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Preparation and Evaluation of Water-Soluble Curcumin-Cyclodextrin-PVP Inclusion Complexes

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Abstract

Curcumin, the principal bioactive constituent of turmeric, has attracted considerable interest because of its therapeutic attributes, which encompasses anti-inflammatory, antioxidant, and antimicrobial effects. Nonetheless, its clinical utilization is impeded by inadequate water solubility and diminished bioavailability. This research sought to improve the solubility and antimicrobial efficacy of curcumin by creating inclusion complexes with *β*-cyclodextrin and polyvinylpyrrolidone. Curcumin-*β*-cyclodextrin-polyvinylpyrrolidone complexes were formulated using the kneading method with different polyvinylpyrrolidone concentrations (0.5%, 1%, and 1.5%). Solubility investigations revealed that the 1.5% polyvinylpyrrolidone complex demonstrated a 30-fold increase in solubility relative to pure curcumin. UV-visible spectrophotometry validated the enhancement of solubility, whereas optical microscopy and particle size analyses underscored the uniformity and stability of the complexes. The dissolution profile of the optimized complex demonstrated markedly improved drug release under physiological conditions. Additionally, antimicrobial assays revealed enhanced efficacy of curcumin-curcumin-*β*-cyclodextrin-polyvinylpyrrolidone complexes against Gram-positive bacteria, specifically *Staphylococcus aureus* and *Enterococcus faecalis*. The findings indicate that Curcumin-*β*-cyclodextrin-polyvinylpyrrolidone inclusion complexes present a viable approach to address the solubility and bioavailability issues of curcumin, facilitating its broader use in pharmaceutical formulations.

Keywords

β-Cyclodextrin, curcumin, polyvinylpyrrolidone, solubility enhancement, spectrophotometry.

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INTRODUCTION

Turmeric (*Curcuma longa*), widely known as the "golden spice" or "Indian saffron," has been a cornerstone of traditional medicine and cultural practices for over 4,000 years, originating from the Vedic culture in India. Its therapeutic value lies in curcumin (CUR), the primary bioactive compound responsible for its vibrant yellow color and extensive medicinal applications. CUR has garnered significant scientific interest for its potent anti inflammatory, antioxidant, antibacterial, and anticancer properties, making it a subject of extensive research in contemporary biomedical science (Hewlings and Kalman, 2017).

CUR, a hydrophobic molecule with a log P of 3.2, is practically insoluble in water and has a short half-life of approximately 10 minutes in phosphate buffer at physiological (pH 7.4) due to its instability in alkaline conditions (Hegde et al., 2023).

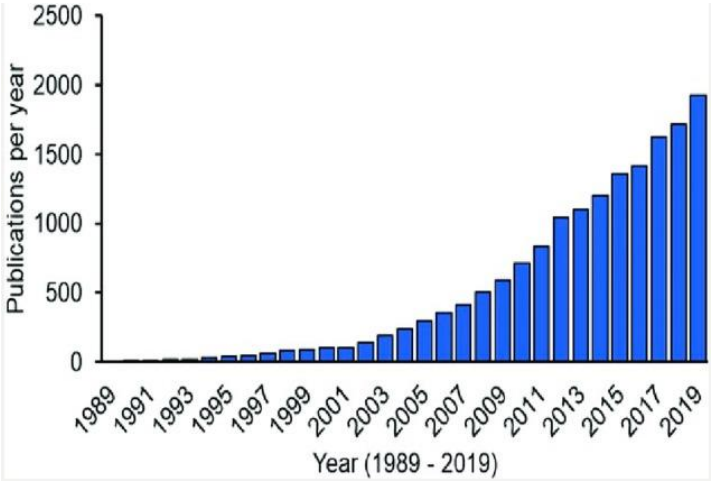


Figure 1: The number of publications indexed by “PubMed” with the topic “curcumin during the last three decades.

As shown in Figure 1, Turmeric and its active component, CUR, have been extensively studied, with nearly 7,000 publications on Turmeric and over 20,000 on CUR indexed in PubMed. (Kunnumakkara et al., 2023).

Turmeric is recognized as a safe food ingredient by the United States Food and Drug Administration (FDA). Turmeric's therapeutic potential has been documented since 1876 when its flower was first reported effective against gonorrhea. Since then, turmeric has been reported for its efficacy against various chronic diseases, including skin conditions, respiratory and gastrointestinal disorders, aches, wounds, sprains, and liver malfunctions. Reports indicate that CUR, along with its

derivatives demethoxycurcumin and bisdemethoxycurcumin, is non-toxic even at high doses of up to 12,000 mg/day. CUR's antibacterial activity was first reported in 1949 when it was shown to inhibit the growth of *Staphylococcus aureus*. Beyond its antimicrobial effects, CUR is recognized for its broad pharmacological benefits, including anti inflammatory, antioxidant, antimutagenic, immunomodulatory, and chemotherapeutic properties. It effectively scavenges reactive oxygen species (ROS), mitigating inflammation and playing a regulatory role in the pathophysiology of chronic diseases by modulating key signaling pathways and enzymes. These attributes underscore CUR's potential as a versatile therapeutic agent for combating infections and chronic disorders (Kunnumakkara et al., 2019; Lao et al., 2006; Schraufstätter and Bernt, 1949).

