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ORIGINAL ARTICLE

Solid-state interactions and drug release of teicoplanin in binary combinations with peracetylated α-, β-, and γ-cyclodextrins

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Abstract Triacetyl α-cyclodextrin, triacetyl β-cyclodextrin and triacetyl γ-cyclodextrin were tested as possible hydrophobic carriers to prolong the release of hydrophilic teicoplanin (TCP). Physical–chemical characterization of individual components, drug-carrier physical mixtures at 0.5, 0.67 and 0.75 mass fraction of carrier, and the respective interaction products by kneading or evaporative crystallization under microwave irradiation was carried out using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). In vitro drug release in pH 7.4 phosphate buffer at 37 °C was determined by intrinsic dissolution rate (IDR) measurements on non disintegrating compressed discs. Solid-state interactions of TCP with triacetyl α-cyclodextrin by evaporative crystallization and kneading and with triacetyl β-cyclodextrin by evaporative crystallization (probably resulting in carrier amorphization) were demonstrated. The role of carrier hydrophobicity, carrier mass fraction and preparation method of solid drug-carrier combinations on solid-state drug-carrier interactions and slowing down of TCP release was assessed. Modulation of drug release can be achieved using TCP-triacetyl γ-cyclodextrin combinations at 0.5 mass fraction of carrier.

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Keywords Differential scanning calorimetry · Intrinsic dissolution rate · Peracetylated α-, β-, and γ-cyclodextrins · Teicoplanin · Thermogravimetric analysis

Abbreviations

TCP	Teicoplanin
MRSA	Methicillin-resistant *Staphylococcus aureus* bacteria
TAαCD	Triacetyl α-cyclodextrin
TAβCD	Triacetyl β-cyclodextrin
TAγCD	Triacetyl γ-cyclodextrin
DSC	Differential scanning calorimetry
TGA	Thermogravimetric analysis
IDR	Intrinsic dissolution rate
TACD	Triacetyl cyclodextrin

Introduction

In clinical situations such as osteomyelitis, prosthetic infections or deep wounds, teicoplanin (TCP) is a valuable alternative to vancomycin to eradicate methicillin-resistant *Staphylococcus aureus* bacteria (MRSA) due to its safety, efficacy and greater capability of bone penetration [1, 2]. Following a similar approach as that for vancomycin [3] for attaining antibiotic-based prolonged release systems for site-specific therapy, in this work triacetyl α- (TAαCD), β- (TAβCD) and γ-cyclodextrin (TAγCD) were tested as possible hydrophobic carriers to prolong the release of hydrophilic TCP. Triacetyl cyclodextrins (TACDs) have been proposed as bioabsorbable sustained-release

carriers for hydrophilic drugs (see [4] and refs. therein). Moreover, thermal and structural solid-state characterization studies that can be exploited for drug-carrier interaction mechanism elucidation were reported (see [5] and refs. therein). Physical–chemical characterization of individual components, TCP-carrier physical mixtures at various mass ratios and the respective interaction products obtained by kneading or evaporative crystallization under microwave irradiation was carried out using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). In vitro drug release was determined by intrinsic dissolution rate (IDR) measurements on non disintegrating compressed discs. The role of carrier hydrophobicity, carrier mass fraction and preparation method of solid TCP–TACD combinations on solid-state drug-carrier interactions and slowing down of TCP release was assessed.

Experimental

Sample preparation

Physical mixtures of TCP (from Pharmatex Italia srl, Milan, Italy) with TAαCD, TAβCD, and TAγCD (a gift from Wacker-Chemie Italia SpA, Milan, Italy) (< 180 μm sieve granulometric fraction) at the 0.50, 0.67 and 0.75 mass fractions of TACD were prepared by mixing in a Turbula apparatus for 20 min. The solid combinations were prepared by kneading and evaporative crystallization under microwave irradiation (PabishCM-Aquatronic, Milan, Italy) at 595 W of 1 g of a TCP and TACD mixture wetted and pasted with 1–2 ml of a 1:1 (v/v) hydroacetonic solution for 30 min or of 1:1 (v/v) hydroacetonic solutions of TCP and TACD (1 g/30 ml) for 1–2 h.

