EVALUATION OF CYCLODEXTRIN POLYMER AS A DISINTEGRATING AGENT

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ABSTRACT. Cyclodextrin polymer was compared to other well known disintegrants concerning the swelling properties /water uptake, moisture uptake, hydration capacity, sedimentation volume in water/. Its high disintegrating effect was proved in directly compressed tablets as well as in tablets made by wet granulation. A remarkable improvement in tablet properties was observed. Not only the disintegration of tablets and the dissolution of the drug was accelerated but also the hardness increased when CDP was used as disintegrant.

Cyclodextrin polymer disintegrant is a crosslinked derivative of β-cyclodextrin (1). Its structure is a three dimensional network which contains rigid cavities of the same shape and size (cavities of the cyclodextrin rings) and flexible cavities of different shape and size formed by the crosslinking agent (2). This porous structure ensures a good compressibility and a rapid penetration of a liquid into the grains. This polymer is completely insoluble in water but due to its highly hydrophylic nature it absorbs water in large extent and a marked swelling occurs (3). The above mentioned properties make this cyclodextrin polymer a potential disintegrating agent.

As cyclodextrin polymer has sufficient flow properties it can be used in directly compressed tablets. Showing some binding capacity that is an increasing effect on the hardness of the tablets it can be considered a binder-disintegrant (4). Its effectivity in different placebo formulations has been compared to other disintegrants

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(Ac-Di-Sol, Polyplasdone XL, Esma Spreng, starch), and cyclodextrin polymer proved to be one of the best among them (3).

An optimum formulation of a model tablet containing furosemide (active ingredient), cyclodextrin polymer (disintegrant) and microcrystalline cellulose (binder) found by a computer optimization process (5) was investigated. The excellent properties of these tablets: high dissolution rate, sufficient dissolution stability, high hardness immediately after the preparation and proper hardness after ageing and also fast disintegration (6), convinced us it is worth to continue the work with this new disintegrant, to involve some other good disintegrants in the comparison, to try its effectivity not only in direct compression systems but also in tablets made by the traditional wet granulation method.

The results of this work have been summarized in this paper.

MATERIALS AND METHODS

Materials:

Cyclodextrin polymer (CDP) was a pilot product of Chinoin Pharmaceutical and Chemical Works (Hungary), a white powder of less than 100 μm grain size. Ac-Di-Sol (internally crosslinked carboxymethyl cellulose, FMC Corp., USA), Ca-CMC (calcium salt of carboxymethyl cellulose, Daicel Chem. Ind., Japan), Esma Spreng (formaldehyde treated casein, Edelfett W., FRG), Polyplasdone XL (crosslinked polyvinylpyrrolidone, GAF Corp., USA), Primojel (carboxymethyl starch, Avebe, Netherland) and corn starch were compared with cyclodextrin polymer concerning their swelling properties.

Avicel pH 102 (FMC Corp. USA) was used as a direct compression carrier in tablet formulations. Furosemide was generously supplied by Wakamoto Pharmaceutical Co., Ltd., Japan.

Bucarban (Chinoin, Hungary), magnesium stearate (Kannae Kagaku, Japan) and talc (Valcisone, Italy) were used in tablets made by wet granulation.

Measurement of swelling properties:

Water uptake, moisture uptake, hydration capacity and sedimentation volume were measured by the previously reported methods (3).

Tablet making by direct compression:

Flat-faced tablets of 13 mm diameter were made by compressing the given amount of powder directly under 300 kg/cm² pressure for 30 sec using a Shimadzu hydraulic

press. Furosemide was the model drug in this experiment. The composition of tablets is given in Table I.

Table I.

	A	B	C
Furosemide	20,0	20,0	20,0
CDP	6,25	-	-
Potato Starch	-	31,25	-
Avicel pH 102	223,75	198,75	230,0

Tablet making by wet granulation:

Bucarban and the intragranular disintegrant were mixed and granulated by a 10 % w/v aqueous gelatin solution using a Manesty MK oscillating granulator. The granula were dried in a Glatt WSC-120 drier, and mixed with the extragranular disintegrant, the lubricant and the antiadhesive agent. Flat-faced tablets of 13 mm diameter were compressed by a Fette P. rotary tablet machine. The composition of tablets is given in Table II.

Table II.