Despite its potential, CUR's effectiveness is significantly limited due to its poor water solubility, instability in aqueous environments, and rapid breakdown in the body, resulting in low bioavailability (Stohs et al., 2020).

Developing novel strategies to enhance CUR's solubility and stability remains a critical focus for researchers aiming to maximize its therapeutic potential. To achieve this, various formulation approaches can be employed to improve CUR's stability, solubility, and bioavailability. These strategies which are widely used to enhance its physicochemical properties include nanoemulsions, liposomes, and nanoparticles (Figure 2). Additionally, cyclodextrin inclusion complexes, particularly with *β*-cyclodextrin (*β*-CD), are effective encapsulation agents that significantly improve CUR's solubility and stability.

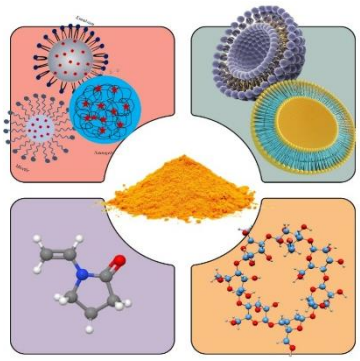


Figure 2: Strategies for increasing curcumins aqueous solubility**.**

Incorporating polyvinylpyrrolidone (PVP) as an excipient further enhances the pharmacokinetic profile of CUR. PVP, a water-soluble polymer, serves as a stabilizing agent by preventing complex precipitation and improving dispersibility

in aqueous environments. This contributes to enhanced formulation stability and improved bioavailability, enabling more efficient absorption of CUR in the body.

Furthermore, the use of cyclodextrins, cyclic oligosaccharides with a well-established ability to enhance the solubility and stability of hydrophobic drugs, is a promising strategy. β-CD, in particular, is known for its ability to form inclusion complexes with poorly soluble molecules, encapsulating them within its hydrophobic cavity while maintaining an outer hydrophilic shell, which improves both stability and solubility. By combining these innovative strategies, CUR can be delivered more effectively, enhancing its therapeutic efficacy (Aiassa et al., 2023; Loftsson and Brewster, 2010b; Sarabia-Vallejo et al., 2023). The synergistic use of β-CD and PVP has shown promise in enhancing the solubility and functional properties of various bioactive compounds.

Even with recent progress, the potential of β-CD and PVP inclusion complexes to boost CUR's solubility and antimicrobial activity has not been fully explored. Previous studies have primarily focused on solubility improvements, with limited emphasis on functional evaluations such as antimicrobial activity (Loftsson and Brewster, 2010a; Schoeman et al., 2024; Stohs et al., 2020). The present study seeks to bridge this gap by not only enhancing CUR's solubility but also evaluating its functional bioactivity including antibacterial assays to assess the functional efficacy against common pathogenic bacteria.

This research stands out for its comprehensive method, merging the solubility-enhancing properties of β-CD and PVP with practical evaluations to showcase the potential of these complexes as cutting-edge drug delivery systems. The primary objective of the study is to develop and characterize CUR-β-CD-PVP inclusion complexes, quantify their impact on solubility, and evaluate their antimicrobial properties. By addressing both the physicochemical and biological aspects of CUR enhancement, the present study aims to contribute to the development of efficient CUR-based formulations, paving the way for broader applications in the pharmaceutical and biomedical fields.

MATERIALS AND METHODS

Materials

Curcumin for synthesis was obtained from Merck (Darmstadt, Germany), methanol was purchased from Merck (Darmstadt, Germany), *β*-Cyclodextrin was obtained from Sigma Aldrich (Saint-Quentin Fallavier, France), PVP K-30 was purchased from Zag Kimya cosmetic grade (Turkiye) and cellulose acetate syringe filters with a pore size of 0.45 µm were from ISOLAB (Eshau, Germany). Studies were conducted using distilled water.

