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Review Article

METHODS FOR IMPROVING ALPHA-MANGOSTIN SOLUBILITY: A REVIEW

NURUL FAJERIYATI[1,3], MUCHTARIDI MUCHTARIDI[1*], IYAN SOPYAN[2]

[1]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Padjadjaran University, Sumedang, Indonesia, [2]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Padjdjaran University, Sumedang, Indonesia, [3]Faculty of Pharmacy, University of Muhammadiyah Banjarmasin, Banjarmasin, Indonesia
Email: muchtaridi@unpad.ac.id

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ABSTRACT

Solubility is an important parameter to achieve for the bioavailability of a drug to reach the therapeutic windows. *Garcinia mangostana* Linn is a plant with great potency for the development of natural medicine. Alpha-mangostin is one of the secondary metabolites of *G. mangostana* and has been reported to have several pharmacological activities. The Biopharmaceutics Classification System (BCS) is a system that classifies drugs based on their solubility and permeability. Due to its low solubility but high permeation, alpha-mangostin is categorized into class II of the Biopharmaceutics Classification System. Therefore, the determination of dosage forms and modification of solubility enhancers is limited due to its physical properties, as mentioned above. This disadvantage requires new methods to improve its solubility to administer alpha-mangostin, especially for oral administration. Here, we discuss the development of the methods to increase alpha-mangostin solubility to be applied to formulate a dosage form to reach a useful plasma level for medication.

Keywords: Alpha-mangostin, Solubility, Drug delivery system

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INTRODUCTION

Solubility is the maximum amount of a compound to be dissolved in a specific solvent at equilibrium. The solubility of a compound increases with the increasing temperature of the solution [1]. In the pharmaceutical setting, the solubility of a drug is an important parameter to achieve the expected concentration, since to be able to reach the useful plasma level, a drug needs to be dissolved in a specific solvent (which must be a non-toxic solvent) at a certain concentration. By knowing the solubility of a drug, it is easier to formulate its dosage form. A proper-formulated dosage form guarantees that molecules of a drug reach its target site resulting in bioavailability. As a result, a specific therapeutic effect is the manifestation of the bioavailability of the drug [2].

Garcinia mangostana Linn is widely known in Indonesia as having the potency to be developed as natural medicine. Among the secondary metabolites of *G. mangostana* Linn, alpha-mangostin has been identified as its major xanthone [3]. Alpha-mangostin is extracted from *G. mangostana* with methanol, followed by purification using chromatographic techniques [4]. In general, xanthone is a group of oxygenated heterocyclic compounds which have extraordinary pharmacological activities and have been reported to have multiple pharmacological effects [5]. Specifically, alpha-mangostin has been reported to have several pharmacological effects such as anticancer [6, 7], cardioprotective [8], anti-inflammatory [9], anti-acne [10], anti-TBC [11], antioxidant [12], antibacterial [13], Recurrent Aphthous Stomatitis (RAS) [14], and antifungal [15]. Based on the aforementioned reports, many pharmaceutical industries are now trying to develop and sell various alpha-mangostin containing products (nutraceuticals, functional foods, food supplements, and medicinal products) as promotive, preventive or curative agents for a particular disease [16].

Alpha-mangostin belongs to the xanthone group, which has hydrophobic properties, and is therefore classified into class II of the Biopharmaceutics Classification System (BCS) due to its low solubility but high permeability. It is not soluble in water resulting in difficulties in determining a dosage form, especially for oral administration [17]. Therefore, the solubility of alpha-mangostin needs to be improved to be able to formulate it into an oral dosage form, in order that its bioavailability in the gastrointestinal and intestinal fluids can be achieved [18].

In this review, we discuss the techniques that have been carried out to increase the solubility of alpha-mangostin. This review is based on a literature study of the reports obtained from Scopus, Google Scholar, ScienceDirect, Springer, and PubChem databases that have been published in the last 15 y, by using specific keywords "solubility", "alpha-mangostin", and "drug delivery system". To obtained reliable reports, we applied the following inclusion criteria (articles and reviews) and exclusion criteria (opinions and material by the topic).

Solubility and influencing factors

The solubility of a compound is dependent on the structure and condition of the solution. The structure of a compound determines its polarity and hydrogen bonds determine the solubility of a compound in a solution. The condition of the solution is influenced by pH, co-solvent, and temperature [19]. Solubility is also influenced by the nature of the compound and the solvent, particle size, molecular size, molecular structure and pressure [20].

