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ORIGINAL ARTICLE

Sertaconazole-HPβCD-pluronic F127 solid inclusion complexes: characterization and effect on drug solubility

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Abstract The influence of Pluronic® F127 (PF127) on hydroxypropyl-β-cyclodextrin (HP-βCD) complexation in solid state with sertaconazole, a highly active but poorly soluble antifungal drug, and its repercussion on drug solubilization and release rate were evaluated. Solid ternary systems comprising sertaconazole: HP-βCD:PF127 were obtained by (i) kneading of blends wetted with methanol:phosphate buffer; (ii) freeze-drying of filtered suspensions; and (iii) cast of films of filtered suspensions in an oven at 37°C. Two levels of PF127 concentrations were evaluated, one below (0.1%) and other above (5%) the critical micellar concentration (CMC). Physical mixtures were used as references. Differential scanning calorimetry, Raman spectroscopy and X-ray difractometry showed that PF127 did not significantly interfere in the complexation process, as confirmed by the total amount of sertaconazole nitrate (SN) dissolved. Nevertheless, the presence of 5% PF127 significantly delayed the release owing to its ability to form a gel layer. These ternary systems are potentially useful to combine drug solubilization ability with control of drug release.

Keywords Drug solubility · Hydroxypropyl-β-cyclodextrin · Inclusion complex · PEO-PPO-PEO block copolymer · Pseudorotaxane · Sertaconazole

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Abbreviations

HP-βCD	Hydroxypropyl-β-cyclodextrin
PF127	Pluronic® F127
SN	Sertaconazole nitrate
CMC	Critical micellar concentration
DSC	Differential scanning calorimetry
WHO	World Health Organization

Introduction

Most drugs considered as essential by the WHO are poorly soluble in water, and near 40% of new chemical entities with potential interest as drugs have to be discarded owing to solubility problems [1]. Aqueous solubility is still a challenging issue when developing either liquid or solid dosage forms [2]. Several technological approaches have been applied to overcome this problem, such as preparation of salt derivatives or inclusion in colloidal systems (e.g., micelles or liposomes). Complexation with cyclodextrins is particularly attractive owing to the relatively easiness of the procedure, the avoidance of organic solvents, and the stability and the high biological tolerance of the complexes [3, 4]. To improve the efficiency of this approach, the combination of cyclodextrins with hydrophilic polymers, such as cellulose ethers or polyvinylpyrrolidone (PVP), is receiving an increasing attention [5, 6]. Although the mechanisms responsible for the increase in drug solubility caused by the polymer are not clear yet, the enhancement in the drug:cyclodextrin complexation constant reported for many of these systems, denotes an absence of competition for the cavity.

Ternary systems comprising drug, cyclodextrin and amphiphilic copolymers have received less attention. Differently from common hydrophilic polymers, the amphiphilic ones can self-aggregate forming micelle-like structures. The greater thermodynamic and kinetic stability of polymeric micelles, which are hence less prone to disassembly upon dilution compared to low molecular weight surfactants, makes them particularly attractive for drug delivery applications [7]. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) copolymers, commercialized under the trade name of Pluronic®, are the most widely used for these purposes [8]. The unimers of the amphiphilic linear copolymers can penetrate the inner cavity of some cyclodextrins to form inclusion complexes through the most hydrophobic segments of the chain. These necklace-like supramolecular structures, named pseudorotaxanes, have been shown useful for modulating the viscosity, gel-responsive behaviour and self-aggregation of copolymer solutions [9, 10]. Therefore, the knowledge of the potential interactions of the amphiphilic polymers and cyclodextrins and of their effect on the micellization process of the polymers is of great importance. The ability of the combination of amphiphilic copolymers and cyclodextrins to solubilize drugs has been scarcely studied. The solubilizing effect can be seen as the result of the balance of the following concomitant phenomena: drug-cyclodextrin complexation, drug inclusion in the micelles, formation of ternary drug-cyclodextrin-amphiphilic unimer complexes, and amphiphilic unimers-cyclodextrin complexation. We have recently observed that the combination of hydroxypropyl-β-cyclodextrin (HP-βCD) and Pluronic® F127 (PF127), at some given proportions, cause an additive effect on the solubility of sertaconazole, a poorly water-soluble antifungal drug. By contrast, at high HP-βCD proportions, an antagonistic effect was observed [11]. The aim of this work was to characterize solid state complexes of sertaconazole with HP-βCD, in the absence and the presence of PF127, and to study the effect of the concomitant presence of both excipients on the drug solubilization from solid systems.

