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Multicomponent Systems of Econazole with Hydroxyacids and Cyclodextrins

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Abstract

The effect of the type of cyclodextrin (α-, β-, γ-, hydroxypropyl-β-CD) and of hydroxyacid (tartaric, citric, gluconic, malic, lactic) on the solubility enhancement by multicomponent complexation of econazole, a poorly water soluble base-type drug, was studied. A synergistic effect was found in ternary systems, largely more effective than corresponding binary complexes and salts. Moreover, the presence of a third component made effective the use of γ-CD, which had no solubilizing power in binary systems. The solubilizing efficiency of multicomponent systems was not related to the solubilities of the corresponding salts or binary complexes. Phase-solubility analysis at different temperatures was also used to investigate the interaction of econazole with cyclodextrins, alone or in the presence of hydroxyacid. The best 1 : 1 : 1 molar ratio system was that with α-CD and malic acid which showed the best solubilizing power and the highest stability constant of the ternary complex. Ternary α-CD products, prepared by co-grinding, co-evaporation or colyophilization, were characterized by Differential Scanning Calorimetry and tested for dissolution properties. The higher solubilizing properties of multicomponent systems were reflected in better drug dissolution rates from their solid systems.

Introduction

Cyclodextrins have received increasing interest in the pharmaceutical field because of their ability to favourably modify physical, chemical and biological properties of drug molecules through the formation of inclusion complexes [1]. Cyclodextrin complexation has been widely used to improve the stability, solubility, dissolution rate and bioavailability of a number of hydrophobic drug molecules [2, 3]. However, due to various reasons (such as their high molecular weight, relatively low water solubility and possible parenteral toxicity), the amount of cyclodextrins that can be used in most solid and liquid drug formulations is limited. Therefore, it should be important to find methods to enhance the complexation and solubilization efficiency, thus making it possible to considerably reduce the cyclodextrin dose. Among the methods proposed with this aim, it has been reported recently that the addition of certain low molecular weight acids or hydroxyacids can enhance the cyclodextrin solubilization of basic drugs by orders of magnitude in comparison to classic drug-cyclodextrin binary systems [4–7]. Nevertheless it was also shown that such multicomponent cyclodextrin complexation was not always effective [8].

Econazole is an imidazole antifungal agent suitable for the treatment of many micotic infections, applied topically, in the treatment of infections of the skin, hair and mucous membranes, and administered by mouth or by intravenous infusion in the treatment of systemic fungal infections [9]. Unfortunately, its very low water solubility (about 5 μg/mL at 25 °C) limits both its therapeutic application and efficacy. We previously showed that conventional complexation with α- and β-cyclodextrins significantly improved both water solubility and antifungal activity of econazole [10]. Other papers reported the favourable effect of cyclodextrin complexation on both the physicochemical properties and biological efficacy of econazole and other imidazole derivatives [11–15]. However, the greatest enhancement of solubility attainable for econazole by this conventional complexation method was not enough to reach the drug concentration required for commercial pharmaceutical formulations (1%w/v) [9].

Preliminary studies showed the effectiveness of multicomponent complexation in the presence of acids to further improve the econazole solubility [16]. Therefore, it seemed of interest to extend our studies and to investigate the effect of the type of cyclodextrins and acids on econazole solubility enhancement by multicomponent complexation. The solubilizing efficiency of the various ternary systems was compared with that of classic drug-cyclodextrin binary complexes or of the simple salts of the drug with the different acids examined. Phase-solubility analysis at different temperatures was used to investigate the interaction of econazole with cyclodextrins, alone or in the presence of a third component. The effect of solubility enhancement on drug dissolution rate was determined by testing, according to the dispersed amount method, solid binary and ternary systems obtained by different techniques (physical mixing, co-grinding, co-evaporation or colyophilization). Differential Scanning Calorimetry was used to check the amorphous

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or crystalline state of econazole in the various solid combinations and to demonstrate possible interactions between the components in the solid state.

