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ORIGINAL ARTICLE

Combined effect of hydroxypropyl methylcellulose and hydroxypropyl-β-cyclodextrin on physicochemical and dissolution properties of celecoxib

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Abstract Investigation on the influence of hydroxypropyl methylcellulose (HPMC) on solubility and dissolution properties of celecoxib/hydroxypropyl-β-cyclodextrin system was carried out, with the ultimate goal of enhancing the drug bioavailability. ^{1}H-NMR and ^{13}C-NMR spectroscopy were first performed to elucidate the type of interactions between celecoxib (CEL) and hydroxypropyl-β-cyclodextrin (HP-β-CD). Then, solubility studies in the absence and in the presence of HPMC were carried out in aqueous solution. After heating in autoclave of CEL/HP-β-CD/HPMC suspensions a synergistic increasing effect on the aqueous solubility of CEL was observed. In fact, the presence of both HP-β-CD (0.05 M) and HPMC (0.25% w/v) gave rise to a 330-fold CEL solubility increase, whereas the cyclodextrin alone provided a 34-fold increase. Gibbs free energy values calculated from phase solubility data were all negative, indicating the spontaneous nature of CEL solubilization, and they decreased in the presence of HPMC, demonstrating that the solubilization conditions became more favorable. CEL/HP-β-CD and CEL/HP-β-CD/HPMC solid systems (physical mixtures and coevaporated products) were characterized by differential scanning calorimetry and infrared spectroscopy. Results suggested that the coevaporation method yields a high degree of amorphous entities and indicated the formation of a CEL/HP-β-CD complex in the coevaporated products. The positive effect of HPMC is particularly evident when looking at the CEL dissolution rate from the binary and ternary solid systems. Specifically, the percent of CEL dissolved after 10 min. resulted 84.21% for ternary coevaporated product and 50.18% for binary coevaporated product with respect to 13.10% for the drug alone.

Keywords Celecoxib · Dissolution · Hydroxypropyl-β-cyclodextrin · Hydroxypropyl methylcellulose · Inclusion complex · NMR · Ternary systems

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Introduction

Celecoxib, 4-[5-(4-methylphenyl)-3-trifluoromethyl-1-H-pyrazol-1-yl]benzene sulphonamide, is the first synthesized NSAID able to selectively inhibit cyclooxygenase-2 (COX-2) activity [1–3]. The drug is recommended for treating osteoarthritis and rheumatoid arthritis, and for the management of the pain of these conditions [4].

Celecoxib (CEL) is a poorly water soluble and highly lipophilic (apparent logP of 3.01) drug and exhibits a low oral bioavailability (between 22% and 40%) that is dissolution rate limited [5]. Hence, the increase of CEL dissolution rate becomes crucial for achieving improved pharmacokinetic parameters, but also for reducing the dosage of the drug with consequent advantages from an economic and toxicological point of view.

A suitable strategy to increase CEL aqueous solubility and dissolution rate can be the co-formulation of the drug with cyclodextrins (CDs). These cyclic oligosaccharides can be used because they possess a hydrophilic outer surface and a somewhat lipophilic central cavity. This property of CDs has been used in the pharmaceutical field to obtain inclusion complexes with various apolar drug molecules to modify the physicochemical characteristics (water

solubility, stability, dissolution rate) of the included compound. However, CD complexation depends on the type and degree of drug-CD interactions. These, in turn, are governed by the structural features of specific drug and the CD.

Recently, studies on complexation of CEL with different cyclodextrins (β-CD, hydroxypropyl-β-CD and dimethyl-β-CD) have been reported in literature [6–9] showing that the CDs significantly increased drug solubility and dissolution rate.

The aim of this study was to improve CEL solubility properties, with a view to enhancing the bioavailability of CEL, utilizing the approach of inclusion complexation of the drug with HP-β-CD in the presence of a water soluble polymer, namely hydroxypropyl methylcellulose (HPMC). In fact, the association of small portion of water-soluble polymers to CDs has been proved to increase their complexation efficiency and solubilizing effect [10–12]. This therefore represents a useful strategy to decrease the CD amount that can actually be used in most solid and liquid drug formulations.

