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Cyclodextrin Polymers in the Pharmaceutical Industry*

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Abstract. The potential applications of cyclodextrin polymers (soluble and insoluble ones) in the pharmaceutical industry are reviewed. The soluble polymers are good solubilizers of drugs thus enhancing their bioavailability. When applied topically the insoluble bead polymer accelerates the healing of burns and ulcers. It can also be used for chromatography and to remove certain components from mixtures. The insoluble ground polymer is an effective tablet disintegrant in direct compression systems as well as in formulations made by wet granulation.

Key words. Cyclodextrin polymer, pharmaceutical industry, drug bioavailability, chromatography, tablets.

1. Introduction

Among cyclodextrin (CD) derivatives increasing attention has recently been devoted to the polymers. The usual mode of their preparation is the crosslinking of cyclodextrins with bifunctional reagents, such as di-epoxides and diisocyanates, or linking the rings to a macromolecular support. With the former method, both soluble as well as insoluble polymers can be obtained; with the latter method insoluble so-called immobilized cyclodextrins are produced.

The structure of the three main types of cyclodextrin polymers is schematically represented in Figure 1. The preparation and properties of the cyclodextrin polymers have recently been summarized [1].

When only a few CD rings are bound to each other the product is soluble in water and shows a much higher solubility than the parent cyclodextrin. This solubility enhancement is especially high in the case of β-cyclodextrin polymer. The complexes of these polymers are also very soluble; they do not precipitate from the solution and therefore these polymers are good solubilizers for the included guest compounds. The range of such products is very diverse, and also contain various substituted monomeric cyclodextrins.

When a larger number of cyclodextrin rings are interconnected, the product cannot be dissolved in any solvents. These products are highly hydrophilic and swell strongly in aqueous systems.

Cyclodextrins can be immobilized by grafting to any natural or synthetic polymers. A great variety of sophisticated methods have been developed for this purpose. These products are used mostly for chromatography. A cyclodextrin-silica bonded phase for HPLC is already on the market (Astec, USA; Ict, FRG).

From the pharmaceutical point of view the soluble and insoluble polymers have a greater importance, especially those prepared with epichlorohydrin, for economical reasons.

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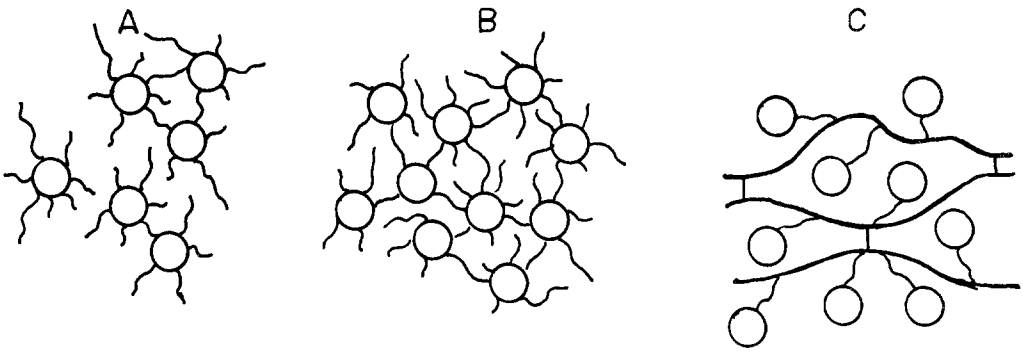

Fig. 1. Scheme of the structure of cyclodextrin polymers: soluble (A), insoluble (B) polymers, immobilized cyclodextrins (C).

2. Soluble Polymers (CDPS)

The molecular weight of the soluble polymer ranges from about 2000 to about 10 000 (Figure 2). The molecular weight distribution curve usually shows two peaks [2]. The first peak corresponds to the fraction of substituted monomers (which is a by-product), the second one belongs to the fraction of compounds consisting of 5–7 cyclodextrin rings in a molecule. As both fractions are very soluble in water and have about the same solubilizing effect [3], there is no need to remove the substituted monomer in most cases and the product can be used without fractionation.