Several factors influence the solubility of a compound. The first factor affecting solubility is polarity, the ability of compounds to form poles. By nature, non-polar compounds dissolve in non-polar solvents, and polar compounds are dissolved in polar solvents. The second factor is hydrogen bonding, an interaction that occurs between the hydrogen bonding donor group and the atoms, which have strong electronegativities such as the halogen, oxygen, and nitrogen groups. Hydrogen atoms form bonds with electronegative atoms based on electrostatic properties and build hydrogen bridges. Hydrogen bonds can occur intramolecular or intermolecular [21]. The third factor is pH, the solubility depends on the pH that will be used [22]. Where an increase in the pH of the alpha-mangostin microgel mixture can cause a decrease in particle size from 548 nm to 200 nm. Alpha-mangostin at low pH shows the shape of the crystals, but with an increase in pH around pH 6, its physical shape changes [4]. Solubility depends on the pH used [22]. The fourth factor is the co-solvent, whose usage in a solution can change the solubility of organic compounds. Co-solvent can increase the solubility of non-polar drugs because it has a small hydrocarbon area. The addition of co-solvent can reduce the interaction between solvents, which leads to a decrease in surface tension and dielectric constant [21]. The fifth factor is temperature, which affects solubility. The solubility will increase due to the increase of temperature in an absorbing energy process. Conversely, in the process of releasing energy, the solubility will decrease due to the decreasing temperature [23]. Generally, an increase in temperature will increase the size of micelles, thereby increasing solubility [20].

The sixth factor is the nature of solutes and solvents, which depend on the concentration of the solute in the solvent to be used, for example, 100 grams of water can only dissolve 1 gram of Pb^{2+}[20]. The seventh factor is particle size; if the particle size decreases, the surface area to volume ratio increases. When the surface area of the particles increases, it will cause a greater interaction with the solvent, and in consequence, the solubility will increase. This basic principle is explained in the equation below [24].

$$\log \frac{S}{So} = \frac{2\,\gamma V}{2.303\ R.T.r}$$

Where so = the solubility of large particles, S = the solubility of fine particles, V = molar volume, γ = the surface tension of solid objects, and r = the radius of fine particles.

The eighth factor is the molecular size and molecular structure. The solubility of a substance will decrease if it has a higher molecular weight because larger molecules are difficult to be surrounded with solvent molecules to dissolve substances [24]. If there is a change in molecular structure it will result in a change in solubility [25]. The ninth factor is pressure; for solid and liquid solutes, solubility is not affected by pressure changes, but for the gas solutes, the solubility will increase with increasing pressure and decrease if pressure is lowered [20].

The techniques to increase the solubility of a compound can be grouped into physical modification, chemical modification, and other techniques. Physical modifications are techniques to change the physical aspects of the compound such as a reduction in particle size (micronization and nanosuspension), crystal modification (polymorph, amorphous, and cocrystal form), solid dispersion, and cryogenic techniques. Chemical modifications deal with the chemical property of the compound, such as changes in pH, using buffer solutions, replacing with derivatives, forming complex compounds, and using the nature of the salt. Other methods such as supercritical fluid processes, the use of auxiliaries such as surfactants, solvents, co-solvent, hydrography, and new excipients can also be used to increase the solubility [18].

Biopharmaceutics classification system (BCS)

The solubility and permeability characteristics of a substance are classified into four categories according to the Biopharmaceutics Classification System (BCS), which can be seen in fig. 1. BCS is one of the prognostics to facilitate the development of oral preparations in recent years and to establish bioavailability standards [26].

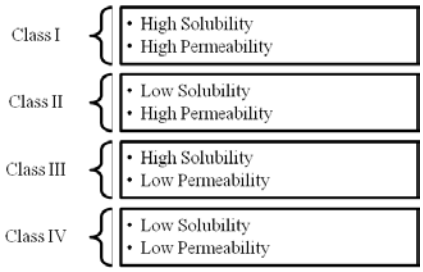
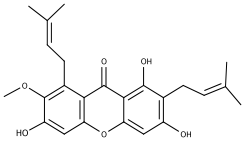


Fig. 1: Biopharmaceutics classification system (BCS)

Class II drugs have high permeation values but are low in dissolution rates. With the low dissolution, the value will be a limitation of the bioavailability of a drug [27]. More than 70% of newly discovered compounds fall into the BCS class II category [28]. One of the natural compounds that is categorized into the class II BCS is alpha-mangostin isolated from mangosteen peel extract [29]. The solubility of alpha-mangostin is 2.03 x 10^{-4} mg/ml in the water at 25 ^{0}C [30]. The solubility of an acceptable compound for a drug is>60 µg/ml [17]. Study of pharmacokinetic profiles *in vivo* shows the limited levels of alpha-mangostin in plasma [31].

