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Evaluation of Cyclodextrin Polymer as an Additive for Furosemide Tablet[1,2]

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The effectiveness of cyclodextrin polymer as a disintegrating agent for directly compressed tablets containing furosemide, cyclodextrin polymer and microcrystalline cellulose was investigated. Regression analysis based on statistically designed experiments made it possible to determine how various tablet characteristics are affected by the amount of excipients. As a result of computer optimization an optimum formulation was obtained exhibiting high dissolution rate, sufficient dissolution stability, fast disintegration, high hardness immediately after preparation and adequate hardness after ageing.

Keywords——cyclodextrin polymer; disintegrating agent; computer optimization; regression equation; experimental design; direct compression; microcrystalline cellulose; furosemide; dissolution; stability

Cyclodextrin is an effective disintegrating agent in tablets made by direct compression.[3] It also shows binding properties besides its accelerating effect on the disintegration of tablets and on the dissolution of a poorly soluble drug (furosemide) as reported in a previous paper.[4]

The purpose of the present study was to find the optimum formulation giving the highest dissolution rate and hardness, the lowest disintegration time, the best dissolution stability, and the minimum softening during storage using the same model drug, furosemide, and the same binder, microcrystalline cellulose, as previously. As the dissolution rate was considered to be of primary interest, the objective was to increase the dissolution rate without adversely changing other properties of the tablets.

Careful experimental design and computer analysis for the solution of such formulation optimization problems have been proved to be advantageous to control the physical and biological properties of tablets[5] and to predict the dissolution parameters of solid dispersions.[6]

In this paper the previously reported method[6] was adapted to deal with two formulation factors: regression analysis was used to describe the tablet characteristics as functions of the amount of cyclodextrin polymer and microcrystalline cellulose, graphical representation was applied to demonstrate how the properties of the tablets are influenced by these excipients, and an optimization program with a set of restrictions was employed to find the optimum formulation.

Experimental

Materials——Cyclodextrin polymer (CDP) used was a pilot product of Chinoin Pharmaceutical and Chemical Works (Hungary),[4,7] a white powder of less than 100 μm grain size, with the following characteristics: β-cyclodextrin content, about 50%, density, 0.63 g/ml; moisture content, 3.1%; sedimentation volume in water, 6.3 ml/g.

Microcrystalline cellulose (MCC) JPX (trade name: Avicel PH 102) was used as a direct compression carrier. Furosemide was generously supplied by Wakamoto Pharmaceutical Co., Ltd.

Tablet Making——Flat-faced tablets of 13 mm diameter were made by compressing a given amount of powder under 100 kg/cm^2 pressure for 30 s in a Shimadzu hydraulic press. Tablets of 9 formulations based on a two-factor composite design graphically illustrated in Fig. 1 were prepared. In this statistical design of experiments the amounts of MCC and CDP were selected as independent variables, X_1 and X_2 respectively, while the quantity of furosemide (20 mg/tablet) and the parameters of the tablet-making procedure (*e.g.* blending conditions, compression pressure) were kept constant for each formulation. The points in Fig. 1 represent the formulations expressed in experimental units as given in Table I. The translation of experimental units was performed on the basis of preliminary experiments[4] (Table II).

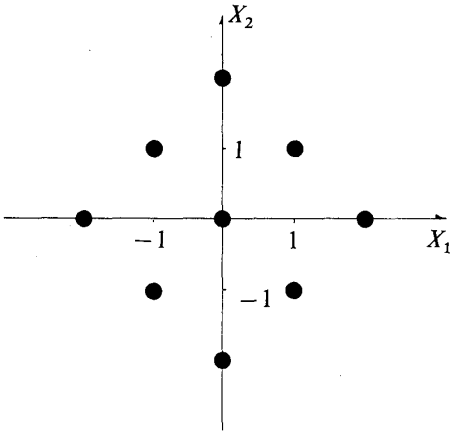

Fig. 1. Geometrical Illustration of the Experimental Design

X_1 and X_2 are the amounts of MCC and CDP, respectively, in tablets expressed in experimental units.