In our investigation, first, NMR and phase solubility studies on the binary system CEL/HP-β-CD were performed to confirm the existence and elucidate the type of interactions between the drug and the carrier. Then, the effect of HPMC, alone or associated with HP-β-CD on CEL solubility was evaluated and data were analyzed through Gibbs free energy calculations. Solid binary and ternary systems were prepared by physical mixing and coevaporation methods and characterized by DSC analysis and FT-IR spectroscopy; for each solid system the dissolution profile was determined and the relative parameters were calculated for evaluating the performance of the different mixtures in enhancing CEL dissolution rate and individuate the one to use for preparing drug formulations with the promise of greater bioavailability than that obtained with the commercial available formulations.

Experimental

Materials

Celecoxib (CEL) was purchased from Unichem Laboratories (Mumbai, India); Hydroxypropyl-β-cyclodextrin DS 0.76 (HP-β-CD) was kindly provided by Roquette (Lestrem, France). Hydroxypropyl methylcellulose 4000 (HPMC) was purchased from Prodotti Gianni (Milan, Italy). These chemicals were used as received, without further purification.

All other chemicals and solvents were of analytical reagent grade purity. Double distilled water was used throughout the study.

Solution studies system CEL/HP-β-CD

NMR spectroscopy

^{1}H and ^{13}C-NMR spectra were recorded on a Varian 400 spectrometer. Solutions containing 2×10^{-2} M of CEL or equivalent amount of CEL/HP-β-CD (1:1 mol/mol) were prepared in CD_3OD-D_2O (1:1 v/v) solution to facilitate drug solubilization. Spinning tube of 4 mm i.d. containing 0.5 mL of solution were employed. Tetramethylsilane was used as external reference and no correction was made for the susceptibility of the capillary. Chemical shifts were calibrated with an accuracy of 0.01 ppm.

Solubility studies

Phase solubility studies were performed in unbuffered water for both binary and ternary systems, according to the Higuchi and Connors method [13]. For binary systems an excess amount of CEL (10 mg) was added to 10 mL of water or HP-β-CD aqueous solutions (from 1×10^{-2} to 1×10^{-1} M) in screw-capped glass vials. The samples were mechanically shaken (SS40-D Grant shaking bath) at 25 °C until equilibrium was reached (3 days at least).

Solubility studies of CEL were also carried out adding HPMC (from 0.1 to 0.5% w/v) to the suspensions in the absence and in the presence of a fixed amount of HP-β-CD (0.05 M). In this case the suspensions formed were also heated in an autoclave in sealed containers to 120 °C for 20 min, and were than allowed to equilibrate in the shaking bath at 25 °C for 7 days. Separate experiments showed that this period of time was sufficient, since longer equilibration times (up to 14 days) did not result in further drug precipitation.

Phase solubility studies for ternary systems were performed in the same manner as for binary systems, but in the presence of a fixed amount of HPMC 0.25% (w/v) and increasing amount of HP-β-CD (from 1×10^{-2} to 5×10^{-2} M). The suspensions were also placed in an autoclave at 120 °C for 20 min and treated as described above. All the suspensions were withdrawn, filtered (filter HA-0.45 μm, Millipore) and spectrophotometrically analysed for CEL content (Shimadzu UV-1204 spectrophotometer) at 248.5 nm. The presence of HP-β-CD and/or HPMC did not interfere with the spectrophotometric assay of the drug. Each experiment was performed in triplicate; the coefficient of variation associated with each measurement was never greater than 3%.

Preparation of solid systems

Binary CEL/HP-β-CD and ternary CEL/HP-β-CD/HPMC solid systems were prepared by physical mixing and co-

evaporation methods. The latter technique is generally useful for obtaining inclusion complexes in the solid state.

Physical mixtures

Equimolar physical mixture (PM_b) of CEL and HP-β-CD was prepared by homogeneous blending in a mortar of exactly weighed amount of the 75–150 μm sieved *(IG3/WET/MS, Giuliani, Torino)* granulometric fractions of the two components, until a homogeneous mixture was obtained.

For ternary physical mixture (PM_t) 2% (w/w) of HPMC was added to the CEL/HP-β-CD (1/1 mol/mol) binary system.

All mixing procedures were performed adopting the geometric method.

Coevaporated products

Coevaporated CEL/HP-β-CD (1/1 mol/mol) binary system (CO_b) was prepared by dissolving equimolar amounts of two components in ethanol, since drug solubility in water is very low, and evaporating the obtained solution under vacuum at 40 °C in a rotatory evaporator (Heidolph, Laborota). Then, the solid residue was dried at 40 °C under a vacuum (Mazzali, Milano) up to constant weight.

