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Research Article

Phase Solubility Study of Quercetin in Presence of Cyclodextrins and Hydrophilic Polymers.

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ABSTRACT
The present study was undertaken to investigate the effect of presence of hydrophilic polymer on the complexation efficiency of cyclodextrins and solubility of quercetin. The phase solubility studies were carried out in presence and absence of hydrophilic polymers (hydroxypropylmethylcellulose, polyvinylpyrrolidone K30 and poloxamer 188) to study their effect on the stability and complexation efficiency of CDs. The phase solubility studies revealed the formation of QUN-βCD and QUN-HPβCD complexes with 1:1 stoichiometry. The incorporation of POLO increased the stability as well as complexation efficiency of CDs.

KEYWORDS
Quercetin, Cyclodextrins, Phase Solubility, Stability Constant, Complexation Efficiency.

INTRODUCTION

Quercetin (QUN) is found in many plants and is a well known bioflavonoid. The scientists have explored its various biological activities like anticancer, antiinflammatory and antibacterial activity. Most of therapeutic benefits of QUN are related to its antioxidant activity. QUN also shows antihypertensive, antiobesity, antihypercholesterolemic and antiatherosclerotic activities [1–4]. Despite of these benefits, it is observed that QUN shows poor bioavailability when administered orally, due to its poor solubility [5].

Cyclodextrins (CDs) are cyclic oligosaccharides which are often used to enhance the solubility of poorly soluble drugs. Some researchers have prepared inclusion complexes of QUN with βCD and HPβCD to increase its solubility [1–5]. Although it is known that the hydrophilic polymers improve the complexation efficiency of CDs, the effect of hydrophilic polymers on the complexation in between QUN and CDs is not investigated.

This study aims at performing the phase solubility analysis to determine the effect of hydrophilic polymers such as hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone K30 (PVP) and poloxamer 188 (POLO) on the complexation in between QUN and CDs (βCD and HPβCD).

MATERIALS AND METHODS

Materials

QUN, βCD and polyvinylpyrrolidone K30 (PVP) were purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India. HPβCD was obtained as a gift sample from Gangwal Chemicals, Mumbai, India. Hydroxypropylmethylcellulose E15LV (HPMC) was purchased from Loba Chemie, Mumbai, India and Poloxamer 188 (POLO) was obtained from Signet Chemicals, Mumbai, India. The analytical grade reagents and glass distilled water were used (for the experimental procedures) throughout the experimental procedures.

Phase solubility studies

The phase solubility studies were performed in distilled water at room temperature (25 ± 2^{o}C) according to the method reported by Higuchi and Connors (6). The excess quantity of QUN was added to 20 mL of βCD and HPβCD solutions (0 to 0.01 M) in the presence and absence of auxiliary substances (0.5%w/v of HPMC, PVP and POLO). The resultant suspensions were shaken for 72 h at 150 rpm using rotary shaker (Lab HOSP, India) to attain equilibrium. Thereafter, suspensions were filtered using Whatman filter paper No. 41, appropriately diluted if necessary and analyzed to determine concentration of QUN using UV-spectrophotometer (Shimadzu 1800, Japan) at 371 nm. The stoichiometry between QUN and CDs was established from the phase solubility curves obtained by plotting the concentration of dissolved QUN (moles/liter) against the respective concentration of CDs (moles/liter). The stability constants (K_S) of the binary and ternary complexes were calculated using the equation (7).

$$K_s = \frac{Slope}{S_0\ (1-Slope\ )} \text{-----(1)}$$

Where, S_0 is the solubility of QUN in distilled water.

The complexation efficiency (C.E.) of CDs was determined by the following equation (7).

$$C.E. = K_s S_0 = \frac{Slope}{(1-Slope)} \text{-----(2)}$$

Gibbs free energy change (ΔG_{tr}) in Joules/mole was also calculated to assess the thermodynamics of the solution and complexation process, using the equation

$$\Delta G_{tr} = -2.303\, RT log \frac{S_c}{S_0} \text{-----(3)}$$

Where, S_c is molar solubility of QUN in aqueous solution of HPβCD or βCD in the presence or absence of hydrophilic polymer, S_0 is molar solubility of QUN in distilled water, R is gas constant and T is temperature in Kelvin.

RESULTS AND DISCUSSION

The phase solubility diagram of QUN in aqueous solutions of βCD and HPβCD in the presence or absence of hydrophilic polymers (HPMC, PVP and POLO) are shown in Fig. 1 (a and b). These diagrams exhibited a linear relationship between the amount of solubilized QUN and concentration of solution of CDs (A_L-type of curves) which signifies formation of water soluble complexes (8).

