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Enhancement of curcumin bioaccessibility: An assessment of possible synergistic effect of γ-cyclodextrin metal–organic frameworks with micelles☆

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ABSTRACT

Biocompatible γ-cyclodextrin metal–organic frameworks (γ-CD-MOFs) have been reported to improve the apparent solubility and bioavailability of encapsulated bioactive compounds, including curcumin, potentially enabling sustained delivery. However, disintegration of γ-CD-MOFs may "release" encapsulated curcumin within the cavity in its insoluble crystallized form. This study evaluated whether the presence of micelles (at a concentration above curcumin's maximum solubility) would be able to take up the "released" curcumin from γ-CD-MOFs to further increase its apparent solubility. Release in the presence of a micellar phase was compared to curcumin encapsulated within γ-CD-MOFs alone. Results demonstrated that Tween 80 solubilized higher curcumin concentrations compared to oleic acid and bile salts. Dispersed in combination with Cur- γ-CD-MOFs, it was found that Tween 80 and oleic acid can improve the apparent solubility of curcumin, 5× and 1.5× higher than in the absence of micelles of these surfactants, respectively, whereas bovine bile salts exhibited a negative effect, due to a displacement of curcumin from within cavity of γ-CD-MOFs. Moreover, it was also found that Tween 80 was less affected by pH and salt concentrations due to its nonionic nature. *In vitro* digestion (via the INFOGEST protocol) revealed an 8-fold increase in apparent solubility of curcumin with bile salts and a 53-fold increase when combining bile salts and γ-CD-MOFs, achieving bioaccessibility of 2 % and 16 %, respectively. In conclusion, this research revealed the evaluation of γ-CD-MOFs' functionality for delivery and controlled release, with the possibility of an emulsion system boosting the fraction of curcumin that would potentially be bioavailable.

1. Introduction

Cyclodextrin (CD) combined with alkali metals can be used to form metal–organic frameworks (CD-MOFs), with edible CD-MOFs being investigated made from γ-CD and potassium ions prepared via a vapor diffusion method (Smaldone et al., 2010). γ-CD-MOFs have attracted growing interest as promising candidate drug carriers due to their non-toxicity, tunability, loading efficiency and reported sustained and controlled drug release (Shen et al., 2021; Si et al., 2024). Several studies have shown that various bioactive compounds and drugs can be successfully encapsulated in γ-CD-MOFs, such as curcumin, ibuprofen, folic acid, quercetin, lansoprazole and many more (Oh et al., 2023; Roy & Stoddart, 2021).

After 'activation' (removal of any excess solvent) from γ-CD-MOFs they remain permanently porous, which enables them to encapsulate and convert drugs from a crystalline state to an amorphous state. This can contribute to the improved solubility and bioavailability of insoluble drugs (Li et al., 2017; Zhou et al., 2020). Several modelling studies as well as Fourier transform infrared spectra (FT-IR) have suggested that not only does curcumin sit within the hydrophobic cavity of γ-CD-MOFs, but also exists in between the γ-CD pairs (Chen et al., 2021; He et al., 2019; Oh et al., 2023; Zhou et al., 2021). According to Lopez and Perez (2023), in the presence of water, the γ-CD-MOFs degrade in two stages. Firstly, water molecules displace the metal-linker coordination bonds of MOFs. Secondly, a hydrolysis process occurs which deprotonates the coordinated water molecule, resulting in the breakdown of metal-linker

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coordination and a hydroxide ion is left attached to the metal center to preserve the charge balance. This supports our previous study where the improved apparent solubility was inferred to be due to the interaction between curcumin and γ-CD pairs because the γ-CD-MOFs alone disintegrate in an aqueous environment, whereas the "release" of trapped curcumin from within the cavity leads to its insoluble crystallized form (Oh et al., 2023).

Surface active agents (surfactants) are amphipathic compounds that are extensively used in a wide variety of applications. Examples include enhancing drug solubility, stabilizing emulsions, lubrication, cleaning and detergency (Kralova & Sjöblom, 2009; Park & Choi, 2006; Tung et al., 2021; Züge et al., 2013). Most applications are highly reliant on the formation of micelles at and above the critical micelle concentration (CMC). The CMC is defined as the concentration at which the surfactant starts to aggregate or self-associate and form discrete structures (micelles) typically no more than 2 to 3× the dimensions of the individual surfactant molecules (Shi et al., 2011; Vinothini & Rajan, 2019). The formation of micelles affects the physical properties of surfactant solutions (e.g., conductivity, density, viscosity, osmotic coefficient, water activity and surface activity) (Abdul Rub et al., 2022; Paddon-Jones et al., 2001; Shadloo et al., 2022). Extensive studies have been conducted on micellization. In fact, two stages of aggregation are sometimes observed: the formation of premicellar aggregates (the critical premicelle concentration, CPMC) at a concentration below the classic single CMC (sometimes now referred to as the first critical micelle concentration, FCMC). At higher surfactant concentrations the initial spherical-like micelles can grow to form spherocylindrical or ellipsoidal micelles, sometimes at a specific concentration termed the secondary critical micelle concentration, or SCMC (Shadloo et al., 2023; Shi et al., 2011). However, micellization depends very much on the nature of the surfactant, the environmental conditions plus the presence of impurities and the molecular weight (Mw) distribution of commercially relevant surfactants.