Table 1: The properties of alpha-mangostin

Property	Description	References
Structure		[30]
Chemical names	1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl)xanthen-9-one	
Molecular formula	$C_{24}H_{26}O_6$	
Molecular weight	410.5 g/mol	
Physical state	Solid	
Color/form	Faint yellow to yellow powder	
Melting point	180-181 ^{0}C	
Solubility	In water 2.03 x 10^{-4} mg/ml at 25 ^{0}C Soluble in methanol	
Dissociation constants	pKa 1 = 3,68 (primary carbonyl) pKa 2 = 7,69 (secondary carbonyl) pKa 3 = 9,06 (tertiary carbonyl)	

The techniques used to improve the solubility of drugs of class II BCS are grouped into three major groups, namely traditional techniques, newer and novel techniques, and solid dispersion techniques. Traditional techniques consist of the use of solvent, hydrotropy, using dielectric constant solvents, amorphous formation, chemical modification of drugs, use of surfactants, the formation of inclusion complexes, solvent pH regulation, use of hydrates or solvents, use of ultrasonic waves, functional polymer technology, pre-precipitation, and evaporation. Newer and novel techniques consist of technology size reduction, nanoparticles, porous nanoparticles, nanocrystals, nanosuspensions, microemulsions, micellar, cryogenic technology, supercritical, lipid-based delivery systems, self-dispersing lipid formulations, micelle blends, and micelle polymers. Solid dispersion techniques consist of amorphous deposition of the crystalline carrier, continuous solid solution, discontinuous solid solution, substitutional solid solution, interstitial solid solution, glass suspension, and glass solution [23].

Several techniques have been carried out to increase the solubility of alpha-mangostin, as presented in table 2.

Nanoparticle technology

The technology of nanoparticles in nanomedicine has an important role in clinical therapy. Because of the size of the particles from 10^{-9} m causes the surface area of the nanoparticles to increase the contact surface with the solvent. The increase of surface area correlates with the increase of the rate of dissolution and absorption of drugs into the body [44]. To overcome the low solubility of an

active ingredient in water, both the active ingredient and the excipient can be reduced into nanosize [45]. The use of nanoparticle techniques can also increase permeation which leads to an increase in oral bioavailability [46]. The formation of nano-or microparticles is strongly influenced by the type and the concentration of the polymer to be used [47]. The use of cellulose derivative polymers forms a nano reservoir in the nanoparticle technique [48]. The use of chitosan polymeric nanoparticles can improve the physicochemical properties and performance of alpha mangostin [49], and in combination with eudragit S 100 [50]. The addition of co-solvents or surfactants to the formula affects the solubility and dissolution of cellulose [51].

Table 2: Techniques to increase the solubility of alpha-mangostin

Technique	Excipient	Result	References
Nanoparticles (nanocarrier, encapsulation)	Ethylcellulose: Methylcellulose (1:1)	Increased activity	[32, 33]
Nanoparticles (nanocarrier)	Proniosome	Increased permeation	[34]
Nanoparticles (nano micelles)	MPEG-PCL (Monomethoxy Poly Ethylene Glycol-PolyCaproLactones)	Increased solubility and activity	[35]
Nanoparticles (nanofiber)	Chitosan thiolated and polyvinylalcohol	Increased solubility	[36]
Self Microemulsion (SME)	Isopropyl myristate, Tween 80, PEG-400	Increased Area Under Curve	[37]
Size reduction	Sodium lauryl sulfate and poloxamer 188	Particle size reduction	[38]
Solid dispersion, Amorphous formation	Polyvinilpirolidon	Increased solubility	[17]
Amorphous formation	PLGA (Poly Lactic-co-Glycolic Acid)	Increased solubility	[39]
Drug carrier	Rice husk silica	Increased solubility	[40]
Solid dispersion	Vegetable oil	Increased bioavailability	[16]
Complex formation	Beta cyclodextrin	Increased solubility	[41, 42]
SNEDDS	Virgin Coconut Oil (VCO), tween 80, PEG 400	Increased permeation	[43]

