



Structural characteristics, binding behaviors, and stability of ternary nanocomplexes of lecithin, polyvinylpyrrolidone, and curcumin

Qiong-Qiong Yang^{a,b}, Wo-Qi Cai^{a,b}, Zhi-Xuan Wang^{a,b}, Yu Li^{a,b}, Yu Zhang^{a,b}, Xiaoling Lin^c, Bao-Lian Su^d, Harold Corke^{c,e}, Bo-Bo Zhang^{a,b,*}

^a Department of Biology, College of Science, Shantou University, Shantou, 515063, Guangdong, China

^b Guangdong Provincial Key Laboratory of Marine Biotechnology, Institute of Marine Sciences, Shantou University, Shantou, 515063, China

^c Biotechnology and Food Engineering Program, Guangdong Technion-Israel Institute of Technology, Shantou, 515063, Guangdong, China

^d Laboratory of Inorganic Materials Chemistry, University of Namur, Rue de Bruxelles, 61, Namur, B-5000, Belgium

^e Faculty of Biotechnology and Food Engineering, Technion-Israel Institute of Technology, Haifa, 320003, Israel

ARTICLE INFO

Keywords:

Curcumin
Bioaccessibility
Lecithin
Hydrophobic compounds
Molecular dynamics simulation

ABSTRACT

Low stability and bioaccessibility are two unfavourable features that limit the application of many hydrophobic compounds. In this study, lecithin was complexed with polyvinylpyrrolidone K30 (PVPK30) to enhance the stability and bioaccessibility of curcumin via a precipitation-ultrasonication method. The curcumin-loaded nanocomplexes exhibited uniform sizes (~120 nm), low polydispersity (~0.22), and negative zeta potential (~−45 mV). Curcumin was molecularly dispersed in lecithin-PVP complexes and exhibited an amorphous state. The curcumin-loaded nanocomplexes possess excellent dilution, thermal, and storage stability. More importantly, *in vitro* simulated gastrointestinal digestion experiment showed that the nanocomplexes could significantly improve the bioaccessibility of curcumin, reaching 105 times. Molecular dynamics simulation study revealed that lecithin and PVPK30 stabilized curcumin through hydrogen bonds, π - π interactions, and hydrophobic interactions. Our study provides a new way for curcumin and other hydrophobic compounds with excellent stability and bioaccessibility.

1. Introduction

Curcumin is a polyphenolic compound mainly isolated from the root of *Curcuma longa* L. and has a wide range of bioactivities, such as antioxidant, anticancer, anti-inflammatory, and antibacterial activities (Yang et al., 2020). Nevertheless, the applications of curcumin are restricted due to its poor solubility and poor oral absorption in the gastrointestinal tract (Zhou, Zheng, & McClements, 2021). Nanoparticles have recently acquired immense importance as delivery vehicles. These nano-formulations not only improve stability but also provide efficient delivery of active compounds to targeted sites and long-term release. Numerous studies have fabricated curcumin into nanoparticles, such as nanocomplexes, polymer micelles, nano-emulsions, nanoparticles, and liposomes, to increase solubility, bioavailability, and absorption (Adsare & Annapure, 2021; Hu et al., 2021; Kim, Kim, & Lee, 2022; Pan, Li, Meng, Xu, & Zhang, 2021; Yang et al., 2020). However, regarding the diversity of commercial food matrices, the development of novel delivery systems to enlarge the

utilization of curcumin has always been a research hotspot.

Lecithin is the main component of biofilm and cell membranes in nature. It is known as the “third nutrient” paralleled with proteins and vitamins (Huang et al., 2022). Lecithin has many health-benefit effects, such as lowering blood lipids, preventing vascular diseases, improving brain and neurological functions, preventing Alzheimer's disease, and anti-inflammatory and antioxidant activities (Miller, 2002). The structure of the lecithin molecule contains polar and nonpolar parts, which can be used as ionic surfactants to emulsify some bioactive compounds, which are commonly used as an emulsifier in the food industry with no limitation on the maximum level (Wang et al., 2021). Since lecithin is a natural cell membrane component, there are no side effects on cells during the whole migration process, they can safely and effectively improve the bioavailability of active substances. A review study has summarized that the complexation of bioactive substances with lecithin can promote the absorption of active compounds in the gastrointestinal tract and improve oral bioavailability (Barani et al., 2021). However, our previous study found that lecithin is a thermally unstable substance and cannot withstand the highly acidic conditions in gastric fluids

* Corresponding author. Department of Biology, College of Science, Shantou University, Shantou, 515063, Guangdong, China.

E-mail address: bbzhang@stu.edu.cn (B.-B. Zhang).

<https://doi.org/10.1016/j.lwt.2023.114489>

Received 19 October 2022; Received in revised form 6 January 2023; Accepted 18 January 2023

Available online 19 January 2023

0023-6438/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Abbreviations

PVPK30	polyvinylpyrrolidone K30
FDA	United States Food and Drug Administration
PdI	polydispersity index
ATR-FTIR	attenuated total reflection Fourier transform infrared spectroscopy
XRD	X-ray powder diffraction
DSC	differential scanning calorimetry
SEM	scanning electron microscope
MD	molecular dynamics
GIT	human gastrointestinal tract
SSF	simulated saliva fluid
SGF	simulated gastric fluid
SIF	simulated intestinal fluid
LEC	lecithin
CUR	curcumin

during gastric digestion.

Polyvinylpyrrolidone (PVP) is a bulky, non-toxic, non-ionic polymer with C=O, C-N, and CH₂ functional groups, which has been approved as an inactive polymer by the United States Food and Drug Administration (FDA) (Kurakula & Rao, 2020). The structure of the PVP molecule contains a strongly hydrophilic component (the pyrrolidone moiety) and a considerable hydrophobic group (the alkyl group), therefore, it is an excellent stabilizer that prevents nanoparticles from aggregating in solvent and interacting with each other through the repulsion generated by hydrophobic carbon chains (steric hindrance effect) (Koczkur, Mourdikoudis, Polavarapu, & Skrabalak, 2015). It is reported that the thermal stability of compounds increases with the increase in PVP dosage (Jelić, Liavitskaya, & Vyazovkin, 2019), indicating that PVP can prevent active compounds from thermal degradation. It was also found that PVP is resistant to acidic conditions in the human gastrointestinal tract (GIT). It was detected in the human stomach, duodenum, and ileostomy fluid, suggesting that it was relatively stable in human GIT (Shoukat et al., 2020). These properties render PVP an ideal building material for lecithin-polymer complexes.

In this study, we speculated that curcumin would be entrapped within the hydrophobic parts of lecithin, and the outer layer of hydrophilic parts of lecithin was further surrounded by PVP, which would retard the decomposition of lecithin during heat treatment and gastric digestion, thereby improving the stability and bioaccessibility of curcumin. Therefore, soy lecithin and PVPK30 were combined used to stabilize curcumin using a simple precipitation-combined ultrasonication method. The physicochemical characteristics such as size, zeta potential, dilution stability, storage stability, and thermal stability of curcumin-loaded nanocomplexes were studied. Moreover, the *in vitro* bioaccessibility and stability of curcumin-loaded nanocomplexes were studied compared to unformulated curcumin. Furthermore, to verify our hypothesis, we further explored the binding behaviour and interaction of the nanocomplexes through molecular dynamics simulation. This study would confirm the excellent stability of lecithin and PVPK30 and provide a theoretical basis for their synergistic applications.

2. Materials and methods

2.1. Materials

Curcumin (98% purity) and PVPK30 were purchased from Bide Pharmatech Co., Ltd (Shanghai, China). Soy lecithin (98% purity) was purchased from Xi'an Pruis Bioengineering Co., Ltd (Shanxi, Xi'an, China). Ethanol (99% purity), NaOH (96% purity), HCl, and acetone were purchased from Xilong Scientific Co., Ltd (Guangdong, China).

2.2. Methods

2.2.1. Preparation of curcumin-loaded nanocomplexes and mixtures

Curcumin-loaded nanocomplexes were prepared via a precipitation-ultrasonication method with modifications (Zhou et al., 2021). Briefly, curcumin, PVPK30, and soy lecithin were dissolved in acetone, distilled water, and distilled water, respectively, at concentrations of 10 mg/mL. PVPK30 and soy lecithin were mixed in the volume ratios of 1:0.5, 1:1, and 1:2 to a total volume was 6 mL. Then 0.6 mL curcumin acetone solution was added into the mixed solution with ultrasonication for 2 min (20.6235 kHz, 340 W), followed by evaporation of acetone at 60 °C under vacuum until no organic solvent remained. The resultant nanocomplexes were defined as K30-L1:0.5, K30-L1:1, and K30-L1:2, respectively. Partitions of the nanocomplexes were kept at 4 °C for further studies, including size, zeta potential, dilution stability, thermal stability, storage stability, and *in vitro* simulated gastrointestinal digestion, and the rest was freeze-dried for SEM, DSC, XRD, and FTIR analysis.

For freeze drying, the liquid samples were first frozen at −80 °C for 24 h and then transferred to the shelf of LGJ-10 bench top freeze dryer (Song Yuan Freeze Dryer Tech Co., Ltd., Beijing, China) at −45 °C, lower than 10 Pa for 2–3 days.

For comparison with the nanocomplexes, physical mixtures of curcumin, lecithin, and PVPK30 were prepared by simply mixing curcumin, lecithin, and PVPK30 in the volume ratios as nanocomplexes without sonification.

2.2.2. Size and zeta potential measurement

Mean particle size, polydispersity index (PdI), and zeta potential of the curcumin-loaded nanocomplexes were determined by a Nano-ZS (Malvern Instruments Ltd., Malvern, U.K.) instrument using dynamic light scattering. Samples were diluted with ultrapure water and determined at 25 °C. All measurements were repeated at least three times, and the results were expressed as mean ± standard deviation.

2.2.3. ATR-FTIR analysis

ATR-FTIR spectra of curcumin powder, blank excipients (PVPK30 and soy lecithin), curcumin-loaded nanocomplexes, and the physical mixture of curcumin powder and excipients were acquired with a PerkinElmer LAMBDA365 (Waltham, MA, USA) equipped with a PerkinElmer Universal ATR sampling accessory consisting of a diamond crystal. The samples were analyzed with the following settings: the spectral range of 4000–550 cm^{−1}, 32 scans, and 4 cm^{−1} resolution. A background was collected for every new sample, and measurements were in triplicate. The 3 mg of each powder was placed under the ATR diamond crystal and the same pressure was applied for each aliquot, resulting in consistent data. All the data were pre-processed to reduce background noise and inputted into multivariate analysis. The analyses were conducted on OriginPro 2022b.