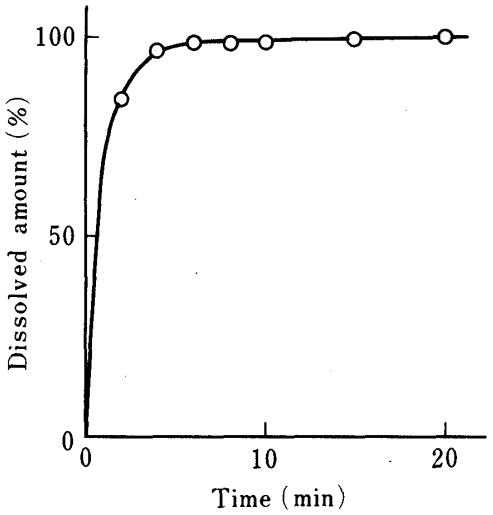

Fig. 2. Dissolution Profile of Furosemide from Tablets of No. 1 Formulation

TABLE I. Experimental Design for Two Factors

Formulation number	Factor level expressed in experimental units	
	X_1	X_2
1	1	1
2	1	−1
3	−1	1
4	−1	−1
5	2	0
6	−2	0
7	0	2
8	0	−2
9	0	0

TABLE II. Translation of Experimental Conditions to Physical Units

Factor	Factor level in experimental units				
	−2	−1	0	1	2
X_1: MCC (mg)	150	170	190	210	230
X_2: CDP (mg)	4	8	12	16	20

Determination of Tablet Characteristics——The thickness of the tablets was measured with a Mitsutoyo micrometer. The measurements of hardness and disintegration time, and the dissolution study were carried out as previously described.[4] In this case, two dissolution parameters, $t_{50\%}$ and $t_{84\%}$ (time passed till the dissolution of 50 and 84% of the drug, respectively), were determined by using Wagner's dissolution model[8] as reported previously.[6] $t_{16\%}$, the third dissolution parameter given by this model was not used because usually 80—90% of the drug was already dissolved at the first sampling (at 2 min), as shown in Fig. 2 in the case of formulation No. 1. The properties of tablets were also measured after storing them for 7 d at 40 °C under 75% relative humidity to test the stability.

All the calculations including regression analysis and optimum search were carried out on a Toshiba PA-7010 series personal computer with the reported programs.[6]

Results and Discussion

Regression Analysis

The characteristics of the tablets, that is hardness, disintegration time and the dissolution parameters measured immediately after the preparation of tablets and after storing them for 7 d at 40 °C under 75% relative humidity (R. H.), are summarized in Table III for the 9

TABLE III. Characteristics of Tablets

Form. number	Immediately after preparation				After the stability test				
	Hardness[a] (kg/mm)	Disint. time (min)	$t_{50\%}$ (min)	$t_{84\%}$ (min)	Weight increase (%)	Hardness[a] (kg/mm)	Disint. time (min)	$t_{50\%}$ (min)	$t_{84\%}$ (min)
1	11.6	0.25	0.642	1.879	2.7	6.62	0.20	1.189	2.499
2	11.2	0.25	1.569	3.211	3.6	7.75	0.25	1.403	3.132
3	10.6	0.20	0.809	1.975	5.2	4.89	0.18	0.809	2.094
4	10.2	0.20	1.008	2.434	1.4	7.68	0.20	0.920	1.980
5	12.6	0.30	1.072	2.390	1.4	7.47	0.22	0.866	2.145
6	10.1	0.20	0.667	1.724	2.2	6.15	0.20	1.002	2.234
7	12.2	0.25	0.703	1.744	3.2	6.58	0.20	0.796	2.025
8	10.8	0.35	3.420	7.051	3.6	7.80	0.32	4.136	8.442
9	10.9	0.25	0.914	2.231	4.7	7.80	0.20	0.736	2.039

a) The hardness is represented per unit thickness of tablet.

