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Properties of Cyclodextrin Polymer as a Tabletting Aid[1,2]

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The binding and disintegrating properties of cyclodextrin polymer as well as its effect on the dissolution of a poorly soluble drug have been evaluated on the basis of the hardness, friability and disintegration time of directly compressed tablets.

The hardness of tablets containing cyclodextrin polymer in addition to potato starch or lactose was lower than that of tablets with microcrystalline cellulose indicating that cyclodextrin polymer has a relatively poor binding capacity. The disintegrating action of cyclodextrin polymer was compared to those of potato starch and lactose, with microcrystalline cellulose as a binder. Equal disintegration times were obtained with 2.5% cyclodextrin polymer, 12.5% potato starch, and 25% lactose. The dissolution rate of furosemide was greatly accelerated by as little as 2.5% cyclodextrin polymer added to microcrystalline cellulose. A somewhat lower dissolution rate was observed with 12.5% potato starch.

As a result it was shown that cyclodextrin polymer, which has excellent disintegrating properties as well as some binding capacity, can be used advantageously in direct compression systems as a binder-disintegrant.

Keywords——cyclodextrin polymer; disintegrating agent; binder; direct compression; tablet; furosemide; microcrystalline cellulose

Various kinds of new directly compressible vehicles are available, providing a high degree of hardness and low friability,[3] but none of them displays sufficiently good disintegration and dissolution characteristics. All such materials must be combined with additives to improve these properties of the tablets. Though microcrystalline cellulose was reported to act as its own disintegrating agent because it swells in water, it is still necessary to add to it a certain level of disintegrant when rapid disintegration and dissolution are required.

Starch is the most commonly used tablet disintegrant, though its disadvantages have been recognized for a long time. A large concentration of starch is necessary to achieve proper disintegration of a tablet, but the use of high concentrations results in soft tablets because of the weak cohesive and adhesive properties of starch.[4] Many attempts have been made to find new disintegrating agents that would improve the disintegration and dissolution behavior without adversely affecting the tablet matrix.[5]

Cyclodextrin polymer, a newly discovered disintegrant,[6] seems to meet this requirement as demonstrated in the present paper by investigating the binding properties of this material together with its accelerating effect on disintegration and its dissolution. Its binding properties were compared to those of microcrystalline cellulose and its disintegrating properties to those of potato starch and lactose. The effect on the dissolution rate was studied by using furosemide as a poorly soluble drug.

Experimental

Materials——Cyclodextrin polymer (CDP) used was a pilot product of Chinoin Pharm. Chem. Works

(Hungary),[6] a white powder of less than 100 μm grain size with the following characteristics: β-cyclodextrin content 50%; density 0.63 g/ml; moisture content 3.1%; sedimentation volume in water 6.3 ml/g; water uptake 4.2 ml/g. Commercial lactose JPX, potato starch (PS) JPX and microcrystalline cellulose (MCC) JPX marketed as Avicel PH 102 were used. Furosemide was generously supplied by Wakamoto Pharmaceutical Co., Ltd.

Measurement of Angle of Repose——The angle of repose of pure MCC and CDP and their mixtures of various compositions were measured with a Tsutsui cylindrical apparatus for angle of fluid surface and repose (Miwa's method) at a rotation speed of 2 rpm.

Tablet-Making——Flat-faced tablets of 250 mg weight, 13 mm diameter, were made by compressing the given amount of powder directly under 300 kg/cm^2 pressure for 30 s using a Shimadzu hydraulic press for KBr tablets for infrared spectroscopy.

Measurement of Hardness of Tablets——A Kiya hardness tester which can be applied to measure hardness below 20 kg was used for the determination of the hardness of 5 tablets of each formulation.

Measurement of Friability of Tablets——Friability was determined by the conventional method using 10 tablets of each formulation and was expressed as a percentage of tablet weight.

Measurement of Disintegration Time of Tablets——The disintegration time of 6 tablets of each formulation was measured with a Toyama Sangyo T-2HS type disintegration tester according to the method in JPX with auxiliary disks, using water as a test fluid.

