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ORIGINAL ARTICLE

Physical chemical characterization of binary systems of prilocaine hydrochloride with triacetyl-β-cyclodextrin

Marco Bragagni · Francesca Maestrelli · Paola Mura

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Abstract Interaction products of prilocaine hydrochloride (PRL), a local anesthetic agent highly soluble in water, with triacetyl-β-cyclodextrin (TAβCD), a hydrophobic CD derivative practically insoluble in water, were prepared to estimate their suitability for the development of a prolonged-release dosage form of the drug. Equimolar PRL-TAβCD solid systems were prepared by different methods (physical mixing, kneading, co-grinding, sealed-heating, coevaporation, spray-drying), in order to investigate their effectiveness and influence on the physical chemical properties of the end products. Differential scanning calorimetry, X-ray powder diffractometry, FTIR spectroscopy and environmental scanning electron microscopy (ESEM) were used for the solid-state characterization of the different PRL-TAβCD systems, whereas their in vitro dissolution properties were determined according to the dispersed amount method. On the basis of the overall solid-state studies results, the ability of the different methods to bring about effective drug-TAβCD interactions varied in the order: spray-drying > co-grinding ≈ coevaporation > sealed-heating > kneading > physical mixing. This rank order was not observed in dissolution studies, where coevaporated, kneaded and sealed-heated products exhibited very similar profiles, practically superimposable to that of pure drug and physical mixture, all reaching 100% dissolution in less than 10 min. Evidently, all these techniques gave rise only to weak surface interactions, rapidly destroyed in solution. Some decrease in dissolution rate was observed for co-ground system (100% dissolved drug after 40 min), probably due to electrostatic and aggregation phenomena associated with the high-energy mechanical treatment. A very different behaviour was shown by the spray-dried system, which give rise to an almost linear slow-dissolving profile, reaching 100% of dissolved drug after 420 min, suggesting in this case the formation of an actual inclusion compound. Thus, the drug-TAβCD product obtained by spray-drying was selected as the best candidate for the future development of a suitable prolonged-release oral dosage form of PRL.

Keywords Prilocaine · Triacetyl-β-cyclodextrin · Complex preparation methods · Solid state characterization · Prolonged release

Introduction

Local anesthetics (LAs) are well established in many areas of clinical practice, including general surgery and post-operative treatments, ophthalmology and dentistry. Local anesthesia is often preferred to general anesthesia for many reasons: wider safety margin, superiority in terms of morbidity, ease of use, maintenance of a state of consciousness, good patient's compliance. Moreover, the interest in LAs has recently grown because of the ever-increasing popularity of anesthetic surgery procedures [1].

Although many new active compounds of this therapeutic class have been developed during the past decades, some important problems still remain partially or totally unsolved. In particular, delayed onset of action, short duration and limited efficiency of the anesthetic effect, and, consequently, need of high drug concentrations and repeated applications are the main drawbacks encountered in case of topical applications on intact skin. Moreover, toxic

M. Bragagni · F. Maestrelli · P. Mura (✉)
Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Florence, Via U.Schiff, 6, 50019 Sesto Fiorentino, Florence, Italy
e-mail: paola.mura@unifi.it

effects, due to systemic absorption of local anesthetics, have been reported [2, 3].

The main strategies which have been proposed to improve the therapeutic efficiency of topically applied LAs, by enhancing and prolonging their effect and, consequently, reducing dosage and risks of systemic toxicity, include: modification of the drugs molecular structure [4]; addition of various chemical enhancers, often arousing doubts about their safety, tolerability and reversibility of their effects on the membranes [5–7]; incorporation in microparticular delivery systems such as microspheres [8] or liposomes [9, 10]; association with viscousizing agents such as dextran, poloxamer or hyaluronic acid [11–13]. Iontophoresis has been proposed to enhance delivery of ionized drugs across the skin, however it requires the use of particular devices and is not completely patient friendly [14]. Complexation with hydrophilic cyclodextrins (CDs) is another interesting approach for improving the therapeutic effectiveness of LAs [15–17]. In fact, numerous studies showed that CDs are able to increase drug permeability through biological barriers, without causing permanent changes within the membranes [18].

