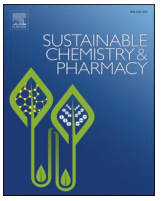
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Overcoming curcumin solubility barriers through cosolvent-modified green deep eutectic solvent systems: Biopolymer-based encapsulation and controlled release

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ABSTRACT

Curcumin, the main compound of the turmeric plant, is widely used as a food supplement. In recent years, it has become one of the popular nutraceutical compounds with its anti-cancer, anti-inflammatory and antioxidant properties. However, the effectiveness of curcumin is limited due to solubility problems in hydrophilic environments. The contribution of deep eutectic solvents (DES), one of the alternative solvents with high performance for many applications, to the bio-accessibility of curcumin was investigated. The best results were obtained using choline chloride-1,2-propanediol-based (CC:PD) mixtures. In addition, the stability and application problems of DESs prepared for high concentration curcumin solutions were solved by modifying them with 0.25 to 7 mol of cosolvent (water and ethanol) per 1 mol of CC. Curcumin solutions in solvent systems containing deep eutectic solvents (DES) and ethanol (EtOH) were encapsulated in alginate-chitosan hydrogels at 10%, 25% and 50% by mass. In vitro controlled release behavior of the obtained curcumin-loaded polymeric beads was studied in simulated gastric fluid (SGF), simulated small intestinal fluid (SIF) and simulated colon fluid (SCF). The results showed that the cosolvent composition of 1:2:2 CC-PD-EtOH exhibited an equilibrium curcumin concentration more than 6 times that of ethanol, the commonly used solvent of curcumin. Drug release studies showed that the highest curcumin release of hydrogel beads occurred in SCF medium. In addition, greenness evaluation using AGREE and AGREEprep metrics confirmed that the developed system is strongly aligned with green chemistry principles.

1. Introduction

Curcumin, obtained from the roots of the *Curcuma longa* plant, is a natural polyphenol compound found in turmeric. This bioactive compound, responsible for turmeric's bright yellow color, has been used for centuries in traditional medicine, particularly in Ayurveda and Chinese medicine, due to its potential therapeutic properties (Sivani et al., 2022). It neutralizes free radicals through the phenolic hydroxyl and methylene groups in its structure, exhibiting strong antioxidant activity both *in vivo* and *in vitro* (Gou et al., 2011). In

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addition to its antioxidant effects, this polyphenol also possesses anti-inflammatory, hypoglycemic, antimicrobial, antiviral, anticancer, and neuroprotective properties (Abd El-Hack et al., 2021; Joe et al., 2004; Pulido-Moran et al., 2016). Furthermore, its low toxicity and limited side effects not only make it suitable for use as a dietary supplement and in medical treatments, but also make it an advantageous option over synthetic antioxidants. Despite these potential health benefits of curcumin, its bioavailability is severely limited (0.05 μg mL−1, <1%), due to its very low solubility in aqueous environments (<8 μg mL−1)(Gunnam and Nangia, 2021; Pantwalawalkar et al., 2021). For this reason, its use as a food and nutritional supplement, as well as its clinical applications, is limited. In addition, poor absorption of curcumin in the small intestine is another factor that reduces its bioavailability. This compound, which is soluble in organic solvents such as dimethyl sulfoxide (DMSO), acetone and methanol, is not suitable for use in biomedical applications, especially due to the limitations of these solvents (Moniruzzaman et al., 2010). Therefore, improving the solubility and bioavailability of curcumin is of critical importance.

Numerous approaches have been adopted to improve the solubility of curcumin for its effective use (Araiza-Calahorra et al., 2018; Barick et al., 2016; Chowdhury et al., 2019; Setthacheewakul et al., 2010; Takahashi et al., 2009; Zheng et al., 2018). Among the proposed green solvents, deep eutectic solvents (DES) have been reported as potential biocompatible media to enhance the solubility of curcumin. Deep eutectic solvents (DES), introduced into the literature by Abbott and colleagues in 2003, are combinations of two or more compounds that come together in specific mole ratios to form mixtures with significantly lower melting points than their individual components (Abbott et al., 2003). The significant melting point reduction and enhanced dissolution properties of DES are attributed to electrostatic and van der Waals interactions (Espino et al., 2016; Mbous et al., 2017; Paiva et al., 2014). These new-generation green solvents are prepared by mixing components that act as hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs). Common HBDs include carboxylic acids, alcohols, sugars, and amino acids, while quaternary ammonium and phosphonium salts serve as HBAs. The tunable nature of DES allows control over key solvent properties such as vapor pressure, density, viscosity, chemical activity, flash point, and stability, making them highly adaptable for various applications (Kist et al., 2021; Liu et al., 2018). As tailor-made solvents, DESs can dissolve many organic and inorganic substances that are otherwise difficult to solubilize, particularly due to their high polarity (Dai et al., 2013; Smith et al., 2014). Furthermore, their entirely non-toxic composition enhances their appeal. The fact that the components of DES are often of natural origin makes these solvents more attractive compared to traditional organic solvents (Jeliński et al., 2019). Additionally, their ability to be designed to enhance the solubility of specific bioactive compounds, thanks to a wide range of compositional diversity, offers a significant advantage (Choi and Verpoorte, 2019). These properties make DES a promising green solvent alternative in many industries, including pharmaceuticals, food, and cosmetics (Jeong et al., 2017; Zainal-Abidin et al., 2019).

Among novel solvent alternatives for curcumin solubility, DESs have garnered significant attention due to their tailor-cut properties, cheap and readily available components that meet the green chemistry requirements (Kist et al., 2021; Liu et al., 2018; Paiva et al., 2014). In comparison to conventional organic solvents such as alcohols, acetone, and chloroform, DESs demonstrated superior efficacy in dissolving bioactive compounds, including phenolic acids, polyphenols, anthraquinones, and flavonoids (Dai and Row, 2019; Torres-Vega et al., 2020; Yue et al., 2020). Recent progress in the literature focuses on the ability of dissolution, stabilization, and conservation efficiency of bioactive compounds in the DES (Abouheif et al., 2022; Alioui et al., 2022; Coelho et al., 2024; Jeliński et al., 2019; Shekaari et al., 2021; J. Silva et al., 2021; Wikene et al., 2015; Yu et al., 2023a). Some types of DESs were reported as considerable alternative solvents for curcumin solubility (Jiang et al., 2019; Li et al., 2020; Murador et al., 2019; Yu et al., 2023).

Even though high curcumin solubility is achieved, the curcumin is still required to be preserved from the disruptive effects of environmental conditions and biochemical processes (Anand et al., 2007; Sahu et al., 2008). Encapsulation systems, in which curcumin dissolved within a solvent gets emulsified in an aqueous medium and stabilized by macromolecules distributed in this aqueous medium are used as release agents with curcumin solution droplets distributed within the aqueous matrix serve as sustained-release reservoirs. Therefore, it is important that the selected solvent, in addition to its high curcumin solubilizing ability, is also suitable for encapsulation applications commonly used in drug delivery systems. To provide emulsion stability, biopolymers are widely used for encapsulation of curcumin (Xu et al., 2007). Among these biopolymers, marine-originated alginate (ALG) and chitosan (CHI) were commonly used (Xu et al., 2007). Polycationic CHI mechanically reinforces the polyanionic ALG network structure due to the electrostatic interactions between the two polymers, and ALG undergoes ionotropic gelation in the presence of divalent cations in aqueous media, such as Ca^{2+}, forming a physically cross-linked hydrogel (Takka and Gürel, 2010; Xu et al., 2007). Hydrogels are water-swollen polymeric networks that comprise mostly of water. Owing to their adjustable parameters, such as cross-link density, polymer concentration, and pore size, hydrogels are favored structures for drug delivery system stabilization and control (Zhang et al., 2019).

In this study, the effectiveness of DESs as an alternative solvent group was investigated in order to create high concentration solutions of curcumin compound with low solubility in hydrophilic environments. In addition, in order to obtain a useable media in biological systems, the physicochemical properties of the selected DES were improved by using a cosolvent without affecting its solubility. It was aimed to create a carrier delivery system by encapsulation method using the developed DES-based curcumin solutions, and the bioaccessibility of the polymeric beads in *in vitro* applications was investigated.