Non disintegrating discs (Φ = 0.8 cm) were prepared by compressing 250 mg of mixture at 2 ton for 1 min by means of a hydraulic press.

Sample characterization

Differential scanning calorimetry (DSC)

Temperature and enthalpy values were measured with a Mettler STAR^e system equipped with a DSC821^e Module and an Intracooler device for subambient temperature analysis (Julabo FT 900) on 3–5 mg (Mettler M3 Microbalance) samples in sealed aluminium pans with pierced lid (β = 10 K min^{-1}, nitrogen air atmosphere (flow rate 50 l min^{-1}), –10 °C–300 °C temperature range). Measurements were carried out at least in triplicate (relative standard deviation ± 4%).

Thermogravimetric analysis (TGA)

Mass losses were recorded with a Mettler TA 4000 apparatus equipped with a TG 50 cell on 8–10 mg samples in open alumina crucibles (β = 10 K min^{-1}, static air atmosphere, 30 °C–300 °C temperature range). Measurements were carried out at least in triplicate (relative standard deviation ± 5%).

Dissolution rate (IDR)

Intrinsic dissolution rate were determined using a rotating disc apparatus immersed in 150 ml of a pH 7.4 phosphate buffer at 37 °C. The amount of drug released was assayed by UV spectroscopy (Lambda20 Perkin Elmer, Milan, Italy) at 280 nm. All experiments were run in triplicate (relative standard deviation ± 3%).

Results and discussion

Thermal behaviour of the TCP–TAαCD system at 0.67 mass fraction of carrier (which corresponds to 0.69 mol fraction) is shown in Fig. 1. The broad endothermal effect for TCP between 30–175 °C was due to loosely bound water (~8% as mass fraction by TGA) (curve a). TAαCD as received (water content ~1.2% as mass fraction by TGA) shows after dehydration a sharp endotherm peaking at 231.0 ± 0.3 °C (ΔH_m = 43 ± 3 J g^{-1}) attributable to melting (curve b). Comparison between the physical mixture as such (curve c) and after treatment (curves d, e) accounted for a solid-state interaction between TCP and TAαCD by evaporative crystallization or kneading. The exothermal effect at about 152 °C indicated that such an interaction resulted in carrier amorphization, which was more pronounced for the evaporative crystallization product. A similar behaviour was recorded for the TCP–TAαCD system at 0.5 and 0.75 mass fraction of carrier (which corresponds to 0.52 and 0.76 mol fraction, respectively) (data not shown).

DSC curves of the TCP-TAβCD system at 0.67 mass fraction of carrier (which corresponds to 0.65 mol fraction) is shown in Fig. 2. Thermal behaviour of TAβCD as received, which contains about 0.8 mol H_2O per TAβCD mol, reflects sample dehydration into a lower-melting anhydrous polymorph I ($T_{m,I}$ = 192.2 ± 1.8 °C; $\Delta H_{m,I}$ = 13 ± 1 J g^{-1}) which in turn recrystallizes into a higher-melting form II ($T_{m,II}$ = 218.5 ± 0.8 °C; $\Delta H_{m,II}$ = 23 ± 2 J g^{-1}) (curve b) [5]. Disappearance of

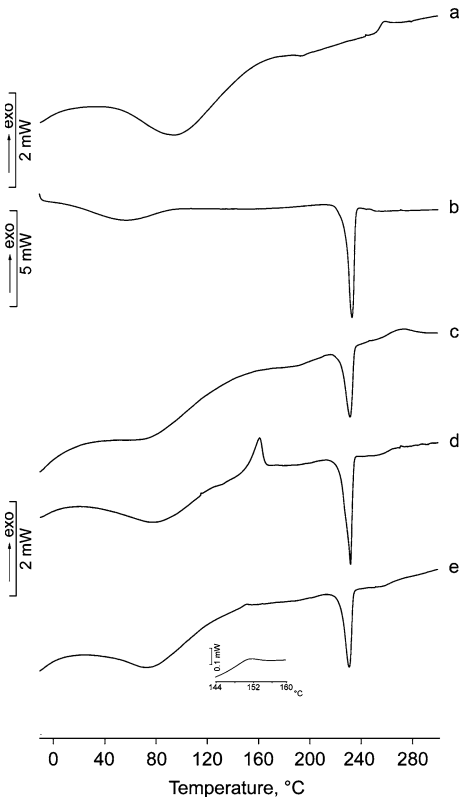

Fig. 1 DSC curves of TCP (**a**), TAαCD (**b**), TCP–TAαCD physical mixture 1:2 (w/w) (**c**) and the respective microwave evaporation (**d**) and kneading (**e**) products