Preparation of curcumin *β*-Cyclodextrin-PVP complex

As shown in Table 1, three formulations were prepared using the kneading method. Precisely weighed quantities of CUR, *β*-CD, and PVP were combined in a mortar. A mixture of water and methanol in a 1:1 ratio was incrementally added to the components, forming a paste. The resulting paste was subjected to drying in an oven maintained at a temperature not exceeding 50°C for a duration of 10 minutes. After drying, the powder was sieved sequentially through 2 mm and 1 mm mesh sieves to ensure uniform particle size.

Table 1: Composition of CUR, PVP, and *β*-CD in each formulation.

	Curcumin	*β*-Cyclodextrin	PVP
Formulation 1	0.364 g	2.70 g	0.5% (0.015 g)
Formulation 2	0.364 g	2.70 g	1% (0.030 g)
Formulation 3	0.364 g	2.70 g	1.5% (0.045 g)

Determination of curcumin content by UV-VIS spectrophotometry

Quantification of CUR in inclusion complexes was analyzed spectrophotometrically using a Shimadzu UV-1800 Spectrophotometer (Shimadzu Corporation, Japan). Standard solutions of pure CUR were prepared in methanol at concentrations ranging from 0.3 to 7.2 µg/ml. The absorbance of the standard solutions was measured at 424 nm.

The quantification of curcumin in inclusion complex by UV-VIS spectrophotometry

To quantify the CUR content in the inclusion complex, 10 mg of the prepared complexes were dissolved in 100 mL of methanol, which was then filtered through a 0.45 MM membrane filter. The necessary dilutions were made, and the absorbance was measured using a UV-visible spectrophotometer.

Solubility studies

For this purpose, excessive amounts of the CUR and previously prepared three formulations were placed in glass test tubes separately, and distilled water was added to each tube to reach 2 ml. After shaking at

120 rpm in an aqueous shaker at 37ºC for 24 hours, the samples were centrifuged at 4000 rpm for 30 minutes. The upper solution was filtered through a 0.45 µm membrane filter, diluted with methanol, and the concentrations were calculated via UV- spectrophotometry (Pozharani et al., 2023).

Characterization studies of curcumin-loaded cyclodextrin complexes

Optical microscopy analysis

The surface morphologies of the physical mixture and CUR-loaded *β*-CD complexes were examined using an optical microscope (OLYMPUS-CX21FS1, Olympus Cor., Japan). Samples were mounted onto clean glass slides and observed under 45x magnification. Images were captured using a high-resolution Canon EOS R digital camera (Canon Inc., Japan).

For enhanced analysis, small fragments of the particles were compressed between two glass slides to create uniform layers, improving visibility. High-resolution images were processed with imaging software to extract detailed morphological features. This systematic approach provided valuable insights into the surface texture, particle size, and structural characteristics of CUR, the physical mixture, and their *β*-CD complexes (Patil et al., 2024).

Particle size distribution, polydispersity index, and zeta potential analysis

Freshly prepared formulations were diluted with distilled water, and their particle size and size distribution were analyzed using a Malvern Zetasizer (Malvern Panalytical Ltd., Malvern, UK) at 25°C. The measurement was conducted to ensure uniformity and consistency in the particle size of the formulations.

For zeta potential analysis, the aqueous suspensions were prepared at a specific concentration and assessed at 25°C using the same Malvern Zetasizer. The measurements utilized a 173°C detection angle to enhance the sensitivity of dynamic light scattering, providing accurate data on the surface charge and stability of the particles within the suspension (Mashaqbeh et al., 2021a).

***In-vitro* dissolution studies**

The dissolution profiles of CUR-*β*-CD: 1.5% PVP complex were compared to pure CUR to assess the impact of complexation on drug release behavior. Dissolution testing was conducted using a USP Type-II (paddle) dissolution apparatus (SOTAX, Switzerland). A 10 mg sample of CUR and an equivalent 10 mg of CUR from the chosen formulation were placed in 900 mL of deionized water at 37 ± 0.5°C, with stirring set at 100 rpm to simulate physiological conditions. For additional testing, simulated intestinal fluid (SIF) was prepared using phosphate buffer at pH 6.8 and 0.1% Tween 80 to replicate small

intestinal conditions. The volume of the dissolution medium was maintained at 900 mL, and the stirring speed was set to 100 rpm at 37°C. At predefined intervals (2, 6, 10, 15, 20, 30, 40, 60, 90, and 120 minutes), 5 mL aliquots were withdrawn using a syringe and filtered through a 0.45 μm PES disc filter. The samples were then appropriately diluted, and CUR concentration was analyzed using UV spectrophotometry. 5 mL of fresh medium was added after each withdrawal to maintain the dissolution medium volume. The experiments were conducted in triplicate to ensure the accuracy and reproducibility of the results (Hagbani and Nazzal, 2017; Jafar et al., 2020a; Mashaqbeh et al., 2021a).

