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ORIGINAL ARTICLE

Production and characterization of a spray-dried hydroxypropyl-β-cyclodextrin/quercetin complex

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Abstract

Background: Quercetin (QC) is a poorly water-soluble and degradation-prone bioflavonoid. *Aim*: This study aimed to investigate the formation of a chemically stable and readily water-soluble solid complex of QC with hydroxypropyl-β-cyclodextrin (HP-β-CD). *Method*: A solid HP-β-CD/QC complex was prepared by spray drying and characterized by high-performance liquid chromatography, Fourier-transform infrared spectroscopy, scanning electron microscopy, laser-diffraction particle sizing, powder X-ray diffraction, thermal analysis, Brunauer–Emmett–Teller nitrogen adsorption, and dissolution testing. *Results*: The complex displayed excellent thermal stability during spray drying, a broad diffuse X-ray diffraction pattern, and a single glass transition temperature (T_g) characteristic of amorphous HP-β-CD. Dissolution testing of the complex in simulated gastric fluid revealed an approximately eightfold increase in the rate and extent of dissolution of QC compared with its molar equivalent physical mixture of QC and blank spray-dried HP-β-CD, although the surface area of QC in the mixture was about seven times that of the complex. *Conclusions*: All these observations can be explained by specific interaction between QC and HP-β-CD in the amorphous solid state, possibly in the form of an inclusion complex.

Key words: *Glass transition temperature; powder X-ray diffraction; solubility enhancement; spray-dried hydroxypropyl-β-cyclodextrin/quercetin complex; stability*

Introduction

Flavonoids are polyphenolic compounds widely distributed in plants. Among the numerous flavonoids known to date, quercetin (QC; Figure 1) has attracted considerable attention in recent years primarily because of its natural abundance and potential health beneficial effects including antioxidant, free radical scavenging, and anticancer activities[1]. Being hydrophobic (log $P = 1.81 \pm 0.46$)[2] and having a near planar molecular structure[3], QC displays poor aqueous solubility[4]. The oral bioavailability of QC in liquid preparations has been shown to be highly dependent on the formulation vehicle used to solubilize the compound; the more soluble the QC is in the vehicle, the higher the oral absorption[5–7]. Thus, solubility enhancement is generally considered as a viable strategy for increasing the oral bioavailability of QC.

Our previous work has demonstrated the ability of various β-cyclodextrins [β-cyclodextrin (β-CD) and the hydroxypropyl and sulfobutyl ether derivatives] to enhance the aqueous solubility and chemical stability of QC via the formation of a 1:1 molecular inclusion complex[4]. The mode of complexation in aqueous solutions has been elucidated using a combination of experimental characterization and computer-aided theoretical molecular modeling techniques[4]. In this study, a complex of hydroxypropyl-β-cyclodextrin (HP-β-CD) with QC in particulate form was prepared by spray drying and characterized by high-performance liquid chromatography (HPLC), Fourier-transform infrared (FTIR) spectroscopy, Scanning electron microscopy (SEM), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), laser-diffraction particle sizing, Brunauer–Emmett–Teller (BET) nitrogen adsorption, and dissolution testing.

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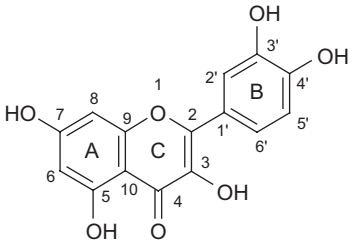

Figure 1. Chemical structure of quercetin (QC).

Our aims were to investigate the formation of the complex in the solid state and to assess the feasibility of using HP-β-CD to prepare a consistent, water-soluble, and chemically stable powder form of QC for subsequent formulation development. While similar characterization studies on the HP-β-CD/QC solid complex have been reported previously[8,9], different methods for preparing the complex (e.g., lyophilization and kneading) were employed in these studies, and the lack of stability control of QC in these reported methods could invalidate the findings obtained. For instance, one of such methods employed an alkaline aqueous medium (ammonia solution with a pH of about 11) to aid the dissolution of QC[8], which could severely compromise the stability of QC through base-catalyzed decomposition[10]. As demonstrated in our previous study[4], only about 5% of QC remained in aqueous solutions at pH 9 and 37°C after 30 minutes of incubation.

Materials and methods

Materials

QC dihydrate and fisetin were purchased from Sigma Chemical Co. (St. Louis, MO, USA). HP-β-CD [Kleptose®; M.S. (Average molar degree of substitution) = 0.8 – 1.0] was donated by Roquette (Lestrem cedex, France). All other chemicals and solvents were of analytical or HPLC grade, and all water used was deionized and double-distilled.