2.2.4. X-ray diffraction (XRD) measurements

The XRD was analyzed by a Rigaku SmartLab9KW X-ray diffractometer (Rigaku, Neu-Isenberg, Germany) with Cu-Kα radiation generated at 40 mA and 40 kV. Curcumin powder, blank excipients (PVPK30 and soy lecithin), curcumin-loaded nanocomplexes, and the physical mixture of curcumin powder and excipients were scanned over an angular range of 3–40° of 2θ, with a step size of 0.02°, scanning rate 8°/min.

2.2.5. Differential scanning calorimetry (DSC) analysis

The thermal behaviours of curcumin powder, blank excipients (PVPK30 and soy lecithin), curcumin-loaded nanocomplexes, and the physical mixture of curcumin powder and excipients were analyzed with a PerkinElmer DSC6000 (Waltham, MA, USA). Samples were sealed in an aluminium pan and heated from 30 °C to 300 °C at a speed of 10 °C/min. The inert atmosphere was maintained by purging nitrogen at a flow

rate of 20 mL/min. The control empty pan under the same heating conditions was taken as a reference.

2.2.6. Scanning electron microscope (SEM) analysis

The morphologies of curcumin powder, blank excipients (PVPK30 and soy lecithin), curcumin-loaded nanocomplexes, and digested curcumin-loaded nanocomplexes were observed with a high-resolution field emission scanning electron microscope (ZEISS GeminiSEM450, Germany). The samples were mounted on an aluminium stub with carbon adhesive discs and coated with gold in an Agar Automatic Sputter Coater B7341. Observations were performed under an accelerating voltage of 3 kV.

2.2.7. Molecular dynamics simulation

Atomistic molecular dynamics (MD) simulations have been performed in the GROMACS (Hess, Kutzner, Spoel, & Lindahl, 2008) (version 2020.6) simulation package. The simulation model is based on OPLS all-atom force field (Kaminsky, Friesner, Tirado-Rives, & Jorgensen, 2001), which has been widely used in MD. The force field has high adaptability to complex organic molecules (Chen, Martin, & Siepmann, 1998; Jorgensen, Maxwell, & Tirado-Rives, 1996; Jorgensen & McDonald, 1998), polymer models (De Nicola et al., 2015; Milano, Santangelo, Ragone, Cavallo & Matteo, 2011; Śiechowski, Borek, Piwowarczyk, & Łuźny, 2015), nanoparticles and other possible interfaces (Bernardes & Joseph, 2015; Ortiz, Nielsen, Klein, & Discher, 2006). The monomer structures of polyvinylpyrrolidone (PVP), lecithin (LEC), and curcumin (CUR) were obtained from the PubChem (CID: 5102882, 26198, and 969516, respectively) (www.pubchem.ncbi.nlm.nih.gov 2021). All initial structures were optimized by Gaussian09. The systems were constructed using the Amorphous Builder in the Materials Studio software with a molecular ratio of 50:50:10 molecules of PVP: LEC: CUR. All molecules were packed randomly in a cubic box with a length of 10 nm, involving appropriate water molecules. The temperature was maintained at 298 K using the V-rescale thermostat (Bussi, Donadio, & Parrinello, 2007) and a time coupling constant of 0.1 ps. The pressure was maintained at 1 bar using the semi-isotropic Berendsen barostat (Berendsen, Postma, van Gunsteren, DiNola, & Haak, 1984) and a time coupling constant of 1 ps. The Verlet cutoff scheme (Nam, Gao, & York, 2005; Qian & Schlick, 2002) was used, along with the particle mesh Ewald method for electrostatics (Hess, Bekker, Berendsen, & Fraaije, 1997). The identification of the interaction between molecules was calculated and analyzed by PyMOL software.

2.2.8. Thermal stability analysis

Curcumin-loaded nanocomplexes and curcumin ethanol solutions were diluted with ultrapure water 100 times and heated at 60 °C and 80 °C for 6 h. The absorbance at 425 nm was recorded every hour. The particle size, PDI, and zeta potential of the diluted curcumin-loaded nanocomplexes were detected every hour. The curcumin retention rate was calculated using the following equations:

$$\text{Curcumin retention rate (\%)} = C_{\text{initial}} / C_t \times 100 \quad (1)$$

Where C_{initial} and C_t were the curcumin concentrations of the samples at 0 h and at the measured time point, respectively.

2.2.9. Storage stability analysis

Curcumin-loaded nanocomplexes and curcumin ethanol solutions were diluted with ultrapure water 100 times and were stored at room temperature (21 °C) and 4 °C for 6 weeks. The absorbance at 425 nm was recorded every week. The particle size, PDI, and zeta potential of the diluted curcumin-loaded nanocomplexes were detected every week.

2.2.10. The pH stability of nanocomplexes

Curcumin-loaded nanocomplexes and curcumin ethanol solutions were diluted with ultrapure water 100 times, and the pH was adjusted to

1.5, and 6.8, and then shaken for 2 h (25 °C, 100 rpm). The absorbance at 425 nm was recorded every half an hour.

2.2.11. Simulated gastrointestinal digestion (GIT)

A gastrointestinal tract (GIT) model that contains oral, gastric, and intestinal phases was used to simulate the potential digestion of curcumin and curcumin-loaded nanocomplexes according to a previous method (Lee, Jung, Rho, & Kim, 2022). Artificially simulated saliva fluid (SSF), simulated gastric fluid (SGF), and simulated intestinal fluid (SIF) were purchased from Dongguan ChangFeng Technology Co., Ltd. Curcumin ethanol solution (1 mg/mL) and curcumin-loaded nanocomplexes containing 1 mg/mL curcumin were used as the primary raw samples. Firstly, the samples were mixed with SSF in a ratio of 1:1 and reacted for 10 min (37 °C, 100 rpm). Thereafter, the mixtures were further mixed with SGF in a ratio of 1:1 and reacted for 120 min (37 °C, 100 rpm). After gastric digestion, the SIF was added to the mixtures in a ratio of 1:1 and reacted for another 120 min (37 °C, 100 rpm).

2.2.12. Bioaccessibility and stability

The bioaccessibility and stability of curcumin were determined according to a previous study (Zheng, Zhou, & McClements, 2021) with slight modifications. After the samples passed through the GIT model, the raw digestates were centrifuged (12000 rpm, 30 min, 4 °C), and the supernatants were regarded as mixed micelle fractions. The droplet size, PDI, and zeta potential of the micelles were measured as described in section 2.2.2, and the morphology of freeze-dried micelles was observed using SEM according to the method described in section 2.2.6.

The curcumin in the raw digestates or the mixed micelle fractions was extracted with ethyl acetate and centrifuged (3000 rpm, 5 min, 4 °C). The ethyl acetate phase was collected and diluted with ethanol, and then measured at 425 nm to calculate the curcumin concentration. The *in vitro* bioaccessibility and stability of curcumin were calculated using the following equations:

$$\text{Bioaccessibility (\%)} = C_{\text{micelle}} / C_{\text{digest}} \times 100 \quad (2)$$

$$\text{Stability (\%)} = C_{\text{digest}} / C_{\text{initial}} \times 100 \quad (3)$$

Where C_{micelle} , C_{digest} , and C_{initial} represent the concentration of curcumin in the mixed micelle fraction, raw digest, and primary raw samples, respectively.

2.2.13. Statistical analysis

All experiments were repeated at least three times and the results are expressed as the mean $\pm$ standard deviation (SD). One-way analysis of variance (ANOVA) was used for data mean comparison, followed by Tukey's-HSD test, with $p < 0.05$ deemed statistically significant.

3. Results and discussion

3.1. Preparation and physicochemical characterization of the curcumin-loaded nanocomplexes

In a preliminary test, PVPK30 or soy lecithin alone could not stabilize curcumin in a weight ratio of 1:10 (drug: stabilizer), the systems even precipitated immediately after preparation. However, the combination of PVPK30 and soy lecithin could stabilize curcumin well. The curcumin-to-stabilizer ratio was fixed at 10%, and the weight ratio of PVPK30 to soy lecithin was adjusted. We found that a ratio of 1:0.5–1:2 could stabilize curcumin well, and when the ratio was lower or higher than this range, curcumin would precipitate. As shown in Fig. 1a, b, c, K30-L1:0.5, K30-L1:1, and K30-L1:2 had small particle sizes (~ 120 nm), and narrow size distribution (0.2–0.25), indicating a relatively homogeneous system (Manca et al., 2014). Zeta potential is a general measurement of the surface charge of particles in the dispersion system and is an index to characterize the stability of nanoparticles. The colloidal system tends to be stable when its zeta potential is higher than $|\pm 30|$ mV because the