Antibacterial activity

Determination of minimum inhibitory concentration (MIC)

The antimicrobial activities of CUR and its combination with *β*-CD were established by broth microdilution technique. The antibacterial activity was investigated against *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, and *Klebsiella pneumoniae* ATCC 700603. The inoculum of each bacterial strain was standardized to 1 x 10^6 cfu/mL, with the final sample concentrations varying from 4 to 0.125 mg/ml. The maximum concentration of samples in Mueller Hinton broth served as a negative control, whereas ciprofloxacin was employed as a positive control. Incubation was carried out for 18 hours at 37°C. The MIC was determined as the lowest concentration of the samples that inhibited the growth of each bacterial strain.

FTIR analysis of curcumin-cyclodextrin-PVP complexes

Infrared (IR) spectra of the formulation components, including pure CUR, β-CD, PVP, the physical mixture, and their supramolecular complex formulation, were recorded using a Shimadzu FTIR-8400s spectrophotometer (Japan). The formation of inclusion complexes was assessed by comparing the IR spectra of the solid complexes with those of the physical mixture containing an equivalent amount of curcumin.

To ensure consistency, the ratio of curcumin to potassium bromide (KBr) remained constant throughout the experiment. Accurately weighed samples and KBr were finely ground, mixed thoroughly, and compressed into pellets for spectrophotometric analysis. The spectra were scanned over a range of 4000–400 cm^{-1} at a resolution of 2 cm^{-1}, allowing for precise identification of functional group interactions and structural changes indicative of complex formation (Mohan et al., 2012; Zhang et al., 2016).

RESULTS AND DISCUSSION

The quantification of curcumin in inclusion complex by UV-VIS spectrophotometry

The calibration curve was established with a linear regression equation y=0.1642x−0.0035 and a high correlation coefficient (r2=0.9998). The spectrophotometric method's validation for the main parameters like assessing linearity, accuracy, precision, repeatability, the limit of detection (LOD), and the limit of quantification (LOQ) was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Accuracy was determined to be 95.73 ± 7.45%, and the linearity range was confirmed as 0.3–7.2 µg/ml. The LOD and LOQ values were calculated as 0.2236 µg/mL and 0.6776 µg/mL, respectively (Figure 3 and Table 2).

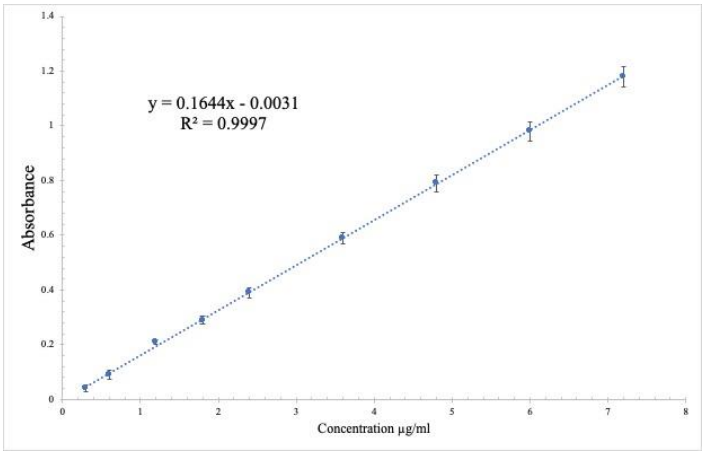


Figure 3: Calibration curve of curcumin.

Table 2: The spectrophotometric method's validation parameters.

Parameter	Value
Accuracy	95.73 ± 7.45
Slope	0.164
Intercept	0.003
Linearity range	0.3 – 7.2 µg/ml
Correlation coefficient (r)	0.999
SE of intercept	0.003
SD of intercept	0.011
LOD	0.224
LOQ	0.677

*SE: Standard Error SD: Standard Deviation; LOD: Limit of detection; LOQ: Limit of quantification.

Pursuant to the construction of the calibration curve, the concentration of CUR in each formulation was quantified via an assay. The recovery percentages illustrated in Figure 4 adhere to pharmacopeial standards.

