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Studies of cyclodextrin inclusion complexes. I. The salbutamol-cyclodextrin complex as studied by phase solubility and DSC

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Summary

Cyclodextrins (CYDs) are cyclic non-reducing oligosaccharides built up from six, seven or eight glucopyranose units (α-, β- or γ-CYD, respectively). Many drugs are able to form an inclusion complex with CYDs, being trapped entirely or at least partially into their slightly apolar cavities. Complexes of CYDs and salbutamol were obtained in both the liquid and solid state. The influence of both temperature and CYD concentration on complex solubility was studied using the method of Higuchi and Connors (*Adv. Anal. Chem.*, 4 (1965) 117–212). This is based on monitoring changes in the solubility of substrate (salbutamol) on the addition of complexing agents (α-, β-, Me-β- and γ-CYD). The rate of increase in substrate solubility with CYD concentration varied with the type of CYD used (Me-β- > β- ≫ γ- > α-CYD). As salbutamol is water soluble and an A_L type diagram is obtained, the solid complex was prepared by freeze-drying (lyophilization). In order to confirm solid complex formation, differential scanning calorimetry (DSC) was used. When guest molecules are incorporated in the CYD cavity, their melting, boiling or sublimation points usually shift to a different temperature or disappear within the temperature range where the CYD is decomposed. The thermograms obtained showed an endothermic peak for the freeze-dried salbutamol and for the physical mixture (salbutamol and β-CYD both freeze-dried) which was eliminated for the inclusion complex.

Introduction

Cyclodextrins (CYDs) are toroidal molecules which have, as their most important structural characteristic, a doughnut-shaped hydrophobic cavity in which various types of drugs ('guest' molecules) may be clathrated (encased). Non-covalently bonded inclusion complexes either in the solid phase or in aqueous solutions are formed (Saenger, 1980; Uekama, 1981; Szejtli, 1982a). This phenomenon has received extensive attention in the pharmaceutical field because of its ability to improve the aqueous solubility, dissolution and release rates, bioavailability, chemical stability (e.g. photodegradation, hydrolysis, decomposition, oxidation, racemization and isomerization), physical stability (heat, dispersed stabilization systems) and modification of the pharmacokinetics, of various drug molecules (Uekama, 1979; Saenger, 1980;

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Fromming, 1987; Uekama and Otagiri, 1987). In addition, the complexation may also suppress the volatility and unpleasant odours or tastes associated with the drug and avoid incompatibility problems with other drugs or excipients in a formulation, reduce the local irritance and haemolysis of a drug, etc. (Uekama, 1979, 1981; Saenger, 1980; Szejtli, 1982b; Jones et al., 1984).

Because of their different internal cavity diameters, each CYD (α, β, γ) shows a different degree of inclusion complex formation with different-sized guest molecules. When the guests have similar molecular dimensions, the more hydrophobic (rather than hydrophilic) molecule or residue has the higher affinity for the CYD cavity in an aqueous solution, because the cavity provides a micro-heterogeneous hydrophobic matrix in such polar solvents (Hirayama and Uekama, 1986).

The objective of the present paper is to examine the feasibility of using drug-CYD complexes in order to produce a sustained-release formulation of short-acting bronchodilators. Recently, it has been shown that CYD derivatives may be useful for controlling (sustaining) the release rate of other classes of drugs by alternative routes of administration (Uekama et al., 1987; Hirayama et al., 1988). The physiology and morphology of the lung eliminates the use of more conventional approaches to achieving sustained release. Salbutamol initially has been selected as a 'model' short-acting bronchodilator. In this paper proof is provided that complexes are formed both in solution and in the solid state and by solubility studies estimates of the stability constants are provided. A subsequent publication seeks to identify the nature of the complex with specific reference to the preferred orientation of the salbutamol molecule within the β-CYD torus.

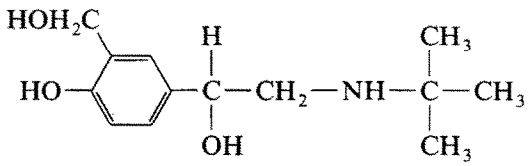
Materials and Methods

Materials

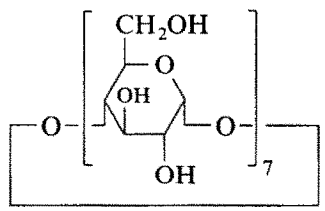
Salbutamol B.P. (base) was a generous gift from the Pharmaceutical Research Department, Glaxo plc. (Ref. No. MR22508W), Lilly Research Centre Ltd, Surrey, U.K. (batch no. 73267023) and from 3M Health Care Ltd, Loughborough, U.K. (batch no. AL260988).

