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SOLUBILITY AND STABILITY ENHANCEMENT OF CURCUMIN THROUGH CYCLODEXTRIN COMPLEXATION

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ABSTRACT

Water insolubility, low potency and instability are inherent problems of several herbal medicines. Identity, strength, quality, purity of herbal products is 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*. The stoichiometric ratios for inclusion complexation of curcumin with various cyclodextrins 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.

Stability constants were 11200 M^{-1}, 1557 M^{-1}, 2858 M^{-1} and 2206 M^{-1} for α, β, γ and dimethyl β-CDs respectively, thus indicating good complex formation. Theoretical amounts of curcumin in binary products were between 80-97 % 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 upto 60, 55, 56 and 1500 folds by α, β, γ and dimethyl β-cyclodxtrin respectively. Inclusion complexation protected the drug from hydrolytic degradations as only 20-40% degradation was observed at the end of 8 hours as opposed to >70% for pure curcumin.

A significant improvement in the solubility and stability was observed with curcumin–cyclodextrin complex as compared to pure curcumin.

Keyword: Curcumin, Dimethyl β-cyclodxtrin, 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 less than one percent **[1]**. Water insolubility, low potency and instability are inherent problems of several herbal medicines. Identity, strength, quality, purity of herbal products is 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, obtaioned from *Curcuma longa* (family. *Zinziberaceae*). It has demonstrated anti-inflammatory **[2]** wound healing **[3]** antioxidant **[4]** hepato-protective **[5]** neuro-protective **[6]**, cardio protective [7] anti-carcinogenic **[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 anti-ulcer properties **[10]**. In spite of extensive researches on this miraculous drug it is still to be fully utilized due to its poor inherent physicochemical properties like water insolubility, photo-instability 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 have been successfully used to enhance either solubility or stability or both of several drugs of plant origin. Previously the effects of cylodextrins like RM β-CD & HP β-CD on the solubility & 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 (Banglore, India.). Dimethyl β-cyclodextrin (DIMEB) was purchased from Sigma Aldarich, Chem.USA. Other cylodextrins like α-CD, β-CD 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.

pH Solubility Profile of Curcumin

As curcumin is a weak base, its solubility might be affected by hydrogen ion concentration, therefore pH solubility profile was studied by method reported by Higuchi and Conners **[14]**. 0.2 M hydrochloric acid buffer (pH 1.2) was prepared by adding 50

ml of 0.2 M potassium chloride to 85 ml of 0.2M HCl in a 200 ml volumetric flask and then diluting with distilled water to make 200 ml. 0.2 M phosphate buffers (pH 2.0-10) were prepared by methods described in I.P. 1996 **[15]**. Saturated solubility of curcumin (S_o) in various buffer solutions ranging from pH 1.2 to pH 10.0 was then determined by using double beam UV spectrophotometer (UV 1601, Shimadzu, Japan) at a λ_{max} of 430 nm using straight-line equation (Y= mX + c) of respective calibration curves of the buffers.

Phase Solubility Studies

Stock solutions of 20 mM of cyclodextrins in distilled water (16 mM in case of β-CD as no clear solution was obtained at 20 mM) were prepared and phase solubility studies were done by method reported by Higuchi and Conners **[14]**. Excess amount of curcumin (30 mg) was placed in separate amber coloured bottles containing 20 ml of aqueous solutions of cyclodextrins and samples were stirred continuously until equilibrium was achieved (five days). Suspensions were filtered using 0.45 micron membrane filter and then analyzed spectrophotometrically at a λ_{max} of 428 nm by using aqueous solutions of respective cyclodextrins as blanks.

Preparation of Inclusion Complexes

The inclusion complexes of curcumin with various cyclodextrins (α-CD, γ-CD and dimethyl β-CD) were prepared in a 1:1 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 cyclodextrins for 30 minutes in a clean dry glass pestle and mortar.

Kneading

Equimolar quantities of curcumin and cyclodextrins 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^o C for 30 minutes, powdered, passed through 100-mesh sieve and stored in a dessicator.

Freeze-drying

Equimolar quantities of curcumin and cyclodextrins 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 over night and freeze-dried over 8 hours in a Lyph-lock 6 apparatus (Labconco). The resulting

amorphous products were powdered in glass mortar, passed through 100-mesh sieve and stored in a dessicator.

