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RESEARCH PAPER

Evaluation of Rapidly Disintegrating Tablets Prepared by a Direct Compression Method

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ABSTRACT

To make rapidly disintegrating tablets with sufficient mechanical integrity as well as a pleasant taste, microcrystalline cellulose (MCC), Tablettose (TT), and cross-linked sodium carboxymethyl cellulose (Ac-di-sol) or erythritol (ET) were formulated. Tablets were made by a direct compression method (1). Tablet properties such as porosity, tensile strength, and disintegration time were determined. The tensile strength and disintegration time were selected as response variables, tablet porosity and parameters representing the characteristics of formulation were selected as controlling factors, and their relation was determined by the polynomial regression method. Response surface plots and contour plots of tablet tensile strength and disintegration time were also constructed. The optimum combination of tablet porosity and formulation was obtained by superimposing the contour diagrams of tablet tensile strength and disintegration time. Rapidly disintegrating tablets with durable structure and desirable taste could be prepared within the obtained optimum region.

INTRODUCTION

With the increase in the average human life span, drug administration for elderly patients has become more important (2). Due to a decline in swallowing ability with age, a great many elderly patients complain that it is difficult to take medication in the form of tablets. Recently, useful dosage forms, such as rapidly disintegrating or dissolving tablets, have been developed and applied clinically (3).

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For example, a suspension or solution of a drug and excipients may be charged in the preformed blister pockets. The suspension and blister tray are then frozen and lyophilized to obtain soft tablets with a very porous structure. When such tablets are placed in the oral cavity, saliva quickly penetrates into the pore to cause rapid tablet disintegration. The main disadvantage of this dosage form is the lack of mechanical strength (4). In fact, the loss of integrity was initially thought to be unavoidable to obtain fast-dissolving or disintegrating oral dosage forms. However, products that could be pushed from a blister pack with minimal damage were prepared not only by a technique similar to that described above (lyophilization) (LYOC®, FARMLYOC Co., Ltd., France), but also by drying a suspension in the depressions of plastic blister packs at room temperature (5).

Another type of fast-dissolving tablet was developed using wet powders containing drugs. Such tablets were produced by two methods: molding (6) and compression (7). These commercially produced tablets have excellent quality, but the cost of manufacture is high.

Previously, we developed a form of tablet by a direct compression method (1). These tablets disintegrated rapidly in the mouth and had sufficient mechanical integrity to be able to withstand handling without substantial breakage. However, as microcrystalline cellulose (MCC) and low-substituted hydroxypropylcellulose were used as excipients in these tablets, their taste was unsatisfactory, as expected. The aim of the present study was to develop a rapidly disintegrating tablet with a taste and texture acceptable to patients and with sufficient structural integrity if made by a low-cost direct compression method.

Microcrystalline cellulose and lactose were used as basic excipients; cross-linked sodium carboxymethylcellulose (Ac-di-sol) was used as a disintegrant. Erythritol (ET) was selected to enhance palatability of the tablets.

MATERIALS

Ethenzamide (ETZ; Yoshitomi Pharmaceutical Industries, Ltd., Japan) was chosen as an active ingredient; MCC (Avicel PH 102, Asahi Kasei Co., Ltd., Japan), lactose (Tablettose, TT; Meggle, Germany), and ET (Nikken Chemicals Co., Ltd., Japan) were used as excipients. Cross-linked sodium carboxymethylcellulose (Ac-di-sol; Asahi Kasei Co., Ltd., Japan) and magnesium stearate (St-Mg; Yoneyama Pharmaceutical Industries, Ltd., Japan) were used as disintegrant and lubricant, respectively.

METHODS

Physical Properties of Excipients

The particle density was measured with a helium-air pycnometer (Model 1302, Micromeritics Instrument Co., Nagoya City). Heywood diameter and shape factor *SF* were determined with an image analyzer (Luzex 500, Nireco Co., Japan). Water solubility was measured at 25°C. Data are listed in Table 1.

Preparation of Tablets

Flat-faced direct compression tablets, 200 mg in weight and 8 mm in diameter, were prepared using a rotary tableting machine (12 HUK-AW, Kikusui Seisakusho, Ltd., Japan) at compression loads of 0.98, 1.96, 2.94, 3.92, and 4.90 kN (precompression force 1/3 of the load in each case). Tablet formulations are shown in Table 2.

