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Original Article

Formulation and Characterization of Bitter Melon Extract (*Momordica charantia*) Loaded Phytosomes

Rhatih Eka Sasongko[1,2], Silvia Surini[1,*], Fadlina Chany Saputri[3]

ABSTRACT

Objective: Phytosomes are a novel drug delivery system that offers better absorption and bioavailability for extract or phytoconstituents. The aim of this study was developing bitter melon extract load phytosomes with appropriate characteristics for transdermal delivery. **Methods:** Three formulas were developed, F1, F2 and F3 with weight ratios of extract and phosphatidylcholine were 1: 1, 1: 2 and 1: 3, respectively. Bitter melon fruit was extracted using a maceration method and the marker compounds were determined by high performance liquid chromatography (HPLC) method. Phytosomes were prepared using thin layer method and then characterized, in terms of morphology, particle size distribution, zeta potential and entrapment efficiency. **Results:** The results of pytosomes characterization reveals that the F3 was the optimal formula. It has a spherical shape, particle size ($D_{V\text{-}mean}$) was 282.3 ± 16.4 nm, zeta potential value at -39.2 ± 0.14 mV and entrapment efficiency of 90.06 ± 1.07 %. **Conclusion:** Bitter melon extract loaded phytosomes with a weight ratio of extract and phosphatidylcholine 1:3 (F3) was selected as an optimal formula with appropriate characteristics for transdermal delivery.

Key words: Bitter melon, Momordica charantia, Phytosomes, Thin layer method, Transdermal delivery.

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INTRODUCTION

Recently, utilization of herbal drugs is increased due to their therapeutic effects and insignificant side effects compared to synthetic drugs. The use of herbal medicines to treat diabetes has been widely used in Asia and other developing countries, one of them is *Momordica charantia*. *Momordica charantia*, also known as bitter melon, bitter gourd, karela and pear balsam have traditionally been used to help treat diabetes, hyperlipidemia, inflammation and microbial infections.[1-3] Among the various therapeutic effects of bitter melon, it's antidiabetic property is the most widely use[3–5] and has been supported by the results of various studies. Hsien-Yi Wang reported that bitter melon extract rich charantin reduce blood glucose significantly in type 1 and type 2 diabetic mice with different mechanisms.[6] A study conducted by Anjana Fuangchan concluded that bitter melon have a simple hypoglycemic effect and significantly reduce fructosamine levels in patients with type 2 diabetic.[7]

The main constituents of bitter melon which responsible for its hypoglycemic effects are triterpenes, proteides, steroid, alkaloids and phenolic compounds. The main compound that has been isolated from bitter melon and identified as hypoglycemic agent are charantin, polypeptide-p and vicine.[3] Charantin is a steroid glycoside and is a mixture of stigmasterol glycosides and β-sitosterol glycosides (Figure 1) with a ratio 1: 1, firstly isolated by Lotlikar and Raja Rama Rao in 1960.[5]

Nowadays, studies and information related to absorption and bioavailability of charantin are very limited. Since charantin is a mixture of two steroid glycosides, which is slightly soluble in water,[5] it can be predicted that its absorption and bioavailability is also limited. Hence, it is necessary to develop a formulation for improving its absorption and bioavailability. According to its structure, charantin which belongs to the steroid glycoside class will be easily hydrolyzed in the gastrointestinal tract. Therefore, some alternative routes such as transdermal route are expected can improve its absorption and bioavailability as well as reduce its dose.

Transdermal drug delivery system (TDDS) is the delivery system of therapeutic agents through the various skin layer into the blood stream for systemic effect. This route can avoid the first pass effect of metabolism drug, reduce plasma concentrations in the blood, hence decrease side effects, reduce fluctuation of plasma levels of drugs. However, TDDS also has limitations, large molecules drug and drugs with very high or low partition coefficient are difficult to be delivered via this route.[8,9] Moreover, stratum corneum, which is the outer layer of skin, is the major barrier for drug delivery.[10] Therefore, to deliver substances such as charantin with unknown P log data and large molecular weight, modification in size and lipophilicity is needed.

