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Research Article

DISSOLUTION ENHANCEMENT OF CURCUMIN BY HYDROXYPROPYL-β-CYCLODEXTRIN COMPLEXATION

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ABSTRACT

Objectives: The purpose of this study describes the formation of inclusion complex by coevaporation of curcumin using hydroxypropyl-β-cyclodextrin as carriers, to improve the solubility and dissolution of drug.

Methods: The preparation of inclusion complex was carried out by using solvent method. The drug and carrier were dissolved in alcohol and subjected to solvent evaporation by a rotary evaporator. The residual powder preparation was allowed to dry overnight in vacuum desiccator, pulverized and sieved through # 60 mesh. The invitro dissolution testing was performed media in HCl 0.1 N aqueous solution. Characterization of inclusion complex and physical mixture was further evaluation using differential thermal analysis (DTA), powder X-ray diffraction (PXRD), FTIR spectrophotometry and a scanning electron microscope (SEM).

The results: Evaluation of the phase solubility studies revealed a A_L type diagram with complexation of equimolar ratio and solubility constant of 30.09 mM^{-1}. In-vitro dissolution studies showed that the curcumin entrapped in coevaporated complexes dissolved much faster than the incomplexed dissolved drug and physical mixtures. X-ray diffraction indicated loss a crystalline nature of the drug, FTIR, DTA studies revealed no interaction between curcumin and HPβCD.

Conclusions: Inclusion complex of curcumin with HPβCD appears to have the advantage of dissolution enhancement and that may lead to improved bioavailability.

Keywords: Curcumin, Hydroxypropyl-β-Cyclodextrin, Inclusion complex, solubility, Dissolution, Characteristic.

INTRODUCTION

Curcumin is a substance obtained from *curcuma longa* Linn which has wide therapeutic activities and practically insoluble in water and has poor bioavailability; it is a biopharmaceutics classification system (BCS) class-IV drug [1,2]. This class of drugs shows dissolution rate limited absorption and hence variable bioavailability [3,4]. To overcome these drawbacks, increasing the dissolution rate and aqueous solubility of curcumin is an important goal [5,6].

Formation of inclusion complexes of drug with cyclodextrin has been reported to enhance the solubility, dissolution rate and bioavailability of poorly water soluble drugs. They are known for the ability to molecularity encapsulates a wide variety of drug into their hydrophobic cavity without the formation of any covalent bounds [7,8,9]. Hydroxypropyl-β-Cyclodextrin (HPβCD), was chosen for the study because of its wide use in the pharmaceutical industry due to its cavity size, efficiency of drug complexation, high aqueous solubility and available used in parenteral formulation [10].

However, the efficiency of complexation is often not very high, and therefore, relatively large amounts of HPβCD must be used to obtained the desired effect. On the other hand, Pharmaceutical dosage forms should contain a little HPβCD as possible because of variety of reason problems of formulation bulk and possible toxicity [11].

The main objective of this study was to investigate the possibly of improving the solubility and dissolution rate of curcumin by complexation with HPβCD. The complex formed was characterized by DTA, PXRD, SEM and FTIR.

MATERIALS AND METDODS

Materials

Curcumin, Mw 368.38 was purchased from E-merck, Germany. Hydroxypropyl-β-Cyclodextrin (HPβCD), Mw 1380 was purchased from Sigma-Aldrich, Japan. All the other reagents were of analytical grade.

Methods

Phase – solubility study

Excess amounts of curcumin (20 mg) were added to 20 ml of HCl 0.1 N aqueous solution of HPβCD in the 0 – 15 mM concentration range. The suspensions were magnetically stirred in thermostatically water bath circulation maintained at 37 ± 0,5^{0}C, until equilibrium was reached (10 h). Aliquots of 5 ml were periodically withdrawn with a syringe – filter (pore size 0.45 μm) and after suitable dilution, assayed for curcumin concentration by UV-Vis spectroscopy at 430.0 nm. The presences of the complexes were calculated from the slope of the straight lines of the phase-solubility diagram [12]. Each experiment was performed in triplicate.