TABLE IV. Optimum Regression Equation for Each Characteristic Determined by Multiple Regression Analysis

Y	$Y=b_0+b_1X_1+b_2X_2+b_3X_1^2+b_4X_2^2+b_5X_1X_2$						
	b_0	b_1	b_2	b_3	b_4	b_5	$r^{2\,c)}$
Hardness[a]	10.667	0.583	0.300	0.156	0.194	—	0.962
Hardness[b]	6.971	0.370	−0.530	—	—	—	0.626
Disint. time[a]	0.230	0.025	−0.017	—	0.015	—	0.767
Disint. time[b]	0.200	0.009	−0.026	—	0.014	—	0.899
$t_{50\%}$[a]	0.793	—	−0.547	—	0.306	—	0.881
$t_{50\%}$[b]	0.768	—	−0.584	—	0.412	—	0.805
$t_{84\%}$[a]	1.949	—	−1.034	—	0.591	—	0.876
$t_{84\%}$[b]	1.880	—	−1.113	—	0.806	—	0.798
Weight increase[b]	3.780	—	—	−0.501	—	−1.175	0.742

a) Determined immediately after preparation of the tablets.
b) Determined after the stability test (7 d at 40 °C, 75% R.H.).
c) Square of the multiple correlation coefficient.

formulations. The thicknesses of the tablets were different from each other, and thus, the value of hardness was represented as the ratio to the thickness of the tablet to allow accurate comparison among the tablets.

The regression analysis of these data was carried out by the reported method[6] after adapting it to two independent variables. The following type of equation was used:

$$Y=b_0+b_1X_1+b_2X_2+b_3X_1^2+b_4X_2^2+b_5X_1X_2$$

where Y is the level of the given characteristic, b_i is the regression coefficient and X_1 and X_2 are the levels of the independent variables (the amounts of MCC and CDP in the tablets, respectively, expressed in experimental units). The optimum regression equation for each dependent variable was selected on the basis of statistical significance from among 31 equations (overall combination of independent variables) generated by the computer. Correlation coefficients with doubly adjusted degrees of freedom[9] were used as an index for the selection of the optimum combination of independent variables. The optimum equations obtained for 9 characteristics are listed in Table IV.

According to the equation obtained for the hardness of tablets measured immediately after preparation, the hardness is a function of four factors, but it is affected by X_1 with about 2 times higher regression coefficient than by X_2. The fact that X_2 also has a positive regression coefficient shows that increase of the amount of CDP in tablets results in higher hardness, in agreement with previous observations that CDP is not only an excellent disintegrant but also has some binding properties.

The hardness after the stability test was represented as a linear function of X_1 and X_2. The negative regression coefficient of X_2 indicates that the hardness of tablets is decreased by CDP upon exposure to moisture. A decrease of binding effect was also observed in the case of MCC, as the regression coefficient of X_1 also decreased after storage. Such softening of tablets at high humidities is quite usual when highly hydrophilic excipients are used for their preparation.[10]

The disintegration times of tablets measured immediately after preparation and after the stability test are described by the same kind of equation. The values varied in as narrow a range as 0.20—0.35 min (before the stability test) or 0.18—0.32 min (after the stability test). The small experimental range might explain the low value of r^2 (square of the multiple correlation coefficient). X_2 has a negative regression coefficient as is expected for a disintegrant. The positive regression coefficient of the amount of MCC is also reasonable in view of the binding effect, though MCC was also reported to have disintegrating properties.[11]

The equations describing the dissolution parameters show that the dissolution of furosemide is fully determined by X_2 and X_2^2, that is, the amount of MCC has no influence on the dissolution rate. The difference between the regression coefficients of the factors in the equations predicting $t_{50\%}$ and $t_{84\%}$ before and after the stability test is not great, indicating good stability of these directly compressed formulations.

The equation describing the increase in weight (moisture sorption) after storage of the tablets for 7 d at 40 °C under 75% R. H. was also generated, but was not involved in the optimization process, being used only for the prediction of this characteristic.

Graphical Representation of Regression Equations[6]

The graphical representation of the regression equations is a useful tool in an optimization problem as it makes it easier to understand the meaning of the equations by demonstrating the contribution of the factors as well as by showing clearly the minimum and maximum positions of the characteristics.