For ternary coevaporated product (CO_t), equimolar amounts of CEL and HP-β-CD were dissolved in ethanol; to this solution an exact volume of a 1% (w/v) HPMC aqueous solution was added, so that the final concentration of HPMC in the solid system was 2% (w/w). The resulting dispersion was magnetically stirred at room temperature until an homogeneous one was obtained and treated as described above.

Both, the CO_b and CO_t systems were sieved and the 75–150 μm granulometric fractions were collected and used for the following tests.

Differential scanning calorimetry

DSC analysis was carried out on a DSC 2920 (TA Instruments, USA). Samples were weighted (2 mg) (Mettler M3 microbalance) in Al pans pierced with a perforated lid, and scanned at 10 °C/min in the 25–200 °C temperature range. Dry nitrogen was used as purge gas.

Infrared spectroscopy

FT-IR spectra (KBr disk) were obtained on a JASCO FTIR-430 apparatus applying Fourier transformation of 8 scans.

Dissolution studies

The dissolution profiles of CEL and its binary CEL/HP-β-CD and ternary CEL/HP-β-CD/HPMC solid systems were evaluated according to the disperse amount method. 25 mg of drug or equivalent amount of the blends were added to 350 mL of water (non-sink conditions) at 37 ± 0.5 °C, in a Sotax AT7 apparatus. Suitable aliquots were removed at scheduled times, filtered and spectrophotometrically analyzed for CEL content (see solubility studies). A correction was calculated for the sampling. Each test was performed in triplicate (coefficient of variation <3%).

Dissolution process was characterized through the percent of the drug dissolved after 10 min (calculated with respect to the highest solubilized drug amount) and the relative dissolution rates of the binary and ternary systems, calculated as the ratio of the amount of drug dissolved at 10 min to that obtained with the pure drug.

Results and discussion

Solution studies on the binary system CEL/HP-β-CD

^{1}H-NMR and ^{13}C-NMR studies on CEL in the absence and in the presence of HP-β-CD were performed to gain insight into the type of interactions between CEL and HP-β-CD in solution. NMR analysis was only performed on drug molecule. The differences in chemical shift values between CEL in the free and in complexed state are presented in Fig. 1. The atoms showing the highest variations in chemical shift are only reported; the negative sign of $\Delta\delta$ (i.e., the difference in CEL chemical shifts in the presence and in the absence of HP-β-CD) refers to an upfield shift, whereas the positive sign indicates a downfield shift.

A significant upfield shift is evident (Fig. 1A) for the H4 proton of the pyrazole nucleus ($\Delta\delta$ = –0.09), which could be due to the shielding effect produced by oxygen atoms of hydroxypropyl groups of the HP-β-CD ring close to H4 atom [9]. On the other hand the downfield shifts observed for H5, H8-10, H13-17, H14-16 protons are probably a consequence of a deshielding effect due to Van der Waals forces between this portion of the drug molecule and carbohydrate chains.

^{13}C-NMR studies provided more specific and supplementary information on the environment of individual carbons and intermolecular interactions. Chemical shift variations of CEL indicated that CEL/HP-β-CD interactions occurred, which could be due to inclusion complexation. In fact, according to Inoue Model [14], carbon atoms deeply inserted in the CD cavity (from the secondary hydroxyl group side) experience a negative shift [15, 16]. Therefore, the great upfield shift of C4 carbon atom ($\Delta\delta$ = –0.22) (see Fig. 1B) could suggest that the heterocyclic ring is included within the HP-β-CD cavity. This hypothesis seems to be corroborated by the low intensity upfield shifts of the C6 and C19 atoms, that are bonded to