Preparation of inclusion complex

Equimolar amounts of curcumin-HPβCD complexes were prepared by solvent evaporation method. The resultant clear solution was evaporating in rotary evaporator at 40^0 – 50^{0}C under vacuum. The dried product (complex) was kept in vacuum desiccators with blue silicate as drying agent. Physical mixture was also prepared by simple blending an equimolar curcumin and HPβCD. Sieved products (75 – 150 μm) were used for all subsequent studies.

Diffrential Thermal Analysis (DTA)

A Mettler Toledo FP85 model Differential Thermal Analysis was used. Sample was sealed in aluminum pans and measured in the temperature range 50 – 250^{0}C at scanning rate 10^{0}C/min.

X –ray Powder-Diffraction (XRPD)

Jeol X-ray powder diffractometer was used. The measure meant condition were as follows : target Cu, filter Ni, voltage 40 KV, Current 20 mA, analyzed in the 2θ range between of 5 - 40°.

Scanning Electron Microscopy (SEM)

A Philips XL – 30 SEM was used. Samples were gold – sputter coated to render them electrically conductive and picture were taken at 500 fold magnification.

FTIR spectroscopy

A FT-IR 5300 spectrophotometer, Jasco Japan, was used. The samples were mixed with KBr powder and then pressed hydraulic press until a transparent disc was obtained. The spectrum was scanned on 8 minute scan time.

Dissolution study

In-vitro dissolution studies were carried out as conditions reported by using USP apparatus I basked method by dispersed powder technique. Accurately weighed sample equivalent to 30 mg of curcumin was placed in a basked (mesh 150) of dissolution vessel and 900 ml of HCL 0.1 N aqueous solution of dissolution medium, maintained at 37 ± 0.5^{0}C was transferred into the vessel and rotated at 100 rpm. An aliquot of 5 ml was withdrawn at different time intervals and filtered through 0.45 µm membrane filter. An equal volume of fresh dissolution medium was immediately replaced. The concentration of curcumin at each sampling time was analyzed spectrophotometrically at 430.0 nm The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The phase solubility diagrams for the complex formation between curcumin and HPβCD in HCl 0.1 N aqueous solution are shown in figure 1. The aqueous solubility of curcumin was increased linearly as a function of the concentration of HPβCD. The phase solubility diagram of curcumin – HPβCD complexes can be classified as type A_L [12]. The results may attributed to the formation of curcumin-HPβCD obtained of the complex 1 : 1 molar ratio was followed an A_L type diagram and its stability constant was 30.09 mM^{-1}.

Dissolution profiles of the pure curcumin, physical mixture and the curcumin – HPβCD complex are shown in figure 2. The rate dissolution of curcumin was rapid and higher from the inclusion complex when compared with pure curcumin and physical mixture equimolar. It was evident that inclusion complex exhibited faster dissolution rates than that of pure curcumin and physical mixture. At the end of 60 minutes, pure curcumin, physical mixture and inclusion complex release: 0.91 %, 1.13 % and 8.63 %, respectively. It was evident that inclusion complex exhibited faster dissolution rates than that of pure curcumin and physical mixture at the end of 60 minutes. The improvement of dissolution rate obtained with inclusion complex could of readily soluble complex of curcumin in the dissolution medium.

DTA was used to characterize the curcumin-HPβCD inclusion complex. The DTA thermogram of pure curcumin, HPβCD, physical mixture, and inclusion complex are shown in figure 3.