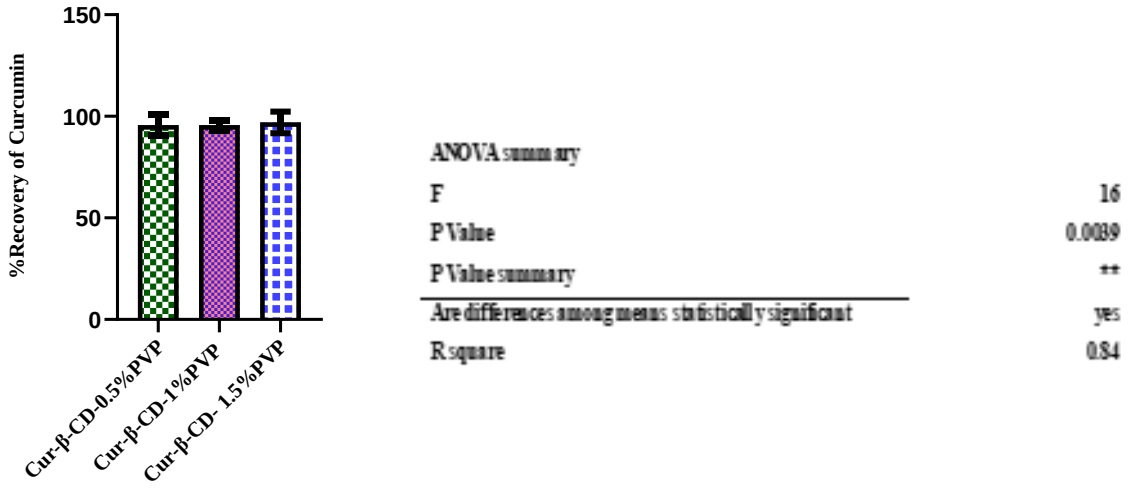


Figure 4: Recovery % of CUR-*β*-CD: 0.5% PVP ; CUR-*β*-CD: 1% PVP; CUR-*β*-CD-1.5% PVP.

Solubility studies

As shown in Figure 5, the aqueous solubility of pure CUR and the CUR-*β*-CD inclusion complex were measured and a notable 30-fold enhancement in CUR solubility through complexation was detected, confirming the 31-fold increase previously documented by Mangolim et al.(2014). The increased solubility of CUR upon the formation of the CUR-*β*-CD inclusion complex was further confirmed by UV-Vis spectroscopy, demonstrating a significant enhancement in solubility relative to pure CUR (Mangolim et al., 2014b). It has been noted that the sample with the highest PVP ratio demonstrated the most significant enhancement in solubility. Therefore, the CUR-*β*-CD: was 1.5% PVP used for further analysis (Jafar et al., 2020b).

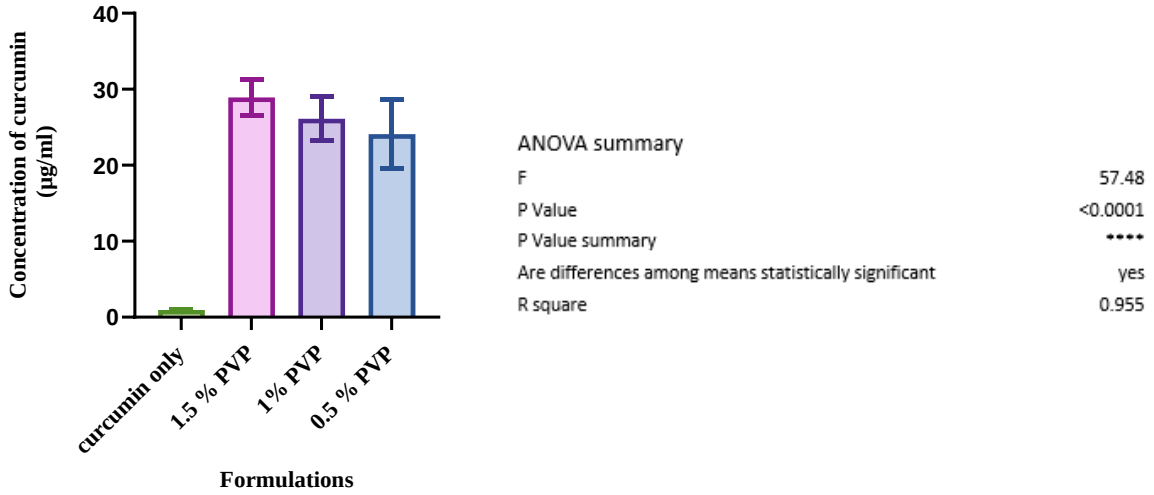


Figure 5: Solubility test of curcumin in comparison with three formulations.

Characterization studies of curcumin-loaded cyclodextrin complexes

Spectral insights from FTIR analysis of curcumin-cyclodextrin-PVP complexes

The FTIR spectra in Figure 6 illustrate the profiles of pure CUR, essential polymers (β-CD and PVP), their physical blends (1:1:1), and the selected formulation. The analysis identified characteristic peaks for CUR, including the phenolic O–H stretching vibration at 3505.6 cm^{-1}, the C=C stretching at 1628 cm^{-1}, the C=O and C=C vibrations at 1508.4 cm^{-1}, and the olefinic C–H bending vibration at 1427.6 cm^{-1}. These findings are all consistent with literature reports. For PVP, the presence of the C=O stretching band at 1650 cm^{-1} and CH_2 stretching vibrations between 2800–3000 cm^{-1} confirmed its polymer structure. Similarly, β-CD exhibited a broad O–H stretching peak between 3100–3500 cm^{-1}, an indicative of hydroxyl groups, and C–O–C stretching vibrations within 1020–1150 cm^{-1}, a characteristic of its ether linkages (Mangolim et al., 2014a; Rahma et al., 2016).