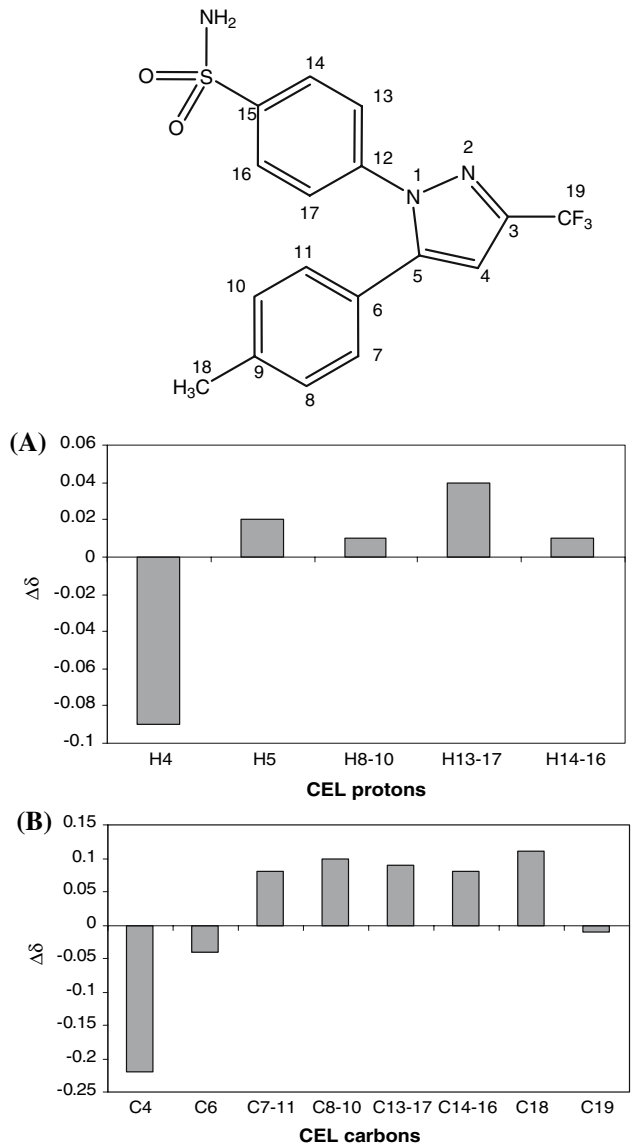

Fig. 1 Chemical shift changes of protons (**A**) and carbons (**B**) of CEL in the presence of HP-β-CD (1:1 molar ratio). $\Delta\delta = \delta$complex-δfree

this ring. Moreover, the downfield shifts of the C7-11, C8-10, C13-17 and C14-16 atoms of the two aromatic rings and that of the C18 atom of the methyl group suggest that these atoms are externally close to the wider rim of the hollow CD cone [17].

The equilibrium phase solubility plot of CEL in aqueous HP-β-CD solutions at 25 °C is reported in Fig. 2. The CEL solubility in water was 2.43 ± 0.06 μg/mL (6.4×10^{-6} M). In the presence of the CD the drug solubility increased proportionally as the HP-β-CD molar concentration increased, proving the formation of an inclusion complex in the solution. At the highest HP-β-CD concentration tested (1.0×10^{-1} M), a 80-fold CEL solubility increase was obtained. According to the Higuchi and Connors classification [13], the diagram obtained was of A_L type, since it was characterized by a straight line pattern. This type of diagram indicates the formation of a soluble drug-CD complex, thereby increasing the total amount of drug in solution.

Assuming a 1:1 stoichiometry of the complex (this assumption is usually made for A_L type diagrams in the absence of additional information), the apparent stability constant of the complex ($K_{1:1}$) was calculated from the slope of the phase solubility diagram using the Higuchi and Connors equation (1):

$$K_{1:1} = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

where S_0 is the CEL water solubility. The calculated $K_{1:1}$ value was 395 ± 9 M^{-1}.

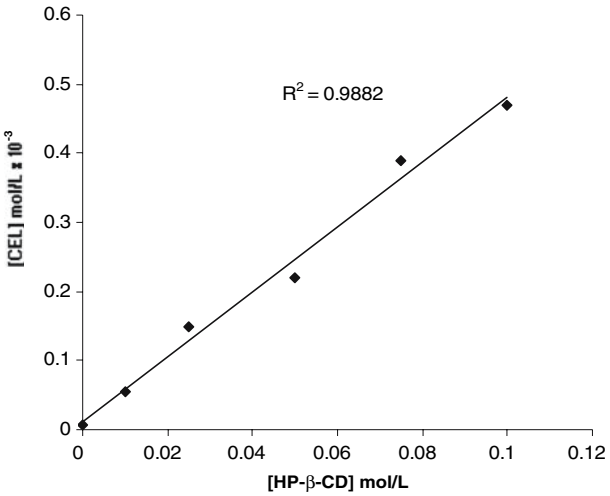

Fig. 2 Phase solubility diagram of CEL at increasing amounts of HP-β-CD (mean of three experiments, CV < 3%)

Effect of HPMC on CEL solubility

Solubility tests on CEL were carried out also in aqueous HPMC solutions (from 0.1 to 0.5% w/v) at 25 °C. Results (Fig. 3) show that the polymer alone was ineffective to increase drug solubility at the tested concentrations. On the other hand data obtained in the presence of both HP-β-CD (0.05 M) and HPMC (from 0.1 to 0.5% w/v) show that the solubilizing effect of HP-β-CD is unaffected by the presence of the polymer at different concentrations.