α-CYD was obtained from Chinoin (Budapest) (Ref. No. 810901) and from Sterling Organics Ltd, Northumberland, U.K. (Lot. No. 10106).

β-CYD was obtained from Chinoin (Budapest) (Ref. No. 850436) and from Berk Limited, Basingstoke, Hants, U.K. (Ensuiko Sugar Refining Co., Ltd).



Salbutamol



Beta-Cyclodextrin

γ-CYD was obtained from Sterling Organics Ltd, Northumberland, U.K. (Lot. No. 30601) (Sanraku Incorporated).

Heptakis (2,6-di-*O*-methyl)-β-CYD (Me-β-CYD) was purchased from Aldrich (27,953-6 05407KM DV). Hydrochloric acid (0.1 M) was prepared using HCl (1.0 M) from BDH and freshly prepared distilled water.

Salbutamol purity was established by comparison of its melting point (154–155 °C) with literature values (155 °C) (British Pharmacopoeia, 1988), and was used without further purification. CYDs were used directly. Other chemicals were reagent grade.

Apparatus

A Uvikon 860 UV spectrophotometer (Kontron Instruments) was used to determine the λ_{max} for salbutamol. An LKB 4050 Ultrospectrophotometer (Biochrom, Cambridge, U.K.) was used for all the fixed-wavelength UV measurements. A constant temperature (± 0.1 °C) shaking water bath (Grant Instrument, Cambridge, U.K.), ultrasoni-

cator cavitator (Scientific Industries Int., Inc. (U.K.) Ltd) and a Modulyo Edwards high vacuum freeze-drier (Crawley, U.K.) were from the indicated suppliers. The DSC spectra were obtained using a DSC-2C (Perkin Elmer, CT, U.S.A.).

Phase-solubility studies

Solubility measurements were carried out and the stability constants (K_s) of the complex were determined according to the phase solubility method of Higuchi and Connors (1965). An excess amount of salbutamol was added to screw-cap glass vials containing aqueous solutions of various concentrations of CYDs. Fresh distilled water was used as a medium. The vials were protected from light, sonicated for 10 min, placed in a water bath and shaken (190 strokes min^{-1}) continuously at 20, 25 and $37 \pm 0.1°C$. After equilibrium was attained, (approx. 24 h) an aliquot was filtered through a 0.2 μm pore size Whatman filter membrane. A portion of the sample (0.2 ml) was diluted (to 50 ml in a 50 ml volumetric flask) with 0.1 M HCl solution and the concentration of dissolved drug determined by UV-absorption spectroscopy at 275 nm. Previous determinations showed that the CYDs did not interfere with the spectrophotometric measurements at the concentrations employed. The experiment was carried out in triplicate for β-CYD and in duplicate for the other CYDs studied.

The increase in solubility in these systems is due to one or more molecular interactions between substrate (S) and ligand (L) to form distinct chemical species or complexes (Higuchi and Connors, 1965). Stability constants (K_s) were calculated from the initial linear portions of the phase solubility diagrams, assuming that a 1 : 1 stoichiometric ratio complex was formed at the initial stage, (as the slope is smaller than 1 for all CYDs). Calculation of K_s was according to Eqn 1 (where S_0 = intercept):

$$K_s = \text{slope}/S_0(1-\text{slope}) \quad (1)$$

It should be noted that some authors use S_0 as the intercept of the curve and others as the solubility of salbutamol in the absence of CYDs. In all these studies S_0 was considered as the intercept, and the slopes were quoted as molar ratios.

