ELSEVIER

International Journal of Pharmaceutics 171 (1998) 19–29

international journal of pharmaceutics

Physical characteristics of inclusion compounds of 5-ASA in α and β cyclodextrins

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Received 2 July 1997; received in revised form 30 April 1998; accepted 11 May 1998

Abstract

Inclusions in α- and β-cyclodextrins (CD) of 5-amino salicylic acid (5ASA), a light and oxygen sensitive drug, were prepared by a kneading method. The inclusions were studied in aqueous solutions and the solid state and compared to physical mixtures by several methods: differential scanning microscopy (DSC), thermomicroscopy, X-ray diffraction, scanning electron microscopy and mass spectrometry. Studies in aqueous solutions did not reveal the inclusion phenomena with α-CD. The stability of inclusion of 5ASA with β-CD was very low in solution. The studies performed in solid state show that 5ASA may be included preferentially in β-CD. Our data allow us to suggest the usefulness of a β-CD-based dosage form to enhance the stability of 5ASA.

Keywords: Cyclodextrins; 5-Amino salicylic acid; Inclusions

1. Introduction

Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α-, β- or γ-cyclodextrin (CD), respectively), arranged into toroidal compounds. In aqueous solution and the solid state, the inner hydrophobic cavity of the cyclodextrin molecule provides accommodation for appropriate guest molecules and the formation of dynamic inclusion complexes leading to the modification of some physical and chemical properties which characterise the drug (Lach and Cohen, 1963; Saenger, 1980; Szejtli, 1982). These modifications have several advantages in the drug formulation by improving the solubility of poorly water soluble drugs (Guyot et al., 1995) and their consequent bioavailibility or by modifying physical and chemical stability of molecules (Bootsma et al., 1983; Uekama et al., 1984; Vikmon et al.,

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0378-5173/98/$19.00
PII: S0378-5173(98)00165-3

1986; Torres-Labanderia et al., 1994). Cyclodextrins are also useful to eliminate the undesirable properties of drugs, like irritation (Otero Espinar et al., 1991) or unpleasant odour and taste (Sanghavi et al., 1995). Through complexation, cyclodextrins may also stabilise and protect unstable compounds from degradation (Krenn et al., 1992). In this respect, 5-amino salicylic acid (5ASA) is a light and oxygen sensitive drug, currently used in the treatment of inflammatory bowel diseases, particularly rectocolitis and Crohn's disease. One mechanism by which 5ASA could degrade appears to be dependent on the production of coloured imine (Fig. 1). Thus, the present work was undertaken to investigate the possibility of complex formation of 5ASA with α- or β-CD in solution and in the solid state, in order to enhance the stability of this drug. As no definite conclusions about the generation of inclusion compounds can be made according to the techniques currently used in aqueous solution, such as phase solubility diagrams and ultra-violet spectrophotometry method, differential scanning calorimetry (DSC), X-ray diffraction, scanning microscopy and others can be used to show if an inclusion phenomena is obtained.

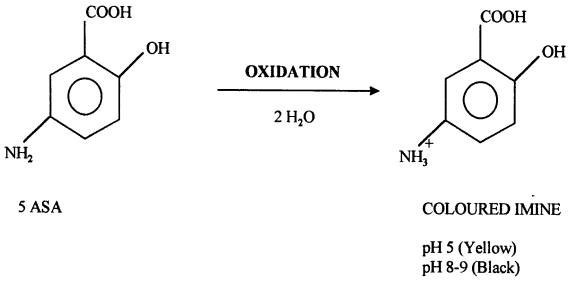


Fig. 1. Oxidative degradation of 5ASA.

2. Materials and methods

2.1. Materials

5ASA was purchased from Bayer (Paris, France). The cyclodextrins were supplied by Ringdex (Paris, France) (α-CD: purity 99%; molecular weight, 972; solubility, 14.5 g/100 ml at 25°C; β-CD: purity, 99%; molecular weight, 1135; solubility, 1.85 g/100 ml at 25°C). All other chemicals and materials were of analytical reagent grade.

