrude with their elongation into enormous fibrils.

Previous research studies have indicated that niosomes are bilayer constructions that has the potential to be applied as nano-carriers for hydrophilic and hydrophobic compounds. The application of niosomes, which has chemical stability against both oxidation and temperature and requiring less care in handling and storage, for encapsulation of artemisia absinthium essential oils is an approach to improve its physicochemical stability due to low solubility in water. In this study, the novel niosomal system containing artemisia absinthium essential oil showed a high encapsulation efficiency (66.73%). The DLS results showed that the mean size of artemisia absinthium essential oil loaded nano-niosomes was 174 nm (zeta potential of -26.5±1/42 mV) whereas the size of empty niosomes was 89.7 nm. The FTIR and SEM results confirmed that the essential oil and nano-carrier did not interact and their particles had a spherical morphology.

In previous studies, the anti-amyloid fibrillation activity of various synthetic and natural products have been investigated. In the present study, artemisia absinthium essential oil loaded nano-niosomes as a novel natural compound which is biocompatible, have less side effects compared to the chemically

synthesized materials shows strong inhibition efficiency against protein amyloid fibrillation. It is noteworthy the inhibitory potential of this essential oil on the aggregation of amyloid-β peptides were confirmed by AFM and Thioflavin T fluorescence measurements.

CONCLUSIONS

In this study artemisia absinthium essential oil has been extracted and encapsulated in nanoniosomes by thin-film hydration method effectively. The physico-chemical properties of as-synthesized nanoniosomal system were then characterized by utilizing FTIR, SEM, Zeta-Sizer, and the amount of drug release was measured at 37° C. The controlled drug release of this nanoniosomal system was successfully investigated and regulated. The FTIR results showed that the drug and nano-carrier did not interact chemically with each other. As described before, plaque forming owing to amyloid-β fibrillation is the main subject matter for its precipitation in the brains of dementia and Alzheimer's disease patients. Relevant structures inhibiting this peptide fibrillation tolerate the capability of noticeable medical value. Therefore, the nano-niosomes containing essential oil from artemisia absinthium were evaluated as an amyloid fibrillation inhibitor. Thioflavin T fluorescence measurement and Atomic force microscopy results indicated that nanoniosomal system inhibited amyloid aggregation properly. The nanoniosomal system could develop the endorsement of the feasible implementation as a novel inhibitor of Aβ fibrillation in Alzheimer's disease.

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