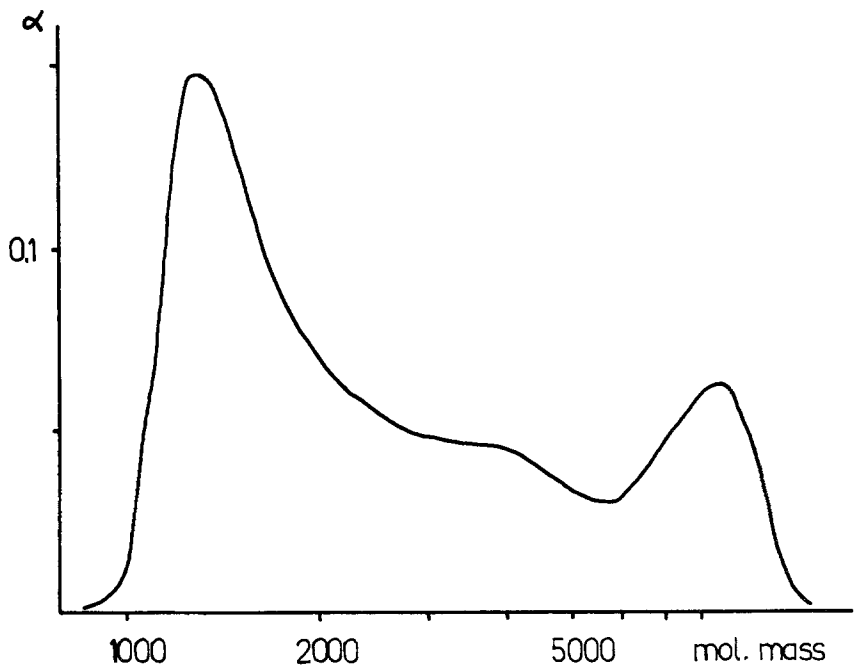

Fig. 2. The molecular weight distribution curve of a water soluble cyclodextrin polymer prepared with epichlorohydrin. The distribution curve was obtained by liquid chromatography on an Ultrogel ACA 34 [2].

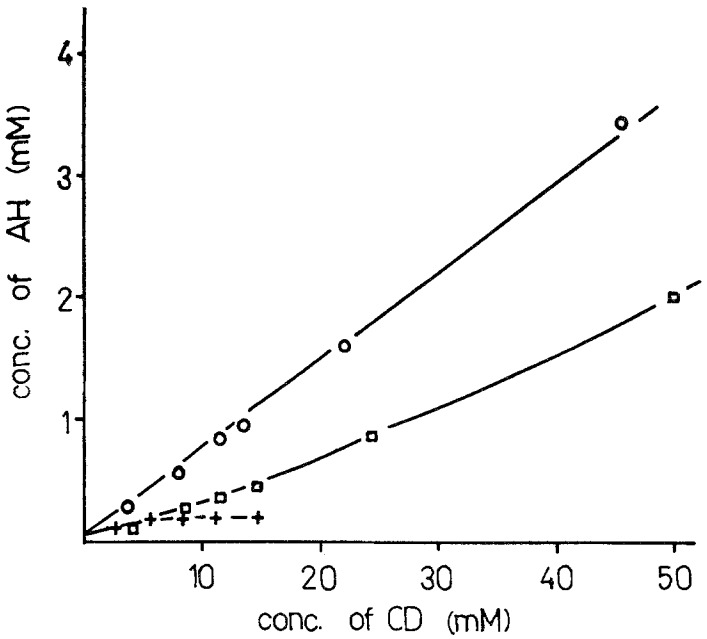

Fig. 3. Phase-solubility diagram of acetohexamide-βCD and acetohexamide-βCD derivative systems in water at 25°C, βCD (+), soluble βCD polymer (○), dimethyl-β-cyclodextrin (□) [3].