2.2. Solubility studies

Phase solubility diagrams were carried out according to the method of Higuchi and Connors (1965). A large excess of 5ASA, exactly 306 mg, was added into glass vials to 20 ml of the appropriate CD solution. 0.1 M phosphate buffer solution (USP XXIII) containing various concentrations of α- or β-CD ($2.5–15 \times 10^{-3}$ M/l). The solubility studies in aqueous solution were investigated over a pH range 3.5, 5.8 and 8.5 because 5ASA can exist under different ionic forms depending on the pH of the solution (Fig. 2). All solutions were protected from the light by wrapping the vials with aluminium foil. The samples were mixed at 25°C over 7 days on a shaking table (Agitelec SL 201). After equilibrium, aliquots of the supernatant were filtered through a membrane filter (0.45 μm, Millipore). The filtrates were diluted with buffer at the corresponding pH and assayed. The drug concentration was determined at $l = 297$ nm using ultra violet spectrophotometer (UV–vis Shimadzu model UV 1201). The

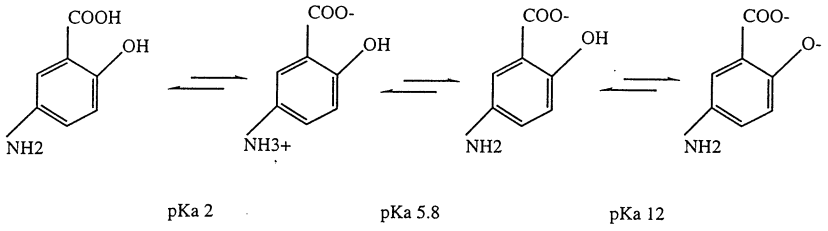


Fig. 2. Ionisation processes for 5ASA.

drug standard followed Beer's law and the cyclodextrins did not interfere with the assay. The apparent stability constants (K_c) were determined, from the initial straight line portion of the phase solubility diagrams. The K_c was calculated by the following equation: $K_c = \text{slope (So } (1 - \text{slope}))^{-1}$ where So represents the saturation concentration of the drug measured without cyclodextrin.

2.3. UV absorption studies

Complex formation between 5ASA and the cyclodextrins in phosphate buffer at pH 5.8 was studied using the spectral shift method (Connors and Mollica, 1966). The concentration of 5ASA was 5×10^{-5} M/l while the α- or β-CD concentration varied from 0.15 to 15×10^{-3} M/l. The mixtures were stirred for 10 min before recording the UV absorption spectra with a double beam spectrophotometer (Shimadzu). The plot of absorbence versus wavelength was made and compared with the plot of free 5ASA. The changes in absorbency of 5ASA by the addition of cyclodextrins were measured at 297 nm.

2.4. Preparation of the inclusion complex

Inclusion in a 1:1 molar ratio were prepared by the kneading method (Vikmon et al., 1986). Cyclodextrins were triturated in a mortar with purified water to obtain a paste before 5ASA was added. The resulting mixture was stirred for 30 min, dried in an oven at 40°C for 12 h and calibrated on a 250 μm opening sieve. The corresponding physical mixtures at similar ratios were prepared for comparison to the inclusions.

2.5. DSC

Samples of approximately 10 mg were accurately weighed (± 0.1 mg) and encapsulated in flat-bottomed aluminium pans with crimped-on lids. The DSC patterns were carried out with a Mettler FP 80 TH (Velizy, France). The measurements from 50 to 360°C were obtained at a scanning speed of 10°C/min under a nitrogen stream.

2.6. Hot stage microscopy (HSM)

Different observations were made during heating using a hot stage device connected to the microscope (Mettler model FP 82 heating system) for thermomicroscopic investigations. Approximately 0.1 mg of the samples were placed on glass slides with coverglasses and heated at 5°C/min.

2.7. X-ray diffractometry

The powder X-ray diffraction patterns were recorded with a Philips X-ray diffractometer (PW 1820) from 2 to 60°C at a 2θ range with a scan speed of 1°C/min using a Ni-filtered CuKa radiation detector ($\lambda = 1.75$ A). The others operating conditions were a voltage of 40 kV and a current of 40 mA with slit width of 0.5°.

2.8. Scanning electron microscopy

An optical (Olympus BH-2) and a scanning electron microscope (model S-250 Hitachi) were used to evaluate the reality and the quality of the inclusion. The advantage of the scanning electron microscopy is the generation of a three-dimensional deep field-picture. The disadvantage is possible damage to the structures due to the electron beam. All photographs were taken using ILFORD FPX 120, 125 ASA film at 20 KV and a magnification of $1000\times$.

2.9. Electro-spray mass spectrometry

This study was performed according to the method described by Sorokine et al. (1992). Mass spectrometry in the electro-spray mode proved to be valuable to show the inclusion compounds and the differences in inclusion ability of native or chemically modified cyclodextrins.