CDs are cyclic oligosaccharides, consisting of (alfa-1,4)-linked alfa-D-glucopyranose units with a hydrophilic outer surface and a lipophilic central cavity where a "guest" molecule can be included to form a host–guest complex. Natural CDs can be differently functionalized in order to conveniently modify their solubility and complexing properties and extend the range of pharmaceutical applications of the parent molecules. Hydrophilic CD derivatives are the most studied and have been extensively used to form inclusion complexes with lipophilic drug molecules, in order to improve their solubility and, consequently, their bioavailability. On the contrary, there are less data regarding the possible applications of hydrophobic CD derivatives, such as the peracylated ones, which have been proposed as sustained-release carriers for highly soluble drugs, in virtue of the formation of poorly water-soluble complexes [19–21].

Prilocaine (Fig. 1a) is an amino-amide type local anesthetic. The use of prilocaine base is limited by its oily nature and its very low aqueous solubility, which gives rise to problems of formulation and variable bioavailability. Therefore, it is mainly used as hydrochloride salt, particularly for intravenous regional anesthesia and in dentistry, even though its therapeutic efficacy is typically limited by the above-described problems. In particular, its high solubility in aqueous environment causes a rapid removal from the tissues by the bloodstream after parenteral administration. Moreover, it presents a low permeability through the biological barriers, due to its hydrophilic properties.

Thus, we considered it worthy of interest to evaluate the effectiveness of triacetyl-β-cyclodextrin (TAβCD), a very poorly water-soluble CD derivative, as a carrier to obtain a lipophilic, slow-dissolving complex of the drug, with the aim of improving its affinity for the skin and prolonging its release over time and then its duration of action. It is known that different methods can be employed for preparing solid drug-cyclodextrin complexes, and the choice of the most efficacious one should be carefully evaluated case by case [22–26]. Therefore, in the present work, equimolar drug-TAβCD solid compounds were prepared by different methods, i.e. physical mixing, kneading, co-grinding, sealed-heating, coevaporation and spray-drying in order to investigate the influence of the preparation method on the physico-chemical properties of the end product and to select the most effective system for slowing down the drug dissolution properties. Differential scanning calorimetry, X-ray powder diffractometry, Fourier transform infrared spectroscopy, and environmental scanning electron microscopy (ESEM) were used to check and evaluate the crystallinity of the drug in the different equimolar drug-cyclodextrin systems and to investigate drug-carrier interactions in the solid state, whereas the drug dissolution properties from the various binary combinations were determined according to the dispersed amount method.

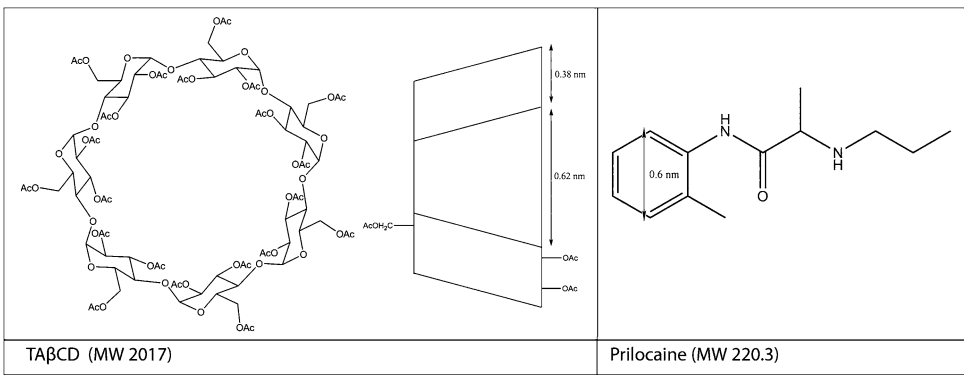

Fig. 1 Schematic representation of chemical structures of prilocaine and TAβCD and their relative dimensions

Materials and methods

Materials

Prilocaine (*N*-(2-methylphenyl)-2-propylaminopropanamide) hydrochloride (PRL) (Fig. 1a) was purchased from Sigma (St. Louis, MO, USA). Triacetyl-β-cyclodextrin (TAβCD) (Cavasol® W7 TA) (Fig 1b) was a kind gift of Wacker-Chemie Italia SpA, Milan, Italy). Eudragit® RLPO (ammonium methacrylic copolymer, type A NF) was kindly provided by Rofarma-Italia srl (Gaggiano, Italy). All other chemicals and solvents were of analytical reagent grade.