2. Materials and methods

2.1. Materials

In the preparation of DES's, choline chloride (99%, Sigma-Aldrich, USA), 1,2-propanediol (99%, Sigma-Aldrich, USA), ethylene glycol (99%, Sigma-Aldrich, USA), butanediol (98%, Sigma-Aldrich, USA), eucalyptol (99%, Sigma-Aldrich, USA), DL-menthol (99%, Sigma-Aldrich, USA), thymol (99%, Sigma-Aldrich, USA), decanoic acid (99%, AmBeed, USA), acetic acid (99%, Sigma-Aldrich, USA),

formic acid (99%, Sigma-Aldrich, USA), lactic acid (80%, Sigma-Aldrich, USA), alanine (98%, AmBeed, USA), glycine (98.5%, Sigma-Aldrich, USA), and L-proline (99%, Sigma-Aldrich, USA) chemicals were used. The chemicals used in solubilization and encapsulation processes were ethanol (99.9%, Sigma-Aldrich, USA), deionized water, curcumin (99%, AmBeed, USA), sodium alginate (90%, Macklin, USA), chitosan (50,000–190,000 Da Mw, Sigma-Aldrich, USA), $CaCl_2$, (98%, AmBeed, USA), HCl (37%, Merck, Germany), NaOH (98%, Sigma-Aldrich, USA), NaCl (99.5%, Merck, Germany), KCl (99%, Sigma-Aldrich, USA), KH_2PO_4 (99%, Merck, Germany), Na_2HPO_4 (99%, Sigma-Aldrich, USA).

2.2. Methods

2.2.1. Preparation of deep eutectic solvents (DES)

In order to obtain a DES with high curcumin (CUR) solubilizing ability, 17 different DES were prepared. For this purpose, quaternary ammonium salt choline chloride, carboxylic acid (formic, acetic, lactic, octanoic, nanonoic), alcohol (1.3-Butanediol, 1.2-Propanediol, Ethylene Glycol), amino acid (alanine, proline, glycine), sugar (fructose, glucose, sucrose), and terpenoid (menthol, thymol, Eucalyptol) group components were used as HBA and HBD. The mixtures prepared according to the determined ratios were prepared by following the procedures in the heating and mixing method (Negi et al., 2024). The DES components were mixed at 343.15 K using a Heidolph MR Hei-Tec model magnetic stirrer equipped with a contact thermometer. Once a colorless and homogeneous liquid was obtained, the resulting DESs were subjected to stability testing by being stored at room temperature in a Memmert UF110 model oven for 24 h.

2.2.2. Solubility and stability tests of curcumin within DESs

Solubility tests were conducted following the procedure outlined by Yu et al. (Yu et al., 2023a). An excess amount of curcumin was added to 5 mL of DES, ethanol (EtOH), or a cosolvent mixture. The mixtures were agitated in a Lab Companion BS-21 thermostatic water bath at 37 °C and 180 rpm for five days. Subsequently, the saturated solutions were centrifuged at 4000 rpm for 30 min using a NÜVE NF400R rotational centrifuge. The supernatant, separated from the excess solid CUR, was subjected to HPLC analysis to determine the CUR concentration. Stability tests were performed with the same experimental procedure for the CUR dissolved in the selected cosolvent composition with the highest CUR solubility. The saturated CUR solution was prepared with this cosolvent mixture. The sample solution was stored under darkroom conditions for one year.

2.2.3. The chromatographic analysis of curcumin

The chromatographic analysis of curcumin was carried out with minor modifications to the method originally developed by Yaman et al. (2025). Chromatographic measurements were performed using a Shimadzu LC-2050C-PDA system. Separation was achieved in isocratic mode on an InertSustain C18 column (250 mm × 4.6 mm, 5 μm) employing mobile phase A (acetic acid:water, 2:100, *v/v*) and mobile phase B (acetonitrile) (60:40, *v/v*) with a run time of 30 min. All calibration standards and samples were passed through a 0.45 μm RC syringe filter prior to injection into the system. The flow rate was maintained at 1.6 mL/min with an injection volume of 10 μL. The retention time of 22.4 min was defined for curcumin. Analytes were identified based on peak areas recorded at 425 nm using the PDA detector. Calibration curves were constructed by plotting the peak areas of standard solutions against their respective concentrations, and the corresponding linear regression equations were derived.

Table 1
The composition of DES-cosolvent systems.

DES Name	CC: PD	Molar Ratio, H_2O	Molar Ratio, EtOH
DES 1	1 : 2	-	-
DES 2	1 : 3	-	-
DES 3	1 : 4	-	-
DES 4	1 : 2	-	0.25
DES 5	1 : 2	-	0.5
DES 6	1 : 2	-	1
DES 7	1 : 2	-	2
DES 8	1 : 2	-	3
DES 9	1 : 2	-	4
DES 10	1 : 2	-	5
DES 11	1 : 2	-	6
DES 12	1 : 2	-	7
DES 13	1 : 2	0.25	-
DES 14	1 : 2	0.5	-
DES 15	1 : 2	1	-
DES 16	1 : 2	2	-
DES 17	1 : 2	3	-
DES 18	1 : 2	4	-
DES 19	1:2	5	-
DES 20	1:2	6	-
DES 21	1:2	7	-

2.2.4. Preparation of DES-based cosolvent systems

The DES mixture (CC-PD; 1:2), which was determined to have the highest CUR solubility as a result of HPLC measurements, was diluted with water and ethanol (EtOH) at certain ratios in order to improve its physicochemical properties. DES-based cosolvent mixtures were prepared with water or EtOH molar ratios of 0.25, 0.5, 1, 2, 3, 4, 5, 6, and 7 in the composition. It was obtained by adding DES and diluting it. The molar ratios of the cosolvent systems formed are listed in Table 1.

2.2.5. Characterization of DESs and cosolvent systems

The densities of DESs with CC:PD composition were measured using a Kem-Kyoto DA645-CHD502 densimeter. Similarly, the refractive indices of the DESs were determined using an Anton Paar Abbemat 350 refractometer. Finally, the viscosity properties were assessed using an AND SV-10 vibro-viscometer with a sample volume of 10 mL.

The theoretical diffusion coefficient (D_s)of the solute (CUR) in the surrounding DES or cosolvent is determined using the Stokes-Einstein equation (Chan and Neufeld, 2009):

$$\boldsymbol{D}_s = \frac{\boldsymbol{k_B T}}{\boldsymbol{6\pi\eta r_H}} \tag{1}$$

In this relation, k_B is the Boltzmann constant, T is the absolute temperature, η is the dynamic viscosity of the solvent, and r_H is the hydrodynamic radius of the solute molecule. This step establishes the baseline mobility of the drug without accounting for the structural hindrance of the hydrogel.

2.2.6. Spectroscopic analysis

The conformational structures of the CC:PD solvent and curcumin solutions prepared with this DES were elucidated using a Shimadzu IRTracer-100 infrared Fourier spectrophotometer. Spectra were acquired within the scanning range of 4000–400 cm^{-1} using a single attenuated total reflectance (ATR) accessory equipped with a diamond prism.

^{1}H NMR spectra were recorded on an Agilent DDR2 spectrometer operating at 400 MHz (9.39 T) at room temperature. The spectra were analyzed to evaluate the molecular interactions between curcumin and DES components.

2.2.7. Preparation of curcumin-loaded alginate-chitosan hydrogel beads

Alginate (ALG) solutions were prepared at a concentration of 6% (*w/v*) in deionized water. The pH of the ALG solution was adjusted to 7. Subsequently, the prepared ALG solutions were homogenized with a saturated CUR solution prepared using DES 7 with the aid of a Daihan Scientific HG-15D digital mechanical stirrer. The homogenization process was carried out at 15,000 rpm for 5 min. To investigate the effect of DES solutions on curcumin loading and release capacities, DES solutions were mixed with ALG solutions at three different mass fractions: 10%, 25%, and 50% (*w/w*).

The prepared ALG-DES solution emulsions were transferred into 20 mL disposable syringes equipped with 18-gauge blunt-tip injection needles. The emulsions were dripped into a coagulation bath at a constant extrusion rate of 1 mL/min using a syringe pump (New Era Pump Systems Inc., Model NE-300). The coagulation bath was prepared using a 0.1 M $CaCl_2$ solution containing 0.2% (*w/v*) chitosan (CHI) and 1% (*v/v*) acetic acid. The pH of the solution was adjusted to 5. The extrusion process was carried out at room temperature, and the coagulation bath was continuously stirred with a magnetic stirrer to prevent droplet aggregation.