Preparation of spray-dried inclusion complex

HP-β-CD/QC complex was prepared by spray drying in a Büchi B-191 mini spray dryer (Büchi Labortechnik AG, Flawil, Switzerland) under the following operating conditions: outlet drying temperature 120°C; pump 10%; flow rate 600 L/h; aspirator level 86%. QC dihydrate and HP-β-CD (molar ratio = 1:5.5) were dissolved in pure ethanol to obtain a clear yellow solution (4 mg/mL QC). The solvent was quickly removed by rotary evaporation (Büchi, Rotavapor R-114, Flawil, Switzerland) at 40–50°C (Büchi waterbath B-480, Flawil, Switzerland). The residue was redissolved in water (adjusted to a pH of about 3) and used as the feed solution. All spray-dried complex samples were stored in desiccators over phosphorous pentoxide at room temperature before characterization. Physical mixture employed as control in the characterization studies was prepared by gentle blending for 5 minutes of the starting QC material and blank spray-dried HP-β-CD in the same molar ratio as that used for the complex by means of an electrical vibrator (Record Power Ltd., Sheffield, UK).

Scanning electron microscopy

The particle shape/morphology and surface features of the spray-dried complex were characterized using a LEO 1450 scanning electron microscope (LEO Electron Microscopy Ltd., Cambridge, UK). A small piece of double-sided adhesive tape was adhered onto an aluminum stub, and a small quantity of particles was sprinkled and dispersed on the stub surface. The particles were immediately coated with gold using a Fisher sputter coater. The electron microscope was operated under the following conditions: accelerating voltage at 20 kV, working distance at 25 mm, magnification at 500 or 2 K, and scale at 20 or 50 μm.

Powder X-ray diffractometry

Small-angle X-ray reflection measurements were performed with a Philips PW1830 powder X-ray diffractometer (Philips Analytical, Eindhoven, the Netherlands) and a Philips PW1830 generator using Cu (λ = 1.540562 Å) as anode material at room temperature. Samples were packed into an aluminum holder, and the diffractograms were recorded in the 2θ angle range from 5.0° to 35° with the following operating parameter settings: scan step size at 0.05° (2θ), scan step time at 2 seconds and scan speed at 0.025° per second.

Specific surface area determination

Specific surface area of sample was determined by BET nitrogen adsorption using a surface area analyzer (Coulter SA 3100, Miami, FL, USA). Accurately weighed sample (~1 g) was placed in a glass sample tube and outgassed under helium (purity > 99.999%) before analysis at 120°C for 1 hour (for the spray-dried complex) or at 25°C for 16 hours (for the QC dihydrate to avoid dehydration). Nitrogen (purity > 99.999%) was used as adsorbate, and BET-specific surface area was recorded as unit surface area per gram of sample. Triplicate measurements were performed on separate batches, and the mean value was calculated.

Particle size analysis

Particle size distribution was measured by an LS 13 320 laser-diffraction particle size analyzer (Beckman Coulter, Miami, FL, USA). The measurement is based on the light-scattering pattern of particles in the sample. Sample (2–3 g) was placed in a disperser sample cup. To compute the size distribution, the composite scattering pattern is deconvoluted into a number of individual but additive functions, one for size classification, and the relative amplitude of each pattern is used to measure the relative volume of spherical particles of that size. This deconvolution is based on either the Fraunhofer or the Mie theory of light scattering. Particle size distribution was expressed as percent frequency based on volume versus size.

FTIR spectroscopy

FTIR spectra were obtained using a Perkin Elmer FTIR system (Spectrum BX, version 2.0, Norwalk, CT, USA) for the complex, QC raw material, blank spray-dried HP-β-CD, and physical mixture of the QC raw material and blank spray-dried HP-β-CD (in the same molar ratio as the complex). As an additional reference material for spectral comparison, a 1:1 binary mixture of HB-β-CD and QC was also prepared by rotary evaporation of a solution containing equal molar quantities of the two components in pure ethanol to complete dryness as described above, but without going through the spray-drying process. Sample was blended thoroughly in a 1% (w/w) dilution with dry potassium bromide (KBr), an infrared transparent matrix, to prepare a disc for FTIR measurement. The KBr disc was prepared by compressing the powder under a force of 8 tons for 3 minutes. The scan parameters were set as follows: number of scan 8, resolution 4 cm^{-1}, scan range 400–4000 cm^{-1} at an interval of 2 cm^{-1}.

