



Pharmaceutical Sciences

Journal of Faculty of Pharmacy

<http://pharm.sci.tabriz.ac.ir>

ISSN: 1735-421X

Quarterly

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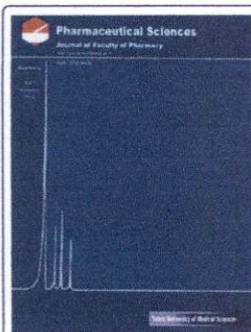
Vol. 3



Tabriz University of Medical Sciences

Pharmaceutical Sciences

ISSN: 1735-403X eISSN: 2383-2886

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pumila), Grape (*Vitis vinifera*), Pomegranate (*Punica granatum L.*) and Common Fig (*Ficus carica L.*) Fruits

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Research Article

Physical Characteristics of Liposomal Formulation Dispersed in HPMC Matrix and Freeze-Dried Using Maltodextrin and Mannitol as Lyoprotectant

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Article Info

Article History:

Received: 18 June 2017

Accepted: 1 November 2017

ePublished: 30 December 2017

Keywords:

-Liposomes
-Lyoprotectant
-Freeze-Drying
-Maltodextrin
-Mannitol
-HPMC

ABSTRACT

Background: The present study aims to design formulation of liposomes that are well-preserved during freeze-drying. The combination of Hydroxy Propyl Methyl Cellulose (HPMC) as dispersion matrix and lyoprotectants; maltodextrin or mannitol, was employed to prevent aggregation and/or recrystallization. The obtained dry products were investigated in terms of their physical characteristics.

Methods: Liposomes were prepared using thin film method and hydrated with the lyoprotectant solution. The formed liposomes were mixed with HPMC gel and freeze-dried. The obtained solid products were characterized using Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), and Scanning Electron Microscopy (SEM).

Results: The DSC thermograms of formulations with maltodextrin were relatively homogenous, yet exhibiting meta-stable properties. In contrast, the formulations using mannitol showed phase separation. These results were confirmed by XRD data, in which formulations with maltodextrin showed no intensive peaks, indicating amorphous solid while the formulations with mannitol exhibited more intensive peaks, indicating the presence of crystalline solids. The SEM images of both maltodextrin and mannitol-containing formulations showed porous matrix with spherical liposomes trapped in the matrices. The SEM images also correspond to the DSC and XRD data, where crystalline solid existed in the mannitol-containing formula.

Conclusion: The developed liposomes formulation using combination of HPMC matrix and maltodextrin showed potential in preserving liposomes structure, contrary to those of using mannitol.

Introduction

Liposomes are spherical vesicles which formed when phospholipids are hydrated with an aqueous solution. Widely used in the pharmaceutical formulation because of its versatility for incorporating both hydrophilic and lipophilic drugs, the liposomes also have particular advantages in vaccine delivery.¹ Many studies have been reported that the activity of liposomes as a vaccine adjuvant is via depot effect, where the injected liposomes are retained on the site and slowly released. The released antigens are then drained into lymph nodes and activate APC (Antigen Presenting Cells) to initiate T cell-mediated immune response.² Therefore; liposomes have great potential in delivering antigens, despite the fact that its physical and chemical instability in liquid forms as the major concern. Mediated by water, the phospholipid

constituents in the bi-layer membrane could undergo oxidation and hydrolysis, which also lead to drug leakage from the vesicles. For instance, liposomes are easily aggregated that lead to bi-layer instability and causing drug leakage.³

To address this problem, researches on producing liposomes into solid materials have been conducted extensively. Decreasing molecular mobility in solid state may also improve chemical and physical stability.⁴⁻⁶ Lyophilization or freeze-drying is a widely known technique to produce dried liposomes formulation.³ Freeze-drying process is also challenging as bilayer membrane may shrink when water molecules are removed from the system. Polyhydroxy compounds, such as saccharides, have been reported replacing water molecules in the dried state and successfully maintain liposomes structure during and after drying. Moreover, saccharides

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could also form glassy matrix during drying that decrease molecular mobility of the system, therefore, preventing neighboring bilayer to collide.^{7,8}