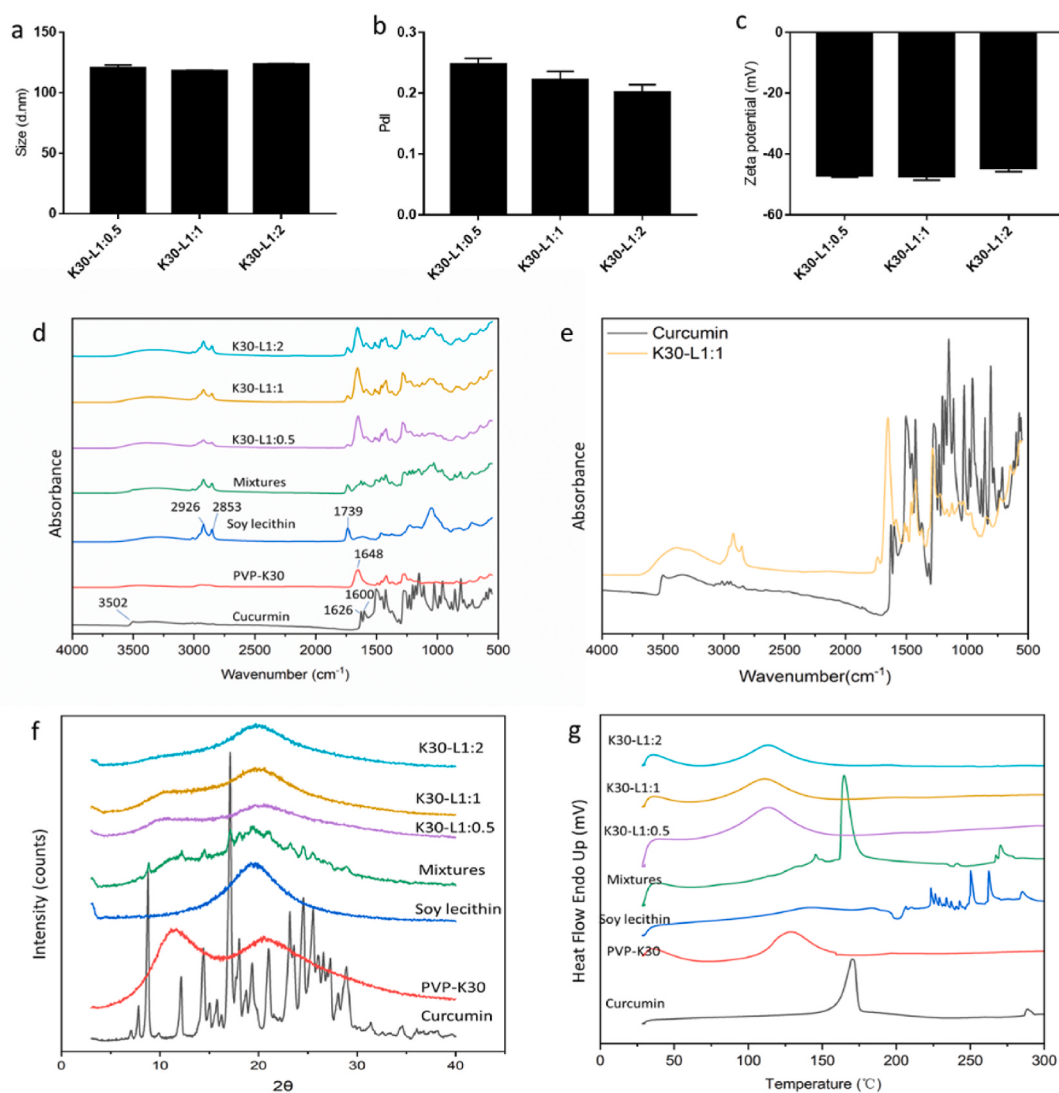


Fig. 1. Characterization of curcumin and related formulas. (a) Particle size of curcumin nanosuspensions; (b) Polydispersity index of curcumin nanosuspensions; (c) Zeta potential of curcumin nanosuspensions; (d) ATR FT-IR spectra of curcumin, PVPK30, soy lecithin, mixtures, and three curcumin nanosuspensions; (e) ATR FT-IR spectra of curcumin and K30-L1:1; (f) XRD curves of curcumin, PVPK30, soy lecithin, mixtures, and three curcumin nanosuspensions; (g) DSC curves of curcumin, PVPK30, soy lecithin, mixtures, and three curcumin nanosuspensions.

surface loads will prevent aggregation between particles (Syamdi, Sidauruk, Munandar, & Haryati, 2020). The three nanocomplexes had low zeta potential (<-44 mV), indicating that they were very stable.

FTIR can be used to elucidate intermolecular interactions (Ma et al., 2022). As shown in Fig. 1d, ATR-FTIR spectra of curcumin demonstrated three typical peaks at 3503 cm^{-1} , 1626 cm^{-1} , and 1605 cm^{-1} , corresponding to the stretching vibration of O-H (Akbari et al., 2020), the stretching vibrations of C=C and C=O groups of the inter-ring chain, and the C=C stretching vibration of aromatic rings (Szegedi et al., 2019), respectively. PVPK30 demonstrated a typical peak at 1628 cm^{-1} corresponding to the C=O stretching of the carbonyl group (Kyaw Oo, Mandal, & Chatterjee, 2017). Soy lecithin exhibits three typical peaks at 2926 cm^{-1} , 2853 cm^{-1} , and 1739 cm^{-1} . The bands at 2926 cm^{-1} and 2853 cm^{-1} correspond to the ν_{as} (CH₂) and ν_{s} (CH₂) of the aliphatic CH₂ group of lipids, while the band at 1739 cm^{-1} corresponds to the ν_{s} (C=O) of glycerides (Kemal, Baillet-Guffroy, Faivre, & Laugel, 2019). As shown in Fig. 1d, after curcumin was prepared into nanocomplexes, the typical bands of curcumin disappeared, while the typical bands of PVPK30 and soy lecithin remained. The formulas of K30-L1:0.5, K30-L1:1, and K30-L1:2 exhibited similar ATR-FTIR spectra because

they contained the same components. As shown in Fig. 1e, curcumin and representative curcumin-loaded nanocomplexes (K30-L1:1) showed some similar peaks, indicating that curcumin was molecularly dispersed in the nanocomplexes (Elbaz, Tatham, Owen, Rannard, & McDonald, 2021).

To study the physical nature of curcumin-loaded nanocomplexes, XRD patterns of pure curcumin, PVPK30, soy lecithin, mixtures, and curcumin-loaded nanocomplexes were investigated (Fig. 1f). The diffractogram of pure curcumin exhibited sharp and intense peaks of crystallinity. Noticeably, the mixtures showed fewer peaks and lower intensity, the peak pattern of mixtures is similar to that of the curcumin-loaded nanocomplexes, however, a number of crystalline peaks belonging to curcumin were still observed, indicating that simple physical mixing is unable to generate enough molecular force to embed curcumin inside the complexes. However, the characteristic peaks of curcumin disappeared in curcumin-loaded nanocomplexes (K30-L1:0.5, K30-L1:1, K30-L1:2). This phenomenon indicates that curcumin-loaded nanocomplexes were molecularly dispersed within stabilizers in a disordered crystalline phase or amorphous or dissolved in phospholipid complex in a solid-state (Li et al., 2021).

To further confirm curcumin was well dispersed in nanocomplexes, DSC thermograms of pure curcumin, PVPK30, soy lecithin, mixtures, and curcumin-loaded nanocomplexes were investigated (Fig. 1g). Thermogram of curcumin showed a sharp endothermic peak at 170 °C, which is the melting point of curcumin. However, the melting points of K30-L1:0.5, K30-L1:1, and K30-L1:2 are all at 113 °C, and the characteristic peak of curcumin was not observed in the curcumin-loaded nanocomplexes (K30-L1:0.5, K30-L1:1, and K30-L1:2), indicating that the curcumin had changed from crystalline state to amorphous state, with curcumin particles being molecularly dispersed within the stabilizers (Aditya, Yang, Kim, & Ko, 2015). DSC results again confirmed the XRD data and showed that PVPK30 and lecithin-stabilized curcumin was in an amorphous state.

3.2. SEM analysis

To further confirm curcumin was dispersed in nanocomplexes, the morphology of pure curcumin, PVPK30, soy lecithin, and curcumin-loaded nanocomplexes were observed with SEM. As shown in Fig. 2a, pure curcumin had a needle-like structure with a large size, PVPK30 was hollow spherical (Fig. 2b), and soy lecithin appeared as big aggregates (Fig. 2c). After ultrasonication, the shape of curcumin did not change (Fig. 2d), but PVPK30 and soy lecithin were disrupted into small fragments (Fig. 2e and f). However, in curcumin-loaded nanocomplexes stabilized by PVPK30 and lecithin, the needle-like structures disappear. Instead, spherical structures (red arrows) embedded in membrane-like structures (green arrows) (Fig. 2g, h, i) were observed. As we previously hypothesized, the hydrophobic regions of lecithin cluster inward to form a sphere, and curcumin molecules were entrapped within it, while the hydrophilic regions of lecithin extended outward and were

further entrapped by PVP, which may provide a suitable steric hindrance for inhibiting aggregation and particle growth (Rahimi, Valeh-e-Sheyda, & Rashidi, 2017). The hypothesized structures were confirmed by SEM morphology, indicating the successful incorporation of this amorphous curcumin into the molecular structures of stabilizers.

3.3. Molecular dynamics simulation

To investigate the binding mechanism of curcumin-loaded nanocomplexes and the way the nanocomplexes protect curcumins. The three-dimensional molecular structure model of the nanocomplexes in an aqueous solution system was constructed. Fig. 3a–d shows the behaviour of nanocomplexes system in different simulation periods from 0 ns to 20 ns. It can be noted that curcumin was initially dissociated from the system. With the simulation process, lecithin molecules gradually gather to form clusters, and curcumins are found to be adsorbed on phospholipid clusters. It can be explained by the aggregation of the hydrophobic tail of the phospholipid molecule to form a hydrophobic cavity, while curcumin is a hydrophobic molecule and binds through hydrophobic interactions (Niu et al., 2012). Interestingly, the MD result shows that the curcumin molecule is not completely anchored to the inside of the phospholipid cluster, instead, curcumin is partially located at the interface of the phospholipid layer. This phenomenon is related to the concentration of curcumin, the type and thickness of the phospholipid layer, and hydration (Barry et al., 2009). During the simulation process, PVP molecules gradually adsorbed on the outer layer of phospholipid molecular groups. At 20 ns, it was observed that PVP molecules were obviously on the outer layer of the complex, forming a shell containing phospholipid and curcumin. Next, we study the interaction among the three molecules. The calculation and analysis results show