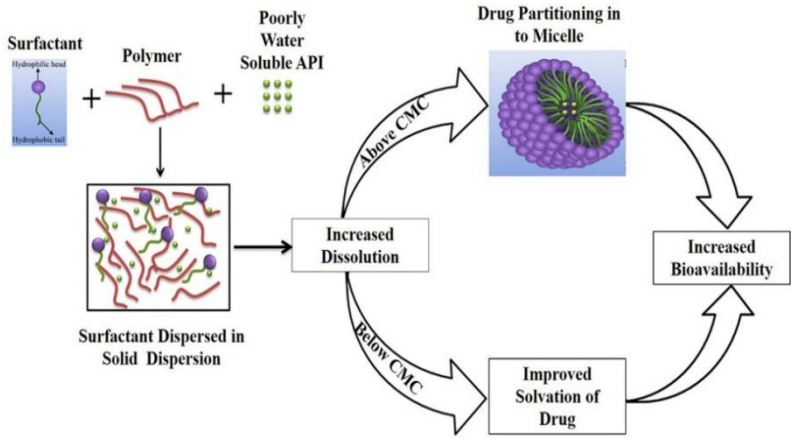


Fig. 2: Mechanisms of adding surfactants and polymers to solid dispersions to increase the bioavailability of a drug [52]

Alpha-mangostin, which is used for the treatment of *H. pylori* infections, is prepared with an encapsulation technique with a stable mucoadhesive nanocarrier in an acid solution. Ethylcellulose and methylcellulose (1:1) are used as a nanocarrier through self-assembly techniques [32]. The selection of polymers is very important, as the branched polymers are more soluble than non-branched (linear) polymers despite having the same molecular weight because the carbon chain is a hydrophobic group [53]. Here, cellulose derivatives are used as polymers in the process of forming encapsulation [54].

This encapsulation technique has been shown to have better cellular absorption and anticancer activity than non-encapsulated alpha-mangostin [33]. The use of cellulose derivates is to absorb large amounts of water, due to its large surface area, high porosity, and low fragility [55]. Cellulose also has an affinity in the formation of complexes with drugs and can reduce the crystallization of drugs in forming an amorphous matrix [56], and in doing so, demonstrates the efficacy of the treatment in mice after oral administration.

Proniosome (spans, soy lecithin, and cholesterol) can be used as an alternative nanocarrier. These compounds can increase the permeation of alpha-mangostin up to 1.8 to 8 times by using the coacervation method [34]. In another example, the formation of alpha-mangostin nano micelles produced a stronger effect on anti-melanoma when compared to free alpha-mangostin, making it suitable for use as a chemotherapy agent [35].

Self-microemulsion (SME)

Alpha-mangostin is loaded into self-microemulsion (SME). The results showed that this technique could increase the area under the curve (AUC) of alpha-mangostin by 4.75 times and the increase in distribution to the lymphatic organs. SME in nanosize is an efficient delivery system to increase the absorption, which will ultimately increase the bioavailability of alpha-mangostin [37]. This drug delivery system can help solve problems related to drug delivery that is difficult to dissolve [57].

Snedds

SNEDDS (self-nano-emulsifying drug delivery system) is defined as an isotropic mixture of oil, surfactant, and co-solvent, cosurfactant, or hydrophilic co-solvent. It has a particle size of less than 100 nm [58]. After the addition of isotropic mixture, it will interact with the fluids of the digestive tract and form an oil nanoemulsion in water. The formation of nanoemulsion will dissolve the drugs in small drops of oil, thereby expanding the surface area, which facilitates the release and absorption of the drug [59]. Illustration of SNEDDS formation can be seen in fig. 6.

The SNEDDS mechanism increases the solubility and bioavailability of drugs. If lipids enter the channel area in the Gastro Intestinal it will cause contraction of the gallbladder, which eventually stimulates the secretion of the bile duct and pancreas. Due to the contractions,

SNEDDS will create a coarse emulsion that increases the dissolution of hydrophobic drugs. Lipids also cause delays in the emptying of the stomach, so the hydrophobic drug transit time slightly increases. In the end, the drug dissolution improves and the absorption increases [60].