A number of investigations have reported the solubilizing effect of cyclodextrin polymer on poorly soluble drugs [3–5]. It is an even better solubilizer than dimethyl-β-cyclodextrin (Figure 3), when the guest is a large molecule having two binding sites for the inclusion. Probably this can be attributed to the cooperative action of the adjacent rings.

The higher solubility often results in higher bioavailability. The first bioavailability study with a soluble cyclodextrin polymer was reported by Uekama *et al.* [4]. Phenytoin was administered orally to dogs in the form of its β-cyclodextrin polymer complex. The area under the plasma concentration curve of the complex was about twice as great as that from phenytoin alone for up to 24 hours post administration. It was assumed that the absorption rate of the complex was negligibly small compared to phenytoin alone owing to the low lipophilicity of the complex. The enhanced absorption of the drug from the complex is probably a consequence of the rapid dissolution and dissociation of the complex.

The percutaneous absorption of tolnaphtate was greatly enhanced by complex formation with soluble β-cyclodextrin polymer when mice were treated topically with the complex [7]. The maximum concentration of tolnaphtate in the skin was approximately 10 times higher, and the maximum concentration in the blood increased to a much higher level compared to the control group treated with tolnaphtate alone (Figure 4).

The absorption-promoting effect of the soluble β-cyclodextrin polymer on the sublingual route has also been demonstrated [8] in the case of steroids. The solubility of steroids can be greatly enhanced by γ-cyclodextrin and the soluble derivatives of β- and γ-cyclodextrin (Table I) [5]. The absorption of testosterone from the oral cavity could be supported with soluble β-cyclodextrin polymer as well as with hydroxypropyl-β-cyclodextrin (HPBCD) in human experiments. A five-fold higher blood level was measured 2 h after administration

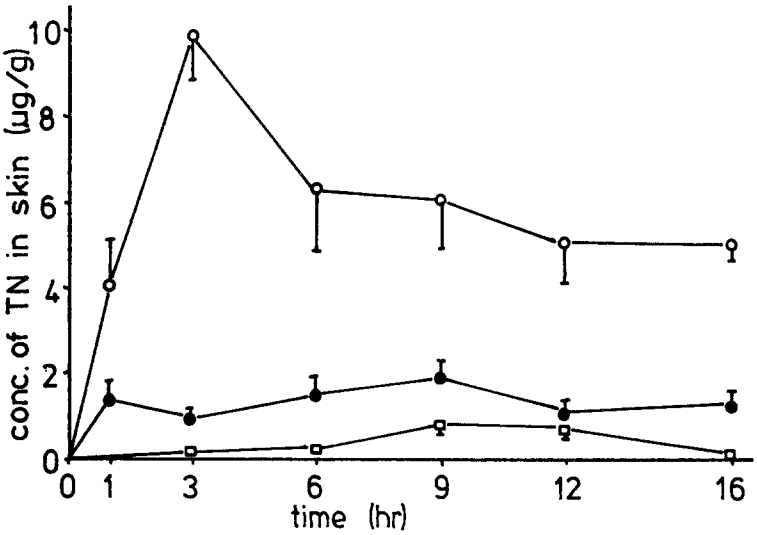

Fig. 4. Concentration of tolnaphtate (TN) in the removed skin of mice after topical application of powders: TN alone (□), TN/βCDPS physical mixture (●), TN/βCDPS complex (○) [7].

of the complex while other solubilizers, e.g. surfactants or dimethyl-β-cyclodextrin, did not influence the absorption rate [8].

The effective absorption of drugs is usually dependent on the rapid dissolution of the drug. It is plausible that cyclodextrin polymer itself is not absorbed, either from the gastrointestinal tract, or from saliva or through the skin, but it serves as a temporary carrier for the drugs. The complex functions as a depot from which the drug is released by dissociation at a rate determined – under physiological conditions – by the stability of the complex and the absorption rate of the free drug.