Saccharides such as glucose, lactose, maltodextrins, and mannitol are commonly used as lyoprotectant for protein and liposomes in their dry products.⁹⁻¹³ Among them, maltodextrins—oligomer of glucose—draw attention to its amorphous nature which became an advantage in preserving protein structure during freeze-drying and maintain its performance after the process.¹⁴ Another compound which also extensively studied as lyoprotectant is mannitol. Mannitol forms a relatively high eutectic point with ice, allowing the use of a relatively high temperature of primary drying and shorten the cycle. However, the tendency of mannitol to crystallize during freeze-drying process become a draw-back of its usage.¹⁵ In this study, hydroxypropylmethylcellulose (HPMC) was employed as dispersing matrix which also works as a polymeric stabilizer to prevent crystallization during storage.¹⁶ HPMC is a cellulose-derived polymer that underwent methylation and hydroxypropylation. It is generally used as bioadhesive material, controlled release matrix, solid dispersion matrix, and thickening agent.¹⁷

The developed liposomal formulation was using bromide salt of dimethyl-dioctadecyl ammonium (DDA) which offers advantages as lipid bi-layer component for antigen delivery.¹⁸⁻²⁰ Due to its positive charge; DDA forms cationic liposomes, therefore, works effectively as a vaccine adjuvant. However, as DDA easily aggregates even in the presence of small amounts of salt,²¹ combining DDA as lipid components with soy phosphatidylcholine could improve the stability of the vesicles.²²

The present study investigated the effects of lyoprotectants as a function of concentration in combination with HPMC as dispersing matrix on physical characteristics of the solid dried products. Scanning Electron Microscopy (SEM), X-Ray Diffraction (XRD), and Differential Scanning Calorimetry (DSC) were used to investigate the characteristics of the products; the procedures were carried out according to our previous work.²³

Materials and Methods

Dimethyl-dioctadecyl ammonium (Sigma Aldrich, Singapore) and soy phosphatidylcholine S-100 (Lipoid GmbH, Germany) were used as liposomal membrane constituent, while cholesterol (Sigma-Aldrich, Singapore) was used as the liposomal membrane stabilizer. Maltodextrin (DE:13-17) and mannitol (Sigma-Aldrich, Singapore) were used as lyoprotectants to promote stabilization of liposomes upon freeze drying process. Hydroxypropylmethylcellulose (Shin-Etsu, Japan) was selected as a dispersion matrix to increase the mass of the resultant liposomes. Methanol (E. Merck) was selected as a solvent to facilitate the mixing of liposomal ingredients. The solvent used was of analytical grade.

Preparation of Liposomes

Liposomes formula was prepared using thin film hydration methods. SPC, DDA, and cholesterol were dissolved in methanol in the molar ratio of SPC: DDA: Cholesterol = 9:3:1. Lipid phase was then evaporated under vacuum condition at 45°C using rotary evaporator (Büchi, Germany) for 60 minutes. Thin film which was formed after the process was then hydrated with pre-warmed 5 mL solution of lyoprotectant in various concentrations (Table 1). Hydration process was conducted at 50°C for 10 minutes. The liposomes formation was signed by the appearance of white-milky suspension. Liposomes suspension sonicated in water bath sonicator for 5 minutes. HPMC powder was weighed according to Table 1, and dispersed in 5 mL purified water to form HPMC gel. Liposomes suspension was incorporated into HPMC gel and stirred homogeneously, and divided into vials for freeze drying (Virtiz Lyophilizer, US). The freezing temperature was conducted in -80°C for 24 hours and continued by drying at -20°C for 48 hours.

Differential Scanning Calorimetry (DSC)

DSC instrument (Mettler Toledo FP 85, Switzerland) was used to detect the solid state of the dried product. Samples were placed in aluminum crucibles and scanned from 30°C to 300°C at the heating rate of 10°C/min.

Table 1. Prepared Formulation of Freeze-Dried Liposome.

