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Combined hydroxypropyl-β-cyclodextrin and poly(alkylcyanoacrylate) nanoparticles intended for oral administration of saquinavir

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Abstract

The aim of this study was to prepare and characterize an hydroxypropyl-β-cyclodextrin–saquinavir inclusion complex with the purpose of incorporating this complex into poly(alkylcyanoacrylate) nanoparticles in order to increase the drug loading. Hydroxypropyl-β-cyclodextrin–saquinavir complex was characterized by thermal (differential scanning calorimetry), crystallographic (X-ray diffractography) and spectroscopic methods (circular dichroism, H^1-NMR). Nanoparticles were prepared by polymerization of alkylcyanoacrylate monomers (isobutyl- and isohexylcyanoacrylate) in a water solution of the complex and further characterized. The apparent solubility of saquinavir was increased 400-fold at pH 7.0 in presence of hydroxypropyl-β-cyclodextrin owing to the formation of a drug–cyclodextrin complex as demonstrated mainly by ^{1}H NMR and confirmed by other techniques. Saquinavir-loaded nanoparticles could be easily prepared in the presence of a drug–cyclodextrin complex. It was found that large amounts of cyclodextrins remained associated with the particles, resulting in a 20-fold increase in saquinavir loading compared to nanoparticles prepared in the absence of cyclodextrins. This study has shown that the loading in saquinavir of poly(alkylcyanoacrylate) nanospheres could be dramatically improved by simultaneously increasing the apparent solubility of the drug in the preparation medium and the amount of cyclodextrin associated with the particles, making these nanospheres a promising system for oral application.

Keywords: Hydroxypropyl-β-cyclodextrin; Inclusion complex; Nanoparticles; Oral administration; Saquinavir

1. Introduction

Saquinavir, a potent HIV-1 and HIV-2 protease inhibitor, has been approved for use in treatments of patients with acquired immunodeficiency syn-

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drome. This drug is effective in reducing viral load and is well tolerated. However, saquinavir has a low oral bioavailability (approximately 4–8%) caused by: (1) an important hepatic first-pass metabolism, (2) a limited absorption due to a poor water solubility and (3) the effect of the multidrug resistance transporter P-glycoprotein, which is responsible for an efflux mechanism resulting in a reduced crossing of the intestinal barrier (Noble and Faulds, 1996; Molla et al., 1998; Williams and Sinko, 1999).

Administering saquinavir by the oral route appears as a formidable challenge due to its poor absorption pattern. Several approaches could be investigated to improve its oral bioavailability, among them, the association of the drug to natural or modified cyclodextrins and the association of the drug complex to colloidal drug carrier systems.

Cyclodextrins (CDs) constitute a family of cyclic oligosaccharides. The repetitive unit in these molecules is glucose and, owing to steric reasons, only six-, seven-, and eight-membered rings (α, β, γ) formed natural CDs. They have the ability to form complexes with molecules that are hosted in the inner cyclodextrin core due to interactions between hydrophobic moieties borne by these molecules and the internal surface of the cyclodextrin cavity. For many years, CDs have been extensively used as potent carriers to increase the solubility, to modify the release and to improve the bioavailability of poorly water-soluble drugs (Loftsson and Brewster, 1990; Stella and Rajewski, 1997; Hirayama and Uekama, 1999; Uekama et al., 1998; Bibby et al., 2000). The most common CDs applied in pharmaceutics are natural CDs substituted on the hydroxyl groups. In particular, hydroxypropyl-β-cyclodextrin (HPβCD) deserves special attention because of a higher solubility, a lower toxicity as well as a more hydrophobic cavity compared to the parent compound (Duchêne and Wouessidjewe, 1990; Leroy-Lechat et al., 1994), making this CD a choice candidate for incorporation into drug formulation.

The other strategy for oral drug delivery is the use of colloidal drug carrier systems and particularly polymeric nanospheres. Drug-loaded nanospheres are very stable systems allowing a molecular dispersion of the drug. Many studies demonstrated their ability in promoting oral bioavailability increases (Kreuter, 1994), particularly by improving their residence time in the intestinal mucus owing to a mechanism of bioadhesion (Durrer et al., 1994; Ponchel and Irache, 1998), making them suitable drug colloidal carrier systems for oral administration of poorly bioavailable drugs like saquinavir. However, in many cases, one of the major problems encountered with these drug colloidal carrier systems appeared during the preparation and resulted from the low water solubility of the drug leading either to low drug loadings or to slow or incomplete release of the drugs (Couvreur et al., 1982).

Silveira et al. have shown that the incorporation of cyclodextrins into polymeric nanoparticles offers a very interesting opportunity to increase the loading of nanoparticles with various lipophilic drugs and to modify drug release (Silveira et al., 1998). Therefore, the aim of this paper was, in a first step, to investigate the interactions between HPβCD and saquinavir leading to an HPβCD–saquinavir inclusion complex and, in a second step, to formulate saquinavir loaded combined hydroxypropyl-β-cyclodextrin and poly(alkylcyanoacrylate) nanospheres.