Micelles have also been extensively studied and reported to be promising candidates as drug delivery carriers. This could include targeted delivery, enhanced solubility and improved permeability and retention (Saha et al., 2023). However, the lack of stability in certain physiological conditions may limit their effectiveness. Hence, in this study, we investigated the capability of micelles formed from different surfactants to take up a bioactive material released from γ-CD-MOFs as they disintegrate, which has not been highlighted before. Furthermore, to our knowledge, this enhanced effect of micelles working with γ-CD-MOFs to enhance the bioaccessibility of a model payload - curcumin - is the first to be reported.

2. Materials and methods

Tween 80 was purchased from Cambridge Bioscience (Cambridge, UK). Tween 60, curcumin (from *Curcuma longa* (turmeric), powder, >65 % purity), and γ-cyclodextrin (γ-CD, >90 % purity), purchased from Sigma-Aldrich Company Ltd (Dorset, UK). Oleic acid (technical grade, 90 %), sodium chloride (NaCl), potassium hydroxide (KOH, pellets, ACS reagent, >85 % purity), hydrochloric acid (HCl, analytical reagent grade, S.G. 1.18, ~37 %) and sodium hydroxide (NaOH, analytical reagent grade, pellets) were purchased from Thermo Fisher Scientific (Loughborough, UK). Pepsin (from porcine gastric mucosa, lyophilised powder, 500 U mg^{-1}), pancreatin (from porcine pancreas, 8 USP) and bovine bile (dried, unfractionated) were purchased from Sigma-Aldrich Company Ltd. HPLC grade methanol (>99.9 %), acetonitrile (>99.9 %), ethyl acetate (>99.7 %), curcumin, demethoxycurcumin, and bisdemethoxycurcumin were purchased from Sigma Aldrich Company Ltd. Formic acid (for mass spectrometry) was purchased from Honeywell (Seelze, Germany). All solutions were prepared with pure deionized water (with a resistivity of not less than 18.4 MΩ cm at 25 °C) (Merck Millipore, Darmstadt, Germany).

2.1. Preparation of micelles

A 1.5 mM Tween 80 solution (100× CMC (Hait & Moulik, 2001; Krstonošić et al., 2019)) was prepared in water. Curcumin was first dissolved in methanol then added into the Tween 80 solution at molar ratio of Tween 80:curcumin at 50:1, 10:1, 5:1 and 3:1. This was similarly prepared for Tween 60 (1.67 mM) (Feng et al., 2022), oleic acid (0.6 mM) (Grippo et al., 2021) and bovine bile salts (10 mM). These solutions were allowed to stand for an hour before any measurements were recorded.

2.1.1. Particle size and polydispersity index

The particle size distribution (PSD) and polydispersity index (PDI) were determined for each miceller solution and after addition of curcumin at each molar ratio using a dynamic light scattering instrument at 25 °C (Zetasizer Nano ZS series, Malvern Instruments, Worcestershire, UK). The particle size measurement was repeated on samples of micellar solution containing increasing curcumin concentration after being filtered through a 0.45 μm organic filter membrane.

2.1.2. Concentration of dispersed curcumin

Micellar solutions containing curcumin were all centrifuged at 5000 rpm for 20 min (Rotina 380R, Hettich, Tuttlingen, Germany). Discarding the supernatant, the sediment was collected and dissolved in methanol. The concentration of undispersed curcumin was calculated from a calibration curve using the SPECORD 210 Plus UV–Vis spectrophotometer (Analytik Jena, Jena, Germany) at 426 nm. The concentration of curcumin or apparent micellar-solubilized curcumin was calculated by difference.

2.2. Effect of pH and presence of salt on micelles

As per section 2.1.2, it was determined that the maximal solubilization of curcumin was at molar concentration of micelles:curcumin at 5:1. Micellar solutions were prepared as described in 2.1 for Tween 80 and oleic acid either in the absence of NaCl or in the presence of 0.1 M NaCl or 1.0 M NaCl. The pH was then adjusted to pH 2 or pH 7 using 1.0 M HCl or NaOH solution. The particle size and concentration of dispersed curcumin was similarly measured as per sections 2.1.1. and 2.1.2.

2.3. Effect of micelles in combination with Cur-CD-MOFs

2.3.1. Preparation of γ-CD-MOFs and encapsulation

The preparation of γ-cyclodextrin metal–organic frameworks (γ-CD-MOFs) and their use for encapsulating curcumin were conducted following established methods. γ-CD-MOF crystals were prepared via the conventional vapor diffusion method as described by Smaldone et al. (2010). Briefly, the process involved dissolving γ-CD and KOH in deionized water, filtering, and allowing methanol diffusion into the sample for 7 days. Following an activation process to remove residual moisture entrapped during synthesis, the crystals were dried under vacuum at 30 °C overnight (Genevac EZ-2 Plus Evaporating System, Marshall Scientific, New Hampshire, USA).

Curcumin was encapsulated using an impregnation method, in which a 10:1 M ratio of γ-CD-MOFs to curcumin was simultaneously dispersed and dissolved in methanol. Subsequently, the mixture was centrifuged, washed with methanol to remove unencapsulated fraction of curcumin, and then dried overnight under vacuum.

Full details are given in a previous publication by Oh et al. (2023).

2.3.2. Concentration of dispersed curcumin

Micellar solutions were prepared of Tween 80, oleic acid and bovine bile salts, each at 100× of their respective CMC concentrations. 10 mg of Cur-γ-CD-MOFs was dispersed in 5 mL of each micellar solution and allowed to stand for 1 h. The solutions were then centrifuged, and the

sediments were collected. The concentration of dispersed curcumin in solution was then similarly recorded as per 2.1.2.

