International Journal on Advanced Science Engineering Information Technology

Vol.10 (2020) No. 6
ISSN: 2088-5334

Molecular Encapsulation of Frankincense Oil (*Boswellia serrata*) in β-Cyclodextrin as a Preliminary of the Stability Study

Hesty Parbuntari[a,1], Sri Benti Etika[a], Melindra Mulia[a]

[a] *Chemistry Department, Universitas Negeri Padang, Jl. Prof. Dr. Hamka, Air Tawar Barat, Padang, 25132, Indonesia*
E-mail: [1]hesty5193@fmipa.unp.ac.id

***Abstract*— Molecular encapsulation is the focus of current research because it is proven to be able to maintain and even to improve the physicochemical properties of their guest molecules. A trapping agent plays an essential role in the success of encapsulation. β-cyclodextrin (β-CD) could be one of the good trapping agents because it has a hydrophobic cavity and a hydrophilic outer surface. β-CD can interact with hydrophobic bioactive compounds as the guest molecules by trapping these compounds into the cavity of β-CD. Frankincense oil (FO) is one of the essential oils. It has been researched and utilized in various fields, but the physicochemical properties of FO make it less stable. This study explains the encapsulation of FO in β-CD. By using the coprecipitation method, this study gives pure crystal, and the efficiency of encapsulation is 78%. The diffraction pattern shown in the ICs identified the pattern of diffraction in crystals with a sharp peak of diffraction, and most of these peaks showed patterns of diffraction in β-CD. The absorption intensity of the pure CD was only 2.5, but after inserting the FO in its cavity, the intensity changed to 2.7 – 2.9. It shows that there is an interaction between the non-covalent part of β-CD and bioactive molecules, which are also known as hosts - guests inclusion complexes (ICs). The results confirmed as well that the ICs formed is more stable as the increase in the boiling point of the ICs in the range of 280-295^{o}C.**

***Keywords*— frankincense; β-cyclodextrin; molecular; encapsulation; stability.**

I. INTRODUCTION

Boswellia is a deciduous tree that has various types such as *Boswellia sacra* in Saudi Arabia, *Boswellia carteri* in China, and East Africa, as well as Boswellia serrata in India, each producing a different kind of resin [1], [2]. The tapped Boswellia tree trunks will produce sap like rubber trees. The sap is in the form of a resin that resembles milk. Frankincense or olibanum is an aromatic resin produced from the genus Boswellia (Burseraceae family). It has been used for centuries as traditional medicines in Asia and Africa. During exposure to air, the resin hardens and changes to an orange-brown color called frankincense. Frankincense oil (FO) is an extract produced from steam distillation of frankincense sap. FO is one of the most used oils in aromatherapy, traditional ceremonies, and perfumes.

Frankincense has been used in various countries such as Africa, China, India, and the Middle East for the prevention and treatment of various diseases, especially the types of chronic diseases (chronic inflammatory disease) [3]. Various benefits of frankincense in the medical fields cannot be maximally related to the common properties of essential oils as volatile compounds. Essential oils are also lipophilic, causing essential oils are immiscible to water, while almost all drugs are designed or consumed with polar solvents such as water. Frankincense is also reactive to chemical reactions in several external factors such as temperature, light, and oxygen [2]. Encapsulation of a compound plays a vital role in trapping the compound in a matrix, so the essential properties of the compound can be protected by various formulation [4].

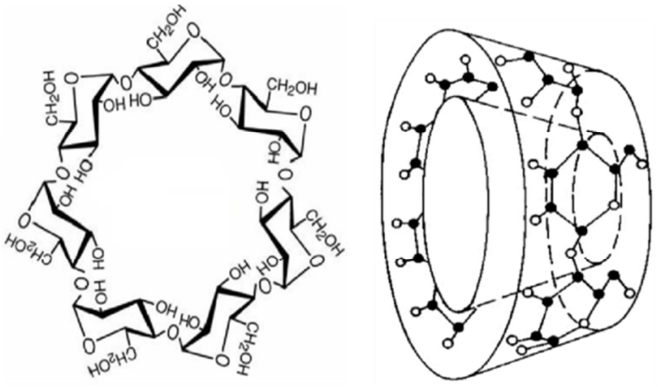
One of the alternatives to increase the physicochemical properties of frankincense is by trapping the molecules [5], [6]. Molecular encapsulation in supramolecular chemistry is a method of entering a guest molecule in the host cavity of a supramolecule. In supramolecular chemistry, host-guest interactions explain the complexity that results from two or more molecules or ions connected in a special interaction structure through several interaction forces that are not covalent bonds.

