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COMMUNICATIONS

The influence of β-cyclodextrin on the solubility and dissolution rate of paracetamol solid dispersions

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Abstract—The effect of cyclodextrin (β-CD) on the solubility and dissolution rate of various paracetamol dispersion powders (1:1 w/w), and tablets was studied. Lower solubility was exhibited by a spray dried solid dispersion made from paracetamol-Ethocel-Macrogol 6000 (95:2:3). The improvement in solubility was influenced by complexation with β-CD and the crystalline nature of the powder products made by different procedures. The difference in crystallinity was confirmed by X-ray powder diffraction patterns. The dissolution rate of paracetamol from tablets made from the solid dispersions was satisfactory compared with paracetamol alone. The differences between the dissolution rate from the examined paracetamol tablets resulted from the different solubility of each powder and from the structural changes of particles which influenced the consolidation of the tablet mass.

The use of cyclodextrin (β-CD) to enhance the solubility and the rate of dissolution of poorly soluble drugs, has been described (Szejtli 1982; Duchêne et al 1987; Uekama & Irie 1987). Solid dispersions of paracetamol and polyvinylpyrrolidone (PVP) or paracetamol and mannitol in various proportions have been reported (El-Banna et al 1977; Lipman & Summers 1980). Recently, inclusion complexes of paracetamol and β-CD have been published with increased dissolution rates (Lin & Kao 1989). In pharmaceutical practice the application of drug inclusion complexes is difficult for high dosage drugs such as paracetamol (100–500 mg).

The aim of this paper was to examine the influence of β-CD on the solubility and dissolution rate of paracetamol in solid dispersions and in tablet formulations.

Materials and methods

Materials. Paracetamol (Ph.Jug.IV grade) was from Vetprom, Belgrade, Yugoslavia.; β-CD was obtained from Chinoin, Budapest, Hungary; ethylcellulose (Ethocel) was from Hercules BV, Rijswijk, Holland; polyethylene glycol 6000 (Macrogol 6000) was from ICI, Welwyn Garden City, UK; Avicel PH 101(Fluca), Ac-Di-Sol (FMC Corporation) and Aerosil 200(Degussa) were from the manufacturers indicated and magnesium stearate was Ph.Jug.IV grade.

Preparation of solid dispersions. Five powder products were included in the experiment as follows: I, paracetamol; II, paracetamol-β-CD physical mixture (w/w 1:1, molar ratio 7·5:1) mixed in a Turbula (W. E. Bachofen, Basel, Switzerland) for 10 min; III, kneaded solid disperson of paracetamol-β-CD (w/w 1:1); the substances were mixed and kneaded with an equal quantity of solvent (water–ethanol 1:1) with a mortar and pestle. The mass was continuously stirred and evaporated under infra-red lamps (4 h) and passed through a sieve (1·2 mm), dried overnight at room temperature (21°C), and sieved again (1·2 mm). IV, spray dried solid dispersion paracetamol-β-CD (w/w 1:1) was produced using a Niro minor atomizer (Copenhagen, Denmark); the substances were dissolved in solvent (water–ethanol 2:1) by heating at 40°C and mixed to a clear solution. The powder-solvent ratio was 1:5; during the spray process the rotation rate on the rotary atomizer was 25 000 rev min^{-1}, the temperature of the inlet air was 105 ± 5°C, the outlet, 70 ± 5°C and the feed rate was 2000 g h^{-1}. V, with the same conditions another spray dried solid dispersion of paracetamol with Ethocel-Macrogol 6000 was prepared; paracetamol (95), Ethocel (2) and Macrogol 6000(3) were dissolved in ethanol (solid-solvent ratio 1:10).

Solubility procedure. Different amounts of paracetamol powder samples were dissolved in 5 mL of distilled water (20 ± 2°C), gently stirred and after 1 h filtered (0·45 μm). The concentration of drug dissolved was determined spectrophotometrically (Specord M 40, Carl Zeiss Jena, Germany) at 245 nm.

Preparation of tablets. The paracetamol powders (plain, physical mixture and three solid dispersions) were used for tableting. The tablet composition was: Avicel PH 101 (5%), Aerosil 200 (1%), Ac-Di-Sol (1%), magnesium stearate (1%) calculated on 460 mg of solid dispersions or physical mixture (paracetamol-β-CD, 1:1 w/w). To the samples made without β-CD (plain and solid dispersion of paracetamol–Ethocel-Macrogol 6000), Avicel was added to make a 500 mg tablet. The mass was mixed in a Turbula mixer for 8 min, then 2 min with magnesium stearate; the mixture was compressed into tablets with a single punch tablet machine (Erweka, Korch, Berlin, Germany) fitted with a 12 mm diametral plane-faced punch, at a constant compression force of 10 kN.