2. Materials and methods

2.1. Chemicals

Saquinavir (sqv) was chemically extracted from Invirase (Roche) according to a procedure described by Parkes et al. (1994). Isobutylcyanoacrylate (IBCA) and isohexylcyanoacrylate (IHCA) were gifts from Loctite (France). Poloxamer 188 (Lutrol F68) surfactant was a gift from BASF (Germany). Hydroxypropyl-β-cyclodextrin (HPβCD) was purchased from Acros Organics (average degree of substitution 3). Other chemicals and solvents were analytical and HPLC grades.

2.2. Hydroxypropyl-β-cyclodextrin–saquinavir inclusion complex

2.2.1. Solubility studies

Phase-solubility studies were carried out according to the method described by Higuchi and Connors (Higuchi and Connors, 1965). An excess of saquinavir was added to deionised water or to pH 2.0 buffered aqueous solution containing increasing amounts of hydroxypropyl-β-cyclodextrin and mixed using a laboratory shaker at 25°C until a solubility equilibrium was reached (7 days). Then, the samples were filtered through a 0.22 μm filter (Millex, SLAP 0225) and, after appropriate dilution with methanol; the filtrate concentration in saquinavir was measured spectrophotometrically at 239 nm. The presence of trace amounts of cyclodextrin did not interfere with the assay.

2.2.2. Preparation of solid inclusion saquinavir–hydroxypropyl-β-cyclodextrin complex

An inclusion complex was prepared by freeze-drying a solution of saquinavir an HPβCD prepared in the molar ratio HPβCD: sqv 4:1. Briefly, saquinavir were dispersed at a concentration of 20 mM in 50 ml of a water containing 80 mM of HPβCD and mixed for 7 days at room temperature. The suspensions were filtered through a 0.22 μm filter (Millex, SLAP 0225). The filtrate was frozen and then freeze-dried.

2.2.3. Preparation of a physical mixture

A physical mixture consisting of saquinavir and HPβCD in the same molar ratio as the freeze-dried complex was prepared by admixing these substances together using a mortar and pestle for 5 min to obtain a homogeneous powder blend.

2.2.4. Differential scanning calorimetry

Thermograms of the different samples (inclusion complex, physical mixture and pure substances) were obtained from a computer-interfaced differential scanning calorimeter equipped with a thermal analysis data system (DSC 7 Differential calorimeter, Perkin-Elmer). Weighted samples (2–4 mg) were contained in holed aluminium pans and scanned at a rate of 10°C/min, between 50 and 260°C, using nitrogen as purging gas. Duplicate determinations were carried out for each sample.

2.2.5. X-ray diffractometry

X-ray diffraction of the samples (inclusion complex, physical mixture and pure components) was performed on the D 43 line of DCI Synchrotron source of the L.U.R.E center (Orsay, France). The wavelength of the radiation was 0.145 nm.

2.2.6. Circular dichroism spectrometry

Circular dichroism spectra of saquinavir alone and in the presence of HPβCD were obtained on a Jobin Yvon Mark V dichrograph (France). The circular dichroism spectra were recorded in the 200–400 nm wavelength domain at room temperature. The saquinavir concentration was fixed at 4.8 mM. Cyclodextrin has no measurable circular dichroic signal in this wavelength domain for the concentration used in the optical experiments.

2.2.7. ^{1}H-nuclear magnetic resonance (^{1}H-NMR)

^{1}H-NMR spectra of free saquinavir or in presence of HPβCD were obtained from a Brücker AM-400 spectrophotometer operating at 400 MHz. Samples were prepared by dissolution in D_2O (99.9% D) or CD_3OD (99.9% D). ^{1}H-NMR spectra of the following samples were recorded: HPβCD (10 mM in D_2O), saquinavir (10 mM in CD_3OD), HPβCD: sqv physical mixture (10 mM of sqv in CD_3OD), HPβCD: sqv freeze-dried complex (10 mM of sqv in D_2O). Chemical shifts were reported in ppm (δ) downfield from tetramethylsilane (TMS) (internal reference).

2.3. Hydroxypropyl-β-cyclodextrin combined poly(alkylcyanoacrylate) nanospheres loaded in saquinavir

HPβCD combined PIBCA and PIHCA nanospheres were prepared by an emulsion polymerization technique (Silveira et al., 1998). Freeze-dried HPβCD–sqv complex prepared as described above was added in the polymerization medium consisting of an aqueous solution of 0.01 M hydrochloric acid (pH = 2.0) containing 1% w/v poloxamer 188. Nanospheres were prepared

by adding 100 μl of IBCA or IHCA in presence of increasing amounts of HPβCD–sqv inclusion complex. The polymerization medium was magnetically stirred (1000 rpm) at room temperature, and the monomer was added drop wise. After 6 h, the suspensions were filtered with a 2 μm prefilter (Millex AP500) in order to remove any aggregates.