The SNEDDS method produces small round particles with oxidative stability and that are free-flowing, so they can be developed as solid dosage forms [61]. SNEDDS is also a promising carrier because it improves the bioavailability and therapeutic effects of the class II BCS drugs [62]. And solubility of drugs that are lipophilic [63]. SNEDDS improve the dissolution and increase intestinal permeation. As a result, the efficacy of orally administered drugs increases [64]. A report showed SNEDDS could increase the diffusion rate of mangosteen peel, taking into account the solubility of the active component in oil, surfactants, and co-solvent to obtain optimal formulation [43].

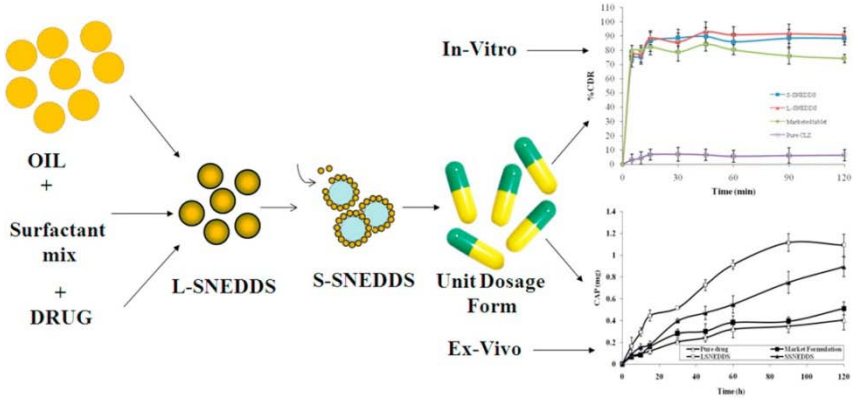


Fig. 3: Illustration of self-nano-emulsifying drug delivery system (SNEDDS) formation [65]

Size reduction

The size reduction of alpha-mangostin using high-pressure homogenization (HPH) with the addition of stabilizers turns out to be effective. The efficiency of reducing the size of alpha-mangostin suspension particles significantly decreases to them micron size by using sodium lauryl sulfate stabilizer and poloxamer 188 [38]. HPH has a principle of cavitation in the aqueous phase. The cavitation force in a particle is high enough to turn microparticles into nanoparticles [18].

Amorphous formation

The amorphous form is an irregular shape of a molecule with a higher energy level than a crystal. In the digestive tract, the amorphous form will cause a higher concentration gradient and cause an increase of permeation through the intestinal membrane [28]. Amorphous formation by using a solid matrix can increase the dissolution, solubility, and bioavailability of a drug, as the amorphous phase has a weak lattice that causes the contact and wetting process of the solvent [66]. The free energy, enthalpy, and entropy produced by amorphous solids are also relatively high when compared to crystalline shapes due to the irregular structure of amorphous solids [67]. Although sometimes amorphous formation is still constrained in terms of stability, the addition of a stabilizer can increase the stability of the amorphous form [68].

The physical changes in crystal alpha-mangostin to amorphous form increase solubility from the original 0.2±0.02 g/ml can be increased to 2743±11 g/ml [17]. The microencapsulation of alpha-mangostin can also change the crystalline form of alpha-mangostin to an amorphous form, which improves its water solubility. As a result, the bioavailability of the drug increases [39]. The use of rice husk silica as the carrier of alpha-mangostin, via the sol-gel method, has been investigated and showed the changing of the crystal form of alpha-mangostin into amorphous form, increasing the solubility of alpha-mangostin [40].

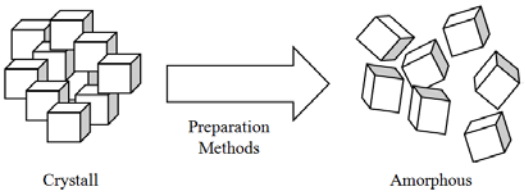


Fig. 4: Crystal and amorphous shapes

Solid dispersion

Solid dispersion is a dispersion technique of one or more active substances into a matrix, or an inert carrier in a solid state. Principles to reduce particle size, better wetting processes, and reducing agglomeration can produce a high concentration of a drug in the gastrointestinal fluids, which will increase the solubility and bioavailability of the drug [69]. Solid dispersions usually have two different components, usually, the matrix is hydrophilic, while the drug or API is hydrophobic. The matrix used can be either a crystal matrix or an amorphous shape matrix [70]. The addition of surfactants in solid dispersions is needed to reduce recrystallization to increase dissolution and stability [52].