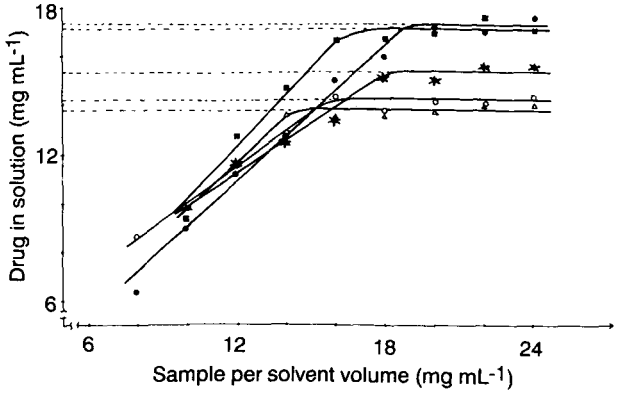

FIG. 1. Solubilities of paracetamol (○), a physical mixture paracetamol-β-CD 1:1 w/w (●), a kneaded solid dispersion paracetamol-β-CD 1:1 w/w (*), a spray dried solid dispersion of paracetamol in β-CD 1:1 w/w (■) and a spray dried solid dispersion of paracetamol in Ethocel-Macrogol 6000 (95:2:3) (△).

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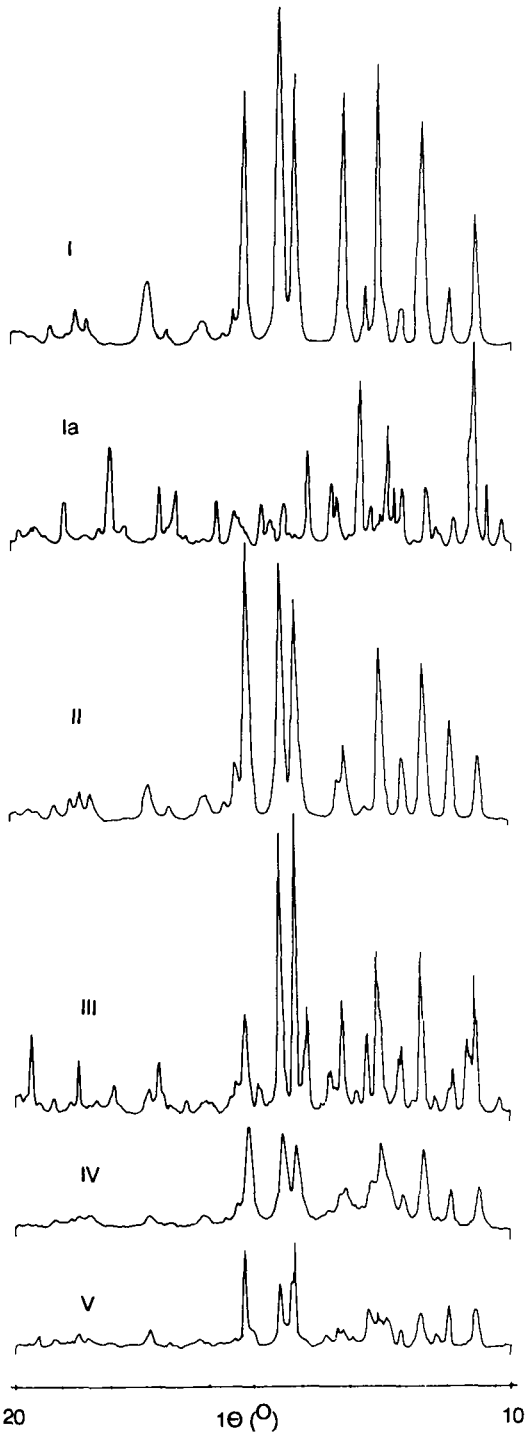

FIG. 2. X-ray powder diffraction patterns for: I paracetamol; I_a β-CD; II physical mixture of paracetamol and β-CD (1:1 w/w); III kneaded solid dispersion of paracetamol in β-CD (1:1 w/w); IV spray dried solid dispersion of paracetamol in β-CD (1:1 w/w); V spray dried solid dispersion of paracetamol in Ethocel-Macrogol 6000 (95:2:3).