According to literature [11, 12, 18], water-soluble polymers may enhance drug solubilization induced by CDs when activated by heating. Consequently the same solutions were heated in autoclave at 120 °C for 20 min. After heating the solubility of CEL resulted remarkably enhanced when HPMC and HP-β-CD were jointly present in the solution, the 0.25% (w/v) of HPMC providing the

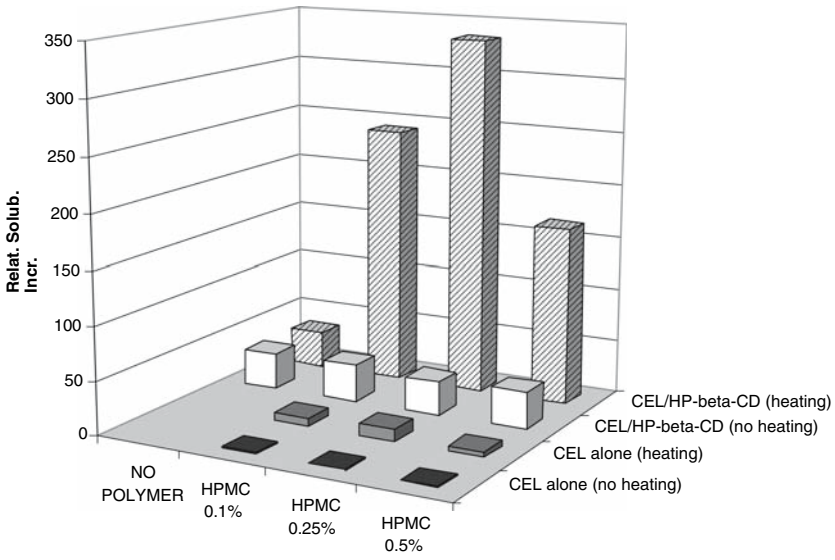

Fig. 3 Relative solubility increase of CEL in aqueous solutions at 25 °C containing different concentrations of HPMC alone or in the presence of 0.05 M of HP-β-CD. Measurements were carried out when no heating was performed and after heating at 120 °C (mean of three experiment, CV < 3%; error bars omitted for the sake of clarity)

best results. In fact, HPMC at 0.25% (w/v) gives a 11-fold CEL solubility increase, HP-β-CD provides a 34-fold increase whereas their association gives rise to a ~330-fold higher drug solubility value. Therefore, the solubilizing effect of the polymer is more then simply additive with that of the cyclodextrin; it is synergistic.

Taking into account these results, phase solubility studies of CEL at increasing amount of HP-β-CD (from 1.0×10^{-2} to 5×10^{-2} M) were carried out in the presence of 0.25% (w/v) HPMC and after heating in autoclave. Figure 4 shows that the presence of HPMC unchanged the type of phase solubility diagram which was still of A_L type, but slightly increased the apparent stability constant of the complex ($K_{1:1}$) that resulted 470 ± 12 M^{-1}.

Several mechanisms have been assumed to explain the improvement of the solubilizing and complexing effects of cyclodextrins in the presence of water-soluble polymers upon heating in autoclave. According to Loftsson [19] the water-soluble polymers alter the hydration of the CD molecule and thus its three-dimensional structure in aqueous solutions. Consequently, we can assume that the improved CEL solubilization after autoclaving could be due to facilitated fitting of the CEL molecule to the HP-β-CD cavity, resulting from differences in flexibility and conformational changes of HP-β-CD molecule in the presence of the polymer.

As a consequence of the improvement of the drug/CD complexation obtained by adding 0.25% (w/v)of HPMC and heating the solution at 120 °C for 20 min, less CD was required to dissolve a given amount of drug. As clearly shown in Fig. 5 the amount of HP-β-CD needed to obtain a CEL aqueous concentration of 200 mg/L was decreased from 151.05 g/L to 14.38 g/L (about 9 folds).