Preparation of drug-CD solid binary systems

Equimolar solid binary products of PRL with TAβCD were prepared with different techniques. The physical mixture (PM) was prepared by gently mixing in a mortar for 15 min the two components previously sieved (75–150 μm) and accurately weighted. The co-ground system (GR) was obtained by ball-milling the PM in a high-energy vibrational micromill (Retsch GmbH, Haan, Germany) at 24 Hz for 30 min. For the preparation of the kneaded system (KN) about 500 mg of PM were wetted in a mortar with 0.3 mL of a water/ethanol 80:20 v/v solution; the slurry was ground thoroughly with a pestle until complete evaporation of the solvent, and the obtained powder was placed in an oven and left to dry for 24 h at 40 °C. The sealed-heated system (SH) was prepared by introducing 300 mg of PM in a 2 mL glass vial with 20 μL of a water/ethanol 80:20 v/v solution; the vial was immediately flame sealed and heated at 90 °C for 2 h. The co-evaporated product (COE) was obtained by dissolving the PM in the minimum amount of a water/ethanol 80:20 v/v solution and removing the solvent by rotary evaporation; the solid product was collected and left drying in an oven for 24 h at 40 °C. The spray-dried product (SP) was prepared by dissolving the PM in a water/ethanol 80:20 v/v solution and then spray-drying using a Mini Spray Dryer B-290 (Buchi GmbH, Essen, Germany) under the following conditions: inlet temperature 135 °C, outlet temperature 70 °C, flow rate 9 mL/min, atomising air pressure 3 kg/m^2, vacuum 70 mm H_2O.

Differential scanning calorimetry (DSC)

Thermal analysis of PRL, TAβCD and drug-TAβCD binary systems obtained with the different methods was performed by a Mettler TA 4000 Star^e system (Mettler Toledo, Greifensee, Switzerland). About 3 mg of each sample were accurately weighted by M3 Microbalance (Mettler-Toledo, Greifensee, Switzerland), placed in sealed aluminium pans with pierced lid and scanned at a heating rate of 10 °C min^{-1} under static air atmosphere, in the 30–300 °C temperature range. The relative degree of drug crystallinity (*RDC*) in the samples was calculated according to the Eq. 1:

$$RDC = \frac{\Delta H_{\text{sample}}}{\Delta H_{\text{drug}}} \times 100\% \quad (1)$$

where ΔH_{sample} and ΔH_{drug} are the measured heat of fusion of the sample and of the crystalline drug, respectively, normalised to the drug content in the sample.

X-ray powder diffractometry (XRPD)

The powder X-ray diffraction patterns were taken at ambient temperature with a theta-theta D8 apparatus (Bruker, Silberstreifen, Germany) using a CuK_α radiation. The samples were analysed in the 5°–30° 2θ range at a scan rate of 0.05°/s.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra were recorded by a Perkin-Elmer Model 1600 spectrometer (Wellesley, USA). The samples were prepared by dispersing each sample in Nujol. One drop of this suspension was placed between two NaCl disks and scanned in the 4000–400 cm^{-1} range, with a 2 cm^{-1} resolution.

Environmental scanning electron microscopy (ESEM)

The samples were fixed on a brass stub using a double-sided adhesive tape and observed using an environmental scanning electron microscope XL 30 ESEM FEG (Philips, Netherlands).

Ultraviolet–visible spectrophotometry (UV–VIS)

A spectrophotometric technique was employed for drug assay in dissolution studies (2.7.), using a Shimadzu UV-1601 double beam UV–VIS spectrometer (Kyoto, Japan). The drug concentration in aqueous solutions was assayed at 232.5 nm, using as blank a saturated filtered solution of TAβCD, to avoid any possible problem of interference The drug calibration curve was obtained starting from an aqueous stock solution of PRL, which was opportunely diluted to obtain a series of solutions with concentrations ranging from 4.4 to 44.4 mg/L: the absorbance at 232.5 nm was recorded for all these solutions, always using the saturated solution of TAβCD as blank, and the values were used for the determination of the calibration curve ($R^2 = 0.9993$).