3. Results and discussion

3.1. Solubility studies

These studies allow us to follow the inclusion phenomena and to evaluate the apparent stability

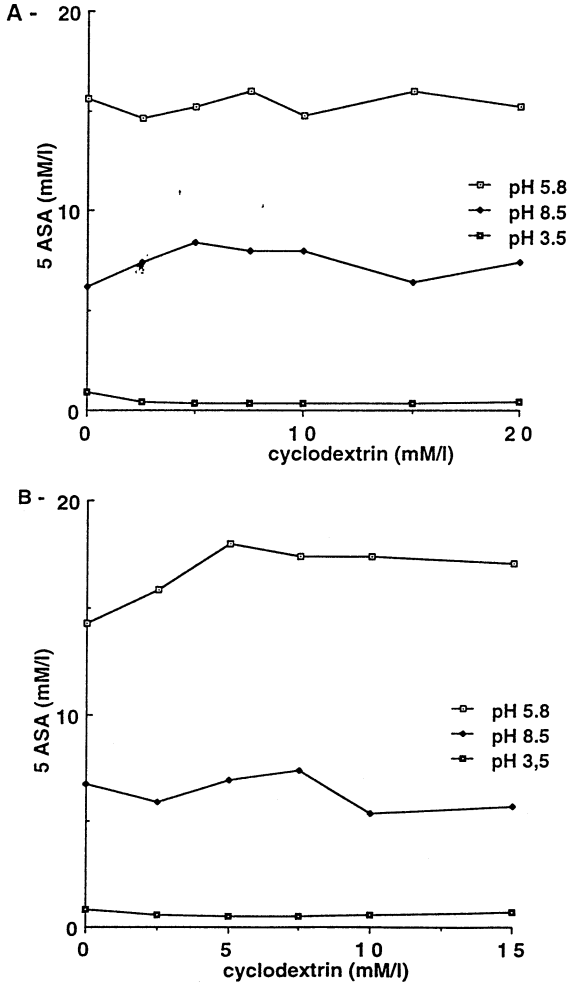


Fig. 3. Phase solubility diagrams of (A) 5ASA–α-CD and (B) 5ASA–β-CD systems in different pH medium.

of the complexes. The type A and type B diagrams are obtained for soluble and insoluble inclusion complexes respectively.

Phase solubility diagrams of 5ASA in the presence of increasing concentrations ($0–15 \times 10^{-3}$ M/l) of α- and β-CD in different pH medium (3.5, 5.8 and 8.5) are shown in Fig. 3. In the pH 3.5 medium, the initial solubility of 5ASA is 1×10^{-3} M/l, no appreciable increase in the solubility was observed in the presence of α- or β-CD, on the contrary, the complexes' solubilities decreased (0.5×10^{-3} M/l). In the pH 5.8 medium, the initial solubility of 5ASA was between 6 and 7×10^{-3} M/l; it was not modified by the presence of α-CD, but it increased slightly upon addition of β-CD. The differential might be due to the narrower cavity size of α-CD as compared to the larger size of β-CD (Eftink et al., 1989). The β-CD system showed a Bs-type behaviour with the microcrystalline complexes precipitating at the highest β-CD concentrations. The rate constant, K_c, was found to be 285/M indicating a relative favourable fitting of 5ASA in the β-CD cavity; furthermore the slope of the straight line is less than 1, thus it was assumed that the increase in the solubility observed was due to the formation of a 1:1 complex. At pH 8.5, the solubility of 5ASA was determined to be between 14 and 16×10^{-3} M/l in the absence of cyclodextrin. The addition of α- or β-CD to the aqueous medium have either no or a minimal effect on the solubility of the drug. Although the samples were protected from light during the seven days of equilibration, it was found that exposure to an alkaline pH medium resulted in a change in colour of the solution. The blackish coloured solution obtained under these conditions may be considered as a qualitative indication of the degree of degradation of 5ASA in an alkaline medium. Furthermore, we may observed in the pH 8.5 medium, an additional peak in the spectrum at 328 nm. These results indicated that the formation of an inclusion complex between 5ASA and β-CD, as previously reported for different drugs (Uekama et al., 1979), was influenced by the pH medium. Indeed, the cyclodextrin cavity has a preferential affinity for the neutral form over the ionised form (Connors and Lipari, 1976). In our experiments, the Bs-type diagram was obtained in the 5.8 pH medium in which 5ASA is less ionised. On the other hand, in an alkaline medium (pH 8.5) the existence on the 5ASA phenyl ring structure of two ionised groups (the carboxyl group, COO^- and the hydroxyl group, O^-) was unfavourable for the formation of an inclusion. However, the weak value of the stability constant obtained at pH 5.8 for the 1:1 5ASA–β-CD inclusion might reflect the weakness of the complexation forces in solution. It is well recognised that the drug–cyclodextrin interactions are not limited only to inclusion phenom-

ena, but can also involve intermolecular forces (Otagiri et al., 1976; Jones et al., 1984). Thus, we have to consider the low calculated stability constant at pH 5.8 as partially representing the inclusion phenomena or an equilibrium reaction.