Phytosomes are one of technology in order to improve the penetration, absorption and bioavailability of herbal extracts or phytoconstituents. Phytosomes are micelles or little cells like structure contain the standardized herbal extracts or active phytoconstituents which bind to phospholipids and producing a lipid compatible

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molecular complexes[10–13] and with this nature of phytosomes can improve its penetration through the skin. Moreover, the nano-sized phytosomes are appropriate for transdermal delivery. Some study has been developing phytoconstituent in phytosomes for transdermal purpose, there is signirin phytosomes which optimally deliver signirin to the skin and can be used for various skin-related disease;[14] patch containing rutin-phytosomes revealed that drug permeates the keratinized horney layer and remain localized for a longer period of time, thus enabling drug targeting to the dermis and feasibility of using rutin for sustained effect;[15] and the phytosomes containing boswellic acid can provide a rapid penetration through the skin.[16]

The objective of this study was to develop phytosomes containing bitter melon extract with appropriate characteristics for transdermal delivery. Phytosomes were prepared in various formulas. The produced phytosomes were characterized including morphology, particle size distribution, zeta potential and entrapment efficiency.

MATERIALS AND METHODS

Materials

Bitter melon fruits were purchased from traditional market in Cilegon city (Banten, Indonesia) and were determined by the Research Center For Biology, Indonesian Institute of Science (Bogor, West Java, Indonesia) with a number of determinations was 106/IPH.1.01/If.07/VII/2018. Stigmasterol glucoside standard was purchased from ChemFaces (China), Beta sitosterol glucoside was purchased from ChromaDex (California, USA), Phosphatidylcholine (Phospholipon 90 G®) was a generous gift from the Lipoid Company (Nattermannallee 1, German) and other chemicals and solvents used were analytical grade.

Extraction of bitter melon fruits

Unripe bitter melon fruits were cleaned, cut and dried. Dried bitter melon fruits were cut into coarse powder[17,18] and macerated with hexane[19] and 80% ethanol.[19,20] The ethanol extracts were concentrated in vacuum and dried using a vacuum oven (nuve® EV 018) at 40°C to obtain the dried bitter melon extracts (BME).[21]

Charantin content in bitter melon extract

Charantin was estimated as stigmasterol glucoside (STG) and β-sitosterol glucoside (BSG) by reversed phase HPLC method which was slightly modified from the study conducted by Desai.[22] Analysis was performed on HPLC instruments (Shimadzu, Japan) with Grace Altima® C-18 column (4.6mm×250mm, 5µm particle). Methanol–water 98:2 (v/v) was set as the mobile phase with flow rate 1 ml/min. Sample was injected in volume 20µl and detected with PDA detector at 204nm. A calibration curve of both standard solutions, STG and BSG, were prepared in methanol medium. One ml of each standard solution with a concentration of 100 ppm were mixed and then injected to find out the chromatogram of a mixture standarts. 10000 µg/ml sample solution in methanol medium was injected and charantin content was analyzed.

Preparation of bitter melon extract loaded phytosomes

Bitter melon loaded phytosomes were prepared using the thin layer method.[23,24] Phytosomes were formulated in various weight ratios[24,25] of bitter melon extract and phosphatidylcholine (PC) as shown at Table 1. The dried bitter melon extract and PC were weighed and then dissolved in dichloromethane until homogeneous. Both solutions then mixed in a round flask and the solvent removed using a rotary evaporator (Heidolph, Germany) at 150 rpm. The solvent was evaporated at 40°C under vacuum until the solvents evaporated completely and thin film was obtained on the flask wall. Nitrogen gas was flowed into flask then stored in a refrigerator for 24 h. The thin film was hydrated with phosphate buffer solution (PBS) pH 7, 4 using rotary evaporator at 150 rpm 37°C to peel off the thin film and forming phytosomes suspension.