Differential scanning calorimetry

DSC thermograms were generated using a Perkin Elmer Pyris 1 DSC (with Pyris Manager software) (Perkin Elmer Corporation, Norwalk, Connecticut, USA) to analyze the thermal behaviors of the samples (including melting point, T_m, and glass transition temperature, T_g). Indium (T_m = 156.6°C; ΔH_f = 28.45 J/g) and zinc (T_m = 419.47°C; ΔH_f = 108.37 J/g) were used for routine calibration. An empty aluminum pan was used as reference, and nitrogen (purity > 99.99%) was used as the purge gas at 20 mL/min. Accurately weighed samples (2–8 mg) were placed in aluminum pans and covered with unsealed lids. The samples were scanned at 10°C/min from 50°C to 240°C (with HP-β-CD) or from 50°C to 350°C (for QC dihydrate). The onset of melting and T_m were recorded for QC dihydrate while the onset of glass transition and half C_p-extrapolated T_g were taken for amorphous samples (including the complex). T_g values were confirmed by at least four repeated scans of the same sample.

Thermogravimetric analysis

The loss in mass of the samples associated with phase transition or decomposition was monitored using a Perkin Elmer Thermogravimetric Analyzer TGA 7 with Thermal Analysis Controller TGA 7/DX (Perkin Elmer Corporation). Sample (2–5 mg) was placed inside an open pan. Nitrogen was used as the purge gas at 20 mL/min, and the sample was heated at 10°C/min from 50°C to 450°C.

Dissolution studies

Dissolution studies were conducted in a standard dissolution tester (Erweka DT80, Heusenstamm, Germany) according to the USP rotating paddle method[11]. The dissolution medium, consisting of 900 mL of enzyme-free simulated gastric fluid (pH 1.2), was maintained at 37°C and stirred at 100 rpm. Accurately weighed samples (~200 mg spray-dried QC complex or equivalent amount of the physical mixture of blank spray-dried HP-β-CD and QC in the same molar ratio) were dropped into the dissolution medium at time zero. At defined time intervals over a period of 60 minutes, 10-mL aliquots of the dissolution medium were withdrawn, filtered with 0.45-μm membrane filters (Spartan 13/20, Schleicher & Schuell GmbH, Dassel, Germany), and analyzed for QC (after discarding the initial 7 mL) by UV absorption spectroscopy at 370 nm (for solid complex) or HPLC (for physical mixture).

High-performance liquid chromatography

Gradient-elution HPLC analysis of QC and potential degradation products employed a Hypersil C_{18} reversed phase column (5 μm, 250 × 4.6 mm^2 I.D., Thermo Hypersil Ltd., Cheshire, UK) and a Waters 2695 LC system equipped with a Waters 996 photodiode array detector (Waters, Milford, MA, USA). The mobile phase consisting of methanol, acetonitrile, and phosphate buffer (pH 2.6; 25 mM) was linearly changed from volume ratio of 5:25:70 to 80:0:20 during the first 15 minutes, and then returned to the initial eluent composition for another 5 minutes. The analysis was conducted at room temperature and an eluent flow rate of 1 mL/min.

To determine the recovery of QC after spray drying, accurately weighed spray-dried samples were dissolved in 50% (v/v) aqueous methanol and diluted to an appropriate concentration for the HPLC analysis. For the dissolution study, aliquots (250 μL each) of the filtered dissolution medium collected at different time intervals were mixed

with an equal volume of 50% (v/v) aqueous methanol. A 120-μL aliquot of the above diluted sample was then mixed with 30 μL of fisetin internal standard solution (4 μg/mL), and 20 μL of the resulting mixture was injected onto the HPLC column for QC analysis at 370 nm. The inter- and intra-day RSD for the analysis was less than 5.2%. Calibration curves constructed with standard QC and fisetin solutions of appropriate concentrations for the assay revealed excellent linearity with $R^2 > 0.999$.

Results and discussions

Preparation of spray-dried HP-β-CD/QC complex

Excess HP-β-CD was employed to ensure the complete complexation of QC in solid form. The appropriate molar ratio of QC to HP-β-CD was determined from initial trial runs to be 1:5.5. Based on the complexation constant (11,048 M^{-1} at 24°C) obtained from our previous phase solubility study[4], complexation between QC and HP-β-CD should essentially be complete at this molar ratio. Furthermore, the resulting feed solution (containing 4 mg/mL QC) exhibited no apparent precipitation and could be efficiently spray-dried at 120°C without compromising the stability of QC. The mean yield of three separate batches of HP-β-CD/QC complex was 71.8 ± 1.5%, and the mean content of QC recovered in the samples was 102.3 ± 0.8%. In addition, the three batches of solid complex were comparable in particle size and specific surface area (Table 1), reflecting good reproducibility of the powder production method.

Particle morphology and particle size distribution

As shown by SEM, QC dihydrate appeared as large clumps consisting mostly of fine irregularly shaped particles while the HP-β-CD raw material displayed an irregular and porous morphology with curved edges (Figure 2A and B). In contrast, the particles in the spray-dried samples were spherical in shape with smooth surfaces for some and shriveled surfaces for the others (Figure 2C). A 'blown-up' morphology was apparent with some particles, which may be attributed to a rapid expansion of highly heated air within the particles and concurrent extensive evaporation of solvent below the particle surface. No crystalline particles of well-defined shapes were visible with the spray-dried sample (Figure 2C), suggesting an absence of phase separation. The three batches of spray-dried HP-β-CD/QC complex showed closely similar morphology and relatively narrow particle size distributions with a median diameter between 5.7 and 6.3 μm (Table 1).

