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INCREASING THE SOLUBILITY OF DRUGS THROUGH CYCLODEXTRIN COMPLEXATION

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ABSTRACT. The bioavailability of pharmaca which dissolve in water only with difficulty is very limited. The cyclodextrins /CDs/, and primarily β-CD and γ-CD, were successfully applied to increase the dissolution characteristics and hence the bioavailability of drugs: furosemide, hydrochlorothiazide, mebendazole, metronidazole, spironolactone, tofisopam, vinpocetine base, etc. From these pharmaca, products were made by mixing, kneading, grinding, freeze-drying, spray-embedding and precipitation.

The more important factors on which the dissolution and bioavailability of the drugs depend are concluded.

Key words: cyclodextrin complexation, solubility characteristics of drugs, increase of bioavailability of pharmaca.

1. INTRODUCTION

Certain non-polar pharmaca dissolve in water only slightly and slowly. The dissolution characteristics of some of these active ingredients can be increased by CD complexation /1-6/. Chiefly those drugs can be taken into consideration which satisfy the following requirements:

- the guest pharmacon molecule should be partly or totally non-polar,
- its relative molecular mass should be between 100 and about 500,
- its chemical structure should permit the formation of inclusion complexes, and
- its single dose should not be more than 30-50 mg.

From such pharmaca, products were made by different methods and were subsequently investigated. It was established how the dissolution characteristics of the drugs change as a function of the CD derivatives, of the % compositions and of the methods of preparation of the products.

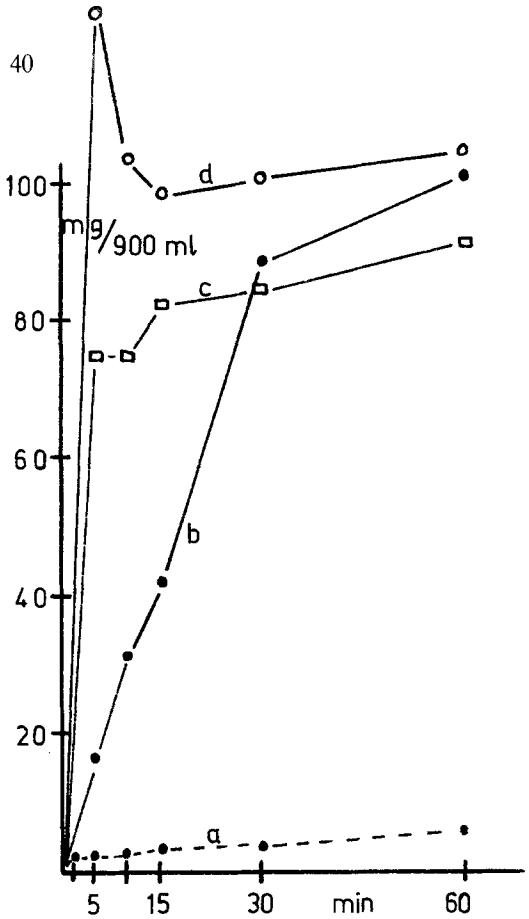

Fig. 1: Spironolactone

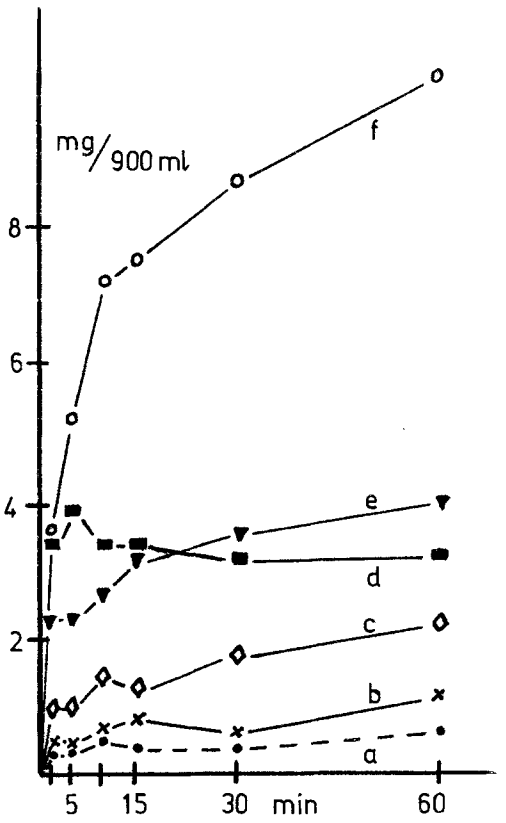

Fig. 2: Mebendazole

2. MATERIALS AND METHODS

The investigated pharmaca meet the pharmacopoeial specifications, and the α-, β-, γ- and dimethyl-β-CD /DM β-CD/ are products of Chinoin Chemical and Pharmaceutical Works Ltd. /Budapest, Hungary/.

The physical mixes were made by mixing, the spray embeddings with a NIRO-Atomizer apparatus, the inclusion complexes by precipitation, the kneaded products by kneading and the freeze-dried products with a Leybold GT 2 apparatus.

Dissolution tests were performed with the rotation basket method, with 900 ml of 37 °C water at 50-100 rpm, according to USP XX and XXI. /7/. The dissolved pharmacon content was measured spectrophotometrically /Spektromom 195 instrument/ and the CD content was measured in solution with concentrated sulphuric acid and anthrone at 625 nm /8/.

The products and inclusion phenomena with CD were studied by means of X-ray diffractometry, DTA and electron microscopy /9/.

