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REVIEW

Inclusion complex essential oil into cyclodextrins and its optimization via experimental designs: a review

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Abstract

The scope of this review gives an insight into the inclusion complex of essential oil (EO) using cyclodextrins (CDs), including mechanism, preparation and characterization. It also mentioned that this process was influenced by the size of the inner cavity of CDs and the chemical profile of EOs. The scope has looked forward to derivative CDs, which are further modifications of native CDs to achieve more solubility and efficiency by adding hydroxyl, sulfobutylether, and methyl groups, and by using an esterification process. Subsequently, the cyclodextrin metal organic frameworks, which correspond to native CDs connected via a metal cation, were anticipated as a biocompatible porous material demonstrating a more sustained release of EOs. Indeed, supramolecular cyclodextrins obtained through the covalent binding between cyclodextrins and cross-linked reagents led to higher water solubility, stability, and sustained release. It then moves on to combining CD with biopolymer by grafting or dual encapsulation, which was studied to modulate the profile of EO release. It then moves on experimental designs used to optimize the encapsulation efficiency to reduce the amount of CD and EO added, minimize energy and time, and optimize the medium efficacy.

Keywords Essential oils · Inclusion complex · Cyclodextrin · Experimental designs

Introduction

Essential oils (EOs) and their components possess a wide range of chemical and biological properties that favor their use in food, health, and beauty fields, making them ubiquitous in our daily lives (Kfoury et al. 2019). However, EOs suffer from their very low solubility in aqueous phases; they are also very volatile and sensitive to extrinsic factors such as temperature, oxygen, light, and other contaminants. These drawbacks can be overcome using an encapsulation process, including inclusion complex via cyclodextrins.

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Cyclodextrins (CDs) are organic natural oligosaccharides made from the enzymatic degradation of starch. The attraction of CDs is mainly attributable to their capacity for inclusion and ability to include desirable physicochemical properties of guest molecules, such as apparent solubility and stability (Krabicová et al. 2020). In addition to their exceptional ability to create host–guest supramolecular interactions due to their toroidal shape and non-polar interior cavity, cyclodextrins could also be bonded in various ways to form more complex structures (Petitjean et al. 2021).

The native cyclodextrins (CDs), also called natural or parent CDs, were obtained directly through the action of Bacillus amylobacter bacteria on starch (Arruda et al. 2021). Generally, they are three native CDs classified according to the number of glucopyranose units; alpha-cyclodextrin (αCD, 6 units), beta-cyclodextrin (βCD, 7 units), and gamma-cyclodextrin (γCD, 8 units) (Fig. 1A). Indeed, native CDs containing 9 or more glucose units conventionally named large ring CDs. The cyclic shape and arrangement of hydroxyl groups formed a hollow cone for CDs, with an exterior face of polar character providing their water solubility and a non-polar interior perfect for incorporating the hydrophobic compounds (Fig. 1B).

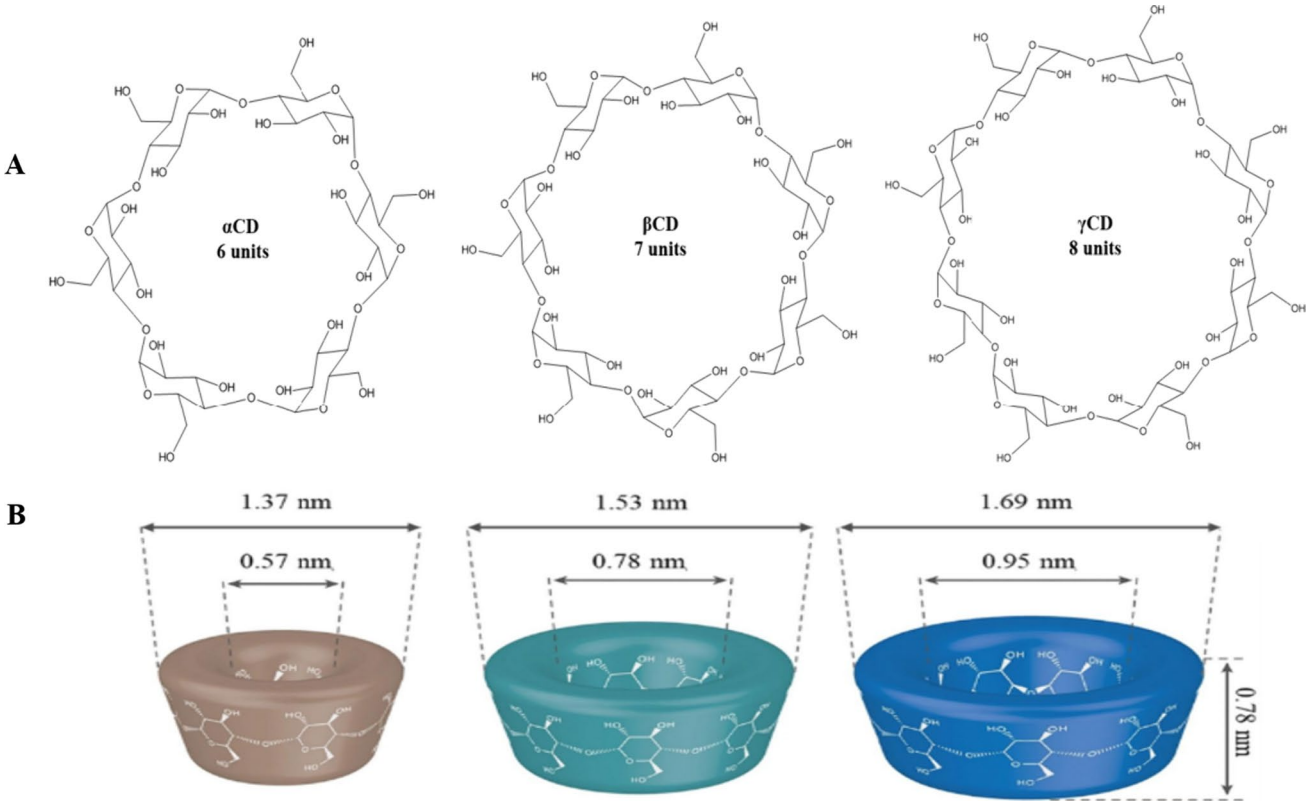

Fig. 1 Chemical structures of native cyclodextrins (**A**). 3D geometry characteristics of native CDs (**B**)

Thus, these geometry characters and varied sized of CDs provide a favorable environment for the accommodation of essential oils and its compounds (Kringel et al. 2017).

During the inclusion complex (IC), no covalent bond is established between CD and essential oil compounds, and it is defined as an equilibrium dissociation-association. Practically, the IC prepared by various methods in which each preparation process affects their physico-chemical and biological properties. Technologies have recently been employed to minimize time and energy consumption, including ultrasound and microwave. Indeed, several of experimental techniques and theoretical studies were combined to confirm and understanding the inclusion process. The native CDs (mainly βCD) led to an inclusion complex with higher physicochemical properties and effective activity over time, despite at times having lower encapsulation efficiency as well as limited solubility, stability, and biological efficacy. Therefore, variety of strategies based via modified cyclodextrins were employed to ensure high efficiency, stability, solubility, and biological activities. In addition to the type of cyclodextrins used, other parameters affected the preparation of the inclusion process essential oil into CDs, which experimental designs were employed to optimize the crucial factors affecting the encapsulation efficiency.

Considering all of this, the scope of this paper gives a deeper understanding of the inclusion complex of EO and the different strategies employed based on CDs. Indeed, experimental designs defined and optimized the key parameters that affect the inclusion efficiency.

Inclusion complex via cyclodextrins (CDs)

Mechanism

Essential oil/cyclodextrin inclusion complexes are a class of supramolecular host/guest assemblies that take place via several non-covalent interactions, such as electrostatic, hydrogen bonding, Van der Waals, and hydrophobic interactions (Abdellatif et al. 2023). Indeed, thermodynamic driving forces, including enthalpy and entropy changes, mainly drive the host–guest complex interaction between essential oil and cyclodextrin (Araújo et al. 2021). The molecular inclusion mechanism was activated when water molecules occupied the hydrophobic cavity of CDs prepared in an aqueous solution, which is energetically unfavorable (Fig. 2). The water molecules then escape from the cyclodextrin cavity, facilitating the substitution of EO via a favorable energetic process and apolar-apolar interactions between the carbon skeleton

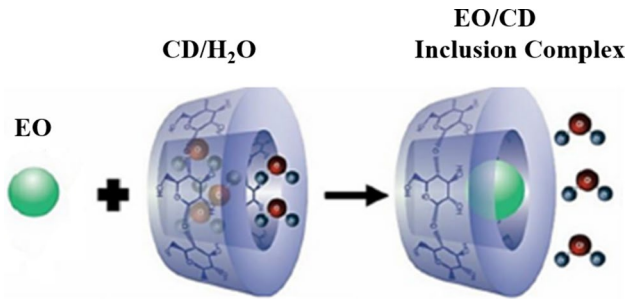

Fig. 2 The mechanism of inclusion complex essential oil/beta-cyclodextrin

of CDs and guest molecules, which decrease its degree of release to a one-dimensional rotational degree. The system EO/CD gains stability due to the Van der Waals involved and sometimes by hydrogen bonding, mainly for oxygenated terpenes.