Experimental

Materials

Econazole (1-[2-(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl) ethyl)-1H-imidazole, ECO) was kindly donated by Italfarmaco (I-Genova); γ-cyclodextrin (γ-CD) and hydroxypropyl-β-cyclodextrin (average substitution degree 0.9 per anhydroglucose unit, HPβCD) were a gift of Wacker Chemie (D-München). Commercial α-cyclodextrin (α-CD) and β-cyclodextrin (β-CD), nitric, citric, D-gluconic acids and racemic malic, tartaric and lactic acids were purchased from Sigma (USA, St. Louis, MO). Equimolar drug-acid salts, drug-CD complexes and drug-acid-CD multicomponent systems were prepared by freeze drying (Lyovac GT2, Leybold-Heraeus) their aqueous solutions.

Solubility studies

Solubility measurements of ECO and its equimolar salts with the different acids, equimolar complexes with the different CDs and equimolar drug-CD-acid systems were performed by adding excess amounts of drug or each product to 10 mL of water in sealed glass containers which were stirred 48 h at 25 ± 0.5 °C. The solutions were then filtered (0.45 μm filter pore size) and assayed for drug concentration by second derivative UV spectroscopy [10] using a Perkin Elmer Mod 552S spectrophotometer (USA-Norwalk). The presence of CD or acid did not interfere with the spectrophotometric assay. Each test was repeated four times (C.V. $< 3\%$).

Phase-solubility diagrams in water at 25, 37 and 45 °C were obtained according to Higuchi and Connors [17]. In binary systems, excess drug was added to 10 mL aqueous solutions containing increasing concentrations of CD in sealed glass containers and electromagnetically stirred (500 rpm) at constant temperature until equilibrium was reached (48 h). In ternary systems, equimolar amounts of ECO and acid were stirred in the presence of increasing amounts of CD, until equilibrium (48 h). Then the solutions were filtered (0.45 μm filter pore size) and assayed for drug concentration by UV spectroscopy as described above. Experiments were performed in triplicate (C.V. $< 3\%$). The 1 : 1 stability constants of drug-CD complexes were calculated from the slope of the initial straight portion of the phase-solubility diagrams [17].

Preparation of α-cd complexes by different techniques

Physical mixtures (P.M.) of binary and ternary systems of ECO with α-CD and malic acid were prepared by tumble mixing for 15 min 4–5 g of the respective single components in equimolar ratios. Ground products (GR) were prepared by grinding for 60 min physical mixtures (about 1 g) in a micro-vibrational mill (Retsch, GmbH, Düsseldorf, Germany) (volume of the mill 12 mL). Co-evaporated products (COE) were obtained by dissolving the physical mixtures in an ethanol-water solution (1.3:1.0 v/v) at room temperature, removing the solvent under vacuum in a rotatory evaporator at 50 °C, and drying the residue under vacuum at room temperature up to constant weight. Colyophilized products (COL) were prepared as described above by freeze-drying ECO-α-CD, ECO-malic acid or ECO-α-CD-malic acid equimolar aqueous solutions (Lyovac GT2, Leybold-Heraeus). Before being subjected to the dissolution test, each product was sieved and the 75–150 μm granulometric sieve fraction was collected.

Dissolution studies

Dissolution studies were performed at 37 ± 0.5 °C according to the dispersed amount method by adding 50 mg of ECO or ECO equivalent to 75 mL in a 100 mL beaker, where a glass three-blade propeller was centrally immersed and rotated at 100 ± 1 rpm. At appropriate time intervals, suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm) and spectrophotometrically assayed for drug content as described above. A correction was calculated for the cumulative dilution caused by replacement of the sample with an equal volume of original medium. Each test was repeated 4 times (C.V. $<2\%$). The parameters used to characterize the dissolution curves were the percentage of drug dissolved at 10min, the dissolution efficiency (calculated according to Khan [18]), and the relative dissolution rate at 2min (ratio between amount of drug dissolved from a given system and amount dissolved from drug alone at 2min).

Differential scanning calorimetry

Temperature and enthalpy values were measured with a Mettler TA4000 system, equipped with a DSC 25 cell, on 3–5 mg samples (Mettler M3 microbalance) in Al pans with perforated lids at the heating rate of 10 K min^{-1} in the 30–200 °C temperature range under a static air atmosphere.