When the drug is targeted into the lymphatic system the rapid dissociation of the complex is a drawback. Carmophur (1-hexylcarbamoyl-5-fluorouracyl), which is an anti-tumor agent, is a drug that is required to enter the lymphatic system. The higher the molecular weight of a drug the more selectively it is transferred into the lymph vessel rather than into the blood vessel. An obvious means for increasing the molecular weight of a drug is by complex formation with soluble cyclodextrin polymer, but somehow the dissociation of the complex must be prevented. A bifunctional delivery system was developed [9] which is a combination of a macromolecular complex as a lymphotropic carrier and a surfactant

Table I. Solubility of testosterone in aqueous solutions of cyclodextrins and their derivatives [5].

Solubilizer	Conc. of solubilizer (%)	Conc. of testosterone (mM)
αCD	5	0.7
βCD	1.5	0.2
γCD	5	5.7
αCDPS	30	4
βCDPS	30	52
γCDPS	30	60
HPβCD	30	100

Table II. Ratio of carmophur concentration in the lymph relative to plasma 2.5 hr after administration [9].

Carrier	lymph/plasma conc. ratio
–	1.0
βCDPS	1.1
surfactant (BL9-EX)	1.1
βCDPS + surfactant	2.5

that forms micelles, providing a lipid-like environment around the complex. On administering carmophur into the large intestine of mice, no lymphotropic selectivity was observed either with CDPS or with a surfactant, but using them in combination a two-fold higher lymph level was measured, as compared with the plasma concentration (Table II).

An interesting idea of Karadake *et al.* is the microencapsulation of a drug complexed with a soluble cyclodextrin polymer [10]. The polymer cannot penetrate through the membrane of the microcapsule: only the drug can do so. The drug release was retarded and the stability against oxidation and degradation was greatly increased when penicillin complexed with soluble cyclodextrin polymer was microencapsulated.

Before the application of soluble cyclodextrin polymer in any drug formulation it was necessary to check its safety [5]. Mice exposed to soluble β-cyclodextrin polymer solutions (1% in their drinking water) for 16 weeks, showed neither visible signs of illness nor were there any deaths among the test animals. The average weights of the mice were recorded, and it was found that the treated groups gained slightly more weight than the controls.

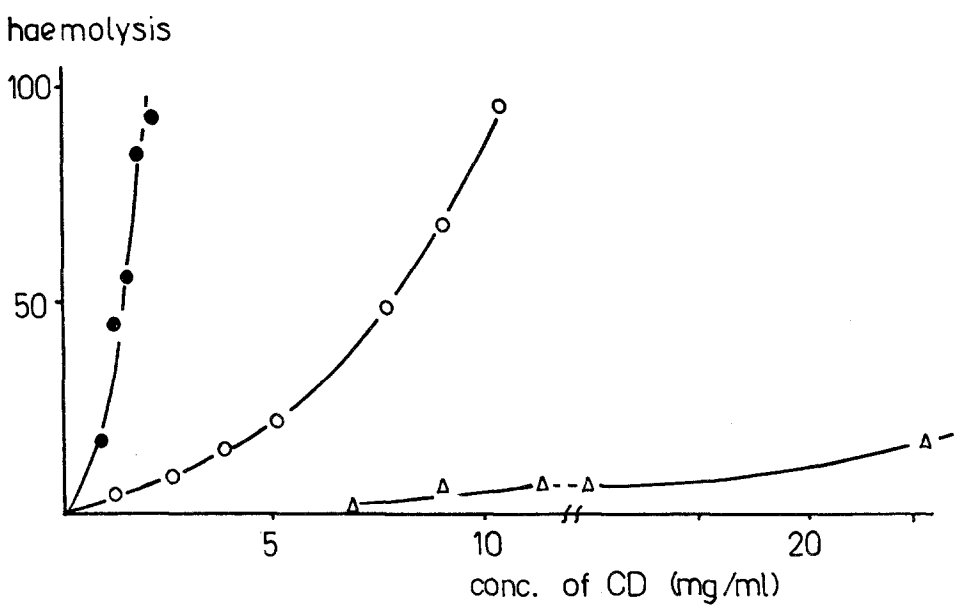

Fig. 5. Haemolysing effect of β-cyclodextrin (○), dimethyl-β-cyclodextrin (○) and soluble β-cyclodextrin polymer (△) [11].