Preparation and drying methods

Practically, reports on the preparation of IC have included various techniques such as co-precipitation, slurry and paste complexation, damp and dry mixing, and extrusion. In line with this, several studies investigated the preparation's impact on its physico-chemical characteristics and biological properties. Tao et al. 2014 investigated the impact of the inclusion complex preparation of thyme essential oil including kneading (KN) and freeze-drying (FD) methods on the entrapment efficiency, particle sizes, and antimicrobial activity, and they reported that FD had the best one. On the other hand, scanning electron microscopy showed a decrease in the size of the inclusion complexes of *Hyptis pectinata* essential oil with βCD obtained by slurry method more than paste procedure (Menezes et al. 2015). Indeed, the inclusion complexes of *Citrus sinensis* essential oil with βCD prepared by the complexation method had largest inclusion content compared to the co-precipitation method. Therein, the thermogravimetric analysis showed that the slurry complexation was the best method inclusion with mass loss of 6.9% over the paste method that was 6.0% (Andrade et al. 2017).

Generally, the inclusion complexes EO/βCD prepared by the co-precipitation method, and the physical mixture is usually used as a control. Firstly, βCD was dissolved in water with continuous stirring under 35 up to 60 °C (Huang et al. 2020), or dissolved into a mixture water/ethanol to increase the water solubility of βCD (Anaya-Castro et al. 2017). After obtaining the βCD solution, the EO was added slowly in the free solvent (Matshetshe et al. 2018; de Santana et al. 2020), or diluted in ethanol (10%) used as a suitable surfactant (Garcia-Sotelo et al. 2019), and by addition of an emulsifying agent usually Tween 80 (Yang et al. 2019). In line with this, Ogata et al. 2020 examined the effect of dilution solvent of cyclamen aldehyde in methanol, and acetone and dropped directly into an aqueous solution of βCD, and obtained that the third condition has a suitable yield. Indeed, Nakhle et al. 2023 investigated the ability to encapsulate EOs and their solvation into a deep eutectic solvent (DES).

The drying process of the inclusion complex of EO was performed using an oven at 40 up to 60 °C (Kringel et al. 2017), and this process was recently was developed using a lyophilizer (Fig. 3) to overcome the possibility of releasing EO and degradation of IC (Alizadeh and Nazari 2022). However, the spray drying method requires a high temperature, which is detrimental to EO due to its heat sensitivity, demonstrating that few studies have been reported (Veiga et al. 2019). Recently, technologies, including ultrasound and microwave, have been employed extensively to minimize time and energy consumption. In line with this, *Cinnamomum zelanicum* EO was encapsulated through βCD with sodium caseinate under ultrasonic conditions (Erfani et al. 2022). Indeed, resveratrol was incorporated into βCD under microwave treatment (Iskineyeva et al. 2022). βCD inclusion complexes containing p-anisaldehyde using the ultrasound/microwave-assisted co-precipitation method (Lin et al. 2022). These

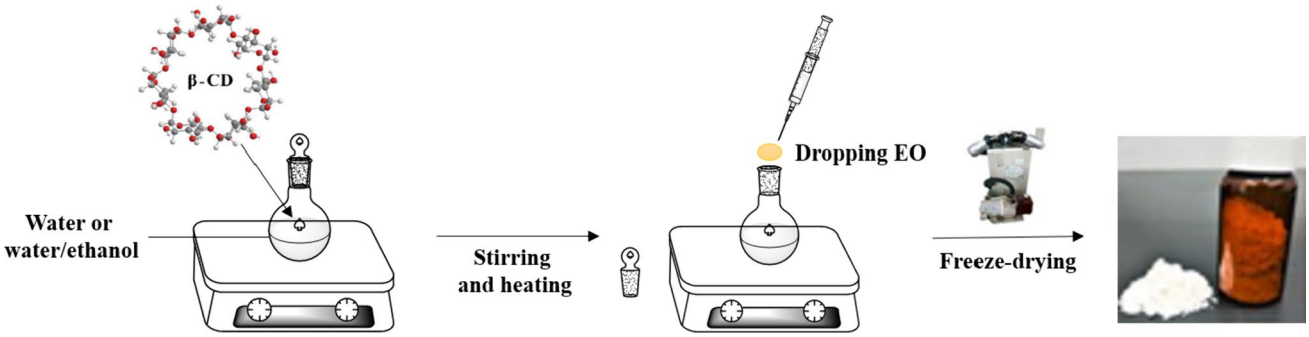

Fig. 3 Preparation of inclusion complex EO/βCD via freeze-drying method

technologies considered as an environmentally friendly and efficient method, significantly reduce synthesis duration, increase the yield and improves the product's quality.

Characterization

Various techniques and methods were combined to confirm the inclusion complex's successful formation, by investigating the morphological and crystalline characteristics, spectroscopic properties, chromatography analysis, thermal behavior and magnetic environment. The morphological examination was assessed via scanning electron microscopy (SEM) and transmission electron microscopy (SEM), which could give a view of the structure changes during the formation of the IC, and estimate the size of the obtained inclusion complex (Wadhwa et al. 2017). Additionally, native CDs are characterized by their crystalline forms and confer unique XRD patterns with intense peaks. Moreover, when the complex was chelated, the crystalline forms recognized a decrease, manifesting by a change in intensity and disappearance of the characteristic peaks (Ogata et al. 2020).

On the other hand, UV–visible spectroscopy is commonly used to determine the inclusion equilibrium constant, phase solubility, and stoichiometric ratio between CD and EO compound, as well as employed to determine the encapsulation efficiency (Xiao et al. 2021). These properties could also be determined via chromatographic analysis including GC (static headspace gas chromatography) and HPLC (High-liquid performance chromatography). Other spectroscopic methods such as infrared, Raman, circular dichroism, and fluorescence spectroscopies were also employed to provide information about the complex's molecular structure and functional properties.

Furthermore, the thermal analysis approves the stability of the complex under heating via thermogravimetric (TG)–differential thermogravimetric (DTG), differential scanning calorimetric (DSC) analysis, and other recent thermal techniques such as isothermal titration calorimetric (ITC) (Hădărugă et al. 2019).

Indeed, nuclear magnetic resonance (NMR) is also effective for analyzing EOs inclusion inside CDs, based on the interpretation of changes in the magnetic environment of the CD nuclei (mainly H and C) during complexation with EOs. NMR could also be used to deduce a complex's stability constant and stoichiometry (Siva et al. 2020). Additionally, the development of two-dimensional NMR techniques like NOESY and ROESY has made it possible to highlight the dipolar interactions between CD and EOs (Locci et al. 2004).

However, experimental techniques are still insufficient to understand the structure and process of the inclusion complex clearly. Therefore, the employment of molecular mechanics (MM), dynamic simulations (MD), Monte Carlo simulations, and quantum calculations (QC) are the theoretical tools to give more information about complexation processes (Dodziuk and Lukin 2000).