Solid dispersion systems have an advantage over other systems for increasing oral bioavailability without changing active targets. It is achieved by forming salts or incorporating polar or ionized group compounds into the structure of the drugs [71]. Solid dispersions are made by various methods, as shown in fig. 4.

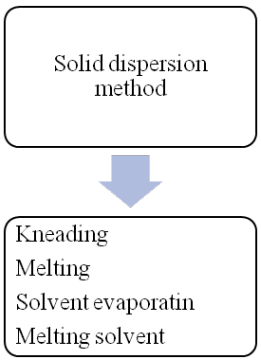


Fig. 5: Solid dispersion method [72]

Solid dispersion technique is applied to alpha-mangostin using a solvent evaporation method, with the formation of a complex between alpha-mangostin and PVP (polyvinylpyrrolidone), to produce alpha-mangostin with increased solubility [17]. PVP is used as a matrix because PVP is a non-toxic substance, has very soluble properties in the water, is inert, and thermostable [73]. PVP also has a small size to increase the wet ability and solubility of a drug [72].

Soft capsules containing alpha-mangostin with vegetable oil as a matrix also can improve the bioavailability of alpha-mangostin. The distribution of alpha-mangostin can be detected in the brain which means alpha-mangostin can cross the blood-brain barrier after oral administration [16].

Complex formation

Chemical modification by forming a complex between alpha-mangostin and quaternate beta-cyclodextrin combined can increase the solubility of alpha-mangostin [41]. Cyclodextrin is a cyclic oligosaccharide that can form non-covalent bonds with several drugs so that it does not change the physicochemical properties of the drug. The primary and secondary hydroxyl cycle of cyclodextrin is a potential site for the modification of a drug [74]. An illustration of cyclodextrin complex formation with drugs can be seen in fig. 5. Cyclodextrin is a carrier of drugs that are non-toxic and biodegradable [75]. Complex formation with cyclodextrin is also preferable because of the increase of free energy (ΔG) and complex energy (ΔE) [76]. The beta-cyclodextrin bond with alpha-mangostin produces about 14 hydrogen bonds [77]. Beta cyclodextrin will attach to the nanoparticle conjugate, which will be positively charged by the ionic bond [78]. Beta cyclodextrin has 2 derivatives of 2.6 dimethyl-□cyclodextrin and 2-hydroxypropyl-□cyclodextrin, which are commonly used to form inclusion complexes with alpha-mangostin. 2-hydroxypropyl-□cyclodextrin is able to bind with alpha mangostin to form complex bonds in hydrogel formulation [79]. The results showed 2.6 dimethyl-□cyclodextrin results in a more soluble complex than 2-hydroxypropyl-□cyclodextrin [42]. The formation of a complex with cyclodextrin usually uses two methods, namely the solvent evaporation and kneading methods, but the solvent evaporation technique showed significant improvement on the drug's release and solubility [80].

The use of surfactants

The use of surfactants increases the dissolution of compounds in water. Surfactants increase the dissolution of lipophilic drugs in aqueous media and reduce surface tension. When the surfactant exceeds the critical micelle concentration, micelle formation occurs trapping the compounds in the micelle (micellization process), which increases the solubility of the compounds. Surfactants also increase the wetting of solids, thereby increasing the rate of disintegration into finer particles [18].

Various methods have been used to increase the solubility of alpha-mangostin as previously described. The results of these various methods were certainly characterized to ensure that there was indeed an increase in the solubility of alpha-mangostin. Characterization was carried out such as FT-IR spectra examination (fig. 7) which showed that there was vibrational streaching of alpha mangostin on the hydroxyl groups that appeared at 3416.1 and 3251.7 cm-1. In the solid dispersion of alpha mangostin mangostin (SDs), the bands at 3416.1 and 3251.7 cm-1 and at 1608.8, 1049.9, 1009.8, 849, 812.4, and 782.7 cm–1 disappeared. The stretching of the PVP carbonyl groups appeared at 1646.5 cm-1 indicating there was a redshift to a mean of 1649±0.8 cm-1 in SDs. These results indicate the participation of the OH group in alpha mangostin in the interaction of the hydrogen bond with the PVP carbonyl group. On the other hand, the peak position of the OH alpha mangostin group in and the physical mixture alpha mangostin (PMs) slightly changed [17].