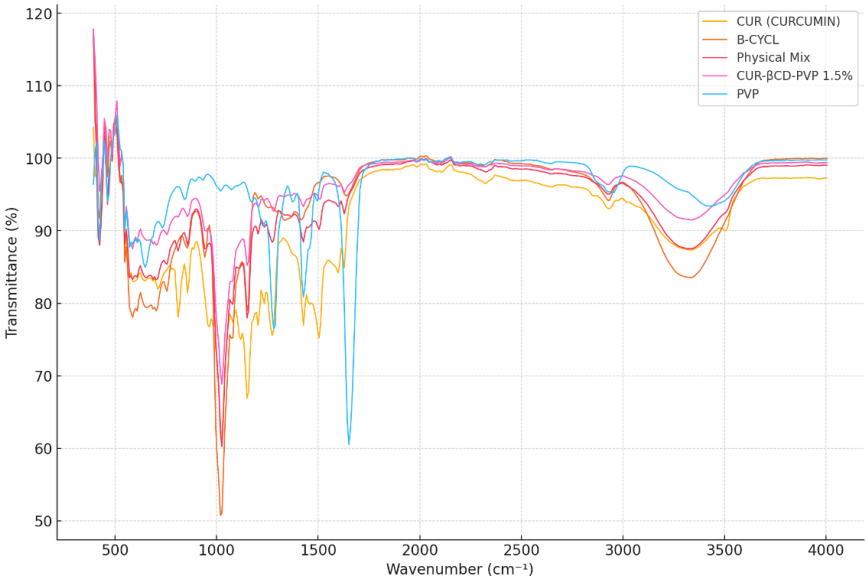


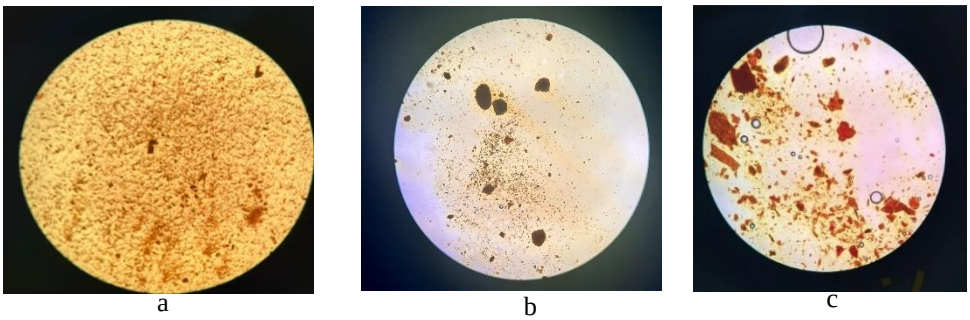
Figure 6*:* FT-IR spectrum of CUR, *β-CD,* PVP, drug-polymer physical mixture (1:1:1, w/w/w) and selected formulation.

The physical mixture displayed a combined spectrum featuring peaks from CUR, *β*-CD, and PVP. A slight weakening of CUR's characteristic peaks was observed in the physical blend and the formulation, likely due to the dilution effect of the polymers. However, the absence of significant peak shifts suggests no notable chemical interactions occurred between the drug and polymers in these preparations.

Optical microscopy analysis

The optical microscopy analysis revealed distinct differences in the surface morphology among CUR, physical

mixture, and CUR-loaded *β*-CD complexes. CUR appeared as irregularly shaped crystalline particles while the physical mixture displayed a heterogeneous composition with separate regions of CUR and *β*-CD. In contrast, the cyclodextrin complexes exhibited a more uniform and smoother surface texture, indicating the successful inclusion of CUR within the cyclodextrin cavities (Figure 7). These observations suggest a significant alteration in the physical properties of CUR upon complexation, which may enhance its solubility and stability for potential pharmaceutical applications (Yallapu, 2010).



a b c

Figure 7: Images of a) Pure CUR b) Physical mixture c) CUR-*β*-CD: 1.5 %PVP.