Various approaches based on cyclodextrins (CDs)

Native CDs

The size of the inner cavity of native cyclodextrin plays a critical role in the inclusion process, promoting beta cyclodextrin (βCD) suitable for the complexation of EOs and its compounds, which have between 200 and 800 g/mol in a molecular weight. Therefore, a huge number of essential oil have increasingly encapsulated through βCD, such as *Rosa damascene* (Hadian et al. 2023), *Plectranthus ornatus* (da Silva et al. 2023), *Rosmarinus offininalis* (Halahlah et al. 2021; Ben Abada et al. 2023), *Origanum vulgare* (Shi et al. 2022), *illicium verum* (Wu et al. 2022), *zanthoxylum bungeanum* (Qin et al. 2022), *Ocimum basilicum* and *Syzygium aromaticum* (Miyoshi et al. 2022), wampee fruit pericarp (Luo et al. 2022), *Lippia grata* Schauer (Beserra-Filho et al. 2022), *Plectranthus ornatus* (Castro et al. 2022), *Callistemon viminalis* (Martins et al. 2021), orange (Kringel et al. 2021) and sea buckthorn fruit essential oils (Zhang et al. 2021). Indeed, the major compound of EOs mainly mono and sesquiterpenes were extensively encapsulated through βCD including thymol, eugenol, resveratrol, and cinnamaldehyde (Ma et al. 2023). On the other side, a few reports indicate the uses of alpha-cyclodextrin (αCD) as the carrier for essential oil and its compounds due to the smaller size of its inner cavity. Thus, Kfoury et al. 2015 demonstrated its limited employment as the carrier for estragole (the main component of bail and tarragon EOs). In addition, Ciobanu et al. 2013a, b were revealed its poor ability to retention of aroma compounds from *Mentha piperita* essential oil (pulgeone, menthone, menthol and eucalyptol). However, αCD has been considered a suitable carrier for linear compounds including methyl 2-octynoate (Decock et al. 2008). On the other side, the large interior cavity of gamma cyclodextrin (γCD) could be more suitable for high molecules such as guaiazulene (Inoue et al. 2019), thymol (Barbieri et al. 2018) and eucalyptol (Ciobanu et al. 2013a). γCD acts as a superior wall material to the βCD in the thyme essential oil (Ahmed et al. 2022). Additionally, the large cyclodextrins (LRCD) have proven to be a perfect wall material for improving the antimicrobial activity of *Litsea cubeba* EO (Cao et al. 2023). Indeed, the encapsulation through LRCD could improve the applications of tea tree EO by enhancing its water solubility more than 329 times (Cao et al. 2021).

Overall, using βCD as an encapsulating agent led to an inclusion complex with higher physico-chemical properties and effective activity over time, despite at times having lower encapsulation efficiency and limited solubility, stability, and biological efficacy. Considering all of this, the scope of the coming sections gives an insight into strategies based on including complex essential oils via modified cyclodextrins to ensure high efficiency, stability, solubility, and biological activities.

Derivative CDs

The chemical modification of native CDs has been widely investigated, which could improve water-solubility, stability, and biological activities (Table 1). Among these modifications, the substitution via hydroxypropyl, sulfobuthylether and methyl CDs are explored, as well the esterification process via succinic acid (Fig. 4). The synthesis modification affords, respectively, hydroxypropyl beta cyclodextrin (HPβCD), sulfobutyl ether betacyclodextrin (SBEβCD), randomly methyl betacyclodextrin (RAMEB) and succinic acid beta cyclodextrin (SACD).

For instance, hydroxypropyl has been attached to the hydroxyl groups on βCD molecules to produce a wall material with relatively high aqueous water solubility (60 g/100 mL), lower toxicity, and satisfactory inclusion ability. Several studies have reported the utilization of hydroxypropyl beta cyclodextrin (HPβCD) such as *Psidium cattleyanum* S. (Mendes et al. 2023), nutmeg (Xi et al. 2023), *Litsea cubeba* (Li et al. 2022a, b, c, d), *Psidium guajava* L. (Mendes et al. 2022), tea tree oil (Jiang et al. 2021a, b), *Eucalyptus staigeriana* (Yuan et al. 2019a, b), lavender (Yuan et al. 2019a, b), star anise (Zhang et al. 2018) and clove (Cetin Babaoglu et al. 2017) essential oils. In addition to higher inclusion complex efficacy, the results showed that the encapsulation of essential oils via HPβCD improved the physico-chemical properties such as water solubility, sustained release, and thermal stability, as well as HPβCD was used as a suitable shell to increase the biological activities of EOs. Similarly, Rakmai and co-workers demonstrated the ability of this shell agent to improve solubility and biological activities (antioxidant and antibacterial) for guava leaf oil (Rakmai et al. 2018), black pepper (Rakmai et al. 2017a), yarrow (Rakmai et al. 2017b) essential oils. Indeed, HPβCD has the potential ability to incorporate monoterpenes including d-limonene (Marinho et al. 2022), carvacrol (Li et al. 2022a, b, c, d), borneol (Santana et al. 2021), thymol (Rodríguez-López et al. 2020) and citral (Campos et al. 2019).

On the other hand, sulfobutyl ether betacyclodextrin (SBEβCD) possesses higher aqueous solubility more than 1200 mg/mL, and lower toxicity. Moreover, Kfoury et al. 2017 were demonstrated that SBEβCD (denoted as Captisol®) has a higher sustained release ability than HPβCD for many essential oils such as *Artemesia dracunculus* (Tarragon), *Citrus aurantifolia* (Lime), *Citrus reticulate Blanco* (Mandarin), *Melaleuca alternifolia* (tea tree), *Rosamarinus offcinalis Cineoliferum* (Rosemary), and *Melaleuca quinquenervia* (Niaouli).

Also, recent studies have investigated the ability of randomly methyl beta-cyclodextrin (RAMEB) to encapsulate thyme, lemon balm, lavender, and peppermint EOs and their main compounds thymol, linalool, borneol, citral, and menthol (Das et al. 2019). The results indicated that encapsulation via RAMEB protects the essential oils against oxidative environments and elevates their antifungal and antimicrobial activities. Indeed, RAMEB not only revealed the ability of RAMEB on the bioavailability, solubility and stability of cuminaldehyde and isoeugenol, but also enhanced their antibacterial and antioxidant effects (Siva et al. 2020). Furthermore, the incorporation of β-caryophyllene into RAMEB increases its water solubility and significantly improves its anti-inflammatory, gastric protection and antioxidant activities (Santos et al. 2017).

In addition to the alkylation process, esterification of the hydroxyl groups of βCD has been recently explored using succinic acid to afford succinic acid beta cyclodextrin (SACD). For instance, Ez-Zoubi et al. 2023 reported that *Artemisia herba-alba* EO encapsulation via SACD could improve its antifungal activity. Indeed, Hu et al. 2022a, b demonstrated that incorporating Artemisinin into SACD improves its solubility, stability, and antibacterial activity.

Overall, the chemical modification of native CDs, notably βCD, could pave other researchers to explore more investigations for the encapsulation of other EOs, and prepare novel CD derivatives based on other functional groups such as amino, azide, and triazole. It could create other derivatives monosubstituted avoiding the large substituents, which prevent the inclusion of EOs due to steric hindrance influences.

Cyclodextrin metal organic frameworks

Cyclodextrin metal–organic frameworks (CD-MOFs), invented by Smaldone et al. 2010, are a class of crystalline porous material consisting of native cyclodextrins (α,β and γCD) crosslinked via metal cation (Fig. 5), which potassium (K) was generally used as a metal unit due to its lower cost (Jiang et al. 2021b).

The inclusion complex of EOs via CD-MOFs (mainly based on β and γCD) offered huge food applications due to bioavailability, biocompatibility and flexibility, as well as afford more ability of various guest molecules due to its different shapes and pores sizes (Han et al. 2018).

As summarized in Table 2, recent studies mainly reported the encapsulation of essential oils via γCD-MOFs, including oregano EO (He et al. 2023), cinnamaldehyde (Che et al. 2022), benzaldehyde (Kathuria et al. 2022), and d-limonene