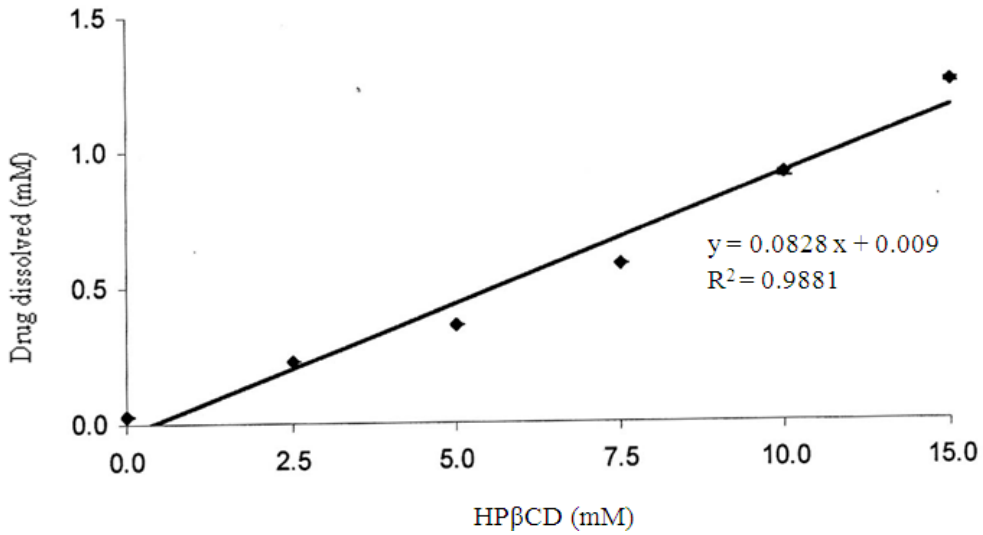

Fig. 1: Phase solubility diagram of curcumin - HPβCD complex.

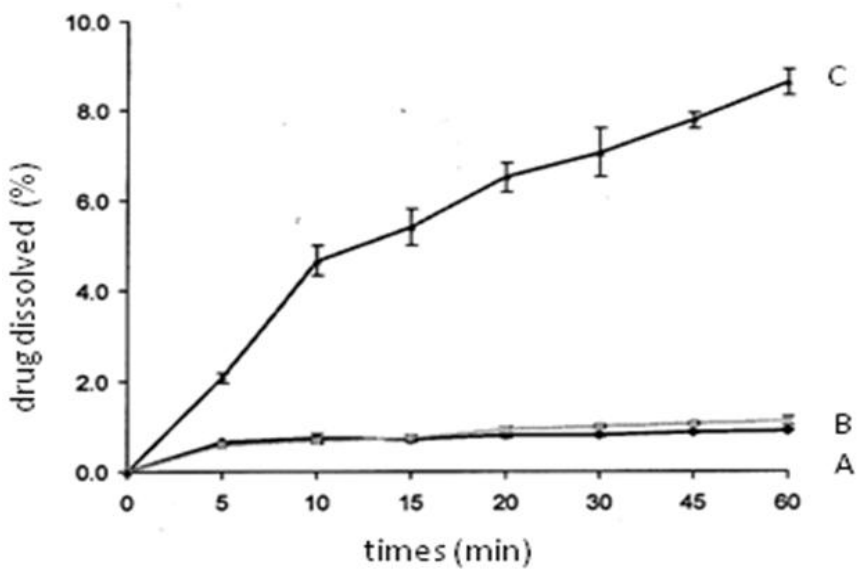

Fig. 2: Dissolution profile of pure curcumin (A), physical mixture (B), and inclusion complex (C) in distilled water at 37^{0}C.

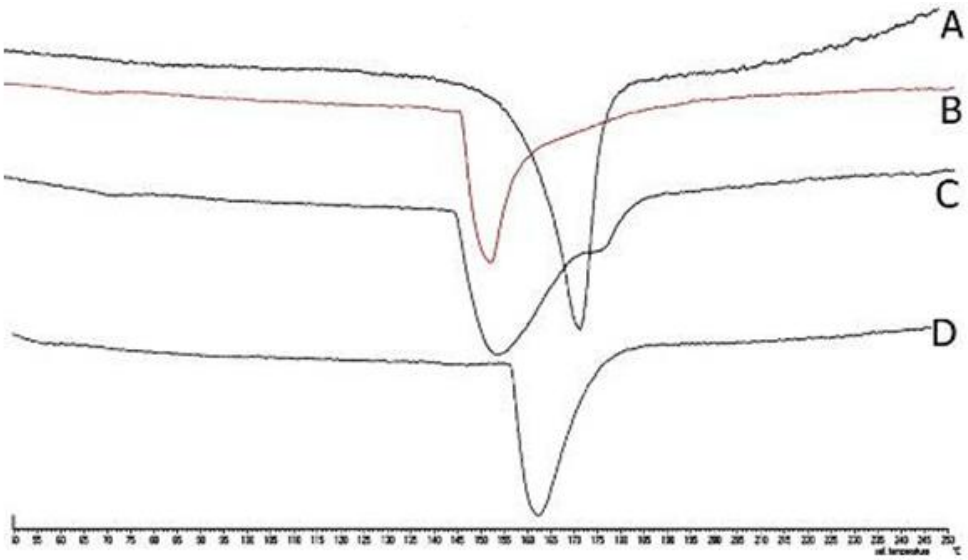

Fig. 3: Thermogram pattern of curcumin (A), HPβCD (B), physical mixture (C), and inclusion complex (D).