The molecules that make up the ICs are generally divided into two types, namely self-assembly and the formation of host-guest interactions between molecules. Both types of ICs are formed depending on the ability of a molecule in the formation of the bond. If the molecule has this capability because of a specific functional group, the ICs with the type of self-assembly can be formed. The bonds that function in the formation of ICs are hydrogen bonds and bonds between metals and ligands. Therefore, some studies do not merely call the bond as a covalent bond. Among these two bonds,

hydrogen bonds provide greater plasticity and faster-reaching equilibrium state. On the other hand, the bonds between metals and ligands provide greater and more rigid strength than hydrogen bonds. In addition to the interactions that occur, the size, shape, and chemical surface of the guest molecule on the host molecule are also important [7].

Cyclodextrin (CD) is a cyclic compound and a water-soluble oligosaccharide. It is produced from enzymatic conversion (CD glycosyltransferase or α-amylase), degradation, and cyclization of starch and compounds that have α-1,4-glucan. CD could also be synthesized from trisaccharide. Furthermore, some studies have successfully produced the precursor of β-CD [8].

CD is not toxic, biodegradable, and not absorbed in the digestive system [9]. Because the inner cavity is hydrophobic and the outer part is hydrophilic, as shown in Fig. 1, the CD has been extensively applied in various fields as encapsulants of several organic compounds such as vanilla, essential oils, and spices, as well as compounds such as carvacrol, thymol, menthol, and ethylene [10], [11]. Moreover, recently some research proved the use of CD as a catalyst for organic synthesis [12]. Therefore, the use of CD as a template or host molecule for essential oil such as frankincense increases not only the solubility of FO in water but also the stability.



(a) (b)

Fig. 1 (a) Structure of β-CD (b) Toroidal shape of β-CD (outer surface is hydrophilic, and the center cavity is hydrophobic

There are several encapsulation methods such as molecular inclusion, coacervation, internal ionotropic gelation, spray drying, spray freeze drying, fluid bed coating, co-crystallization, emulsification, and extrusion. They can be used as an alternative to improve the stability of the physicochemical properties of frankincense [13]. This study focused on the method of giving higher purity of crystal, namely coprecipitation. The results in the form of ICs are characterized using different analytical techniques.

II. Material and Method

A. Research Materials

The chemicals used in this study were premium quality FO (*Boswellia sacra*) obtained from Young Living, β-cyclodextrin (β-CD) with 99% purity, ethanol (CH_3CH_2OH) with pro-analysis quality (Merck), n-hexane, magnesium sulfate anhydrous and ethyl acetate (EtOAc) purchased in Sigma Aldrich and Merck. During the preparation process, double deionized water was needed to dissolve the CD.

B. Synthesis of the FO-β-CD

1) Preparation of the FO-β-CD ICs: Procedure of the study refers to the research procedure with some modifications in the preparation of the FO-β-CD ICs using the coprecipitation method [12]. 1.5-gram β-CD was dissolved in 60 mL of ethanol and deionized water (DW) (20:80 v/v) at 65 ± 2°C for 45 minutes. FO was added with a various volume of 0.5 mL, 0.75 mL, and 1.0 mL, respectively, in a solution of β-CD. The mixture is stirred on a magnetic stirrer at a speed of 1400 rpm for 3 hours at 65ºC. It is left for 1 hour at room temperature. The ICs were then vacuumed with a vacuum pump until the complex dries. The ICs were stored in an airtight glass and a cooler or refrigerator for further stability test and characterization (FTIR, UV VIS, XRD, and sem analysis). FTIR, UV VIS, and XRD analysis were performed in the chemistry and physics laboratories, Universitas Negeri Padang, Indonesia. SEM analysis was performed in the Indonesian Institute of Science (LIPI), Indonesia. The magnification of SEM was controlled from 1000x to 5000x.

2) Determination of FO Encapsulation Efficiency: The research procedure refers to the previous research that has been modified in determining the efficiency of essential oil encapsulation [14]. The total essential oil content in the ICs represents the amount of oil included in the β-CD cavity, plus the amount of oil adsorbed on the surface of the β-CD molecule.

To determine the total content of essential oils in the encapsulation product (ICs), as much as 0.5 g of the ICs were suspended in 50 mL deionized water and 15 mL n-hexane followed by low-speed stirring using a magnetic stirrer. Organic phases containing free oil are separated. The water phase was extracted with 5 mL n-hexane three times. The extract was dried with magnesium sulfate anhydrous. After evaporation of the solvent vacuum using a rotary evaporator, oily residues are weighed and expressed as (m_1). 20 mL of n-hexane was added to 0.5 g of the ICs powder and then stirred using a magnetic stirrer at 400 rpm at room temperature for 30 minutes to determine the oil adsorbed on the surface of the β-CD molecule. The mixture is filtered, and the powder is washed with 10 mL n-hexane. The organic filtrate is dried with magnesium sulfate anhydrous. Magnesium sulfate was decanted, the final extract was vacuumed using a rotary evaporator, and oily residues were weighed and expressed as (m_2).