Formulation	Lyoprotectant	Lyoprotectant concentration	HPMC Concentration
F2M1	Maltodextrin	5%	2.5%
F2M2		10%	2.5%
F2M3		5%	7.5%
F2M4		10%	7.5%
F3Mn1	Mannitol	5%	2.5%
F3Mn2		10%	2.5%
F3Mn3		5%	7.5%
F3Mn4		10%	7.5%

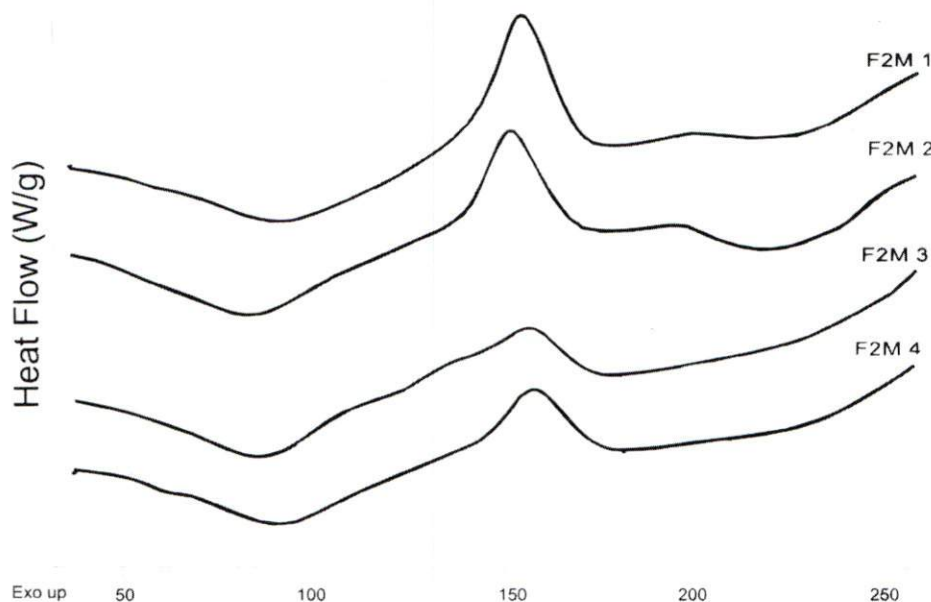


Figure 1. The thermal profile of freeze-dried liposomes formulations, in which maltodextrin was employed as lyoprotectant and HPMC as dispersion matrix. Each formulation has a different composition of maltodextrin and HPMC according to the Table 1. Downward peaks indicated endothermic (energy input to the system) responses, while upward peaks indicated exothermic (energy output from the system) responses.

X-Ray Diffraction Analysis (XRD)

Powder X-Ray Diffraction Instrument (Phillips X'Pert PRO PANalytical, Netherlands) was used to observe crystallinity of the dried products. The sample was placed on the sample holder and flatted to prevent particle orientation during preparation. The condition of analysis was as follows: Cu metal target, K α filter, the voltage of 40 kV, 40 mA performed at room temperature. The analysis was carried out in range of 2 theta of 5-40°.

Scanning Electron Microscopy (SEM)

The morphology of the liposomes contained in the solid gel was analyzed using SEM. The portions of the dried product were scattered and glued onto 25 mm diameter plates, which were attached to SEM specimen mounts. The specimens were sputter-coated with a layer of Au-Palladium approximately 5 nm in thickness and specimens were examined with an electron microscope (Phenom, U.S.).

Results

Thermal Analysis using Differential Scanning Calorimetry

All maltodextrin-containing formulations showed miscible solid dispersion (Figure 1), characterized by single and wide endothermic transition peak ranging from 85°C to 92°C. These results might imply that the solid product were relatively homogenous, in which all components were intimately mixed at the molecular level.²⁴ However, the system might be meta-stable, as the exothermic peaks of re-crystallization were observed around 155°C to 157°C. The amorphous material can

crystallize when sufficient molecular mobility provided by energy input in the form of heat exists.²⁵ The increased molecular mobility may enable molecular re-arrangement in the system; results in long-range ordered structures.