After 16 weeks the mice were killed and the weights of their organs were measured. There was no significant difference compared with the control group except for the liver. Even in the case of the liver there was no morphological histological change. It is plausible that CDP forms complexes with bile acids, and thus inhibits the uptake of bile acid from the intestine. This leads to an increase of bile acid synthesis and may cause the observed enlargement of the liver. A comparison of cholesterol concentration levels in treated and control mice, however, showed no significant difference between the groups.

Cyclodextrin polymer shows a lower haemolytic effect than the cyclodextrins themselves and their methylated derivatives (Figure 5) [11].

3. Insoluble Bead Polymers

The insoluble crosslinked cyclodextrin polymers can be prepared either as regular beads or as grains of irregular shape. The bead polymers seem to be applicable as wound healing accelerating agents for the treatment of oozing wounds like burns and ulcers. The mechanism of action of a swelling bead polymer in wound healing is demonstrated in Figure 6. The effect is essentially the same with any swelling bead polymers, e.g. Debrisan, Sherisorb [12]. When dry beads are placed on a wound, the secretion of the wound is sucked up by the beads, if the molecular weight of the substance is small enough for penetration into the pores of the beads. A continuous flow between the beads towards the less hydrated beads is created by capillary forces and this whirls along the large molecular substances, debris and bacteria. The wound secretion is removed from the surface as long as dry beads are available. In consequence of this effective outward drainage mechanism the wound becomes clear, less hydrated, penetration of bacteria into the deeper layer of tissues is decelerated, the blood supply of the tissues gets better and so the granulation tissue develops faster.

The wound healing effect was tried first on rats [13]. Wounds were inflicted on the back skin of rats by burning and simultaneous administration of sodium hydroxide. According to histological studies CDP was mixed with the exudatum and cellular debris. The new skin formation began on the second day of the treatment. On the 4th day a newly formed continuous epithelium covered the wound under the protective polymer layer. Wounds

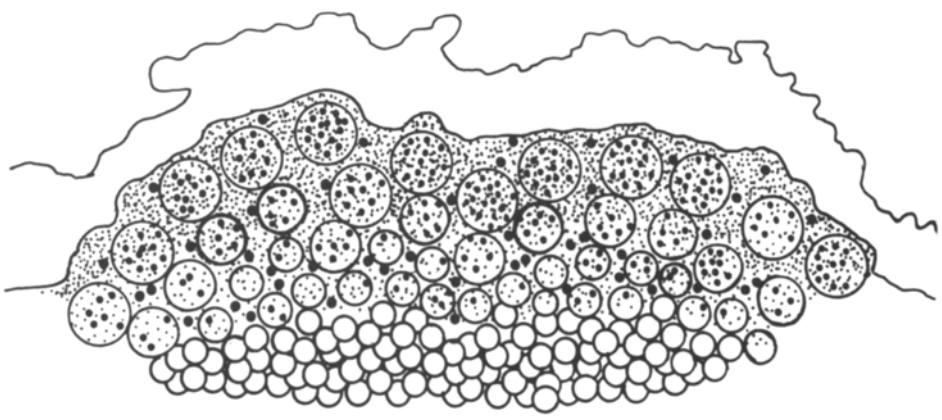

Fig. 6. Mechanism of action of a swelling bead polymer in an oozing wound. Large dots indicate the high molecular weight substances, debris and bacteria, whirling with the flow in the interspaces. Small dots indicate the small molecular weight substances which are evenly distributed [12].

were healed within 7 to 8 days (epithelization of the control wounds took 8 to 10 days). No inflammation could be observed around the wounds or in the deeper layer of subcutis.