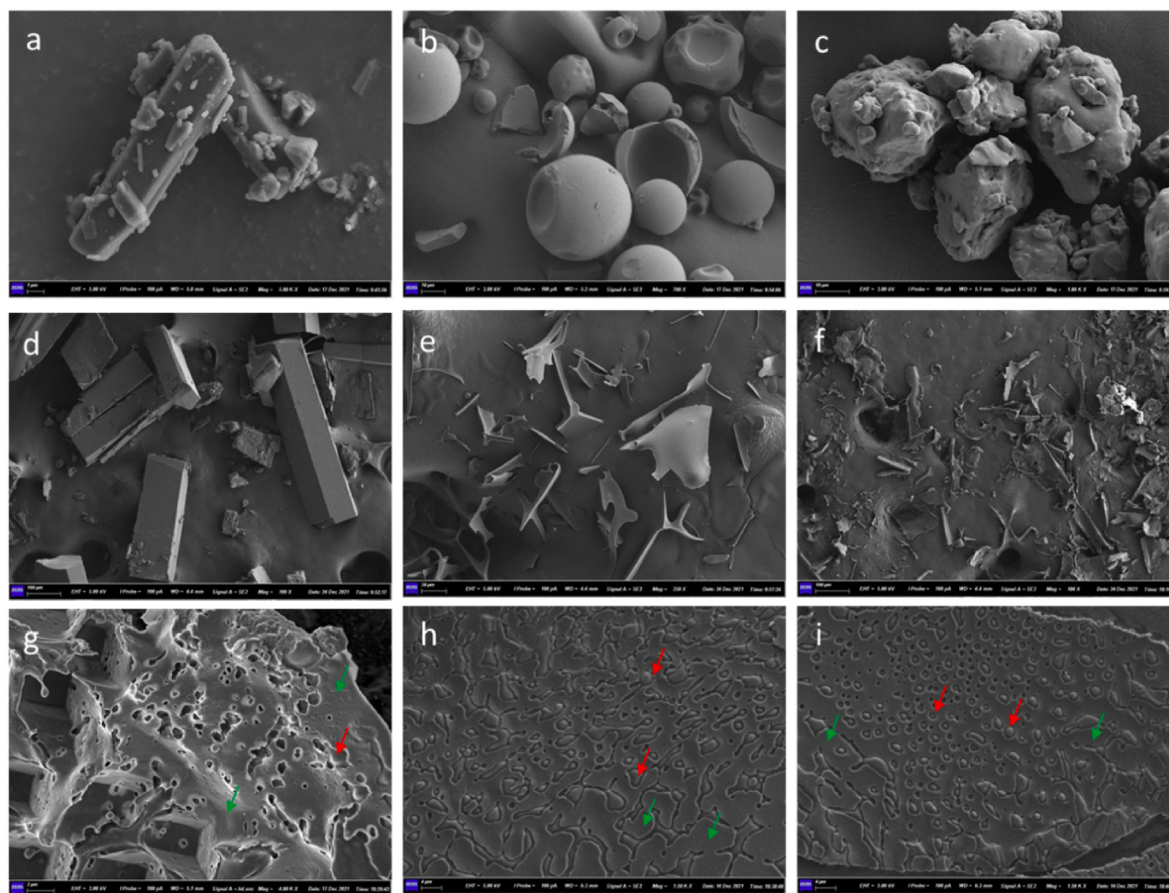


Fig. 2. SEM images of materials and samples. Raw materials of curcumin (a), PVPK30 (b), soy lecithin (c); ultrasonicated materials of curcumin (d), PVPK30 (e), soy lecithin (f); samples of K30-L1:0.5(g), K30-L1:1(h), K30-L1:2(i).

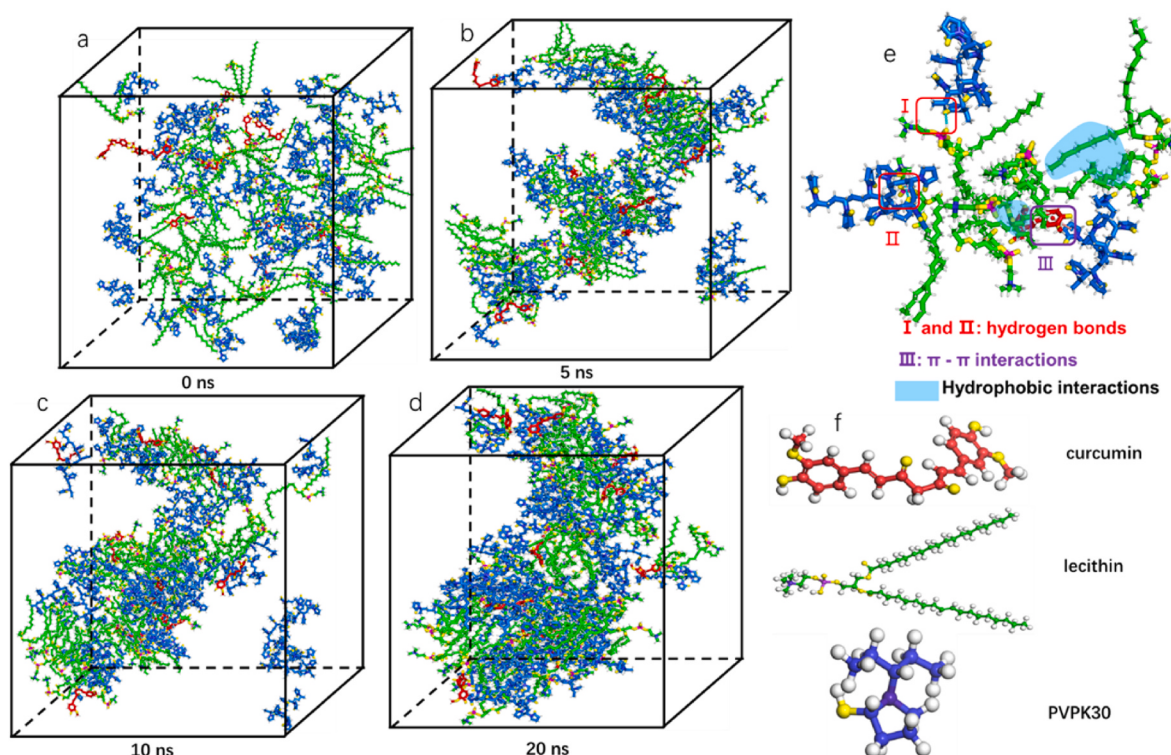


Fig. 3. Molecular dynamics simulation. (a) MD simulation model of nanocomplexes (0 ns). (b) MD simulation model of nanocomplexes (5 ns). (c) MD simulation model of nanocomplexes (10 ns). (d) MD simulation model of nanocomplexes (20 ns). (e) A part of MD simulation model of nanocomplexes in 20 ns. (f) Three dimensional structures of three molecules involved in simulation.

that there are hydrogen bonds, π - π interactions, and hydrodynamic interactions between the three molecules. Hydrogen bond mainly exists between the H atom and electronegative atom (such as O, F, and N), which is a relatively weak force with a strength of 10–40 kJ/mol (Le et al., 2018; Steiner, 2002). As presented in Fig. 3e, the oxygen atom on the pyrrole ring of PVP forms a hydrogen bond with the H on the phosphate group of the phospholipid molecule, providing a force for PVP to combine with phospholipid. In addition, the hydrophobic interaction between phospholipids and curcumins has also been reflected, which is consistent with our conclusion that phospholipids and curcumin are adsorbed by hydrophobic interaction. Moreover, the C=O bond in N-methyl pyrrolidone and the aromatic ring of curcumin can be attracted to each other by π - π interaction (Azimzadeh, Akbari, & Omidkhan, 2017), which corresponds to Fig. 3e. The MD results revealed the formation mechanism of nanocomplexes, in which hydrogen bond, hydrophobic interaction, and π - π interaction play roles in forming and maintaining the structure. Meanwhile, the formation of nanocomplexes is also related to curcumin concentration, phospholipid layer thickness, and hydration. The exploration of the formation mechanism can help us to better design and application of curcumin-loaded nanocomplexes.

3.4. Thermal stability analysis

In our preliminary experiment, curcumin ethanol solution was diluted 100 times with ultrapure water and then heated at 60 °C or 80 °C for 1 h. The yellow colour disappeared and the absorbance at 425 nm could not be detected, indicating that the curcumin solution was highly unstable during heat treatment.

The thermal stability of the three curcumin-loaded nanocomplexes is shown in Fig. 4. When the nanocomplexes were heated at 60 °C for 1–6 h, the droplet sizes did not increase significantly (Fig. 4a). The PDI of the samples were all lower than 0.26 (Fig. 4b), indicating a homogeneous system. The zeta potential of the samples was stable at all heating times

(Fig. 4c). These results confirmed that heat treatment at 60 °C for 6 h did not affect the curcumin-loaded nanocomplexes. As shown in Fig. 4d, the three formulas were heated for 6 h, and the curcumin retention rates were all higher than 85%, with K30-L1:1 exhibiting the highest thermal stability and a curcumin retention rate of up to 92%.

When the temperature was increased to 80 °C with heating for 1–4 h, the particle sizes of the three formulas did not change significantly, however, after heating for 5 h, the sizes were slightly increased ($\sim$ 10 nm), and thereafter decreased (Fig. 4e). The PDI of the three formulas were all lower than 0.25 (Fig. 4f), indicating a homogeneous system. The zeta potential of K30-L1:0.5 was higher than -30 mV all the time, and the zeta potentials of K30-L1:1 and K30-L1:2 increased to about -30 mV at the first 5 h, then decreased. As shown in Fig. 4h, the retention rate of curcumin decreased with the extension of heating time. After heat treatment for 6 h, the curcumin retention rates were still higher than 50%, higher than in our previous study (Yang, Sui, Lu, & Corke, 2021).

PVPK30 is a thermodynamically stable polymer and has steric prevention on particle stability (Tashan, Karakucuk, & Celebi, 2019), which may suggest that the enhanced thermal stability of curcumin-loaded nanocomplexes is due to the formation of additional protective barriers around the particle surface by PVPK30, thereby suppressing the dissociation of lecithin from the particles and preventing curcumin leakage from inside. Nanocomplexes are thermodynamically unstable systems with a tendency to agglomerate or crystal growth, which is still a limitation for their pharmaceutical or industrial applications (Wang, Zheng, Zhang, Wang, & Zhang, 2013). However, our study found that curcumin-loaded nanocomplexes stabilized with PVPK30 and lecithin have excellent thermal stability, and these may have potential applications in food or industrial fields.

3.5. Storage stability analysis

In our preliminary experiment, curcumin ethanol solution was diluted 100 times with ultrapure water and then stored at 4 °C or room