In case of mannitol-containing formulations, they showed different results from those using maltodextrin. Based on their DSC thermograms (Figure 2), the formulations were phase-separated in which three distinctive endothermic peaks were observed. Conversely, the wide endothermic peaks detected in the range of 72°C to 81°C might be indicated that the solid systems were partially amorphous. The phase separation was indicated by double endothermic peaks observed at 153-155°C and 164-166°C possibly formed by the polymorphs of mannitol upon freeze-drying.²⁵ These findings were conformed to the previous investigation which determined the melting point of meta-stable δ -mannitol at 155°C, followed by the stable form at 166°C.²⁶

X-Ray Diffraction Analysis

The solid systems of maltodextrin-containing formulations were completely amorphous in fact that there was no intensive peak detected in the powder X-Ray diffractogram analysis (Figure 3). This is a good indication that the employed freeze-drying process was successfully produced an amorphous solid. Amorphous system could protect the liposomes in the formula since crystal components could damage the integrity of bi-layer membrane,¹² and can be detrimental to the structure of labile bio-molecules such as proteins.²⁵

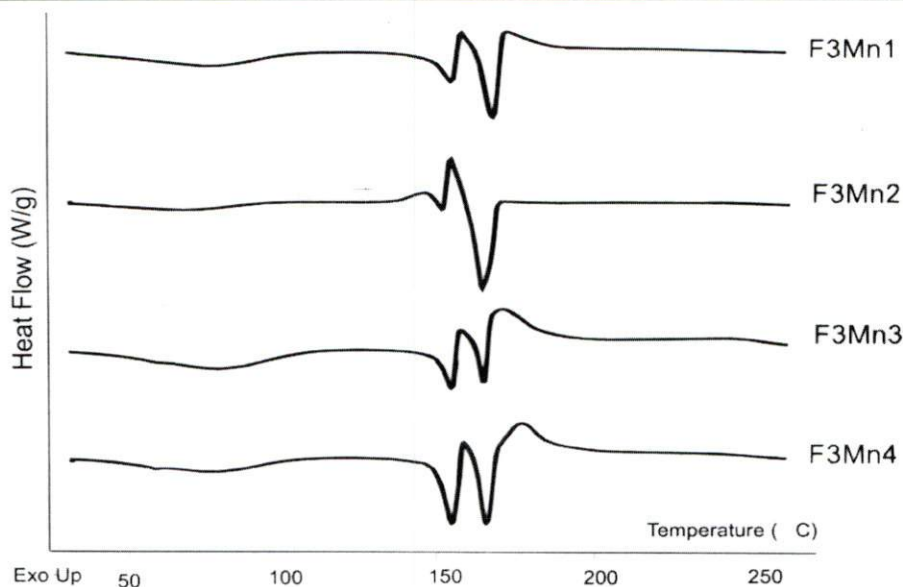


Figure 2. Differential Scanning Calorimetry (DSC) analysis of freeze-dried liposomes in mannitol-containing formulations with HPMC as dispersion matrix. Each formula has a different composition of maltodextrin and HPMC according to the Table 1. Only endothermic peaks were detected in these profiles, indicating the phase separation.

In contrast, The X-Ray diffractogram of all mannitol-containing formulations showed sharp and intensive crystallization peaks (Figure 4). These findings support the DSC data where two intensive endothermic peaks in mannitol-containing formulations were detected. Thus, it was confirmed that the formulations using mannitol as lyoprotectant have crystalline properties. The HPMC which was supposed to inhibit crystallization may not too effective in these formulations. Furthermore, it was suspected that the crystals might be the meta-stable δ -mannitol form as it was confirmed by similar investigation on its polymorph in $9.6-9.7^\circ 2\theta$ angle.²⁷ However, lesser intensive peaks were detected in F3Mn3 which contained lowest concentration of mannitol (5%) and highest concentration of HPMC (7,5%) compared to the other formula. We hypothesized that the optimum

ratio of mannitol and HPMC played a role in preventing re-crystallization of mannitol upon the freeze-drying process.

Morphology Analysis by Scanning Electron Microscopy

As observed in SEM microphotograph shown in Figure 4, the liposomes in spherical structures were successfully preserved upon freeze-drying. The porous solid matrices (Figure 5A) might be caused by ice crystal removal during sublimation in freeze-drying processes. Due to the fact that the porosity of the matrix will allow water infiltration, we expect the solid product to be porous as it may ease the rehydration of liposomes. Interestingly, the increase of HPMC concentration tends to reduce the porosity of the solid products (Figure 5B).