2.4. In vitro gastrointestinal digestion (static model)

A static digestion model was used in the *in vitro* digestion experiments with slight variation from the protocol published by Brodkorb et al. (2019), omitting the oral and gastric phases as it was assumed that the intended method of delivery (capsule form) would remain intact until it reaches the intestinal phase. The volumes of curcumin suspensions and Cur-γ-CD-MOFs were measured to each make up a curcumin starting concentration of 2 mg/mL. The samples were mixed with 8.5 mL of simulated intestinal fluid (SIF), consisting of 6.8 mM potassium chloride (KCl), 0.8 mM potassium phosphate monobasic (KH_2PO_4), 85 mM bicarbonate of soda ($NaHCO_3$), 38.4 mM sodium chloride (NaCl), and 0.33 mM magnesium chloride hexahydrate ($MgCl_2(H_2O)_6$), 40 μL of 0.3 M calcium chloride ($CaCl_2$), as well as 2.5 mL of bile (10 mM) and 5.0 mL pancreatin solution (100 U/mL trypsin activity) that were made up in SIF electrolyte stock solution. The *in vitro* intestinal digestion was carried out for 2 h at pH 7 and 37 °C under agitation using a shaking incubator (Incu-Shake MAXI, SciQuip Ltd, Shropshire, UK) at 115 rpm.

2.5. Bioaccessibility of curcumin

The bioaccessibility of curcumin was determined for both samples at the end of the 2 h of *in vitro* digestion. The digesta obtained at the end of the digestion process were centrifuged at 13,000 × g for 15 min at 4 °C. Solubilized curcumin was assumed to be in the micellar phase, within the supernatant fraction. Curcumin was extracted from the supernatant with ethyl acetate, repeated three times. The ethyl acetate was evaporated off in vacuum and the extracted curcumin was redispersed in acetonitrile. The concentration of curcumin was analyzed using ultra high-performance liquid chromatography (UHPLC) analysis. An Agilent 1260 Infinity II LC system coupled with DAD detector was used for the analysis. The measurement wavelength was 425 nm, and the separation column was Ascentis Express C18 (150 mm × 4.6 mm, 2.7 μm) fitted with a Phenomenex guard column. The mobile phase A was a 0.1 % aqueous solution of formic acid, and the mobile phase B was 0.1 % formic acid in acetonitrile, with a flow rate of 1 mL/min and maximum pressure limit at 400 bars. The gradient elution program was: 0 min, 82 % of A; 10.8–16.8 min: 68 % of A; 16.8–19.2 min: 40 % of A; 19.2–21.7 min: 0 % of A; 21.7–23.8 min: 82 % of A. The column temperature was maintained at 35 °C. The injection volume was 10 μL and external curcuminoid standards (bisdemethoxycurcumin, demethoxycurcumin and curcumin) were used for quantitative analysis. A calibration curve was prepared with standard curcuminoids in acetonitrile in concentrations ranging from 0.1 μM to 20.0 μM. Bioaccessibility of curcuminoids were calculated by dividing the detected amount of total solubilised curcuminoids by the initial amount of curcumin the sample.

$$Bioaccessibility\ (\%) = C_{micelle}/C_{initial} \times 100$$

Here, $C_{micelle}$ was the concentration of curcumin solubilized in the simulated intestinal phase, $C_{initial}$ was the concentration of curcumin initially added before digestion.

2.6. Statistical analysis

Statistical analysis was carried out using OriginPro 2024 (OriginLab, Northampton, USA) and the statistical significance was taken as at $p < 0.05$. Data were collected in triplicate. Results in tables are expressed as mean ± standard deviation where applicable and error bars in figures represent standard deviation.

3. Results and Discussion

Based on the mean particle size in the micellar solutions (Table 1), the size of micelles increases in the sequence of Tween 60 < Tween 80 < oleic acid < bovine bile salts. The PDI values suggest that the Tween 80 and oleic acid micelles were fairly homogeneous, but Tween 60 and bovine bile salts formed highly polydisperse micelles.

The measurements were carried out at 100× the accepted CMC concentrations. The CMC can be determined by various methods such as surface tension, conductivity, viscosity, light scattering, fluorimetry, calorimetry, spectrophotometry, and nuclear magnetic resonance (NMR) spectroscopy (Hait & Moulik, 2001; Shi et al., 2011; Szymczyk et al., 2018). Unfortunately, the CMC values obtained via different methods often disagree. The CMC values reported for Tween 60, Tween 80 and oleic acid are 0.0167 mM, 0.015 mM and 6 μM, respectively (Feng et al., 2022; Grippo et al., 2021; Hait & Moulik, 2001; Krstonošić et al., 2019). The complexity of bovine bile, which contains various bile acids, makes it particularly difficult to specify a single CMC concentration. It was suggested that the CMC could range between 0.9 – 18 mM, resulting in varying micellar proportions for different bile acids and hence no clear consensus could be made on the CMC concentration (Naumann-Gola et al., 2019; Parker et al., 2014). Therefore, in this study a nominal CMC value of 10 mM was assumed.