For control, PIBCA and PIHCA nanoparticles were prepared in absence of cyclodextrin in the polymerization medium. Saquinavir-loaded nanoparticles were prepared by dissolving the drug in 0.01 M hydrochloric acid (pH = 2) in the presence of 1% w/v of poloxamer 188. The polymerization process was conducted as described above.

2.3.1. Determination of saquinavir into the nanoparticles

The different suspensions of nanoparticles were centrifuged at 82 000 *g* for 30 min at 25°C (Beckman, L5-65 Ultracentrifuge, rotor type 70.1 Ti) and resuspended in 5 ml of distilled water. The suspensions were finally freeze-dried (Christ HED 10 Freeze Dryer, Germany). For determining the amount of saquinavir in the particles, the lyophilized products were diluted in HPLC-grade methanol, and the solutions were analysed by high-performance liquid chromatography (HPLC). The HPLC system consisted of a Waters (St-Quentin-en-Yvelines, FRANCE) 510 solvent delivery unit, a WISP 712 auto sampler, which was operated at 239 nm and interfaced with a 746 data module. The flow rate was 1.0 ml/min and the mobile phase was a (40.5:59.5) mixture of acetonitrile and water containing 25 mM sodium acetate adjusted to pH 4.0 with hydrochloric acid 37% (Hoetelmans et al., 1997). Results were expressed as the mean of three determinations.

2.3.2. Determination of 2-hydroxypropyl-β-cyclodextrin into nanoparticles

For HPβCD quantification, the freeze-dried nanoparticles were hydrolysed with NaOH 0.2 M. After incubating for 12 h, the pH was adjusted to 7.0 ($\pm$ 0.5), and the HPβCD was quantified by a spectrophotometrical determination of the fading of phenolphthalein solutions in the presence of HPβCD. Briefly, phenolphthalein forms stable colourless inclusion complexes with cyclodextrins. The intensity of the coloration decreases in proportion to the increase in cyclodextrins in the medium. Standard solutions and samples were prepared by diluting one part of a cyclodextrin stock solution or samples with four parts of an alkaline borate buffer solution at pH 10.0 containing 2% of an ethanolic solution of phenolphthalein 0.006 M. The standard curve ($\lambda = 550$ nm) was linear for HPβCD concentrations ranging from 1 to 100 μg/ml (Vikmon, 1981).

2.3.3. Nanoparticle characterization

The nanosphere diameter was determined after suitable dilution of bulk suspensions in demineralised water using dynamic laser light scattering (Nanosizer ND4, Coultronics, FRANCE). Each analysis lasted 200 s. The temperature was 20°C, and the analysis angle was 90°. The zeta potential was determined by laser Doppler velocimetry (Zetasizer4®, Malvern, UK) after suitable dilution of the preparations in a 1.0 mM KCl solution.

3. Results and discussion

A significant number of studies suggested that nanoparticles might be useful drug delivery systems for oral administration. Entrapping drugs into nanoparticles was shown to enhance bioavailability and efficacy in comparison to a solution of these drugs. Like most molecules of its class, saquinavir has a poor water solubility. Usually, when using classical water emulsion polymerization procedures, a poor aqueous solubility results in a very low drug loading. This was presently the case as saquinavir loadings in poly(-isobutylcyanoacrylate) and poly(isohexylcyanoacrylate) nanospheres were 2.4 and 2.9 μg of saquinavir per milligram of particles, respectively, impairing any practical interest in these formulations for oral delivery.

In order to overcome this problem, Silveira et al. proposed, in the case of poly(isobutylcyanoacrylate), adding the drug in the preparation medium in the form of a drug–cyclodextrin complex. This resulted in large increases in drug

loadings, which could be due not only to an increase in the drug concentration in the polymerization medium but also to an increase in the number of hydrophobic sites in the nanosphere structure, due to the association of large amounts of cyclodextrin to the particles.

In the present study, saquinavir-loaded PIBCA and PIHCA nanospheres were prepared by adding HPβCD–sqv complex previously characterized in the polymerization medium.