Dissolution rate studies

Dissolution rate studies of PRL alone and from the drug-carrier binary systems prepared with the different techniques were performed according to the *dispersed amount* method: samples containing 30 mg of drug or its equivalent as binary system with TAβCD were added in a 300 mL beaker containing 150 mL of water at 37 ± 0.5 °C, and stirred at 100 rpm with a glass three-blade propeller (19 mm diameter) immersed in the beaker 25 mm from the bottom. At given time intervals, samples (3 mL) were withdrawn with a syringe-filter (pore size 0.45 μm), replaced with an equal volume of fresh medium, and spectrophotometrically assayed as described in the "Ultraviolet–visible spectrophotometry (UV–VIS)" section. The effect of the dilution was calculated in the assay of the drug according to the formula:

$$C_{i_{\text{corr}}} = C_i + \left(\frac{V_p}{V_o}\right) \sum C_i$$

where $C_{i\ \text{corr}}$ is the corrected concentration, V_p the volume of the withdrawal, V_0 the total volume of water in the flask. Each test was repeated three times (coefficient of variation <5%).

Results and discussion

Solid-state studies

Solid-state studies were performed on pure components and on the different binary systems in order to investigate and compare the effectiveness of the different techniques in inducing drug-carrier solid-state interactions. In order to exclude possible solid-state modifications due to the sample treatment, also pure components were subjected to these same processes.

Differential scanning calorimetry (DSC)

The thermal curves of pure PRL, TAβCD and their equimolar binary systems are shown in Fig. 2, while drug thermal data and its relative crystallinity degree (RDC) values in the different binary systems with TAβCD are reported in Table 1.

The DSC curve of PRL (Fig. 1a) exhibited a sharp endothermic peak at 169.9 °C (ΔH 118.7 J/g), indicative of its crystalline anhydrous state. The thermal curve of TAβCD was typical of a crystalline pseudopolymorph that, after the initial water loss indicated by the broad endothermic band between 30 and 100 °C, transformed into a lower melting anhydrous polymorph I ($T_{fus,I}$ = 192 °C), which then recrystallized into a higher-melting form II ($T_{fus,II}$ = 220 °C). A similar thermal behaviour has been reported by Bettinetti et al. for commercial TAβCD [27].

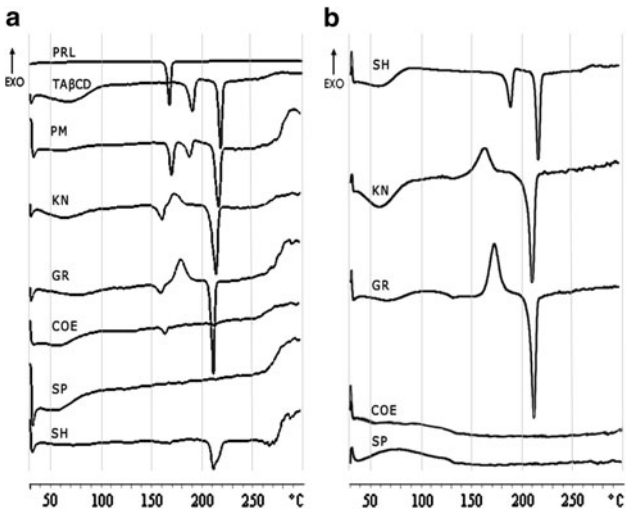

Fig. 2 DSC curves of (**a**) pure prilocaine hydrochloride (PRL), TAβCD, and their equimolar physical mixture (PM), kneaded (KN), co-ground (GR), coevaporated (COE), spray-dried (SP) and sealed-heated (SH) systems; (**b**) pure TAβCyD after sealed-heating (SH), kneading (KN), grinding (GR), evaporation (EV) or spray-drying (SP) procedures

Table 1 Melting peak temperature, fusion enthalpy and relative degree of crystallinity (RDC) of prilocaine HCl alone and in its equimolar binary systems with TAßCD

Sample	Melting temp. (°C)	Enthalpy (J/g)	RDC (%)
Prilocaine HCl	169.9	118.6	100
Physical mixture	169.9	99.3	83.7
Kneaded	163.1	84.1	70.8
Co-ground	161.5	33.2	28.0
Coevaporated	166.0	18.6	15.8
Spray-dried	–	–	0
Sealed-heated	169.5	2.5	2.1

The thermal profile of the drug was almost unaffected by the different treatments (DSC curves not shown); on the contrary, in the case of TAβCD this happened only for the sealed-heated product (Fig. 2b). In fact, the DSC profiles of TAβCD treated with kneading and grinding techniques were different from that of the original sample, showing the appearance, after the initial dehydration band, of a glass transition at about 135 °C, followed by an exothermic effect at about 165 °C, and then by the fusion at 220 °C of the higher melting form. This thermal behaviour can be attributed to the recrystallization of an amorphous form, obtained during the mechanical treatment of the sample, into the higher-melting crystalline form of TAβCD, in

agreement with previous results [28]. Finally, samples subjected to evaporation and spray-drying exhibited a flat profile with complete disappearance of both exothermic and endothermic phenomena, suggesting the formation of a more stable amorphous form of TAβCD.