To be used as references for comparison, two different series of hydrogel beads were prepared: in the first series, ALG solution was directly added dropwise to the $CaCl_2$–CHI coagulation bath, and the ALG-CHI beads without the DES phase were formed. In the second reference series, the DES phase that does not include CUR was mixed with the ALG solution with the same mass ratios of 10%, 25% and 50% (*w/w*). The beads were allowed to harden by stirring in the coagulation bath for 1 h. Once hardened, the beads were separated by filtration and washed 3–5 times by stirring in 100 mL of distilled water. The obtained hydrogel beads were dried under vacuum (Weightlab Instruments, model WFHT25-V) at −0.8 atm at 40 °C for 5 days and stored under darkroom conditions.

2.2.8. Characterization of DES and curcumin-loaded alginate-chitosan hydrogel beads

Morphological imaging was conducted to characterize the prepared hydrogel beads. The scanning electron microscope micrographs were obtained using SEM, FEI Versa 3D Dual Beam equipment. The micrographs were taken for each DES mass ratio-bead with 150x and 1000x magnifications, under vacuum without metallic coating.

The rheological properties of the prepared deep eutectic solvent (DES) and curcumin-loaded DES (CUR-DES) hydrogel beads were determined using a Discovery HR 30 (TA Instruments) rheometer. Measurements were conducted at 25 °C using a 25 mm parallel plate geometry with a 500 μm gap. To evaluate the viscoelastic behavior, a frequency sweep test was performed, analyzing the storage modulus (G'), loss modulus (G''), and loss tangent (tan δ) within an angular frequency range of 1–100 rad/s.

The crosslink density of the 10, 25 and 50% (*w/w*) CUR-DES-loaded hydrogel beads was calculated theoretically from their swelling ratios, according to the methodology explained in Borges et al.'s (Borges et al., 2020) and Chan & Neufeld's (Chan and Neufeld, 2009) work.

Initially, the volumetric swelling ratio (Q_v) and the corresponding polymer volume fraction (ϕ_2) were determined by measuring the equilibrium diameters of the beads in their swollen and dry states, assuming an isotropic swelling behavior for the spherical geometry. To evaluate the physical crosslinking intensity, the Flory-Rehner equation was employed to calculate the average molecular weight between crosslinks (M_c). This calculation explicitly accounted for chain-end corrections by utilizing the number average molecular weight of the primary alginate chains (M_n), ensuring a more accurate representation of the elastically effective network segments. The

thermodynamic interactions between the sodium alginate and the aqueous medium were characterized using a Flory-Huggins interaction parameter (χ) of 0.495, as reported for similar biopolymeric systems (Chan and Neufeld, 2009).

An additional network parameter, the degree of crosslinking (X_n), was calculated to correlate the structural tightness of the hydrogels with their rheological performance and drug release kinetics.

Detailed mathematical derivations, including all parameters and the specific forms of the Flory-Rehner and the degree of crosslinking equations used in this study, are provided in the Supplementary Information (Equations S1–S5).

2.2.9. Swelling tests of vacuum-dried hydrogel beads

Swelling tests were conducted by immersing vacuum-dried hydrogel beads in simulated gastrointestinal fluids (SGIF) until equilibrium was reached. The test environments included simulated gastric fluid (SGF, pH = 1.2 ± 0.1), simulated intestinal fluid (SIF, pH = 6.8 ± 0.1), and simulated colonic fluid (SCF, pH = 7.4 ± 0.1). These fluids were selected to investigate the effect of environmental pH on the swelling behavior of ALG-CHI hydrogel beads. Additionally, *in vitro* drug release studies were also conducted in these fluids.

The optimal swelling equilibrium times, determined experimentally, were determined to be 2 h, 45 min, and 30 min for SGF, SIF, and SCF, respectively. Swelling tests were performed by immersing 30 mg of dry hydrogel beads in 3 mL of SGIF-filled beakers and stirring at room temperature using a magnetic stirrer for the specified durations.

At the end of the swelling periods, the hydrogels were carefully blotted to remove excess SGIF from their surfaces, and weighed. The swelling ratios by mass were calculated using the following equation.

$$\textbf{Mass swelling ratio} = \frac{\textbf{Swollen} - \textbf{state mass}}{\textbf{Vacuum} - \textbf{dried state mass}} \tag{2}$$

The mass measurements of hydrogel beads were triplicated and the average of these values was used for calculations.

2.2.10. In vitro drug release studies

Stimulated gastric fluid (SGF – pH = 1.2 ± 0.1), stimulated intestinal fluid (SIF – pH = 6.8 ± 0.1) and stimulated colonic fluid (SCF – pH = 7.4 ± 0.1) were used as *in vitro* drug release media. The buffer solutions were prepared according to the procedure reported elsewhere (Marques et al., 2011; Martins et al., 2013). The preparation of simulated gastrointestinal fluids for *in vitro* release studies follows standard protocols where simulated gastric fluid (SGF, pH 1.2) is formulated by dissolving 2.0 g of NaCl in water, adding 7.0 mL of concentrated HCl, and diluting to 1000 mL. For simulated intestinal fluid (SIF, pH 6.8), 6.80 g of is dissolved in water and mixed with 77 mL of 0.20 mol/L NaOH to reach a final 1000 mL volume. Simulated colonic fluid (SCF) can be prepared as a simple phosphate-based saline buffer (SCoF1, pH 7.0) containing KCl, NaCl, KH_2PO_4 and Na_2HPO_4 to reflect the colonic environment. All release media were prepared enzyme-free. Hydrogel beads prepared from 10, 25 and 50% (*w/w)* emulsions were vacuum-dried. Beads weighing 35–40 mg were incubated in 3 mL of simulated gastrointestinal fluids. In vitro release studies were performed for a total of 4 h for SIF and SCF, and 8 h for SGF at 37 °C and a constant rotation speed of 60 rpm. 0.8 mL aliquots were sampled at specified time intervals and cumulative curcumin release was measured and reported by HPLC analysis. The withdrawn 0.8 mL volume was then replaced with an equal volume of release medium to maintain volumetric consistency.

CUR loading capacities of beads were determined according to the following procedure: 10 mg of vacuum-dried beads were disrupted until homogenization with the digital mechanical homogenizer in 3 mL of pure ethanol, for 1 min. Later, the solution was kept in an ultrasonic bath at 37 °C for 1 h. Finally, the homogeneous mixture was centrifuged at 4100 rpm for 30 min to avoid the inclusion of any excessive amount of CUR. The aliquots of 0.8 mL were taken from saturated solutions and the CUR concentrations were measured with HPLC. To ensure reproducibility, all experiments were independently repeated three times ($n = 3$). The CUR loading capacities of hydrogel beads were determined according to the following formula:

$$\textbf{CUR Loading Capacity} = \frac{\textbf{HPLC Concentration } \textbf{x } \textbf{0.8 mL}}{\textbf{10 mg of beads}} \tag{3}$$

The drug distribution homogeneity experiments were conducted with 10, 25 and 50% (*w/w)* CUR-DES-loaded dry beads with a similar methodology. 10 mg of dried beads were weighed in 5 mL of pure ethanol, and completely disrupted using the Daihan Scientific HG-15D digital mechanical stirrer, for 1 min. Resulting systems were kept in an ultrasonic bath at 37 °C for 1 h, and centrifuged at 4100 rpm for 30 min. The supernatant liquids were quantified in CUR concentrations with HPLC measurements.

The release kinetics of CUR from the ALG-CHI hydrogel bead system were evaluated across simulated gastric (SGF), intestinal (SIF), and colonic (SCF) fluids using four mathematical models: Zero-order, First-order, Higuchi (1963), and Korsmeyer-Peppas (Korsmeyer et al., 1983). The equations from which the kinetic data were derived are given in Supplementary Table S1.

3. Result and discussion

In the present work; experimental studies were carried out on obtaining a DES with high curcumin dissolving ability. The deep eutectic solvent detected was modified using a cosolvent in order to improve its suitability and stability for release systems. After the obtained DES-based curcumin solutions were encapsulated, their release behaviors in different environments were investigated.