		A	B	C	D
Bucarban	granula	500	500	500	500
CDP	granula	-	20	-	20
corn starch	granula	20	-	20	-
gelatin	granula	14	14	14	14
magnesium stearate		10	10	10	10
talc		10	10	10	10
CDP		-	26	13	26
corn starch		26	-	-	-

Determination of tablet characteristics:

The directly compressed tablets were characterized by the peviously given methods (4). In the case of Bucarban tablets the average weight was measured by a Sartorius automatic tablet weighing machine, the friablity, the disintegration time and the hardness were determined according to USP XX., the latter one by an Erweka hardness tester. The dissolution study was carried out by an Erweka dissolution tester using the rotating basket method at 120 rpm rotating speed. The test fluid was 0,1 N HCl solution. 50 ml samples were withdrawn at appropriate intervals and immediately replaced with an equal volume of the test medium. The Bucarban content of the samples was determined by titration potentiometrically with 0,05 N $NaNO_2$ solution.

RESULTS

Swelling properties

The high swelling capacity seems to be one of the most important requirements against a good disintegrant, though the high swelling alone does not ensure the disintegrating effect. The swelling properties of cyclodextrin polymer compared to Ac-D-Sol, Polyplasdone XL, Esma Spreng and corn starch have been published (3). Two more disintegrants have been involved in the comparison since that time: Primojel and Ca-CMC, both belong to the group of the so called superdisintegrants. The results are summarized in Table III.

Primojel showed the highest values for all the investigated swelling property. Its outstanding behaviour appears first of all in the rate of water uptake /Fig.1. and 2./.

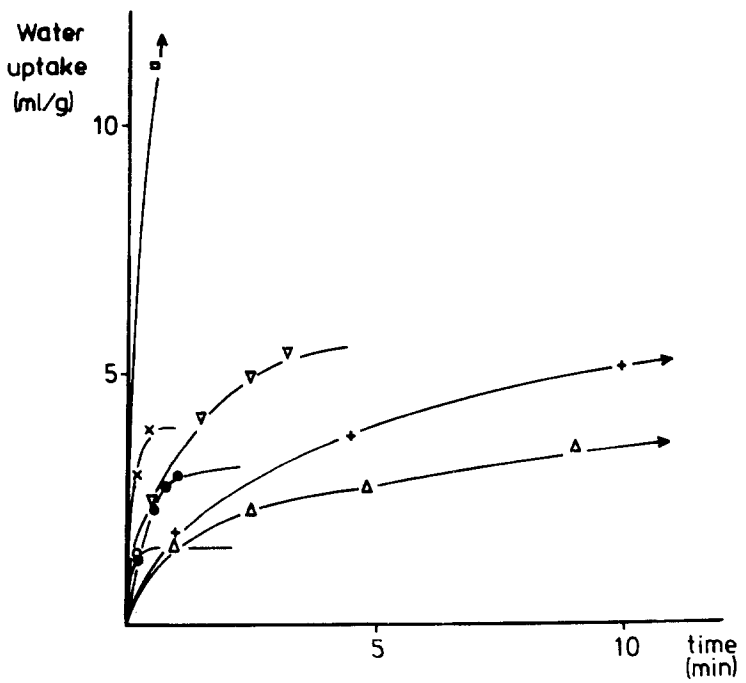

Fig.1. Water uptake of the disintegrants (the samples were compressed under 0,1 MPa for 15 minutes before the measurement) CDP /+/, Primojel /□/, Ac-Di-Sol /△/, Ca-CMC /▽/, Polyplasdone XL /×/, Esma Spreng /●/ and corn starch /o/ .

Table III.

	CDP	Pri-mojel	Ac-Di-Sol	Ca-CMC	Poly-plas-done XL	Esma Spreng	Corn Starch
Water a uptake /ml/g/b	6,1	29,5	6,7	5,3	3,8	3,0	1,1
	6,5	29,6	6,5	6,4	3,7	2,6	1,0
Incre- a ase in volume b /%/	340	2900	350	200	50	60	10
	780	4100	600	800	400	260	100
Moisture uptake from vapour phase /%/	70	190	110	68	54	30	23
Hydration capacity	8,1	26,7	9,8	6,4	5,5	4,8	1,9
Sedimentation volume in water /ml/g/	9,0	24,1	11,0	10,0	7,0	8,5	1,5

a = the samples were pressed under 0,1 MPa pressure for 15 min.
b = the samples were pressed under 1000 MPa for 2 min.