Testing of tablets. Tablets were tested immediately after production. Weight uniformity was determined according to Ph.Jug.IV. The crushing strength of tablets was determined by using a Heberlein tester (Heberlein WTP 3, Zurich, Switzerland). The results noted are average values of ten determinations. The friability of tablets was measured using a Roche friabilator (ten tablets/5 min). Results quoted are the average values of two determinations. Disintegration time was determined on each batch of tablets by Ph.Jug.IV method using an Erweka disintegration test unit (Disintegration tester ZT 3, Erweka, Heusenstamm, Germany).

Dissolution test. Dissolution of paracetamol from tablets was determined according to USP XXI for Paracetamol tablets (basket method used instead of paddle). The results were the mean of 6 determinations.

X-Ray diffraction. All X-ray diffraction spectra (Philips PW 1050/25 diffractometer) were obtained by scanning at 1° min^{-1}, in terms of a 1 θ angle. The change in powder crystallinity of the samples was studied by comparing their diffraction patterns.

Differential scanning calorimetry (DSC). A Dupont 9900 DSC was used. Samples were weighed (7–9 mg) in pierced aluminium pans (DSC) and scanned at 10°C min^{-1} between 25–250°C.

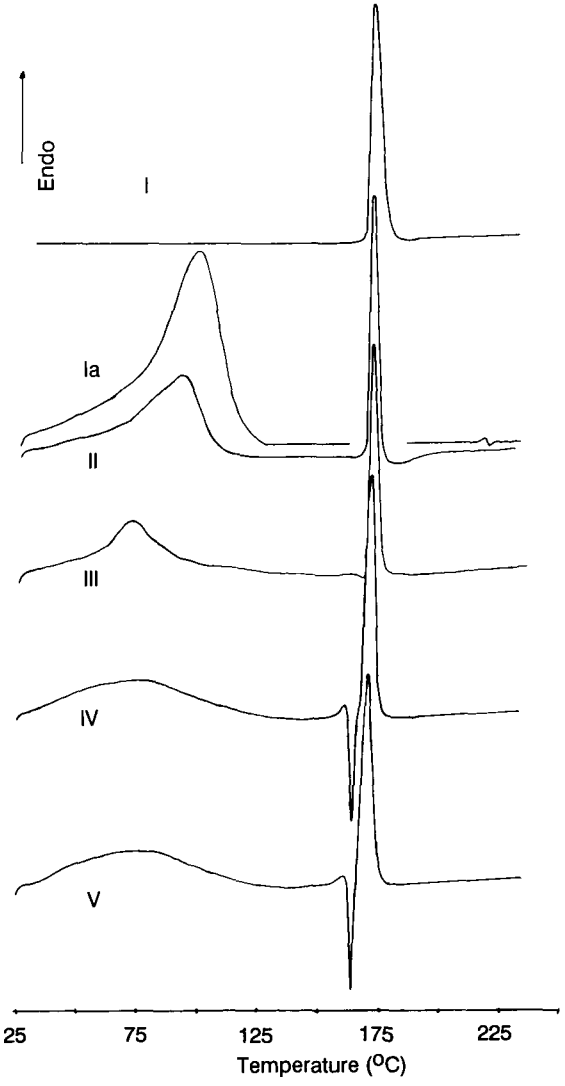

FIG. 3. DSC curves of: I paracetamol; I_a β-CD; II physical mixture of paracetamol in β-CD (1:1 w/w); III kneaded solid dispersion of paracetamol in β-CD (1:1 w/w); IV spray dried solid dispersion of paracetamol in β-CD (1:1 w/w); V spray dried solid dispersion of paracetamol in Ethocel-Macrogol 6000 (95:2:3).

Table 1. Physical characteristics of tablets made from different powders.

Paracetamol powder	Weight* (mg)	Crushing* strength (kp)	Disintegration time (min)	Friability (%)
Alone	517·7	16·15	0·60	0·54
Physical mixture with β-CD (1:1 w/w)	523·5	9·64	0·45	1·87
Kneaded solid dispersion with β-CD (1:1 w/w)	524·6	17·50	0·87	1·35
Spray dried solid dispersion with β-CD (1:1 w/w)	524·4	20·00	14·93	1·90
Spray dried solid dispersion with Ethocel/Macrogol 6000 (95:2:3)	524·7	20·00	1·73	0·58

* s.d. < 2%.