3.1. Solubility of saquinavir at different concentrations of HPβCD

The solubility of saquinavir in deionised water and in pH 2.0 buffer was very low (35.8 μg/ml). The addition of HPβCD resulted in a considerable increase in apparent drug solubility. For example, the addition of 10% w/w HPβCD resulted in 15.8 and 9.3 mg/ml solubilities corresponding to a 400- and 240-fold increase in solubility of saquinavir at pH 7.0 and 2.0, respectively. The phase-solubility diagrams at pH 7.0 and at 2.0 were linear in a wide range of HPβCD concentrations and corresponded to an A_L type profile (Fig. 1). The apparent stability constants (K_C) were estimated from the slope of the straight line according to the equation of $K_C = \text{slope}/S_O(1 - \text{slope})$, where the solubility values (S_O) of saquinavir. The calculated constants were 4086 and 2353 M^{-1} at 25°C in deionised water and pH 2.0 buffer, respectively.

3.2. Characterization of the saquinavir–hydroxypropyl-β-cyclodextrin complex

3.2.1. Thermal analysis

To verify the existence in the solid state of the interaction between saquinavir and HPβCD, each sample was analysed by differential scanning calorimetry (DSC) and X-ray diffractometry. The DSC results presented in Fig. 2 demonstrated an endothermic peak for saquinavir at 249°C corresponding to the melting point. The physical mixture thermogram was nearly identical to that of pure saquinavir and showed an endothermic peak at 249°C. The HPβCD and the inclusion complex did not show any sharp endothermic peak in the temperature range investigated, indicating the amorphous character of both samples. The disappearance of the endothermic peak from the thermogram obtained for saquinavir compared with the thermogram obtained for the complex may indicate the occurrence of an inclusion complex between saquinavir and HPβCD.

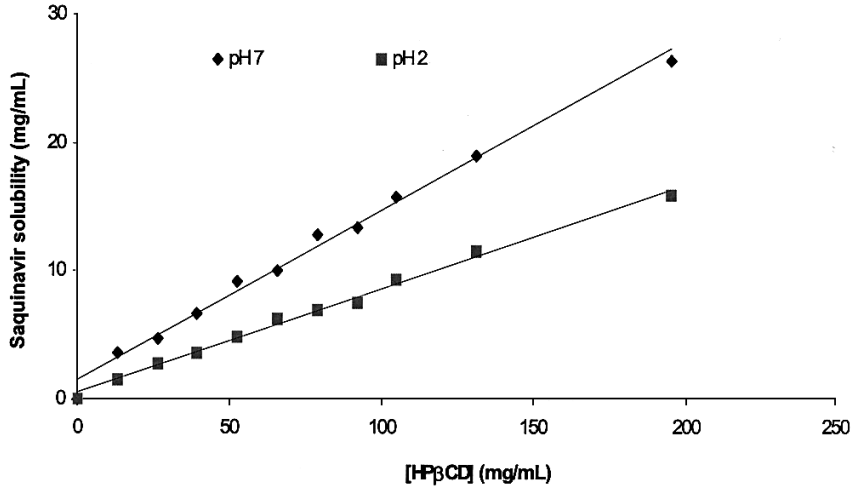


Fig. 1. Solubility diagram of saquinavir in the presence of HPβCD at pH 7.0 and pH 2.0 ($n = 3$).

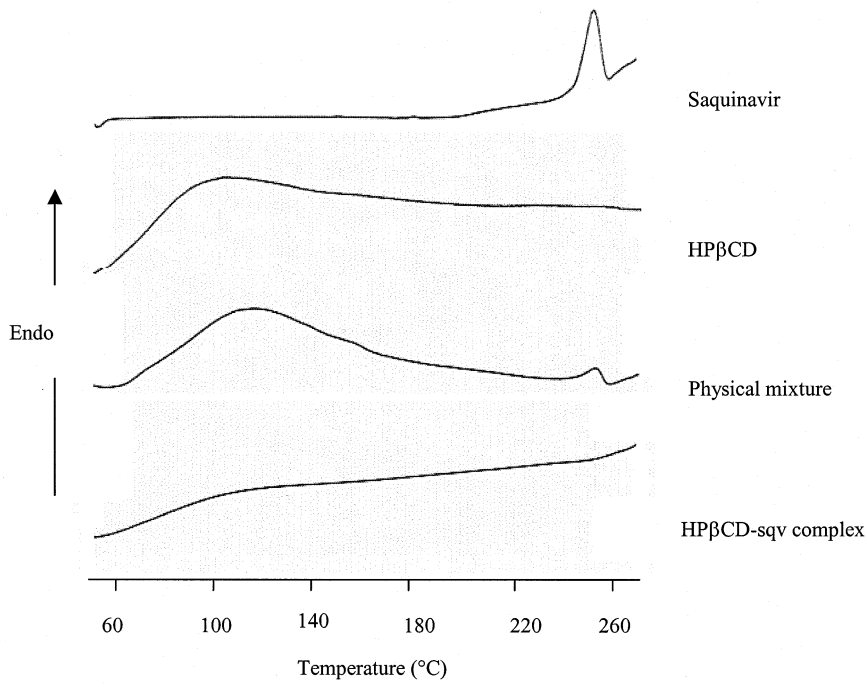


Fig. 2. DSC thermograms of HPβCD–sqv systems. (a) Saquinavir; (b) HPβCD; physical mixture; (d) HPβCD–sqv complex.