DTA thermogram of curcumin showed one endothermic peak at 172.4 °C corresponding to the melting point of curcumin. Thermogram HPβCD did not show any endothermic peaks in the melting point region of curcumin. The lost of crystal water is observed at a lower temperature (120-130°C) as an endothermic peak [13,14]. The endothermic peak as 172.4°C, which is characterize of curcumin, is present in the thermogram of the physical mixture but not in those of the inclusion complex prepared by coevaporating method.

Supporting evidence for complex formation was also obtained from X-ray diffraction analysis confirm the DTA result. In fact, its can be seen in figure 4, some diffraction peaks attributable to curcumin crystal are still detectable in physical mixture, whereas they are absent in the respective inclusion complex product.

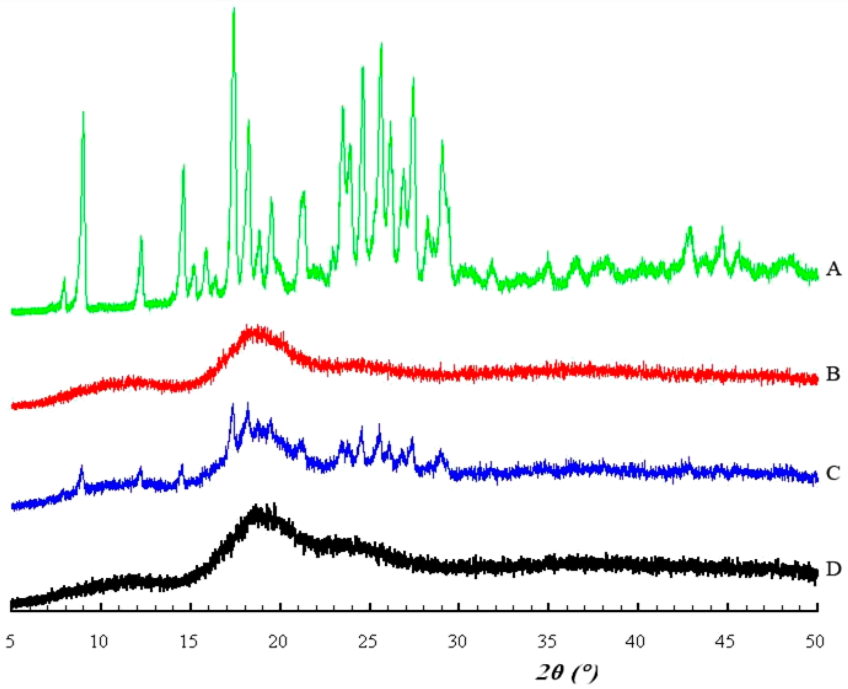

Fig. 4: PXRD pattern of curcumin (A), HPβCD (B), physical mixture (C), and inclusion complex (D).

Supporting evidence for complex formation was also obtained from FTIR studies (figure 5). In the IR-spectrum, the characterize absorption of HPβCD are superimposed over the curcumin. The phenomenon is due to the differences between molecular weight of the components even it the molar ratio of the inclusion is 1:4 w/w. The IR-spctrum of the inclusion complex indicate spesific absorption peaks of 3370, 1627, and 1243 cm^{-1} (H streching and bonding) characteristic for HPβCD. The patterns of physical mixture were the simple superimposition of those single components, where those of the corresponding inclusion complex system of the functional group of phenolic OH, C=O and aromatic C=C which shows the peak 1625-1640 cm^{-1} and 1520-1400 cm^{-1} indicated no interaction. These peak were observed in both pure drug as well as in inclusion complex indicating no interaction.