Table 1 Encapsulation of essential oils via CD derivatives

CD derivatives	Essential oils	Functional properties	References
HPβCD	*Psidium cattleyanum* EO	Water solubility	(Mendes et al. 2023)
		Thermal stability	
		Larvicidal activity	
	Myristica fragrans Houtt. (nutmeg) EO	Thermal stability	(Xi et al. 2023)
		Control release	
		Antioxidant activity	
	Litsea cubeba EO	Volatility	(Li et al. 2022a, b, c, d)
		Thermal stability	
		Antifungal activity	
	Psidium guajava L. EO	Larvicidal activity	(Mendes et al. 2022)
	Tea tree *oil*	Thermal stability	(Mendes et al. 2022)
		Sustained release	
		Antifungal activity	
	Eucalyptus staigeriana EO	Thermal stability	(Yuan et al. 2019a, b)
		Antimicrobial activity	
	Lavender *EO*	Thermal stability	(Yuan et al. 2019a, b)
		Antibacterial activity	
	Star Anise *EO*	Volatile stability	(Zhang et al. 2018)
		Antimicrobial activity	
	Guava leaf, black pepper and yarrow EOs	Water solubility	(Rakmai et al. 2018)
		Antioxidant and antimicrobial activities	
	Clove EO	Thermal stability	(Cetin Babaoglu et al. 2017)
		Control release	
		Antioxidant activity	
	D-limonene	Antiarrhythmic effects	(Marinho et al. 2022)
	Carvacrol	Water solubility	(Li et al. 2022a, b, c, d)
		Thermal stability	
	Borneol	Thermal stability	(Santana et al. 2021)
	Thymol	Antifungal activity	(Rodríguez-López et al. 2020)
	Citral	Anti-hyperalgesic and anti-inflammatory activities	(Campos et al. 2019)
SBEβCD (Captisol®)	Tarragon, Lime, Mandarin, Tea tree, Rosemary and Niaouli EOs	Water solubility	(Kfoury et al., 2017)
		Sustained release	
RAMEB	Lemon balm, lavender, peppermint and thyme EOs	Water solubility	(Das et al. 2019)
		Antioxidant, antifungal and antimicrobial activities	
	Cuminaldehyde and isoeugenol	Water solubility	(Siva et al. 2020)
		Thermal stability	
		Antioxidant and antibacterial activities	
	β-Caryophyllene	Water solubility	(Santos et al. 2017)
		Anti-inflammatory, gastric protection and antioxidant activities	
SACD	*Artemisia* herba-alba EO	Thermal stability	(Ez-Zoubi et al. 2023)
		Antifungal activity	
	Artemisinin	Water solubility	(Hu et al. 2022a, b)
		Thermal and heat stability	
		Antimicrobial activity	

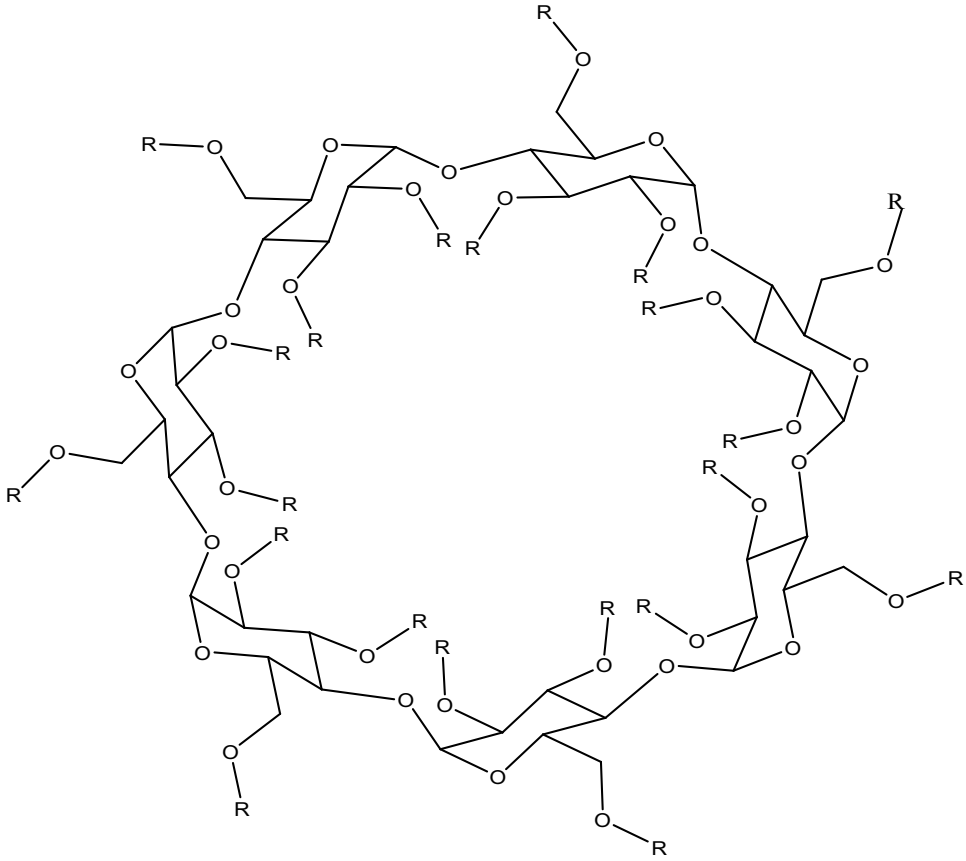

Fig. 4 Structures of βCD derivatives including HPβCD (R=CH_2–CHOH–CH_3), SBEβCD (R=$(CH_2)_4$-SO_3Na), RAMEB (R=CH_3) and SACD (R=CO–$(CH_2)_2$–COOH)

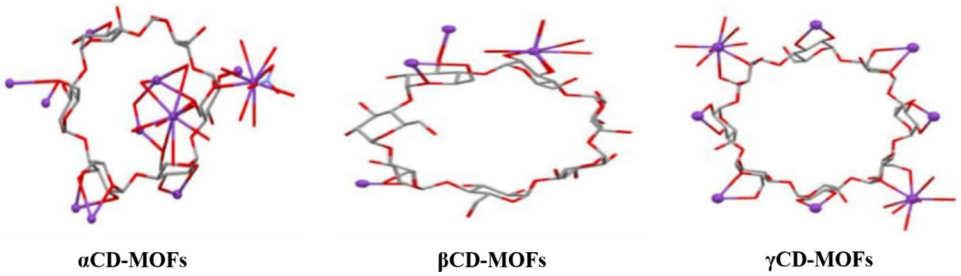

Fig. 5 Cyclodextrin metal organic frameworks consisting of K^+ ions and native CDs

(Zhou et al. 2021). These studies concluded that γCD-MOFs exhibited outstanding effective carriers to deliver EO. Indeed, the inclusion complex of thymol via γCD-MOFs showed higher stability, sustainability and antibacterial activity compared to γCD (Pan et al. 2022). Additionally, γCD-MOFs showed higher incorporation ability to encapsulate terpene fragrances (myrcene and limonene), and superior sustained release compared to γCD (Zhang et al. 2019). On the other hand, βCD-MOFs have considerable potential as an alternative carrier and demonstrates their uses as effective agents for EOs, such as *Origanum compactum* (Ez-zoubi et al. 2023), lavender (Wang et al. 2021) EOs. Indeed, the microencapsulation of *Syzygium aromaticum* (clove) EO by βCD-MOFs preserves its antioxidant activities and improves thermal and pH stability (Wang et al. 2023). Furthermore, menthol was released from βCD-MOFs significantly slower under simulated saliva environments (Hu et al. 2022a, b).

The impact of native CDs on the ability of MOFs to incorporate EOs has been the subject of numerous comparative investigations. In line with this, Li et al. 2022a, b, c, d obtained that γCD-MOFs have a high ability compared to βCD-MOFs and αCD-MOFs, for encapsulation efficacy, sustained release and fruit preservation of thymol inclusion complex. Furthermore, Hu et al. 2021 revealed that βCD-MOFs appears as suitable encapsulating agent for menthol much higher than α, γCD-MOFs and native CDs. However, the inclusion complex via αCD-MOFs in the case of menthol had lower encapsulation efficiency than pure αCD (Hu et al. 2021).

Table 2 Encapsulation of essential oils via cyclodextrin metal organic frameworks

Essential oils	CD unit	Metal cation	Functional properties	References
Oregano EO	γCD	K^+	Thermal stability Sustained release	(He et al. 2023)
Clove EO	βCD	K^+	Thermal and pH stabilities Antioxidant activity	(Wang et al. 2023)
Origanum compactum EO	βCD	K^+	Thermal stability Antioxidant activity	(Ez-zoubi et al. 2023)
Lavender EO	βCD	K^+	Thermal and pH stabilities Intracellular antioxidant activities	(Wang et al. 2021)
Cinnamaldehyde	γCD	K^+	Thermal stability Control release Antibacterial activity	(Che et al. 2022)
Benzaldehyde	γCD	K^+	Thermal stability	(Kathuria et al. 2022)
Thymol	γCD	K^+	Release control Antibacterial activity	(Pan et al. 2022)
	αCD βCD γCD	K^+	Encapsulation efficacy Sustained release Fruit preservation effect	(Li et al. 2022a, b, c, d)
Menthol	βCD	K^+	Encapsulation efficiency Thermal stability Temperature and moisture effects Kinetic release	(Hu et al. 2022a, b)
	αCD βCD γCD	K^+	Menthol content Encapsulation efficiency Thermal stability	(Hu et al. 2021)
D-limonene	γCD	K^+	Water solubility volatility bioavailability	(Zhou et al. 2021)
Ethyl propionate Ethyl-2methyl butyrate Myrcene Limonene	γCD	K^+	Thermal stability Kinetic release	(Zhang et al. 2019)

However, the effect of the nature of metals has never been investigated before in the preparation of MOFs as encapsulating agents for essential oils. Therefore, other studies are needed to investigate the effect of metal nature on the inclusion complex (EO/CD-MOFs), because no studies have been carried out on the utilization of cyclodextrin derivatives MOFs.