Encapsulation efficiency (% EE) is calculated by the equation:

$$\%EE = \frac{m_1 - m_2}{m_{inclusion\ complex}} \quad (1)$$

Where;

$$m_{inclusion\ complex} = \frac{m_{total\ oil} + m_{surface\ oil}}{2} \quad (2)$$

Total oil is the total mass of oil trapped in the β-CD surface oil is the total mass of oil adsorbed on the surface of β-CD.

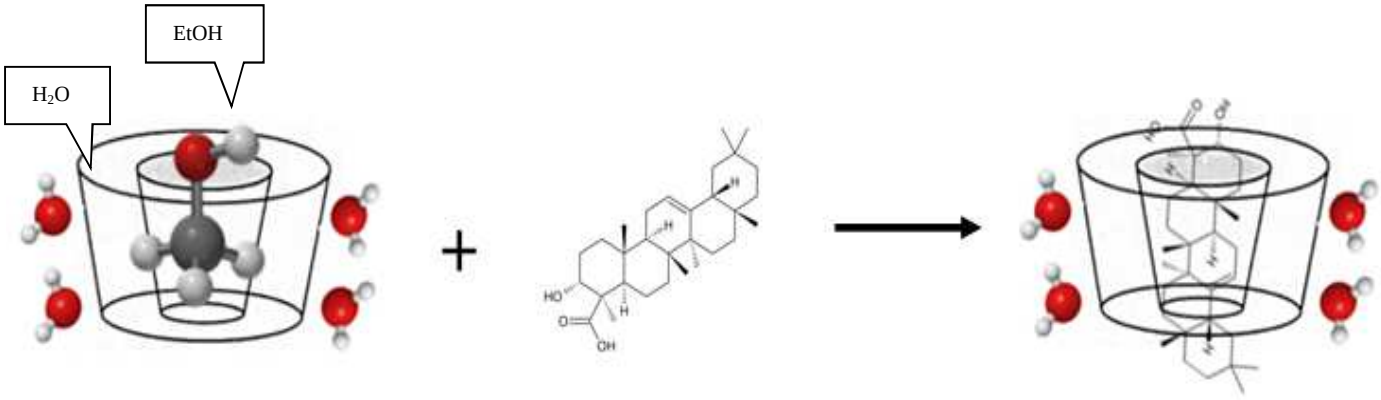


Fig. 2 The ICs formation (FO: β-CD)

III. Results and Discussion

The ICs of FO:β-CD was produced by coprecipitation method based on the previous research with some modifications [15], [16]. This study carried out some volume variations of FO and β-CD, as shown in Table I. FO as a guest molecule would be trapped in the β-CD because it replaced the more polar organic solvent (ethanol). The hydrophobic cavity in the β-CD plays an essential rule in the trapping steps. So that if there were more nonpolar molecules than the polar molecules trapped inside, the cavity would be replaced by the nonpolar molecules, as shown in Fig. 2. The use of the coprecipitation method is beneficial for the encapsulation of molecules that are not soluble in water or other words, nonpolar molecules. The crystals of the ICs formed were then washed with ethanol to remove FO that is not encapsulated. The use of organic solvents in the recrystallization stage will yield pure results and produce a stable crystalline IC.

TABLE I
THE VOLUME RATIO OF FO AND β -CD

No.	V of FO (mL)	V of β-CD (mL)
1	0.5	0.93
2	0.75	0.93
3	1	0.93

In this study, the organic solvent used in the washing stage was ethanol. Hence, the boiling point of ethanol was low, so that the ICs crystals formed had a high enough purity level after vacuum filtration.

A. Mechanism of the ICs Formation

The formation of ICs (FO:β-CD) is a unique complex chemical form showing a trapped molecule in another molecular cavity (host molecule). Guest molecules must have the appropriate size or shape to enter the cavity in the host molecule. Stereochemistry and polarity of host and guest molecules determine the effectiveness of encapsulation [16]. In aqueous solution, β-CD can form complexes with several guest compounds (guest) by inserting guest molecules into the middle cavity of the β-CD molecule. There are no covalent bonds that are damaged or formed during complex formation. Some molecular interactions that may occur when forming ICs are hydrophobic, Van der Waals interactions, hydrogen bonds, the release of high energy water from the CD cavity during the inclusion process, and the presence of conformational forces [16].

In this study, the mechanism of complex formation begins with the guest molecule and the β-CD molecule which approaches each other. Then, there is a breakdown in the structure of water or ethanol in the cavity. It results in these molecules coming out of the β-CD cavity caused by a guest molecule that will enter the cavity of the β-CD. This process is then followed by the interaction between the functional groups of the guest molecule and the groups located in the CD cavity. It produces hydrogen bonds between the guest molecule and the CD. The process then continued with reconstructing the water structure around the guest molecule, which was not covered by β-CD [16], [17].