Figure 3 shows the contour graph of tablet hardness measured immediately after

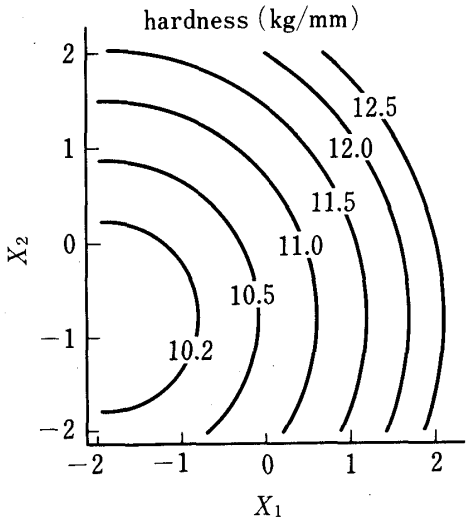

Fig. 3. Contour Graph of Tablet Hardness Measured Immediately after Preparation

Both X_1 and X_2 are expressed in experimental units.

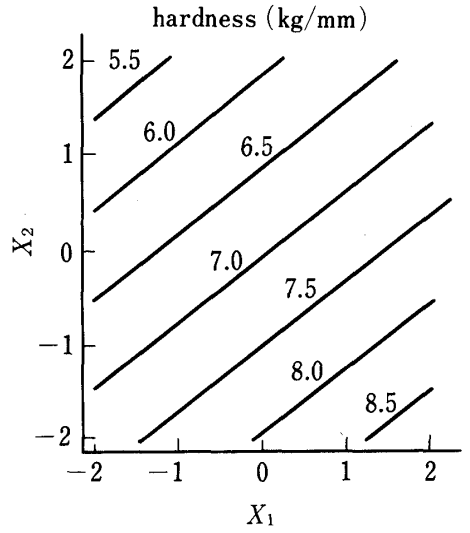

Fig. 4. The Hardness Measured after the Stability Test as a Function of X_1

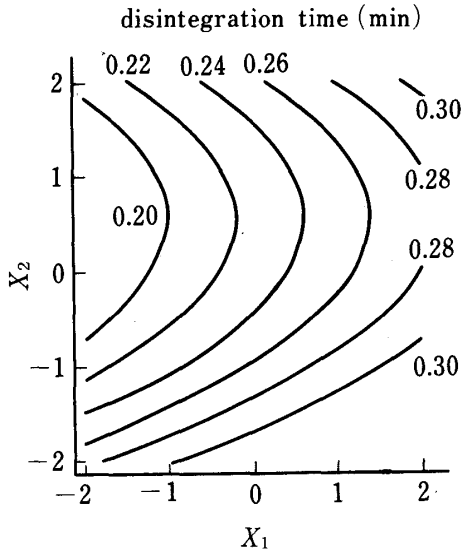

Fig. 5. Contour Graph of the Disintegration Time of Tablets Measured Immediately after Preparation

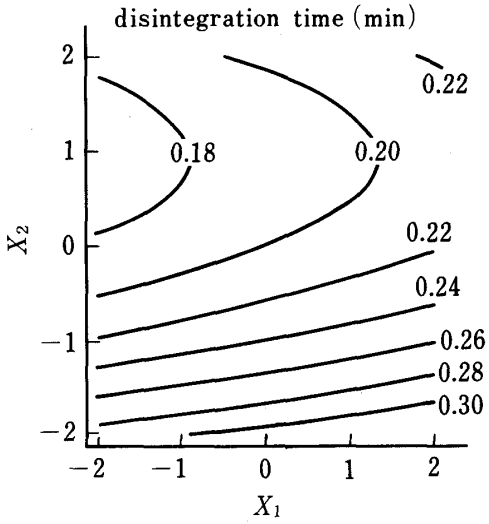

Fig. 6. Contour Graph of the Disintegration Time of Tablets Measured after the Stability Test

7d at 40 °C, 75% R.H.

preparation. It can be seen that the contribution of X_1 is much higher than that of X_2.