Procedure for Dissolution Study——The dissolution of furosemide was determined by the rotary basket method according to JPX at 100 rpm. rotating speed using 1000 ml of No. 2 test fluid (pH 6.8). A tablet containing 20 mg furosemide was tested. Five ml of the solution was withdrawn at appropriate intervals through a filter (Fine Filter F, Ishikawa Manufactory) and immediately replaced with an equal volume of the test medium. The sample, after dilution with No. 2 test fluid, was analyzed for furosemide by the ultraviolet (UV) absorption method at 276 nm using a Hitachi 124 spectrophotometer. The time required for dissolution of 50% of furosemide ($t_{50\%}$) was calculated from the mean of 3 determinations according to Wagner's dissolution model.[7]

Results and Discussion

Relationship between the Angle of Repose of Powder Mixture and the Concentration of CDP

Powder mixtures containing microcrystalline cellulose and cyclodextrin polymer in various ratios were tested. Both pure MCC and CDP showed poor fluidity. A clear tendency for a decrease of angle of repose was observed in the case of powder mixtures, with a minimum at 30% CDP concentration (Fig. 1), but the decreasing effect was not remarkable. These results indicate that addition of a lubricant is necessary when MCC–CDP powder mixture is subjected to direct compression.

Binding Properties of CDP Compared to MCC

The fact that CDP is directly compressible in pure form to provide tablets of higher than 5 kg hardness and low friability suggests that it has useful binding properties. In combination with PS, tablets of the same hardness were obtained in the 25—100% CDP concentration

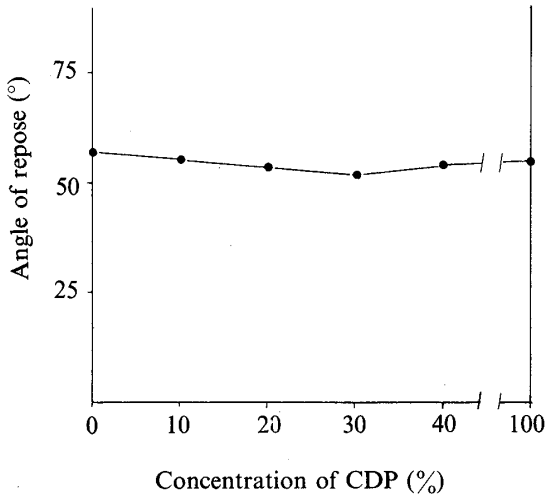

Fig. 1. The Angle of Repose of MCC–CDP Powder Mixture as a Function of the Concentration of CDP

range (Fig. 2). Though the values of hardness are lower than those for tablets containing MCC, the difference is less at higher concentrations of PS. Addition of less than 12.5% CDP or MCC resulted in failure of tablet formation.

A comparison of the friability of CDP–PS and MCC–PS tablets revealed no considerable difference above 50% concentration of CDP or MCC (Fig. 3). When the concentration of PS was more than 50% the friability of the tablets containing CDP was higher than that of the tablets with MCC.

Similar results were obtained when CDP and MCC were combined with lactose (Figs. 4 and 5). Lactose itself is compressible, giving tablets of lower than 5 kg hardness and unacceptably high friability. The hardness of MCC–lactose tablets increased to a considerable extent with increasing concentration of MCC. A slight increase was also observed in the case of CDP–lactose tablets. The decrease in friability with addition of CDP or MCC was very similar, and 80% CDP or MCC was needed to achieve less than 1% friability.

Disintegrating Properties of CDP Compared to PS and Lactose

CDP, PS or lactose was added in various ratios to MCC to compare the disintegrating