Gibbs free energy analysis

Indication about the process of solubilization of CEL in the presence of the CD alone or associated with the polymer was obtained from the values of Gibbs free energy change. The Gibbs free energy values of transfer ($\Delta G°_{tr}$) of CEL from pure water to the aqueous solutions of HP-β-CD and

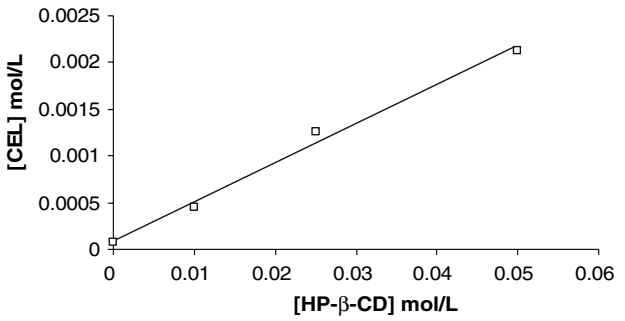

Fig. 4 Phase solubility diagram of CEL in aqueous HP-β-CD solutions containing 0.25% (w/v) of HPMC after heating at 120 °C (mean of three experiments, CV < 3%)

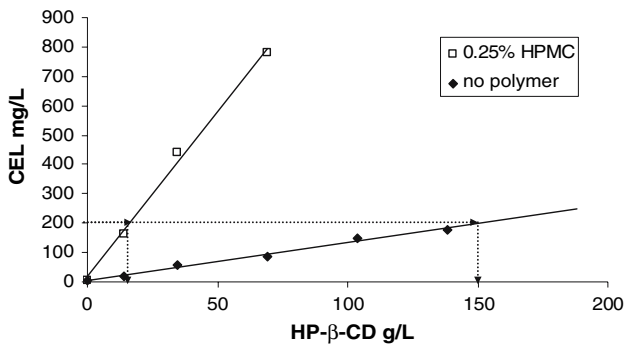

Fig. 5 Solubility of CEL in aqueous HP-β-CD solutions in the absence and in the presence of 0.25% (w/v) of HPMC

HP-β-CD/HPMC systems were calculated from phase solubility data using Eq.(2) [20]:

$$\Delta G^{\circ}_{tr} = -2.303RT \log \frac{S_S}{S_0} \quad (2)$$

where S_S/S_0 is the ratio of molar solubility of the drug in aqueous carrier solutions to that in pure water. The obtained values of Gibbs free energy are presented in Table 1. Data provide the information whether the reaction condition is favorable or unfavorable for drug solubilization in the aqueous carrier solutions, negative Gibbs free energy values indicating favorable conditions. ΔG°_{tr} values were all negative for HP-β-CD solutions at various concentrations, indicating the spontaneous nature of CEL solubilization, and they decreased with an increase in carrier concentration, demonstrating that the process became more favorable as the concentration of HP-β-CD increased. Moreover, it is worth of note that, when HPMC was added to HP-β-CD solutions, the ΔG°_{tr} values became much lower than in its absence, demonstrating that the condition of solubilization became more favorable when the water soluble polymer was present.

The synergistic effect of polymer on CEL solubility upon heating in an autoclave can be also due to its stabilizing action since it does not only enhance drug solubility by improving the stability of CEL/HP-β-CD complex but the water soluble polymer can retard or hinder the precipitation of CEL from its saturated solution formed by autoclaving [18].

Table 1 Thermodynamic parameters of the solubility process of CEL in HP-β-CD and HP-β-CD/HPMC solutions at 25 °C

HP-β-CD (mol/L)	ΔG°_{tr} (kJ/mol)	
	CEL/HP-β-CD	CEL/HP-β-CD/HPMC
0.01	–52.60	–103.97
0.025	–77.13	–129.14
0.05	–86.50	–142.04
0.075	–100.50	–
0.1	–105.06	–

Solid state studies

Binary (drug/HP-β-CD) and ternary (drug/HP-β-CD/HPMC) systems were prepared in the attempt to individuate the one to include in a innovative CEL formulation. Specifically, co-evaporated products were prepared and characterized by DSC and FT-IR analysis. Physical mixtures were also studied to make a comparison.