The particle sizes reported in Table 1 for Tween 60, Tween 80 and oleic acid coincided within the range of previously reported values of the corresponding micelle sizes (Bide et al., 2021; Pisárčik et al., 2013; Salentinig et al., 2010). Studies have shown that Tween 60 forms a bimodal size distribution, with small micelles of 7 nm diameter plus larger aggregates of 60–120 nm, which contribute to higher PDI values (Lohmann et al., 2022; Pisárčik et al., 2013). The larger apparent values of the micelle size and PDI for the bile acid mixture are presumably a result of the complexity of the mixture, each individual bile acid have its own CMC and aggregation number (N_{agg}). It is known that bile salts do not orient themselves like classic amphiphiles – they have a facial structure based on a tetracyclic steroid ring, with polar hydroxyl groups orientating to the concave side and a hydrophobic convex side (Madenci & Egelhaaf, 2010). This tends to result in low N_{agg} so that it is debatable whether they should be termed micelles at all, but rather surfactant aggregates. The large apparent size observed here suggests that these mixed aggregates maybe be even larger and more complex in structure.

The particle size measurements were repeated with the addition of curcumin (Table 2). Following the addition of curcumin into the micellar environment, the micelles increased in average particle size. Samples of Tween 80, oleic acid and bovine bile salts showed a gradual increase in average particle size as the molar concentration of curcumin was increased – the sizes showed a 50–60 % increase in average particle size. The size distribution curves, pre- and post-addition of curcumin, are provided in the Supplementary material (Fig. S1) and these confirm the large PDI values. This is attributed to curcumin occupying the hydrophobic core which increased the N_{agg} value, resulting in a higher packing density and increased particle size of micelles. This has been observed in many other studies (Deng et al., 2016; Huang et al., 2024; Kuru et al., 2021). It is worth noting that due to the bimodal size distribution of Tween 60 micelles, a clear trend in particle size distribution could not be identified with the gradual increase in curcumin concentration (Fig. S1a). This resulted in a highly polydisperse system (PDI =

Table 1
Average hydrodynamic diameter and polydispersity index (PDI) measured from samples at 100× critical micelle concentrations (CMC).

Sample	Hydrodynamic Diameter (nm)	Polydispersity Index (PDI)
Tween 60	7.0 ± 5.1	0.72 ± 0.25
Tween 80	10.7 ± 3.0	0.16 ± 0.06
Oleic acid	85.6 ± 23.5	0.44 ± 0.09
Bovine bile salts	219.0 ± 24.8	0.94 ± 0.08

Table 2
Average hydrodynamic diameter and polydispersity index (PDI) measured from samples with addition of curcumin at 100× critical micelle concentrations (CMC).

Sample	Molar Concentration Ratio	Hydrodynamic Diameter (nm)	Polydispersity Index (PDI)
Tween 60	50:1	89.6 ± 114.2	0.79 ± 2.94
	10:1	466.5 ± 576.5	0.97 ± 0.64
	5:1	352.7 ± 427.1	1.00
	3:1	624.0 ± 776.8	1.00
Tween 80	50:1	13.7 ± 0.8	0.19 ± 0.01
	10:1	14.6 ± 1.1	0.20 ± 0.08
	5:1	15.9 ± 2.4	0.25 ± 0.02
	3:1	16.2 ± 0.1	0.30 ± 0.01
Oleic acid	50:1	103.2 ± 18.2	0.43 ± 0.07
	10:1	141.7 ± 23.5	0.42 ± 0.06
	5:1	288.6 ± 13.3	0.12 ± 0.11
	3:1	379.1 ± 9.6	0.63 ± 0.25
Bovine bile salts	50:1	169.1 ± 12.9	0.84 ± 0.02
	10:1	188.1 ± 23.5	0.94 ± 0.05
	5:1	205.6 ± 5.6	0.86 ± 0.04
	3:1	309.3 ± 22.3	0.93 ± 0.06

1), even at low concentrations of curcumin. Hence, Tween 60 was not considered for further experiments.

As shown in Fig. 1a, the three micellar systems Tween 80, oleic acid and bovine bile salts showed micelles taking up curcumin, with a maximal solubility at molar ratio of micelles: curcumin at 5: 1. All 3 systems have shown the capability of taking up curcumin where the apparently solubilized fraction is retained in the supernatant. Similarly, as the concentration of curcumin added to these systems of constant micellar concentration was increased, a limit in their capability to solubilize curcumin was seen. Any further addition of curcumin into the micellar systems resulted in the formation of curcumin sediments. This was also apparent visually (Fig. 1b). With increasing concentration of curcumin, the intensity of the distinct yellow color of curcumin increases, whilst visible sedimentation of curcumin was observed at a higher molar ratio of 3:1. Although not shown, Tween 80 and bovine bile salts had similar visual characteristics when curcumin was added, with the only difference being the varied intensity of the yellow color due to their differing ability of solubilizing curcumin.

The capability of a certain type of micelle to solubilize curcumin will be limited by a combination of factors, but most especially the N_{agg}. The value of N_{agg} will determine the number of micelles available for solubilization within the system, their size and therefore ability to accommodate curcumin molecules into their structure. Hence, an inverse relationship between N_{agg} and number of micelles is expected (Kuru et al., 2021). The balance between N_{agg} and the number of micelles is crucial for optimizing solubilization (Medoš et al., 2020). Moreover, specific interactions (hydrogen bonding, van der Waals interactions, polarity of micelle core) between curcumin and the micelle structure add to the complexity of the relationship.