B. Confirm the Existence of ICs in the solution

The Formation of ICs could be identified using Fourier transform IR (FT-IR) spectra. Spectra bands showing the presence of guest molecules tend to shift slightly, or spectral intensity is different, but if the mass of the guest molecule is not more than 5-15% of the mass of the ICs formed, the increase will be disrupted by the host molecule spectrum. Nonetheless, current studies can prove the existence of ICs marked by shifts in IR. Like the shifts that occur in carbonyl groups (carbonyl stretching bands), which initially were at 1650 cm^{-1} and 1700 cm^{-1} shifted around 40 cm^{-1} to higher wavelengths in the ICs [18]. This result is probably due to the intermolecular hydrogen bond in the disturbed guest molecule and causes the dispersion of each molecule in the host molecule.

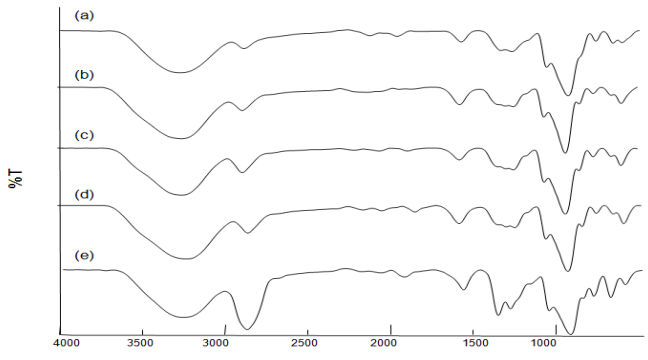


Fig. 3 (a) Infrared spectra of pure β-CD, (b) FO (0.5 mL): β-CD, (c) FO (0.75 mL): β-CD (d) FO (1 mL): β-CD, (e) pure FO

The interaction between host molecules (β-CD) and guest molecules (FO) in the ICs of this study also addressed to change of the spectrum shown in vibration spectroscopic (FTIR) data. The difference in shape, shift, or intensity of the spectra at the IR absorption peaks of FO and β-CD to the ICs could prove that the ICs had been formed. IR spectra for pure ICs, as shown in Fig. 3.

As shown in Fig. 3, the absorption peak shift to higher wavenumber showed reduced water inside the β-CD molecules. The shift of OH stretching peak to a higher wavenumber direction upon heating is often attributed to the weakening of the hydrogen bonding interaction, which gradually changes the vibrational frequency of this band. This trend confirms that there is a new interaction. The hydrogen bond between β-CD molecules and water are replaced by the Van der Waals interaction between FO and β-CD [18].

The presence of FO inside β-CD will increase electron cloud density, which leads to an increase in the frequency. On the other hand, the decrease in frequency between the ICs and its constituent molecules is due to changes in the microenvironment that lead to the formation of hydrogen bonds and the presence of Van der Waals forces during interactions to form ICs.

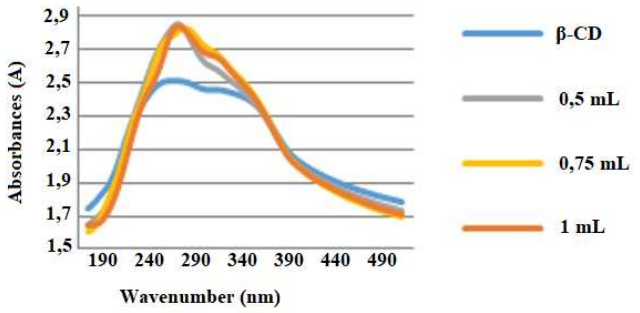


Fig. 4 UV VIS spectra of Inclusion Complex (ICs)

Some formation of ICs in CD affects ultraviolet or UV VIS absorption spectra possessed by the molecules, sometimes appearing in bathochromic or hypochromic shifts. As shown in Fig. 4, the absorption intensity of the pure CD was only 2.5, but after inserting the FO in its cavity, the intensity changed to 2.7 – 2.9. UV shift with maximum absorption in complex formation could occur due to the protection of some of the electrons, which should be excited in the cyclodextrin cavity. The high electron density in the CD cavity makes it easier for electrons in the guest molecule to be trapped in the CD to move. In this study, the ICs were shown at a wavelength of about 380 nm. Considerable differences between the absorption intensity of pure CD and ICs also show hyperchromic effects [19].

TABLE II
MAXIMUM ABSORBANCE FOR EACH INCLUSION COMPLEX

Sample	Wavenumber (nm)	Maximum Absorbance (A)
β-CD	282,0 nm	2,5084 A
FO 0,5 mL	285,0 nm	2,8356 A
FO 0,75 mL	293,0 nm	2,8295 A
FO 1,0 mL	286,0 nm	2,8456 A

Based on Table II, There was an increase in the number of Absorbance in each ICs. The interaction between guest molecules (FO) and β-CD molecules play a vital role in this phenomenon. In β-CD cavities, FO will form various interactions with β-CD molecules, such as hydrogen bonds, dipole-dipole interactions, and dispersion forces. They will contribute differently to the conformational variations of guest molecules and guest immobilization.