Characterization of Inclusion Complexes

Aqueous Solubility Determination of the Solid Complexes

Excess amount of complexes were kept in amber coloured bottles containing 10 ml of distilled water and stirred on thermostated mechanical shaker (25 ^{o}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 coloured 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 cyclodextrins were found to be linear (A_L type) in cases of α, γ and dimethyl β-cyclodextrin indicating 1:1 ratio whereas β-CD showed a non-linear limited solubility diagram (Bs type), which indicated a molar ratio of 1: 2 between curcumin β-cyclodextrin complexation system **(Figure 1)**. Apparent stability constants were found to be satisfactory for the formation of inclusion complexes as shown in the **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 upto 60, 54, 46 and 1500 folds by α-, β-, γ- and dimethyl β-cyclodextrin respectively as shown in the **Figure 2**. Therefore it is obvious that all tested cyclodextrin significantly enhanced the solubility of curcumin and this is in agreement with other reports **[16-17]**. It was also observed that there was no significant difference in solubility enhancement capacities amongst natural cyclodextrins, however, di-methyl beta cyclodextrin exhibited approximately 300 fold higher solubility enhancement as compared to natural cyclodextrins.

pH Stability Profile of Solid Inclusion Complexes

From stability study, it is evident that curcumin degraded rapidly both in acidic as well as in basic conditions, however, degradation was much faster in neutral or basic conditions as compared to acidic pH, and this was in agreement with other reports

[18]. More than 70 % curcumin degraded in basic conditions where as 40-60 % degradation was observed in acidic pH conditions at the end of 8 hours. Cyclodextrin inclusion complexation of curcumin was found to protect the drug from hydrolytic degradations. Only 5-10 % degradation was observed at 0.5 hour and a maximum of 20-40% degradation was observed at the end of 8 hours. Graphs between % amount remained and time are plotted as shown in **Figure 3**.

Table I: Comparative phase solubility parameters of curcumin-cyclodextrin systems

S No.	Types of cyclodextrin	Types of phase solubility diagram	Stability constant K_s (M^{-1})	Correlation coefficient (R^2)
1	α-CD	A_r (1:1)	11200	0.9935
2	β-CD	B_S (2:1)	1457	0.9991
3	γ-CD	A_L (1:1)	2858	0.9995
4	Dimeb	A_L (1:1)	2206	0.9977