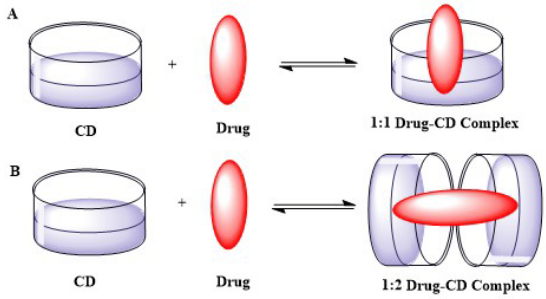


Fig. 6: Illustration of cyclodextrin complex formation with drugs [81]

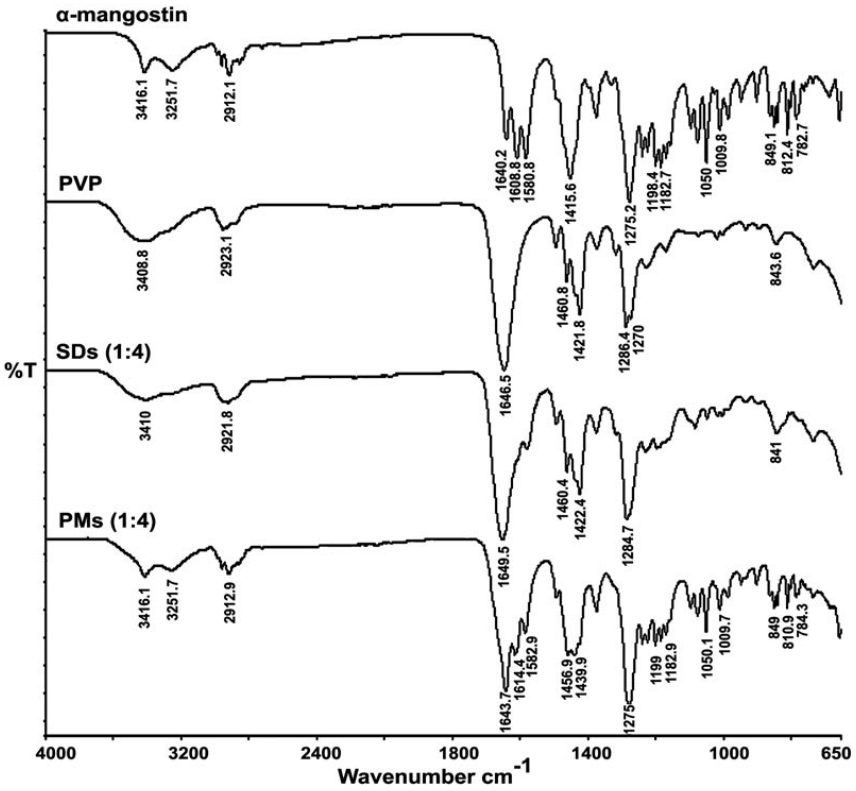


Fig. 7: FT-IR spectrum [17]

Characterization using Differential scanning calorimetry (DSC) of alpha mangostin, PVP, solid dispersion alpha mangostin (SDs) and physical mixture alpha mangostin (PMs) is illustrated in fig. 8. Alpha Mangostin produces sharp endothermic peaks at 180 °C according to its melting point, while PVP shows wide peaks in the temperature range of 100 °C-160 °C. The endothermic peaks of alpha mangostin disappeared in all SDs and PMs, indicating an interaction between alpha mangostin and PVP [17].