C. A preliminary study of the chemical stability of complex inclusions

This study also used X-ray Diffractometer (XRD) to support data from FTIR. XRD is a simple method to detect the ICs in amorphous or crystal phases. The diffraction pattern in the ICs seems different from the superposition of each compound if an inclusion complex has been formed. Even in guest molecules in the form of liquid (oil or volatile compounds), XRD is very suitable to be used in identifying the formation of its ICs. The guest molecule in the form of liquid will not show diffraction patterns on XRD, and if the diffractogram is different from the ICs that have not been fully formed, then the formation of crystals from the guest molecule shows a new form of the crystal lattice.

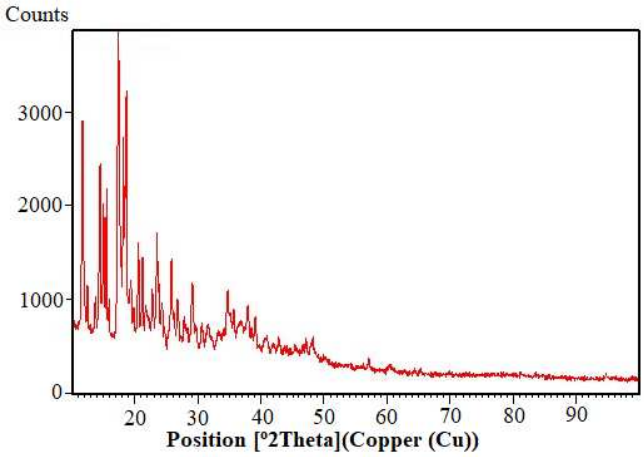
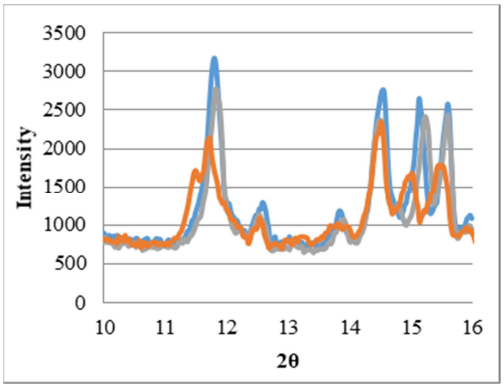


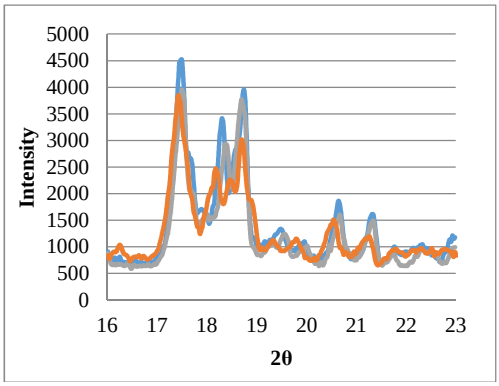
Fig. 5 The diffraction pattern of the ICs

This result supports that the ICs have been formed. XRD results in the study can be seen in Fig. 5. The diffraction pattern shown in the ICs identified the pattern of diffraction in crystals with a sharp peak of diffraction, and most of these peaks showed patterns of diffraction in β-CD. In addition to the peak diffraction of β-CD, there were different diffraction patterns.

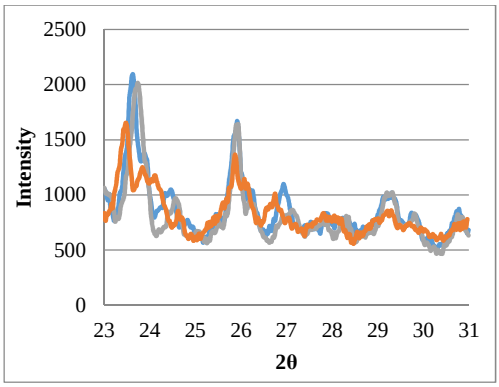
Guest molecules would show a more complex crystal pattern which reflects the existence of guest molecules in β-CD. The diffraction pattern shown in the ICs (Fig. 5) is mostly more like the β-CD diffraction pattern, but the intensity of the XRD pattern between β-CD and ICs gives different sharpness of peak. The intensity of XRD patterns in β-CD is higher compared to the three ICs. The XRD pattern of β-CD proves the crystal properties are evident because of its sharp and robust peak [20]. The difference in intensity, diffraction distribution pattern, and sharpness of the peaks indicates that the ICs have been formed.