Measurement of Tablet Properties

Measurement of Tablet Tensile Strength

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using a tablet hardness tester (TS-50N, Okada Seiko Co., Ltd., Japan). The plunger was driven down at a speed of 20 mm/min. Tensile strength for crushing T was calculated using the following equation:

$$T = 2F/(\pi\, dt) \quad (1)$$

where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Measurement of Tablet Porosity

Tablet porosity ε was calculated as follows:

$$\varepsilon = 1 - m/(\rho_t V) \quad (2)$$

where ε is the true density, and m and V are the weight and volume of the tablet, respectively.

Measurement of Wetting Time

The same testing method for wetting time was used as described in our previous report (1).

Table 1

Physical Properties of Excipients

	MCC	TT	ET	Ac-di-sol
Particle size (μm)[a]	56.4	49.5	26.3	34.5
$SF = (A/ML)4\pi$[b]	0.336	0.563	0.516	0.378
Particle density (g/cc)	1.56	1.51	1.44	1.60
Solubility (w/w%)	—	20.0	36.0	6.2[c]

[a] Heywood diameter ($n = 1000$).
[b] Shape factor *SF* represents sphericity of particles (when particle is spherical, $SF = 1$). *ML* = maximum length of particle; *A* = projection area of particle ($n = 1000$).
[c] About 6.2% of Ac-di-sol was water soluble.

Measurement of Disintegration Time

The disintegration test was carried out using a modified JP XIII dissolution apparatus as described in Ref. 1. The in vitro disintegration data obtained under these mild testing conditions were reproducible and were closely related to those from oral cavity tests.

Values are shown as averages of 10 determinations.

Statistical Analysis

Tablet porosity has been demonstrated to be closely related to water absorption (8), which is a very important step of the disintegration process. It is also an important factor in reflecting the structure of tablets. In this study, tablet porosity and parameters representing the characteristics of formulation were selected as controlling factors, and tablet tensile strength and disintegration time were selected as response variables. A polynomial regression algorithm was used to relate the controlling factors to the response variables. The levels of controlling factors were transformed using the following equation:

$$T_{ran} = \{2A - (Max + Min)\}/(Max - Min) \quad (3)$$

where T_{ran} is the transformed value, *A* is the actual value of the factor being transferred, and *Max* and *Min* are the maximum and minimum values in the range of the factor being transferred, respectively. Response surface plots and contour plots were also constructed to analyze each factor that would optimize the response variables.

RESULTS AND DISCUSSION

MCC has good compressibility, as well as compactibility, according to its plastic deformation, strong hydrogen bond among hydroxyl groups, and concave-convex shape (1). It can also be used as a disintegrant, with disintegrating properties in water attributable to either capillary action or swelling (9). TT is an agglomerate of α-lactose monohydrate, with much better flowability and compressibility than α-lactose monohydrate; it is a commonly used additive in direct tableting. In this study, MCC and TT were used as basic excipients, and they

Table 2

Tablet Formulations

Materials	Lot A						Lot B						
(Percentage)	A1	A2	A3	A4	A5	A6	B1	B2	B3	B4	B5	B6	B7
ETZ	—	—	—	—	—	—	—	—	—	—	—	—	20
MCC	65	55	50	45	40	50	40	40	40	30	20	10	32
TT	30	40	45	50	55	40	30	20	10	20	30	40	16
ET	—	—	—	—	—	—	30	40	50	50	50	50	32
Ac-di-sol	5	5	5	5	5	10	—	—	—	—	—	—	—
St-Mg	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

were formulated with either Ac-di-sol or ET to complete our design specification.

Tablets Consisting of Microcrystalline Cellulose, Tablettose, and Ac-di-sol

Ac-di-sol was used as a disintegrant and was formulated with MCC and TT. Ac-di-sol is one of the ''super-disintegrants'' and has excellent disintegrating ability. It swells to a large extent when it comes into contact with water to disintegrate tablets and has a fibrous nature that allows intraparticulate, as well as extraparticulate, wicking of water even at low concentration levels (10). As Ac-di-sol is often added into formulations at less than 10%, we used this agent at 5% or 10%. The tensile strength, porosity and wetting and disintegration times of each resultant tablet are shown in Fig. 1.

The tensile strength of tablets containing 10% Ac-di-sol was less than that of tablets with an Ac-di-sol content of 5%. Furthermore, the wetting time and the disintegration time of the former were much longer than those of the later.