Preparation of the solid complex

There are several methods for the synthesis of the CYD-guest complexes depending on the physical properties of the guest molecules: kneading (Saenger, 1980; Hirayama and Uekama, 1986; Rajagopalan et al., 1986), neutralisation (Tokumura et al., 1984), co-pulverizing or grinding (Nakai et al., 1978; Fujioka et al., 1983), co-precipitation (not based on the phase solubility) (Kurozumi et al., 1975; Saenger, 1980; Jones et al., 1984; Hirayama and Uekama, 1986), co-precipitation (based on the phase solubility) (Saenger, 1980; Uekama et al., 1982; Tokumura et al., 1984; Chow and Karara, 1986; Hirayama and Uekama, 1986; Rajagopalan et al., 1986), and freeze-drying or lyophilization (Kurozumi et al., 1975; Saenger, 1980; Fujioka et al., 1983; Jones et al., 1984; Hirayama and Uekama, 1986; Rajagopalan et al., 1986). Lyophilization was used in these studies because it is suitable for substances like salbutamol which are water soluble or for drugs which decompose on drying (Saenger, 1980) and it produces a powdered sample with a very good yield (Jones et al., 1984).

Thus, the solid salbutamol-β-CYD complex was prepared by dissolving the appropriate amounts of salbutamol (0.3590 g) and β-CYD (1.7025 g) in water (100 ml) giving a molecular ratio of 1 : 1, whereafter this sample was freeze-dried for 48 h (protected from light).

Preparation of the physical mixture

The mode of the preparation of the physical mixture consisted of pulverization in a ceramic mortar and careful mixing of the calculated and exactly weighed (1 : 1 molar ratio) amounts of salbutamol and β-CYD (Erden and Çelebi, 1988).

Differential scanning calorimetry (DSC)

The DSC scans were recorded with sample weights between 2.84 and 3.15 mg. Each sample was scanned at 20 K min^{-1} in the range 400–460 K.

Results and Discussion

Inclusion complexation in solution

Figs 1–3 show the solubility isotherms representing the effects of increasing concentrations of the four CYDs on the apparent solubility of salbutamol. An increase in the solubility of the complex with respect to the free form was observed for all CYDs and at all temperatures studied. Linear plots (A_L type diagrams) were obtained up to the maximum solubility of all CYDs in water for the three temperatures (20, 25 and 37 °C). According to Higuchi and Connors (1965) these A_L type curves indicate the formation of soluble complexes between the substrate (salbutamol) and the ligand (each CYD) and a first-order dependency of the interactions on the CYDs concentrations (i.e., SL, S_2L, ... S_nL).

The solubility of salbutamol complex increased in the order Me-β- > β- ≫ γ- ≫ α-CYD. Accessibility of the ring of the salbutamol molecule must be the primary factor for interaction with CYDs. Overall, the cavity size of β-CYD and its derivative seems to be optimal for entrapment of the salbutamol molecule and consequently provides the greatest solubilization effect.

The effect of the temperature on the solubility of salbutamol is minimal in the absence and presence of the various CYDs, as shown in Fig. 4 (for β-CYD). All other CYDs were similarly not sensitive to changes of temperatures in the range of 20–37 °C.

Table 1 lists the values for the maximum solubility of salbutamol in water at each temperature (S_0), the stability constant (K_s) of the complex for each interaction calculated from Eqn 1, the correlation coefficient of the regression line, and the molar ratio (salbutamol : CYDs) which was obtained from the slope. Attempts were made

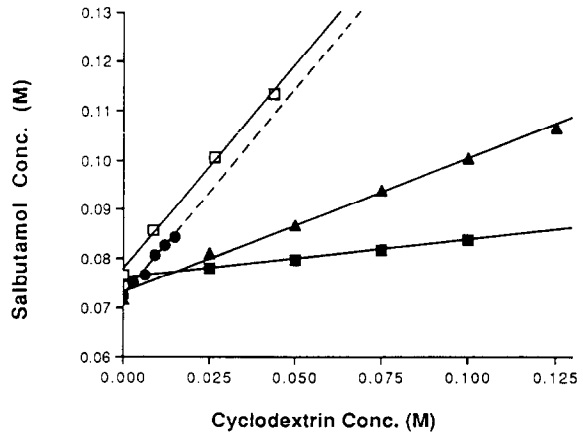


Fig. 2. Phase solubility diagrams for salbutamol with α- (■), β- (●), γ- (▲) and Me-β-CYD (□) at 25 °C. Each data point is the mean of duplicate samples ± < 5% except for β-CYD (●) which is the mean of three determinations (S.E. < 0.0017).