As the molar concentration of curcumin increases, the micellar system of a finite number of micelles approaches the maximal limit for solubilization of the curcumin, and sedimentation will occur as there will be no micelles to effectively solubilize the remaining curcumin (Torres et al., 2011). Tween 80 and oleic acid had comparable capabilities of solubilizing curcumin which is attributed to the similar

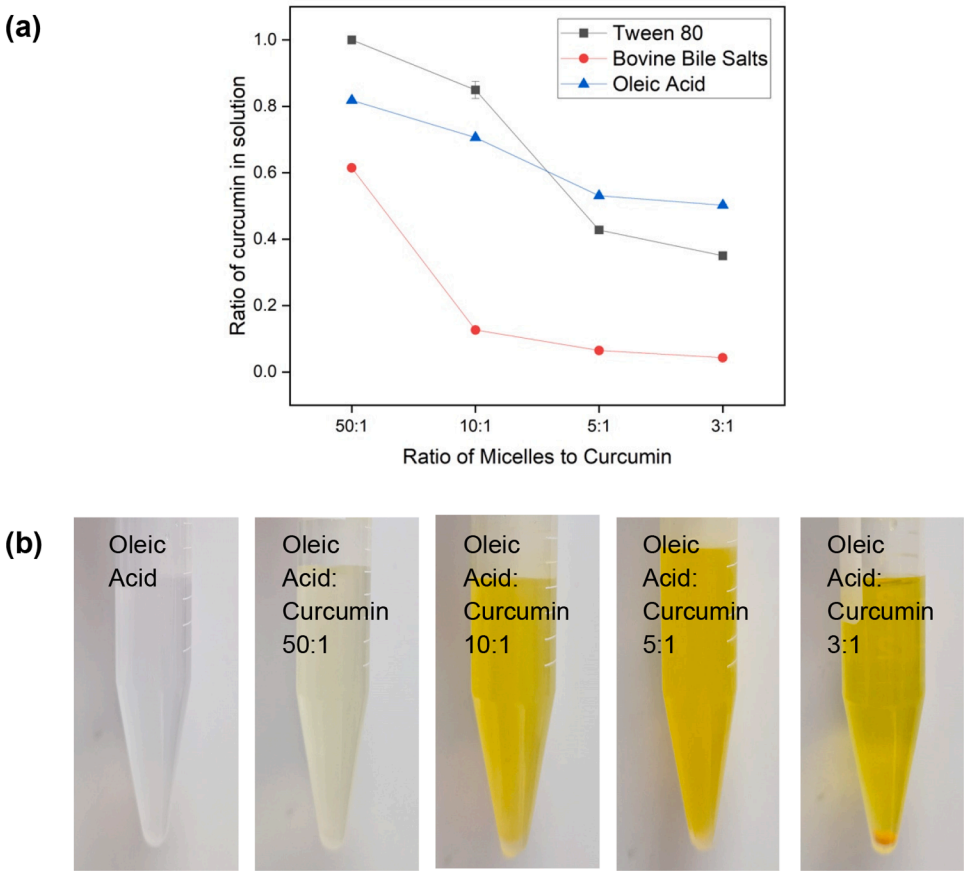

Fig. 1. (a) Fraction of curcumin measured in solution (dissolved, not as particles) based on molar ratio of respective micelles at 100× CMC concentration, (b) images of oleic acid micelles with curcumin at increasing molar concentration of 50:0, 50:1. 10:1, 5:1, and 3:1.

reported range of N_{agg} from 20 to 100 (Arai et al., 2016; Glenn et al., 2005; Penttilä et al., 2019). The N_{agg} of individual bile salts is reportedly very low (3–26), and so should have provided sufficient micelles to the system to solubilize curcumin (Madenci & Egelhaaf, 2010). However, the reduction in efficacy of solubilizing curcumin may be due to the large aggregation evident in Table 1 as well as the variability of bile acids present.

The particle size of the Tween 80 micelles remained relatively stable under all conditions tested (see Table 3), indicating that the micelles were neither affected by pH nor salt concentrations and therefore more stable than those of oleic acid. The micelle sizes increased on addition of curcumin and the increases might be expected to be similar if similar amounts of solubilization occurred. The concentrations of curcumin apparently retained in solution by the micelles were also consistent under all conditions (see Fig. 2), further demonstrating the stability of the micelles with solubilized curcumin. Tween 80 is a non-ionic surfactant and therefore the effect of salt and pH on Tween 80 micelles are generally reported as negligible (Qazi et al., 2020).

Conversely, with oleic acid, there was a large variability in the results obtained with regard to pH and salt conditions. With the addition of curcumin to oleic acid, the micelles clearly increased in size, but there was no identifiable trend. Moreover, the resulting micelles were very polydisperse under all conditions. The concentration of curcumin retained in solution also remained consistently lower than that with Tween 80, with only the pH 2 condition having a spike at the lowest salt concentration.

In acidic pH, the particle size of oleic acid micelles nearly doubled. Oleic acid is an anionic surfactant that on dissolution in water will generate a negatively charged ionic head and positively charged counter ion (Saha et al., 2023). It is well-documented that the aggregation of oleic acid is highly affected by pH and the degree of protonation of the head group determines whether either micelles, vesicles, or oily droplet phases are formed (Edwards et al., 1995; Janke et al., 2014; Kaibara et al., 1997; Nakano et al., 2002; Salentinig et al., 2010). At pH above 9.85 (above the apparent pK_a value of the oleic acid carboxyl group), the fatty acid is deprotonated, and the solution exists as a suspension of spherical micelles at the CMC. As the pH decreases to a value close to the apparent pK_a (8.0–8.5), there is a balance of protonated and deprotonated micelles and spontaneous formation of highly polydisperse vesicles that may be multilamellar. Additionally, oleic acid would exist in its protonated form with a further decrease in pH values, resulting in the transition to nonlamellar liquid-crystalline structures and subsequently formation of oil droplets due to the reduced hydrophilic nature of the head group. According to Salentinig et al. (2010), it was reported that the particle size of oleic acid also changes with pH, with micelles being approximately 120 nm in diameter and decreasing to 60 nm for vesicles (Salentinig et al., 2010). These transitions of oleic acid with pH are known to be reversible. At pH 2, oleic acid would be totally protonated causing the formation of oil droplets, resulting in a large increase in particle size. It is possible that with such structures most of the curcumin would be trapped in the oil droplets, rather than existing in its insoluble crystalline form within the sediment.