Experimental

Materials

Sertaconazole nitrate (SN) (batch 0I0695) was from Ferrer Internacional, Spain; HP-βCD (degree of substitution of 4.6, MW 1300 Da; batch 102302254) from Janssen Pharmaceutische, Belgium; and Pluronic® F127 (PF127; PEO_{99}-PPO_{69}-PEO_{99}) from Sigma-Aldrich (USA). Water was purified by reverse osmosis (MilliQ®, Millipore Spain). All other reagents were of analytical grade.

Preparation of the physical mixtures

SN: HP-βCD 1:1 molar ratio mixtures (with 0.1 and 5% w/w PF127) were prepared by sieving the powders through 0.5 mm meshes and mixing for 10 min in a Turbula T2C (WAB, Switzerland).

Preparation of the inclusion complexes

Kneading method

Amounts of SN and HP-βCD in a 1:1 or 1:2 molar ratio and F127 (0.1 or 5% of the SN + HP-βCD weight) were placed in a mortar, and methanol:phosphate buffer (pH 5.8) 50:50 solution was slowly added to have a final solid:liquid 70:30 ratio. The systems were kneaded for 45 min and, then, dried at 40°C for 2 days. Control SN samples were kneaded under the same conditions without HP-βCD nor PF127.

Freeze-drying method

An excess of SN was added to 10 or 20% (w/v) HP-βCD solutions prepared in pH 5.8 phosphate buffer containing 0.1 or 5% PF127. The systems were shaken at 25°C for 5 days and filtered using 0.22 μm cellulose acetate membranes (Millipore®, Spain). The filtered solutions were immersed in liquid nitrogen and lyophilized in a Labconco Lyph-lock six apparatus (Kansas City MO, USA). SN content in the freeze-dried product was determined spectrophotometrically at 302 nm ($E_{1\%1\ cm}$ = 73.4).

Films

Samples of filtered solutions prepared as described above, were desiccated in an oven at 37°C.

Characterization of the inclusion complexes

Differential scanning calorimetry (DSC)

The experiments were carried out, in duplicate, using a DSC Q100 apparatus (TA Instruments, USA) fitted with a refrigerated cooling accessory. Nitrogen was used as purge gas (50 ml min^{-1}). The calorimeter was calibrated with indium (melting point 156.61°C, enthalpy of fusion 29.71 Jg^{-1}) and sapphire standards for cell constant temperature and heat capacity,

respectively. Two to 5 mg of sample were accurately weighed in non-hermetic aluminium pans and then just covered with the lid. The samples were heated from 30 to 162°C, afterwards cooled to 0°C, and finally heated again to 250°C, always at 10°C min^{-1}.

Raman spectroscopy

Raman spectra were recorded at 20°C using a FT-Raman Bruker spectrometer (Germany) equipped with a FRA 106 Raman module and a Nd:YAG laser.

X-ray diffractometry

Powder diffraction patterns were recorded in a Philips X-ray diffractometer (PW1710, The Netherlands) using Cu Kα radiation and 20 scans at a scan rate of 2°C/min.

Dissolution test

Drug release rates from physical mixtures and from solid-state complexes obtained by kneading and freeze-drying (samples containing 4.5 mg of SN) were evaluated, in triplicate, at 37°C in a 100 ml beaker containing 50 ml water under magnetic stirring (25 rpm). SN concentration in periodically withdrawn samples, filtered using 0.22 μm cellulose acetate membranes (Millipore®, Spain), was determined at 302 nm (Agilent 8453, Germany). Samples of pure SN powder (4.5 mg) were also tested.