Supramolecular polymers based on CDs

Other strategies based on utilizing organic units in place of metal anion to crosslink the cyclodextrin units and afford cyclodextrin polymers (Table 3). These last have abundant affinity sites, high specific surface, stable structure, good biocompatibility, and better water solubility (Zhao et al. 2022). Cyclodextrin polymers numerous CD units cross-linked through its hydroxyl groups by polyfunctional substances (Fig. 6). Among these cross-linker agents, epichlorohydrin (EP) one of the first and most crosslinker frequently used, which contains two reactive functional groups and can react with βCD to form ether functions. Historically, Ciobanu et al. 2012 first reported the potential retention of EP-CDs polymer for linalool and camphor (two main compounds of *Lavandula angustifolia* EO), and its higher ability for release profile of these aroma fragrances compared to other CDs. After that, an additional study investigated the higher ability of these polymers for the controlled release of *Mentha piperita* EO (Ciobanu et al. 2013a, b). Recently, Bai et al. 2022 demonstrated that the inclusion complex of cinnamaldehyde and thymol using CD polymers had a good retarding effect on the sustained release of the two compounds.

After that, cyclodextrin nanosponges (CD-NS) were employed due to high solubility, stability, and potential use for antimicrobial food packaging, which is obtained through

Table 3 The inclusion complex via CD polymers

Essential oils	CD units	Cross-linker agents	Main objectives	References
Coriander EO	αCD βCD HPβCD	Carbonyldiimidazole	EO content Antibacterial activity	(Silva et al. 2019)
Cinnamon EO	αCD βCD HPβCD	Carbonyldiimidazole	EO content Control release Antibacterial activity	(Simionato et al. 2019)
Babchi oil	βCD	Diphenyl carbonate	Water solubility EO content Thermal stability Cytotoxicity Photogedradation effect Antibacterial activity	(Kumar et al. 2018)
Salvia officinalis EO	βCD	2,6-Naphthalene dicarboxylic acid	EO content Storage stability Antimicrobial activity	(Bachir et al. 2017)
Mentha piperita EO	βCD	Epichlorohydrin	EO content	(Ciobanu et al. 2013a, b)
Lavandula angustifolia EO	βCD	Epichlorohydrin	Sustained release	(Ciobanu et al. 2012)
Cinnamaldehyde and thymol	βCD	Epichlorohydrin	EO content Sustained release	(Bai et al. 2022)
Linalool	βCD	Diphenyl carbonate	Thermal stability Release control	(Trotta et al. 2012)

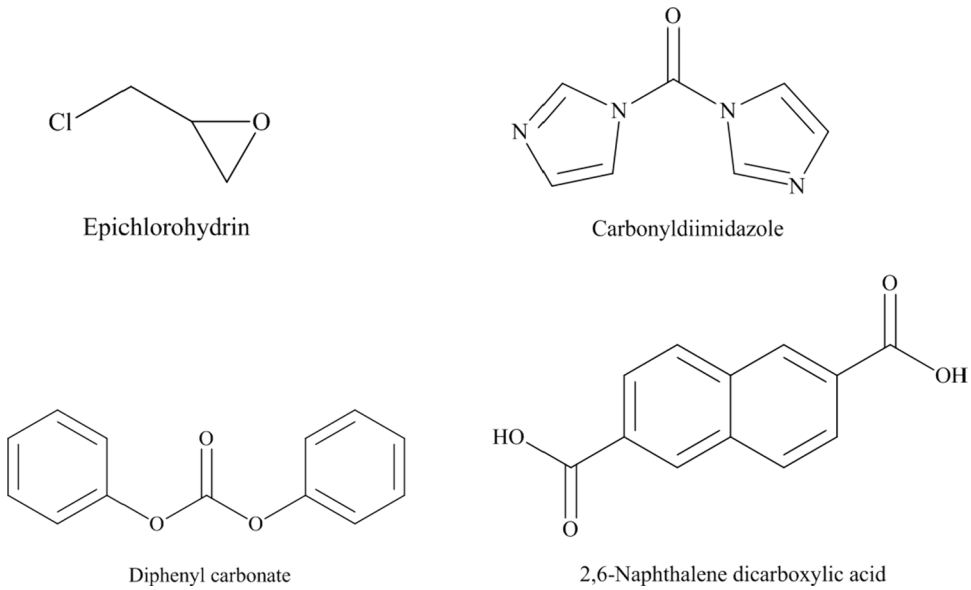

Fig. 6 The chemical structures of cross-linker agents used

the covalent binding between cyclodextrins and various multifunctional reactants such as diisocyanates, carbonyl, dianhydrides, polycaroboxylic acids and epoxide groups (Fig. 4). Silva et al. 2019 investigated the potential of nanosponges based on αCD, βCD, and HPβCD with carbonyldiimidazole (CDI) to load and release coriander essential oil (CEO) to exert their antimicrobial activity and demonstrated that CEO incorporated into α and HPβCD-NS exhibited a predominant bactericidal activity. Other studies showed that α and βCD-NS (CDI as cross-linking agent) were able to encapsulate higher cinnamon EO amounts compared to HPβCD-NS, and these three encapsulating agents allowed EO to be effective in culture medium at lower concentrations (Simionato et al. 2019). Furthermore, water solubility of *Psoralea corylifolia* (Babchi) oil was enhanced five times when encapsulated into βCD-NS (βCD was crosslinked

with diphenyl carbonate), and a substantial improvement in photo-stability was also observed (Kumar et al. 2018). Indeed, the nanoencapsulation of *Salvia officinalis* EO into nanosponges (βCD and 2,6-naphthalene dicarboxylic acid) enhances its therapeutic efficacy (Bachir et al. 2017). Also, βCD-NS (diphenyl carbonate as cross-linking agent) showed higher control release of linalool (half release after 2 h) than βCD, thereby indicating that NSs stabilize the molecule in their structure (Swaminathan et al. 2010; Trotta et al. 2012). Collectively, these studies demonstrated that nanosponges could give a potential opportunity to incorporate EO and be used as antimicrobial food packaging.

Indeed, other studies are needed to investigate the type of cross-linker agents and degree of cross-linking, as well as the ability of formation nanosponges under greener environments to avoid the of organic petroleum solvents (DMF and DMSO).

Cyclodextrin combined with biopolymer (BP)

Cyclodextrin's stability, solubility, and controlled release qualities could be improved by combining them with biopolymers (BP) that have high availability, biodegradability, renewability, and biocompatibility. Recently, the grafting of cyclodextrin and loading of the inclusion complex into biopolymers were investigated as an appropriate approach to enhance the properties of the inclusion complex.