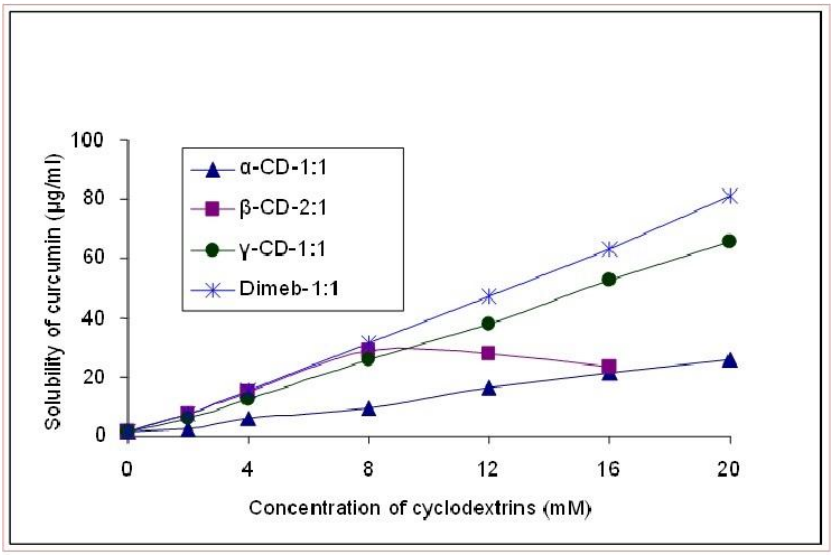

Figure 1: Comparative phase solubility diagrams of curcumin-cyclodextrin systems

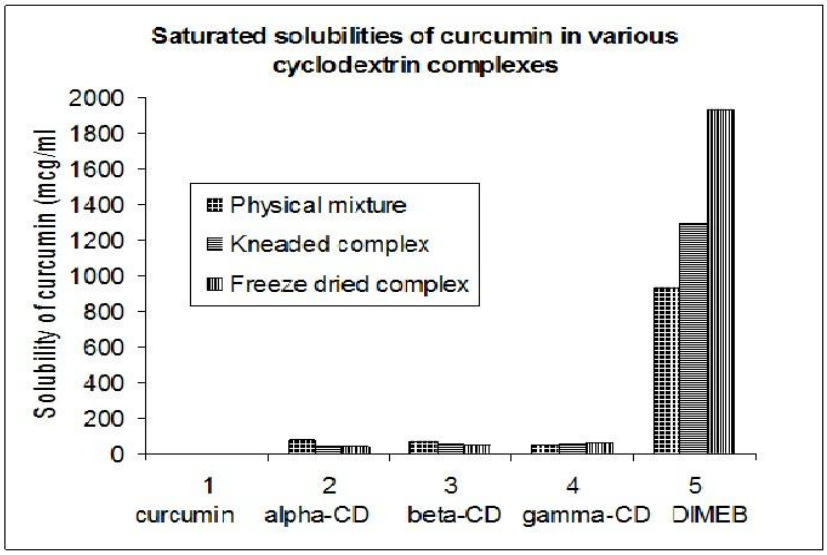

Figure 2: Aqueous solubility of curcumin and solid inclusion complexes

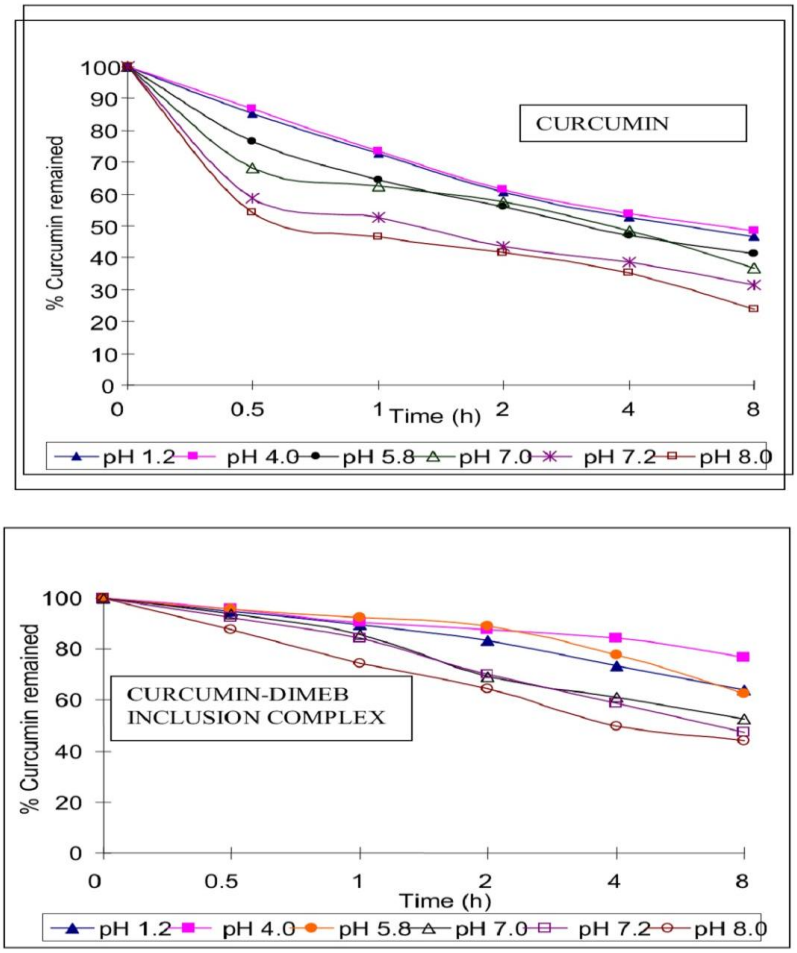

Fig 3 pH stability profile of pure curcumin and curcumin-Dimeb complex

CONCLUSION

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