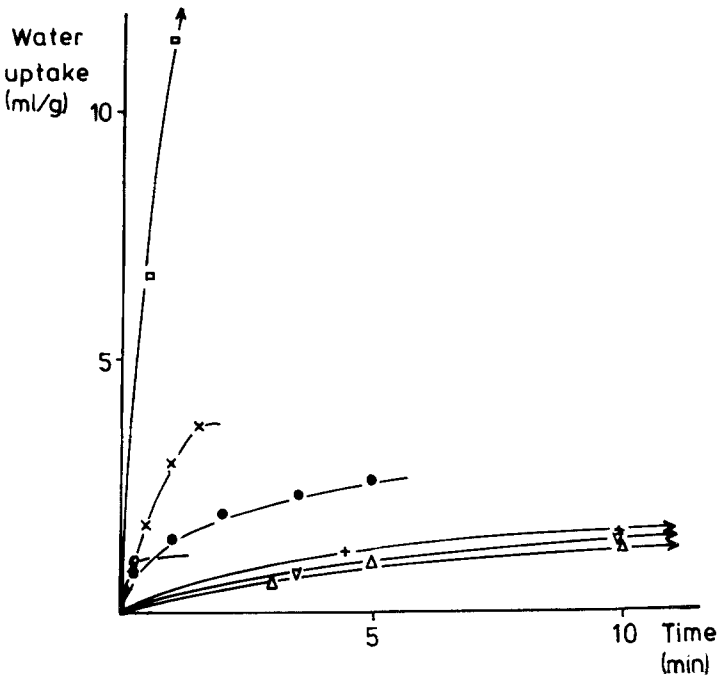

Fig.2. Water uptake of the disintegrants /the samples were compressed under 1000 MPa for 2 minutes before the measurement/ For symbols cf. Fig.1.

Not so high differences were found among the characteristics of the two kinds of carboxymethyl cellulose and the cyclodextrin polymer. The rate of water uptake of this group is the slowest especially for the samples compressed at higher pressure.

Lower values were measured for Polyplasdone XL, Esma Spreng and corn starch.

There was not proved a close relationship between the disintegrating effect and any of the investigated swelling property (3). The disintegration time values of placebo formulations however showed approximately the same order as the measured characteristics except the sedimentation volume in water which contains a high experimental error. The best agreement was found between the order of the rate of moisture uptake /Fig.3./ and the disintegration time.

The swelling properties of cyclodextrin polymer are very close to those of Ac-Di-Sol, it belongs to the group of the most effective disintegrants.

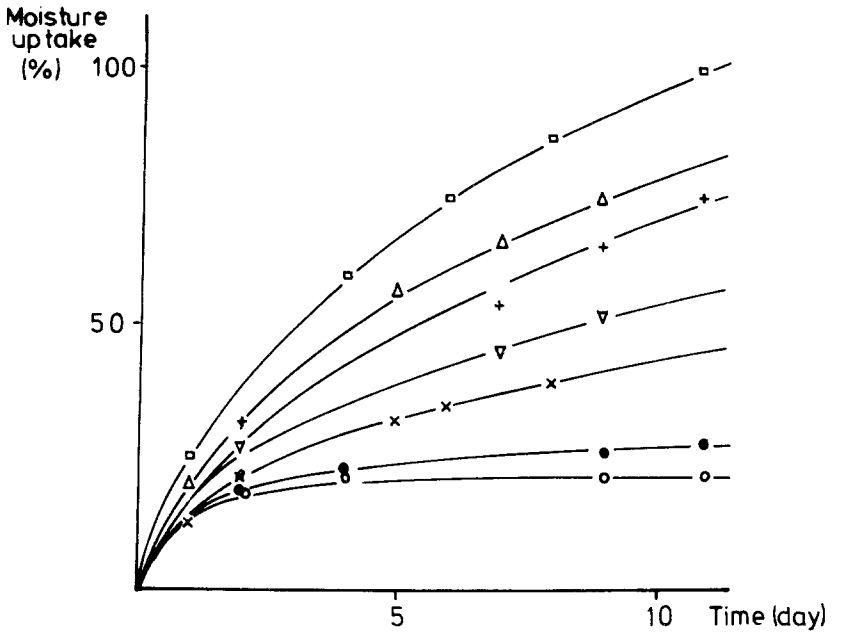

Fig.3. Moisture uptake from vapour phase. For symbols cf. Fig.1.

The effectivity of CDP in direct compression system (4).

Tablets of 8 % furosemid content were compressed with or without disintegrant using microcrystalline cellulose as binder. 2,5 % CDP or 12,5 % potato starch played the role of disintegrant. The properties of tablets are listed in Table IV.

Table IV.

Tablet properties	Formulations A	B	C
Weight /mg/	240	230	233
Thickness /mm/	1,27	1,24	1,25
Hardness /kg/	> 20	> 20	> 20
Disintegration time /min/	0,8	0,7	4,5
t_{50} % /min/	4,0	4,2	52,4

Inspite of the high hardness the disintegration time of the tablets containing disintegrant was less than

1 minute. About the same disintegration time was measured for the tablets with five times lower amount of CDP as for the tablets with potato starch, what shows an excellent effectivity of CDP.

The dissolution study was very important in this case to see how the dissolution of furosemide, a good complex forming guest molecule (7) is influenced by the presence of cyclodextrin polymer. The results are comforting: somewhat higher dissolution rate was observed with CDP than with potato starch /Fig.4./. This might be explained by the low concentration of CDP in the tablets which is enough for the fast disintegration but too low to affect the dissolution by complex formation.