Phytosomes characterization

Morphology

Vesicles morphology of phytosomes was observed by Transmission Electron Microscopy (TEM).[23–27] Sample was prepared at room temperature using 1% phosphotungstate acid (pH 6.0) as a negative staining agent.[24] After drying the specimen was seen under a microscope with a magnification of 7,000 – 71,000 times.

Fourier transformation infrared spectroscopy (FTIR)

Sample was added to KBR powder which had previously dried in a ratio of 1: 100 then mixed homogeneously. Identification using FTIR (Shimadzu, Jepang) was performed at wave number 400 to 4000 cm^{-1}. FTIR analysis

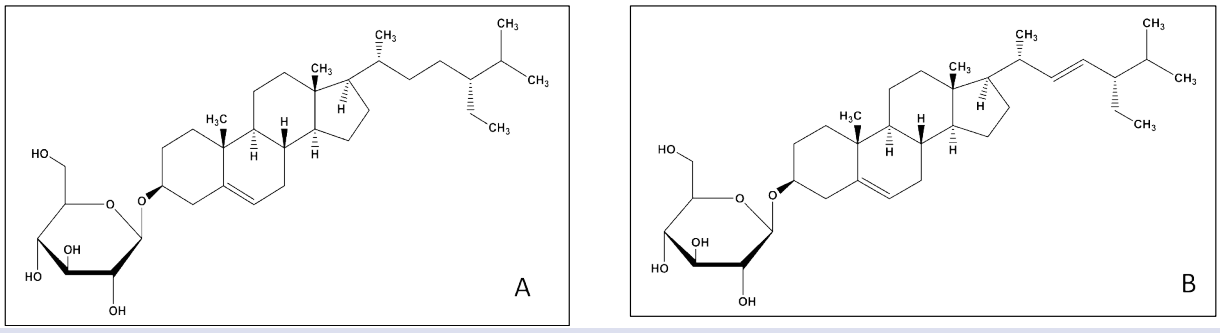

Figure 1: Structure of β-sitosterol glucoside (A) and stigmasterol glucoside (B).

Table 1: BME loaded-phytosomes formulation.

Materials	Formula		
	F1	F2	F3
Bitter melon extract (BME) (gram)	1	1	1
Phospholipon 90 G (gram)	1	2	3
Phosphate Buffer pH 7.4 (ml)	20	20	20

was carried out on the dried bitter melon extract, phosphatidylcholine and prepared phytosomes.[24,27]

Particle size distribution and zeta potential

The particle size distribution and zeta potential (ZP) of prepared phytosomes were determined using the nano zetasizer (Malvern, UK).[16,24,26,28] Phytosomes were diluted with double distillate water and the sample was transferred to disposable cell to perform the measurement.

Entrapment efficiency

Entrapment efficiency of the obtained phytosomes were determined by direct method.[16] One milliliter of phytosomes suspension were taken in centrifuge tube and centrifuge at 13,000 rpm for 60 min at 4°C. The sediment and supernatant were separated. The sediment was dissolved in 1.0 ml methanol and filtered through 0, 45µm millipore filters. The samples were analyzed by HPLC to estimate the charantin content. The charantin present in the sediment was the entrapped-charantin in the phytosomes and the entrapment efficiency (EE) was determined by the following equation:

% Entrapment Efficiency = (Entrapped drug)/(Total Drug) × 100 (1)

Total drug was the total amount of charantin in bitter melon extract added to preparation phytosomes.

RESULTS

Characterization of bitter melon extract

The dried bitter melon extract has a dark brown color and a distinctive odor. HPLC analysis of BME reveals that both markers were present in this extract with mean retention times of STG and BSG was at 11.323 and 13.227 min, respectively. The yield of the extraction process and charantin content was listed in Table 2.