According to Eq. 4, proposed by Washburn (8), the water penetration rate into the powder bed (dl/dt) is proportional to the pore radius and is affected by factors such as the hydrophilicity of powders (which is expressed by the contact angle between water and powder θ and surface tension γ) and liquid viscosity η.

$$dl/dt = r\gamma/(4\eta l) \tag{4}$$

where l is the length of penetration, r is the capillary radius, and t is the time.

The porosity of the 10% Ac-di-sol tablets was slightly greater than that of Ac-di-sol 5% tablets, and both

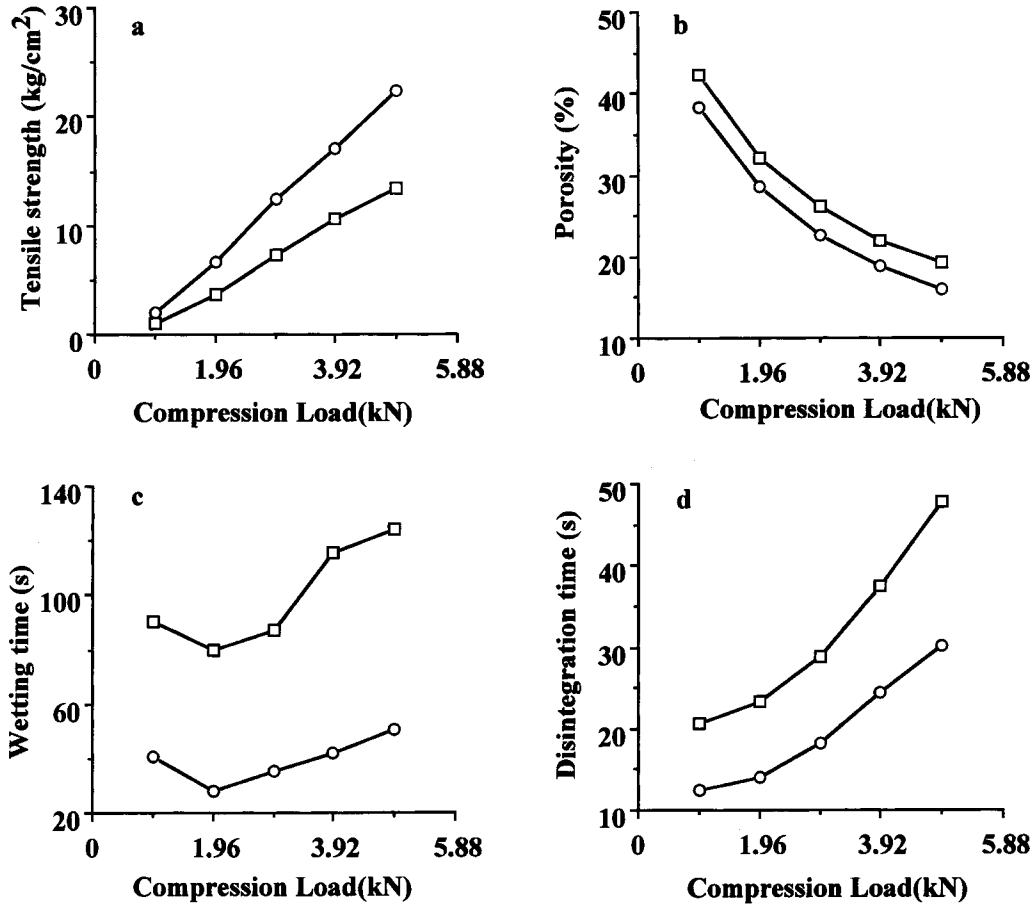

Figure 1. Effects of Ac-di-sol content on tablet properties: (a) tensile strength; (b) porosity; (c) wetting time; (d) disintegration time. Ac-di-sol content: □, 10% (A6 tablets); ○, 5% (A2 tablets).

showed similar hydrophilicity. Hence, according to the equation above, the delayed wetting of the former was considered to have been caused by the rise in viscosity. Ac-di-sol is made by a cross-linking (esterfication) reaction of sodium carboxymethylcellulose. This cross-linking greatly reduced the water solubility of sodium carboxymethylcellulose, while permitting the material to swell and absorb many times its weight in water without losing individual fiber integrity (11). However, because a water-soluble content of about 6% remains, which tends to become viscous and adhesive when hydrated, when Ac-di-sol is added to tablet formulations at a high concentration, its absorption of water might cause an increase in viscosity of the liquid within the tablet, and further water penetration would be delayed. As water absorption is an important step in the disintegration process, disintegration of the tablets showed the same tendency as wetting time.