Results and discussion

Pluronic® F127 self-aggregate in water and in phosphate buffer solutions, owing the hydrophobic interactions between the PPO segments, at a concentration above 0.5% [11]. In solution, HP-βCD can be threaded onto the PPO blocks slightly increasing the CMC. The free energy of interaction of PF127 with this cyclodextrin in phosphate buffers was estimated to be –2.72 kJ/mol, which denotes a relatively weak association. Despite of that, competition of PF127 with SN for forming the inclusion complex with HP-βCD was observed at certain proportions [11]. Therefore, the aim of this work was to evaluate if such PF127-HP-βCD complexation and competition with SN also occurs and is maintained when the complexes are obtained using a lower volume of medium and then subjected to desiccation, as it is usual when preparing kneaded or freeze-dried systems, or films. Additionally, since the additive/antagonistic effects of PF127 on the drug phase-diagram solubility are more evident when the amphiphilic copolymer concentration is above the CMC, two PF127 proportions were chosen: one below (0.1%) and other above (5%) CMC.

The behaviour of the ternary systems at the solid state was evaluated by DSC, Raman spectroscopy and X-ray spectroscopy, using as reference the pure components. DSC curves of pure SN (Fig. 1A) shows an endothermic melting point at 160°, which is characteristic of the polymorph A, and an exothermic peak at 190°C owing to the thermal decomposition. When the test was carried out up to only 165°C, the SN sample just melted without decomposition. After a

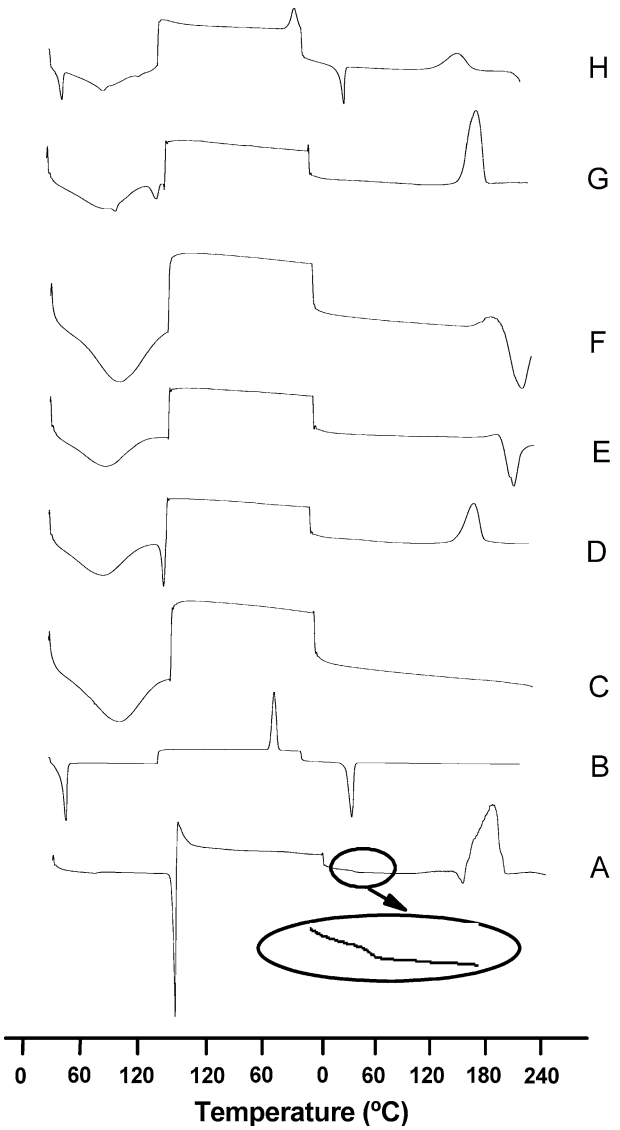
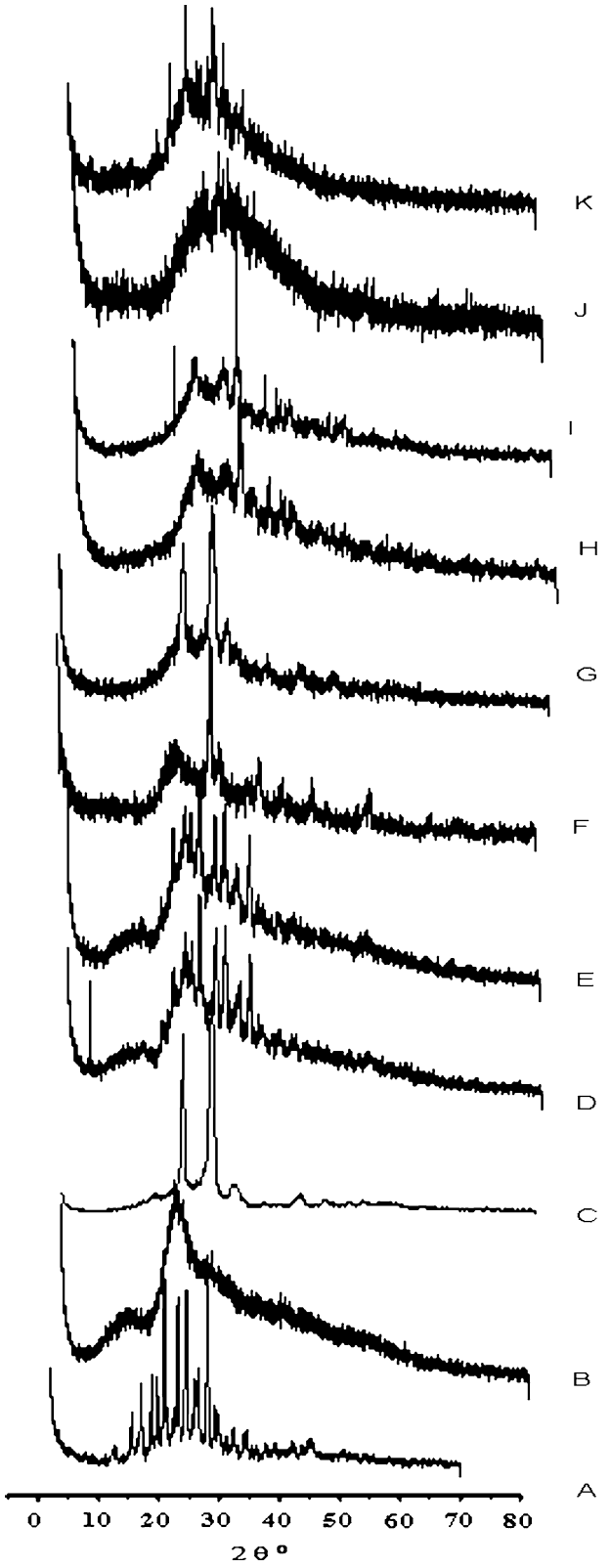