3.1. Preparation of different deep eutectic solvents for Investigation of curcumin solubility and diffusivity

In order to examine the curcumin solubilizing abilities of DESs, alternative solvents were prepared using carboxylic acid, alcohol,

amino acid and sugar group components that are widely used in the preparation of these new generation solvents. (Jeliński et al., 2019; Yu et al., 2023a). Hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) in the DES composition were preferred to form hydrophilic or amphiphilic DES compounds. Thus, it was aimed to increase the accessibility of the prepared curcumin solutions to hydrophilic biological systems. In this context, the compositions of deep eutectic solvents (DES) formulated in different molar ratios and the CUR solubility values (mg/mL) determined using HPLC in these solvents are presented in Table 2.

As a result of the analysis, it was observed that sugar and amino acid-based DES systems generally have solubility values below 1 mg/mL. On the other hand, terpene and choline chloride-based DES systems were found to be able to dissolve curcumin at higher rates than those containing sugar compounds in their composition. Curcumin solubility values of DESs with choline chloride - acetic acid, thymol - decanoic acid and choline chloride - ethylene glycol compositions were measured as 7.58, 6.92 and 4.14 mg/mL, respectively.

It was determined that the highest CUR solubility value (19.74 mg/mL) was obtained in the DES system consisting of choline chloride (CC) and 1,2-propanediol (PD) at 1:2 M ratios. This value is more than 2.5 times that of other DES types. Similarly, in the study conducted by Yu et al. on curcumin solubility, it was stated that positive results were obtained in curcumin solubility with DESs prepared with this duo (Yu et al., 2023a).

However, among three different DES formulations where CC and PD were used in different molar ratios (1:2, 1:3 ve 1:4), an increase in CUR solubility was observed with the increase in the CC molar ratio.

Structurally, the curcumin molecule is a diketone compound formed by the conjugation of two ferulic acid molecules connected by a methylene bridge and is in equilibrium with the enol form. This keto-enol structure likes a dipolar solvent environment. As the choline chloride ratio increases, the ionic character of the system increases, which can have a positive effect on the solubility of curcumin. In addition, the choline hydroxyl group forms a hydrogen bond with the carbonyl or phenolic –OH groups of curcumin, which can be said to contribute positively to the solubility of curcumin. However, as the amount of CC in the DES content increases, the viscosity of the solvent increases, and more importantly, crystallization is observed even under room conditions. For this reason, in the literature, DESs prepared using 3 or more moles of PD per 1 mol of CC with a curcumin solubility capacity have been preferred due to both obtaining a stable solvent and ease of application (Abbott et al., 2003a; Cui et al., 2021; Yu et al., 2023a).

In our study, it was aimed to obtain a more stable form of CC-PD solvent with a 1:2 M ratio at room conditions and with high curcumin dissolving properties. In this context, studies were carried out on reducing the viscosity and increasing the stability of CC-PD DES by adding a cosolvent.

3.2. *Physicochemical and curcumin solubility properties of DES-cosolvent systems*

In order to improve the physicochemical properties of the eutectic mixture prepared with CC and PD having the highest curcumin solubility among the prepared eutectic mixtures at a mole ratio of 1:2 (DES 1), water and ethanol were used as cosolvents and added to DES in different amounts. The effects of all prepared mixtures on the solubility of curcumin were investigated. In this context, DES 1 was diluted with ethanol (EtOH) and water at different mole ratios. The mole ratios used were determined as the molar amounts of H_2O and EtOH according to CC. The compositions, density, viscosity and refractive index values of these prepared DES–cosolvent mixtures are presented in detail in Supplementary Table S3.

The obtained data revealed that among the DES systems without cosolvent, density values decreased with the increase in PD mole ratio. In DES-cosolvent systems containing EtOH, the density and refractive index of all formulations were observed to be lower compared to the DES 1 system; it was determined that these parameters decreased even more with the increase in EtOH mole ratio.

Table 2
DES mixtures at different HBA:HBD molar ratios and CUR solubilities of the respective mixtures (mg/mL).

DES Composition	CUR Solubility (*mg/mL*)
Choline Chloride: 1,2-Propanediol (1:2)	19.74
Choline Chloride: 1,2-Propanediol (1:3)	12.12
Choline Chloride: 1,2-Propanediol (1:4)	7.34
Choline Chloride: Ethylene Glycol (1:2)	4.34
Choline Chloride: 1,4 Butanediol (1:2)	<1
Choline Chloride: Formic Acid (1:4)	1.58
Choline Chloride: Lactic Acid (1:4)	1.26
Choline Chloride: Acetic Acid (1:4)	7.58
Alanine: Lactic Acid (1:4)	<1
Glycine: Lactic Acid (1:4)	<1
L-Proline: Lactic Acid (1:4)	<1
L-Poline: Octanoic Acid (1:4)	2.24
L-Proline: Nonanoic Acid (1:4)	2.02
Menthol: Acetic Acid (1:2)	4.14
Thymol: Acetic Acid (1:2)	6.92
Eucalyptol: Acetic Acid (1:2)	3.53
Acetic Acid: Fructose: Water (1:5:5)	1.24
Acetic Acid: Glucose: Water (1:5:5)	<1
Acetic Acid: Sucrose: Water (1:5:5)	<1

Similarly, in mixtures containing water, both density and refractive index values were observed to decrease with the increase in water mole ratio.

Physicochemical properties are one of the effective factors in the dissolution process. For example, low viscosity can accelerate dissolution by allowing the solute and solvent to interact more easily. However, viscosity is not the only determinant. It should be evaluated together with other factors such as solvent-solute interaction, temperature, and polarity.

Solubility tests were performed in order to make the most appropriate selection for the release systems to be prepared by the encapsulation method among the DES-cosolvent mixtures with determined physicochemical properties. In this way, it was aimed to make a selection by evaluating both viscosity and curcumin dissolving ability together. The measured viscosity values and CUR solubility values of all prepared mixtures are shown in Fig. 1.

HPLC analyses of CUR solubility values revealed that cosolvents added to DESs significantly affected solvent performance. According to the measurements, DES 7 (1:2:2 CC–PD–EtOH) provided the highest CUR solubility with 26.815 ± 0.385 mg/mL. In addition, the CUR solution prepared in DES 7 was stored under dark conditions at room temperature for approximately one year. The results demonstrated that the system retained a high level of its initial solubilization capacity throughout the storage period, with only a moderate decrease in curcumin content. Importantly, no precipitation or phase separation was observed, indicating that the DES matrix effectively preserves curcumin in a solubilized state over time. Overall, these findings confirm the favorable long-term physical stability of the CUR-DES system, supporting its robustness and potential suitability for further formulation and application studies. This formulation reduced the viscosity of DES 1 from 94.1 cP to 17.2 cP (DES 7). It is observed that adding a certain amount of EtOH to DES both reduces the viscosity and increases the solubility of curcumin.

However, it was understood that the positive effects of EtOH added to DES caused a decrease in CUR solubility at higher EtOH ratios. It is thought that this effect is due to the fact that, as previously reported in the literature, although the addition of cosolvents in some DESs initially increased the solubility, it caused a decrease in solubility after a certain threshold due to the deterioration of the DES structure (Dai et al., 2013). By evaluating all the findings, it was decided that DES 7, which provides maximum CUR solubility in terms of solubility and physicochemical properties, will be used as a carrier phase in the preparation of encapsulated systems and in *in vitro* applications.

3.3. Spectrophotometric analysis of DES and CUR-DES solution systems

The composition of the CC-PD type deep eutectic solvent selected for use in the encapsulation stage and its interactions with curcumin were evaluated by FTIR analysis. FTIR spectra of pure CC and PD, DES and CUR-DES systems are shown in Fig. 2.

FTIR spectra of pure components CC, PD and DES prepared in 1:2 molar ratio reveal molecular interactions that occur due to hydrogen bonds. It is observed that O–H stretching bands (~3200–3500 cm^{-1}) of CC and PD broaden and shift upon DES formation. C–N stretching band (~1000–1100 cm^{-1}) of CC and C–O stretching band (~1050–1150 cm^{-1}) of PD also shifted upon DES formation. These shifts indicate molecular interactions between the components within DES. Similarly, C=Ostretching band (~1625–1650 cm^{-1}) corresponding to the β-diketone structure of CUR exhibited a slight shift in the CUR-DES spectrum and this is thought to indicate hydrogen bond interactions between CUR and DES components.