CDs grafted onto biopolymer

This strategy is based on a double effect; incorporating EOs via the hydrophobic cavity of CD and its hydrophilic exterior promotes more solubility by establishing a covalent bond with a biopolymer (Ma et al. 2023). The advantages of the grafting process of CD into biopolymers are summarized as follows; high biocompatibility and solubility, direct inclusion complex, and self-assembly into micelles (Liu et al. 2021). These biopolymers have been widely studied due to their high abundance and biocompatibility (Table 4). However, as these biopolymers have hydroxyl and amine groups, respectively, it is necessary to use cross-linker agents or modify one (or both) of the two moieties (cyclodextrin and biopolymer) to connect them. Monochlorotriazine-beta cyclodextrin (MCT-βCD) was commonly used to form an ester bond between the chlorotriazine ring of the MCT-βCD and the hydroxyl groups of the cellulose of cotton (Fig. 7). In

Table 4 Inclusion complex of essential oils via cyclodextrin grafted biopolymer

Essential oils	CD	Biopolymer	Cross-linker agents	Functional properties	References
Wormwood EO	MTC-βCD	Cotton	–	Thermal stability	(Chen et al. 2015)
Cedarwood EO Clove EO Eucalyptus EO Peppermint EO	MTC-βCD	Cotton	–	Release control	(Khanna et al. 2015)
Cedarwood EO Lavender EO Peppermint EO	βCD	Cotton	CA	Insecticidal activity	(Khanna and Chakraborty 2018)
Clove EO Jasmine EO Eucalyptus EO	MTC-βCD	Cotton	–	Release control	(Khanna and Chakraborty 2017)
Lavender EO	βCD	Chitosan	CA	Release control	(Singh et al. 2017)
Citronella EO	βCD	Wool	BTCA	Thermal stability Control release	(Bezerra et al. 2019)
Carvacrol Cuminaldehyde Cinnamaldehyde Hydroxytyrosol	βCD	Cellulose Bleached pulp Starch	BTCA	Kinetic release	(Aguado et al. 2021)
Carvacrol and linalool	βCD	Chitosan	Chloroacetic acid	Insecticidal activity	(Campos et al. 2018)
Carvacrol	βCD	TEMPO-oxidized cellulose	–	Control release and Antimicrobial activity	(Saini et al. 2017)
		Cellulose	Succinic acid Fumaric acid	Control release Antimicrobial activity	(Castro et al. 2016)
		Cellulose	CA	Control release	(Lavoine et al. 2014)

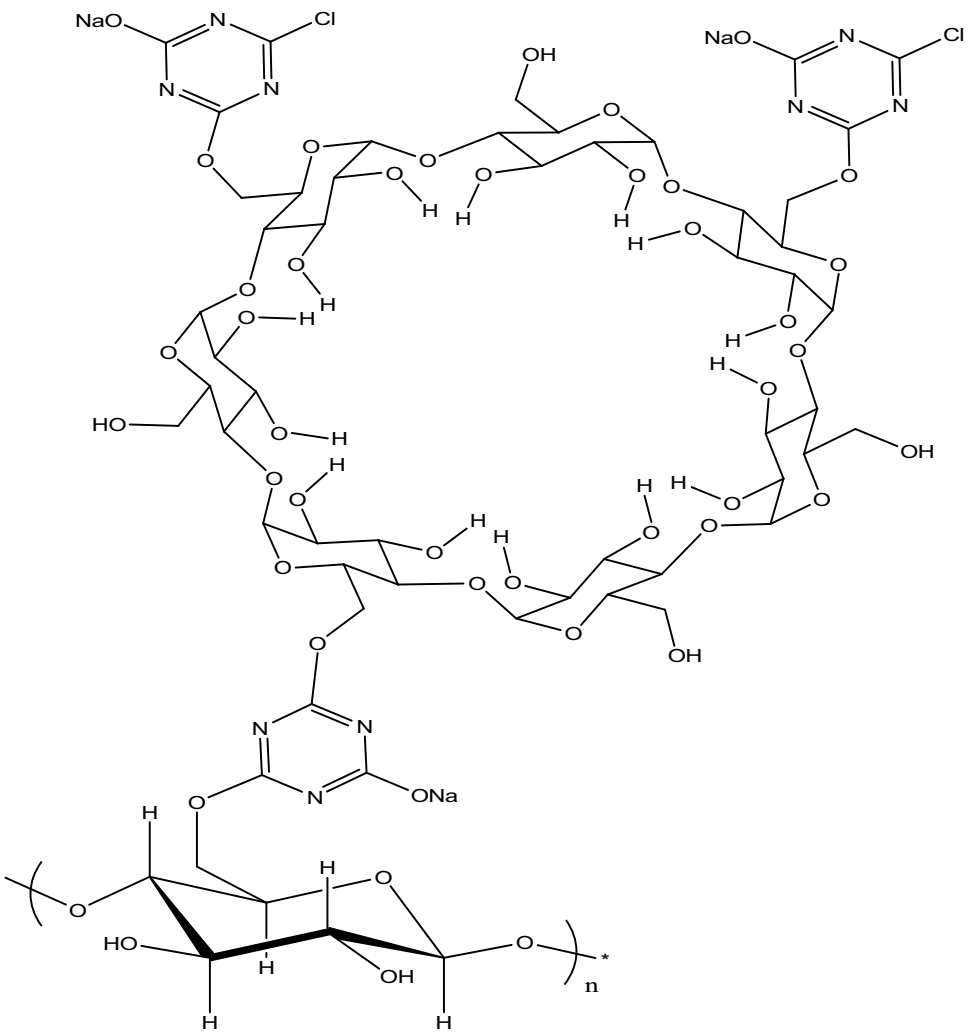

Fig. 7 The monochlorotriazine-beta cyclodextrin (MCT-βCD) chemical structure grafted to cellulose

line with this, various essential oils including; wormwood, cedarwood, lavender, peppermint, clove, jasmine, and eucalyptus EOs were subject of incorporation into MCTβCD grafted onto cellulose cotton (Chen et al. 2015; Khanna et al. 2015; Khanna and Chakraborty 2017). The direct grafting of βCD into TEMPO-cellulose nanofibers was investigated as new biobased packaging, with the sustained release and antibacterial activity of carvacrol (Saini et al. 2017).

Otherwise, crosslinking of biopolymers was mediated by the esterification process of βCD via polycarboxylic acids mainly citric acid (CA) and 1,2,3,4-butanetetracaroxylic acid (BTCA). For example, CA-βCD was grafted onto cotton, to improve the control release and the adulticidal activity of six essential oils cedarwood, lavender, peppermint, clove, jasmine, and eucalyptus (Khanna and Chakraborty 2018). Similarly, grafting βCD via CA onto cellulose enhances the biological activity of lavender EO (Singh et al. 2017) and carvacrol (Lavoine et al. 2014). Furthermore, by a two-step-esterification via BTCA, βCD was attached to wool (Bezerra et al. 2019), cellulose, and starch (Aguado et al. 2021) for sustained the release of citronella EO and monophenolic compounds. Two dicarboxylic acids (succinic and fumaric acids) were applied as cross-linker agents between βCD and cellulose, to study their effect on the antibacterial activity and prolonged release of carvacrol (Castro et al. 2016). Indeed, chloroacetic acid another cross linker agent was employed for attaching βCD onto chitosan to increase the insecticidal activity of linalool and carvacrol (Campos et al. 2018).

Other studies are needed to establish a covalent network between βCD and biopolymer using the azide-alkyne cycloaddition.

Inclusion complex loaded into biopolymer

The second strategy was developed using a dual encapsulation of EOs with an inclusion complex into βCD then loaded into biopolymers. This strategy could enhance the physicochemical and biological characteristics of the IC while combining with suitable biopolymers more

Table 5 The inclusion complex loaded biopolymer

Essential oils	CD	Biopolymer	Properties	References
Pelargonium graveolens EO	βCD	Chitosan	Storage stability Release study	(Ez-zoubi et al. 2023b)
Vladimiriae Radix EO	HPβCD	Chitosan	Stability Release profile Bioavailability	(Yan et al. 2021)
Lavender EO	βCD	Chitosan/Sodium alginate	Encapsulation efficiency Thermal stability Release profile	(Zhang et al. 2020)
Cinnamomum zeylanicum EO	βCD	Chitosan	Release profile	(Matshetshe et al. 2018)
Lippia sidoides EO *Syzygium aromaticum* EO	HPβCD	Liposome	Thermal stability Release profile	(Baldim et al. 2022)
Clove EO	HPβCD	Liposome	Encapsulation efficiency Antioxidant activity	(Sebaaly et al. 2016)
Thymol	βCD	Chitosan	Antioxidant and antibacterial activities	(Alizadeh and Nazari 2022)
Eugenol	SBEβCD	Chitosan	Release profile Antioxidant and antibacterial activities	(S. Li et al. 2022a, b, c, d)
α-Pinene	HPβCD	Liposome	Storage stability Antioxidant activity	(Hammoud et al. 2021)
Eucalyptol	HPβCD	Liposome	Release profile	(Gharib et al. 2020)
Estragole	HPβCD	Liposome	Release profile	(Gharib et al. 2019)
Anethole	HPβCD	Liposome	Storage stability	(Gharib et al. 2017)