In another experiment cyclodextrin bead polymer was injected into the femoral muscle of rats [13]. No pathological symptoms were observed during the 6 weeks of the study. The polymer did not react with the surrounding tissues. On the 3rd week a characteristic foreign body granuloma was formed. There was no inflammation reaction even in the 6th week.

Patients suffering from venous leg ulcers of different origin (post-thrombotical ulcer, scleroderma, rheumatoid arthritis) were treated with cyclodextrin polymer [14]. The overinfected, coated wounds became clear on average after 5 days. On the granulation tissue formed the epithelization began under essentially more favourable conditions. Both the depth and the area of the ulcers decreased quickly. During the application no complaints of pain occurred. No allergenic process, eczematisation, toxic effect etc. was observed.

Besides the wound healing application cyclodextrin bead polymers can be applied as column packings for liquid chromatography to separate geometrical and optical isomers [15]. The main advantage of these packings as compared to different immobilized cyclodextrin columns known from the literature is that the separations can be scaled up. Semipreparative resolutions of optical antipodes have already been reported [16]. Isolation or purification problems (similar to the debittering of citrus juices by CDP [17]) can be solved by this method in the pharmaceutical industry too. For example, phenylalanine can be removed from a protein hydrolysate to make it digestable for children suffering from phenylketonuria [18]. The phenylalanine content of a casein hydrolysate was reduced to less than 0.05% by a simple elution through a CDP column. The taste of the product obtained was much better than that of the other protein hydrolysates now available for the same purpose.

Environmental protection is increasingly demanded of manufacturers, and cyclodextrin polymers offer a method in waste water treatment (e.g. selective removal of carcinogenic biphenyls [19]).

4. Insoluble Ground Polymer

The hydrophilic nature and the high water absorption capacity utilized in wound healing are the desirable properties of cyclodextrin polymer making it a powerful disintegrant in tablet formulations. In this case no regular bead shape is required, a grain of approximately 100 μm average diameter will do as a tabletting aid to accelerate the disintegration.

The effectivness of a CDP-disintegrant was studied using a poorly soluble model drug (furosemide) and a reasonably soluble one (salicyclic acid) in direct compression systems. In furosemide formulations it proved to be a more effective disintegrant than potato starch

Table III. Properties of the furosemide/CDP/microcrystalline cellulose tablets of the optimum formulation.

	After preparation	After ageing at 40°C, R.H. 75%
Hardness (kg)	11.2	6.7
Disint. time (min)	0.26	0.32
$t_{50\%}$ (min)	0.56	0.55