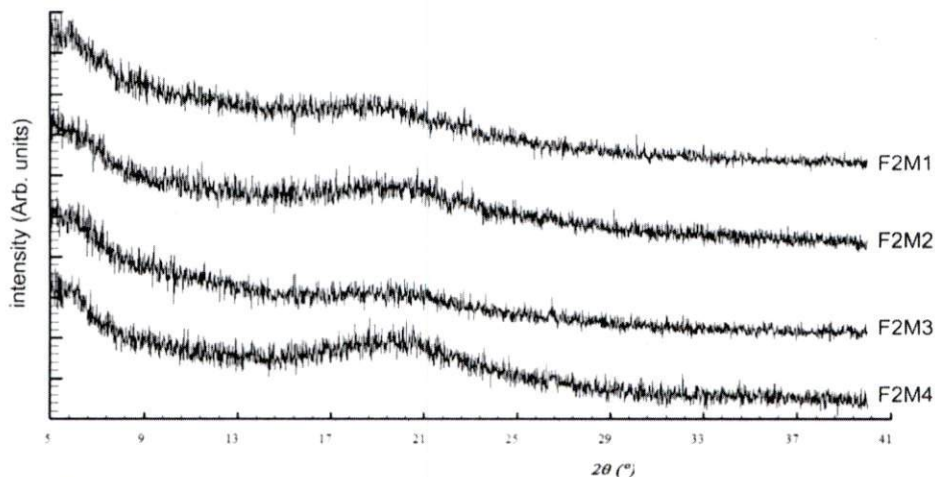


Figure 3. X-Ray Diffractogram of freeze-dried liposomes formulation with maltodextrin as lyoprotectant and HPMC as dispersion matrix according to Table 1 composition. No intensive peaks were detected; indicating the amorphous behavior of the system.

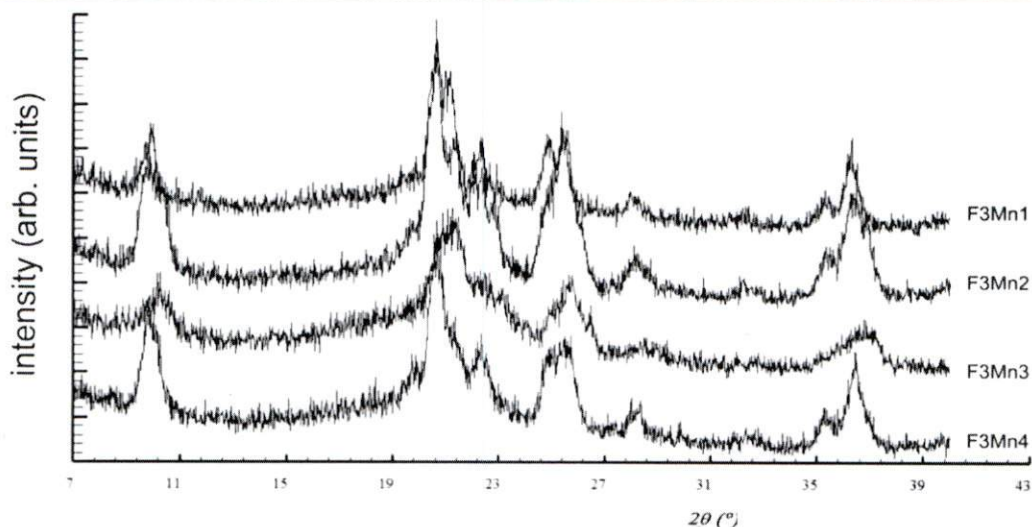


Figure 4. X-Ray Diffractogram of freeze-dried liposomes formulation with mannitol as lyoprotectant and HPMC as dispersion matrix according to Table 1 composition. There were sharp peaks detected; indicating a higher degree of crystallinity compared to the maltodextrin-containing formulations.