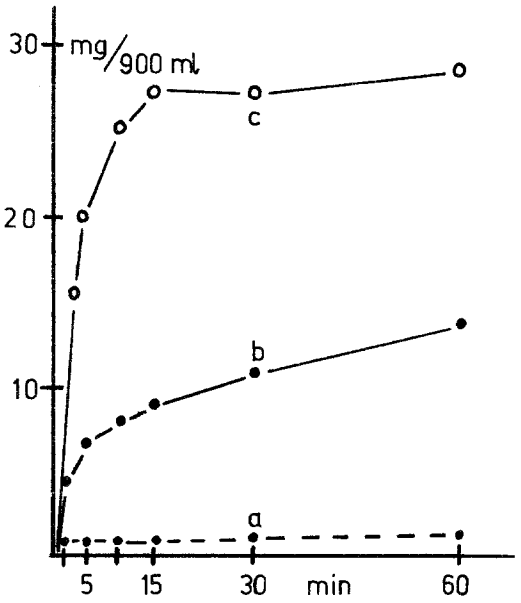

Fig. 3: Tofisopam

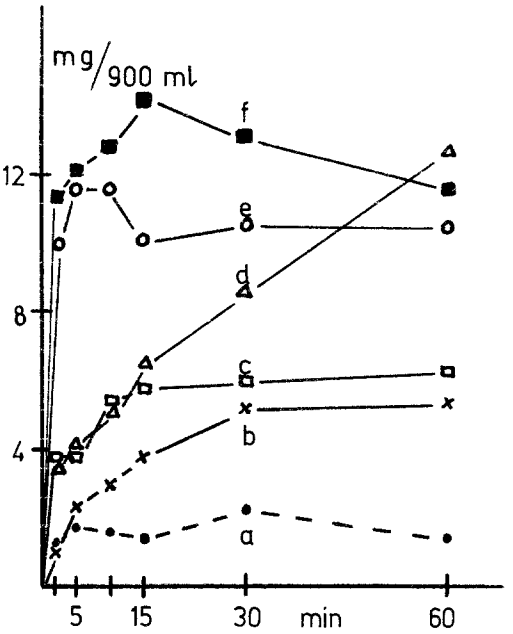

Fig. 4: Vinpocetine base

3. RESULTS AND DISCUSSION

Spironolactone is practically insoluble in water /3.86 mg/ /900 ml/h//Figure 1:a/. The increase of the dissolution depends on both the drug content and the method of making the products; for the 10.9% combinations, essentially more dissolves from the kneaded products and from tablets made with this kneaded product. The increase of the dissolution is 11 times, and 25 mg spironolactone is liberated within 5 minutes /1 tablet contains 25 mg drug/.

The internal diameter of α-CD is larger than that of β-CD, and α-CD yields complexes more easily with spironolactone. During 1 hour, the total pharmacon dissolves from the physical mix /Figure 1:b/; this quantity is 25 times more than that from pure spironolactone. The preparation of a physical mix is the simplest and cheapest drug technological operation.

DM β-CD also increases the solubility. In probability, the decrease of the surface tension plays a part in this. The dissolution starts more quickly, but after 15 minutes it slows down; overall, it is essentially better /Figure 1:c/.

The product made with a 1:1 mix of α-CD and DM β-CD combines the advantage of both CD derivatives: the total quantity of spironolactone dissolves, and quickly /Figure 1:d/.

Mebendazole is an antihelminthic agent used in veterin-

ary medicine. Its solubility is less than 0.05% /Figure 2:a/. Mebendazole always dissolves in the highest quantity and most quickly from the 11.5% spray-embedded product /Figure 2:f/ [physical mix /b/, kneaded product with formic acid /c/ and with ethanol /d/, inclusion complex /e/]. The dissolution is 15 times better.

β-CD enhances the dissolution of all of the metronidazole products. The best are the 40.0% products, among them the kneaded products, spray-embeddings and physical mixes.

Tofisopam does not dissolve well: 1.22 mg/900 ml/h /Figure 3:a/. The commercially available 50 mg Grandaxin^{R} tablets yield somewhat more dissolved product /b/, but from the tablets made with 25.2% kneaded β-CD product 23 times more Tofisopam is released than from the pure drug /c/.

The furosemide tablet contains 40 mg of active ingredient. During 1 hour, only one-tenth of this quantity dissolves. From the 11.3% kneaded β-CD and DM β-CD products, the full 40 mg is liberated within 5 minutes.

Vinpocetine base is the pharmacon of Cavinton^{R} tablets, the most successful Hungarian medicine in the past decade. It is a base that dissolves in water only very slightly /20 µg/ml/ /Figure 4:a/. One tablet contains 5 mg vinpocetine base. However, with 11.9% γ-CD it releases more than 7 times as much from kneaded products /f/, and 10 mg, twice as much as the usual dose of vinpocetine base, was liberated within 5 minutes [physical mix /b/, co-pulverizate /c/, ditto + Tween-20 /d/, and spray-embedding /e/].

In the case of hydrochlorothiazide, the rate of dissolution depends both on the drug content and on the method of making the products. The best liberation of hydrochlorothiazide was generally achieved from the kneaded products. The most drug was liberated and most quickly
- from the kneaded product for the 10.4% combinations,
- from the spray-embedding for the 20.8% combinations, and
- from the physical mix for the 31.2% combinations.

Besides these drugs, cinnarizine /10/, griseofulvin, hydrocortisone, iomeglamic acid, salicylic acid and triamcinolone were also investigated.

4. CONCLUSIONS

From about one thousand dissolution tests, it can established that the following factors influence the release of the pharmaca from the products containing CDs:
- the material characteristics of the pharmaca,
- the type of CD derivative / α-, β-, γ- or DM β-CD/,
- the combinations of two or more CDs and their ratio,
- the ratio of pharmacon and CD,
- other auxiliary substances /tensides or cellulose derivatives/,

- the content of the drug in the product, and
- the method of manufacturing the products.

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