Original Article

Solubility and stability enhancement of curcumin: Improving drug properties of natural pigment

Abstract

Aim: Water insolubility, low potency, and instability are inherent problems of several herbal medicines. Identity, strength, quality, and purity of herbal products are further compromised during manufacturing and storage. The aim of present work was to evaluate solubility and stability of curcumin, a pigment obtained from dried rhizomes of plant *Cucrcuma longa*. **Materials and Methods:** The stoichiometric ratios for inclusion complexation of curcumin with various cyclodextrins (CDs) were determined by phase solubility analysis. Grinding, kneading, and freeze-drying were employed to determine optimum complexation. Complexes were evaluated for drug inclusion, solubility, and stability. **Results:** Stability constants were 11200 M^{-1}, 1557 M^{-1}, 2858 M^{-1}, and 2206 M^{-1} for α-, β-, γ-CD, and dimethyl β-CD (DIMEB), respectively, thus indicating good complex formation. Theoretical amounts of curcumin in binary products were between 80% and 97% with a maximum of 96.8% in curcumin-β-CD freeze-dried product. The complexation resulted in a marked improvement in the solubility of curcumin up to 60, 55, 56, and 1500 folds by α-, β-, γ-CD, and DIMEB, respectively. Inclusion complexation protected the drug from hydrolytic degradations as only 20–40% degradation was observed at the end of 8 h as opposed to >70% for pure curcumin. **Conclusion:** A significant improvement in the solubility and stability was observed with curcumin-CD complex as compared to pure curcumin.

Key words:
Curcumin, dimethyl β-cyclodextrin, solubility enhancement

Introduction

Quest for safer and natural option for treatment of diseases led about 80% of the world population to rely on herbal medicines accounting a global market of about 83 billion dollar of which India contributes < 1%.[1] Water insolubility, low potency, and instability are inherent problems of several herbal medicines. Identity, strength, quality, and purity of herbal products are further compromised during manufacturing and storage. Modification of the herbal drugs can deal with such issues to a large extent. Curcumin is a natural polyphenol, obtained from *Curcuma longa* (family. *Zingiberaceae*). It has demonstrated anti-inflammatory,[2] wound healing,[3] antioxidant,[4] hepatoprotective,[5] neuroprotective,[6] cardioprotective,[7] anticarcinogenic,[8] and anti-AIDS potentials.[9] The most interesting feature of curcumin is that it is devoid of gastrointestinal side effects (ulcerogenic activity) rather it is reported to have antiulcer properties.[10] In spite of extensive researches

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on this miraculous drug, it is still to be fully utilized due to its poor inherent physicochemical properties such as water insolubility, photoinstability, and hydrolysis leading to poor bioavailability. It was found unstable at basic pH and undergoes hydrolytic decomposition even in *in vitro* physiological condition.[11] Photodecompositions in solid as well as solution form further contribute in poor bioavailability of curcumin.[12] Cyclodextrins (CDs) have been successfully used to enhance either solubility or stability or both of several drugs of plant origin. Previously the effects of CDs such as random methyl-beta-CD and 2-hydroxylpropyl-β-CD on the solubility and photochemical stability of the curcumin and curcuminoids in solution have also been reported.[13] This paper presents the development and evaluation of solid inclusion complexes of curcumin that may be further exploited for the industrial purposes.

Materials and Methods

Curcumin was purchased from Loba chemicals (Bengaluru, India.). Dimethyl β-CD (DIMEB) was purchased from Sigma-Aldrich, Chem. USA. Other CDs such as α-, β-, and γ-CD were obtained from S. D. Fine Chemicals (India). All other compounds and solvents used in this study were of analytical–reagent grade.

Phase solubility studies

Stock solutions of 20 mM of CDs in distilled water (16 mM in case of β-CD as no clear solution at 20 mM) were prepared, and phase solubility studies were done by the method reported by Higuchi and Conners.[14] Excess amount of curcumin (30 mg) was placed in separate amber-colored bottles containing 20 mL of aqueous solutions of CDs, and samples were stirred continuously until equilibrium was achieved (5 days) then analyzed spectrophotometrically at λ_{max} of 428 nm by using aqueous solutions of respective CDs as blanks.

Preparation of inclusion complexes

The inclusion complexes of curcumin with various CDs (α-, γ-CD, and DIMEB) were prepared in a 1:1 (w/w) molar ratio (1:2 molar ratio was used in case of curcumin:β-CD) using following methods.

Grinding

Physical mixtures were prepared by triturating together the accurately weighed equimolar quantities of curcumin and different CDs for 30 min in a clean, dry glass pestle and mortar.

Kneading

Equimolar quantities of curcumin and CDs were blended in clean, dry glass pestle and mortar then wetted by ethanol and triturated to get a paste-like consistency. Trituration was continued until the product started drying on the walls of mortar. The products were further dried in the hot air oven at 60°C for 30 min, powdered, passed through a 100-mesh sieve, and stored in a desiccator.

Freeze-drying

Equimolar quantities of curcumin and CDs were dissolved in distilled water with a small amount of ammonia (27%) to aid dissolution of curcumin and sonicated for 15 min to get clear solutions. The solutions were frozen in ultra-freezer by keeping overnight and freeze-dried over 8 h in a Lyph-lock 6 apparatus (Labconco). The resulting amorphous products were powdered in glass mortar, passed through the 100-mesh sieve, and stored in the desiccator.

Aqueous solubility determination of the solid complexes

Excess amount of complexes were kept in amber-colored bottles containing 10 mL of distilled water and stirred on thermostated mechanical shaker (25°C) for 5 days. Suspensions were filtered through 0.45 μ Millipore filter, diluted adequately, and analyzed spectrophotometrically at 430 nm.

pH stability profile of inclusion complexes

Curcumin and complexes with equivalent amounts were kept in amber-colored bottles containing 10 mL of buffer solutions (pH 1.2–8). Aliquots were taken at different time intervals, diluted adequately, and analyzed spectrophotometrically at 430 nm.