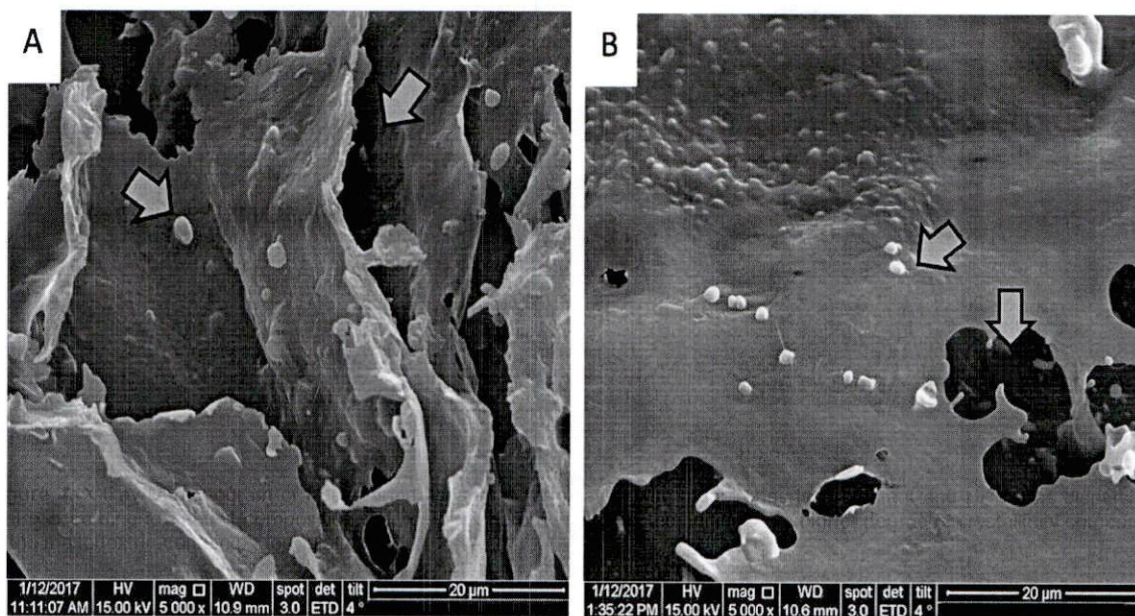


Figure 5. Representatives of SEM photograph in maltodextrin-containing formulation (5% of Maltodextrin). (A) F2M1 contains 2,5% HPMC and (B) F2M3 contains 7,5% HPMC. Pink arrows point to the porous matrix and spherical liposome. The images were captured with 5000x magnification.

The same phenomenon was observed in mannitol-containing formulations. As the HPMC concentration went higher, the less porous it became (Figure 6A and 6B). The remarkable difference was the presence of crystalline materials detected in the formula containing a lower concentration of HPMC (Figure 6A). These results were in accordance with the XRD data that indicated the presence of crystalline in the mannitol-containing formula (Figure 4). Liposomes in spherical shaped were also observed, despite the fact that the presence of re-crystallized materials may damage the liposomes during storage.¹²

Discussions

The most important factor to preserve liposomes in dried solid is to prevent collapse when the water is removed from the system since the water act as a stabilizer which maintains liposomes spherical structure in liquid form. In the present study, two different sugars with distinctive characteristics were employed in the formulations. Maltodextrin, which is amorphous in nature, was selected to provide vitrification effect that may conserve the liposomes integrity.²⁸ In contrast, mannitol is a crystalline sugar alcohol which was reported to have role in maintaining integrity of dry solid as scaffold structure, thus preventing micro-collapse.¹¹