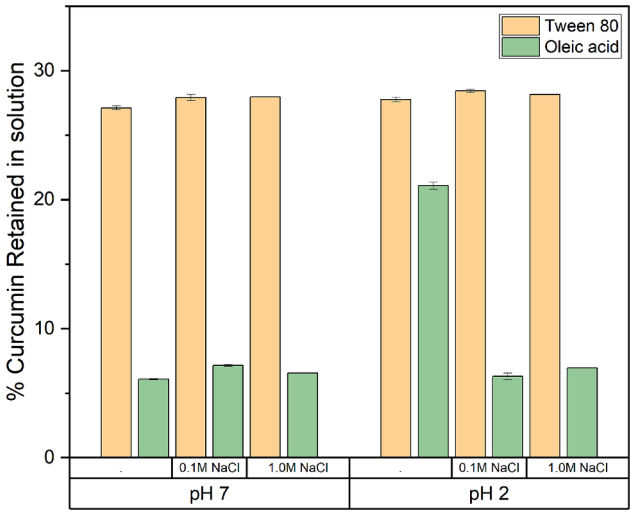

Fig. 2. Concentration of curcumin remaining in solution at varying conditions of pH and salt concentrations in micellar solutions of Tween 80 and Oleic acid after 1 h.

Oleic acid aggregation is also known to be sensitive to salt concentration as electrostatic repulsion between headgroups of oleic acid influences the phase stability. Although at low salt concentration (0.1 M), there was a slight increase in size, at high salt concentrations (1.0 M), micelle sizes decreased slightly – but this was not consistent. At pH 7, which is close to the apparent pK_a of 8.0–8.5, the oleic acid should exist in both its protonated and deprotonated form, with its protonated form slightly dominating (Edwards et al., 1995; Salentinig et al., 2010). At low salt concentrations, the electrostatic repulsive interaction between the head group and Na^+ is large, which may result in an increase in area of lipid headgroup (Aota-Nakano et al., 1999). Consequently, this repulsion can lead to the formation of larger micelles or vesicles, or even increased CMC concentrations. Conversely, the addition of salt at higher concentration introduces more Na^+ and Cl^- ions that could potentially screen the electrostatic charges (Hoque et al., 2021). The screening effect would reduce the repulsion between partially ionized head groups that would allow a tighter packing, forming smaller micelles.

According to Kaibara et al. (1997), at low pH (pH 2) the carboxyl group of oleic acid is in its completely protonated form. This would have led to the increased hydrophobic interaction and formation of oil droplets, hence the effect of addition of salt at low concentration is less pronounced. At higher salt concentration, the ions may still screen any residual charges. However, due to the low ionization state, the size was not observed to decrease significantly. Moreover, any further increase in salt concentrations would have not been feasible as an aggregation of vesicles would occur, which is likely caused by a "salting out" effect of NaCl (Maurer & Nguyen, 2016).

Generally, curcumin is known to be poorly soluble in water, with a typical solubility limit of 0.6 μg/mL (Górnicka et al., 2023). When γ-CD-

Table 3
Average hydrodynamic diameter measured before and after addition of curcumin into micellar solutions at varying pH (pH 7 and 2), and at NaCl concentrations of 0.0 M, 0.1 M and 1.0 M.

Samples	Hydrodynamic diameter (nm)											
	Before addition of curcumin						After addition of curcumin					
	pH 7			pH 2			pH 7			pH 2		
		0.1 M NaCl	1.0 M NaCl		0.1 M NaCl	1.0 M NaCl		0.1 M NaCl	1.0 M NaCl		0.1 M NaCl	1.0 M NaCl
Tween 80	11.6 ± 0.5	11.7 ± 0.6	12.1 ± 0.6	11.4 ± 0.4	11.5 ± 0.1	13.2 ± 0.6	15.4 ± 0.1	17.3 ± 0.4	17.5 ± 0.9	17.2 ± 0.6	17.2 ± 0.1	20.4 ± 0.7
Oleic acid	98.1 ± 2.5	232.4 ± 12.4	105.5 ± 0.5	166.6 ± 2.6	190.1 ± 0.1	107.4 ± 41.3	175.2 ± 4.6	211.3 ± 67.4	191.7 ± 1.7	337.5 ± 50.7	199.5 ± 6.4	189.3 ± 0.8