The dissolution mechanism and successful incorporation of curcumin into the DES (CC:PD:EtOH) system were elucidated using ^{1}H NMR spectroscopy. As depicted in Fig. 3, the stacked spectra of pure DES and CUR-DES reveal critical structural interactions. The appearance of distinct signals in the aromatic region (6.4 - 7.8 ppm) for the CUR-DES system confirms the presence of structurally intact curcumin within the solvent. Furthermore, significant peak broadening and chemical shifts observed in the highlighted regions (~2.2-2.6 ppm and ~4.4-5.0 ppm) indicate alterations in the surrounding hydrogen-bonding environment. Importantly, the absence of any newly formed, unassigned peaks confirms that no chemical reaction or degradation occurred during the dissolution process. These

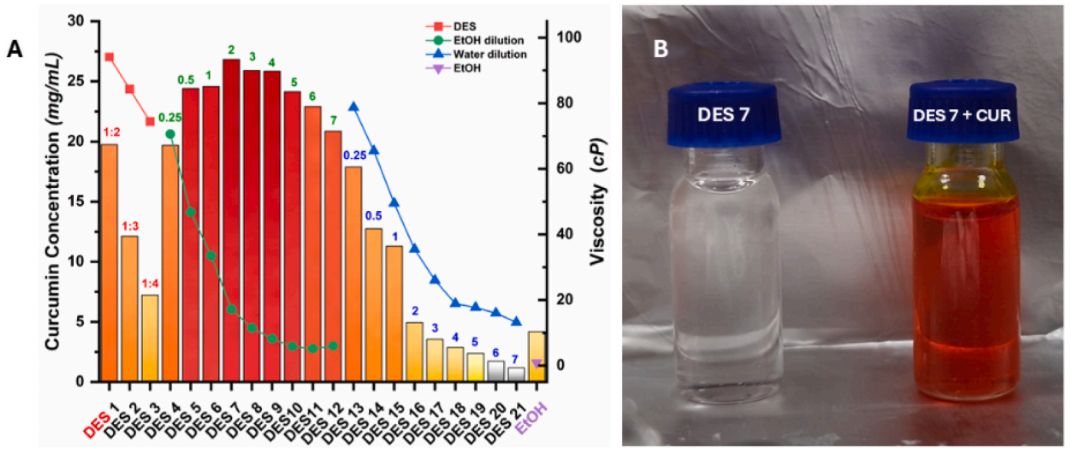


Fig. 1. (A) Curcumin solubility and viscosity values of DES and DES-cosolvent mixtures. (B) Pure DES 7 and saturated curcumin solution prepared with DES 7.

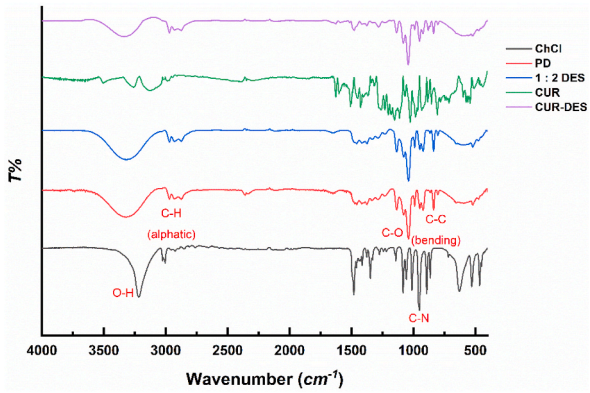


Fig. 2. FTIR spectra of choline chloride (CC), 1,2-propanediol (PD), DES 1, curcumin (CUR) and DES with CUR dissolved in it (CUR-DES) solution.

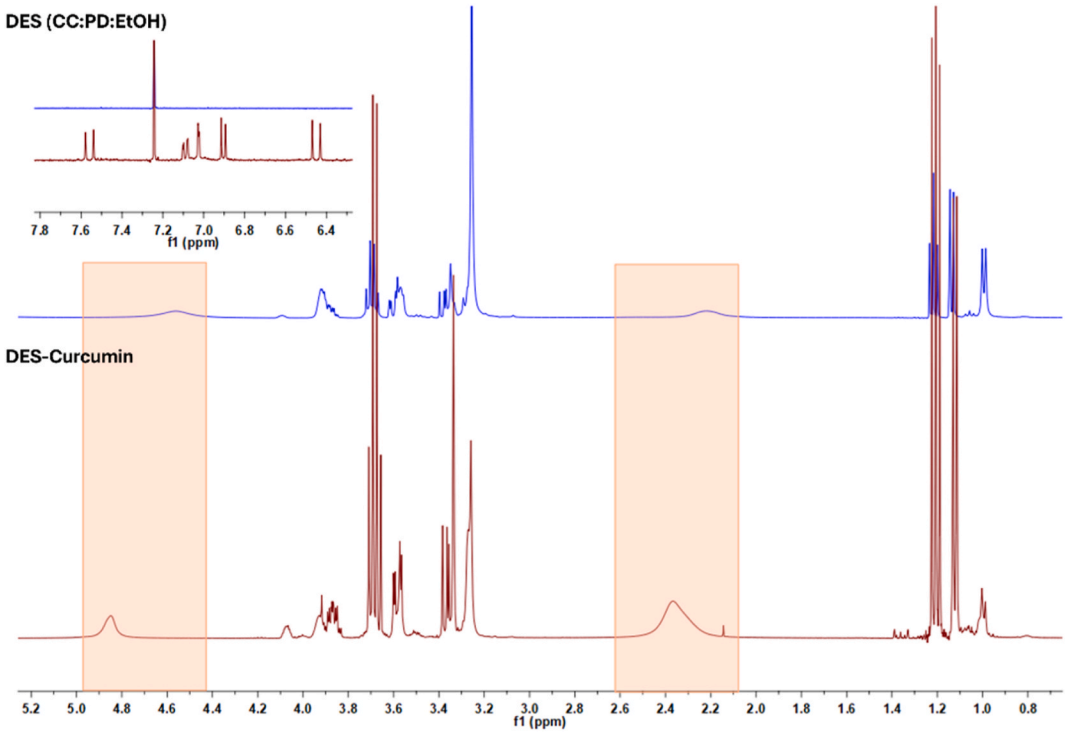


Fig. 3. Comparative ^{1}H NMR spectra of pure DES and the CUR-DES system.

spectral changes collectively suggest strong intermolecular hydrogen-bonding interactions between the functional groups of curcumin and the DES components. This supramolecular reorganization demonstrates that curcumin is physically dissolved and stabilized within the deeply connected hydrogen-bond network of the DES, preserving its chemical integrity. ^{1}H NMR spectra of curcumin, DES, and CUR-DES are shown in Supplementary Figs. S1, S2, and S3, respectively.

3.4. Swelling properties, crosslink density and rheological analyses of curcumin-loaded alginate-chitosan hydrogel beads

CUR-DES solution, which was obtained by using the eutectic solvent with the highest curcumin (CUR) dissolving ability, was used in the encapsulation process together with polymer solutions containing calcium alginate (ALG) and chitosan (CHI). Emulsions were prepared by adding CUR-DES solution to ALG solutions at 10%, 25% and 50% (*w/w*) ratios. In order to evaluate the effects of CUR-DES solution on the encapsulation system, beads containing only ALG-CHI (without DES) were prepared by the same method. Hydrogel beads containing CUR solution were produced from these emulsions by using the syringe extrusion method. Fig. 4 shows the post-synthesis and vacuum-dried states of hydrogel beads containing CUR-DES.

All hydrogel beads were dried in a vacuum oven after synthesis and *in vitro* swelling tests were performed in three different SGIF

liquids. Graphs showing the mass swelling values of hydrogel beads are presented in Fig. 5. The CUR loading capacities determined using the previously explained method are also presented in Fig. 5(B).