3.2. UV spectroscopy

The putative formation of an inclusion complex of 5ASA in aqueous buffered solution in a pH 5.8 medium have been studied by UV spectroscopy. Fig. 4 show the effects of β-CD on the spectra of 5ASA. The absorption spectrum of 5ASA varied by adding β-CD, although the changes were shown to be slight. No bathochromic shift was observed. At 297 nm, which are the absorption maximum wavelength, the addition of low quantity of β-CD ($0.15–5 \times 10^{-3}$ M/l) to the 5ASA solution resulted in a decrease in the optical density of the drug. In the presence of 0.15 and 1.2×10^{-3} M/l of β-CD, the spectral changes were such that the intensity of the maximal absorbency difference at 297 nm were 0.011 and 0.039, respectively. These changes were larger than those in the case of adding α-CD (data not shown). This hypochromic shift indicated that the concentration of 5ASA in solution increased by adding β-CD. These data might suggest the possibility of an interaction between 5ASA and β-CD

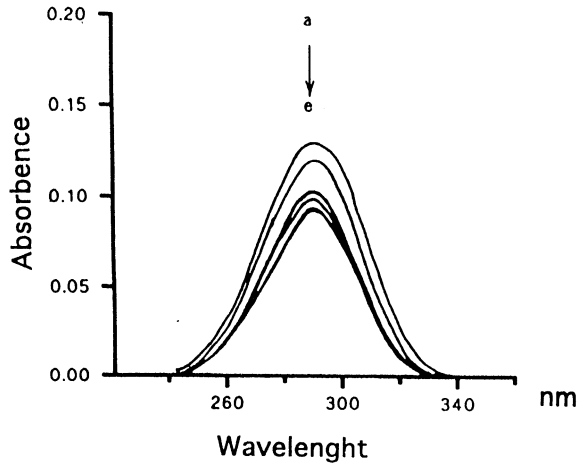


Fig. 4. Effects of β-CD increasing concentrations (a, 0; b, 0.15; c, 0.5; d, 1.2; and e, 5×10^{-3} M/l) on the UV spectrum of 5ASA (5×10^{-5} M/l) in buffer phosphate (pH 5.8, 25°C).

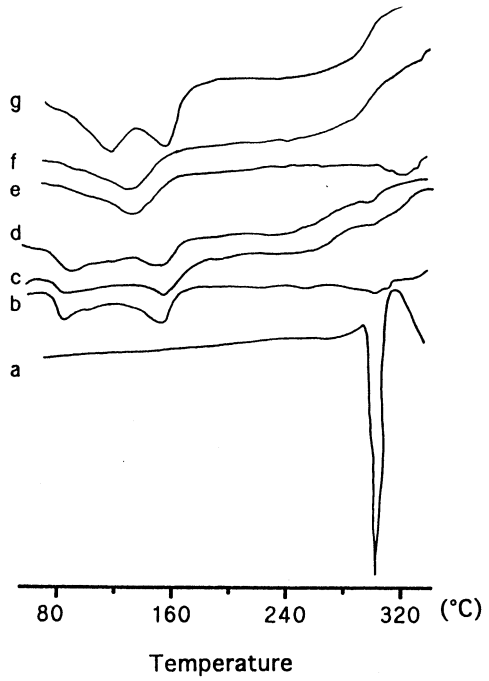


Fig. 5. DSC thermograms of: (a) 5ASA, (b) α-CD, (c) physical mixture 5ASA–α-CD (d) inclusion complex 5ASA–α-CD, (e) β-CD, (f) physical mixture 5ASA–β-CD and (g) inclusion complex 5ASA–β-CD.

as a result of a partial shielding of the chromophore electrons in the β-CD cavity. Similar results have been previously reported for β-CD with ibuprofen (Chow and Karara, 1986) and allopurinol (Ammar and El-Nahhas, 1995).

3.3. Differential thermal analysis

The thermograms of the 5ASA, α- and β-CD physical mixtures and kneaded complexes are depicted in Fig. 5. The active substance 5ASA showed a characteristic thin endothermic peak at 297°C indicating the melting point of the drug (Fig. 5a). Pure α- and β-CD had no defined melting peaks. The α-CD melting peaks consisted of two isolated signals appearing at 80 and 150°C (Fig. 5b). On the other hand, the β-CD thermogram exhibited a broad thermal rise peak phenomena in the zone between 60 and 140°C which attained a maximum around 120°C (Fig. 4c). This phenomena might be attributed to the loss of

water and was observed in different studies with hydrocortisone butyrate (Chun and Yun, 1993). The presence on the DSC curves of a thermal rise near 300°C is generally attributed to the beginning of decomposition of the cyclodextrins (Glomot et al., 1989). The thermal analysis of the 5ASA–α-CD kneaded complexes and their corresponding physical mixtures revealed the disappearance of the melting phenomenon described for the drug. Taken together, these results confirm not only an interaction between 5ASA and cyclodextrin but lead us to suggest the possibility of a real inclusion complex formed by kneading. However, the conclusions must be used carefully because two phenomena may be accounted for: (i) the inclusions can be made during the fusion process; and (ii) the other limitation is the dilution of 5ASA in the samples. Indeed, the concentration of 5ASA for the 1:1 composition corresponded to only 10% of the complex total mass, the possibility that the dilution of 5ASA in the cyclodextrin may mask the detection of the endothermic peak.