Results and discussion

Solubility studies

ECO solubility improvement obtained by classic binary complexation with natural cyclodextrins, though effective at improving its antimicotic activity [10–12, 14, 15], was nevertheless inadequate for practical utilization in liquid pharmaceutical dosage forms, all marketed at 1% w/v [9]. Therefore, since ECO is a basic drug, multicomponent complexation with acids was attempted to intensify solubilization by cyclodextrins [4, 19] and several acids were selected to test their effectiveness as possible ternary components. Citric, D-gluconic, (±) tartaric, (±) lactic and (±) malic acids were chosen as promising candidates due to their potential ability, all being hydroxy and/or polycarboxylic

Table 1. Aqueous solubility (mg/mL) at 25 ± 0.5 °C (standard deviations in brackets) of ECO and its 1 : 1 salts with various acids, 1 : 1 complexes with cyclodextrins and 1 : 1: 1 ECO-CD-acid ternary systems, and Relative Increment (R.I.)[a] of drug solubility

Acid	–		α-CD		γ-CD		β-CD		HPβCD	
	mg/mL	R.I.	mg/mL	R.I.	mg/mL	R.I.	mg/mL	R.I.	mg/mL	R.I.
	0.0050	–	0.620	120	0.0070	1.4	0.235	50	0.260	50
	(±0.0004)		(±0.020)		(±0.0004		(±0.007)		(±0.008)	
Nitric	0.48	100	5.6	1120	1.90	380	3.5	700	3.1	620
	(±0.01)		(±0.1)		(±0.05)		(±0.1)		(±0.1)	
Lactic	3.35	670	11.6	2320	6.8	1360	11.6	2320	11.4	2280
	(±0.09)		(±0.3)		(±0.1)		(±0.3)		(±0.3)	
Gluconic	2.70	540	11.5	2300	6.9	1380	10.5	2100	8.7	1740
	(±0.07)		(±0.2)		(±0.1)		(±0.2)		(±0.2)	
Tartaric	0.95	190	10.1	2020	8.4	1680	9.1	1820	8.4	1680
	(±0.02)		(±0.2)		(±0.2)		(±0.2)		(±0.2)	
Citric	3.50	700	12.4	2480	7.7	1540	12.3	2460	12.2	2440
	(±0.09)		(±0.3)		(±0.2)		(±0.3)		(±0.4)	
Malic	1.70	340	12.8	2560	8.6	1720	11.9	2380	9.9	1980
	(±0.04)		(±0.3)		(±0.2)		(±0.3)		(±0.2)	

[a] R.I.= ratio between drug solubility in binary or ternary system and that of drug alone.

Table 2. Aqueous solubility (mg/mL) at 25 ± 0.5 °C (standard deviations in brackets) of ECO in ternary systems at 1 : 1 : 2.5 ECO-CD-acid molar ratios and Relative Increment (R.I.)[a] of drug solubility

Acid	α-CD		γ-CD		β-CD		HPβCD	
	mg/mL	R.I.	mg/mL	R.I.	mg/mL	R.I.	mg/mL	R.I.
Lactic	22.5	4500	17.7	3540	17.7	3540	22.0	4420
	(±0.6)		(±0.5)		(±0.5)		(±0.6)	
Gluconic	21.3	4260	16.3	3260	18.4	3680	20.8	4160
	(±0.5)		(±0.4)		(±0.5)		(±0.6)	
Tartaric	12.8	2560	10.3	2060	14.3	2860	16.9	3380
	(±0.3)		(±0.2)		(±0.3)		(±0.4)	
Citric	19.2	3840	16.9	4160	16.6	3320	18.3	3660
	(±0.5)		(±0.5)		(±0.4)		(±0.5)	
Malic	12.4	2280	6.5	1310	10.9	2180	9.1	1830
	(±0.3)		(±0.1)		(±0.2)		(±0.2)	

[a] R.I. = ratio between drug solubility in ternary system and that of drug alone.

acids, to interact with cyclodextrin molecules by forming hydrogen bonds with their numerous hydroxyl groups [5]. Nitric acid was selected as well, because ECO-nitrate is the only salt at present used in commercial pharmaceutical formulations [9]. As for cyclodextrins, in addition to the natural ones (α-, β-, and γ-CDs), HPβCD was selected, due to its higher solubility than the parent β-CD, the least soluble of the natural cyclodextrins (about 18 mM at 25 °C).