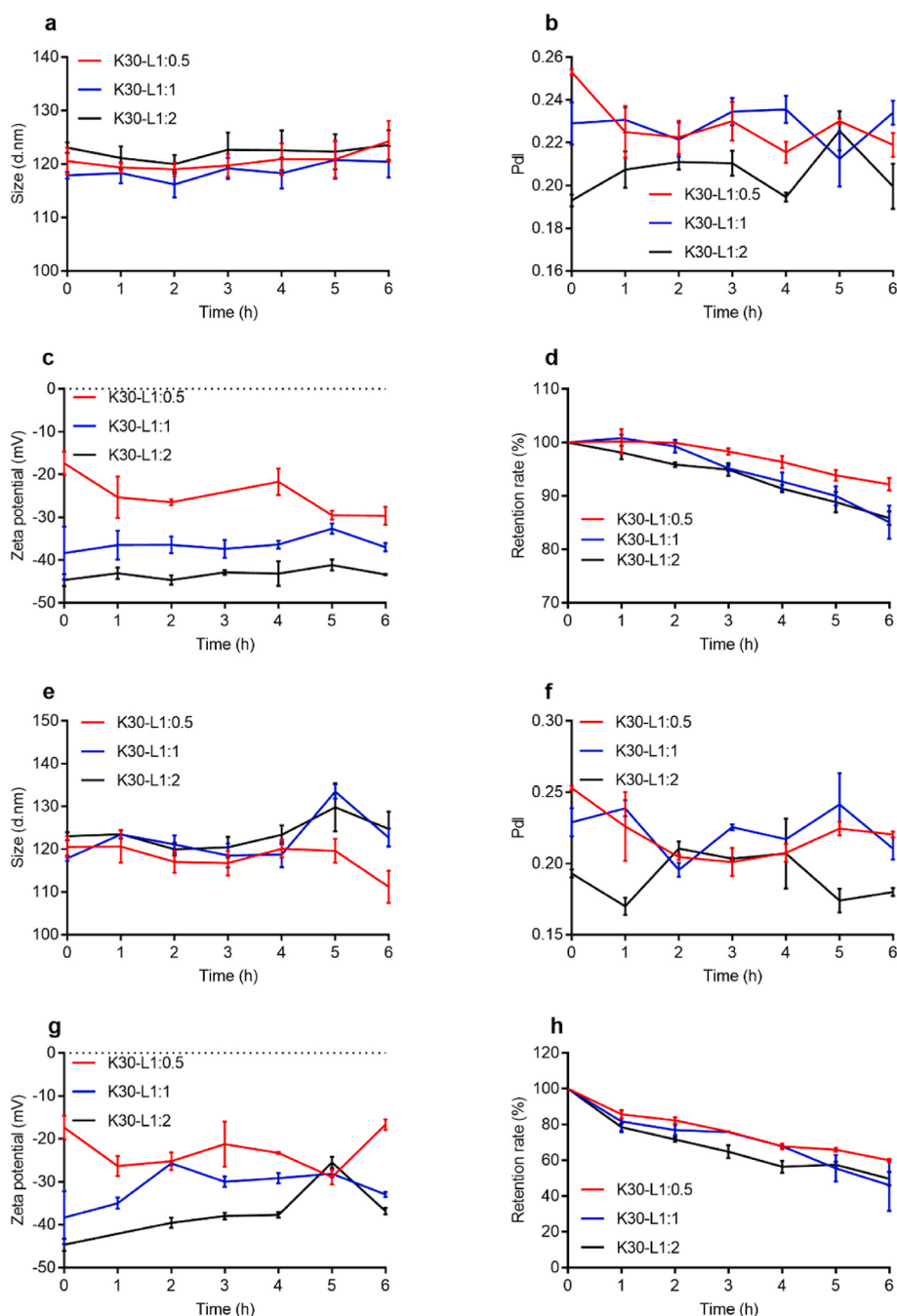


Fig. 4. Thermal stability of three formulas. The particle size (a), polydispersity index (b), zeta potential (c), and curcumin retention (d) of three formulas at 60 °C; The particle size (e), polydispersity index (f), zeta potential (g), and curcumin retention (h) of three formulas at 80 °C.

temperature (21 °C) for 1 week. The yellow colour disappeared and the absorbance at 425 nm could not be detected, indicating that the curcumin solution was highly unstable during storage.

As shown in Fig. 5a, the particle sizes of the three curcumin-loaded nanocomplexes slightly increased in 0–3 weeks, and then decreased, with a particle size range of 118–135 nm. A previous study also found that PVP stabilized curcumin nanoparticles had good storage stability within one month, and the particle size increased slightly (Rachmawati, Shaal, Müller, & Keck, 2013). Similar trends were also found for PDI which slightly increased in 0–3 weeks, and then decreased, with a PDI range of 0.2–0.4 (Fig. 5b). As shown in Fig. 5c, K30-L1:0.5 and K30-L1:1 showed similar trends in that the zeta potential slightly increased in 0–3 weeks and then decreased. However, the zeta potential of K30-L1:2 decreased sharply in 0–1 week and then increased. Overall, the zeta

potential of the three curcumin-loaded nanocomplexes was lower than −25 mV, indicating that they were very stable during storage at 4 °C for 6 weeks. This conclusion was further confirmed in Fig. 5d. The curcumin retention rates in the three nanocomplexes decreased slightly in 0–6 weeks, and more than 90% of curcumin was retained after 6 weeks of storage.

Unlike curcumin-loaded nanocomplexes stored at 4 °C, when they were stored at room temperature (21 °C), the particle sizes of the three curcumin-loaded nanocomplexes increased gradually from 0 to 6 weeks, and from 120 nm to 200 nm (Fig. 5e). Similarly, the PDI also gradually increased from 0 to 6 weeks, and was close to 0.5 in the third week, indicating that there were some big aggregates in the systems (Fig. 5f). A similar phenomenon was also observed in curcumin-loaded nanocomplexes stabilized by VE-TPGS (Kim, Lee, Lee, & Hong, 2021). As

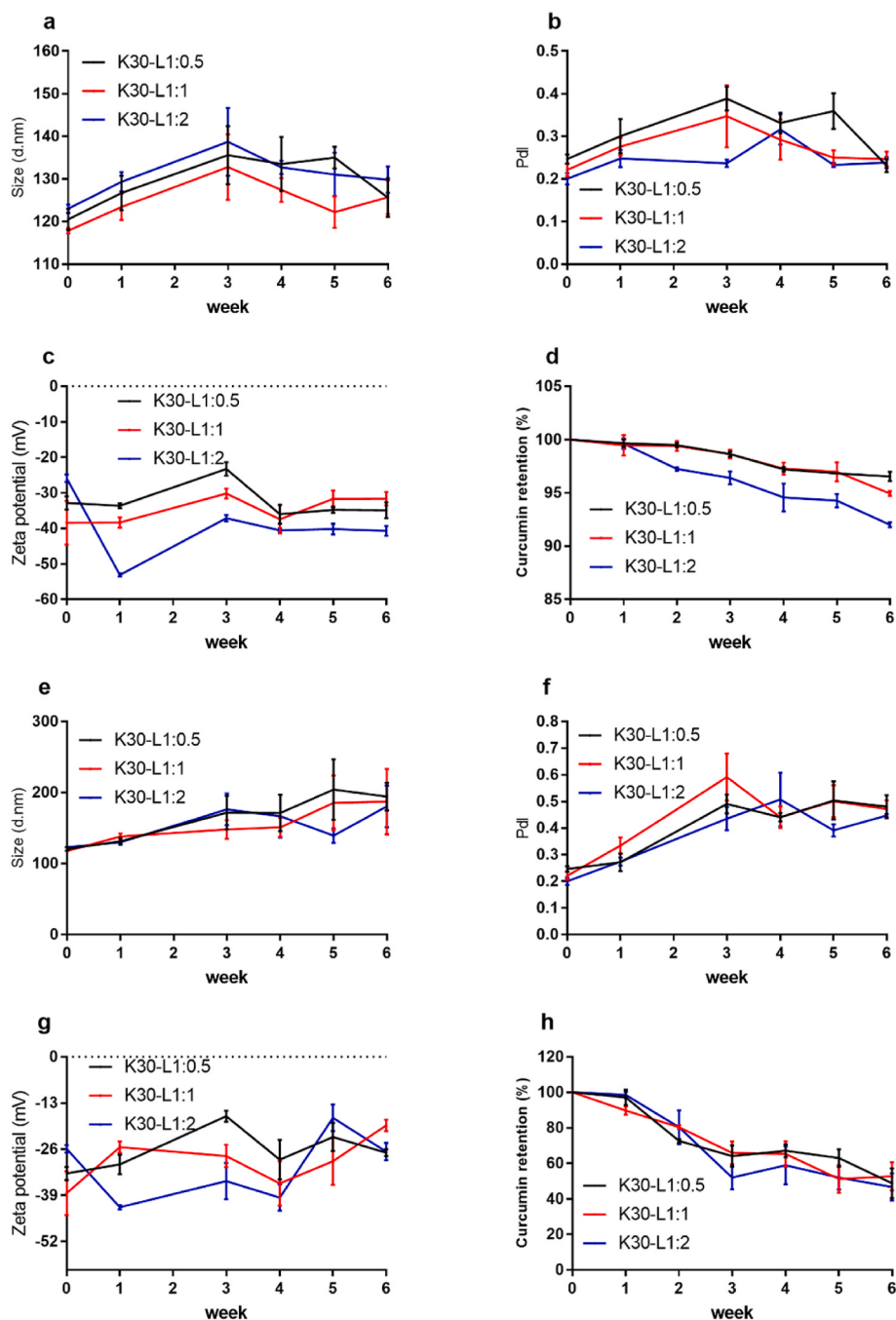


Fig. 5. Storage stability of three formulas. The particle size (a), polydispersity index (b), zeta potential (c), and curcumin retention (d) of three formulas at 4 °C; The particle size (e), polydispersity index (f), zeta potential (g), and curcumin retention (h) of three formulas at room temperature.

shown in Fig. 5g, the zeta potential of the three curcumin-loaded nanocomplexes was close to -25 mV after 6 weeks of storage, indicating that the systems were at the edge of stability and instability, and inclined to instability. Fig. 5h showed that the retention rates of curcumin decreased gradually from 0 to 6 weeks, and about 50% of curcumin remained in the systems after 6 weeks of storage.

As shown in Fig. 5, storage temperature is a pivotal determinant of particle stability. Compared to ambient storage, curcumin-loaded nanocomplexes stored at 4 °C displayed superior stability. This may be due to the system entropy decreasing with the decrease in temperature. Therefore, under equilibrium conditions, the maximum coverage of stabilizers can be increased at lower temperatures (Pavan, Crepaldi, Gomes, & Valim, 1999), thereby further strengthening the steric

stability. In addition, at a lower temperature, the dissociation rate of stabilizers from the particle surface will decrease, which is crucial for maintaining the integrity of particles and reducing the leakage of drugs from the particle surface (Chow et al., 2015). Besides, a reduced temperature can reduce the Ostwald ripening rate of particles, the frequency of particle collision, and the resulting particle aggregation (Liu, Kathan, Saad, & Prud'homme, 2007).

3.6. The pH stability of nanocomplexes

The pH stability contributes supporting information to curcumin application in oral administration. Many studies have shown that the chemical properties of curcumin are unstable in a digestive environment

in vivo, especially sensitive to the near neutral pH environment. In phosphate buffer, about 90% of curcumin will degrade within 15 min after incubation under neutral conditions (Gómez-Mascaraque, Sipoli, de La Torre, & López-Rubio, 2017). Thus, we evaluate the protective ability of the three formulas of nanocomplexes in a simulated digestion pH environment (pH 1.5 and pH 6.8). In our work, free curcumin was totally degraded after reacting at both pH values for 1 h, which was consistent with the reported results (Gómez-Mascaraque et al., 2017). As shown in Fig. 6a and b, the nanocomplexes retain more than 90% after 2 h of reaction at two different pH values, which has obvious acid-base resistance compared with free curcumin. Interestingly, the absorbance of nanocomplexes will rise in the first half hour under the environment of pH 1.5, which may be due to the color increasing effect of curcumin under acidic conditions (Tang, Ma, Wang, & Zhang, 2002). Interestingly, liposomal curcumin could not withstand harsh pH stress with less than 60% curcumin retained after 6 h at pH 2.5, 5.0, or 7.4 (Wei, Zhu, Wang, & Ba, 2020). However, the incorporation of polymers into liposomes can significantly enhance the pH stability of curcumin, and more than 90% of curcumin is retained after 3 h at pH 7.4 (Li et al., 2018). Similar to our results. The high retention rate provides a good potential for the application of curcumin.