The above results suggested that 5% of Ac-di-sol should be added to the formulation rather than 10%. Therefore, in the following formulations (A1, A2, A3, A4, and A5), 5% of Ac-di-sol was used as a disintegrant, and tablets with various TT/MCC ratios were prepared at five compression load levels, and 25 kinds of tablets with various porosities, tensile strengths, and disintegration times were obtained. Then, based on these 25 groups of data, tensile strength was expressed as a function of TT/MCC ratio and tablet porosity by the polynomial regression method, yielding the following equation:

$$\begin{aligned} Ts &= -1.430x - 8.830y + 2.109x^2 \\ &\quad + 5.528y^2 + 3.412 \\ N &= 25 \quad R = .981 \quad T(20) < 0.05 \\ \mathrm{SD} &= 1.368 \quad F(4,20) = 94.726 \end{aligned} \tag{5}$$

where *Ts* is tablet tensile strength, *x* stands for the transformed TT/MCC ratio, *y* refers to the transformed tablet porosity, *N* is the number of samples, and *R* is the multiple correlation coefficient. *T* denotes the *P* value determined by a Student *t* test, and *F* that obtained by an *F* test. The Student *t* test showed that the coefficients for all the components at the right side of Eq. 5 are very significant ($P < .05$).

Three-dimensional surface and contour plots of tensile strength could also be constructed by statistical analysis of these 25 groups of data using a computer (Fig. 2).

The negative coefficient for *x* in Eq. 5 indicates that the TT/MCC ratio contributes negatively to the tensile strength of tablets; the term x^2 is responsible for the curvature in the surface plot. In the contour plot, points on the same line represent the same tensile strength value, and the value is marked next to the corresponding line. It is apparent that a low TT/MCC ratio resulted in tablets with high tensile strength, and tablet tensile strength decreased with increases in TT/MCC ratio when the ratio was less than 0.85. The strong interparticle force between MCC particles can explain this phenomenon. When the TT/MCC ratio exceeded 0.85, however, the tensile strength showed only a slight increase with increases in the TT/MCC ratio. It was supposed that, at a high TT/MCC ratio, TT granules break into small crystals during the compression process, which generates many fresh contact surfaces, and tablet integrity is accordingly improved (12). At a TT/MCC ratio of around 0.85, the interparticle force in tablets was depressed to the largest extent.

As all the controlling factors were transformed to the range from -1 to 1 before polynomial regression, the absolute value of *y* was always larger than that of y^2. In Eq. 4, the negative effect of *y* is always larger than the positive effect of y^2, indicating that porosity contributes negatively to tablet tensile strength at all times. This could also be visualized from the contour plot and is very easily understood because, when tablet porosity increases, the contact area over which interparticle force acts would be decreased.

Equation 6 is the polynomial equation of disintegration time of the above tablets, and it was obtained in the same way as Eq. 5.

$$\begin{aligned} Dis &= 2.351x - 5.301y - 1.308x^2 \\ &\quad - 2.191xy + 20.168 \\ N &= 25 \quad R = .991 \quad T(20) < 0.05 \\ \mathrm{SD} &= 0.958 \quad F(4,20) = 85.439 \end{aligned} \tag{6}$$

where *Dis* is the disintegration time, and other symbols are the same as in the equations above.

The signs of the coefficients of *x* and *y* in Eq. 6 indicate that the TT/MCC ratio increases, whereas porosity decreases the disintegration time. The term x^2 is the response for curvature in the *x* direction. The positive coefficient for the interaction term *xy* suggests a synergistic effect between the TT/MCC ratio and porosity. Response surface and contour plots of disintegration time are shown in Fig. 3.