The DSC profiles of CEL and of the respective binary and ternary systems are shown in Fig. 6. The thermal curve

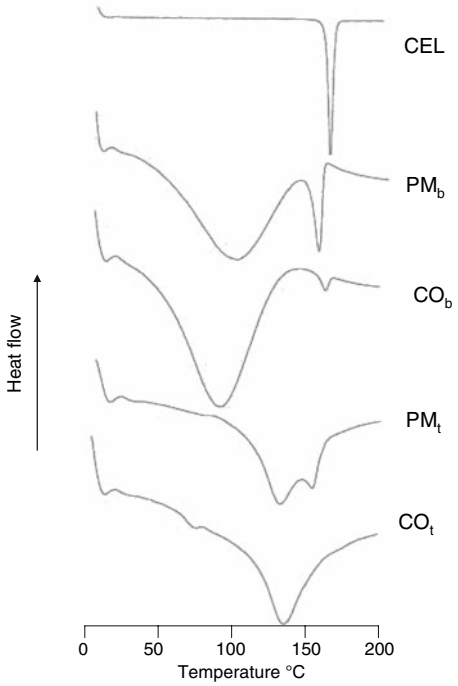

Fig. 6 DSC curves of drug alone (CEL), CEL/HP-β-CD binary systems (PM_b and CO_b) and CEL/HP-β-CD/HPMC ternary systems (PM_t and CO_t)

of pure CEL was typical of a crystalline anhydrous substance with a sharp endothermic peak at 163 °C corresponding to the melting point of the drug. The comparison of DSC curves from binary systems with those belonging to ternary systems resulted in significant differences. Both characteristic peaks of CEL (drug melting) and HP-β-CD (water loss) were clearly distinguishable in binary and ternary physical mixtures, being the DSC curves of those the superposition of the individual components, but in PM_t the peaks are broader than in PM_b. As far as the coevaporated products are concerned, the endothermic melting peak of CEL is significantly reduced in CO_b, whereas the same peak completely disappears in CO_t. A reduced intensity of drug melting peak can be the consequence of interaction between CEL and HP-β-CD. Specifically, the disappearance of an endothermic peak may be attributed to

Table 2 FT-IR characteristic bands (cm^{-1}) for CEL, for CEL/HP-β-CD systems (PM_b and CO_b) and for CEL/HP-β-CD/HPMC systems (PM_t and CO_t)

Sample	SO_2	CF_3	
CEL	1347.03	1230.36	1274.72
PM_b	1348.96	1230.36	1274.72
CO_b	1334.98	1237.59	1272.79
PM_t	1348.01	1237.11	1274.72
CO_t	1335.46	1237.59	1272.79

an amorphous state and/or to an inclusion complexation [21]. DSC results suggest that HPMC enhances drug/CD interaction and/or amorphization.

FT-IR spectroscopy has also been used to assess the interaction between CD and guest molecules in the solid state. Upon complexation, a significant shift in the characteristic peaks of the guest molecule to either a higher or lower frequency can be observed [22]. CEL alone shows strong absorption bands at 1166 cm^{-1} and at 1347 cm^{-1} assigned to the sulphonyl (SO_2) group for asymmetric and symmetric stretching respectively. Moreover, bands at 1230 cm^{-1} and 1275 cm^{-1} are evident, which are attributed to the trifluoromethyl (CF_3) group [23]. These bands are of diagnostic value to elucidate drug-CD interactions. In Table 2 the wavenumbers relative to the bands of CEL for the different samples are listed (the band at 1166 was masked by the CD signals). The absorption bands of the pure drug appeared unchanged in the PM_b. In the PM_t and in both CO_b and CO_t the band at 1230 cm^{-1} assigned to CF_3 group was recorded to higher wavenumber. On the contrary, the SO_2 band appeared markedly shifted to lower wavenumber in the CO_b and CO_t. These results suggest the formation of hydrogen bonding between the carrier and the drug molecule during inclusion complexation [6]. Furthermore, the presence of the polymer did not produce any significant change in the characteristic peaks of the drug when binary systems were compared with ternary systems.

Dissolution studies

The mean dissolution curve of CEL and those of its solid binary and ternary systems prepared to evaluate the effect of the presence of HPMC and of the preparation method are shown in Fig. 7. Mixtures containing polymer concentrations different than 2% (from 0.5 to 5%) were prepared and tested for dissolution rate but their performances did not result so good as that of the selected formulation (data not shown).