As a result of the swelling tests, it was observed that increasing DES and CUR-DES ratios in all formulations caused a decrease in the mass swelling ratios. Similarly, it was determined that the mass swelling ratios increased with the increase in the pH of the medium. However, while the mass swelling value in beads containing 50% CUR-DES was higher in the SIF medium (pH 6.24), it was slightly lower in the SCF medium (pH 5.19). It is thought to be due to the fact that more partial disintegration occurred in beads that reached swelling equilibrium in the SCF medium compared to the SIF medium. The mass swelling ratios of the hydrogel samples containing only DES at 10%, 25% and 50% (*w/w*) were found to be higher compared to the gels containing CUR dissolved DES (CUR-DES) at the same ratios. It is thought that this difference is due to the physicochemical changes that occur in the system with the addition of CUR to the DES phase. In addition, a general decrease in the swelling ratio of the gels was observed as the DES content increased. This situation is considered to be related to the increased CUR release observed especially in gels containing high CUR-DES content and to limit the swelling behavior. The CUR loading capacity values were seen increasing with the increasing mass fraction of CUR within the encapsulation system, as expected. The standard deviations of curcumin loading capacity for beads containing 10%, 25%, and 50% (*w/w*) CUR-DES were 0.0040, 0.0042, and 0.0059, respectively ($n = 3$), indicating acceptable reproducibility across all formulations.

The rheological measurement results for hydrogel beads containing only DES are presented in Supplementary Fig. S4. The analysis revealed that increasing the mass fraction of DES led to a reduction in G', G'', and tan δ values. Specifically, for the 0% (ALG) reference gel compared to the 10% (DES) formulation, the G' values at an angular velocity of 0.1 rad/s decreased from 53,141 Pa to 38,497 Pa, while at 100 rad/s, the values dropped from 130,323 Pa to 92,404 Pa.

The tan δ value (the ratio of the loss modulus to the storage modulus) showed a significant initial decrease from 0.24 to 0.208 between the 0% and 10% formulations. However, with further increases in DES mass fractions, tan δ values were measured at 0.229 and 0.254, respectively. These results suggest that while the addition of DES initially weakens the elastic character of the alginate matrix, higher mass fractions enhance gel rigidity, causing the viscous character to become more dominant compared to the pure alginate hydrogel. This transition from a viscous-dominant to an elastic-dominant character due to DES incorporation aligns with observations reported in recent literature (Verger et al., 2024).

The rheological data for hydrogel beads loaded with curcumin-containing DES (CUR-DES) are summarized in Supplementary Fig. S5. It was observed that the 10% (*w/w*) (CUR-DES) formulation exhibited a maximum elastic modulus of 105,192 Pa, which is slightly higher than the modulus observed in beads containing DES alone. For higher mass fractions, however, the CUR-DES hydrogels displayed lower elastic modulus values compared to the formulations containing only DES.

Furthermore, the CUR-DES loaded beads exhibited a shift from a viscous-dominant character to a more elastic-dominant character, as evidenced by the increase in tan δ values from 0.207 to 0.235. This behavior indicates that the presence of the curcumin payload within the DES phase further modulates the physical cross-linking and internal network stability of the alginate-based hydrogel system.

The crosslink density of the 10, 25 and 50% (*w/w*) CUR-DES-loaded hydrogel beads was evaluated regarding the methodology explained in Section 2.2.8. The resulting numerical values for each hydrogel formulation are summarized in Supplementary Table S3. The calculated network parameters reveal that 50% (*w/w)* CUR-DES-loaded hydrogel beads possess the highest degree of crosslinking ($X_n = 0.0295$) and the lowest average molecular weight between crosslinks (6701 g/mol), which directly correlates with its superior mechanical stability. This structural tightness is reflected in the rheological data, where the incorporation of higher concentrations of curcumin-containing deep eutectic solvent leads to an increase in the storage modulus (G') and a transition from a viscous-dominant to an elastic-dominant character (increased tan δ compared to 10% (*w/w)* gels), indicating a more rigid and tightly crosslinked biopolymeric network.

Consequently, the significantly more abundant crosslinking in 50% (*w/w)* CUR-DES beads effectively suppresses initial burst release and limits the diffusion of the hydrophobic payload in upper gastrointestinal environments, as evidenced by its adherence to Fickian diffusion regimes ($n \leq 0.43$) in simulated gastric fluid. In contrast, 25% (*w/w)* CUR-DES-loaded beads exhibit a looser network ($M_c = 11459$ g/mol) and the highest volumetric swelling capacity ($Q_v = 15.22$), facilitating a faster transition toward non-Fickian transport and higher release rates in simulated colonic fluid. Ultimately, the dense crosslinking and polymer entanglement in 50% (*w/w)* CUR-DES-loaded hydrogel beads provide a robust, pH-responsive delivery mechanism that triggers rapid structural relaxation and Super Case-II transport ($n = 1.24$) specifically in colonic conditions, thereby ensuring colon-targeted delivery and maximizing the

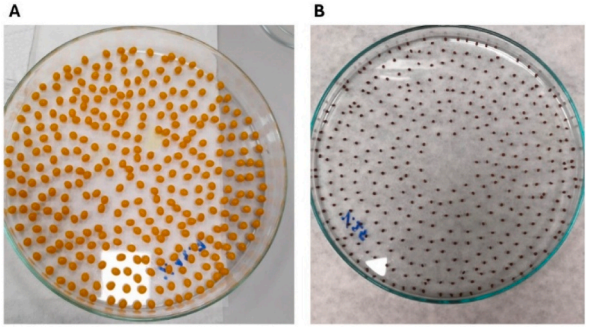


Fig. 4. CUR-DES loaded hydrogel bead (A) after synthesis and (B) vacuum dried.

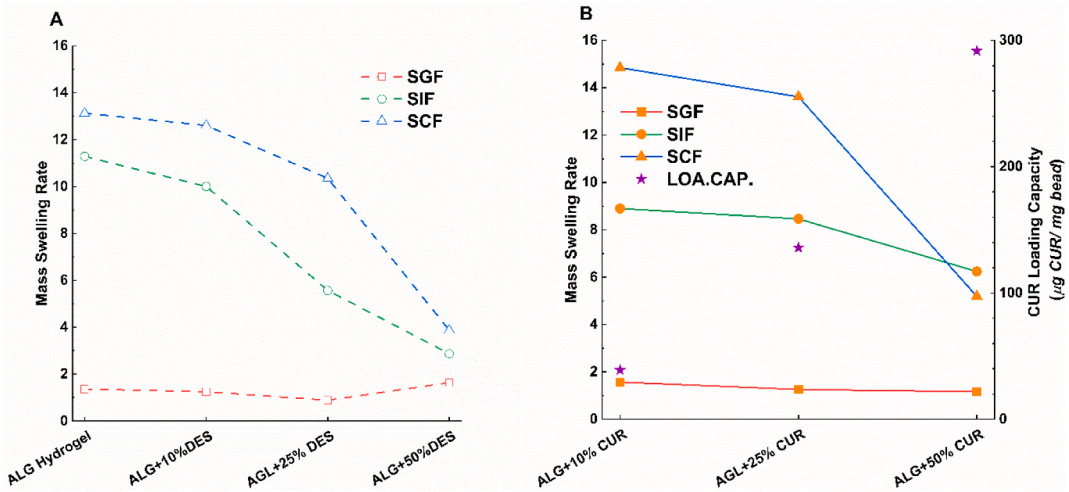


Fig. 5. (A) Swelling ratios by weight of DES-loaded hydrogel beads. (B) CUR loading capacity values and swelling ratios by weight of CUR-DES-loaded hydrogel beads in three different simulated gastrointestinal fluids (SGF, SIF, and SCF).

therapeutic efficacy of curcumin.

3.5. Structural analyses and SEM imaging of hydrogel beads

In order to investigate the effect of DES and CUR-DES loading on the morphology of beads, scanning electron microscopy (SEM) images of empty (containing only calcium alginate and chitosan), DES-containing and CUR-DES-containing hydrogel bead samples were obtained. SEM images of hydrogel beads loaded only with DES and CUR-DES-loaded are given in Figs. 6 and 7, respectively.