The DSC curve of the physical mixture was the simple superimposition of the curves corresponding to pure PRL and TAβCD, suggesting complete lack of interactions between the two components. A clear reduction of intensity of the drug melting peak, together with a broadening and shift to lower temperature, was instead observed in the thermal curves of kneaded and co-ground products, followed by the appearance of an exothermal effect, and finally by the fusion peak of the higher-melting polymorphic form of TAβCD. DSC analysis of pure components made it possible to correctly attribute such exothermal phenomenon to the presence of a TAβCD unstable amorphous form, obtained during the sample mechanical treatment, which, during the DSC heating, recrystallizes into the more stable higher-melting crystalline form (see Fig. 2b). On the contrary, the modifications observed for the drug melting peak feature, more evident in the co-ground systems, can be actually ascribed to drug-TAβCD solid-state interactions occurring during sample preparation, and to loss of drug crystallinity as a consequence of such interactions.

The reduction of drug fusion enthalpy was even more evident in the coevaporated product, until to almost complete or total disappearance of the drug melting peak, respectively, in sealed-heated and spray-dried products, indicative of more intense drug-carrier interactions. The disappearance of melting phenomena related to TAβCD observed in the thermal curves of coevaporated and spray-dried products, indicative of its total amorphization, was observed also in the corresponding pure samples. On the contrary, the absence of the drug melting peak in spray-dried and sealed-heated products is a consequence of its interaction with the carrier and not of the sample treatment. In fact, the thermal behaviour of the drug alone subjected to these same treatments (curves not shown) was very similar to that of the untreated sample. Finally, the modification of TAβCD thermal behaviour in the sealed-heated product, i.e. the broadening and lowering of its higher-melting crystalline form, can be ascribed to drug-TAβCD solid-state interactions, since it did not occur on pure sealed-heated TAβCD.

The data pointed out the importance of the sample preparation method in promoting drug-carrier solid-state interactions and drug amorphization, as suggested by the progressive reduction of drug crystallinity degree, passing from kneaded to co-ground, coevaporated up to sealed-heated products, until the achievement of complete amorphization in spray-dried systems (Table 1).

X-Ray powder diffractometry (XRPD)

XRPD has been employed for a further characterization of the binary systems in the solid state. The X-ray diffraction patterns of PRL, TAβCD, and their respective equimolar binary systems obtained with the different techniques are shown in Fig. 3. Both PRL and TAβCD present numerous sharp diffraction peaks, suggestive of their crystalline state. The diffraction peaks characteristics of the individual components were maintained also in their physical mixture, excluding the occurrence of interactions and/or amorphization phenomena during blending of the components, in complete accordance with the results of DSC analysis. The pattern of the sealed-heated system shows some modifications with respect to that of the physical mixture, exhibiting a general reduction of intensity of crystallinity peaks, mainly attributable to drug amorphization, as indicated, by the disappearance of typical drug peaks such as those at 7.0, 14.8 and 24.6° 2θ. A more evident loss of crystallinity was observed in the kneaded product, probably as a consequence of drug-carrier interactions brought about by the mechanical treatment. On the other hand, coevaporated and co-ground compounds showed diffractograms