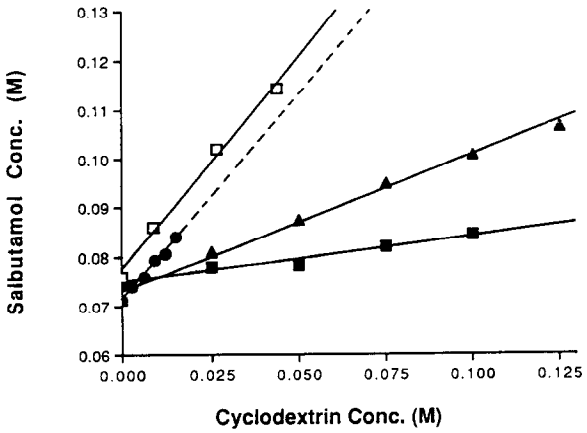


Fig. 1. Phase solubility diagrams for salbutamol with α- (■), β- (●), γ- (▲) and Me-β-CYD (□) at 37 °C. Each data point is the mean of duplicate samples ± < 5% except for β-CYD (●) which is the mean of three determinations (S.E. < 0.0015).

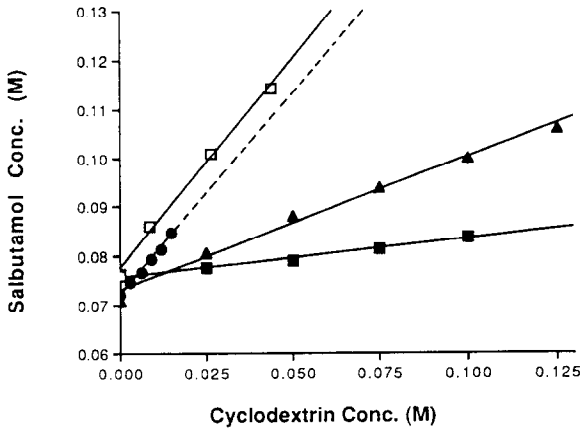


Fig. 3. Phase solubility diagrams for salbutamol with α- (■), β- (●), γ- (▲) and Me-β-CYD (□) at 20 °C. Each data point is the mean of duplicate samples ± < 5% except for β-CYD (●) which is the mean of three determinations (S.E. < 0.0017).

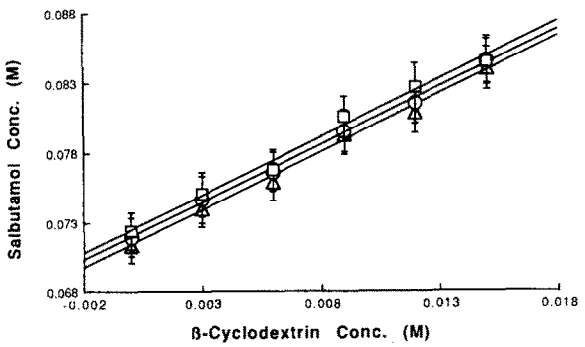


Fig. 4. Effect of temperature on the β-CYD-salbutamol system at 20 (○), 25 (□) and 37 °C (△). Each point is the mean of three determinations with S.E. bars.

according to the method of James (1986) to prove that complexes of different order were formed but the correlation factors of the regression lines were very small. Therefore, we concluded that a 1 : 1 complex is the only species formed under the conditions studied.

The interaction of salbutamol with α- and γ-CYD is just detectable and very weak with equilibrium constants of 1.1–1.3 and 5.1–5.2 M^{-1}, respectively, confirming the poor interactions between the complex components. Larger constants are observed for β- and Me-β-CYD (66–69 and 62–83 M^{-1}, respectively), indicating that salbutamol interacts more strongly with these CYDs. The stability constants reflect a favorable positioning of the guest molecules inside the cavity of the CYD host molecules (Duchêne et al., 1986). Uekama et al. (1982) demonstrated that the hydrophobic nature of the guest molecule and steric factors between the host and guest molecules were responsible for these interactions. The salbutamol structure is therefore not compatible either with the internal cavity of α-CYD, which clearly too small to allow penetration of a benzene ring, or with γ-CYD, which may be too large to allow a close fit, and an optimal binding. Interaction of salbutamol with β-CYD and Me-β-CYD is more sterically favoured than with α- or γ-CYD. Jones and Parr (1987) reached similar conclusions for *o*-, *m*- and *p*-acetotoluide complexation.