Results and Discussion

Phase solubility study of curcumin

Phase solubility diagrams of curcumin with CDs were found to be linear (A_L type) in cases of α-, γ-CD, and DIMEB indicating 1:1 ratio whereas β-CD showed a nonlinear limited solubility diagram (Bs type), which indicated a molar ratio of 1:2 between curcumin β-CD complexation system [Figure 1]. Apparent stability constants were

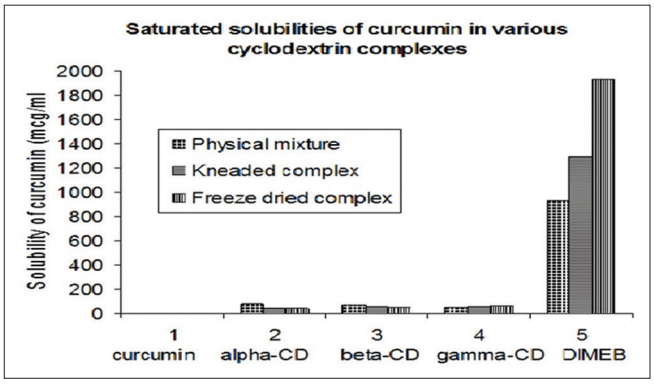

Figure 1: Comparative phase solubility diagrams of curcumin-cyclodextrin systems

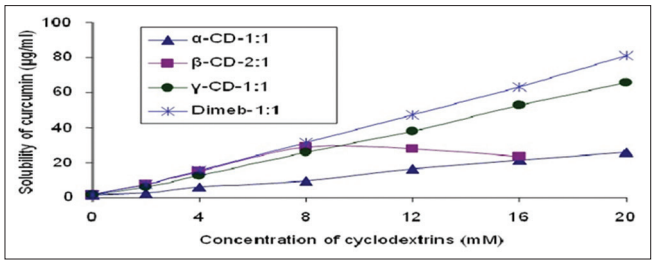

Figure 2: Aqueous solubility of curcumin in various cyclodextrin complexes

Table 1: Comparative phase solubility parameters of curcumin-cyclodextrins systems

Types of CD	Types of phase solubility diagram	Stability constant K_s (M^{-1})	Correlation coefficient (R^2)
α-CD	A_L (1:1)	11,200	0.9935
β-CD	B_S (2:1)	1457	0.9991
γ-CD	A_L (1:1)	2858	0.9995
Dimethyl β-CD	A_L (1:1)	2206	0.9977

CD – Cyclodextrin

found to be satisfactory for the formation of inclusion complexes [Table 1].

Aqueous solubility determination of the solid complexes

Curcumin is reported to be practically insoluble in water, its saturated solubility in distilled water at room temperature was found to be 1.29 µg/ml. Inclusion complex formation of curcumin greatly enhanced the aqueous solubility up to 60, 54, 46, and 1500 folds by α-, β-, γ-CD, and DIMEB, respectively [Figure 2].

pH stability profile of inclusion complexes

Curcumin degraded rapidly both in acidic as well as in basic conditions. More than 70% curcumin degraded in basic conditions, whereas 40–60% degradation was observed in acidic pH conditions at the end of 8 h. CDs inclusion complexation of curcumin was found to protect the drug from hydrolytic degradations. Only 5–10% degradation was observed at 0.5 h and a maximum of 20–40% degradation were observed at the end of 8 h. Graphs between percent amount remained and time are plotted [Figure 3].

Conclusion

Prepared solid inclusion complexes showed promising results with 50–1500 folds increase in the solubility of practically insoluble curcumin. The pH adjustment does not significantly enhance the solubility of curcumin. Inclusion complex formation resulted in amorphous compounds with improved solubility and stability of

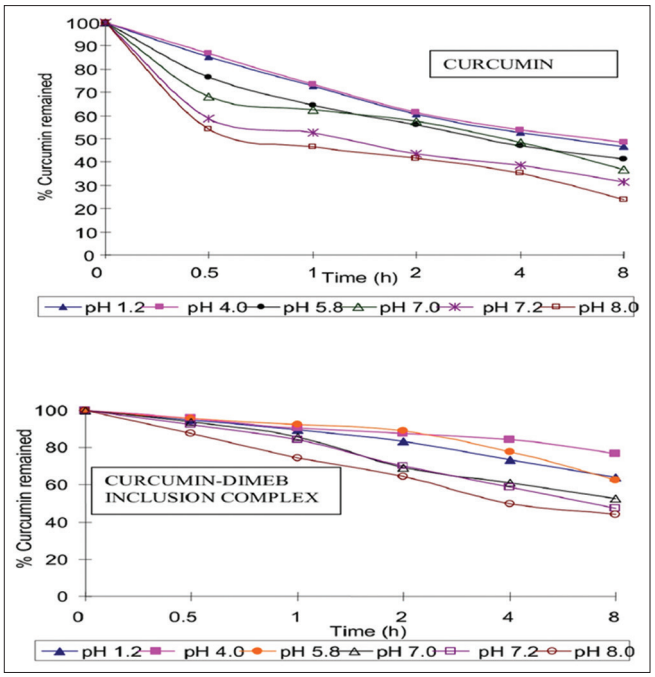

Figure 3: pH stability profile of curcumin and curcumin dimethyl β-cyclodextrin inclusion complex

curcumin. DIMEB has the greatest solubilizing effect on the curcumin. Freeze-dried complexes have greater solubility than kneading one, but it is much costlier than the later.

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Conflicts of interest

There are no conflicts of interest.

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