The contour plot shows that, for tablets with the same TT/MCC ratio, disintegration time decreases with increases in porosity. The rapid disintegration of tablets with high porosity is thought to be due to rapid water absorption. For tablets with the same porosity, when tablet porosity is low, disintegration time increases significantly with increases in the TT/MCC ratio, but the tendency decreases with increasing porosity. When tablet

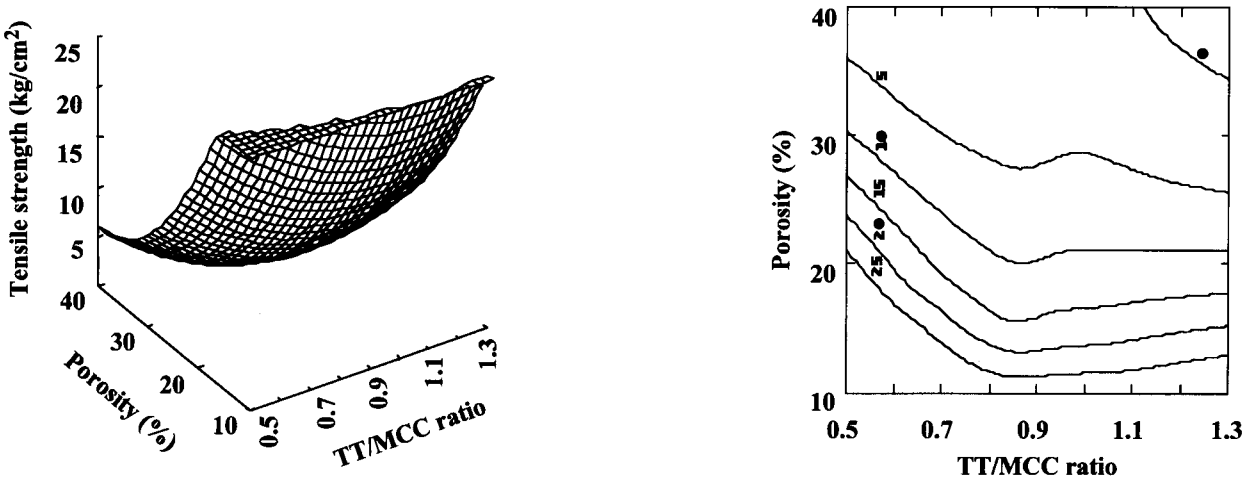

Figure 2. Response surface and contour plots of tensile strength of tablets containing MCC, TT, and 5% Ac-di-sol.

porosity exceeds a certain limit, the TT/MCC ratio has almost no effect on disintegration.

When tablet porosity is very high, water can be absorbed easily, and destruction of tablets is not very difficult. Disintegration is hardly affected by tablet formulation. However, when tablet porosity is not extremely high, disintegration will be influenced by the properties of the excipients used. In these tablets, Ac-di-sol was used as a disintegrant. In tablets containing large amounts of water-soluble TT, the pores along the Ac-di-sol fiber will be enlarged by the dissolution of TT, so the swelling of Ac-di-sol will have less effect on destruction of the tablet matrix compared with tablets containing more insoluble MCC. This may be one reason why tablet disintegration time increased with increasing TT/MCC ratio. Furthermore, this may also have been due to differences in the disintegration abilities of MCC and TT. MCC is a swellable material, and its disintegration characteristics in water have been attributed to either capillary action or swelling. TT is not a swellable material that undergoes