Results and discussion

In Fig. 1 the solubility data of paracetamol alone, as a physical mixture with β-CD and in solid dispersions, are presented. Tangential extrapolation of the curves gave the solubility (C_s) values of the examined samples. The solubility of paracetamol ($C_s = 14{\cdot}2$ mg mL^{-1}) was in agreement with the literature value (USP XXI). The solid dispersion of paracetamol in Ethocel-Macrogol 6000 shows a lower solubility than paracetamol alone. A possible explanation for these results is increased viscosity in the diffusion layer caused by the polymer (Lipman & Summers 1980). The best improvement of paracetamol solubility was shown by the physical mixture of paracetamol and β-CD ($C_s = 17{\cdot}3$ mg mL^{-1}), followed by the spray dried solid dispersion paracetamol-β-CD ($C_s = 17{\cdot}1$ mg mL^{-1}) and the kneaded solid dispersion paracetamol-β-CD ($C_s = 15{\cdot}33$ mg mL^{-1}). It is suggested that in the physical mixture, β-CD is available to dissolve readily in water. During the solubility measurement, the concentration of β-CD in solution is increased. It is known that the structure of β-CD inclusion compounds in solution may differ appreciably from that in the crystalline state. Recent experimental evidence reveals that in solution the guest molecule fits wholly or partially into the central cavity of the β-CD host molecule and the whole complex is surrounded and solvated by water molecules (Jones et al 1984), which would be consistent with the best paracetamol solubility being shown by the physical mixture. In the spray-dried process small amorphous particles of paracetamol-β-CD solid dispersion (8–50 μm), were produced. In the kneading procedure coarse granular particles, mostly in a crystalline form, were formed (400 μm) (Hódi et al 1991). The X-ray diffraction patterns support these observations (Fig. 2). The amorphous nature is indicated by the diffused X-ray patterns, observed in both spray dried solid dispersions (with and without β-CD). The kneaded solid dispersion and physical mixture of paracetamol-β-CD shows some sharpness of the X-ray patterns, an indication of the crystalline structure of these powders. The thermal behaviour of paracetamol dispersions was investigated by DSC. In Fig. 3 the DSC data of the examined samples are presented. The melting peak of paracetamol was present in all samples (mp 170°C). In the DSC curve of samples II and III we can see similar solid-solid transitions which occurred during heating. These phase transitions may be due to water loss from the samples and are moved to lower temperatures (compared with sample I, from 97 to 92 and 72°C). The phase transitions in sample IV and V were characterized by an exo/endo peak as a result of structural changes of these dispersions during production. Spray drying produces amorphous particles. In Table 1 the physical characteristics of the examined tablets are presented (weight, crushing strength, disintegration time and friability) and proved acceptable. Fig. 4 shows the dissolution rate of paracetamol from tablets. The dissolution rate of paracetamol from plain tablets was not satisfactory, according to USP XXI (80% of drug was not dissolved in 30 min). Other samples showed satisfactory, though different, dissolution rates. During compression many changes in surface area could occur due to deformation, fragmentation or bonding, and could affect the drug dissolution rate (Rees 1978). There is a difference in crystallinity between the different powders, which may affect the compression mechanism, and this could also contribute to different dissolution rates. The paracetamol in tablets made by spray dried solid dispersion (paracetamol-Ethocel-Macrogol 6000) showed a good dissolution rate, in spite of poor solubility of its powder dispersion. The presence of 55% Avicel in this sample and its good disintegration behaviour (presumably caused by a capillary effect), could be the explanation. The best dissolution rate of paracetamol was with a kneaded solid dispersion of paracetamol-β-CD. In this sample the granular form of the solid dispersion was used. Tablets containing ungranulated powder generally possess a narrower pore size distribution than those prepared from granulated material and in the latter the coarse extragranular voids widen the pore size distribution, and enhance the ability of dissolution fluid to penetrate the pore structure of the tablet (Rees 1978).

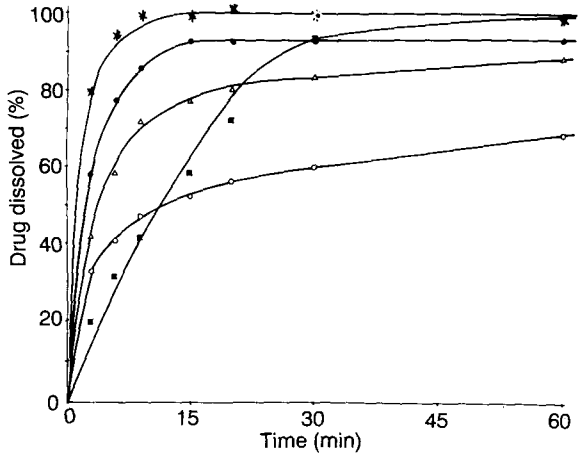

FIG. 4. Dissolution rate of paracetamol from tablets made from different powders (symbols see Fig. 1).