3.4. HSM

The differential thermal studies were completed by microscopic analysis to follow the fusion phenomena whilst increasing the temperature. The photographs of 5ASA are shown in the Fig. 6a. The pure drug was characterised by the presence of crystals in a needle shape with a melting point at 280°C. The feasible formation of an inclusion was examined by exposing the different samples to HSM study. The presence of 5ASA was observed for the kneaded product with the α-CD (Fig. 6b), but not for the kneaded product with the β-CD (Fig. 6c). Moreover, the melting process of 5ASA was only observed by HSM for the kneaded product with α-CD. These results confirm the reality of the formation of inclusion complexes in the case of using β-CD.

3.5. X-ray diffractometry

The X-ray diffraction patterns obtained for the kneaded complexes and their physical mixtures are presented in Fig. 7. The physical mixture patterns are apparently only the superposition of each product. On the other hand, the spectra of the 5ASA–β-CD complex clearly differed from those of each component, it showed a less crys-

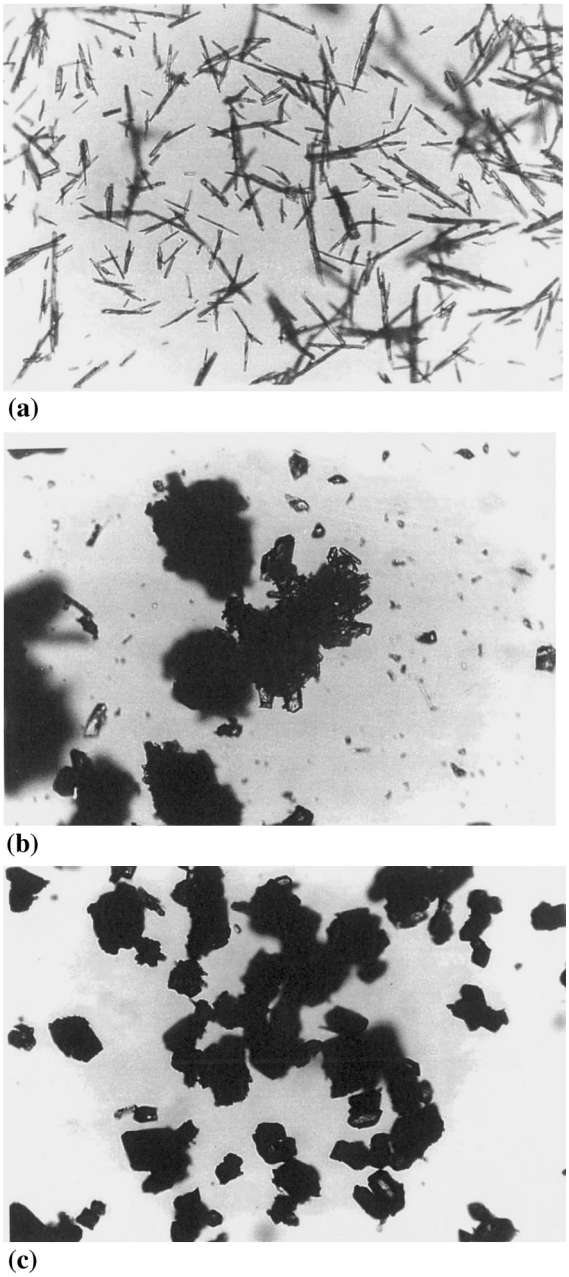


Fig. 6. Hot stage microscopy: (a) 5ASA, (b) 5ASA–α-CD and (c) 5ASA–β-CD.