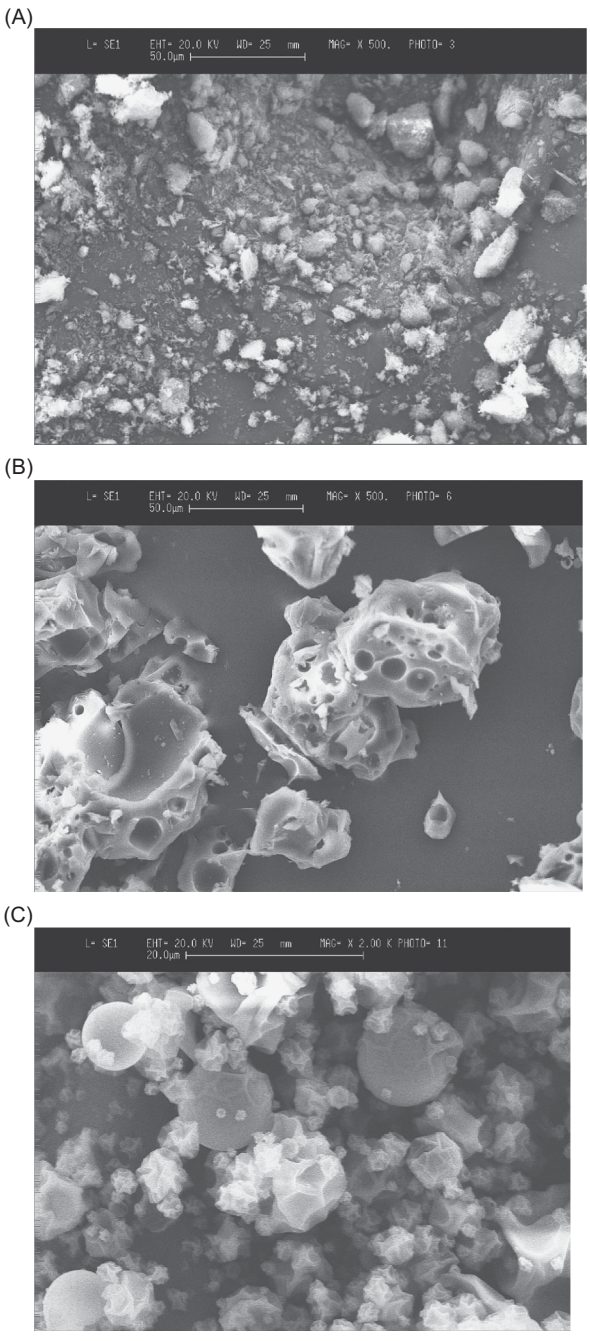

Figure 2. Scanning electron micrographs of: (A), QC dihydrate (MAG: 500); (B), HP-β-CD raw material (MAG: 500); (C), spray-dried complex of QC with HP-β-CD (1:5.5 molar ratio) (MAG: 2K).

Table 1. Specific surface areas and particle sizes of three separate batches of spray-dried HP-β-CD/quercetin complex.

Batch no.	Specific surface area ±SD (m^2 g)	Particle size (μm)		
		D_{10}	D_{50}	D_{90}
1	2.257 ± 0.010	2.7	6.3	10.8
2	2.249 ± 0.017	2.7	6.2	14.5
3	2.316 ± 0.006	2.5	5.7	9.9

D_{10}, D_{50}, and D_{90} are the particle size at 10%, 50%, and 90%, cumulative frequency, respectively.

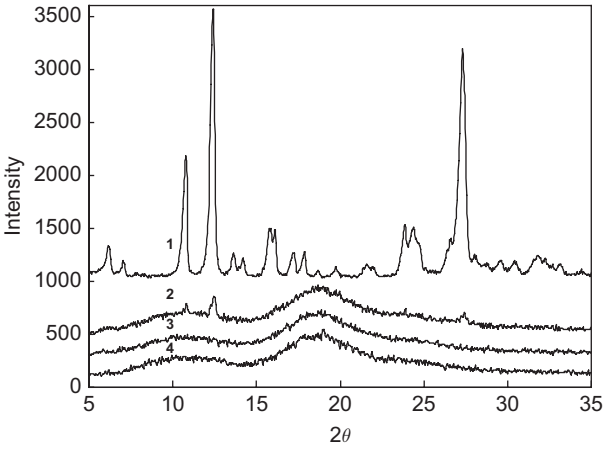

Figure 3. Powder X-ray diffraction patterns of (1), QC dihydrate; (2), physical mixture of QC dihydrate and blank spray-dried HP-β-CD (1:5.5 molar ratio); (3), spray-dried complex of QC with HP-β-CD (1:5.5 molar ratio); (4), blank spray-dried HP-β-CD.