Fig. 1 DSC scans of the indicated formulations. Key: (A) SN; (B) Pluronic F-127; (C) HP-βCD; (D) SN:HP-βCD:0.1% (w/w) F127 physical mixture; (E) SN: HP-βCD:0.1% (w/w) F127 freeze-dried system; (F) SN:HP-βCD:0.1% (w/w) F127 film; (G) SN:HP-βCD:0.1% (w/w) F127 kneaded system; (H) SN:HP-βCD:5% (w/w) F127 kneaded system



◀ **Fig. 2** X-ray diffraction patterns of the indicated formulations. Key: (A) SN; (B) Pluronic F-127; (C) HP-βCD; (D) SN:HP-βCD:0.1% (w/w) F127 physical mixture; (E) SN:HP-βCD:5% (w/w) F127 physical mixture; (F) SN:HP-βCD:0.1% (w/w) F127 freeze-dried system; (G) SN: HP-βCD:5% (w/w) F127 freeze-dried system; (H) SN:HP-βCD:0.1% (w/w) F127 film; (I) SN:HP-βCD:5% (w/w) F127 film; (J) SN:HP-βCD:F127 (0.1% w/v) kneaded complex; (K) SN:HP-βCD:5% (w/w) F127 kneaded complex

cooling ramp of 10°C/min, the second heating scan evidenced a glass transition (Tg) at 34°C and a melting process at 155°C with a much lower enthalpy than that observed in the first run, suggesting that the melted SN evolved to the amorphous state. The DSC curve of HP-βCD showed the endotherm of evaporation of adsorbed water between 50 and 150°C. The typical melting peak of PF127 was recorded at 50°C. The physical mixtures and the kneaded systems of SN:HP-βCD:PF127 exhibited the endothermic melting and the exothermic decomposition peaks of the drug (Fig. 1D), which were seen neither in the freeze-dried systems nor in the films (Fig. 1E and F). These observations indicate that the solvent promotes the incorporation of the drug to either the HP-βCD cavities or to the PF127 micelles, and that the solid complexes obtained show a high thermal stability. The endothermic peak that appeared at 190–200°C may be related to the carbonization of the excipients. The melting peak of F127 at 50°C was clearly seen in systems prepared with the greatest amphiphilic copolymer concentration (i.e. 5% w/w; data not shown). This means that although this copolymer may penetrate some HP-βCD cavities, most of the chains remain not physically included in the cyclodextrins.

Sertaconazole nitrate is a crystalline drug that presents a number of peaks between 10 and 30 °2θ (Fig. 2) The X-ray spectra of samples that were kneaded, freeze-dried or prepared as films mainly showed the peaks of PF127, whilst the SN peaks were almost imperceptible. These results confirm the complexation of SN with HP-βCD, and indicate that PF127 recovers its crystalline structure when dried. In the Raman spectra (data not shown), the SN bands remained practically unperturbed in the physical mixtures, but became narrower and shifted to higher wavenumbers in the kneaded systems; these changes being characteristic of host-guest interactions [12].

Sertaconazole nitrate release rate profiles are shown in Fig. 3. Remarkable differences in both release rate and total drug solubilized were observed among the different systems. In all cases, the presence of HP-βCD efficiently promoted drug solubilization. The amount of SN dissolved at the end of the experiment raked in the order: freeze-dried systems >> kneaded systems >> physical mixture >> SN powder. These results confirm the formation of solid-state SN: HP-βCD complexes in the kneaded and the

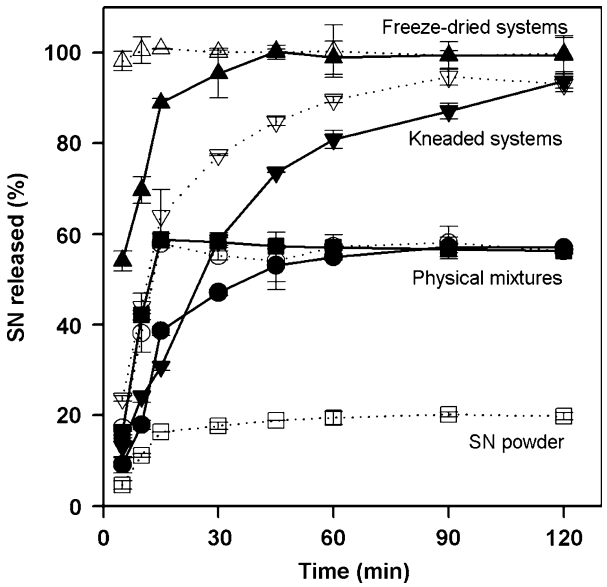


Fig. 3 Sertaconazole nitrate release rate profiles in water at 37°C from SN powder (□); SN:HP-βCD 1:1 molar ratio physical mixture (■); SN:HP-βCD 1:1 molar ratio physical mixture prepared with 0.1% (○) or 5% (•) PF127; SN:HP-βCD 1:1 molar ratio kneaded systems containing 0.1% (Δ) or 5% (▲) PF127; and SN:HP-βCD :SN:HP-βCD1:1 freeze-dried systems containing 0.1% (∇) or 5% (▼) PF127

freeze-dried systems. The proportion of PF127 did not affect to the total amount solubilized but modified the dissolution rate; the release rate was lower for the 5% PF127. This effect is the result of the formation of a gel layer on the solid particles of the complexes owing to the gelation of PF127. The high porosity of freeze-dried systems makes this gel-effect less marked.

Conclusions

Complexation of SN and HP-βCD can be achieved by kneading of blends with methanol:phosphate buffer, or by freeze-drying or oven-dessication of solutions. The presence of PF127 did not substantially affect such complexation and, hence, drug solubilization. The temperature-responsive gel properties of this amphiphilic copolymer enable tuning of drug dissolution rate. Therefore, ternary systems comprising cyclodextrins and Pluronic are potentially useful to combine drug solubilization ability with control of drug release.

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