For a preliminary screening to select the best combinations, aqueous solubilities of ECO in binary (1 : 1 molar ratio) and ternary (1 : 1 : 1 molar ratio) systems with CDs and acids at 25 °C were determined (please see Table 1). As regards binary systems, among the examined cyclodextrins, α-CD showed the highest solubilizing power, followed by HPβCD and β-CD, whereas γ-CD was practically ineffective. Salt formation was always more effective than classic CD complexation in increasing drug solubility, except in the case of the nitrate salt. However the highest solubility values obtained by salt formation (0.33–0.35% w/v with lactic or citric acids) were still lower than the desired level for an optimal utilization and efficacy of the drug. The simultaneous presence of acid and CD always gave a synergistic effect and was clearly more effective in increasing the aqueous solubility of ECO, in comparison with both binary complexation (up to more than 20 or 50 fold in comparison with α-CD or β-CD alone) and salt formation (up to more than 7 fold). The most surprising results were obtained in ternary systems containing γ-CD, where high levels of drug solubility were achieved (up to more than 1800 fold the original drug solubility and 1200 fold that with γ-CD alone) even though a very poor solubilizing power was shown by this CD in binary combination with ECO. In ternary systems with β-CD, a simultaneous solubility enhancement both for the drug and the CD was observed, as already reported in the literature [19–21]. Nevertheless, in our case, the increase in the initial aqueous solubility of β-CD (about 18 mM at 25 °C) was rather limited and ranged from 40% (in ternary systems with malic acid) to 80% (in ternary systems with gluconic acid), or at most about 100% (in ternary systems with lactic or citric acids). However, among the various examined tern-

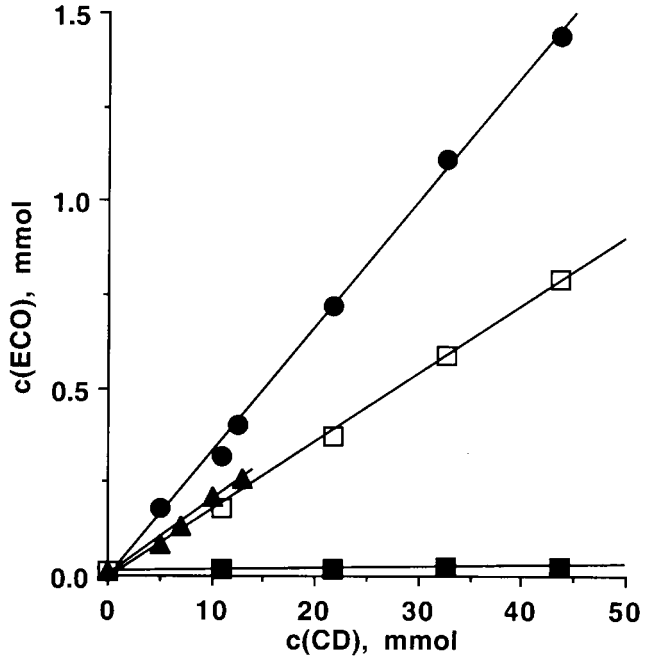

Figure 1. Phase-solubility diagrams of ECO with (●) α-CD, (▲) β-CD, (□) HPβ-CD, and (■) γ-CD in water at 25 °C.

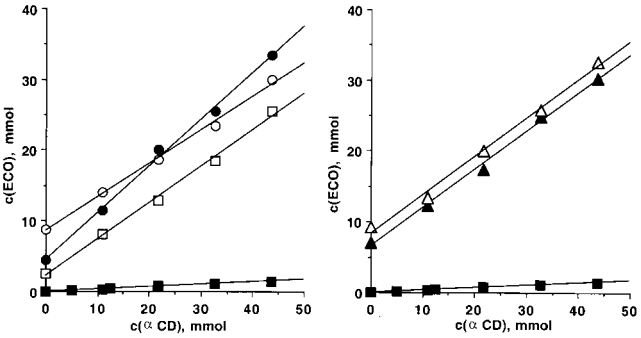

Figure 2. Phase-solubility diagrams of ECO with α-CD (■) alone or in the presence of equimolar amounts of (□) tartaric, (●) malic, (○) lactic, (▲) gluconic, and (△) citric acids in water at 25 °C.

ary systems, those containing α-CD were generally the best, giving in almost all combinations with the various acids the highest improvement of drug solubility and reaching or even exceeding the desired drug solubility level (1% w/v), except in the combination with nitric acid.