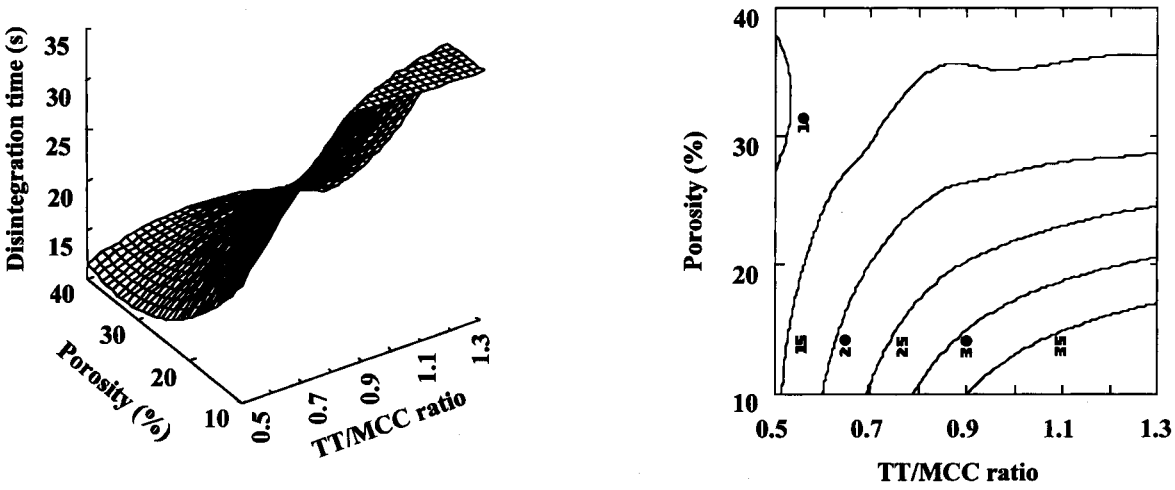

Figure 3. Response surface and contour plots of disintegration time of tablets containing MCC, TT, and 5% Ac-di-sol.

so-called self-disintegration or spontaneous disintegration, the mechanism of which has been proposed to be bond (hydrogen bond) annihilation and consequent repulsion between particles. Bond annihilation is thought to be not as efficient for tablet disintegration as swelling of particles. This may also explain why tablets with a low TT/MCC ratio disintegrated rapidly.

Based on the above analysis, the optimal TT/MCC ratio and porosity combination was analyzed. With the expected tensile strength and disintegration time, we can superimpose these two contour plots and find the optimum region of porosity and TT/MCC ratio combination. With 5 kg/cm^2 as the minimum expected tensile strength and 15 sec as the maximum expected disintegration time, we superimposed the contour plots and recognized the optimum porosity and TT/MCC ratio combination as the shaded region in Fig. 4. The optimum region is the point at which the TT/MCC ratio is less than 0.7 and porosity is less than 30%. Thus, only tablets containing more than 56% MCC have acceptable characteristics.

These tablets have improved taste in comparison with those described previously (1), but because large amounts of insoluble MCC must be included in the formulation, residual powder remains when these tablets disintegrate in the mouth. To overcome this problem, the addition of another sugar alcohol, ET, was considered.

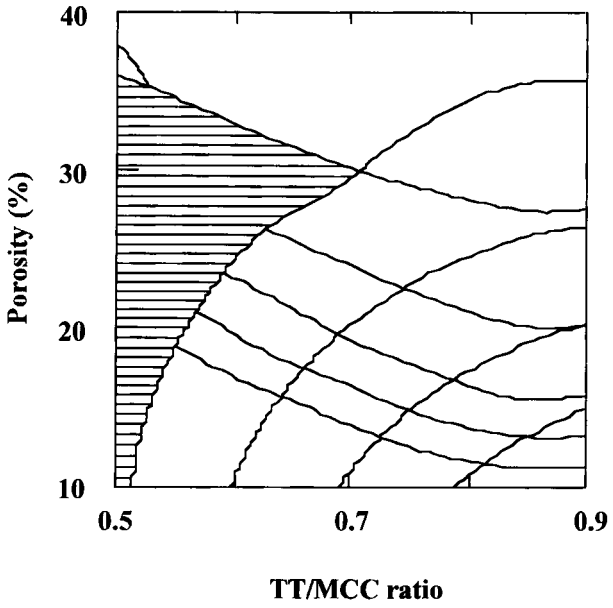

Figure 4. Optimum region of tensile strength and disintegration time as a function of TT/MCC ratio and porosity for tablets in which Ac-di-sol content was 5%.

Tablets Consisting of Microcrystalline Cellulose, Tablettose, and Erythritol

Erythritol is a tetrose alcohol with about 75–80% of the sweetness of sucrose. As it is noncariogenic, ET has recently attracted the interest of diet food and beverage manufacturers (13). The heat of solution of ET is −320 J/g, and hence it has a cool and mild taste. It is also heat stable and nonhygroscopic and was therefore selected as a filler to improve the taste and texture of tablets. Here, Ac-di-sol was excluded from all formulations since its disintegration effect was shown to be poor in formulations containing large amounts of water-soluble material, as described above.