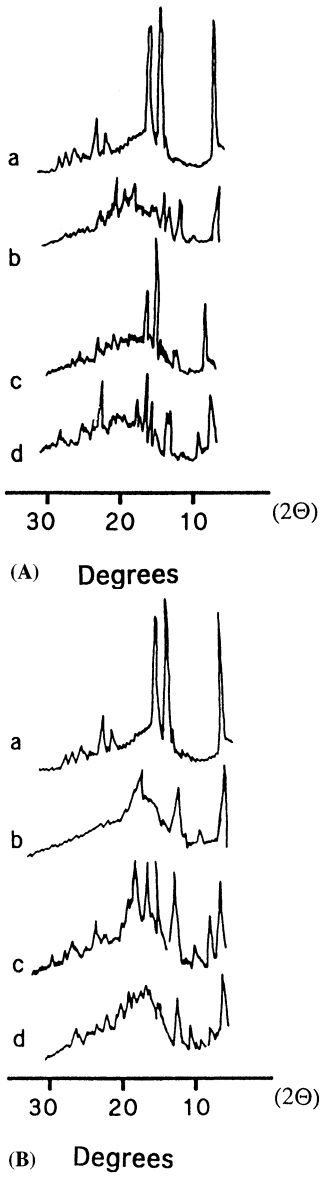


Fig. 7. (A) Powder X-ray diffraction patterns of (a) 5ASA, (b) α-CD (c) physical mixture and (d) inclusion complex 5ASA–α-CD; and (B) powder X-ray diffraction patterns of (a) 5ASA, (b) β-CD, (c) physical mixture and (d) inclusion complex 5ASA–β-CD.

tallisation state as evidenced by fewer and broader peaks of lower intensity. Furthermore, we observed the modification of the diffractogram to an halo pattern and the disappearance of the two peaks corresponding to 2θ degree values of 14 and 16 A (Fig. 7B). The formation of a different crystal structure may be considered as an indirect proof for inclusion formation between the drug and the β-CD (Uekama et al., 1984). In the case of the α-CD, we observed some differences in the patterns of 5ASA–α-CD inclusion from those of the initial products and the physical mixture, the formation of the complex is not easy to identify because the physical mixture and the inclusion obtained by kneading have a similar spectra (Fig. 7A).

3.6. Scanning electron microscope

Analysis by the scanning electron microscope shows the crystallisation of α- and β-CD in polyhedral form with relative large dimensions (Fig. 8b,d) while 5ASA occurs in the form of fine needles (Fig. 8a). The observation of the 5ASA–β-CD complex obtained by kneading (Fig. 8e) reveals the absence of needles which assesses the existence of a single component in the preparation. Furthermore, the microscopic studies prove that 5ASA and α-CD have a marked tendency to aggregation (hydrogen bounds), as demonstrated by the 5ASA crystals confined outside the toroid (Fig. 8c).

3.7. Electro-spray mass spectrometry

Mass spectrometry in the electro-spray mode allows us to see the formation of inclusion compounds and the differences in inclusion ability between the cyclodextrins This method bring a better understanding of their inclusion capability (Sorokine et al., 1992). According to the mass spectra obtained in our study (Fig. 9), we identify the following ionic peaks: α-CD ($m/z = 973$), β-CD ($m/z = 1135$), kneaded complexes 5ASA–α-CD 1:1 ($m/z = 1127$) and 5ASA–β-CD 1:1 ($m/z = 1289$). In view of our data, the spectra analysis attempts to consider that 5ASA forms preferentially complexes with β-CD by a physical mixture and kneading. In the case of the physical mixture, it could be that complexed products occurred during the preparation of the samples; however, kneading provide a greater included compounds ratio as compared to the physical mixture.