The effect of the acid was found to be dependent on the cyclodextrin and there was not an acid which was always the most effective in all the examined ternary systems, even though nitric acid was in all cases the worst and therefore it was no longer considered in further studies. The synergistic effect of various acids on cyclodextrin drug solubilization was not related to either the pH of the aqueous solution or the solubility of the corresponding drug salts. In fact, for example, citric and tartaric acid showed a considerably different behaviour in ternary systems with ECO and the various examined CDs, even though their aqueous solutions had about the same pH (pH $\approx$ 3 in the presence of 30 mM citric or tartaric acid). Furthermore, malic acid was more efficacious than gluconic or lactic acids, even though the ECO-malate salt was clearly less soluble than the gluconate or lactate salts. Moreover, even though a further increase of drug solubility was generally obtained by further increasing the acid amount in the ternary system (passing from 1 : 1 : 1 to 1 : 1 : 2.5 molar ratios), such effect was of very different degree for the various acids, and even in the case of malic acid a decrease of drug solubility was observed (Table 2). In fact, whereas for example malic and citric acids were the best in 1 : 1 : 1 molar ratio ternary systems with α-CD, followed by gluconic and lactic acids, if one considers the same systems at 1 : 1 : 2.5 molar ratios, lactic and gluconic acids became the best, followed by citric acid, and malic acid became the worst.

Phase-solubility studies of ECO in binary and ternary systems with cyclodextrins and acids were then performed to obtain more information about the drug solubilization mechanisms and the multicomponent complex formation. Solubility diagrams with all the examined cyclodextrins were of the A_L type [17], indicating the formation of soluble binary complexes of probable 1 : 1 stoichiometry (Figure 1). The values of the 1 : 1 stability constants were 2630 ± 260, 1540 ± 150, 1420 ± 130 and 20 ± 2 M^{-1} for α-CD, HPβCD, β-CD and γ-CD, respectively, i.e., in the same order of their solubilizing power, thus confirming the stronger interaction of ECO with α-CD and indicating that in aqueous media its cavity size better accommodates the molecular portion of the drug involved in the inclusion. This was also proved by Nuclear Magnetic Resonance and Nuclear Overhauser Effect studies which showed that either of the ECO phenyl moieties can be favourably inserted into the α-CD cavity [22]. On the other hand, γ-CD confirmed the very low interaction with ECO observed in solubility studies. Owing to the higher affinity of ECO for α-CD, further phase-solubility studies on ternary systems with acids were therefore performed only with this cyclodextrin. Solubility diagrams obtained by adding increasing amounts of α-CD to 1 : 1 mol/mol ECO-acid mixtures, all showed a linear increase of drug aqueous solubility as a function of CD concentration (Figure 2). The intercepts of the various curves corresponded to the solubilities of the relevant 1 : 1 salts, whereas the slopes were directly related to the solubilizing power of the system. Therefore we assumed as an index of the solubilizing efficiency of a given ternary system the ratio between the slope of its solubility phase curve (S_t) and that of the corresponding drug-CD binary system (S_b) (please see Table 3). The apparent stability constants of 1 : 1 : 1 multicomponent complexes ECO-acid-α-CD were calculated from the slope and intercept of the straight line portion of the phase-solubility diagrams according to Higuchi and Connors [17] (Table 3). It is evident that all the examined ternary systems were clearly more effective than the simple binary system with α-CD in improving drug solubility, and their relative solubilizing efficiency (S_t / S_b) was from 14 to 20 fold higher than the binary complex. However, in all cases a decrease of drug-CD interaction was observed, as indicated by the sharp reduction of the stability constant values. Such an effect was explained on the basis of the higher initial drug solubility, due to the salt formation, and of

Table 3. Stability constants ($K_{1:1}$) at 25 °C (standard deviations in brackets) of complexes of ECO with α-CD, alone or in the presence of acids, and relative solubilizing efficiency (S_t/S_b)[a]

Acid	$K_{1:1}$ (M^{-1})	S_t/S_b
–	2630 (±260)	–
Tartaric acid	429 (±38)	15.7
Citric acid	130 (±12)	16.5
Malic acid	448 (±42)	20.1
Gluconic acid	169 (±16)	16.4
Lactic acid	103(±10)	14.4

[a] Ratio between the slopes of the solubility phase curves of ternary (S_t) and binary (S_b) systems.