Powder X-ray diffraction

The PXRD patterns of QC dihydrate raw material, physical mixture, spray-dried complex, and spray-dried HP-β-CD are shown in Figure 3. The diffractogram of QC dihydrate exhibited a series of intense peaks, indicative of its crystalline nature[3]. However, no diffraction peak was apparent with HP-β-CD, suggesting that it is essentially amorphous. The PXRD pattern of the physical mixture of QC dihydrate with blank spray-dried HP-β-CD was a composite pattern of the individual compounds, indicating no formation of new physical form. Only the crystalline peaks characteristic of QC dihydrate at 2θ = 12.4° and 27.3° could be observed in the physical mixture. The PXRD of the spray-dried QC complex with HP-β-CD showed broad and diffuse pattern with no intense peaks, indicating an essentially amorphous nature. Thus, it would appear that QC was molecularly dispersed in the amorphous HP-β-CD matrix.

Fourier-transform infrared spectroscopy

Previous FTIR studies on the HP-β-CD/QC complex in solid form have employed samples prepared with equal molar amounts of the two materials by either lyophilization[8] or kneading[9]. The former method involved the use of an alkali (ammonia solution at ~pH 11) to enhance the solubility of QC in water while the latter entailed trituration of the solid mixture with a small amount of ethanol–water (1:1 v/v). However, in addition to the lack of stability control alluded to earlier, neither method can achieve complete complexation for the substrate. To maintain the stability of QC and to ensure its full conversion to the complex form, this study has used HP-β-CD in excess (i.e., at a QC to HP-β-CD molar ratio of 1:5.5) to prepare the solid complex from aqueous solution by spray drying. Presented in Figure 4 are the spectra of the spray-dried complex and the reference 1:1 solid sample prepared from ethanol by rotary evaporation. Comparison of the spectrum of the spray-dried complex with those of the pure QC and blank HP-β-CD revealed that the spectra of the spray-dried complex and blank HP-β-CD were virtually identical (Figure 4A), indicating substantial masking of the absorption bands of QC by those of HP-β-CD present in excess. In contrast, the rotary-evaporated 1:1 sample showed absorption bands characteristic of QC in the 1500–1800 cm^{-1} range (Figure 4B). In addition, the carbonyl absorption band at 1667.9 cm^{-1} (corresponding to the aromatic ketonic carbonyl stretching) was shifted to 1654.48 cm^{-1}, consistent with the spectral changes reported for a similarly prepared 1:1 binary mixture of QC and HP-β-CD[9]. This would suggest the formation of a complex between QC and HP-β-CD, but similar spectral shifts of QC in the spray-dried complex could not be verified because of the excess amount of HP-β-CD present.

Thermal analysis

As shown in Figure 5A, QC dihydrate displayed a broad dehydration endotherm at 80–130°C (substantiated by mass loss in TGA), followed by a melting endotherm of the anhydrate at 310–330°C (T_m = 318.2°C). The expected exotherm because of molecular rearrangement to give the anhydrate form was not discernible. No sharp endothermic transition above 100°C was observed with the spray-dried HP-β-CD (Figure 5B), indicative of its amorphous nature. For the physical mixture of QC dihydrate with HP-β-CD (Figure 5C), only the endotherm corresponding to the dehydration of QC could be observed at around 80–130°C in the first scan. For the spray-dried HP-β-CD/QC complex (Figure 5D), neither endotherm nor exotherm could be observed, suggesting that the complex is amorphous. This was further substantiated by the presence of broad diffuse maxima and coherent scatters instead of sharp defined peaks in the X-ray diffraction patterns of the complex (Figure 3). In addition, as HP-β-CD was found to decompose at temperatures below the melting point of QC, the melting behaviors of QC in the physical mixture or spray-dried samples containing HP-β-CD could not be monitored by DSC.