Morphology of phytosomes

TEM microphotographs of bitter melon loaded-phytosomes were presented in Figure 2. The vesicle seemed to have a spherical shape and the sized was ranging from 100 to below 500 nm.

Fourier transformation infrared spectroscopy (FTIR)

FTIR spectrum in Figure 3 shows a shifting of strength at some peaks, which indicate the interaction between the extract and phosphatidylcholine.

Particle size distribution and zeta potential

Particle size and zeta potential of the bitter melon extract loaded-phytosomes were summarized on Table 3 and particle size distribution of the phytosomes was presented in Figure 4.

Table 2: Characterization of bitter melon extract (BME).

Yield	Marker Content *	
	STG	BSG
(% w/w)	(% w/w)	(% w/w)
20,45	0.26 ± 0.005	0.31 ± 0.001

*(mean ± SD; n = 3)

Table 3: BEM loaded-phytosomes characteristics.

Phytosomes Formula	Morphology	D_{mean} (nm)	Zeta potential (mV)	Entrapment Efficiency (%)
F1	Spherical	160.9 ± 0.56	-29.9 ± 0.28	61.65 ± 0.40
F2	Spherical	221.4 ± 9.30	-36.3 ± 0.10	71.59 ± 0.57
F3	Spherical	282.3 ± 16.4	-39.2 ± 0.14	90.06 ± 1.07

All value was represented as mean ± SD (n = 3)

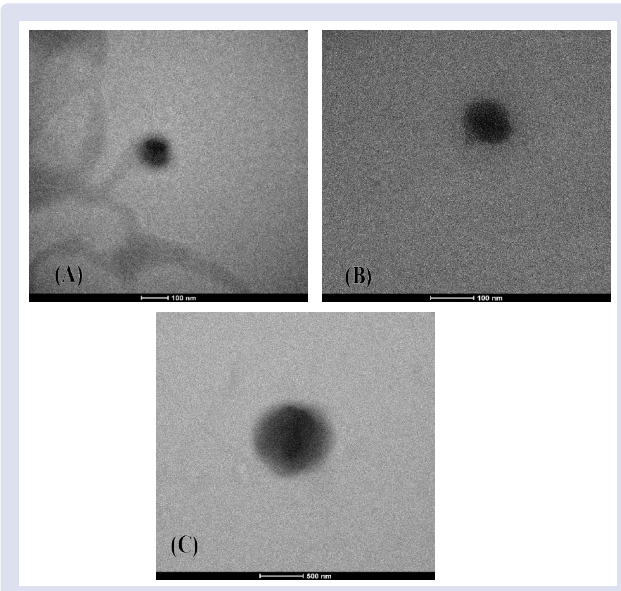

Figure 2: TEM micrographs of F1 with magnification 43,000x (A); F2 with magnification 71,000x (B); and F3 with magnification 15,000x(C).

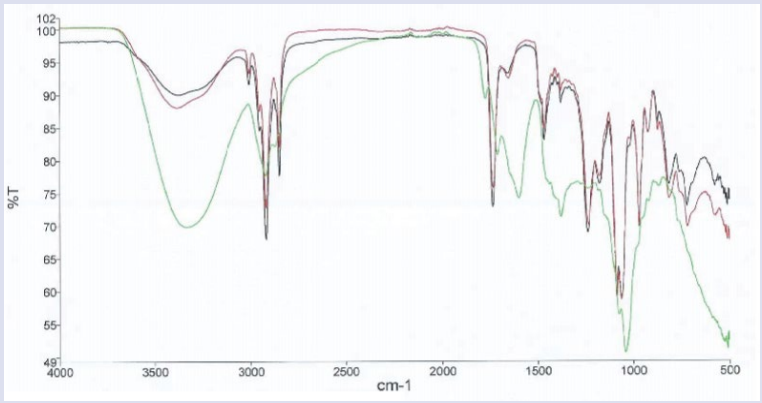

Figure 3: FTIR spectrum of BME (green line); phospholipid (red line) and phytosomes (black line).