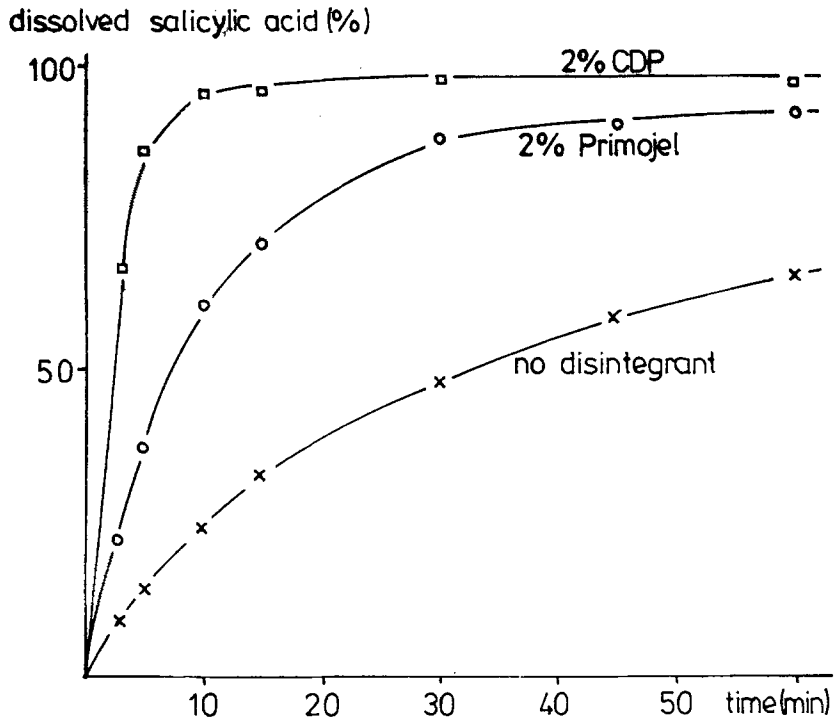

Fig. 7. Dissolution profiles of salicyclic acid formulations without disintegrant (×), with 2% Primojel (○) and 2% CDP (□).

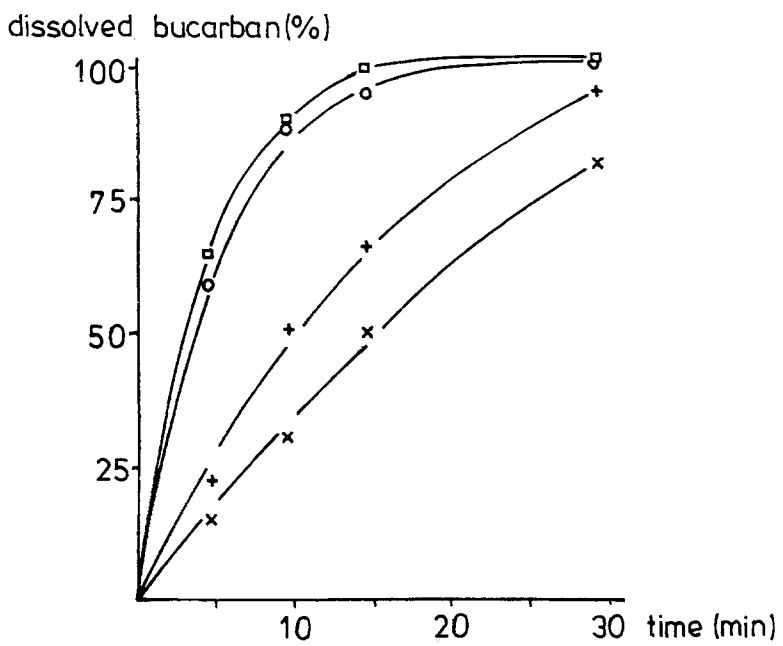

Fig. 8. Dissolution profiles of bucarban formulations. Original formulation (both intra- and extragranular disintegrants are starch) (×), the intragranular starch is replaced by CDP (+), the extragranular starch is replaced by CDP (○), both intra- and extragranular starch is replaced by CDP (□) [22].

and lactose [20]. Besides the shortening of the disintegration time a friability lowering effect was also observed showing that CDP acts also as a binder. An optimum furosemide/CDP/microcrystalline cellulose formulation with the properties listed in Table III was found by computer optimization [21] (furosemide: 20 mg, CDP 14 mg, Avicel pH 102: 220 mg).

In salicyclic acid formulations the effect of cyclodextrin polymer was even higher than that of Primojel. The disintegration times of tablets with no disintegrant, with 2% Primojel and 2% CDP were 15, 2 and 1 min and the $t_{50\%}$ values were 31, 7.5 and 0.9 min, respectively [22]. The drug dissolution is compared in Figure 7.

Bucarban tablets were selected as a model for wet granulation systems [23]. Originally both the intra- and extra-granular disintegrant was corn starch in this formulation. On replacing the extra-granular corn starch by cyclodextrin polymer a remarkable improvement in tablet properties was observed. The drug dissolution curves are shown in Figure 8.