Particle size, polydispersity index (PDI) and zeta potential

The particle size analysis revealed that the average particle size of the prepared formulations was 463.6 ± 30.19 nm, with a PDI of 0.472. These values suggest a moderate particle size distribution, indicating homogeneity in the formulation. The relatively small particle size aligns with expectations for enhanced drug delivery potential, particularly for topical applications, as smaller particles are associated with improved penetration and absorption. The smaller particle size observed in this study compared to typical cyclodextrin complexes could be attributed to factors like aggregate formation or the preparation method, highlighting the impact of formulation techniques on the final characteristics (Figure 8).

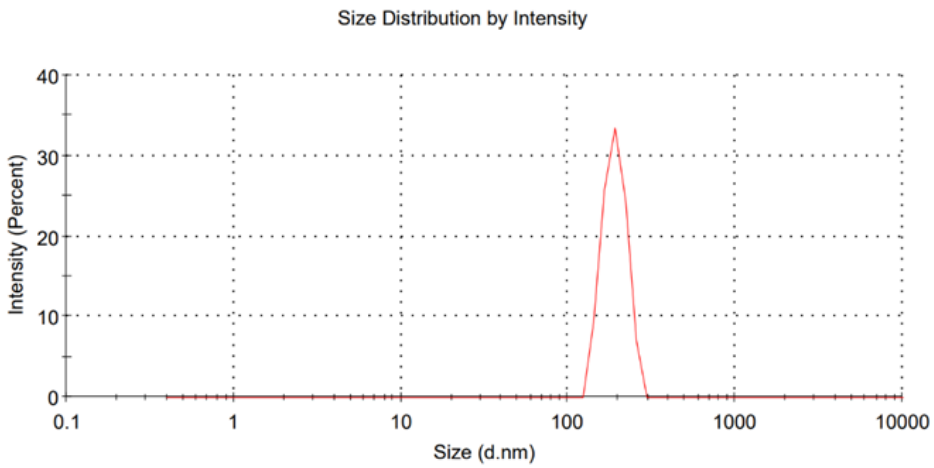


Figure 8: Size distribution by intensity of the CUR-*β*-CD: 1.5%.PVP.

The zeta potential measurements yielded a value of -13.3 ± 5.56 mV, indicating a negative surface charge (Figure 9). This result suggests that the formulation has modest electrostatic stability. The obtained zeta potential value implies that the formulation demonstrates adequate stability under the tested conditions. This finding is in agreement with a previous study which reported a similar trend in zeta potential values, highlighting the impact of cyclodextrin complexation on surface charge and stability (Mashaqbeh et al., 2021a).

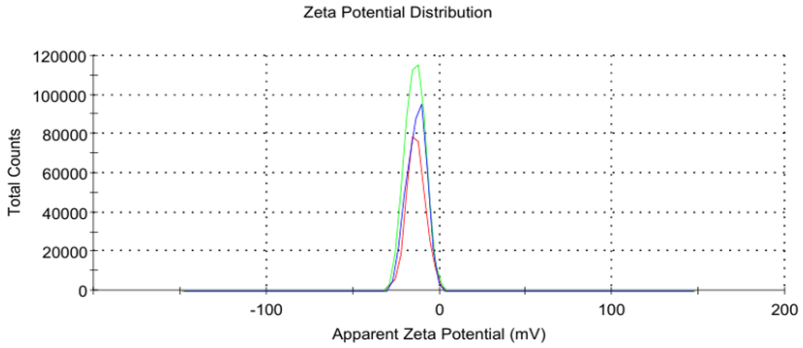


Figure 9: Zeta potential distribution of CUR-*β*-CD-1.5%.PVP.

These findings underscore the critical role of particle size, PDI, and zeta potential in determining the stability and functional performance of the formulations. Further studies are warranted to correlate these physicochemical properties with drug release profiles and therapeutic outcomes (Darandale and Vavia, 2013; Mashaqbeh et al., 2021b; Serri et al., 2017).

Dissolution studies

The in vitro dissolution profiles of CUR and the selected CUR-*β*-CD: %1.5 PVP complex, prepared using the kneading technique, demonstrates a superior enhancement in CUR's release (Figure 10).