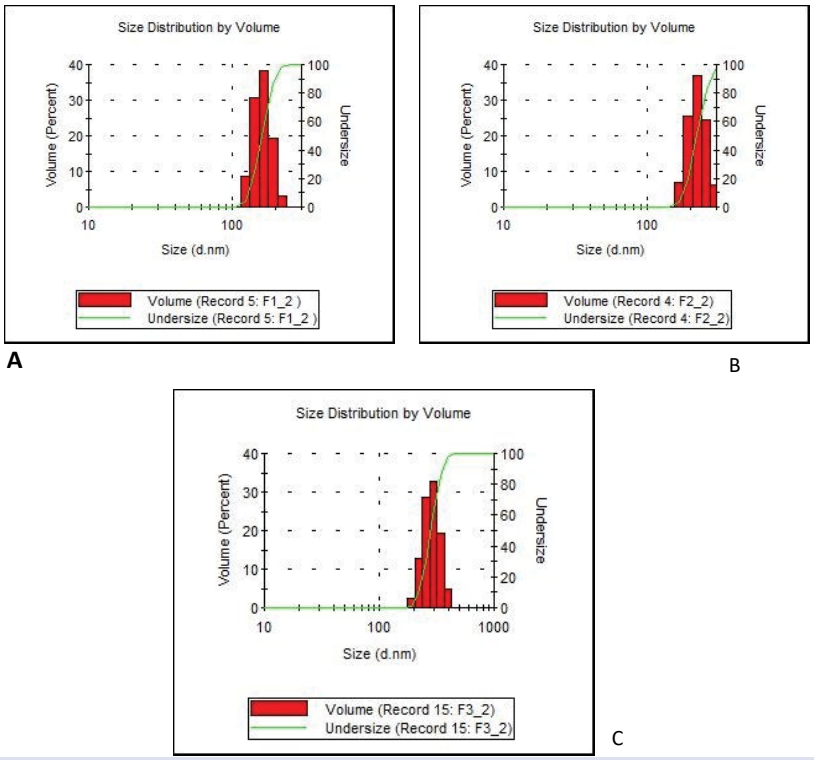

Figure 4: Particle size distribution of BME loaded-phytosomes of F1 (A), F2 (B) and F3 (C).

The entrapment efficiency

Entrapment efficiency (EE) of prepared phytosomes was summarized in Table 3. F3 with the highest ratio of phospholipid has the largest EE (Table 3).

DISCUSSION

Extraction of bitter melon fruits and charantin content in bitter melon extract

Extraction of bitter melon fruits using a maceration method is preferred due to it is a simple, easy implementation and compatible for the thermolabile phytoconstituent, since no heating during the process.[29] Ethanol 80% is selected as a solvent, due to it is an optimal solvent to dissolve charantin[30] and environment friendly. HPLC analysis of the mixed standard solution shows that this system well separated STG and BSG with retention times 11.323 and 13.227 min, respectively. HPLC analysis of the generated extract reveals that it contained two steroidal glycosides, STG and BSG, in ratio almost 1: 1 (Table 2) which known as charantin.[5]

Formulation and characterization of phytosomes

In this study, The preparation of the phytosomes was utilized a thin layer method, which widely used in many studies.[23,24,27,28,31] This method consists of two stages, there is forming thin layer and hydration process. This method is selected, because it is suitable for water insoluble substances like charantin and relatively easy to implement. Thin layers are prepared by dissolving phospholipids and substances that will be entrapped in the appropriate organic solvents.[32] Dichloromethane was chose since it can dissolve both either PC and charantin contained in bitter melon extract (BME).