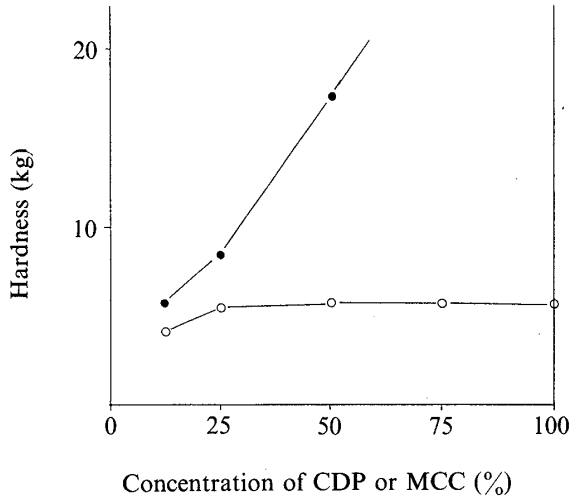

Fig. 2. Hardness of Tablets Containing CDP (○) or MCC (●) in Addition to PS

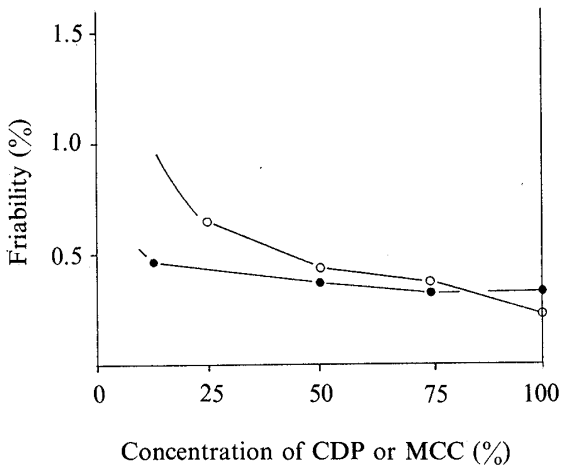

Fig. 3. Friability of Tablets Containing CDP (○) or MCC (●) in Addition to PS

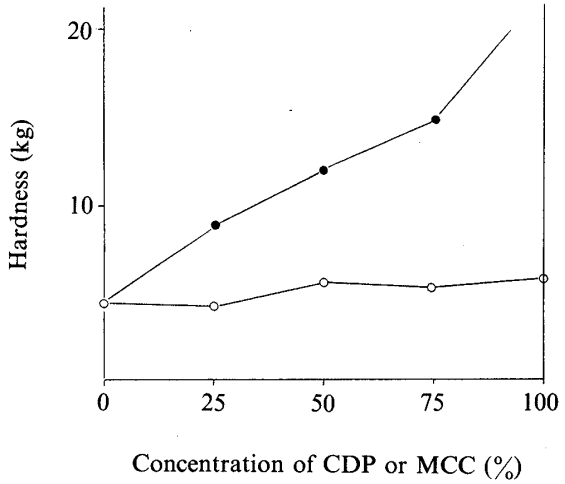

Fig. 4. Hardness of Tablets Containing CDP (○) or MCC (●) in Addition to Lactose

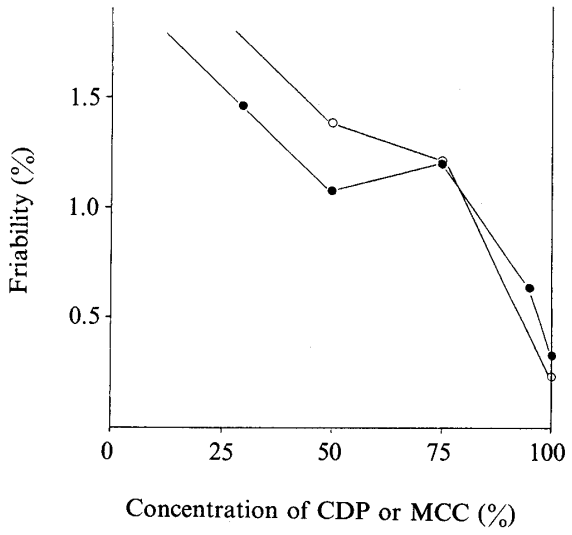

Fig. 5. Friability of Tablets Containing CDP (○) or MCC (●) in Addition to Lactose

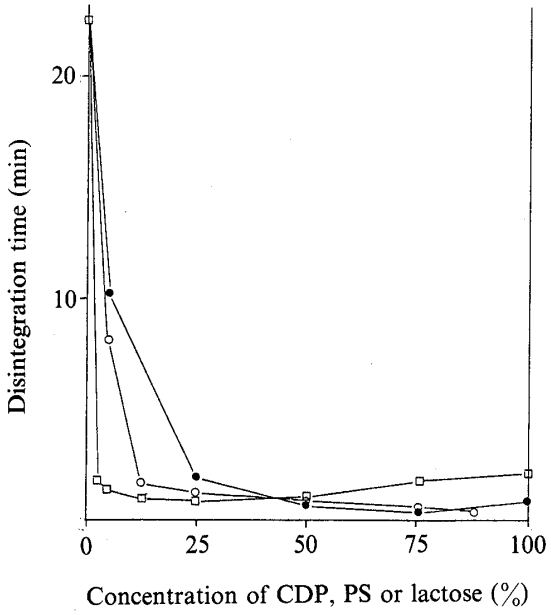

Fig. 6. Disintegration Time of Tablets Containing CDP (□), PS (○) or Lactose (●) in Addition to MCC