TABLE 1

Summary of the findings from the phase solubility studies

CYD (No. of experiments)	K_s (M^{-1})	Temperature (°C)	$r(n)$	Molar ratio	S_0 (M^{-1})
β-CYD	68.9	37	0.997(6)	0.83	0.071
(3)	69.3	25	0.995(6)	0.83	0.073
	66.4	20	0.999(6)	0.82	0.072
α-CYD	1.3	37	0.982(5)	0.09	0.075
(2)	1.1	25	1.000(5)	0.08	0.076
	1.1	20	0.992(5)	0.08	0.076
γ-CYD	5.2	37	0.995(6)	0.28	0.073
(2)	5.1	25	0.998(6)	0.27	0.073
	5.1	20	0.995(6)	0.27	0.073
Me-β-CYD	82.7	37	0.996(4)	0.87	0.078
(2)	61.9	25	0.998(4)	0.83	0.078
	78.7	20	0.997(4)	0.86	0.077

Uekama et al. (1983a) calculated K_s for the system benzaldehyde(BA)-α-CYD (1 : 1 molar ratio) to be 7 M^{-1} according to the method of Higuchi and Connors (1965). They explained that the relatively small K_s obtained may be due to the less hydrophobic nature of the BA molecule compared to other monosubstituted benzene derivatives (Saenger, 1980). The spatial relationship between host and guest molecule seems also to be responsible for the K_s and stoichiometry of the complexes (Uekama et al., 1983a). In spite of the low value of K_s, oxidation and photodegradation were completely inhibited (Uekama et al., 1983a).

Similarly low K_s values were determined by Uekama et al. (1983b) and Andersen and Bundgaard (1982) in benzodiazepine systems. They explained these results as an effect of their low lipophilicities and poor adjustment to the CYD cavity. Other authors have also found K_s values of between 10 and 80 M^{-1} for α- and β-complexes with non-steroidal anti-inflammatory drugs (Hamada et al., 1975), thiazides (Corrigan and Stanley, 1982), furosemide (Szeman et al., 1987), warfarin (Lin and Yang, 1986) and famotidine (Hassan et al., 1990). Even with such K_s values, these complexes still exhibit favourable biopharmaceutical properties.

In order to measure the maximum solubility of salbutamol in the presence of increasing concentrations of α-, β- and γ-CYDs, excess salbutamol was placed in screw-cap glass vials

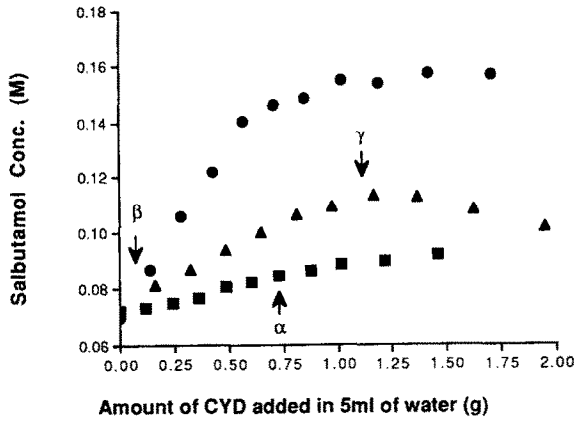


Fig. 5. Effect of increasing concentrations of α- (■), β- (●) and γ- (▲) CYDs (above and below their solubility limits) on the apparent solubility of the salbutamol at 25 °C (arrows represent the maximum solubility of each CYD at 25 °C).

together with accurately weighed amounts of CYDs. The concentrations of CYDs studied were in the range of 0.0–0.3 M which represent concentrations above and below the aqueous solubility of CYD. From these studies it is seen that both salbutamol increases the solubility of the CYDs and the CYDs increase that of salbutamol (Fig. 5). α- and β-CYD-salbutamol complexes are freely soluble under the experimental conditions studied, but the γ-CYD system precipitates as a microcrystalline salbutamol-γ-CYD complex. At the other temperatures studied (20 and 37 °C) the graphs also follow the same trends.

Studies performed above the limits of solubility of the CYDs (α-, β- and γ-CYD) in aqueous solution showed that:

(a) For α-CYD an A_N diagram is observed for all temperatures (20, 25 and 37 °C). The curves at the different temperatures are almost superimposable. The solubility of salbutamol increased up to 0.3 M of α-CYD (the maximum concentration tested). The maximum increase in the solubility of salbutamol in the presence of the CYD (for the concentrations studied) was from 0.07 to 0.09 M, i.e., 1.29-fold (28.6%).