In this study, optimization of the rotation speed and time of solvent evaporation was conducted to obtain a homogeneous thin layer. Rotation at speed of 150 rpm for 2 h allow the optimal results. According to the study of Maryana *et al*. evaporation time is either the variables that can affect the thickness and uniformity of the generated thin layer, in addition to evaporation time, hydration media, hydration time and temperature.[27] Evaporation is carried out at 40°C, since dichloromethane can evaporate at this temperature and prevent loss of the thermolabile active compounds in BME. Phosphate buffer pH 7.4 was selected as a hydration medium due to charantin is stable in normal pH. Selection of hydration media, mainly refers to certain considerations, including the stability of the active compound, formulas application, final dosage form and route of administration.[24]

Morphology of phytosomes

The morphology of phytosomes vesicles was observed microscopically using TEM. In this study, all formulas of BME loaded-phytosomes were observed. According to micrograph presented in Figure 2, phytosomes vesicle from all formula seem to have a spherical shape. This shape is formed after the choline head of the phosphatidylcholine molecule binds to the phytoconstituent and the fat-soluble part of phosphatidylcholine then envelops the material bound to choline[33] and produces small cells such as missels in the water environment. An explanation about the bond will be discussed further in the FTIR spectrum section bellow. The vesicle size that seems in TEM result should confirm to the result of the particle size that measure by particle size analyzer.

Fourier transform infrared spectroscopy (FTIR)

The formation of the BME loaded phytosomes can be confirmed by FTIR spectroscopy. Spectrum of phytosomes complex compared with both spectrum, bitter melon extract and phosphatidylcholine as shown in Figure 3. In the area 3200 - 3600 cm-1 (O-H stretching), there are wave number shift and intensity changes between the bitter melon extract spectrum and the phytosomes spectrum. This result shows that the hydrogen bond between phosphatidylcholine and phytoconstituent in bitter melon extract leading the formation of phytosomes.[24] Furthermore, at the band area N-O (1250 -1650 cm-1), the intensity in the phytosomes spectrum stronger than the bitter melon extract spectrum. It reveals there is an interaction between N atoms in the choline group of phosphatidylcholines and O atoms in phytoconstituent in bitter melon extract.[23]

Particle size and zeta potential

Particle size of BME loaded-phytosomes shows in Table 3, which F3 with a weight ratio of 1: 3 has the largest particle size. These results indicate that the increasing of the amount of phosphatidylcholine (PC) in the formula will increase the particle size gradually. This is possible because when the number of phospholipids in the phytosomes formula increases, the availability of phospholipid molecules compared to phytoconstituent molecules which contact during phytosomes formation becomes excessive. Hence, the physical interactions such as collisions between particles will occur more frequently and increase a potential of agglomeration and the size of vesicles.[24,34]

Particle size is an important factor in transdermal drug delivery. Reducing particle size will increase the rate of penetration (flux) and in the end increase drug delivery.[35] Average particle size (Dmean) of BME loaded-phytosomes is varied between 160 -282 nm (Table 3) and with this size reveals that the BME loaded-phytosomes is appropriate to transdermal delivery purpose. In a previous study, phytosomes with higher particle size such as Rutin phytosomes[34] with particle size 1202 nm and Boswelia extract phytosomes with particle size 514 nm[16] are able to penetrate through to the skin with greater flux rather than its free phytoconstituent or conventional extract.

Homogeneity of particle size distributions also supported by zeta potential values (Table 3). Particle size of dispersion systems such as phytosomes is also influenced by the value of zeta potential. In this study the zeta potential value is high at above -25mV. The higher of the absolute value of the zeta potential then the electric repulsion of particles are more greater.[36] It can prevent interactions between particles and reduces the possibility of particle aggregation.