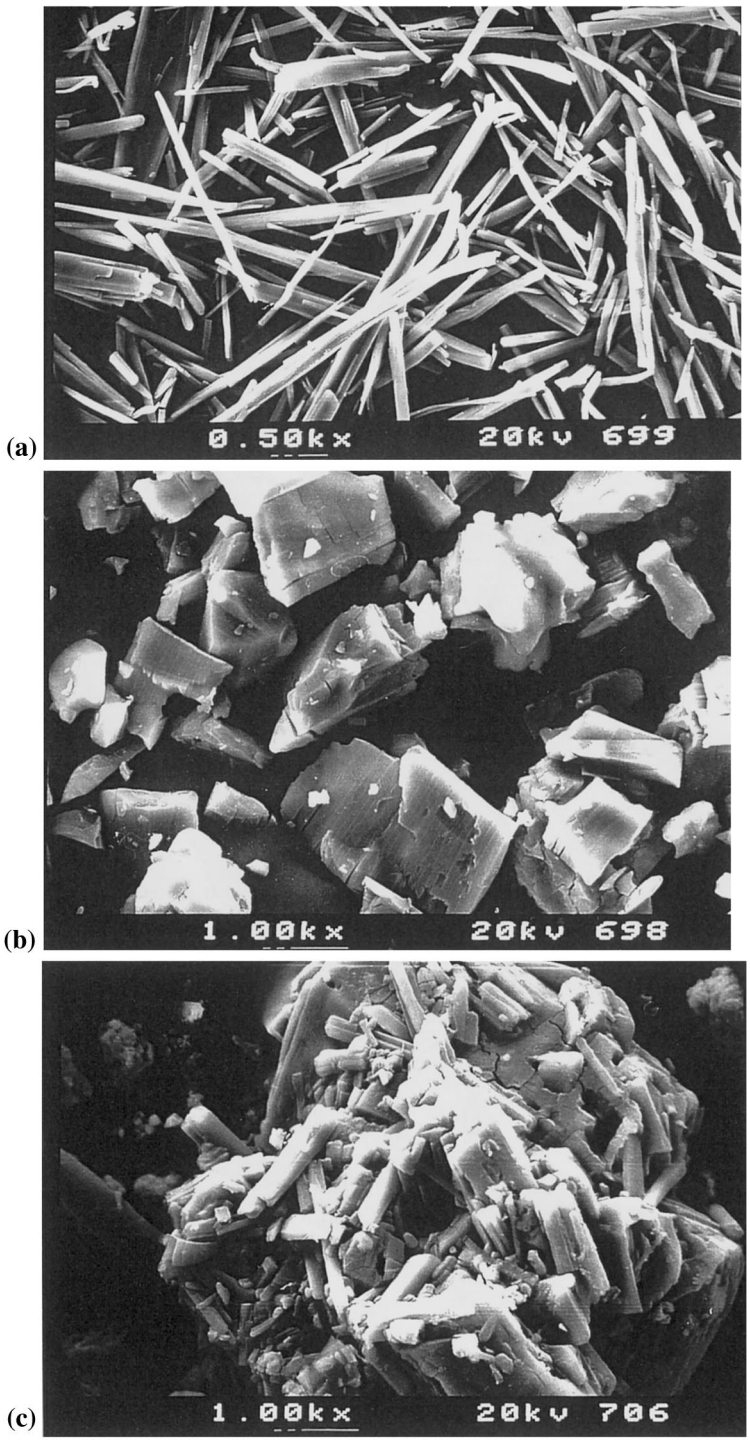
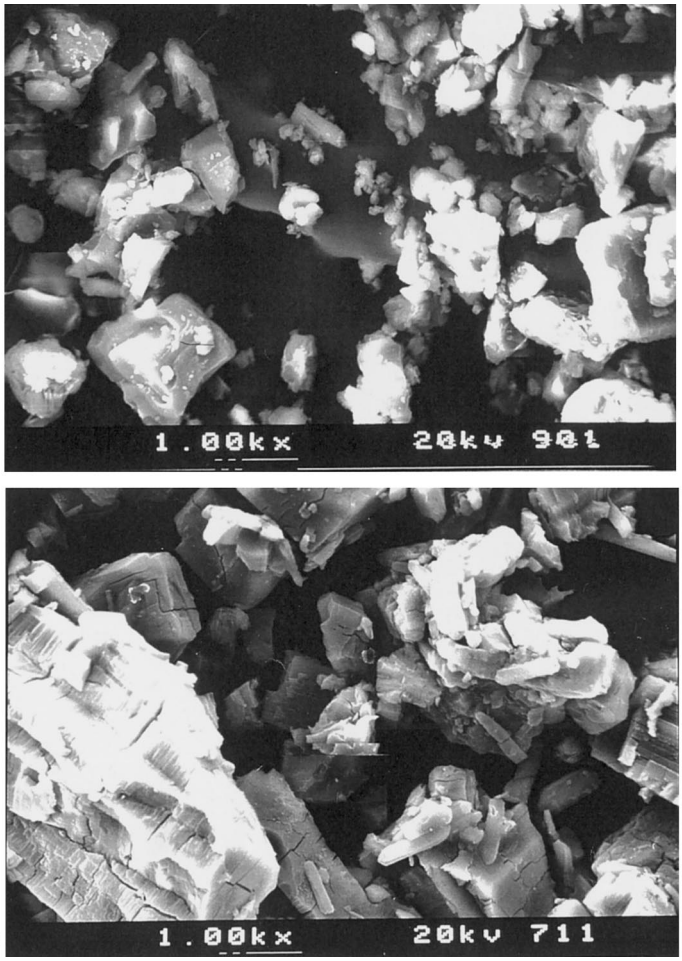


Fig. 8. Scanning microscopy of (a) 5ASA, (b) α-CD, (c) 5ASA–α-CD, (d) β-CD and (e) 5ASA–β-CD.