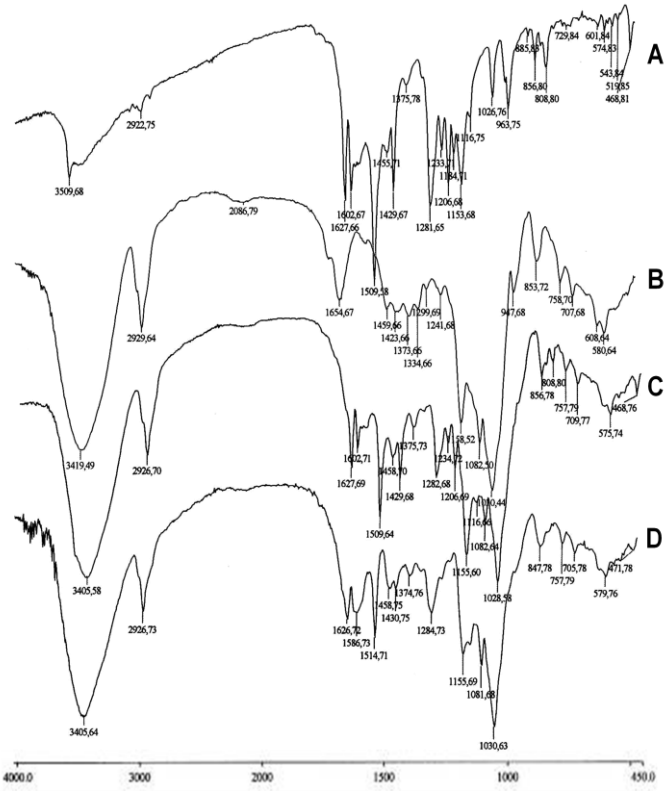

Fig. 5: FTIR pattern of curcumin (A), HPβCD (B), physical mixture (C), and inclusion complex (D).

The SEM analysis of pure curcumin (A), HPβCD (B), physical mixture (C), and inclusion complex (D) are reported three dimensional particles with parallelogram shape (figure 6). A picture HPβCD appared as three-dimensional particles with parallelogram shape. Curcumin appared no irregular and three-dimensional particles. The inclusion complex product showed amorphous and homogenous aggregates, which may be due to the molecular encapsulation curcumin molecule in the HPβCD.

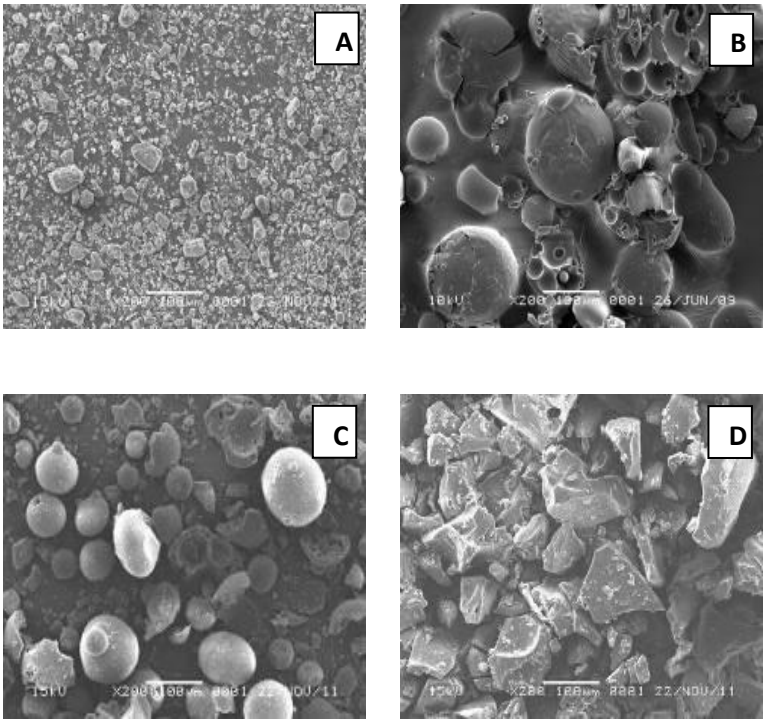

Fig. 6: SEM analysis of curcumin (A), HPβCD (B), physical mixture (C), and inclusion complex (D).

CONCLUSIONS

Complexation with HPβCD was successfully applied for improving the solubility and dissolution of curcumin. The solid state analysis of inclusion complex product by DTA, PXRD, FTIR, and SEM studied showed that it is possible to obtain an inclusion complex of curcumin-HPβCD. The coevaporation technique produced amorphous and homogenous complex.

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