MOFs with encapsulated curcumin are placed in contact with water the γ-CD-MOFs disintegrate and so the trapped curcumin within its cavity should be "released". In the absence of micelles, the released curcumin should therefore rapidly crystallize. The presence of micelles showed a positive influence in the uptake of curcumin, so it was inferred that if the γ-CD-MOF system was augmented with the same surfactant micelles, at least some of the "released" curcumin would be taken up by these micelles and thereby improve its potential bioaccessibility. Based on encapsulation efficiency calculations, 10 mg of Cur-γ-CD-MOFs dispersed in water was predicted to give a maximal 64 μg/mL of curcumin released in the aqueous phase. The results show (Fig. 3) that on their own Cur-γ-CD-MOFs resulted in 14.08 % (9.01 μg/mL) of this maximal value of curcumin dispersed in the aqueous 'solution'. With Tween 80 micelles in combination with Cur-γ-CD-MOFs there was an increase in the apparent solubility of curcumin to 71 % (45.89 μg/mL) of this maximal value. This was followed by oleic acid micelles, which increased the apparent solubility by 9 % of this maximal value (to 14.78 μg/mL). Conversely, bile salts were observed to have a slightly negative effect in solubilizing curcumin, giving a reduction of the apparent solubility of curcumin to 7.49 μg/mL.

Based on the results shown in Fig. 1(a), Tween 80 and oleic acid exhibited similar capabilities of taking up curcumin within the micelles formed. However, Fig. 2 shows that the curcumin retained in solution by Tween 80 was at least double that of oleic acid, which also corresponded to results collected in Fig. 3. With the reported N_{agg} of Tween 80 and oleic acid being within the same range, the lowered curcumin retention may be characterized as being due to the different hydrophile-lipophile (HLB) values of the surfactants. The HLB value is a nondimensional numerical value allocated to surfactant molecules that characterizes their balance between hydrophilic and lipophilic portions (Schmidts et al., 2012). The value can be used, with caution, to indicate the likely suitability of the surfactant for certain formulations and/or stabilization of a system. The HLB values reported for Tween 80 and oleic acid are approximately 15 and 1, respectively (Barkat et al., 2011; Hait & Moulik, 2001). Tween 80 is thus much more hydrophilic in nature, dispersible in water, and its high HLB value indicates that the molecule is better able to stabilize oil-in-water (O/W) emulsions (Hong et al., 2018; Wang et al., 2023). In contrast, oleic acid is lipophilic in nature, largely immiscible with water and in fact may precipitate when added to water. This leads to inferior lowering of the surface tension and its better suitability for stabilizing W/O emulsions (Yu et al., 2015). Since the Cur-γ-CD-MOFs were dispersed in water, Tween 80 would therefore have an advantage over oleic acid in solubilizing curcumin in water.

Although the bile salts showed a slight capability of solubilizing curcumin in water, it was observed that when used in combination with Cur-γ-CD-MOFs, there was a *reduction* in apparent solubility of curcumin in water. It is probable that in the presence of both bile salts and γ-CD-MOFs, the curcumin ends up in several different states: partly solubilized in micelles, partly remaining encapsulated within γ-CD-MOFs and/or partly molecularly dissolved. However, studies have shown that when bile salts interact with drug-cyclodextrin-complexes, bile salts may displace or compete with the molecules within the cyclodextrin cavity, which may have led to the adverse effect of reduced apparent solubility of target compounds (Cuoco et al., 2023). It was also postulated that the dynamic exchange between bile salts and drug complexes would actually boost the free drug concentration to exceed supersaturation, which would induce a higher permeation or bioavailability. However, this was not demonstrated in a study conducted by Eriksen et al. (2022) due to the variation of bile salt concentration in rats and humans, and it was concluded that the competitive displacement was affected by several factors.

Commercially available curcumin is composed of bisdemethoxycurcumin, demethoxycurcumin and curcumin, all classed as curcuminoids. Based on Fig. 4, it appears that curcumin, in the presence of bile salts, has an increased bioaccessibility resulting from its increased apparent solubility as compared to the reported solubility of 0.6 μg/mL in water. The bioaccessibility of curcumin + bile salts is approximately 2 %, measuring at 5 μg/mL. On the other hand, when encapsulated in γ-CD-MOFs the apparent solubility of curcumin is significantly improved and sustained throughout intestinal digestion conditions, thereby improving its bioaccessibility (16 %). A comparison of the results shown in Fig. 3 indicates that Cur-γ-CD-MOFs dissolved in pure water resulted in a retention of curcumin concentration of nearly 10 μg/mL, whereas with the addition of bile salts during *in vitro* digestion, the apparent solubility increased nearly 3.2× to approximately 32 μg/mL and is also approximately 6× more bioaccessible than curcumin + bile salts. Moreover, the displacement of curcumin from the γ-CD-MOFs by bile salts was not observed. Due to the susceptibility of the γ-CD-MOFs to amylase activity from the pancreatin, it is suggested that the collapse of γ-CD-MOFs may counteract the negative displacement effect (Pan et al., 2022). Thus, it has been proven that in the presence of the appropriate type of micelles, the bioaccessibility of a bioactive compound could be further enhanced when used in conjunction with γ-CD-MOFs.