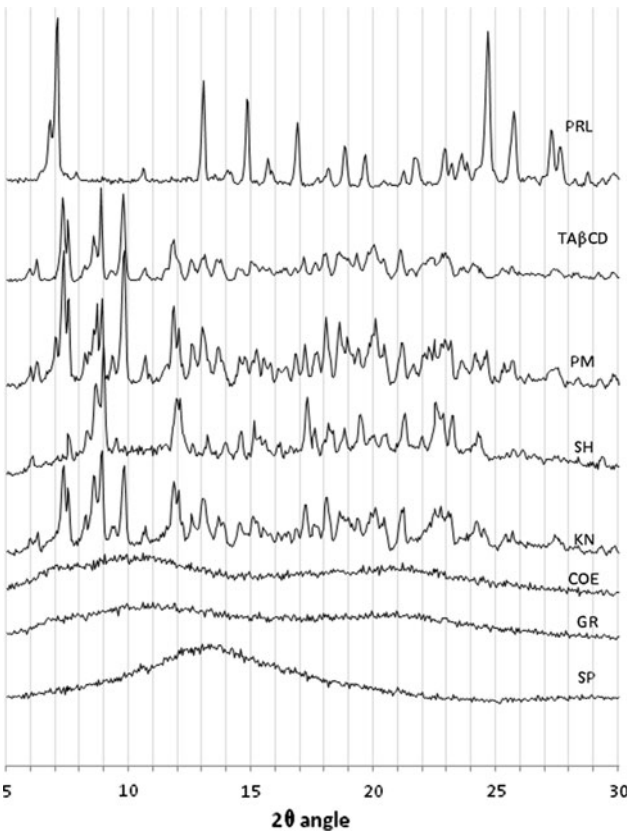

Fig. 3 X-ray powder diffractograms of prilocaine hydrochloride (PRL), TAβCD, and their equimolar physical mixture (PM), kneaded (KN), co-ground (GR), coevaporated (COE), spray-dried (SP) and sealed-heated (SH) systems

typical of amorphous powders, where the traces of residual crystalline drug, evidenced by DSC analysis, were practically undetectable. Finally, the completely amorphous pattern of spray-dried product was in full keeping with DSC data, confirming the actual total sample amorphization. This result may be imputable to the formation of strong solid-state interactions between drug and TAβCD and/or to the possible drug inclusion complexation during the spray-drying process.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy studies were performed to further shed light about PRL-TAβCD interactions induced by the sample preparation method, as inferable by variations in intensity and/or position of the spectrum peaks of each product with respect to the simple physical mixture.

Unfortunately, the spectrum of the equimolar drug-TAβCD physical mixture was very similar to that of pure TAβCD, and most of the drug representative peaks were overlapped by the host bands, due to its greater content in weight in its equimolar systems with PRL. In particular, the zone of the PRL amidic C = O stretching, peaked at 1683 cm^{-1} for the plain drug [21], did not provide any useful information regarding host–guest interactions, since it was completely overlapped by the very strong and broad band peaked at 1741 cm^{-1}, due to the C = O vibration of the acetyl group of TAβCD [21]. However, a typical peak at 1539.6 cm^{-1}, attributable to the bending of the amidic NH group of PRL [29], was detectable in the FTIR spectra of all the samples, since there was not overlapping with the spectrum of TAβCD, which does not present a band in this spectral region [21]. Therefore, its position and intensity in the physical mixture was assumed as a reference, and the variations in terms of shift and intensity of this band, observed in the other binary products with TAβCD obtained by the different preparation techniques, are shown in Table 2. A light shift of this peak to higher frequencies and a concomitant marked broadening and reduction in its intensity have been observed in all the samples. This latter effect was particularly evident in the spray-dried product spectrum, where this peak nearly disappeared. These results, in accordance with those of DSC and XRPD analysis, accounted for the occurrence of the strongest solid-state interaction between the components in the compound prepared by spray-drying.

Table 2 Changes of characteristic FTIR NH amidic band of prilocaine (PRL) in its equimolar physical mixture, sealed-heated, kneaded, co-ground,coevaporated, and spray-dried products with TAβCD

PRL-TAβCD system	% peak intensity	Wave number (cm^{-1})
Physical mixture	100.0	1539
Kneaded	29.4	1541
Co-ground	26.8	1543
Coevaporated	24.6	1545
Sealed-heated	35.0	1546
Spray-dried	16.6	1546

Environmental scanning electron microscopy (ESEM)

ESEM analysis was used in order to investigate the possible morphological changes of the spray-dried product with respect to the raw materials and their simple physical mixture (Fig. 4). The raw PRL appeared as crystalline needle-shaped sticks, with rather homogeneous dimensions, while TAβCD showed the presence of rhomboidal-shaped crystal with different dimensions, which tended to agglomerate. The physical mixture was characterized by the presence of unmodified crystals particles of TAβCD, mixed with the small crystalline sticks typical of PRL. A remarkable change in the morphology of the materials was instead observed in the system obtained by spray-drying, where it was not more possible to detect and differentiate the distinctive crystals of PRL and TAβCD. In fact, the spray-dried product showed an amorphous appearance, with the presence of particles of irregular shape and dimensions and fluffy aspect, completely different form the mother components. This result, even though scarcely conclusive, seems to indicate the presence of a single solid phase in the spray-dried compound, and, consequently, can be considered suggestive of the formation of an inclusion complex.