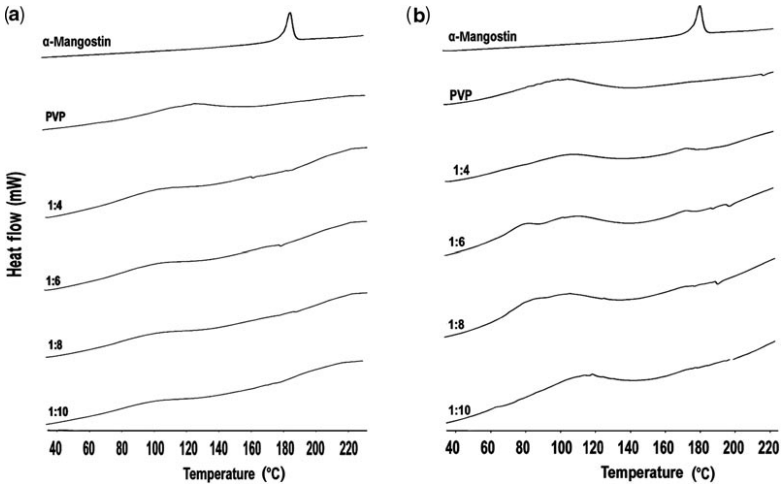


Fig. 8: Differential scanning calorimetry thermograms of (a) "-mangostin solid dispersions and (b) physical mixtures [17]

Characterization of powder XRD pattern showed alpha mangostin peaks appeared at the diffraction angle of 2θ at 15.9°, 18.2°, 20°, 23.3°, 26°, 30.6°, and 32.2° (fig. 9) indicating that alpha mangostin was present in crystalline form. PVP (K29/32) is an amorphous powder and does not show any peaks. The SD diffraction pattern showed loss of alpha-mangostin crystal peaks, indicating that alpha-mangostin was converted from crystals to amorphous forms. This results in an interaction between alpha-mangostin and PVP and may help explain the increase in solubility of the compound [17].

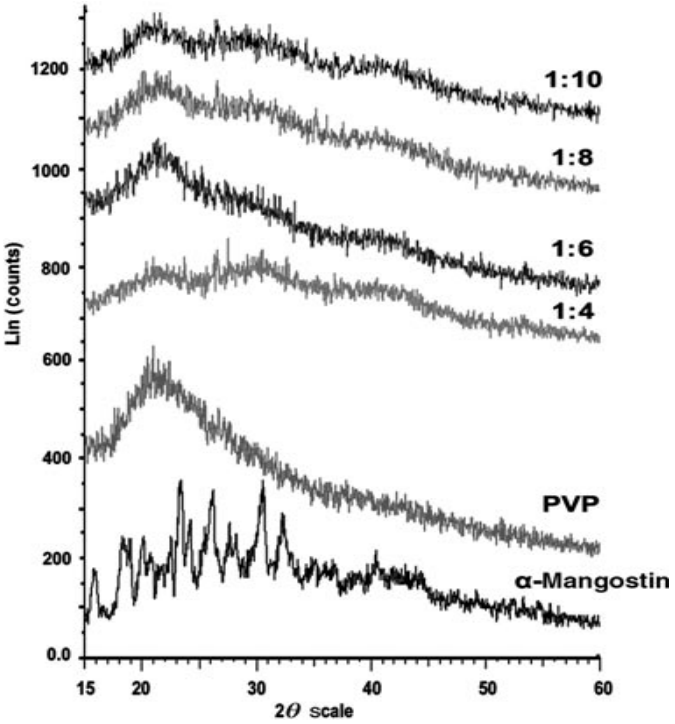


Fig. 9: X-ray diffraction patterns of alpha-mangostin solid dispersions [17]

CONCLUSION

Alpha-mangostin has been known to have low solubility, correlated with its low bioavailability in the blood. However, alpha-mangostin has many pharmacological activities, therefore, various techniques are needed to increase the solubility of alpha-mangostin. Currently, many techniques have been developed to increase the solubility of alpha-mangostin through physical modifications such as a reduction in particle size (nanoparticle technology), amorphous formation, solid dispersion, and chemical modification, such as the formation of complex compounds by adding surfactants and co-solvent. Among the various techniques, nanoparticle technology is most widely used to

increase the solubility of the alpha-mangostin because it has many ways and mechanisms to increase solubility. Among them, as previously discussed, the reduction in particle size in nanotechnology increases the solubility of drugs by means of expanding the surface area of the particles. The use of water-soluble (hydrophilic) excipients as a component of nanoparticles increases the solubility of the drug due to the hydrogen bonding interaction between the excipient used and water molecules. The use of surfactants also increases the solubility of drugs with high lipophilicity properties through reduced interfacial tension in nanotechnology.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declare none

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