Table 3 shows the relative parameters of the dissolution process, i.e. the percentage of CEL dissolved within 10 min (DP) in the presence or in the absence of HP-β-CD and of HPMC, and the relative dissolution rate (RDR) of the binary and ternary systems calculated at t = 10 min. It is clear that all the blends exhibit faster drug dissolution than CEL alone. At each time point, the amount of CEL dissolved from the samples was higher with respect to CEL alone. Both PM blends provided a slight improvement of dissolution profile of CEL. In fact, the percent of active ingredient dissolved at 10 min was 22.98% for PM_b and 32.40% for PM_t with respect to 13.10 % for the drug alone. This slight increase of dissolution can be attributed to both improvement in drug wettability and formation of readily soluble complex in the dissolution medium [24].

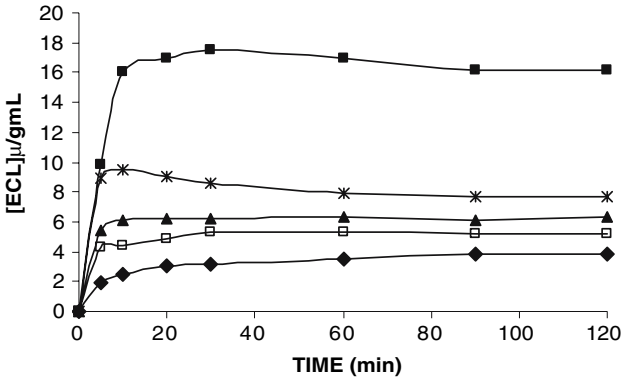

Fig. 7 Dissolution curves of CEL (◆), CEL/HP-β-CD systems: physical mixture (□) and coevaporated product (*), and CEL/HP-β-CD/HPMC systems: physical mixture (▲) and coevaporated product (■) (mean of three experiments, CV < 3%, error bars omitted for the sake of clarity)

Table 3 Percent of active ingredient dissolved (DP) and relative dissolution rate (RDR) at time = 10 min of CEL and its binary and ternary systems (± indicates the SD of the respective values)

Sample		DP	RDR
CEL	–	13.10 ± 0.3	1
CEL/HP-β-CD	PM_b	22.98 ± 0.6	1.75
	CO_b	50.18 ± 1.3	3.83
CEL/HP-β-CD/HPMC	PMt	32.40 ± 0.9	2.47
	COt	84.21 ± 2.3	6.43

The dissolution curves of CO samples evidenced dissolution rates higher than the PM products. The good performance of CO product can be explained by the decrease of drug crystallinity, as well as by a higher degree of drug-CD interaction occurring in the solid state. The highest amount of solubilized drug was obtained with the CO_t sample (DP = 84.21%) that exhibited a 6.43 RDR compared to the CO_b that exhibited a 3.83 RDR (DP = 50.18%).

The results obtained with CO_t can be attributed to the joint presence of HPMC and HP-β-CD which brings about stronger dissolution promoting effect of both increase of complex formation and drug amorphization, along with the filming effect of HPMC layer covering the surface of the solid that results in increased wettability, owing to the hygroscopicity of the polymer [25].

Conclusions

Complexation of CEL with HP-β-CD was obtained in aqueous medium as confirmed by the NMR analysis and phase solubility studies. The stability constant of the complex was increased through the addition of HPMC to

the complexation medium and after brief heating in an autoclave. Indeed, the addition of 0.25% (w/v) HPMC to solutions containing HP-β-CD induced a synergistic solubilizing effect on CEL, allowing a reduction of the amount of carrier necessary for drug solubilization.

The physicochemical characterization of binary and ternary solid systems (physical mixtures and coevaporated samples) gave evidence of the achievement in coevaporated samples of amorphous phases and/or of the formation of an inclusion complex CEL/HP-β-CD. All the systems exhibited better dissolution parameters than the drug alone, the best performance being showed by the CEL/HP-β-CD/HPMC coevaporated sample. Thus, coevaporation is a useful and effective method for obtaining ternary systems with enhanced dissolution properties.

Based on these results we believe that the interaction between CEL, HP-β-CD and HPMC, through the formation of an inclusion complex can lead to important modifications in physicochemical and biopharmaceutical properties of the guest molecule, which might eventually have relevant pharmaceutical potential in view of decreasing dose and side effects of CEL.

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