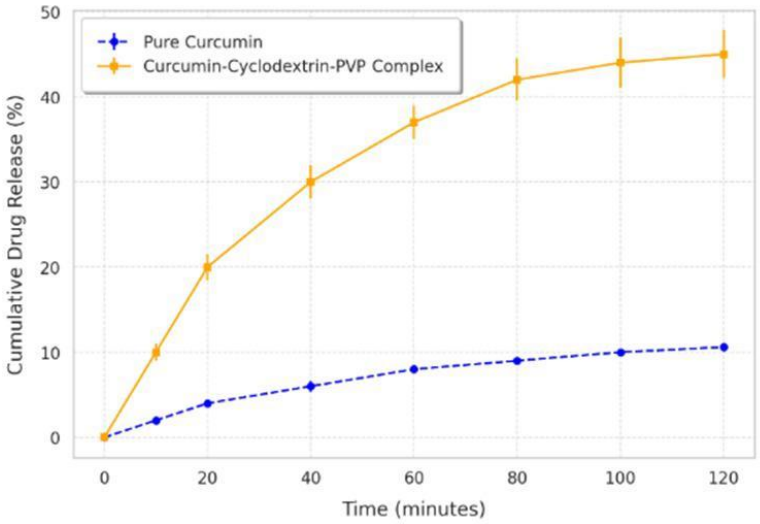


Figure 10: Comparative drug release profile of pure CUR and the CUR-*β*-CD-1.5% PVP in simulated intestinal fluid (pH 6.8) over 120 minutes.

The drug release profile of pure CUR demonstrated minimal release over 120 minutes, which can be attributed to its inherent poor aqueous solubility and strong hydrophobicity at near-neutral pH. Conversely, the *β*-CD-PVP inclusion complex showed significantly enhanced drug release, indicating the efficacy of this formulation in improving CUR's solubility and dissolution rate in a basic medium.

The enhancement in the release can be attributed to multiple factors: the ability of β-CD to encapsulate hydrophobic molecules, thereby increasing CUR's wettability and reducing its crystalline nature, and the auxiliary effect of PVP which acts as a solubilizing agent and further improves the dispersibility of the drug complex in the aqueous medium. Additionally, the greater ionization of the phenolic groups at pH 6.8 further enhances the solubility and release of CUR from the inclusion complex by increasing its hydrophilicity and reducing aggregation tendencies. These effects collectively reduce the thermodynamic barriers to dissolution.

This observed improvement highlights the potential of the *β*-CD-PVP inclusion system as a robust formulation strategy to address the solubility limitations of CUR under physiological pH conditions. Such advancements are crucial for developing efficient delivery systems for CUR, particularly for applications in topical or oral drug delivery systems (Hassan, 2018; Jafar et al., 2020a; Rezaei and Nasirpour, 2019).

Antibacterial activity of curcumin alone and in combination with cyclodextrin and PVP

In order to assess the antimicrobial activities associated with the CUR and CUR-β-CD combination, the microdilution

method was used to measure the MIC against *E. faecalis*, *S. aureus*, *E. coli*, and *K. pneumoniae* (Table 3). CUR revealed selective activity against Gram-positive bacteria including *S. aureus* (0.25 mg/mL) and *E. faecalis* (0.125 mg/mL). Furthermore, CUR, when combined with β-CD, demonstrated higher antibacterial activity with an MIC of 0.25 mg/ml against *S. aureus* and 0.0625 mg/ml against *E. faecalis*. However, no activity was observed against Gram negative bacteria (*E. coli*, and *K. pneumoniae).* This could be due to the structural difference in the cell wall of Gram positive and Gram negative bacteria. The outer lipopolysaccharide membrane found in Gram negative bacteria may act as a barrier for compounds containing antibacterial activity, making them intrinsically impermeable (Liscano et al., 2019).

Table 3: MIC of curcumin alone and in combination with cyclodextrin against Gram-negative and Gram-positive bacteria.

Agents		Gram positive bacteria		Gram negative bacteria	
		S. aureus **ATCC 25923**	***E. faecalis*** **ATCC 29212**	***E. coli*** **ATCC 25922**	***K. pneumoniae*** **ATCC 700603**
Sample (mg/mL)	Curcumin	0.25 ± 0	0.125 ± 0	>4	>4
Sample (mg/mL)	Curcumin +*β*- CD*	0.125 ± 0	0.0625	>4	>4
Control (mg/L)	Ciprofloxacin	0. 25 ± 0	1 ± 0.083	0.008 ± 0	0.25 ± 0.021

Data represented as the standard error of the mean (±S.E.M).
*CD-cyclodextrin.

CONCLUSION

The inclusion complexes of CUR with *β*-CD and PVP markedly improved the solubility and bioavailability of curcumin, mitigating its principal constraints as a medicinal agent. The improved formulation, including 1.5% PVP, exhibited a significant 30-fold enhancement in solubility, confirmed by UV-visible spectrophotometry and particle size characterization. The improved dissolving profiles and antimicrobial tests highlighted the effectiveness of these complexes, especially against Gram positive bacteria, including *S. aureus* and *E. faecalis*. The findings underscore the efficacy of *β*-CD and PVP inclusion complexes as delivery methods for curcumin, facilitating its broader utilization in pharmaceutical and biological domains. Subsequent studies may examine the practical application of the results and assess other functional characteristics of the formed complexes.

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