In beads containing only DES, it was observed that the average bead diameter decreased due to the increasing DES content. It can be said that this situation is due to the decrease in the total amount of polymer in the system with the increasing DES ratio. It was also confirmed by SEM analyses that the beads were organized as elliptical spherical structures. It is thought that the curved protrusions observed on the outer surface of the beads are the result of the hardening and dense packing that develops due to the vacuum drying process. Such tightly packed and rigid structures have been reported in the previous literature for hydrogel beads dried under vacuum conditions (J. M. Silva et al., 2021).

Similarly, compact and rigid outer surface morphologies were observed in beads containing CUR-DES. It can be interpreted that the surface defects formed in these beads are related to the rapid water removal process in the first stage of vacuum drying. Indeed, it has been reported that small particles can form on the outer surface of hydrogel beads in both vacuum drying and freeze-drying processes (J. M. Silva et al., 2021). It is thought that these particles are formed by the diffusion of water out of the hydrogel during the drying process, causing the CUR dissolved in DES to precipitate and accumulate as agglomerates on the surface. The observed structures indicate these agglomerates.

3.6. In vitro drug release tests and release kinetics

In vitro drug release experiments were performed by adding vacuum-dried hydrogel beads into three different SGIF liquids and incubating them. The dry hydrogels were released in capped glass tubes using a magnetic stirrer in a water bath. Photographs of the release media taken at different time intervals are given in Supplementary Fig. S6.

According to the microscopic and optical imaging findings, it was seen that the hydrogels were generally completely disintegrated

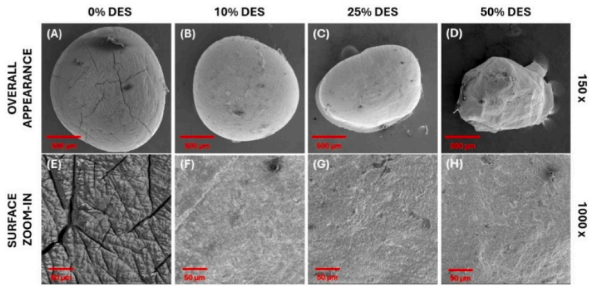


Fig. 6. SEM images of the outer surface overviews of the hydrogel beads loaded with DES only, at 500 μm (A-D) and 50 μm (B–H).

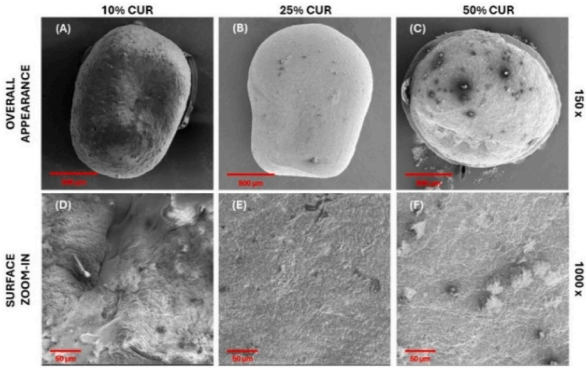


Fig. 7. External surface general views of CUR-DES loaded hydrogel beads, 500 μm (A-C) and 50 μm (D-F) SEM images.

after 4 h. Therefore, cumulative CUR release amount measurements were performed from the moment of observation to 240 min. Graphs showing the CUR release amounts (in μg) measured against time for three different SGIF liquids are presented in Fig. 8.

Experiments showed that CUR release increases significantly with increasing CUR-DES mass fraction. The highest cumulative CUR release amounts for all three release media were measured in 50% (*w/w*) hydrogels. However, increasing pH values were observed to have an increasing effect on CUR release. In the measurements performed, the maximum amount of CUR were measured as 3.02 μg, 5.03 μg and 7.15 μg in low pH (pH 1.2 ± 0.1 for SGF) medium in 10%, 25% and 50% (*w/w*) beads after 240 min, respectively. These values are well below the maximum release values in high pH medium. Optical imaging (Supplementary Fig. S6) showed that the beads maintained their structural integrity in low pH medium throughout the release process. According to these findings, it can be said that CUR is protected from the degradative effects of body environments with low pH with the current encapsulation method. On the other hand, it is observed that cumulative CUR release amounts increase with increasing pH values. This effect is a natural result of the pH-sensitive swelling behavior of ALG-CHI hydrogel beads, as reported in the literature (Dai et al., 2008; Wang et al., 2023). It is observed that CUR release increases with increasing CUR-DES weight fraction at the same pH. The reason for the sudden increase between the release values from 25% to 50% in SIF and SCF environments can be attributed to the hydrogel bead walls, which become thinner and weaker as the DES fraction increases, disintegrate more easily at this pH. Early peaks were observed in cumulative CUR release values due to the disintegration of hydrogel beads observed in release tests conducted in high pH environments after certain periods and in microscope images. This is called 'disintegration release'. In 50% (*w/w*) hydrogels, degradation release was observed at 60 and 30 min in SIF (26.01 μg) and SCF (29.31 μg). After this point, a plateau region in the concentration occurred. It is observed that the release system reached equilibrium after 4 h in high pH environments and after 8 h in low pH environments.

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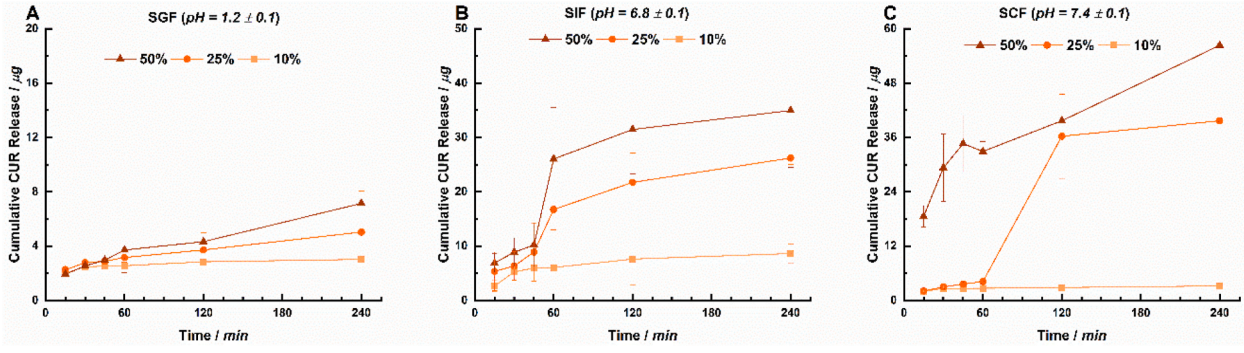


Fig. 8. Cumulative CUR release amounts versus time for vacuum-dried hydrogel beads in (A) simulated gastric fluid (SGF), (B) simulated small intestinal fluid (SIF), and (C) simulated large intestinal fluid (SCF).

release values from 25% to 50% in SIF and SCF environments can be shown as the hydrogel bead walls, which become thinner and weaker as the DES fraction increases, disintegrate more easily at this pH. Early peaks were observed in cumulative CUR release values due to the disintegration of hydrogel beads observed in release tests conducted in high pH environments after certain periods and in microscope images. This is called 'disintegration release'. In 50% (*w/w*) hydrogels, degradation release was observed at 60 and 30 min in SIF (26.01 μg) and SCF (29.31 μg). After this point, a plateau region in the concentration occurred. It is observed that the release system reached equilibrium after 4 h in high pH environments and after 8 h in low pH environments.

The release kinetics of CUR from the ALG-CHI hydrogel bead system were evaluated across simulated gastric (SGF), intestinal (SIF), and colonic (SCF) fluids using four mathematical models: Zero-order, First-order, Higuchi (1963), and Korsmeyer-Peppas (Korsmeyer et al., 1983). The graphics of various kinetic models were given in Supplementary Fig. S7.