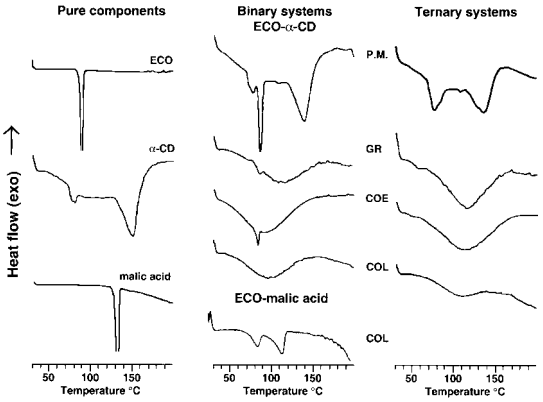

Figure 3. DSC curves of pure components and binary and ternary physical mixtures (P.M.), ground (GR), co-evaporated (COE) and colyophylized (COL) products of ECO-α-CD, ECO-malic acid, and ECO-α-CD-malic acid systems.

increased ionization of ECO in the presence of various acids (pH 3.2-4) with consequent less affinity for the apolar CD cavity [23, 24]. However, the differences observed between the stability constant values obtained in the presence of the various acids did not result from either the different drug ionization degree, because the pH of the various solutions was practically the same, or from the different solubilities of the various salts and therefore they might be reasonably attributed to the more or less good steric fit the hydroxy acid provides for the drug with CD. A study performed to examine the effect of several alcohols, with varying alkyl chains, on the β-CD-pyrene complex, demonstrated the importance of the proper size of the third component on the stability of ternary complexes [25]. Such a factor could concur to explain the best solubilizing efficiency of multicomponent systems containing malic acid, even though the solubility of the corresponding salt with ECO is less than that of citrate or lactate salts or higher than that of tartrate salt, which was on the contrary the least effective. The role of the third component to stabilize the multicomponent complex was particularly evident in the case of γ-CD, where the acid probably acts as a space-regulating molecule [26], narrowing the CD cavity and thus allowing the drug inclusion and solubilization. In confirmation of this, preliminary results of phase-solubility studies performed on ternary systems with γ-CD (unpublished data) showed that, contrary to that observed with α-CD, the stability constants at 25 °C of 1 : 1 : 1 ternary complexes ECO-acid-γ-CD were from 4 up to 8 fold higher (in the presence of lactic or citric acid, respectively) than that of the corresponding binary complex.

Standard thermodynamic parameters related to the complexation process of binary and ternary systems of ECO with α-CD and malic acid were calculated from phase-solubility diagrams on the basis of the temperature dependency of the apparent stability constant within the 25–45 °C temperature range (Table 4). The unfavourable entropy changes obtained for both systems were outweighed by the large negative enthalpy values and the net results were negative ΔG values. The negative enthalpy values suggested that both dipolar or induced dipolar and van der Waals interactions, as well as hydrogen bonds, are involved in the complex formation. This may be a result of interactions between host and guest