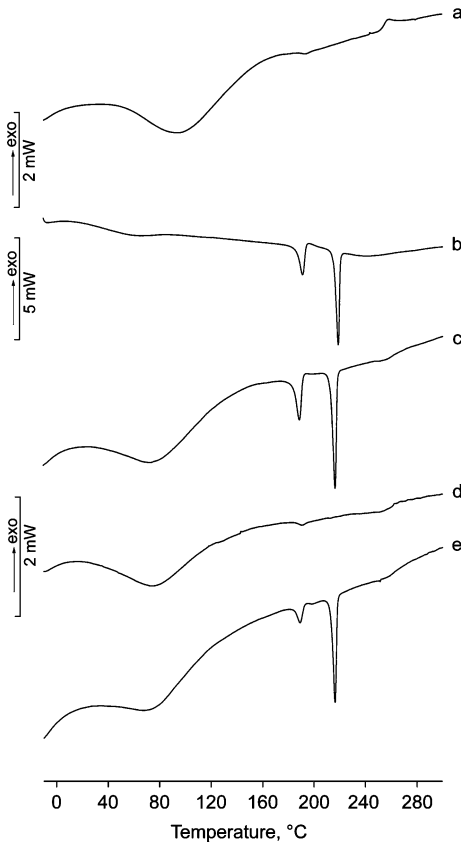

Fig. 2 DSC curves of TCP (**a**), TAβCD (**b**), TCP–TAβCD physical mixture 1:2 (w/w) (**c**) and the respective microwave evaporation (**d**) and kneading (**e**) products

both melting peaks in the DSC curve of the evaporative crystallization product showed total TAβCD amorphization due to interaction (curve d), whereas in the kneading product interaction resulted in a decrease in the relative amount of the lower melting phase ($\Delta H_{m,I} = 6 \pm 2$ J g^{-1} vs. $\Delta H_{m,II} = 24 \pm 1$ J g^{-1}). A similar behaviour was recorded for the TCP–TAβCD system at 0.5 and 0.75 mass fraction of carrier (which corresponds to 0.48 and 0.74 mol fraction, respectively) (data not shown).

Thermal behaviour of the TCP-TAγCD system at 0.50 mass fraction of carrier (which corresponds to 0.45 mol fraction) is shown in Fig. 3.

TAγCD as received (water content ~1% as mass fraction by TGA) shows after dehydration a sharp endotherm peaking at 223.5 ± 0.3 °C ($\Delta H_m = 25.3 \pm 0.2$ J g^{-1}) attributable to melting (curve b). The presence of this peak with very similar thermal parameters in the DSC curves of the TCP–TAγCD physical mixture as such (curve c) and treated (curves d, e) accounted for the absence of apparent solid-state interactions between TCP and TAγCD. A similar behaviour was recorded for the TCP-TAγCD system at 0.67 and 0.75 mass fraction of carrier (which corresponds to 0.62 and 0.71 mol fraction, respectively) (data not shown).

Slowing down of drug release in pH 7.4 phosphate buffer at 37 °C from compressed non disintegrating discs of physical mixtures in terms of IDR constant was as more pronounced as higher the hydrophobic character of the carrier (Table 1). Thus TAγCD was the most efficient carrier in this respect, followed by TAβCD and TAαCD in decreasing order. Within each system, the mass fraction of the carrier also played a role in retarding drug release, which was linearly related to the relative amount of carrier present.