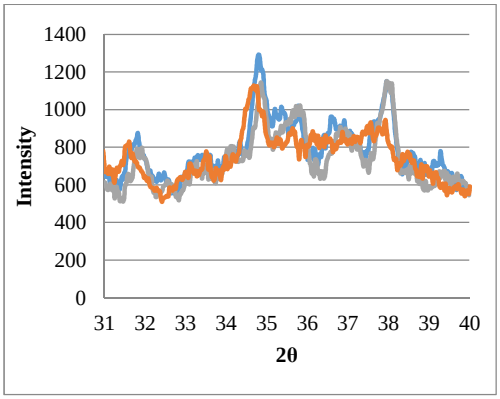
(a)



(b)



(c)

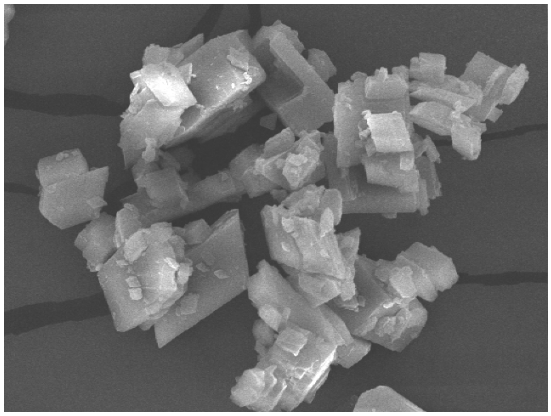


(d)

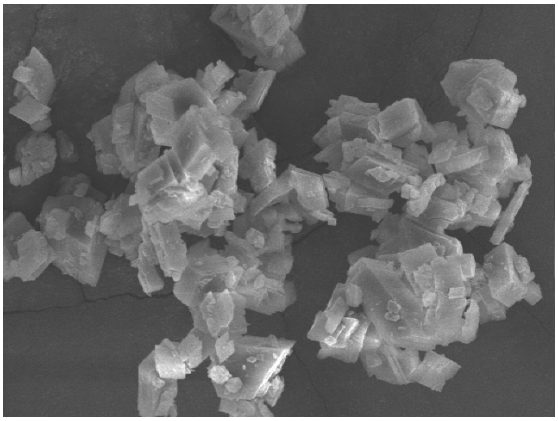
Fig. 6 XRD Difractogram Inclusion Complex (a) 2θ at 10º-16º, (b) 2θ at 16º-23º, (c) 2θ at 23º-31º , and (d) 2θ at 31º-40º

Compared to the diffraction pattern between the three ICs in Fig. 6, there was a decrease in the intensity of each ICs. The intensity of the 0.5 mL ICs (blue peaks) was generally higher than the ICs intensity of 0.75 mL (gray peaks) and 1.0 mL (orange peaks), as well as for the ICs of 0.75 mL with a 1.0 mL ICs. That is, the more frankincense essential oil is added, the lower the intensity of the ICs and the degree of crystallinity of an ICs.

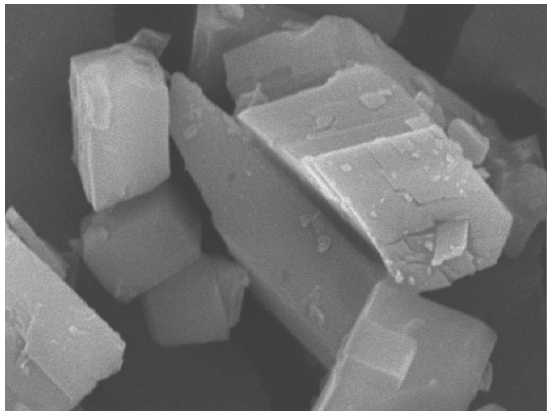
To confirm the formation of ICs, this study performed another analysis, i.e. SEM. Fig. 7 shows the scanning electron micrographs of FO/β-CD in 1,000x and 5,000x. The volume of FO to perform this analysis was 0,75 mL. The image was produced from the above and side perspectives. Small pebbles in the picture indicate the ICs.



(a)



(b)



(c)

Fig. 7 SEM micrographs of FO/β-CD in 1000x from (a) above (b) side (c) in 5000x

Encapsulation of volatile compounds could affect the properties of guest molecules comparing to the properties before being trapped in the encapsulation medium. The formation of crystalline phases of the ICs increased the molecular stability of essential oil. It includes physical stability, such as melting point, and chemical stability such as volatility, photodegradation, dehydration, hydrolysis, sublimation, oxidation, thermal decomposition, stereochemistry, and isomerization.

TABLE III
THE MELTING POINT OF FO- ß-CD INCLUSION COMPLEX

The volume of FO (mL)	The melting point of inclusion complex (°C)
1.0	280
0.75	286
0.5	295

One of the stability tests of essential oil is by measuring the melting point of the ICs. The use of β-CD as the coating material for frankincense essential oil can increase the stability of FO because the ICs are solid or crystalline complexes, which make the melting point of the ICs of FO-β-CD almost resembles the pure melting point of β-CD (> 290 °C) as shown in Table III.