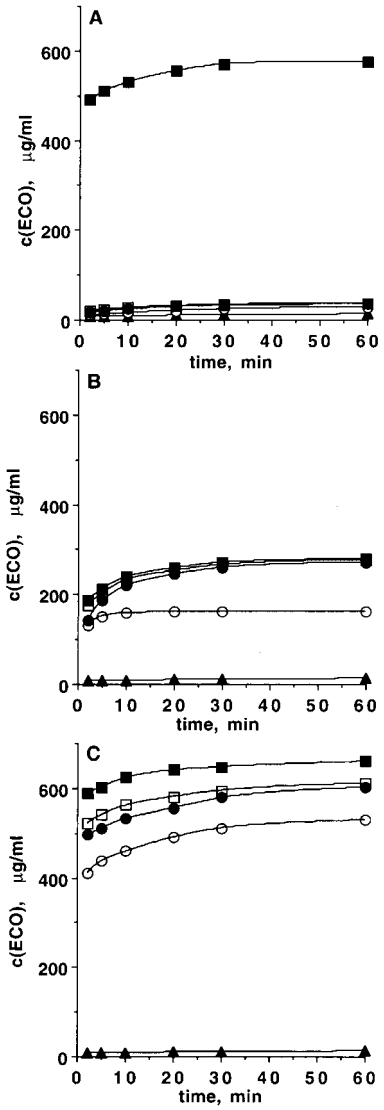

Figure 4. Dissolution curves of ECO alone (▲) and from binary and ternary (○) physical mixtures, (□) ground, (●) coevaporated and (■) colyophylized products of (A) ECO-α-CD, (B) ECO-malic acid and (C) ECO-α-CD-malic acid systems. (Mean of four experiments, CV<2%, error bars omitted for the sake of clarity).

Table 4. Thermodynamic parameters of ECO binary complexation with α-CD and ternary complexation with α-CD and malic acid

	ECO-α-CD			ECO-α-CD-malic acid		
Temperature	25 °C	37 °C	45 °C	25 °C	37 °C	45 °C
$K_{1:1}$ (M^{-1})	2630	1310	610	448	235	186
ΔG (kJ/mol)	−19.5	−18.5	−16.9	−15.1	−14.1	−13.8
ΔH (kJ/mol)	−44.5	–	–	−41.4	–	–
ΔS (J/mol K)	−83.8	–	–	−88.2	–	–

Table 5. Percent drug dissolved of the total amount added, dissolution efficiency,[a] and relative dissolution rate[b] of ECO from binary and ternary physical mixtures (P.M.), ground (GR), co-evaporated (COE) and colyophilized (COL) products with α-CD and malic acid (standard deviations in brackets)

Sample	% dissolved at 10 min	Dissolution efficiency	Relative dissolution rate at 2 min
ECO	1.30 (±0.02)	1.60 (±0.03)	1
ECO-α-CD, P.M.	2.40 (±0.05)	3.30 (±0.06)	1.4
ECO-malic acid, PM.	24.2 (±0.5)	23.1 (±0.4)	18
ECO-α-CD-malic acid, P.M.	69.2 (±1.5)	73.3 (±1.4)	56
ECO-α-CD, GR	4.10 (±0.08)	4.72 (±0.09)	2.7
ECO-malic acid, GR	35.0 (±0.6)	37.1 (±0.7)	24
ECO-α-CD-malic acid, GR	84.3 (±1.5)	86.2 (±1.7)	71
ECO-α-CD, COE	3.60 (±0.07)	4.41 (±0.08)	2.3
ECO-malic acid, COE	32.2 (±0.6)	36.1 (±0.7)	20
ECO-α-CD-malic acid, COE	80.1 (±1.5)	84.0 (±1.6)	68
ECO-α-CD, COL	79.2 (±1.4)	81.1 (±1.5)	67
ECO-malic acid, COL	36.2 (±0.7)	38.0 (±0.7)	25
ECO-α-CD-malic acid, COL	93.3 (±1.7)	94.3 (±1.8)	80

[a] Calcu1ated from the area under the dissolution curve at 60 min and expressed as % of the area of the rectangle described by 100% dissolution in the same time of the total amount added.
[b] Ratio between amount of drug dissolved from a given system and amount dissolved from drug alone at 2 min.

molecules and/or changes on complex formation of the behaviour of the water associated with interacting molecules. Analogous values found for both systems seem to indicate similar basic mechanisms of complexation and inclusion mode of the guest molecule in the host cavity. However, due to the greater complexity of the ternary systems, no definite conclusion can be made on the basis of the present data, and further studies are in progress to better elucidate the role of malic acid on the multicomponent complex formation.