To characterize the amorphous state of the various materials, T_g measurements were conducted. T_g of an amorphous material is normally sensitive to the presence of foreign molecules if there is significant physical interaction between the host and the guest molecules. For instance, water is a well-documented plasticizer that can lower the T_g of hydrophilic polymeric materials by enhancing their molecular mobility and rearrangement in the solid state[12]. In this study, if QC was indeed

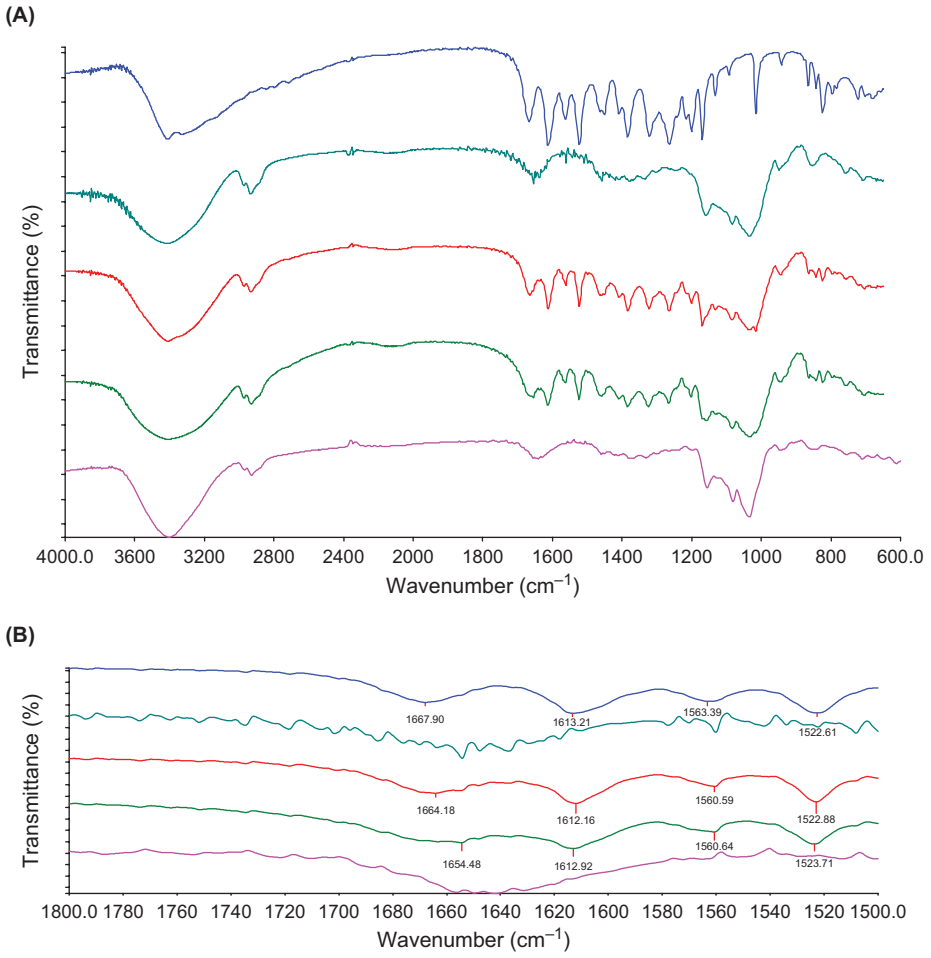

Figure 4. FT-IR spectra at full range (A), and within the 1500–1800 cm^{-1} range; (B), of QC dihydrate, HP-β-CD, physical mixture of QC and HP-β-CD (1:1 molar ratio), binary mixture of QC and HP-β-CD (1:1 molar ratio) prepared from ethanol by rotary evaporation, and spray-dried complex of QC with HP-β-CD (1:5.5 molar ratio) (from top to bottom).

molecularly dispersed in HP-β-CD, the amorphous complex would only display a single T_g.

As shown in Figure 5B–D, the blank spray-dried HP-β-CD material, its physical mixture with QC dihydrate, and the spray-dried complex of HP-β-CD with QC all exhibited a single and essentially the same T_g (220.4°C, 220.4°C, and 219.6°C, respectively), which was not significantly altered by repeated scans. Similar results could be observed at different DSC-scanning rates (10, 20, 30, and 40 K/min; data not shown). The T_g (~220.4°C) observed with HP-β-CD is consistent with that reported in the literature[13,14].

The single and virtually identical T_g values for the blank spray-dried HP-β-CD and the complex samples are open to two interpretations. First, the binary complex is a homogeneous mixture (i.e., with complete miscibility), and QC may stay mostly within the hydrophobic cavity of HP-β-CD such that it exerts negligible impact on the intermolecular interactions (which are assumed to occur predominantly at the outer molecular surface of HP-β-CD) and hence on the molecular mobility and rearrangement of HP-β-CD. Second, the T_g of QC may be masked by the excess amount of HP-β-CD present. Li et al.[15] have demonstrated that the number of T_g observed for various lyophilized binary mixtures of quinapril and β-CD depended on the relative proportion and miscibility of the two components in the mixtures. Physical mixture of these two compounds in a 1:1 molar ratio displayed two T_g values, one for β-CD (50°C) and the other for quinapril (70°C). Lyophilized mixtures prepared in two different molar ratios (i.e., with β-CD or quinapril in excess) also exhibited two T_gs, one for a homogeneous binary system (64°C) and the other for a separate β-CD (50°C) or quinapril (70°C) phase when present in excess[15]. In this study, the T_g of QC could not be measured by DSC, as rescanning of its melt resulted in significant decomposition. Spray drying also could not be used to prepare pure amorphous QC material for T_g measurement because of similar thermal decomposition problem; only about 5% of QC could be recovered