Regression analysis indicates that the cumulative release profiles for all three formulations exhibit poor adherence to the Zero-order matrix model in SGF and SIF. The release data exhibited a strong correlation with the Higuchi and Korsmeyer-Peppas models during the initial stages, particularly when the structural integrity of the hydrogel matrix was maintained. However, for the 50% (*w/w*) CUR-DES loaded formulations, significant deviations from these classical kinetic models were observed in SIF and SCF media due to rapid matrix erosion and the resulting 'burst release' mechanism. While the early stages of release follow a predictable diffusion-relaxation path, the subsequent rapid breakdown of the polymer network in high-pH environments explains the lower values observed in these specific series, as the systems transition from matrix-controlled diffusion to a total disintegration phase. The high correlation coefficients derived from the Higuchi plots confirm that the depletion of the hydrophobic curcumin payload is predominantly governed by a classical matrix-controlled diffusion gradient through the biopolymeric network. The formulation components used in this work, including choline chloride-based DES systems, alginate, and chitosan, have previously been investigated in pharmaceutical and biomaterial-related applications (Paiva et al., 2014; Zainal-Abidin et al., 2019). In addition, Silva et al. (2021) reported the use of therapeutic deep eutectic solvents in alginate–chitosan hydrogel systems for curcumin encapsulation.

In the upper gastrointestinal environments, the release kinetics are characterized by the diffusion exponent (*n*) values extracted from the Korsmeyer-Peppas model. In gastric conditions (pH 1.2), 10, 25, and 50% (*w/w*) CUR-DES-loaded beads showed values (slopes) of 0.142, 0.298, and 0.433, respectively. According to established literature, these values correspond to Fickian diffusion (Korsmeyer et al., 1983). This indicates that the ALG-CHI system effectively suppresses burst release in the acidic environment of the stomach due to the stability of the polyelectrolyte complex.

In intestinal conditions (pH 6.8), the values for the 25% and 50% (*w/w)* formulations shifted to 0.643 and 0.668, respectively. These values ($0.43<n<0.85$) indicate a transition toward non-Fickian or anomalous transport, so-called Case II (relaxational) transport where both diffusion and polymer relaxation/swelling contribute to the release process (Ristic et al., 2024; Kavousi et al., 2018).

A significant kinetic shift occurs when the hydrogel beads are exposed to Simulated Colonic Fluid (SCF). For the highest loading formulation (50% (*w/w)* CUR-DES), the Korsmeyer-Peppas plot recorded a significant increase in the slope, reaching an *n* value of 1.24. In drug delivery kinetics, an *n* value greater than 0.89 represents a Super Case-II transport mechanism. This behavior is driven by the structural relaxation, extensive swelling, and erosion of the alginate-chitosan network in colonic conditions, facilitating a rapid release of the remaining payload.

3.7. Evaluation of greenness assessment

The originality of our study lies in the development of a new generation DES to overcome the limited solubility and bioavailability issues of curcumin, an important antioxidant compound. At the same time, this system was adapted to a polymeric platform to be used for release applications. For the *in vitro* tests of the study, curcumin release experiments were carried out in artificial gastric fluids (SGF) under relevant conditions. In these systems, curcumin concentrations were determined by HPLC analysis. Although acetonitrile was used in the HPLC mobile phase for curcumin quantification, it was limited only to the analytical step and was not involved in the preparation of the DES formulations or hydrogel systems. Nevertheless, its use reduces the overall greenness of the analytical method, and greener chromatographic alternatives may be considered in future studies.

Another important aspect of the work is that the processes employed are fully compatible with sustainability and largely in line



Fig. 9. AGREEPrep Analysis result of CUR encapsulated bead preparation procedure.

with the principles of green chemistry. Therefore, both the sample preparation and analytical stages were evaluated using appropriate greenness assessment tools. For accurate evaluation of the processes, the preparation of curcumin-loaded beads was assessed using the AGREEPrep software, while the subsequent *in vitro* curcumin analysis process was evaluated with the AGREE software. In the AGREEPrep evaluation, all steps were considered with default equal weighting (3).

The AGREEPrep analysis of the CUR-loaded hydrogel bead preparation is presented in Fig. 9 and demonstrated that the method is highly green and sustainable. The major factors contributing to the high sustainability score were the complete absence of toxic or hazardous chemicals, the use of renewable or sustainable resources for almost all components, and the lack of waste generation during the process. The main limiting factors for sustainability were identified as moderate energy consumption and the semi-automated, four-step nature of the method.

The AGREE analysis of the HPLC-PDA method for curcumin determination is presented in Fig. 10 and yielded a score of 0.6, indicating a moderate level of environmental sustainability. Considering the chromatographic conditions employed, solvent consumption (48 mL per injection), and analysis time (30 min), the method could be further improved, particularly in terms of the mobile phase composition especially due to the use of acetonitrile, a solvent with known toxicity and its overall consumption. In contrast, the analysis time, energy usage, and waste generation were found to be within acceptable limits. Overall, these findings suggest that the method offers a balanced profile in terms of both analytical performance and environmental impact.

4. Conclusion

The main rationale behind the search for alternative solvents for curcumin lies in its extremely poor solubility in aqueous environments (8 μg/mL), which is a critical parameter for improving its bioaccessibility. Furthermore, its solubility in common hydrophilic solvents remains limited (e.g., 4.17 mg/mL in ethanol). In the present work, the solubilizing abilities of various deep eutectic solvent (DES) and cosolvent formulations for curcumin (CUR) were investigated, followed by the encapsulation of high-concentration curcumin solutions and their performance in different *in vitro* release media.

Among the formulations studied, the choline chloride and 1,2-propanediol (CC–PD, 1:2) mixture exhibited the highest solubility for CUR (19.74 mg/mL). However, this formulation demonstrated limited stability at room temperature. Although previous studies attempted to overcome this by modifying the component ratios, such approaches led to decreased CUR solubility. To address this issue, ethanol was introduced as a cosolvent, providing not only enhanced physicochemical properties but also improved CUR solubility.

The optimal DES–cosolvent composition was achieved at a 1:2:2 M ratio of CC–PD–EtOH (DES 7). The incorporation of ethanol significantly reduced the viscosity from 94.1 cP to 17.2 cP and increased CUR solubility from 19.74 mg/mL to 26.82 mg/mL, highlighting a synergistic effect of the cosolvent addition.

Encapsulation of the DES-based CUR solution was successfully carried out using alginate–chitosan hydrogel beads with 10%, 25%, and 50% mass loading ratios. In vitro release studies revealed that the highest CUR release occurred in simulated colonic fluid (SCF, pH 7.4), with a maximum cumulative release of 29.31 μg observed for the 50% CUR–DES-loaded beads. These findings demonstrate the potential of DES-based encapsulation systems for targeted and controlled drug delivery applications. The kinetic findings validate the smart, pH-responsive performance of these formulations. The ALG-CHI system remains relatively stable in the upper gastrointestinal tract (SGF/SIF) due to physical cross-linking and ionic interactions between the polymers. However, it undergoes rapid relaxation and erosion in colonic conditions (SCF), ensuring colon-targeted delivery. This targeted release profile is essential for improving the bioavailability of lipophilic compounds like curcumin, which otherwise suffer from poor solubility and rapid metabolism in the small intestine.

In conclusion, this study presents a promising solvent system for curcumin with enhanced solubility, improved physicochemical stability, and successful encapsulation performance. The ability of these systems to protect CUR in acidic environments while enabling controlled release in higher pH conditions highlights their applicability in targeted gastrointestinal delivery.

Additionally, greenness assessment using AGREE and AGREEprep tools confirmed the sustainability and environmental compatibility of the developed formulation. In future studies, these HDES-based encapsulation release systems are thought to be valuable for use in more detailed *in vitro* and *in vivo* studies.

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CRediT authorship contribution statement

Yahya Baş: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Adalet Nur Altunkaya:** Data curation, Formal analysis, Investigation. **Melisa Lalikoğlu:** Investigation, Methodology, Writing – original draft. **İrem Zehra Kublay:** Formal analysis. **Mustafa Bener:** Data curation, Formal analysis, Writing – original draft. **Yavuz Selim Aşçı:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft.

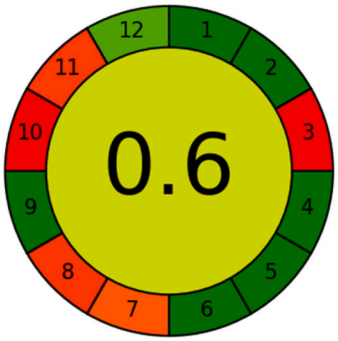


Fig. 10. AGREE Analysis result of HPLC-PDA analysis of curcumin.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Yavuz Selim ASCI reports financial support was provided by Istanbul University. If there are other authors, they 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.scp.2026.102469.

Data availability

Data will be made available on request.

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