Dissolution rate studies

The dissolution profiles of PRL alone and from its different binary systems with TAβCD in water are shown in Fig. 5. PRL completely dissolved within a few minutes, reflecting its very high aqueous solubility. The dissolution from the physical mixture showed the same behaviour of pure PRL, in spite of the presence of the hydrophobic carrier, according to the absence of drug-TAβCD interactions revealed by solid-state studies. However, unexpectedly, coevaporated, kneaded and sealed-heated products exhibited very similar dissolution profiles, almost superimposable to that of pure drug and physical mixture, irrespective of the different degrees of drug amorphization and intensity of drug-carrier interactions obtained with these techniques and pointed out by solid-state investigations. In all these cases in fact, the drug was completely dissolved in less than 10 min. The PRL dissolution rate from the co-ground product was instead significantly retarded, reaching 100% of dissolved drug after about 40 min. Evidently, all these preparation techniques did not give rise to actual inclusion

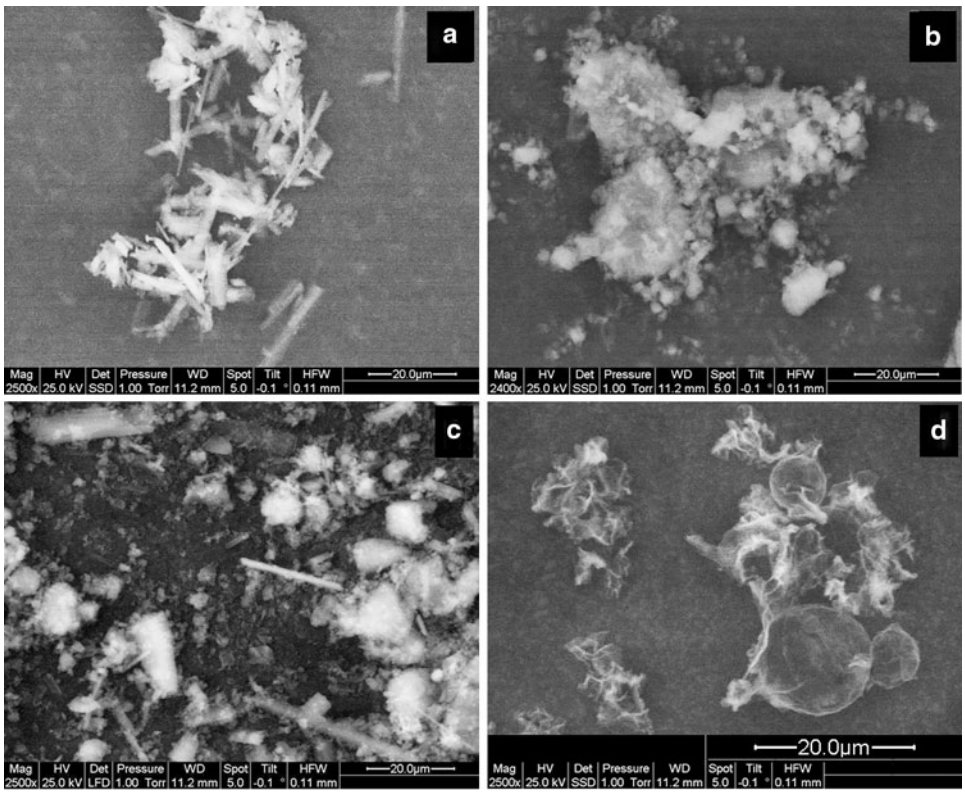

Fig. 4 ESEM photographs of pure prilocaine hydrochloride (**a**), TAβCD (**b**) and of thier equimolar physical mixture (**c**) and spray-dried product (**d**)