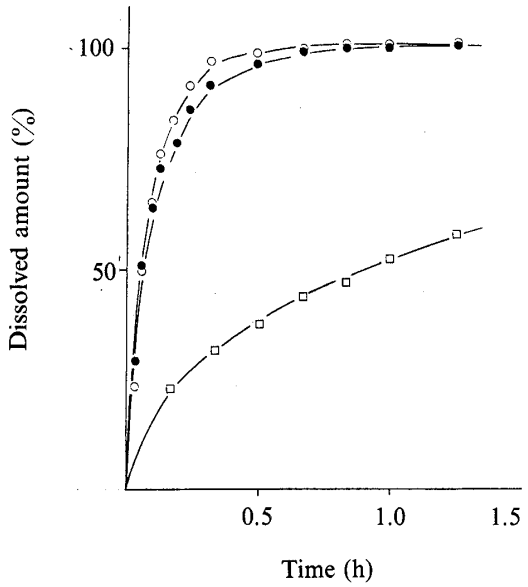

Fig. 7. Dissolution Profiles of Furosemide Tablets without Disintegrant (□), with 2.5% CDP (○) or with 12.5% PS (●)

Table I. Friability of Tablets Containing Various Concentrations of Additives and Microcrystalline Cellulose

Concentration (%)	Friability (%)		
	0	5	25
CDP	0.33	0.29	0.31
PS	0.33	0.36	0.33
Lactose	0.33	0.64	1.21

Table II. Compositions of Furosemide Tablets (mg)

	A	B	C
Furosemide	20.00	20.00	20.00
CDP	6.25	—	—
PS	—	31.25	—
MCC	223.75	198.75	230.00

properties of these materials. Figure 6 shows the disintegration time of the tablets as a function of the concentration of the additives. The tablets of pure MCC disintegrated very slowly. Adding as little as 2.5% CDP to MCC caused the disintegration time of the tablets to decrease from 22.5 to 1.7 min. A similar disintegration time was obtained when 12.5% PS or 25% lactose was used. Above 25% concentration of the disintegrants, no remarkable difference was observed among the effects of CDP, PS, and lactose.

The hardness of tablets containing 0—25% additive was more than 20 kg with all the three disintegrants studied.

The friability values are listed in Table I. The lowest friability was measured for the

tablets containing CDP and more than 1% friability was observed when 25% lactose was used.

CDP can be considered to be a 5 times more effective disintegrant than PS and a 10 times more effective one than lactose, since to achieve less than 2 min disintegration time, at least 2.5% CDP, 12.5% PS, and 25% lactose were necessary. The other advantage of CDP is that it slightly decreased the friability of MCC tablets while PS and especially lactose increased the friability.

Accelerating the Dissolution Rate of a Poorly Soluble Drug

Furosemide was studied as a model drug having low solubility in water (3.7 mg/100 ml). Tablets containing 8% furosemide were compressed with or without disintegrant using MCC as a binder. The composition of the tablets is shown in Table II.

The hardness of tablets of all the three formulations was higher than 20 kg. The disintegration times measured for A, B, and C formulations were 0.8, 0.7, and 4.5 min, respectively. It is noteworthy that 2.5% CDP (A formulation) proved to be nearly equivalent in effect to 12.5% PS (B formulation) in the presence of an active ingredient. The dissolution profiles of the three formulations are shown in Fig. 7. The $t_{50\%}$ values calculated from the dissolution curves to characterize the dissolution rates were 4.0, 4.2, and 52.4 min for A, B, and C formulations, respectively. Somewhat higher dissolution rate (that is, lower $t_{50\%}$) was obtained for the tablets with CDP than with PS, though the disintegration time of the latter tablets was lower suggesting that the dissolution behavior is determined not only by the disintegration time of the tablets, but also by some other properties of the disintegrants.

The data presented in this paper demonstrate that cyclodextrin polymer is a powerful disintegrant with favorable properties such as compactibility and ability to decrease tablet friability and disintegration time, as well as to accelerate the dissolution rate of a poorly soluble drug.

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References and Notes

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