With reports of bioaccessibility of curcumin exceeding 50 % when

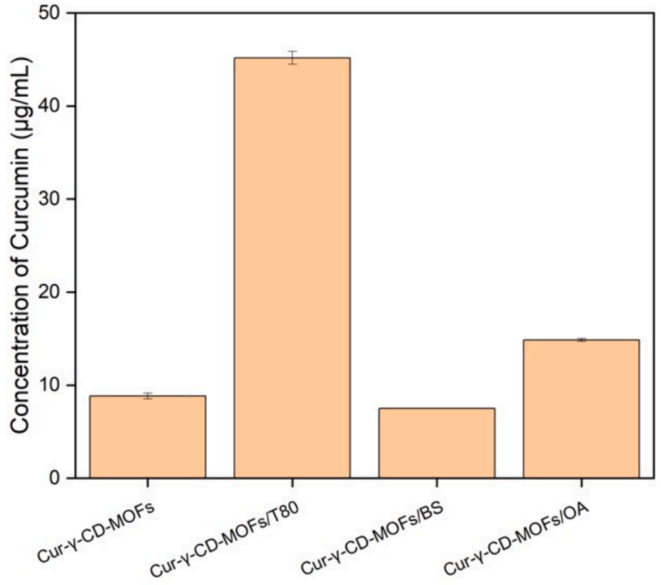

Fig. 3. Concentration of curcumin remaining in solution after dissolution of Cur-γ-CD-MOFs in distilled water ± solutions containing micelles of Tween 80 (T80), bovine bile salts (BS), and oleic acid (OA) at 100× their CMC.

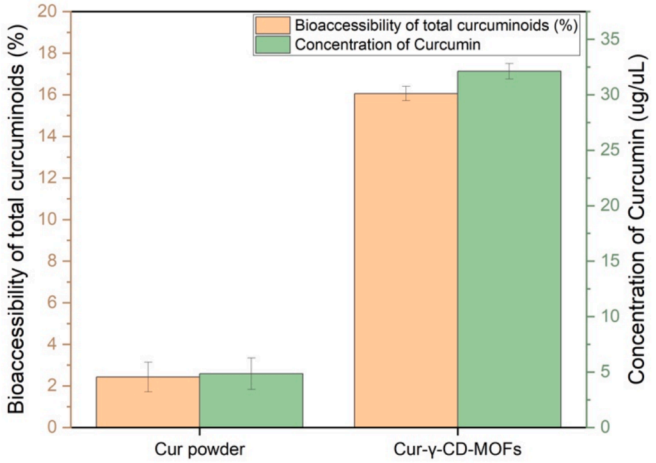

Fig. 4. Bioaccessibility and concentration of total curcuminoids of curcumin (Cur powder) and curcumin encapsulated in γ-CD-MOFs (Cur-γ-CD-MOFs) after *in vitro* gastrointestinal digestion.

delivered in emulsions, solid lipid particles and oleogels, a 15 % bioaccessibility in Cur-γ-CD-MOFs may not seem comparable (Gonçalves et al., 2024; Ma et al., 2024; Verma et al., 2021). This could be influenced by the method of quantifying bioaccessibiity and sample preparation involved. Compounds which are insoluble in water generally require an extraction procedure for further quantification and the extraction efficiency plays a role in the subsequent quantification of curcumin within the micellar phase. In some instances, the quantification of curcumin could be either spectrophotometrically or with the use of HPLC. Although the spectrophotometric method has proven to be simple, the precision is low. Non-curcumin colour interfering pigments would cause an overestimation, and the detection method does not provide relative composition of individual curcuminoids (Kotra et al., 2019). HPLC could effectively separate and quantify curcuminoid mixtures, but the method is still limited by various factors in the optimization of method (e.g. flow rate, run time, gradient elution, etc.).

The stability of encapsulated material, photochemically and thermally, is known to be improved by γ-CD-MOFs (Chen et al., 2021). Due to its unique host–guest structure, the degradation of curcumin within the cavities and pores of γ-CD-MOFs were significantly delayed and instead protected. With formulations involving the use of lipids or proteins, at certain physiological conditions, the dispersibility may be impacted due to coalescence, aggregation or separation, which would in turn limit the action of lipase and pancreatin in simulated intestinal conditions (Dong et al., 2022). Moreover, as these interfaces degrade due to enzymatic reactions, curcumin could be degraded due to exposure to free radicals (Araiza-Calahorra et al., 2018). Furthermore, the biocompatibility of γ-CD-MOFs could potentially favour the absorption of curcumin and thereby influence its bioavailability. This will be further explored in the future studies.

4. Conclusion

This study found that micelles of the surfactants Tween 80, Tween 60, oleic acid and bovine bile salts showed a positive retention of curcumin, an otherwise insoluble crystalline material, within micellar solutions. All the micelles had a maximum limit by which they could solubilize curcumin – at a molar concentration of micelles:curcumin = 5:1. This was thought largely due to the N_{agg} of the micelles and the amount of surfactant molecules available to form micelles at a fixed concentration. Depending on the nature of the surfactants, pH and salt concentrations can significantly influence the ability of the surfactant to form micelles and the stability of the resulting encapsulating structures. Dispersed in combination with γ-CD-MOFs, Tween 80 and oleic acid markedly improved the apparent solubility of curcumin when compared to using Cur-γ-CD-MOFs alone. Although bovine bile salts are known to displace curcumin and compete for the cavity spaces of the γ-CD-MOFs, this negative effect was not seen in *in vitro* intestinal digestion. This may be due to the susceptibility of γ-CD-MOFs to amylase.

This study has therefore shown the potential for γ-CD-MOFs for sustained release, particularly if they are supplemented by the presence of an appropriate surfactant micelle system. In future studies, an emulsion system in combination with Cur-γ-CD-MOFs + micelles could be investigated for further improvement of the bioaccessibility and bioavailability of curcumin.

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CRediT authorship contribution statement

Jia X. Oh: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Alan R. Mackie:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rammile Ettelaie:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Taskeen Niaz:** Writing – review & editing, Supervision. **Brent S. Murray:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodres.2025.115869.

Data availability

Data will be made available on request.

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