Cyclodextrin polymer seems to be a promising tabletting aid for the acceleration of the disintegration and drug dissolution both with soluble and insoluble drugs in direct compression as well as in wet granulation systems. It provides high hardness, low friability and a good stability against ageing. The application of cyclodextrin polymer in tablets is supposed to be safe as it proved not to be absorbed from the gastrointestinal tract [24].

References

1. J. Szejtli: *Cyclodextrin Technology*, Kluwer Academic Publishers, 1988.
2. É. Fenyvesi, M. Szilasi, B. Zsadon, J. Szejtli, and F. Tüdös: *Proc. Ist. Int. Symp. on Cyclodextrins*, ed.: J. Szejtli, D. Reidel Publ., Dordrecht, p. 345 (1981).
3. J. Szemán, H. Ueda, J. Szejtli, É. Fenyvesi, Y. Machida, and T. Nagai: *Chem. Pharm. Bull.* **35** (1987) 282.
4. K. Uekama, M. Otagiri, T. Irie, H. Seo, and M. Tsuruoka: *Int. J. Pharm.* **23** (1985) 35.
5. J. Pitha and J. Pitha: *J. Pharm. Sci.* **75** (1986) 165.
6. A. Harada, M. Furue, and S. Nozakura: *Polymer J.* **13** (1981) 777.
7. J. Szemán, H. Ueda, J. Szejtli, É. Fenyvesi, Y. Watanabe, Y. Machida, and T. Nagai: *Drug Design and Delivery* **1** (1987) 325.
8. J. Pitha, S. M. Harman, and M. E. Mitchel: *J. Pharm. Sci.* **75** (1986) 165.
9. Y. Kaji, K. Uekama, H. Yoshikama, K. Takada, and S. Muranishi: *Int. J. Pharm.* **24** (1985) 79.
10. K. Karadake, T. Morimoto, and K. Tsuda: *Japan Kokai* 57-130914 (1982).
11. I. Jodal: Unpublished results.
12. G. Arturson, L. Hakelius, S. Jacobsson, and U. Rothman: *Burns* **4** (1978) 225.
13. A. Gerloczy, T. Neumark, É. Fenyvesi, and J. Szejtli: *Tissue Compatibility of Cyclodextrin Bead Polymer in Rats*, in press.
14. I. Felméray: unpublished results (1985).
15. B. Zsadon, M. Szilasi, L. Décsei, A. Ujházi, and J. Szejtli: *J. Chromatogr.* **356** (1986) 428.
16. B. Zsadon, L. Décsei, M. Szilasi, F. Tüdös, and J. Szejtli: *J. Chromatogr.* **270** (1983) 127.
17. P. E. Shaw and C. W. Wilson: *J. Food Sci.* **50** (1985) 1205.
18. M. Specht, M. Rothe, L. Szente, and J. Szejtli: *Ger. (East) Patent* 147,615 (1981).
19. R. B. Friedman, D. J. Gottneid, D. J. Mauro, and R. L. Owen: 19th ACS National Meeting, Div. Carbohydrate Chem., Chicago (1985).
20. É. Fenyvesi, O. Shirakura, J. Szejtli, and T. Nagai: *Chem. Pharm. Bull.* **32** (1984) 665.
21. É. Fenyvesi, K. Takayama, J. Szejtli, and T. Nagai: *Chem. Pharm. Bull.* **32** (1984) 670.
22. É. Fenyvesi and B. Antal: Unpublished results (1987).
23. É. Fenyvesi, T. Nagai, B. Antal, B. Zsadon, and J. Szejtli: *J. Incl. Phenom.* **2** (1984) 645.
24. A. Gerlóczy, A. Fónagy, É. Fenyvesi, and J. Szejtli: *Carbohydr. Polym.* **5** (1985) 343.