complex formation, but only to weak surface interactions, which were rapidly destroyed in solution, and were not able to effectively slow down the high drug dissolution rate. The more evident decrease in drug dissolution rate obtained in the case of the co-ground system could be attributed to the formation of electrostatic interactions and aggregation phenomena, which are frequently associated with high-energy mechanical treatment of powders [30]. Finally, a very different behaviour was shown by the spray-dried system, which exhibited a very important retarding effect on the dissolution rate of PRL, and allowed obtainment of an almost linear slow-dissolving profile, reaching 100% of dissolved drug only after about 7 h. The clearly marked effectiveness of the spray-drying method in modifying the drug release behaviour, together with the most evident ability of this technique in inducing the formation of powerful drug-TAβCD interactions, as emerged from solid-state studies, suggest in this case the formation of an actual inclusion compound.

In order to further confirm this hypothesis and to gain more insight the role played by the carrier structure and the specificity of the interaction between PRL and TAβCD on the obtained results, co-ground and spray-dried products were prepared under the same experimental conditions, but replacing TAβCD with an inert hydrophobic component, such as Eudragit® RLPO, a methacrylic copolymer practically insoluble in water, which has been often used as excipient in the development of controlled release

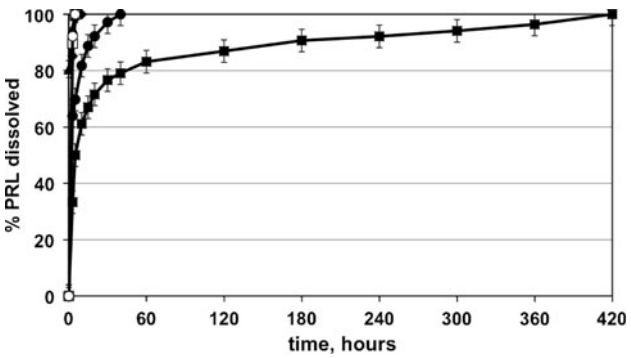

Fig. 5 Dissolution curves in water at 37 °C of prilocaine hydrochloride (PRL) alone (*open circle*) and from its equimolar physical mixture (*open circle*), kneaded (*filled diamond*), coevaporated (*open square*), sealed-heated (*filled triangle*), co-ground (*filled circle*), and spray-dried (*filled square*) systems with TAβCD

formulations [31, 32]. Dissolution rate studies showed the complete PRL dissolution from both these products in less than 10 min, definitely demonstrating that the effectiveness of the hydrophobic CD in reducing the drug dissolution rate is strictly related to its ability in the establishment of specific drug-carrier interactions.

Conclusion

The present work has demonstrated that the actual ability of the hydrophobic cyclodextrin-derivative TAβCD as a

carrier for achieving a slow-dissolving form of PRL is markedly influenced by the preparation method utilised for obtaining the drug-carrier system. In fact, the results have evidenced the fundamental importance of the preparation technique in inducing effective interactions between the components, suitable to purposely modulate the drug dissolution rate. Solid state studies performed to investigate the effects of the preparation technique on the physical chemical properties of the products, revealed different degrees of drug crystallinity reduction as well different intensity levels of drug-carrier solid-state interactions, depending on the preparation method, and indicated the spray-drying as the most powerful technique, followed by co-grinding, coevaporation and sealed-heating.

However, unexpectedly, despite the differences pointed out by solid-state studies, the products obtained with the different techniques showed very similar dissolution profiles, analogous to that of pure drug and simple physical mixture, giving rise to 100% dissolved drug within the first 5-10 min (coevaporated, sealed-heated and kneaded products) or showing, in the case of the co-ground product, only a little slowing down (40 min to achieve 100% dissolution). The only clear exception was given by the product obtained by spray-drying, which presented a very intense effect on the drug dissolution rate, requiring 420 min for obtaining complete drug dissolution, indicating that this was the only technique able to bring about effective drug-carrier interactions and/or inclusion complex formation. Moreover, the significant role of this specific carrier in establishing effective interactions with the drug, suitable to adequately reduce its dissolution rate, has been proved.

Therefore, the PRL-TAβCD spray-dried product was selected as the best candidate to use, in proper ratios with the drug alone, for the future development of a well-timed sustained-release dosage form, such as buccal films, suitable to achieve a controlled and prolonged local anesthetic effect, in the treatment of common oral diseases such as dental caries, peridontitis, aphthous stomatitis, mucositis, etc., with better patient compliance and reduction in side effects with respect to systemic administration.

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