3.7. Particle size, zeta potential, and morphology of the GIT mixed micelle fractions

The characteristics of nanoparticles may change when they are

exposed to digestive fluids, thus affecting the stability and absorption rate of encapsulated drugs (Berardi & Baldelli, 2019). Thus, in the present work, the particle size and zeta potential of the micelles were determined. As shown in Fig. 6d, the bioaccessible components of the three nanocomplexes exhibited a small particle size of around 200 nm. A previous study reported that vesicles below 300 nm can effectively penetrate the epidermis and dermis (Iqbal, Ali, & Baboota, 2018). Therefore, the micelle fractions of the three nanocomplexes may be well absorbed through the epithelial layer of the GIT. Compared to the raw nanocomplexes, the particle sizes of the micelles (~200 nm) were higher. The increase in droplet size after the GIT digestion may be due to the relatively high ionic strength of the gastrointestinal phase, and hydrolysis of lecithin by pepsin to expose its hydrophobic domain, resulting in aggregation. In addition, the micelles exhibited large PDI (~0.5) (Fig. 6e) and reduced negative zeta potentials (>−25 mV) (Fig. 6f), which further confirmed that the micelles are unstable and exhibited large aggregates. To observe the micelle fractions, the micelles were freeze-dried and observed with SEM. As shown in Fig. 6g, h, i, after GIT digestion, the outer layer of the nanocomplexes was destroyed, showing spherical structures (red arrows), indicating that curcumin was still encapsulated in the micelles and could be absorbed through the epithelium.

3.8. Bioaccessibility and stability of curcumin

Bioaccessibility is the fraction of an ingested biocomponent that

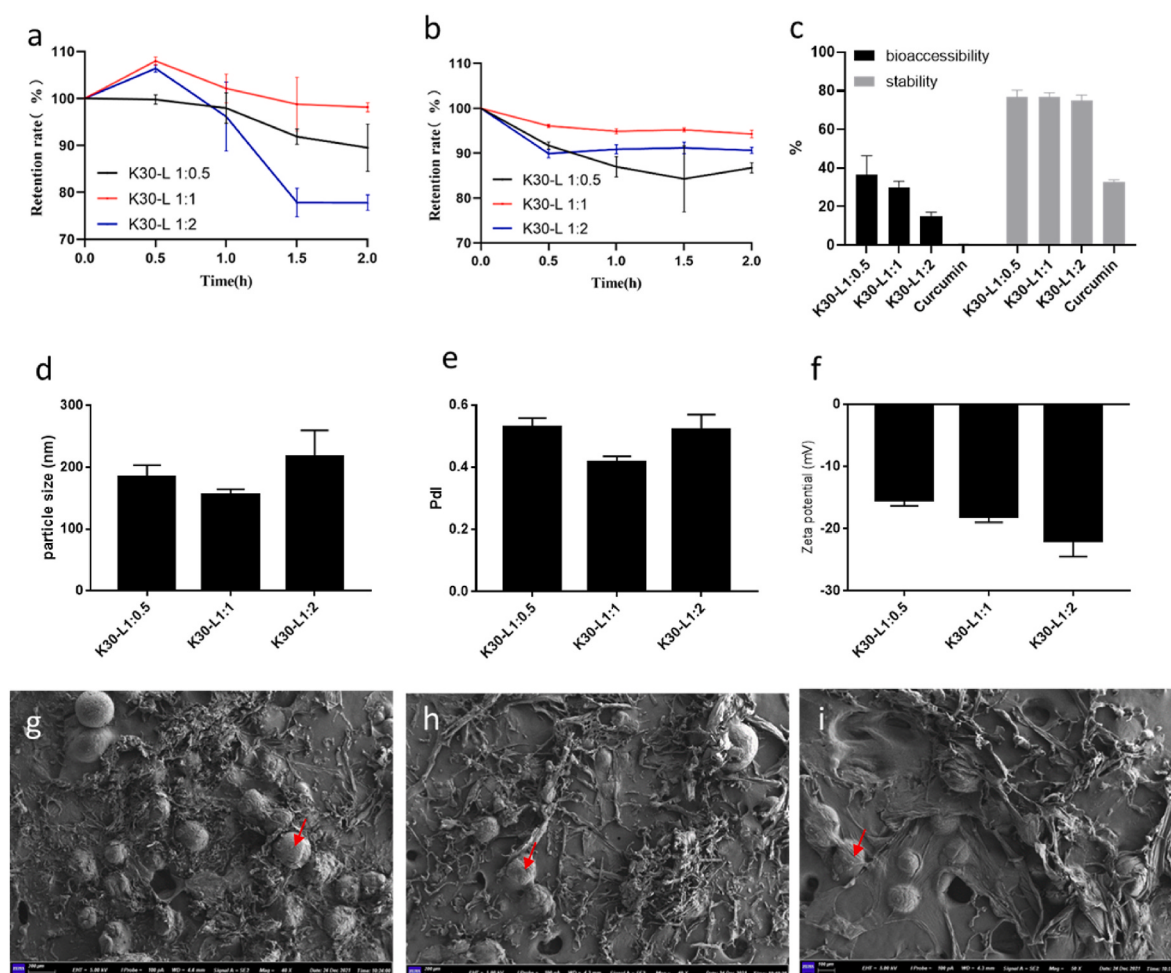


Fig. 6. The pH stability and GIT digestion stability of three formulas. The retention rate of curcumin loaded in three formulas at pH of 1.5 (a), and at pH of 6.8 (b); the bioaccessibility and stability of curcumin in three nanosuspensions (c); the particle size (d), polydispersity index (e), zeta potential (f) of the bioaccessible fraction of the three formulas; SEM images of the bioaccessible fraction of K30-L1:0.5 (g), K30-L1:1(h), K30-L1:2(i).

becomes accessible for absorption through the epithelial layer of the gastrointestinal tract (GIT) (Dima, Assadpour, Dima, & Jafari, 2020). In this study, the bioaccessibility of curcumin in the formulas was significantly higher than in the free form (Fig. 6c). The bioaccessibility of curcumin was only 0.34%, similar to previously reported data (Yang et al., 2021). The bioaccessibility of curcumin in K30-L1:0.5, K30-L1:1, and K30-L1:2 was 36.7%, 29.8%, and 15.1%, respectively, which were 105-, 85-, and 43-fold of free curcumin, respectively. As the lecithin ratio increased, the bioaccessibility of curcumin decreased, which may be because lecithin cannot resist the acidic gastric environment. In this study, after the GIT model, curcumin was encapsulated in PVPK30, which is a highly water-soluble component that can be solubilized within mixed micelles, suggesting that the potential mechanism of the nanocomplexes in increasing the bioaccessibility of curcumin may be to enhance the stability of curcumin in GIT or increase the water solubility of curcumin in GI fluids (Yao, McClements, & Xiao, 2015).

Theoretically, the stability of bioactive compounds is the amount of the compounds that still exist as bioactive forms after small intestine digestion (Cuomo, Perugini, Marconi, Messina, & Lopez, 2019). As shown in Fig. 6c, the stability of the three micelle factions was similar (~75%) and was significantly higher than the stability of free curcumin (32.5%). The increase in the stability of curcumin-loaded nanocomplexes may be due to the effect of the gastro-resistant polymers (PVPK30), which can protect curcumin from the harsh gastrointestinal environment, giving a higher solubility and controlled-release characteristics (Ma, Wang, He, & Tang, 2019).

Based on all of the results above, the *in vitro* bioaccessibility of curcumin can be greatly increased by nanocomplexes stabilized with PVPK30 and lecithin. The PVPK30 and lecithin nanocomplexes are ideal effective delivery systems that could protect curcumin degradation in GIT.

4. Conclusions

Here, we propose a facile and effective method of fabricating curcumin-lecithin-PVP ternary nanocomplexes using a simple precipitation-combined ultrasonication method for the efficient delivery and protection of curcumin. The synthesized nanocomplexes perform uniform size distribution and excellent curcumin encapsulation capability. Characterization results show that curcumin was first anchored at the hydrophobic area of lecithin and then further surrounded by PVP. Hydrogen bonding, hydrophobic interaction, and π - π interaction are the main forces in the formation of nanocomplexes. The encapsulated curcumin exists in an amorphous state, which facilitates dissolution and oral absorption. Furthermore, curcumin-lecithin-PVP ternary nanocomplexes are quite effective for enhancing physical stability, including dilution, thermal, and storage stability, which suggests the promising potential of curcumin-lecithin-PVP ternary nanocomplexes as delivery systems for food products. More importantly, the nanocomplexes could effectively enhance the bioaccessibility and digestive stability of curcumin, which lays the foundation for the application of curcumin or other nutraceuticals as functional supplements in commercial products with high potential bioavailability. Therefore, this study opens a window for future research where lecithin and PVP can be used in combination to effectively increase the stability of hydrophobic bioactive compounds, ultimately improving their well-known performance in achieving health benefits.

Although this study found a potential mechanism for lecithin and PVP to stabilize curcumin, future research could further explore whether lecithin and other polymers exhibit similar effects in enhancing the stability of curcumin and similar hydrophobic compounds. In addition, the curcumin-lecithin-PVP ternary nanocomplexes exhibit good bioaccessibility and digestive stability *in vitro*, more *in vivo* studies are still needed to fully understand the biological behaviour of curcumin-loaded nanocomplexes.

Notes

The authors declare no competing financial interest.

CRediT authorship contribution statement

Qiong-Qiong Yang: Writing – original draft, Writing – review & editing, Visualization, Formal analysis, Investigation, Validation, Supervision, Project administration, Funding acquisition. **Wo-Qi Cai:** Software, Investigation, Formal analysis. **Zhi-Xuan Wang:** Methodology, Data curation. **Yu Li:** Methodology, Data curation. **Yu Zhang:** Methodology, Data curation. **Xiaoling Lin:** Resources. **Bao-Lian Su:** Resources. **Harold Corke:** Writing – review & editing, Visualization. **Bo-Bo Zhang:** Resources, Writing – review & editing, Funding acquisition.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

Acknowledgements

This work was supported by the Research Start-up Foundation of Shantou University (Grant No. NTF22003, Grant No. NTF20003) for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.lwt.2023.114489>.