The difference in the melting point of the three ICs is related to the number of FO trapped in the β-CD cavity. The melting point of the 1.0 mL ICs was lower than the melting point of the ICs of 0.75 mL and 0.5 mL, the ICs with the addition of 1.0 mL essential oil showed that the number of frankincense essential oil molecules trapped more than the ICs 0.75 mL and 0.5 mL as evidenced by total oil data on the encapsulation efficiency of frankincense essential oil molecules. The difference in the melting point of the three ICs is also due to the presence of hydrogen bonds, Van der Waals forces, covalent bonds between β-CD and the incense oil molecules. The endothermic effect on the three variations of kneading time is related to the loss of the hydroxyl group in the FO-β-CD ICs, which is obtained as a melting point. The types of changes in thermal properties in the ICs indicate the possible interaction between β-CD and FO oil, which causes the formation of more stable ICs [21].

D. The Efficiency of FO Encapsulation

Total oil is related to the amount of oil trapped in a microcapsule, such as β-CD, while surface oil is related to the amount of oil adsorbed on the surface of the microcapsule, the amount of total oil and surface oil in the ICs dramatically influences the efficiency of encapsulation.

TABLE IV
EFFECT OF INCREASING VOLUME OF FO ON THE EFFICIENCY OF INCLUSION COMPLEX ENCAPSULATION

β-CD: FO (gram)	Total Oil (mg)	Surface Oil (mg)	Encapsulation efficiency (%)
1,5 : 0,8650	47	13	68
1,5 : 0,6487	44	7	74
1,5 : 0,4325	42	3	78

Total oil affects encapsulation efficiency because of the increasing number of coated ingredients to be packaged to decrease as much oil sticks to the surface. Consequently, it will damage the oxidative stability of the microcapsule [21].

Based on the data of encapsulation efficiency obtained (Table IV), there is an increase in the mass of essential oil trapped in the β-CD (total oil) cavity. The mass of essential oil on the surface of the β-CD (surface oil) cavity also increases. Hence, it will result in decreased encapsulation efficiency as the volume of frankincense essential oil increases. The result is related to the physicochemical properties of β-CD (cavity diameter, derivative properties), and guests (geometry, volume, hydrophobicity) of FO [21].

IV. CONCLUSION

The amount of FO determines the efficiency of the encapsulation of frankincense oil (FO) in the β-CD cavity through the coprecipitation method. The highest number of efficiencies is 78% when adding FO 0,4328 gram. The presence is confirmed by instruments such as UV VIS, FTIR, and XRD. The stability of FO increases after it is encapsulated. This result is indicated by the formation of the crystalline phase and the increase in the ICs melting point.

ACKNOWLEDGMENT

This work was supported by a grant from Universitas Negeri Padang, Indonesia.

REFERENCES

[1] M. A. Ayub, M. A. Hanif, R. A. Sarfraz, and M. Shahid, "Biological activity of *Boswellia serrata* roxb. Oleo gum resin essential oil: Effects of extraction by supercritical carbon dioxide and traditional methods," *Int. J. Food Prop.*, vol. 21, no. 1, pp. 808–820, 2018, doi: 10.1080/10942912.2018.1439957.

[2] C. Bandaiphet and J. F. Kennedy, *Encyclopedia of Common Natural Ingredients used in Food, Drugs and Cosmetics (2nd Edition)*, vol. 58, no. 2. 2004.

[3] R. Hamidpour, S. Hamidpour, M. Hamidpour, and R. Hamidpour, "iMedPub Journals Frankincense (Boswellia Species): The Novel Phytotherapy for Drug Targeting in Cancer Abstract," *Arch. Cancer Res.*, vol. 4, no. 1:46, pp. 1–5, 2016.

[4] S. S. Sagiri, A. Anis, and K. Pal, "Review on Encapsulation of Vegetable Oils: Strategies, Preparation Methods, and Applications," *Polym. - Plast. Technol. Eng.*, vol. 55, no. 3, pp. 291–311, 2016, doi: 10.1080/03602559.2015.1050521.

[5] Y. Chi *et al.*, "Microencapsulation of Bacillus megaterium NCT-2 and its effect on remediation of secondary salinisation soil," *J. Microencapsul.*, 2020, doi: 10.1080/02652048.2019.1705409.

[6] N. Kamrudi, S. Akbari, and M. Haghighat Kish, "The odour assessment of thyme essential oils in electrospun fibre mat with a virtual sensor array data and its relation to antibacterial activity," *J. Microencapsul.*, 2020, doi: 10.1080/02652048.2020.1713241.

[7] S. Das, J. Maharana, S. Mohanty, and U. Subuddhi, "Spectroscopic and computational insights into theophylline/β-cyclodextrin complexation: inclusion accomplished by diverse methods," *J. Microencapsul.*, vol. 35, no. 7–8, pp. 667–679, 2018, doi: 10.1080/02652048.2019.1572239.