Solid state studies

Binary and ternary equimolar solid systems of ECO with α-CD and malic acid were prepared by physical mixing, co-grinding, co-evaporation and colyophilization techniques. The DSC curves of pure components and the respective drug-CD or drug-CD-acid equimolar systems prepared by the various methods are shown in Figure 3. The thermal curve of ECO (T_{peak} = 89.0 °C, ΔH_{fus} = 73.9 J g^{-1}), as well as that of malic acid (T_{peak} = 132.0 °C, ΔH_{fus} = 213.6 J g^{-1}), indicated their crystalline anhydrous state. Liberation of crystal water from α-CD (7.2 ± 0.2% as mass fraction) was observed as a broad endothermal effect ranging between 60 and 160 °C. The thermal curve of the ECO α-CD physical mixture was the simple superimposition of those of the pure components and the typical drug melting endotherm was clearly sharp and intense (T_{peak} = 86.4 °C, ΔH_{fus} = 67.0 J g^{-1}). Instead it shifted to lower temperature and markedly reduced in intensity in co-evaporated and even more in co-ground products as a consequence of interaction between the components [27]. The total disappearance of the drug endothermal effect observed for systems obtained by freeze-drying indicated the complete formation of amorphous product and/or inclusion complexation. It was verified that the lyophilization process did not substantially affect the solid state properties of ECO. In fact the thermal behaviour of the lyophilized drug alone was similar to that of the untreated sample, indicating that it maintained its crystallinity almost unchanged [10]. In the case of ECO-malic acid equimolar systems, a clear broadening and reduction in intensity of both drug and acid melting peaks was observed even in the DSC curve of the physical mixture (not shown); nevertheless, both the thermal effects were always well detectable, also in the corresponding colyophilized product. As for the ternary systems, the physical mixture displayed

a marked lowering (T_{peak} = 76.0 °C) and broadening of the ECO melting peak, indicative of an evident loss of crystallinity and more marked interactions between the components than in the corresponding binary system. The malic acid endothermal effect was almost completely hidden by the dehydration band of α-CD. The complete disappearance of the drug melting peak was observed in all the other systems, a phenomenon undoubtedly indicative of strong interactions in the solid state.

Dissolution rate studies

The mean dissolution curves of ECO from various binary and ternary systems are presented in Figure 4. The results in terms of dissolution efficiency, percent of active ingredient dissolved and relative dissolution rate are collected in Table 5. It was verified that different treatments of pure drug, including grinding and lyophilization, did not produce appreciable variations of its dissolution properties, and the various dissolution curves were practically superimposable. It appears evident that all the examined systems exhibited faster dissolution rates than of the drug alone. The increased dissolution rate of the binary drug-CD physical mixture is attributable both to improvement in drug wettability and to formation of readily soluble complexes in the dissolution medium [28]. As for the other binary systems with α-CD, colyophilization was definitely the most effective technique in achieving the enhancement of drug dissolution rate (80% of drug dissolved at 10 min), probably due to complete drug complexation and/or amorphization, whereas co-ground and co-evaporated products were only slightly better than the simple physical mixture. The ECO-malic acid physical mixture was more effective than co-evaporated or co-ground products with α-CD, but clearly worse than the colyophilized one. Co-evaporation, co-grinding or colyophilization only slightly improved the performance of the ECO-malate salt. The multicomponent systems with malic acid always showed much better dissolution properties than the corresponding ones with α-CD alone, confirming their higher effectiveness. In fact not only was the ternary colyophilized product absolutely the best (about 93% of drug dissolved at 2 min), but the co-evaporated and co-ground products (80 and 84% respectively of drug dissolved at 10 min) were also as effective as the binary colyophilized product, and the simple ternary physical mixture was clearly better than both binary drug-CD co-ground or co-evaporated products and ECO-malate salt.

Conclusions

The multicomponent complex formation between a base-type drug, such as ECO, a CD and a hydroxyacid as third component was confirmed as an optimal tool for enhancing the drug solubility. Enhancement of the drug solubilizing power of α-CD by multicomponent complex formation allowed the attainment of the solubility level of ECO required for pharmaceutical formulations (1%w/v) using only 3.7% of α-CD, whereas it was not possible to attain such a value in simple binary systems, not even at the saturation concentration of α-CD (14.5%w/v). However, our studies showed that the best combination for an optimal drug solubilization can be determined only on the basis of experimental observations. In fact the solubilizing capacity of a given multicomponent system was not related either to the corresponding salt or binary complex solubility and the optimal drug:CD:acid molar ratio was different for the various systems. Interestingly it was found that the presence of a third component made it possible to consider the utilization of γ- CD, which instead had no complexing power for ECO in simple binary systems. The best 1 : 1 : 1 molar ratio system was that with α-CD and malic acid, which combined the greatest solubilizing efficiency with the highest stability constant of the ternary complex. The effect of higher drug solubility enhancement obtained with multicomponent systems was also reflected in better drug dissolution rates of ternary solid products.

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