3.2.2. X-ray diffraction analysis

The X-ray diffraction pattern of the sqv-HPβCD product demonstrated the amorphous state of the sample (Fig. 3). The X-ray powder diffraction patterns of pure saquinavir displayed crystallinity, whereas an amorphous pattern lacking crystalline peaks was observed for HPβCD. The diffractogram of the physical mixture consisted of the superimposed figures of each of the pure components with the peaks of saquinavir being attenuated due to dilution and particle size reduction during mixture. When compared to the diffraction patterns of pure saquinavir and HPβCD, the diffractogram of the inclusion complex was superimposable with that of the amorphous HPβCD, indicating the existence of molecular interactions between the two species.

3.2.3. Circular dichroism

The drug molecule can develop molecular interactions not only with the surface of the internal cavity, forming a real inclusion compound, but also with the external surface of the cyclodextrin molecule. Moreover, two or more cyclodextrin molecules can be involved in these different types of interactions. Circular dichroism and ^{1}H-NMR spectroscopy were used to prove the occurrence of an inclusion complex. Circular dichroism spectra of saquinavir in the presence or absence of HPβCD are reported in Fig. 4. A negative circular dichroism band was observed at 239 nm for saquinavir alone. In the presence of HPβCD, the intensity of this band was decreased due to the perturbation of the electronic transition of the drug caused by the inclusion in the cavity of cyclodextrin following complexation (Engle et al., 1994; Ventura et al., 1998). The relatively important decrease in intensity suggested that an interaction existed between saquinavir and HPβCD, leading to a confirmation of the formation of an inclusion complex between HPβCD and saquinavir.

3.2.4. ^{1}H-NMR studies

Previous studies tended to prove the formation of an inclusion complex between saquinavir and

HPβCD, but only ^{1}H-NMR spectroscopy can afford the most direct evidence for a true inclusion complex formation by evidencing interactions between the guest molecule and H-3 and H-5 protons belonging to the host cyclodextrin and pointed toward the interior of the cavity. The ^{1}H-NMR spectra between 3.5 and 4.5 ppm, reporting the C–H protons of free HPβCD in D_2O and complexed with saquinavir have been performed. Table 1 summarizes the chemical shifts, δ_{free} and $\delta_{complex}$, for the protons of HPβCD both in the absence and in the presence of saquinavir, respectively. Significant changes were observed in the signal due to H-3 and H-5, whereas H-1, H-2, H-4 and H-6 (located outside the cavity) were relatively unshielded by saquinavir (data not shown). The shifts observed for these HPβCD protons were indicative of the occurrence of an inclusion of saquinavir into the CD cavity (Djedaïni and Perly, 1991). The chemical shifts for the protons belonging to saquinavir, both in the absence and in the presence of HPβCD, are noted in Table 2 as δ_{free} and $\delta_{complex}$. As can be seen, a significant upfield shift for the resonance of the protons of the two aromatic cycles of saquinavir (isoquinoleine ring: H-a, H-c, H-d, H-e and