References

- Aditya, N. P., Yang, H., Kim, S., & Ko, S. (2015). Fabrication of amorphous curcumin nanosuspensions using β -lactoglobulin to enhance solubility, stability, and bioavailability. *Colloids and Surfaces, B: Biointerfaces*, 127, 114–121. <https://doi.org/10.1016/j.colsurfb.2015.01.027>
- Adsare, S. R., & Annappure, U. S. (2021). Microencapsulation of curcumin using coconut milk whey and gum Arabic. *Journal of Food Engineering*, 298, Article 110502. <https://doi.org/10.1016/j.jfoodeng.2021.110502>
- Akbari, J., Saeedi, M., Enayatifard, R., Morteza-Semnani, K., Hashemi, S. M. H., Babaei, A., et al. (2020). Curcumin niosomes (curcusesomes) as an alternative to conventional vehicles: A potential for efficient dermal delivery. *Journal of Drug Delivery Science and Technology*, 60, Article 102035. <https://doi.org/10.1016/j.jddst.2020.102035>
- Azimzadeh, H., Akbari, A., & Omidkhah, M. R. (2017). Catalytic oxidative desulfurization performance of immobilized NMP.FeCl₃ ionic liquid on γ -Al₂O₃ support. *Chemical Engineering Journal*, 320, 189–200. <https://doi.org/10.1016/j.cej.2017.03.027>
- Barani, M., Sangiovanni, E., Angarano, M., Rajizadeh, M. A., Mehrabani, M., Piazza, S., et al. (2021). Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. *International Journal of Nanomedicine*, 16, 6983. <https://doi.org/10.2147/IJN.S318416>
- Barry, J., Fritz, M., Brender, J. R., Smith, P. E. S., Lee, D. K., & Ramamoorthy, A. (2009). Determining the effects of lipophilic drugs on membrane structure by solid-state NMR spectroscopy: The case of the antioxidant curcumin. *Journal of the American Chemical Society*, 131(12), 4490–4498. <https://doi.org/10.1021/ja809217u>
- Berardi, A., & Baldelli, B. F. (2019). Oral delivery of nanoparticles-let's not forget about the protein corona. *Expert Opinion on Drug Delivery*, 16(6), 563–566. <https://doi.org/10.1080/17425247.2019.1610384>
- Berendsen, H. J. C., Postma, J. P. M., van Gunsteren, W. F., DiNola, A., & Haak, J. R. (1984). Molecular dynamics with coupling to an external bath. *The Journal of Chemical Physics*, 81, 3684. <https://doi.org/10.1063/1.448118>
- Bernardes, C. E. S., & Joseph, A. (2015). Evaluation of the OPLS-AA force field for the study of structural and energetic aspects of molecular organic crystals. *The Journal of Physical Chemistry A*, 119(12), 3023–3034. <https://doi.org/10.1021/jp512349r>
- Bussi, G., Donadio, D., & Parrinello, M. (2007). Canonical sampling through velocity rescaling. *The Journal of Chemical Physics*, 126(1), Article 014101. <https://doi.org/10.1063/1.2408420>
- Chen, B., Martin, M. G., & Siepmann, J. I. (1998). Thermodynamic properties of the williams, OPLS-AA, and MMFF94 all-atom force fields for normal alkanes. *The*