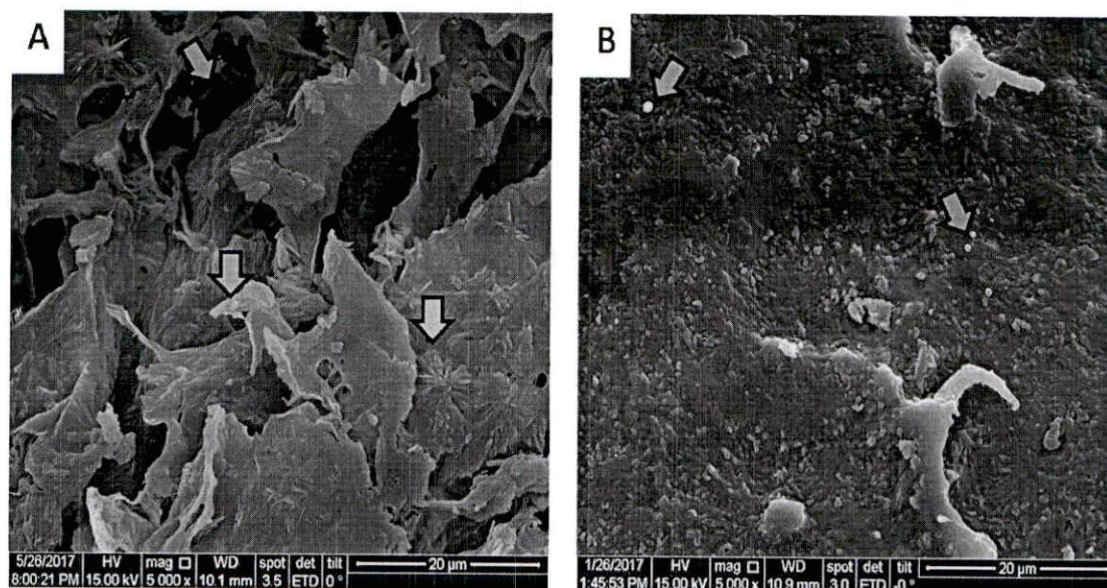


Figure 6. Representatives of SEM photograph in mannitol-containing formulation (5% of Mannitol). (A) F3Mn1 contains 2,5% HPMC and (B) F3Mn3 contains 7,5% HPMC. Pink arrows point to the porous matrix and spherical liposome, while blue arrow points to the crystalline mannitol. The images were captured with 5000x magnification.

HPMC was selected in the study for its protective effect to prevent particle agglomeration in water dispersion.¹⁷ The use of a polymer as dispersion matrix produce amorphous solid following the dissolution of crystalline materials in the polymer and the solvent removal in the drying process.²⁹ This feature is beneficial for liposomes or protein preservation where crystallization can be prevented. All of the maltodextrin-containing formulations showed amorphous characteristics, because maltodextrin is amorphous by nature, and the presence of HPMC helped to prevent re-crystallization of the other components such as DDA and cholesterol.¹⁴

However, we suggested that the mannitol experienced polymorphism upon freeze-drying, which may possibly not beneficial for such formulation. These were confirmed by the crystal profile from x-ray diffraction analysis in which meta-stable δ -mannitol were detected in all formula. Mannitol molecules might have arranged themselves in two different manners,²⁵ resulted in the different melting point,³⁰ which consequently were detected as splitting endothermic peaks in DSC profile. These results were the same conclusion with previous studies which reported mannitol alone could not provide protection as its crystal formation during drying process could cause rupture of liposomes membrane and failed to provide drug retention.¹² Some studies suggested the use of a combination of mannitol with another lyoprotectant such as sucrose and glucose for such issues.^{12,15} Moreover, the presence of HPMC in the formulation was not effective, either because of too high concentration of mannitol or the concentration of HPMC was not sufficient

In contrast to this, maltodextrin-containing formulations successfully provide a glassy amorphous matrix which might have inhibited molecular mobility and avoiding phase-separation.¹⁴ This was confirmed by the results of X-Ray diffraction analysis, DSC thermogram and SEM data. Therefore, the combined strategy using maltodextrin as lyoprotectant and HPMC as dispersed matrix construct a good formula that showed potential and could be further developed for dry liposomal formulation.

Conclusion

In the present study, we demonstrated that freeze-dried liposomal formulation containing SPC, DDA, and cholesterol can be prepared with lyoprotectant maltodextrin and mannitol that is dispersed in HPMC matrix (2,5-7,5%). All concentration of maltodextrin tested (5-10%) applied to the mixtures is miscible with all components in mixtures, while mannitol showed re-crystallization and phase separated from the mixtures. The protective mechanism of maltodextrin as lyoprotectant was probably via vitrification mechanism and HPMC as dispersed matrix might inhibit re-crystallization of the component in the formula which causes phase separation; indicated by DSC, XRD, and SEM.

Acknowledgements

This research received funding from the Directorate General of Higher Education, The Republic of Indonesia.

Conflict of interests

The authors claim that there is no conflict of interest.

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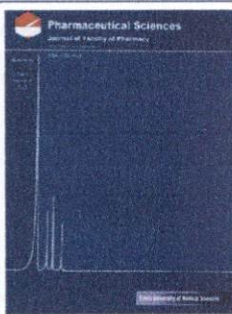
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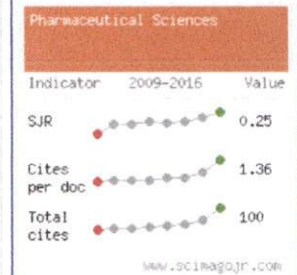


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