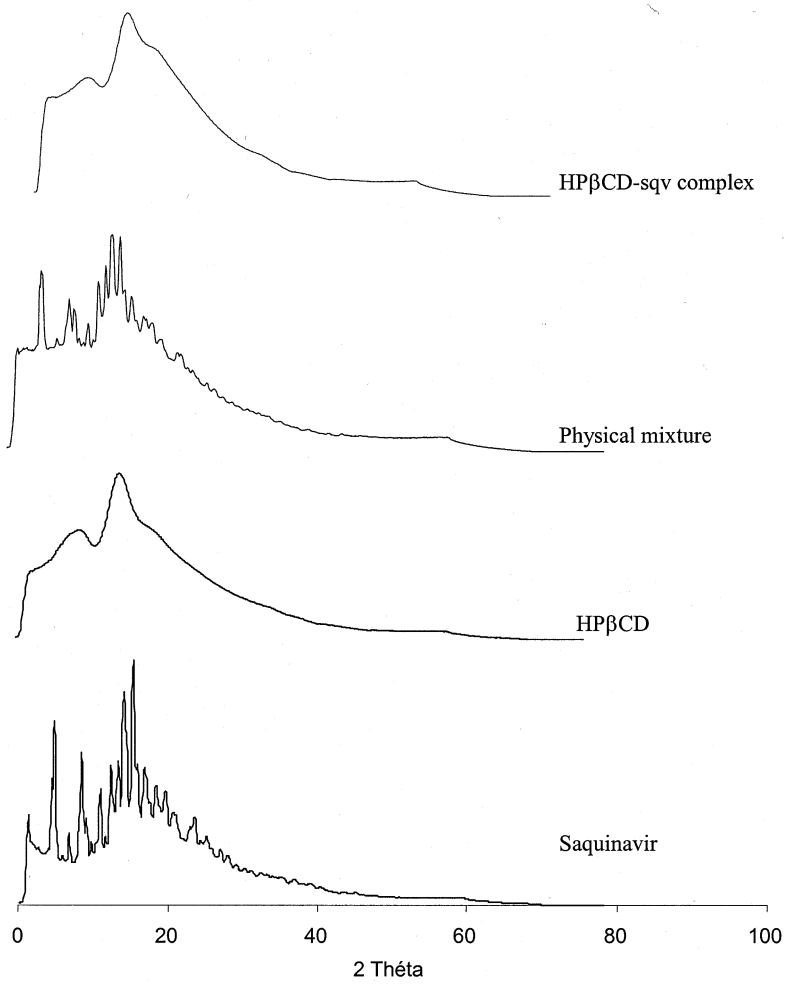


Fig. 3. X-ray diffraction pattern of HPβCD–sqv systems. (a) Saquinavir; (b) HPβCD; (c) physical mixture (d) HPβCD–sqv complex.

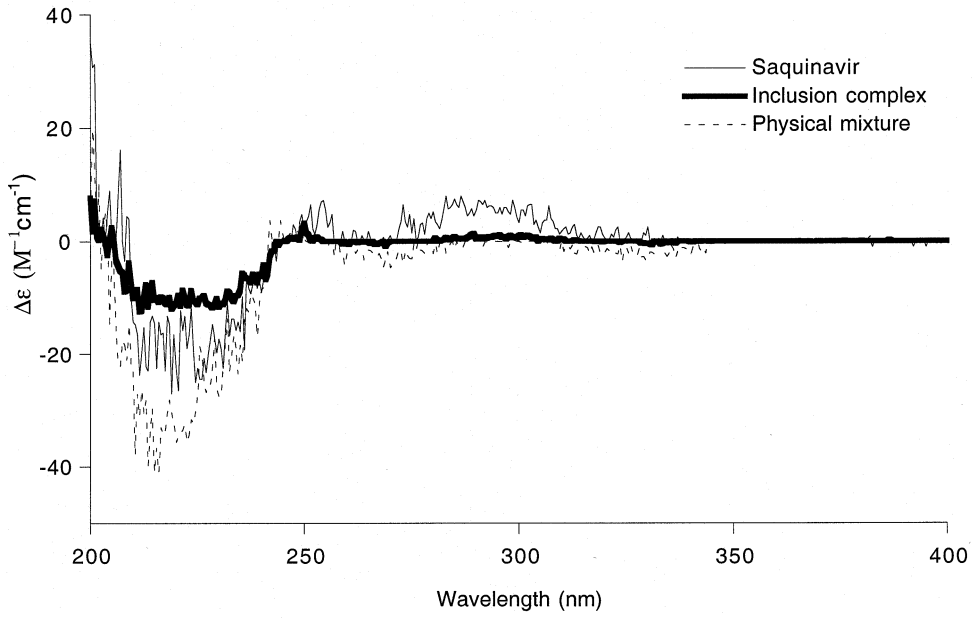
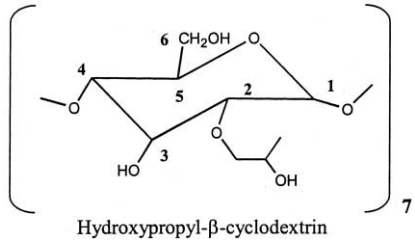


Fig. 4. Circular dichroic spectra of free sqv and in the presence of HPβCD.

phenyl ring: H-g, H-h, H-i) was observed in the presence of HPβCD. This upfield shift noted for the resonance of aromatic protons indicated that the two aromatic cycles of saquinavir were mainly involved in the formation of the complex. Moreover, these results confirmed a previous inspection of the structure of saquinavir, suggesting that both the isoquinoleine and phenyl ring moieties would be expected to be included within the cyclodextrin cavity due to their hydrophobicity and satisfactory geometry. These considerations led to the expectation that both 1:1 and 2:1 HPβCD:sqv complexes were likely to be formed (Johnson et al., 1994).