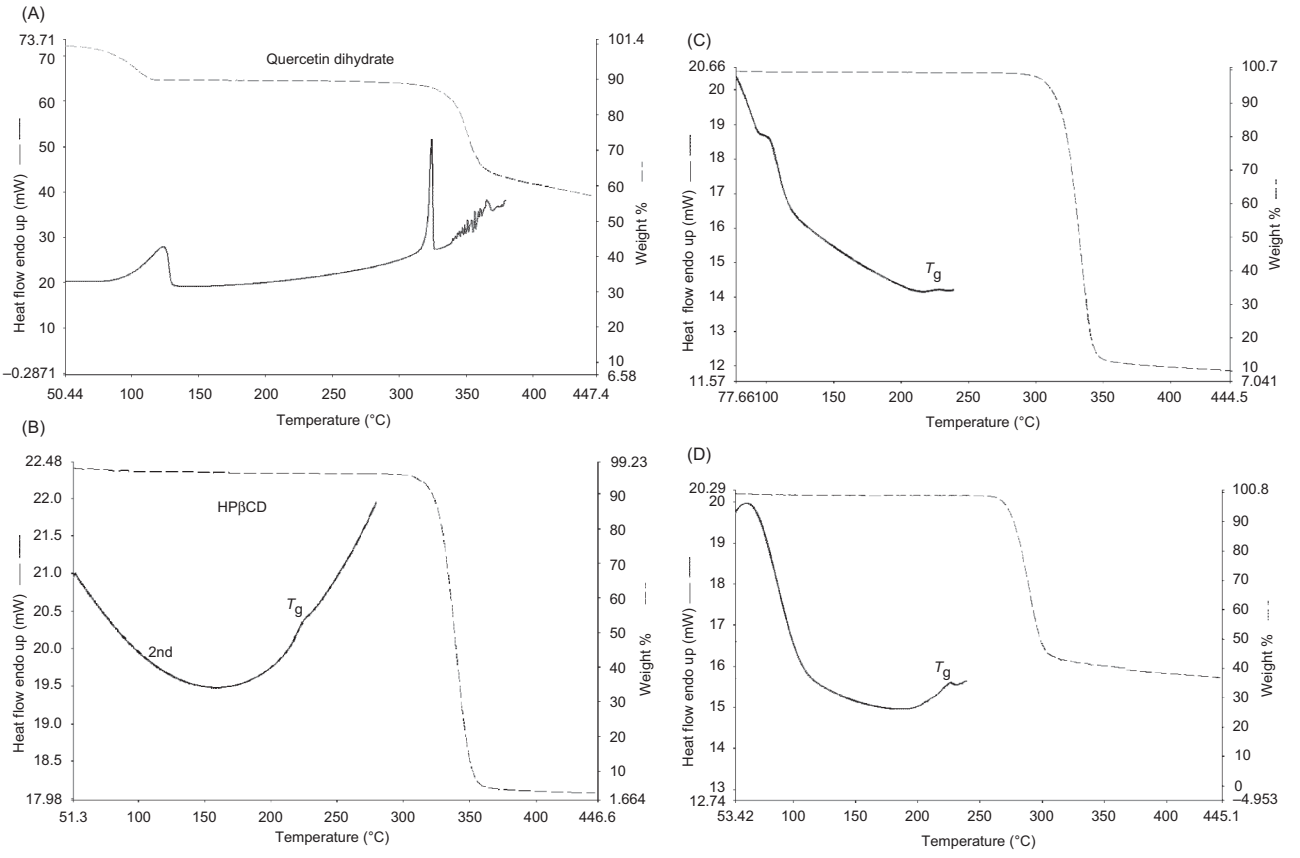

Figure 5. DSC and TGA profiles obtained at a heating rate of 10°C min^{-1} for (A), QC dihydrate; (B), blank spray-dried HP-β-CD; (C), physical mixture of QC dihydrate and blank spray-dried HP-β-CD (1:5.5 molar ratio); (D), spray-dried complex of QC with HP-β-CD (1:5.5 molar ratio).

from spray-dried samples. Furthermore, the HP-β-CD was found to degrade rapidly once the scanning temperature reached 300°C. Thus, the T_g determination of the complex and the physical mixture had to be confined to the temperature range of 50–240°C. Fortunately, the T_g of HP-β-CD (~220.4°C) falls within this scanning range, which makes possible the reliable measurement of this thermal parameter. For the physical mixture of QC dihydrate with HP-β-CD, the observed T_g (~220.4°C) appeared to be independent of the number of heating scans and entirely attributable to the HP-β-CD. This is perhaps not unexpected since the anhydrous QC with a T_m of 318.4°C is unlikely to show any phase transition within this scanning range.