[8] H. Parbuntari, N. Sakairi, B. Purwono, and R. T. Swasono, "Synthesis and characterisation of a partially methylated dodecyl thiomaltotrioside derivative as a precursor of cyclodextrin analogue," *J. Phys. Conf. Ser.*, vol. 1317, no. 1, 2019, doi: 10.1088/1742-6596/1317/1/012032.

[9] M. Kfoury, D. Landy, and S. Fourmentin, "Characterisation of cyclodextrin/volatile inclusion complexes: A review," *Molecules*, vol. 23, no. 5, pp. 1–23, 2018, doi: 10.3390/molecules23051204.

[10] S. Kumar, K. K. Singh, and R. Rao, "Enhanced anti-psoriatic efficacy and regulation of oxidative stress of a novel topical babchi oil (Psoralea corylifolia) cyclodextrin-based nanogel in a mouse tail model," *J. Microencapsul.*, vol. 36, no. 2, pp. 140–155, 2019, doi: 10.1080/02652048.2019.1612475.

[11] R. Li *et al.*, "[6]-Shogaol/β-CDs inclusion complex: preparation, characterisation, in vivo pharmacokinetics, and in situ intestinal perfusion study," *J. Microencapsul.*, vol. 36, no. 5, pp. 500–512, 2019, doi: 10.1080/02652048.2019.1649480.

[12] C. C. Bai, B. R. Tian, T. Zhao, Q. Huang, and Z. Z. Wang, "Cyclodextrin-catalysed organic synthesis: Reactions, mechanisms, and applications," *Molecules*, vol. 22, no. 9, 2017, doi: 10.3390/molecules22091475.

[13] E. Martins, D. Poncelet, R. C. Rodrigues, and D. Renard, "Oil encapsulation techniques using alginate as encapsulating agent: applications and drawbacks," *J. Microencapsul.*, vol. 34, no. 8, pp. 754–771, 2017, doi: 10.1080/02652048.2017.1403495.

[14] Z. Hadian, M. Maleki, K. Abdi, F. Atyabi, and A. Mohammadi, "Preparation and Characterization of Nanoparticle β-Cyclodextrin : Geraniol Inclusion Complexes," *Irian J. Pharm. Res.*, vol. 17, no. February 2016, pp. 39–51, 2018.

[15] B. Fumić, J. Jablan, D. Cinčić, M. Zovko Končić, and M. Jug, "Cyclodextrin encapsulation of daidzein and genistein by grinding: implication on the glycosaminoglycan accumulation in mucopolysaccharidosis type II and III fibroblasts," *J. Microencapsul.*, vol. 35, no. 1, pp. 1–12, 2018, doi: 10.1080/02652048.2017.1409819.

[16] G. Al-Nasiri, M. J. Cran, A. J. Smallridge, and S. W. Bigger, "Optimisation of β-cyclodextrin inclusion complexes with natural antimicrobial agents: thymol, carvacrol and linalool," *J. Microencapsul.*, vol. 35, no. 1, pp. 26–35, 2018, doi: 10.1080/02652048.2017.1413147.

[17] M. Kotronia, E. Kavetsou, S. Loupassaki, S. Kikionis, S. Vouyiouka, and A. Detsi, "Encapsulation of oregano (Origanum onites l.) essential oil in β-cyclodextrin (β-CD): Synthesis and characterisation of the inclusion complexes," *Bioengineering*, vol. 4, no. 3, pp. 1–15, 2017, doi: 10.3390/bioengineering4030074.

[18] N. Rafati, A. Zarrabi, F. Caldera, F. Trotta, and N. Ghias, "Pyromellitic dianhydride crosslinked cyclodextrin nanosponges for curcumin-controlled release; formulation, physicochemical characterisation and cytotoxicity investigations," *J. Microencapsul.*, vol. 36, no. 8, pp. 715–727, 2019, doi: 10.1080/02652048.2019.1669728.

[19] K. P. Sambasevam, S. Mohamad, N. M. Sarih, and N. A. Ismail, "Synthesis and characterisation of the inclusion complex of β-cyclodextrin and azomethine," *Int. J. Mol. Sci.*, vol. 14, no. 2, pp. 3671–3682, 2013, doi: 10.3390/ijms14023671.

[20] J. Jayanudin, R. Rochmadi, M. K. Renaldi, and P. Pangihutan, "Pengaruh Bahan Penyalut Terhadap Efisiensi Enkapsulasi Oleoresin Jahe Merah the Influence of Coating Material on Encapsulation Efficiency of Red Ginger Oleoresin," *ALCHEMY J. Penelit. Kim.*, vol. 13, no. 2, pp. 275–287, 2017, doi: 10.20961/alchemy.v13i2.5406.

[21] J. Xu, Y. Zhang, X. Li, and Y. Zheng, "Inclusion complex of nateglinide with sulfobutyl ether β-cyclodextrin: Preparation, characterisation and water solubility," *J. Mol. Struct.*, vol. 1141, pp. 328–334, 2017, doi: 10.1016/j.molstruc.2017.03.116.