Entrapment efficiency

Entrapment efficiency (EE) of BME loaded-phytosomes was varied as shown in Table 3 and F3 with weight ratios for extract and PC is 1: 3 generated the highest EE. This result reveals that EE increases gradually with increasing of weight or molar ratios between PC and extract or phytoconstituent. Other studies that have similar result, that is formulation of Rutin phytosomes[37] and grape seed phytosomes.[24] A possible explanation about this result is increasing the amount of PC in the formula will increase the number of PC molecules that can interact with phytoconstituents in bitter melon extracts. Furthermore, PC can provide more than one site for binding with phytoconstituents, consequence more phytoconstituents are trapped.[37]

CONCLUSION

Bitter melon extract loaded-phytosomes with a weight ratio between extract and phosphatidylcholine of 1: 3 (F3) were successfully produced and had the best properties of entrapment efficiency, spherical shape, particle size and zeta potential, which is appropriate for transdermal delivery.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors have no conflict of interest

ABBREVIATIONS

BME: Bitter melon extracts; **BSG:** β-Sitosterol glucoside; **EE:** Entrapment efficiency; **FTIR:** Fourier transformation infrared spectroscopy; **HPLC:** High performance liquid chromatography; **PC:** Phosphatidyl choline; **PBS:** Phosphate buffer solution; **PDA:** Photodiode array; **Ppm:** Part per million; **STG:** Stigmasterol Glucoside; **TEM:** Transmission electron microscopy; **TDDS:** Transdermal drug delivery system; **ZP:** Zeta potential.

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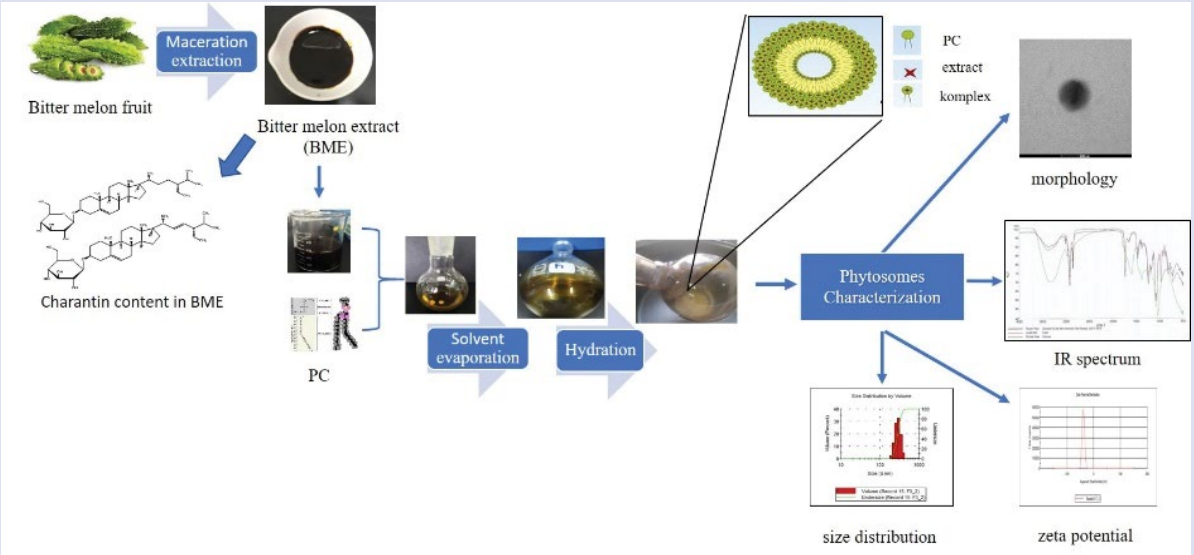
GRAPHICAL ABSTRACT



SUMMARY

This study was carried out to develop bitter melon extract load phytosomes with appropriate characteristics for transdermal delivery. Three formulas of phytosomes were prepared by thin layer method and various weight ratio of extract and phosphatidylcholine. Phytosomes formula with a weight ratio of extract and phosphatidylcholine 1:3 was selected as an optimal formula. They showed a spherical shape, particle size ($D_{V\text{-}mean}$) was 282.3 ± 16.4 nm, zeta potential value at -39.2 ± 0.14 mV, and entrapment efficiency of 90.06 ± 1.07 %, which appropriate for transdermal delivery.

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