As regard to evaporative crystallization and kneading products, no significant retarding effect in comparison with the respective physical mixtures was observed for TCP–TAαCD and TCP–TAβCD systems,

Table 1 IDR values for TCP–TACD physical mixtures (mg cm^{-2} min^{-1}) (IDR TCP alone 5.2 mg cm^{-2} min^{-1})

Physical mixture	1:1 (w/w)	1:2 (w/w)	1:3 (w/w)
TCP–TAαCD	0.333 ± 0.006	0.231 ± 0.004	0.087 ± 0.003
TCP–TAβCD	0.267 ± 0.004	0.093 ± 0.002	0.058 ± 0.002
TCP–TAγCD	0.187 ± 0.003	0.083 ± 0.002	0.048 ± 0.001

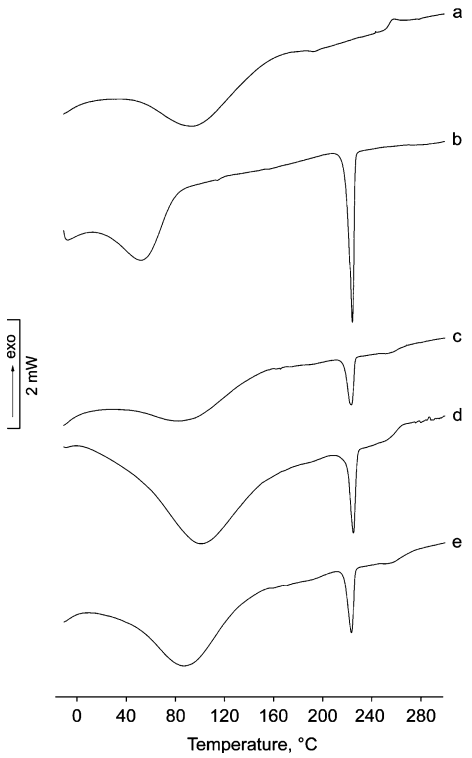

Fig. 3 DSC curves of TCP (**a**), TAγCD (**b**), TCP–TAγCD physical mixture 1:1 (w/w) (**c**) and the respective microwave evaporation (**d**) and kneading (**e**) products

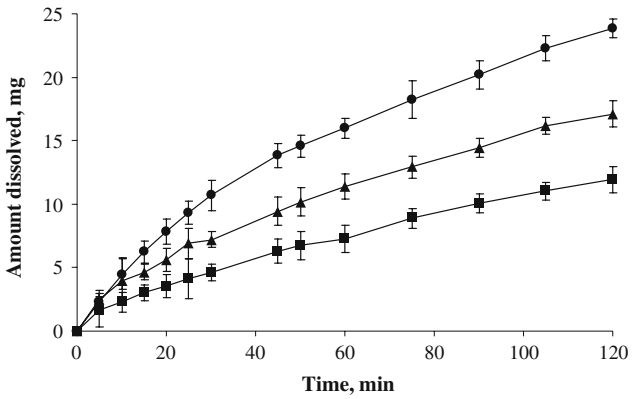

Fig. 4 IDR profiles for TCP–TAγCD physical mixture (■), microwave evaporation product (●) and kneading product (▲) at 0.50 carrier mass fraction

whereas for the TCP–TAγCD combination the physical mixture worked better than the respective evaporative crystallization or kneading products (Fig. 4).

Conclusion

DSC data account for solid-state interactions of TCP with TAαCD by evaporative crystallization and kneading and with TAβCD by evaporative crystallization (probably resulting in carrier amorphization), while no interaction was observed with TAγCD under the same experimental conditions. TCP in vitro release from physical mixtures as non disintegrating discs shows a slowing down directly related to the carrier hydrophobicity and its proportion in a given drug-carrier system. TCP–TAγCD combinations at 0.5 mass fraction of carrier as physical mixture (IDR 0.187 mg cm^{-2} min^{-1}), kneading product (IDR 0.250 mg cm^{-2} min^{-1}), and evaporative crystallization product (IDR 0.358 mg cm^{-2} min^{-1}) allow to modulate the release of TCP which is rapidly released from compressed discs of free drug (IDR 5.2 mg cm^{-2} min^{-1}).

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