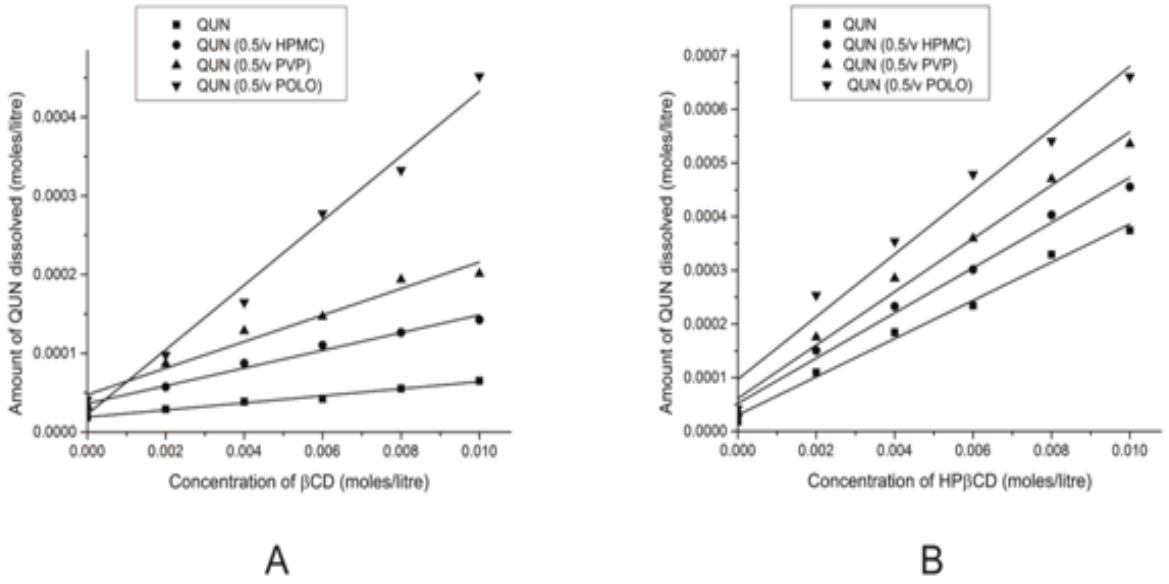

Figure 1. Phase solubility profile of QUN-βCD (A) and QUN-HPβCD (B) systems in distilled water (■) and in presence of 0.5 %w/v HPMC (●), 0.5 %w/v PVP (▲) and 0.5 %w/v POLO (▼).

Table 1 shows the values of slope, stability constant (Kc) and complexation efficiency of the systems considered under phase solubility studies. The slope of phase solubility curves for all the systems was found to be less than one indicating 1:1 stoichiometry between QUN and CDs (6). The presence of hydrophilic polymer caused increase in the stability of the formed complexes along with enhancement in the complexation efficiency of the CDs. This can be attributed to the molecular interactions in between QUN, CDs and hydrophilic polymers such as hydrogen bonding, formation of hydrophobic bonds and van der Waals interaction (9–11).

Table 2 represents the Gibbs free energy change ($G_{tr}\circ$) in the systems with increase in the concentration of CDs. A decrease in the $G_{tr}\circ$ values with respect to increase in the CD concentration indicated the spontaneous nature of QUN solubilization suggesting that the reaction became more favorable with the increase in the concentration of CDs. The negative $G_{tr}\circ$values indicated the exothermic nature of the complexation process (12). The system comprised of QUN, HPβCD and POLO showed maximum stability, high complexation efficiency and lowest value of $G_{tr}\circ$. This may be due to high solubility of HPβCD than βCD and ability of POLO to change the microstructure of the complex along with the rheological properties which in turn can enhance the complexation efficiency of HPβCD.

Table 1. Phase solubility data of binary and ternary inclusion complexes of QUN with βCD and HPβCD.

QUN/CD systems	**Phase solubility parameters**		
	Slope	**$K_{c,1:1}$ (M^{-1})**	**C.E.**
QUN/βCD	0.0044	240.29	0.0045
QUN/βCD/HPMC (0.5%w/w)	0.0112	597.07	0.0113
QUN/βCD/PVP (0.5%w/w)	0.0168	888.86	0.0171
QUN/βCD/POLO (0.5%w/w)	0.0409	2111.71	0.0427
QUN/HPβCD	0.0355	1842.43	0.0368

QUN/βCD/HPMC (0.5%w/w)	0.0445	2286.90	0.0466
QUN/HPβCD/PVP (0.5%w/w)	0.0495	2531.76	0.0521
QUN/HPβCD/POLO (0.5%w/w)	0.0634	3193.08	0.0677

Kc,1:1: stability constant; QUN: quercetin; βCD: β-cyclodextrin; HPβCD: hydroxypropyl-β-cyclodextrin; HPMC: hydroxypropyl-methylcellulose; PVP: polyvinylpyrrolidone K30; POLO: poloxamer 188.

Table 2. Gibbs free energy change (ΔG_{tr}) in Joules/ mole.

Moles of CDs	**QUN/βCD system**				**QUN/HPβCD system**			
	Without polymer	**HPMC (0.5% w/v)**	**PVP (0.5% w/v)**	**POLO (0.5% w/v)**	**Without polymer**	**HPMC (0.5% w/v)**	**PVP (0.5% w/v)**	**POLO (0.5% w/v)**
0.002	-1106.59	-2763.41	-3775.98	-4066.73	-4351.07	-4784.12	-5493.93	-5882.08
0.004	-1787.38	-3788.49	-4734.52	-5344.12	-5618.43	-6189.87	-6686.10	-7215.45
0.006	-2019.85	-4359.08	-5057.65	-6619.67	-6204.44	-6823.86	-7253.22	-7956.97
0.008	-2671.12	-4692.82	-5739.18	-7060.87	-7040.59	-7535.44	-7911.77	-8254.63
0.01	-3065.31	-4988.21	-5829.53	-7812.84	-7353.55	-7949.54	-8228.41	-8896.33

CDs: cyclodextrins; QUN: quercetin; βCD: β-cyclodextrin; HPβCD: hydroxypropyl-β-cyclodextrin; HPMC: hydroxypropylmethylcellulose; PVP: polyvinylpyrrolidone K30; POLO: poloxamer 188.

CONCLUSION

The stability and complexation efficiency of βCD and HPβCD was markedly improved by POLO than the other hydrophilic polymers. Therefore, POLO can be used for the preparation of the multicomponent inclusion complexes of QUN to enhance its solubility and hence its bioavailability.

CONFLICT OF INTEREST

Authors declare no conflict of interests.

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