3.3. Combined poly(alkylcyanoacrylate) and hydroxypropyl-β-cyclodextrin nanoparticles

Nanoparticles could be easily obtained by emulsion polymerization. Depending on the HPβCD concentration, the diameter ranged from 250 to 350 nm. As shown in Fig. 5, the addition of HPβCD–sqv complex in the polymerization medium resulted in an important increase in the drug loading because the amount of saquinavir directly available in the polymerization medium for entrapment into particles during their polymerization was considerably improved when using the HPβCD–sqv complex instead of the saquinavir solution. The total amount of encapsulated saquinavir increased progressively up to 45 and 50 μg of sqv per mg of particles for PIBCA

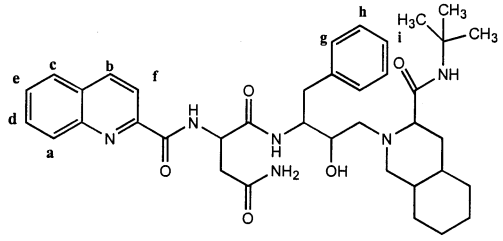


Hydroxypropyl-β-cyclodextrin 7

Table 1
^{1}H chemical shifts corresponding to HPβCD in the sqv–HPβCD complex[a]

HPβCD protons	δ_{free}	$\delta_{complex}$	$\Delta\delta$
H-3	3.825	3.815	−0.010
H-5	3.530	3.500	−0.030

[a] $\Delta\delta = \delta_{complex} - \delta_{free}$.



Saquinavir

Table 2
^{1}H chemical shifts corresponding to saquinavir in the sqv–HPβCD complex[a]

Sqv protons	δ_{free}	$\delta_{complex}$	$\Delta\delta$
H-a	8.460	8.510	0.050
H-b	8.170	8.165	0.005
H-c	8.125	8.055	−0.070
H-d	8.020	7.890	−0.130
H-e	7.815	7.740	−0.070
H-f	7.690	7.69	0.000
H-g	7.110	6.910	−0.230
H-h	6.870	6.500	−0.370
H-i	6.705	5.800	−0.900

[a] $\Delta\delta = \delta_{complex} - \delta_{free}$.

and PIHCA nanospheres, respectively, and reached a plateau when the concentration in HPβCD–sqv complex attained 5 and 7.5 mg/ml, respectively. These values correspond for both nanospheres to a 20-fold drug loading increase compared to the drug loading obtained with conventional nanospheres of PIBCA and PIHCA (respectively 2.4 and 2.9 μg of sqv per milligram of particles).

The addition of HPβCD–sqv complex in the polymerization medium resulted also in the association of large amounts of HPβCD with the nanoparticles. The amount of HPβCD associated with the particles was continuously increased and could be as high as 30% of the weight of the particles. Moreover, the zeta potential of saquinavir-free nanoparticles (−36.9 and −37.1 mV for PIBCA and PIHCA nanoparticles, respectively) was turned into slightly positive values on the whole range of HPβCD–sqv complex concentrations under study (+3.5 and +15 mV, for PIBCA and PIHCA nanoparticles respectively).

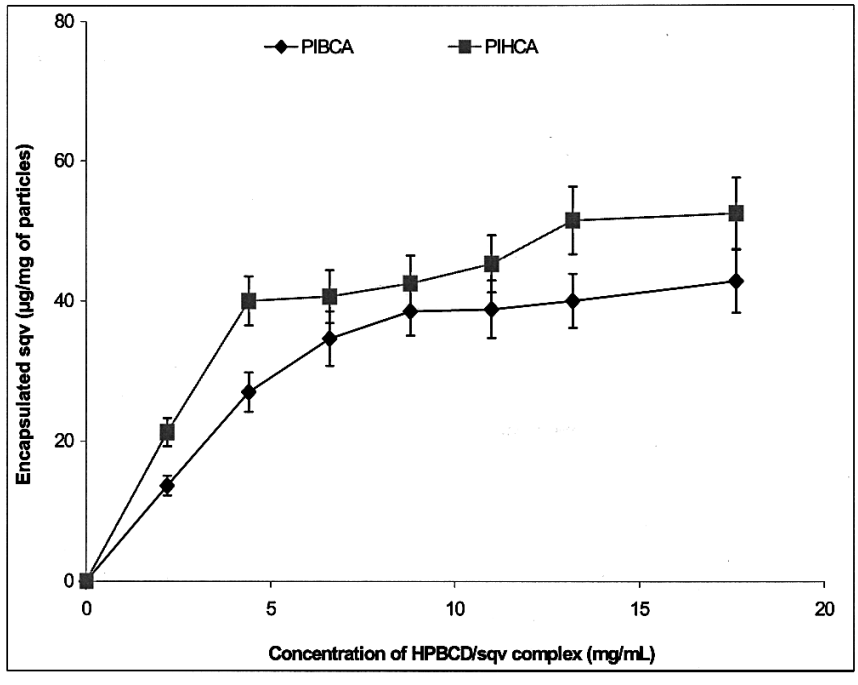


Fig. 5. Saquinavir load of poly(isobutylcyanoacrylate) and poly(isohexylcyanoacrylate) nanoparticles as a function of the amount of HPβCD–sqv complex added in the polymerization medium ($n = 3$).