In summary, the single T_g observed for the solid complex suggests that the QC is molecularly dispersed in the HP-β-CD matrix, possibly in the form of an inclusion complex, because the T_g is essentially the same as that of amorphous HP-β-CD. This is further substantiated by the observation that the QC retained fully its chemical integrity when co-spray dried with HP-β-CD whereas only about 5% of QC was recoverable when being spray-dried alone. As shown by Li et al.[15], molecular dispersion of quinapril in β-CD in a 1:1 molar ratio afforded almost full protection of the guest quinapril from thermal decomposition by the host β-CD in the solid state whereas the trehalose and dextran matrices offered no such protection. The authors attributed this protective effect to a possible carryover of specific interactions (possibly complexation) between β-CD and quinapril from solution to the solid state[15].

Dissolution studies

Comparative dissolution studies were conducted on the three different batches of spray-dried complex versus the physical mixture of QC and HP-β-CD in the same molar ratio (which serves as the control), as shown in Figure 6. QC was rapidly released from the complex and reached saturation equilibrium within minutes. In contrast, only about 10% of QC could be dissolved from the physical mixture, and the equilibrium was reached at a much lower saturation concentration, equivalent to the intrinsic solubility in simulated gastric fluid (pH 1.2) at 37°C (about 1.1 μg/mL). The dissolution profiles of the three separate batches of spray-dried complex were comparable within experimental errors (Figure 6). The drastic enhancement of dissolution of the spray-dried complex compared

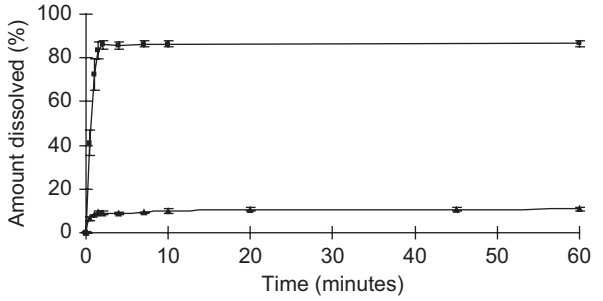

Figure 6. Dissolution-time profiles of spray-dried QC/HP-β-CD complex and physical mixture of equivalent composition in simulated gastric fluid (pH 1.2) at 37°C. Key: (■), QC/HP-β-CD complex; (▲), physical mixture ($n = 3$).

with the physical mixture may be explained by either the formation of a water-soluble complex (>4 mg/mL) as substantiated by the observed A_L-type behavior in our previous phase solubility study[4] or the molecular dispersion of QC in an amorphous HP-β-CD matrix.

According to the Noyes–Whitney equation[16], the amount of solute dissolved per unit time, dm/dt, is proportional to the surface area, A, and the difference between the concentration at time t, C_t, and the solubility, C_s (i.e., $C_s - C_t$). Under sink conditions, i.e., when $C_s >> C_t$, $dm/dt = KAC_s$ where K is a constant incorporating the diffusion coefficient (D), solution volume (V), and diffusion thickness (h) terms, assuming that dissolution is diffusion-controlled. In this study, the formation of a water-soluble complex or solid dispersion of QC in HP-β-CD will lead to an increase in C_s and hence an increase in dissolution rate. Surface area (as depicted by the 'A' term in the equation) was probably not a dissolution-controlling factor here because the specific surface area of the QC dihydrate powder (14.2 ± 0.07 m^2 g) was about seven times that of the spray-dried complex (Table 1), and yet, the dissolution rate of the complex was about eightfold higher than that of the QC dihydrate in the physical mixture.

Conclusion

Consistent batches of amorphous solid complex of QC and HP-β-CD could be readily obtained by spray drying, as verified by HPLC, SEM, thermal analysis, PXRD, BET surface analysis, laser-diffraction particle sizing, and dissolution testing. The amorphous complex exhibited excellent thermal stability during spray drying, a broad diffuse X-ray diffraction pattern, and a single glass transition temperature (T_g) characteristic of amorphous HP-β-CD. The apparent lack of influence of incorporated QC on the T_g of HP-β-CD in the complex possibly reflects preferential inclusion of QC within the hydrophobic cavity of HP-β-CD. In addition, the complex displayed extremely rapid dissolution in simulated gastric fluid compared with its molar equivalent physical mixture of QC and blank spray-dried HP-β-CD, although the surface area of QC in the mixture was much larger than that of the complex. All these observations may be explicated by specific interaction between QC and HP-β-CD in the solid state, possibly in the form of an inclusion complex.

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***Declaration of interest*:** The authors report no conflicts of interest.

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