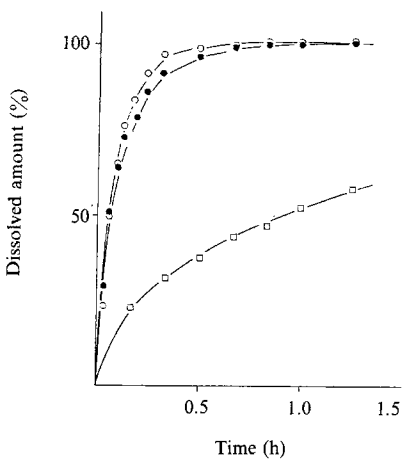

Fig.4. Dissolution curves furosemide tablets. Formulation A /○/, B /●/ and C /□/.

The effectivity of CDP in wet granulation systems

Bucarban tablets were selected as a model for wet granulation systems. Originally both intra- and extragranular disintegrant is corn starch in this formulation. In our experiment CDP was replaced instead of corn starch in 3 different ways /Table II/. The characteristics of tablets are given in Table V. and the dissolution curves are presented on Fig.5.

Table V.

Tablet properties	Formulations A	B	C	D
Weight /mg/	581,3	587,0	581,1	583,0
Thickness /mm/	3,99	4,27	4,00	4,25
Friability /%/	0,17	0,17	0,08	0,08
Hardness /kg/	12,5	>15	>15	>15
Disintegration time /min/	>20	14,5	5,5	5,0
$t_{50\%}$/min/	15,5	10,5	4,0	3,5

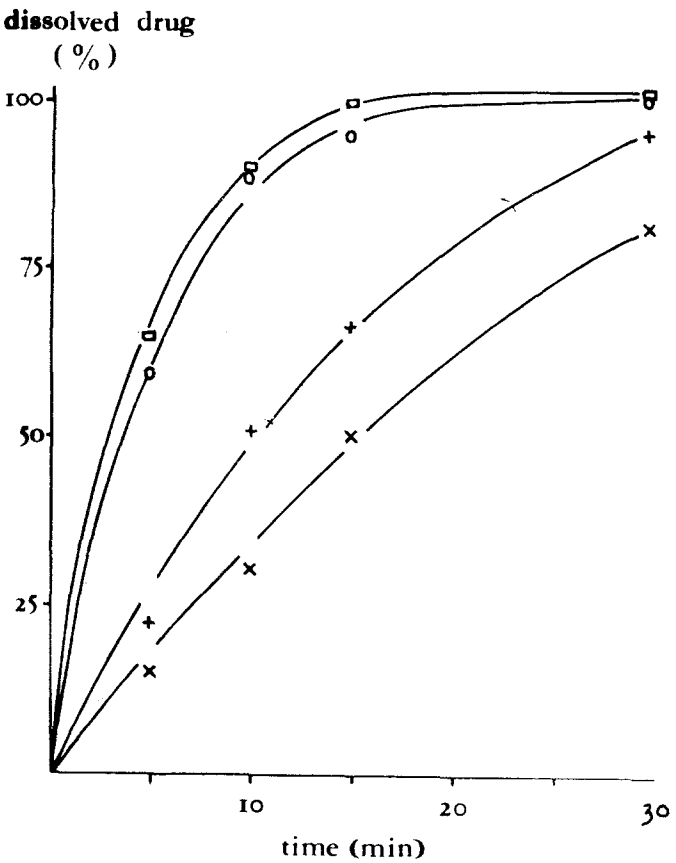

Fig.5. Dissolution rate of Bucarban. Formulation A /×/, B /+/, C /o/ and D /□/.

The hardness of tablets increased in all the three formulations in which CDP was used. /The maximum hardness is 15 kg that can be measured with the Erweka hardness tester./

The disintegration time and the time necessary for the dissolution of the 50 % of the drug /$t_{50\%}$/ changed similarly: some decrease was observed when CDP was the intragranular disintegrant /formulation B/ and a considerable improvement was obtained when extragranular corn starch was replaced by CDP /formulation C/. Only a slight difference was found between formulations C and D, that is the disintegration and the dissolution are mostly determined by the extragranular CDP. It is worth to mention that in formulation C half amount of CDP produced this result.

The results presented in this paper show that cyclodextrin polymer which has excellent swelling properties, similar to those of the best disintegrants available is an effective disintegrant. Its effectivity was proved not only in directly compressed tablets but also in tablets made by wet granulation. Especially remarkable improvement in disintegration and dissolution behaviour of tablets was observed when cyclodextrin polymer was used as an extragranular disintegrant.

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