(b) For β-CYD an A_N type diagram is observed. The first portion of the graph is coincident but the plateau reaches higher values in the order of 37 > 20 > 25 °C. The maximum increase in the solubility of salbutamol in the presence of the CYD (for the concentrations studied) was from 0.07 to 0.17 M, i.e., 2.43-fold (142.9%).

(c) For γ-CYD a B_S type diagram was observed at all temperatures; the first portion of the curve (straight line) was almost coincident for all the temperatures studied (20, 25 and 37 °C). However, the plateaux and the descending portions of the curves are higher in descending order: 37 > 25 > 20 °C. The solubility of salbutamol increases with the concentration of γ-CYD up to 0.18 M and the maximum increase in the solubility of salbutamol in the presence of the CYD (for the concentrations studied) was from 0.07 M to 0.1 M, i.e., 1.43-fold (42.9%).

Inclusion complexation in the solid state

Although the results obtained by the solubility studies strongly indicate the formation of a true complex of salbutamol-β-CYD, they do not preclude the possibility that the product is simply a physical mixture. Thus, the thermal behaviour of CYD inclusion compounds was studied by DSC in order to confirm the formation of a solid complex. When guest molecules are incorporated in the CYD cavity or in the crystal lattice, their melting, boiling and sublimation points usually shift to a different temperature or disappear within the temperature range where the CYD lattice is decomposed. Sztatisz et al. (1981) showed that DSC was the best method for detecting paracetamol-β-CYD complexes. β-CYD (apart from an endotherm due to water loss) did not produce any peaks of interest when examined by DSC (Jones and Parr, 1987). Samples, between 2.84 and 3.15 mg, were examined using DSC scanning at 20 K min^{-1} in the range 400–460 K. The thermograms (Fig. 6) showed an endothermic peak for the freeze-dried salbutamol at 431 K and for the physical mixture (salbutamol and β-CYD both freeze-dried) at 423 K. The fact that the peak of the mixture changed relative to that of the pure salbutamol showed that there was a weak interaction (Erden and Çelebi, 1988). Evidence that the freeze-dried complex is a true inclusion compound and not a simple physical mixture was based upon the fact that the endothermic peak due to the phase transition profile of the salbutamol was not

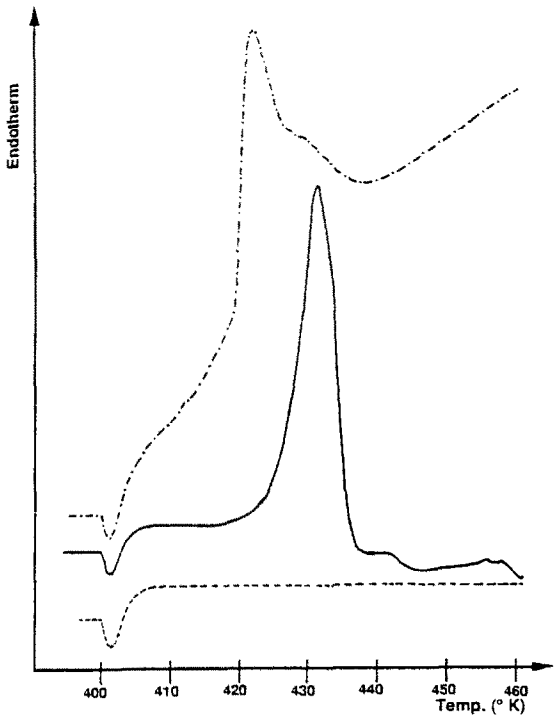


Fig. 6. DSC curves of salbutamol (———), β-CYD-salbutamol complex (- - -) 1 : 1 molar ratio and physical mixture of β-CYD and salbutamol (·-·-·) 1 : 1 molar ratio.

observed for the preparation which was thought to contain the inclusion compound. The disappearance of the endothermic peak may be attributed to the formation of the inclusion compound.

Conclusions

Increasing concentrations of CYDs result in an increase in the solubility of salbutamol (in the region of the solubility of CYDs) in the order Me-β- > β- ≫ γ- > α-CYD. Increase in temperature produces only a very small effect on the solubility of salbutamol in the presence and absence of CYDs. There is formation of a β-CYD-salbutamol complex in aqueous solution and this complex, prepared by the freeze-drying method, also exists in the solid state. DiMe-β-CYD possesses the advantage of having a higher aqueous solubility and forms a slightly stronger complex with salbutamol than β-CYD.

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