(d)

(e)

Fig. 8. (*Continued*)

This preliminary study was used to examine the feasibility of complex formation between 5-ASA and α- or β-CD and to assess cyclodextrin as a potential vehicle for improving the stability of the drug. Interestingly, our data confirm that the study of an inclusion phenomena must be done with several complementary methods. Our first investigations were in aqueous solutions. The calculations from the solubility diagrams and the spectroscopic studies have been performed to give quantitative parameters. These parameters associated with the formation a complex between 5ASA and cyclodextrin have mitigated the formation of an inclusion. Moreover, the results obtained from studies either in aqueous solution or the solid state indicate that the steric features of 5ASA are of crucial importance in the formation of 5ASA–cyclodextrin inclusion. This assumption is supported by the absence of any detectable amount of complexation with α-CD as illustrated by the solubility diagram for 5ASA with α-CD and confirmed by the X-ray diffractometry and scanning electron microscopy methods. On the basis of size consideration, we can suppose that the presence of the hydroxyl group and the amine substituents, respectively, in *ortho* and *meta* related to the carboxylic group of the 5ASA phenyl ring, increase theorically the length of the C_2–C_5 axis and consequently affect the access of the substrate into the cavity of the α-CD. However,

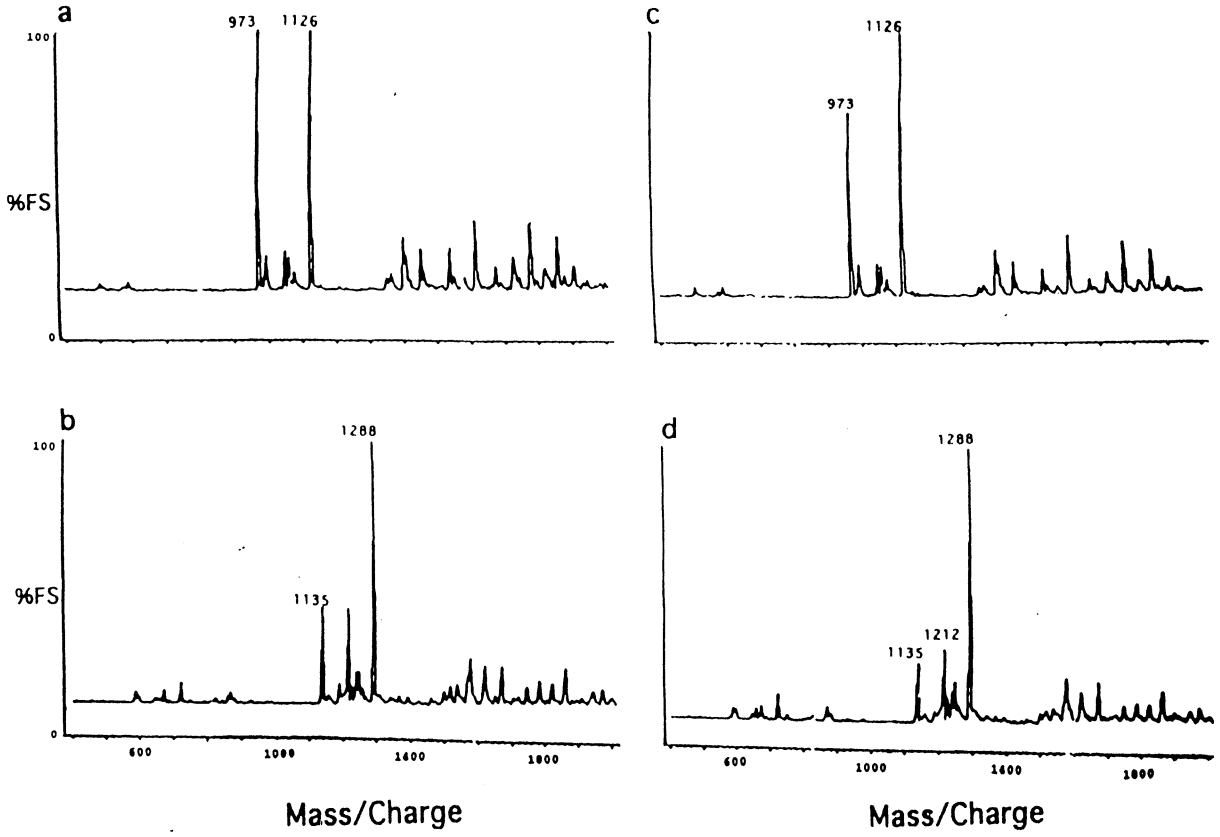


Fig. 9. Mass spectra of (a) physical mixture 5ASA–α-CD, (b) physical mixture 5ASA–β-CD, (c) inclusion complex 5ASA–α-CD and (d) inclusion complex 5ASA–β-CD.

studies in the solid state have provided evidence for the inclusion of 5ASA in β-CD. These data allow us to suggest the usefulness of a β-CD-based dosage form to examine in the future the efficiency of this type of inclusion on the stability of 5ASA. In conclusion, these preliminary results must be completed by studies of stability to confirm that the inclusion compounds might be a means to protect a light and oxygen sensitive drug like 5ASA from degradation.

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