It can be concluded that the physical mixture of paracetamol with β-CD and its solid dispersions, show increased solubility and dissolution rates of paracetamol from tablets as compared with plain paracetamol. The process of preparing dispersions with β-CD influenced the different increases of solubility; for example spray dried products exhibited an increased rate compared with the kneading process. Dissolution rates of paracetamol from tablets made with these solid dispersions were different, with the kneading process resulting in the largest increase in the rate of paracetamol dissolution.

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Salivary excretion of mexiletine after bolus intravenous administration in rats

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Abstract—Salivary excretion of mexiletine was investigated following bolus intravenous administration (10 mg kg^{-1}) in rats. Parotid and mandibular saliva was collected separately by stimulating salivation with constant rate infusion of pilocarpine (3 mg kg^{-1} h^{-1}). The mexiletine levels in blood plasma and parotid and mandibular saliva declined biexponentially with time in almost parallel fashion. Although the mexiletine levels in both types of saliva were lower than that in plasma, the drug level in parotid saliva was always higher than that in mandibular saliva. Significant correlations were observed when all data relating mexiletine concentration in plasma and saliva were included ($P < 0.001$). The saliva/plasma drug concentration ratios (S/P ratios) did not vary to a large extent (0.56 ± 0.10 for parotid saliva, 0.21 ± 0.06 for mandibular saliva), but there was a consistent tendency for the higher plasma drug levels in the distribution phase to produce relatively high S/P ratios for both parotid and mandibular saliva. Moreover, the plasma mexiletine levels calculated by the equation of Matin et al (1974) employing the observed values for the saliva drug level, saliva pH and free fraction of mexiletine in plasma were significantly higher than the observed drug levels. Therefore, it is suggested that the salivary excretion of mexiletine could not be explained quantitatively by simple, passive secretion based on pH-partition theory.

The salivary excretion of drugs has been studied essentially from a clinical point of view, namely to find a reliable method to utilize the saliva drug level for therapeutic drug monitoring. It has been suggested that saliva samples might be substituted for plasma (or serum) in therapeutic drug monitoring or in clinical pharmacokinetic studies if there is a constant correlation of saliva and plasma drug levels over a wide range of concentration (Dvorchik & Vesell 1976; Horning et al 1977). However, relatively large variations in the saliva to plasma concentration (S/P) ratio for several drugs have limited the clinical use of saliva in monitoring drug levels (Danhof & Breimer 1978).

Mexiletine, which is one of the class Ib antiarrhythmic drugs, has been widely used in arrhythmic patients. Since the therapeutic range is relatively narrow (0·5–2·0 μg mL^{-1} (Talbot et al 1973)), its therapeutic monitoring by using blood samples from the patients is desirable. It has been reported that mexiletine was excreted into the saliva with higher levels than those in plasma or serum of man (Beckett & Chidomere 1977; Katagiri et al 1989, 1991), so that a possible utilization of the saliva sample in place of blood plasma (or serum) may provide a non-invasive, sensitive method to monitor this drug. However, pharmacokinetic studies on the salivary excretion mechanism of mexiletine have only been carried out on whole saliva samples (Katagiri et al 1989, 1991).

In the present study, salivary excretion kinetics of mexiletine was investigated following bolus intravenous administration in rats using parotid and mandibular saliva.

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Materials and methods

Materials. Mexiletine hydrochloride was kindly supplied by Boehringer Ingelheim Japan Co. Ltd (Kawanishi, Japan). Fluorescamine used for fluorometric derivatization was purchased from F. Hoffman-La Roche Co. Ltd (Basle, Switzerland). 1-Pentane sulphonic acid (Pic B-5) used as an ion-pairing reagent was purchased from Waters (Milford, USA). All other reagents and solvents were commercial products of analytical grade.

Animals. Male Wistar rats (360–380 g, 12 weeks old) were anaesthetized with pentobarbitone (50 mg kg^{-1}, i.p.) after overnight fasting for 12 h. Body temperature was kept at 37·5°C by using a heated pad placed under the supine rat.

Drug administration and collection of blood and saliva samples. After tracheotomy and catheterization, cannulae were made according to the method described by Watanabe et al (1987).