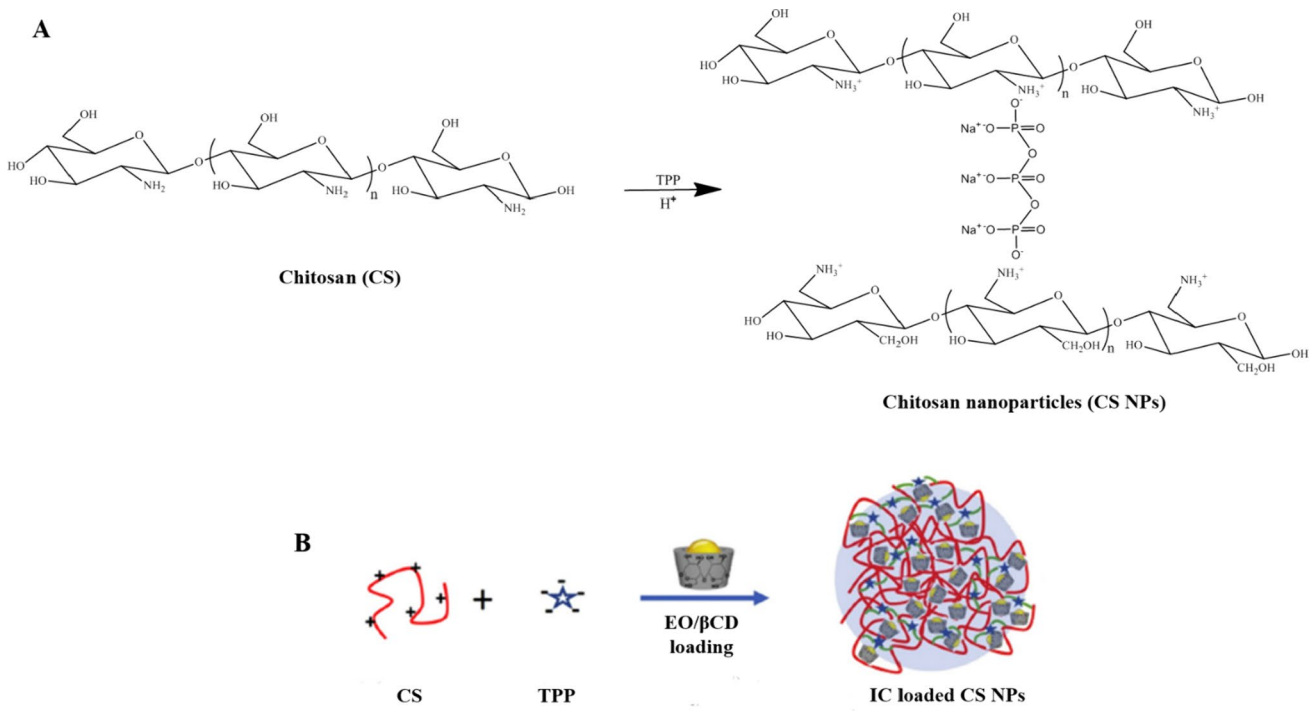

Fig. 8 Formation of chitosan nanoparticles via ionic gelation (**A**). The inclusion complex EO/βCD loaded chitosan nanoparticles (**B**)

extensively used (Table 5). Amid them, chitosan is the most abundant biopolymer available on the planet produced next to cellulose by the deacetylation of chitin. As shown in Fig. 8A, it is made up of β-(1 → 4) linked D-glucosamine units with a rather portion of N-acetyl–D-glucosamine units, which can be easily chemically cross-linked with tripolyphosphate (TPP) of chitosan nanoparticles (CS NPs).

Several research groups have reported the preparation of nanoparticles using CS NPs for loading the inclusion complexes (Fig. 8), promoting enhancing stability, and also increasing efficacy and modulation release of essential oils. Ez-zoubi et al. 2023b investigated the ability of this strategy to enhance the storage stability and modulation release under the gastrointestinal environment of *Pelargonium graveolens* (known as geranium) EO. Indeed, the inclusion complex of thymol with βCD loaded CS NPs exhibited more antioxidant activity properties compared to the IC (Alizadeh and Nazari 2022). Additionally, SBEβCD has a polyanionic nature, which promotes its interaction with other chitosan as a cationic polymer. In line with this, Li et al. 2022a, b, c, d prepared a formulation containing an inclusion complex of eugenol into SBEβCD loaded in chitosan nanoparticles. Indeed, this strategy of dual encapsulation using HPβCD and chitosan could improve the bioavailability and protective effect on the gastric mucosa of *Vladimiriae Radix* EO (Yan et al. 2021). A double-layered microcapsule was prepared via the inclusion complex with βCD into chitosan and sodium alginate to improve the long-term effectiveness of lavender EO (Zhang et al. 2020). Besides, another study demonstrated that combining β-cyclodextrin and chitosan could improve the therapeutic effect of *Cinnamomum zeylanicum* EO (Matshetshe et al. 2018).

On the other hand, liposomes are phospholipid molecules containing one or more bilayers and exhibiting an amphiphilic character, which offers the ability to encapsulate both hydrophilic and lipophilic compounds. Therefore, liposomes offer a suitable approach to incorporate the inclusion complex EO/CD. In line with this, the use of system *Lippia sidoides* and *Syzygium aromaticum* EOs in CD (HPβCD) and liposome (denoted as DCL) has remarkable potential in the assessment of the release and toxicological profiles, as well as the enhancement of biological activity (Baldim et al. 2022). Similar studies using clove EO in the DCL system maintained higher antioxidant activity (Sebaaly et al. 2016). Indeed, the physico-chemical properties, mainly release control, of α-pinene (Hammoud et al. 2021), eucalyptol (Gharib et al. 2020) and estragole (Gharib et al. 2019) were improved using DCL. Indeed, Gharib et al. 2017 demonstrated that HPβCD and liposomes improved the photoprotection of anethole. It should be mentioned that CD was investigated as a cryoprotectant to protect the essential oil into liposomes during the freeze-drying process (Lin et al. 2018, 2019).

Optimization of inclusion complex efficiency

Experimental designs

The application of experimental designs in determining and optimizing of formulation and processing parameters is explored in this contest. Experimental designs are statistical techniques used to model and analyze complex relationships between multiple variables, aiming to identify the optimal combination of factors that yield the desired outcome (Paul and Boves 2021). In the formulation and processing of various products, experimental designs offer a systematic approach to comprehensively assess the effects of individual parameters and their interactions on the final product's quality and characteristics (Xiao et al. 2022).

Through these chemometrics tools, researchers can systematically vary the input parameters while observing the corresponding changes in the complexation efficiency of essential oil into cyclodextrin. This approach could minimize the consumption of resources to achieve optimum inclusion efficiency.

The literature review indicates that the optimization of the essential oils encapsulation within cyclodextrin are based on two powerful experimental design methodologies, screening design (Plackett–Burman) (Quinlan and Lin 2015), response surface methodology (RSM) (Montgomery 2017) and mixture designs (Khuri and Mukhopadhyay 2010).

Screening experimental design is helpful in identifying the most influential factors from a large pool of potential candidates is crucial. Among them, the Plackett–Burman design (PBD) offers an efficient approach for this purpose (Quinlan and Lin 2015). PB designs allow the evaluation of a relatively large number of factors (up to N-1, where N is the number of runs) with a minimal number of experiments. This is achieved by strategically combining factors at high and low levels, enabling the estimation of main effects while acknowledging potential confounding between factors.

RSM is a statistical technique that allows us to model and optimize the relationship between multiple independent variables (factors) and a single dependent variable (response) (Montgomery 2017). By conducting experiments at carefully chosen combinations of these factors, we were able to build a mathematical model that predicts the desired responses across the entire experimental region.

Mixture designs, a specialized subset of RSM, are also employed to optimize the proportions of different cyclodextrin derivatives within the inclusion complex. Such designs ensure that all possible combinations of component proportions sum to 100% while efficiently exploring the experimental space (Khuri and Mukhopadhyay 2010). This allows to determine the optimal blend of encapsulation medium components to reach the best possible response.

Optimization

The encapsulation efficiency (EE) refers to the mass ratio of encapsulated EO to the total oil added, and is also denoted inclusion rate (IR) or inclusion efficiency (IE). While, the loading efficiency (LE) is the ratio of the encapsulated EO to the total mass of the inclusion complex (mass of CD and EO). These two physical properties provide key information about the efficiency of the inclusion process (Luo et al. 2022).

As illustrated in Table 6, several studies used response surface methodology (RSM) to determine the optimal conditions of amount and ratio of EO to CD (Maleki et al. 2021), temperature, time, and energy. The optimization was generated via response surface RSM combined with Box- Behnken Design (BBD), Face-Centered Central Composite Design (FCCDD), Rotatable Central Composite Design (RCCD), or Central Composite Design (CCD).