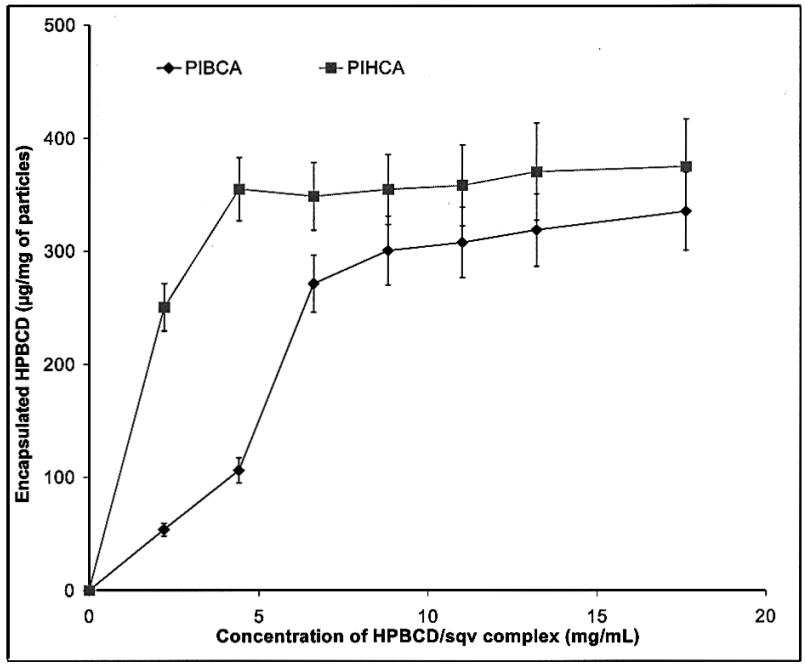


Fig. 6. Amount of HPβCD associated with the poly(isobutylcyanoacrylate) and poly(isohexylcyanoacrylate) nanoparticles as a function of the amount of HPβCD–sqv complex added in the polymerization medium ($n = 3$).

This suggested a shielding of the negative surface charges due to the present in surface of saquinavir and HPβCD.

Fig. 5 shows that the affinity of saquinavir for the particles depended not only on the amount of saquinavir available in the polymerization medium but also on the nature of the nanoparticle itself. The association of saquinavir was higher with the particles prepared from PIHCA compared to PIBCA. This could be due to the higher hydrophobicity of PIHCA compared to PIBCA (which depends on the length of the lateral alkyl chain) as the partition coefficient between the polymerization medium and the particle itself was at least one of the driving forces of the loading process.

More surprisingly, with regard to cyclodextrin, Fig. 6 shows that these molecules were also associated in large amounts with the particles depending on the nature of the polymer forming the particles. As suggested previously (Silveira et al., 1998), cyclodextrins combined with the nanoparticles can have at least four different localizations, which are not exclusive. They can be: (i) adsorbed at the surface of the particles, (ii) bonded to the poly(alkylcyanoacrylate) chains, (iii) entrapped in the polymeric matrix or (iv) exist as inclusion complexes with alkyl moieties borne by the polymeric chain of poly(alkylcyanoacrylate).

In view of the hypothetical structure of the HPβCD and poly(alkylcyanoacrylate) combined nanoparticles, a general mechanism can been suggested for explaining drug loading. The saquinavir–cyclodextrin complex in the polymerization medium constitutes a soluble reservoir that feeds the nanoparticles formation process. It is part of a dynamic equilibrium between the complex, the dissociated species and the forming polymeric particle. Therefore, these different species are likely to be associated with the particles. When particle formation takes place, the free drug is progressively incorporated into the polymer network, driven by the drug partition coefficient between the polymer and the polymerization medium (Duchêne et al., 1999). Simultaneously, direct entrapment of the drug–cyclodextrin complex in the nanoparticles cannot be excluded.

Finally, it is suggested that the present formulation may be considered as a valuable tool for improving the delivery of saquinavir. Firstly, many studies have shown that nanoparticles as drug carriers could improve the delivery of antiviral agents to the mononuclear phagocyte system in vivo, enhancing the activities of antiviral drugs for the treatment of HIV infection and AIDS (Bender et al., 1996; Leroux et al., 1996a). Secondly, nanoparticles have been shown to result in vivo in significant improvements of oral absorption (Leroux et al., 1996b), and therefore, the present formulation may have a potential for improving saquinavir bioavailability and simultaneously reducing the oral dosing of saquinavir in HIV-infected patients.

4. Conclusion

This study has shown that cyclodextrins are not only well-known solubilizers described in the literature. They constitute very powerful tools in drug targeting because they can increase dramatically the loading capacity of nanoparticles. For these reasons, saquinavir-loaded poly(alkylcyanoacrylate)/HPβCD nanoparticles are likely to constitute a promising system for improving oral delivery of saquinavir in the treatment of HIV infection.

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