- Journal of Physical Chemistry B*, 102(14), 2578–2586. <https://doi.org/10.1021/jp9801065>
- Chow, S. F., Wan, K. Y., Cheng, K. K., Wong, K. W., Sun, C. C., Baum, L., et al. (2015). Development of highly stabilized curcumin nanoparticles by flash nanoprecipitation and lyophilization. *European Journal of Pharmaceutics and Biopharmaceutics*, 94, 436–449. <https://doi.org/10.1016/j.ejpb.2015.06.022>
- Cuomo, F., Perugini, L., Marconi, E., Messina, M. C., & Lopez, F. (2019). Enhanced curcumin bioavailability through nonionic surfactant/caseinate mixed nanoemulsions. *Food Engineering, Materials Science, & Nanotechnology*, 84(9), 2584–2591. <https://doi.org/10.1111/1750-3841.14759>
- De Nicola, A., Avolio, R., Della Monica, F., Gentile, G., Cocca, M., Capacchione, C., et al. (2015). Rational design of nanoparticle/monomer interfaces: A combined computational and experimental study of *in situ* polymerization of silica based nanocomposites. *RSC Advances*, 5(87), 71336–71340. <https://doi.org/10.1039/C5RA13154E>
- Dima, C., Assadpour, E., Dima, S., & Jafari, S. M. (2020). Bioavailability and bioaccessibility of food bioactive compounds: overview and assessment by *in vitro* methods. *Comprehensive Reviews in Food Science and Food Safety*, 19(6), 2862–2884. <https://doi.org/10.1111/1541-4337.12623>
- Elbaz, N. M., Tatham, L. M., Owen, A., Rannard, S., & McDonald, T. O. (2021). Redispersible nanosuspensions as a plausible oral delivery system for curcumin. *Food Hydrocolloids*, 121, Article 107005. <https://doi.org/10.1016/j.foodhyd.2021.107005>
- Gómez-Mascaraque, L. G., Sipoli, C. C., de La Torre, L. G., & López-Rubio, A. (2017). Microencapsulation structures based on protein-coated liposomes obtained through electrospraying for the stabilization and improved bioaccessibility of curcumin. *Food Chemistry*, 233, 343–350. <https://doi.org/10.1016/j.foodchem.2017.04.133>
- Hess, B., Bekker, H., Berendsen, H. J. C., & Fraaije, J. G. E. M. (1997). Lincs: A linear constraint solver for molecular simulations. *Journal of Computational Chemistry*, 18(12), 1463–1472. [https://doi.org/10.1002/\(SICI\)1096-987X\(199709\)18:12<1463::AID-JCC4>3.0.CO;2-H](https://doi.org/10.1002/(SICI)1096-987X(199709)18:12<1463::AID-JCC4>3.0.CO;2-H)
- Hess, B., Kutzner, C., Spoel, D. V. D., & Lindahl, E. (2008). Gromacs 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation. *Journal of Chemical Theory and Computation*, 4(3), 435–447. <https://doi.org/10.1021/ct700301q>
- Huang, J., Lu, F., Wu, Y., Wang, D., Xu, W., Zou, Y., et al. (2022). Enzymatic extraction and functional properties of phosphatidylcholine from chicken liver. *Poultry Science*, 101(6), Article 101689. <https://doi.org/10.1016/j.psj.2021.101689>
- Hu, Y., Qiu, C., McClements, D. J., Qin, Y., Fan, L., Xu, X., et al. (2021). Simple strategy preparing cyclodextrin carboxylate as a highly effective carrier for bioactive compounds. *Journal of Agricultural and Food Chemistry*, 69(37), 11006–11014. <https://doi.org/10.1021/acs.jafc.1c02722>
- Iqbal, B., Ali, J., & Baboota, S. (2018). Recent advances and development in epidermal and dermal drug deposition enhancement technology. *International Journal of Dermatology*, 57(6), 646–660. <https://doi.org/10.1111/ijd.13902>
- Jelić, D., Liavitskaya, T., & Vyazovkin, S. J. T. A. (2019). Thermal stability of indomethacin increases with the amount of polyvinylpyrrolidone in solid dispersion. *Thermochimica Acta*, 676, 172–176. <https://doi.org/10.1016/j.tca.2019.04.011>
- Jorgensen, W. L., Maxwell, D. S., & Tirado-Rives, J. (1996). Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids. *Journal of the American Chemical Society*, 118(45), 11225–11236. <https://doi.org/10.1021/ja9621760>
- Jorgensen, W. L., & McDonald, N. A. (1998). Development of an all-atom force field for heterocycles. Properties of liquid pyridine and diazenes. *Journal of Molecular Structure: THEOCHEM*, 424(1), 145–155. [https://doi.org/10.1016/S0166-1280\(97\)00237-6](https://doi.org/10.1016/S0166-1280(97)00237-6)
- Kaminsky, G. A., Friesner, R. A., Tirado-Rives, J., & Jorgensen, W. L. (2001). Evaluation and reparametrization of the OPLS-AA force field for proteins via comparison with accurate quantum chemical calculations on peptides. *Journal of Physical Chemistry B*, 105(28), 6474–6487. <https://doi.org/10.1021/jp003919d>
- Kemel, K., Baillet-Guffroy, A., Faivre, V., & Laugel, C. (2019). ATR-FTIR characterization of janus nanoparticles—Part II: Follow-up skin application. *Journal of Pharmaceutical Sciences*, 108(10), 3366–3371. <https://doi.org/10.1016/j.xphs.2019.06.018>
- Kim, Y. J., Kim, B. K., & Lee, M. H. (2022). Improving curcumin retention in oil-in-water emulsions coated by chitosan and their disperse stability exposed to thermal treatments. *Journal of Food Engineering*, 319, Article 110918. <https://doi.org/10.1016/j.jfoodeng.2021.110918>
- Kim, S. H., Lee, E. S., Lee, K. T., & Hong, S. T. (2021). Stability properties and antioxidant activity of curcumin nanosuspensions in emulsion systems. *CyTA - Journal of Food*, 19(1), 40–48. <https://doi.org/10.1080/19476337.2020.1852315>
- Koczkur, K. M., Mourdikoudis, S., Polavarapu, L., & Skrabalak, S. E. (2015). Polyvinylpyrrolidone (PVP) in nanoparticle synthesis. *Dalton Transactions*, 44(41), 17883–17905. <https://doi.org/10.1039/C5DT02964C>
- Kurakula, M., & Rao, G. S. N. K. (2020). Pharmaceutical assessment of polyvinylpyrrolidone (PVP): As excipient from conventional to controlled delivery systems with a spotlight on COVID-19 inhibition. *Journal of Drug Delivery Science and Technology*, 60, Article 102046. <https://doi.org/10.1016/j.jddst.2020.102046>
- Kyau Oo, M., Mandal, U. K., & Chatterjee, B. (2017). Polymeric behavior evaluation of PVP K30-poloxamer binary carrier for solid dispersed nisoldipine by experimental design. *Pharmaceutical Development and Technology*, 22(1), 2–12. <https://doi.org/10.3109/10837450.2015.1116568>
- Le, Z., Chen, Y., Han, H., Tian, H., Zhao, P., Yang, C., et al. (2018). Hydrogen-bonded tannic acid-based anticancer nanoparticle for enhancement of oral chemotherapy. *ACS Applied Materials & Interfaces*, 10(49), 42186–42197. <https://doi.org/10.1021/acsami.8b18979>
- Lee, J., Jung, Y., Rho, S. J., & Kim, Y. R. (2022). Physicochemical characteristics and *in vitro* bioavailability of licorice (*Glycyrrhiza glabra* L.) extract complexed using cyclic glucans. *LWT—Food Science and Technology*, 167, Article 113841. <https://doi.org/10.1016/j.lwt.2022.113841>
- Li, Z., Lin, Q., McClements, D. J., Fu, Y., Xie, H., Li, T., et al. (2021). Curcumin-loaded core-shell biopolymer nanoparticles produced by the pH-driven method: Physicochemical and release properties. *Food Chemistry*, 355, Article 129686. <https://doi.org/10.1016/j.foodchem.2021.129686>
- Li, Z. L., Peng, S. F., Chen, X., Zhu, Y. Q., Zou, L. Q., Liu, W., et al. (2018). Pluronics modified liposomes for curcumin encapsulation: Sustained release, stability and bioaccessibility. *Food Research International*, 108, 246–253. <https://doi.org/10.1016/j.foodres.2018.03.048>
- Liu, Y., Kathan, K., Saad, W., & Prud'homme, R. K. (2007). Ostwald ripening of β -Carotene nanoparticles. *Physical Review Letters*, 98(3), Article 036102. <https://doi.org/10.1103/PhysRevLett.98.036102>
- Manca, M. L., Manconi, M., Nacher, A., Carbone, C., Valenti, D., Maccioni, A. M., et al. (2014). Development of novel diolefin-niosomes for cutaneous delivery of tretinoin: Influence of formulation and *in vitro* assessment. *International Journal of Pharmaceutics*, 477(1–2), 176–186. <https://doi.org/10.1016/j.ijpharm.2014.10.031>
- Ma, Z., Wang, N., He, H., & Tang, X. (2019). Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. *Journal of Controlled Release*, 316, 359–380. <https://doi.org/10.1016/j.jconrel.2019.10.053>
- Ma, Z., Yao, J., Wang, Y., Jia, J., Liu, F., & Liu, X. (2022). Polysaccharide-based delivery system for curcumin: Fabrication and characterization of carboxymethylated corn fiber gum/chitosan biopolymer particles. *Food Hydrocolloids*, 125, Article 107367. <https://doi.org/10.1016/j.foodhyd.2021.107367>
- Milano, G., Santangelo, G., Ragone, F., Cavallo, L., & Di Matteo, A. (2011). Gold nanoparticle/polymer interfaces: All atom structures from molecular dynamics simulations. *Journal of Physical Chemistry C*, 115(31), 15154–15163. <https://doi.org/10.1021/jp201374h>
- Miller, D. L. (2002). Health benefits of lecithin and choline. *Cereal Foods World*, 47(5), 178–184.
- Nam, K., Gao, J., & York, D. M. (2005). An efficient linear-scaling Ewald method for long-range electrostatic interactions in combined QM/MM calculations. *Journal of Chemical Theory and Computation*, 1(1), 2–13. <https://doi.org/10.1021/ct049941i>
- Niu, Y., Wang, X., Chai, S., Chen, Z., An, X., & Shen, W. (2012). Effects of curcumin concentration and temperature on the spectroscopic properties of liposomal curcumin. *Journal of Agricultural and Food Chemistry*, 60(7), 1865. <https://doi.org/10.1021/jf204867v>
- Ortiz, V., Nielsen, O., Klein, M. S. L., & Discher, D. E. (2006). Computer simulation of aqueous block copolymer assemblies: Length scales and methods. *Journal of Polymer Science Part B: Polymer Physics*, 44(14), 1907–1918. <https://doi.org/10.1002/polb.20836>
- Pan, Y., Li, X. M., Meng, R., Xu, B. C., & Zhang, B. (2021). Investigation of the formation mechanism and curcumin bioaccessibility of emulsion gels based on sugar beet pectin and laccase catalysis. *Journal of Agricultural and Food Chemistry*, 69(8), 2557–2563. <https://doi.org/10.1021/acs.jafc.0c07288>
- Pavan, P. C., Crepaldi, E. L., Gomes, G. d. A., & Valim, J. B. (1999). Adsorption of sodium dodecylsulfate on a hydrotalcite-like compound. Effect of temperature, pH and ionic strength. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 154(3), 399–410. [https://doi.org/10.1016/S0927-7757\(98\)00847-4](https://doi.org/10.1016/S0927-7757(98)00847-4)
- Qian, X., & Schlick, T. (2002). Efficient multiple-time-step integrators with distance-based force splitting for particle-mesh-Ewald molecular dynamics simulations. *The Journal of Chemical Physics*, 116(14), 5971–5983. <https://doi.org/10.1063/1.1458542>
- Rachmawati, H., Shaal, L. A., Müller, R. H., & Keck, C. M. (2013). Development of curcumin nanocrystal: Physical aspects. *Journal of Pharmaceutical Sciences*, 102(1), 204–214. <https://doi.org/10.1002/jps.23335>
- Rahimi, M., Valeh-e-Sheyda, P., & Rashidi, H. (2017). Statistical optimization of curcumin nanosuspension through liquid anti-solvent precipitation (LASP) process in a microfluidic platform: Box-Behnken design approach. *Korean Journal of Chemical Engineering*, 34, 3017–3027. <https://doi.org/10.1007/s11814-017-0201-3>
- Shoukat, H., Pervaiz, F., Noreen, S., Nawaz, M., Qaiser, R., & Anwar, M. (2020). Fabrication and evaluation studies of novel polyvinylpyrrolidone and 2-acrylamido-2-methylpropane sulphonic acid-based crosslinked matrices for controlled release of acyclovir. *Polymer Bulletin*, 77(4), 1869–1891. <https://doi.org/10.1007/s00289-019-02837-5>
- Śniechowski, M., Borek, R., Piwowarczyk, K., & Łuźny, W. (2015). New structural model of PANI/CSA conducting polymer system obtained by molecular dynamics simulations. *Macromolecular Theory and Simulations*, 24(4), 284–290. <https://doi.org/10.1002/mats.201400105>
- Steiner, T. (2002). The hydrogen bond in the solid state. *Angewandte Chemie International Edition*, 41(1), 48–76. [https://doi.org/10.1002/1521-3773\(20020104\)41:1<48::AID-ANIE48>3.0.CO;2-U](https://doi.org/10.1002/1521-3773(20020104)41:1<48::AID-ANIE48>3.0.CO;2-U)
- Syamdi, Sidauruk, H., Munandar, A., & Haryati, S. (2020). The production of nanoparticles chitosan from crustaceans shell using the top-down method. *E3S Web of Conferences*, 147, Article 03025. <https://doi.org/10.1051/e3sconf/202014703025>
- Szegedi, A., Shestakova, P., Trendafilova, I., Mihayi, J., Tsacheva, I., Mitova, V., et al. (2019). Modified mesoporous silica nanoparticles coated by polymer complex as novel curcumin delivery carriers. *Journal of Drug Delivery Science and Technology*, 49, 700–712. <https://doi.org/10.1016/j.jddst.2018.12.016>
- Tang, B., Ma, L., Wang, H., & Zhang, G. (2002). Study on the supramolecular interaction of curcumin and β -cyclodextrin by spectrophotometry and its analytical application. *Journal of Agricultural and Food Chemistry*, 50(6), 1355–1361. <https://doi.org/10.1021/jf0111965>

- Tashan, E., Karakucuk, A., & Celebi, N. (2019). Optimization and *in vitro* evaluation of ziprasidone nanosuspensions produced by a top-down approach. *Journal of Drug Delivery Science and Technology*, 52, 37–45. <https://doi.org/10.1016/j.jddst.2019.04.024>
- Wang, M., Yan, W., Zhou, Y., Fan, L., Liu, Y., & Li, J. (2021). Progress in the application of lecithins in water-in-oil emulsions. *Trends in Food Science & Technology*, 118, 388–398. <https://doi.org/10.1016/j.tifs.2021.10.019>
- Wang, Y., Zheng, Y., Zhang, L., Wang, Q., & Zhang, D. (2013). Stability of nanosuspensions in drug delivery. *Journal of Controlled Release*, 172(3), 1126–1141. <https://doi.org/10.1016/j.jconrel.2013.08.006>
- Wei, X. Q., Zhu, J. F., Wang, X. B., & Ba, K. (2020). Improving the stability of liposomal curcumin by adjusting the inner aqueous chamber pH of liposomes. *ACS Omega*, 5, 1120–1126. <https://doi.org/10.1021/acsomega.9b03293>
- Yang, Q. Q., Farha, A. K., Kim, G., Gul, K., Gan, R. Y., & Corke, H. (2020). Antimicrobial and anticancer applications and related mechanisms of curcumin-mediated photodynamic treatments. *Trends in Food Science & Technology*, 97, 341–354. <https://doi.org/10.1016/j.tifs.2020.01.023>
- Yang, Q. Q., Sui, Z., Lu, W., & Corke, H. (2021). Soybean lecithin-stabilized oil-in-water (O/W) emulsions increase the stability and *in vitro* bioaccessibility of bioactive nutrients. *Food Chemistry*, 338, Article 128071. <https://doi.org/10.1016/j.foodchem.2020.128071>
- Yao, M., McClements, D. J., & Xiao, H. (2015). Improving oral bioavailability of nutraceuticals by engineered nanoparticle-based delivery systems. *Current Opinion in Food Science*, 2, 14–19. <https://doi.org/10.1016/j.cofs.2014.12.005>
- Zheng, B., Zhou, H., & McClements, D. J. (2021). Nutraceutical-fortified plant-based milk analogs: Bioaccessibility of curcumin-loaded almond, cashew, coconut, and oat milks. *LWT—Food Science and Technology*, 147, Article 111517. <https://doi.org/10.1016/j.lwt.2021.111517>
- Zhou, H., Zheng, B., & McClements, D. J. (2021). *In vitro* gastrointestinal stability of lipophilic polyphenols is dependent on their oil–water partitioning in emulsions: Studies on curcumin, resveratrol, and quercetin. *Journal of Agricultural and Food Chemistry*, 69(11), 3340–3350. <https://doi.org/10.1021/acs.jafc.0c07578>