The hardness after the stability test is a linear function of X_1 and X_2, that is, the highest hardness corresponds to the highest X_1 and lowest X_2 (Fig. 4).

The disintegration time is determined by both X_1 and X_2 as shown in Figs. 5 and 6. The minimum positions are outside the graphs at lower X_1 values. As regards the disintegration time determined immediately after the preparation the best formulation corresponds to $X_1 = -2$, $X_2 = 0.5$ in experimental units. After the stability test, the formulation of $X_1 = -2$, $X_2 = 1$ is predicted to give a lower disintegration time. A slightly longer disintegration time resulted from a higher level of X_2, so binding characteristics might appear with increase in amount of CDP. It is important to note, however, that the contribution of X_1 is low and the whole experimental range is narrow.

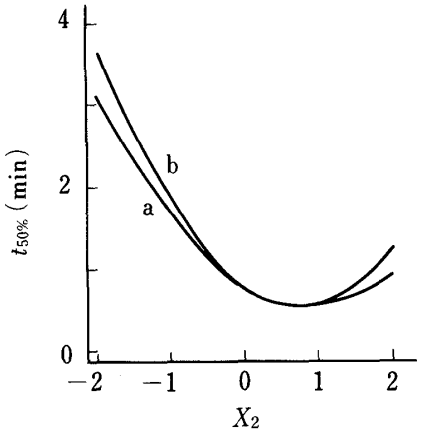

Fig. 7. $t_{50\%}$ before (a) and after (b) the Stability Test as a Function of X_2

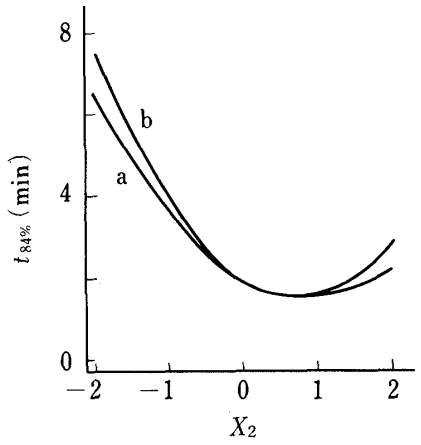

Fig. 8. $t_{84\%}$ before (a) and after (b) the Stability Test as a Function of X_2

TABLE V. The Predicted Maximum and Minimum Values of Each Characteristic and the Weighting in the Optimization Program

Characteristic	Predicted		Weight[c]
	Maximum	Minimum	
Hardness[a] (kg/mm)	13.833	10.019	0.5[d]
Hardness[b] (kg/mm)	8.771	5.171	0.5[d]
Disint. time[a] (min)	0.374	0.175	0.5[d]
Disint. time[b] (min)	0.326	0.170	0.5[d]
$t_{50\%}$[a] (min)	3.111	0.552	1.0[e]
$t_{50\%}$[b] (min)	3.584	0.579	1.0[e]
$t_{84\%}$[a] (min)	6.385	1.507	1.0[e]
$t_{84\%}$[b] (min)	7.330	1.525	1.0[e]

a) Determined immediately after preparation of the tablets.
b) Determined after the stability test (7 d at 40 °C, 75% R.H.).
c) Constraints were relaxed at 1/5 width *d*), or 1/10 width *e*) of the difference between the predicted maximum and minimum values of each characteristic in the first searching step.

The dissolution parameters are parabolic functions of X_2 (Figs. 7 and 8). The minimum of $t_{50\%}$ at $X_2 = 0.89$ is 0.55 min, and it changed to $t_{50\%} = 0.56$ min at $X_2 = 0.71$ after the stability test. Similarly the minimum position of $t_{84\%}$ moved to lower X_2 value (from $X_2 = 0.87$ to $X_2 = 0.69$), while the value of the minimum was unchanged (1.50 min). The change in the dissolution parameters in the accelerated stability test is negligible in the range of $-1 < X_2 < 1$ as regards the predicted data. This result shows the stability of dissolution behavior of these formulations. The contribution of CDP to the dissolution of furosemide is very similar to the case of tablet disintegration time. Thus, it was considered that the disintegration time is closely related to the drug dissolution from the tablet containing CDP.