In line with this, Yin et al. 2021 used a molar ratio of 0.99 of 1,8 cineole to HPβCD under 30.1 °C for 2.30 h to achieve the optimum EE (83.17%). Also, the optimized parameters for the encapsulation of lavender EO via βCD obtained as follows: 2.27 mL of EO, 3.19 h for encapsulation time, and 52.95 °C as temperature environment (Zhang et al. 2020). Indeed, the microencapsulation of *Litsea cubeba* EO into βCD was optimized by Wang et al. 2020 to achieve the highest EE (33.60%) using βCD/EO mass ratio of 4.2 for 2 h at 44 °C. Similarly, Ma et al. 2018 indicated that the optimum inclusion rate (64.64%) process of clove essential oil (CEO) via βCD as follows: CEO:βCD (1:9) at 43 °C for 2.5 h. Furthermore, Li et al. 2018 attained 50.32% corresponding to 5.66 g of sweet orange EO, 53.7 °C and 3.24 h. In addition to the above parameters, minimizing energy was another crucial parameter; Jiang et al. 2021a, b investigated a range power ultrasonic condition (from 60 to 180W) for the encapsulation of tea tree EO, and revealed that 120 W was the optimum one (Ning and Yue 2019; Liu et al. 2022).

On the other hand, the quantities of water and/or ethanol used are crucial conditions for optimum medium performance via RSM. Obedient, Yan et al. 2022 found that the mass ratio of aqueous solution to βCD was 9.6:1 for optimum inclusion of *Cinnamomum longepaniculatum* EO. Other studies were focused on the concentration of essential oil in the ethanol solution including lemon (Shi et al. 2023), *Origanum compactum* (Ez-zoubi et al. 2023a), and *Rosamarinus officinallis* EOs (El Kharraf et al. 2021). The results demonstrated that using a high ethanol amount (higher than 50%) reversely correlated with the EE, which might disrupt the non-covalent bonds necessary for stabilizing the inclusion complex.

In some cases, a pretreatment of the key factors was performed via Plackett–Burman Design (PDB) to determine the RSM experiment's central level (Ning and Yue 2019; Liu et al. 2022).

Mixture design, another chemometric tool, was additionally used to explore the impact of medium efficiency, whereas Ez-zoubi et al. 2022 examined the impact emulsifying agent (glycerol) on the medium efficacy using a binary mixture design, and obtained 58.86% of EE corresponding to volume ratio ethanol and glycerol (0.73:0.27).

In this stage, experimental designs aimed to investigate the effect of different factors for achieving higher inclusion efficiency with respect to reducing the amount of CD and EO added, optimizing the medium efficacy as well and minimizing time and energy.

Thus, encapsulation efficiency is currently the most crucial characteristic of EO inclusion ability into CDs. Therefore, further investigation is required via an efficient machine-learning model to estimate the EE as a function of the quantities of CD and EO, as well as the water and ethanol contents, also the temperature and duration of inclusion.

Conclusion and perspectives

Despite the performances achieved in the inclusion complex of essential oils and their compounds via native cyclodextrins, their modifications are sometimes required to improve their relative weaknesses properties, such as lower solubility and entrapment efficiency, stability, profile release and biological efficacy. Native CDs have been modified by replacing their hydroxyl groups, combining them with a cation metal, crosslinking them with functional groups, and associating their properties with those of a biopolymer. The modified CDs lead to have better physicochemical properties and biological efficacy. Experimental designs could minimize resource consumption (EO, CD, water and ethanol), time and energy.

In future, monosubstituted cyclodextrin should be explored to avoid the steric hindrance effect. In addition, the CD-MOFs based on derived CDs need to be explored, as no report is available in this respect. The green medium was required to replace the petroleum solvent to prepare supramolecular CDs. Also, tria- and tetrazole rings could be explored as a suitable link between CD and biopolymer via cycloaddition. Indeed, an effective machine- learning model will be employed to predict the EE as a function of the amounts of CD and EO, the contents of water and ethanol, and the temperature and time of encapsulation.

Table 6 Various factors optimized via experimental designs

Essential oils	CDs	Used experimental deign	Conditions	Results	
				Optimum factors	Responses (%)
Sweet orange EO (Li et al. 2018)	βCD	RSM (BBD)	Mass of EO (3–7 g)	5.66 g	EE = 50.32
			Time (2–4 h)	3.24 h	
			Temperature (40–60 °C)	53.7 °C	
Litsea cubeba EO (Wang et al. 2020)	βCD	RSM (BBD)	βCD/EO (2–6 w/w)	4.2	EE = 33.60
			Temperature (30–50 °C)	44 °C	LE = 9.07
			Time (1.5–2.5 h)	2 h	
Clove EO (Ma et al. 2018)	βCD	RSM (BBD)	Temperature (30–60 °C)	43 °C	IR = 64.64
			Time (1–2.5 h)	2.5 h	
			βCD:EO (6–12:1 w/w)	9:1	
Lavender EO (T. Zhang et al. 2020)	βCD	RSM (BBD)	EO mass (1–3 mL)	2.3 mL	EE = 80.75
			Time (2–4 h)	3.2 h	
			Temperature (40–60 °C)	53 °C	
1,8 Cineole (Yin et al. 2021)	HPβCD	RSM (BBD)	Time (1–3 h)	2.30 h	EE = 83.17
			Temperature (20–50 °C)	30.1 °C	
			EO/HPβCD molar ratio (0.5–1.5)	0.99	
Cinnamomum longepaniculatum EO (Y. Yan et al. 2022)	βCD	RSM (BBD)	H_2O/βCD (5:1–25:1 mL/g)	9.6:1 mL/g	EE = 68.31
			βCD/EO (4:1–12:1 g/mL)	8:1 g/mL	
			Temperature (20–60 °C)	20 °C	
Lemon EO (Shi et al. 2023)	βCD	RSM (BBD)	Time (2–4 h)	3 h	EE = 91.57
			EO/βCD (1:2–1:6 w/w)	1:4	
			EO/ethanol (25–5%)	25%	
Rosmarinus officinalis EO (El Kharraf et al. 2021)	βCD	RSM (FCCDD)	βCD/EO (10:90–20:80 w/w)	16.85:83.15	IE = 99.98
			Ethanol/water (1:1–1:3 v/v)	1.55:1	
Geraniol (Maleki et al. 2021)	βCD	RSM (RCCD)	βCD (80–95%)	95%	LE = 10.45
			EO (5–20% w:w)	12.50%	EE = 87.25
Tea tree EO (S. Jiang et al. 2021a, b)	HPβCD	RSM (BBD)	EO/HPβCD (1:4–1:12 w/w)	1:10	EE = 80.63
			Power (60–180 W)	120 W	
			Time (30–70 min)	70 min	
			Temperature (30- 70 °C)	40 °C	
Origanum Compactum EO (Ezzoubi et al. 2023a)	βCD-MOFs	RSM (CCD)	Water/ethanol (1:5–4:5 v/v)	4:5	EE = 35.34
			EO/βCD-MOFs (1:1–1:12 w/w)	1:12	
Mosla Chinensis EO (Liu et al. 2022)	βCD	PBD	βCD/EO (4–12:1 w/w)	8.73	LE = 8.92
			Time (15–45 min)	213.56 W	EE = 86.17
		RSM (CCD)	Power (180–360 W)	1:2	
			Temperature (40–60 °C)	–	
			EO/ethanol (0.5–2:1 w/w)	1:2	
Eucalyptus EO (Ning and Yue 2019)	βCD	PBD	Temperature (30–50 °C)	46 °C	EE = 71.17
		RSM (CCD)	Time (1.5–2.5 h)	108 min	
			βCD/EO (6–10 w/v)	9.59 g/mL	
			Ethanol/water (15–25:1 v/v)	20:1 mL/mL	
			Water/ βCD (8–12 v/w)	10:1 mL/g	
Lavandula Stoechas EO (Ezzoubi et al. 2022)	βCD	Mixture design	Ethanol/glycerol (v/v)	0.73:0.27	EE = 58.86

Author contributions AEZ: Conceptualization, Writing-original draft, Writing—review editing, Investigation, Methodology. HZ: Writing—review editing, Visualization. YEZ: Writing—review editing. MF: Writing—review editing. AF: Writing—review and editing, Conceptualization, Supervision.

Data availability This article's published data set contains all information created or analyzed during this investigation.

Declarations

Conflict of interest The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this study.

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