Optimization of Furosemide–MCC–CDP Tablet Formulation

As is typical in optimization problems, the best formulations for different tablet characteristics are different. The formulation with the highest dissolution rate has relatively low hardness, and the lowest disintegration time is not accompanied by optimum hardness.

The optimization process used was the same as described previously:[6] the predicted minimum and maximum values of each tablet characteristic were selected as first constraints

TABLE VI. Experimental and Predicted Values of the Characteristics of Tablets of the Optimum Formulation ($X_1=1.5$, $X_2=0.5$)

Characteristic	Experimental	Predicted
Hardness[a] (kg/mm)	11.2±0.5[c]	12.1
Hardness[b] (kg/mm)	6.66±0.49[c]	7.26
Disint. time[a] (min)	0.26±0.08[d]	0.26
Disint. time[b] (min)	0.32±0.08[d]	0.20
$t_{50\%}$[a] (min)	0.561	0.596
$t_{50\%}$[b] (min)	0.554	0.579
$t_{84\%}$[a] (min)	1.66	1.58
$t_{84\%}$[b] (min)	2.21	1.53
Weight increase[b]	3.1	1.8

a) Determined immediately after preparation of the tablets.
b) Determined after the stability test (7 d at 40 °C, 75% R.H.).
c) Each value represents the mean ± S.D. of 5 determinations.
d) Each value represents the mean ± S.D. of 6 determinations.

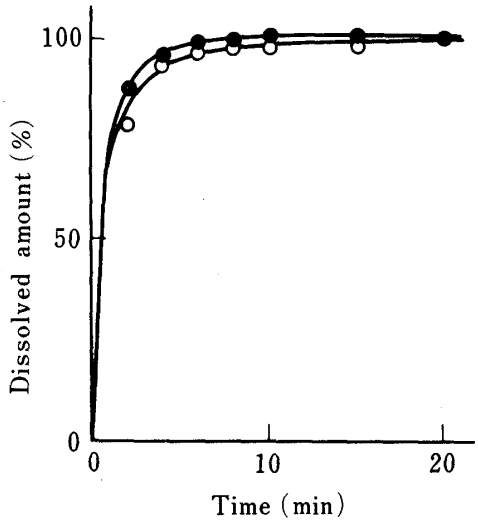

Fig. 9. The Dissolution Profile of Furosemide from Tablets of the Optimum Formulation before (●) and after (○) the Stability Test

in the optimization program and the constraints were relaxed systematically till solutions were found. In this study the characteristics were ranked arbitrarily in order of importance. The dissolution parameters were considered to be the most important characteristics of a formulation of a poorly soluble drug, being given twice the weight of hardness and disintegration time. The degree of the relaxation of the constraints varied according to the assigned weighting on the basis of the above consideration. The predicted maximum and minimum values as well as the weights used in the optimization program are listed in Table V.

Thus the optimum formulation was selected as follows: 220 mg MCC ($X_1=1.5$), 14 mg CDP ($X_2=0.5$) and 20 mg furosemide. Tablets of this formulation were prepared and their characteristics were compared to the predicted values (Table VI). There is good agreement between the measured and the predicted data for most of the characteristics.

The optimum formulation has excellent properties: high dissolution rate, sufficient dissolution stability (Fig. 9), high hardness immediately after preparation and adequate hardness after ageing, and also fast disintegration. Some of the characteristics ($t_{50\%}$ before and after the stability test $t_{84\%}$ before the stability test) were better than those of any of the 9 formulations previously prepared.

It is evident from the results that the use of cyclodextrin polymer in tablets has many advantages, such as improving the disintegration and the dissolution rate, increasing the

hardness of the tablets and providing good stability of dissolution profile. Thus, the use of the computer optimization technique provided a formulation with extremely good properties.

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References and Notes

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