Tablets Containing 40% Microcrystalline Cellulose

As a high MCC concentration in tablets has an adverse effect on both texture and taste, the MCC content was kept at 40% in the following three formulations (B1, B2, and B3). Under five compression load levels, 15 kinds of tablets with various porosities and TT/ET ratios were prepared. The polynomial equations of tensile strength and disintegration time of these tablets were as follows:

$$\begin{aligned} Ts &= 0.499x - 8.181y - 0.702x^2 \\ &\quad + 4.592y^2 - 0.834xy + 6.867 \\ N &= 15 \quad R = .999 \quad T(9) < 0.05 \\ \mathrm{SD} &= 0.343 \quad F(5,9) = 768.437 \end{aligned} \tag{7}$$

$$\begin{aligned} Dis &= -11.397y + 14.784y^2 \\ &\quad - 4.913xy + 12.325 \\ N &= 15 \quad R = .972 \quad T(11) < 0.05 \\ \mathrm{SD} &= 2.790 \quad F(3,11) = 61.935 \end{aligned} \tag{8}$$

where x stands for the transformed TT/ET ratio, and all other symbols are the same as for Eq. 5 and Eq. 6.

The small coefficients for x, x^2, and xy in Eq. 7 suggest that TT/ET ratio has little effect on tablet tensile strength. In Eq. 8, there are no x and x^2 terms, but the coefficient of interaction term xy is large, suggesting that synergistic effects between TT/ET ratio and tablet porosity could not be neglected.

The response surface plots and contour plots of tablet tensile strength and disintegration time are shown in Figs. 5 and 6, respectively. From the contour plot shown in Fig.5, it is obvious that tablet tensile strength decreases

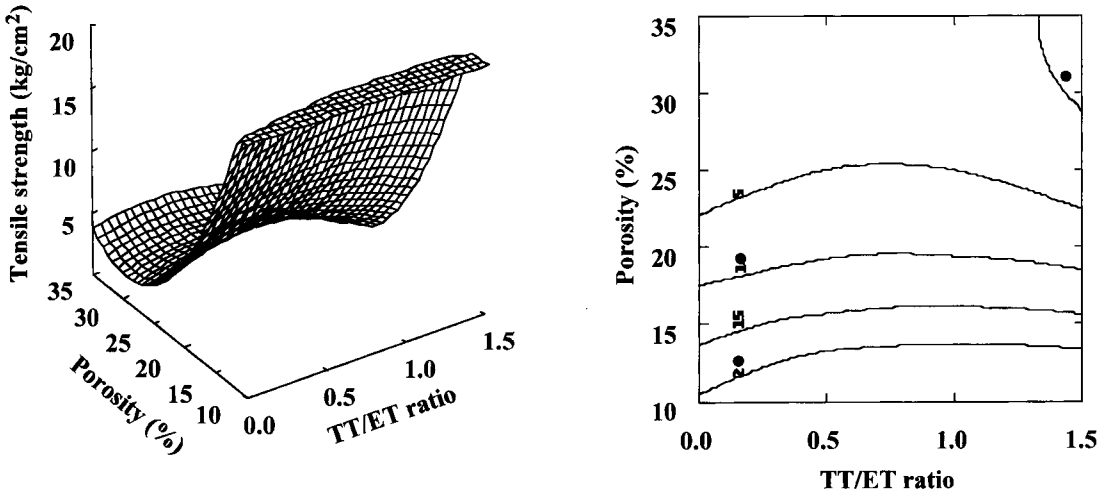

Figure 5. Response surface and contour plots of tensile strength of tablets containing TT, ET, and 40% MCC.

with increasing porosity. When the TT/ET ratio is between 0.7 and 1.0, all contour lines have a very broad peak, which is in accordance with the x^2 term in Eq. 7.

The two primary parameters on which the mechanical strength of tablets depends are the dominating bond mechanism and the surface over which these bonds are active (14). TT and ET are both crystal sugar alcohols, and their main intermolecular force is the same (i.e., the hydrogen bonds between hydroxyl groups). As the intermolecular force mechanism of the two are similar, the TT/ET ratio has little effect on intermolecular force. The broad peak of the contour lines is thought to be due to the difference in particle size of the two materials. When the TT/ET ratio is between 0.7 and 1.0, the small ET particles are thought to just fill the spaces among the large MCC and TT particles, resulting in an increase in contact surface area and thus increased tensile strength.

Figure 6 indicates that the disintegration time of these tablets increases slightly with increasing TT/ET ratio. The solubility of ET is almost twice that of lactose, which is thought to be the reason for the difference in disintegration times of these tablets.

The optimum combination for the TT/ET ratio and porosity of these tablets is shown as the shaded region

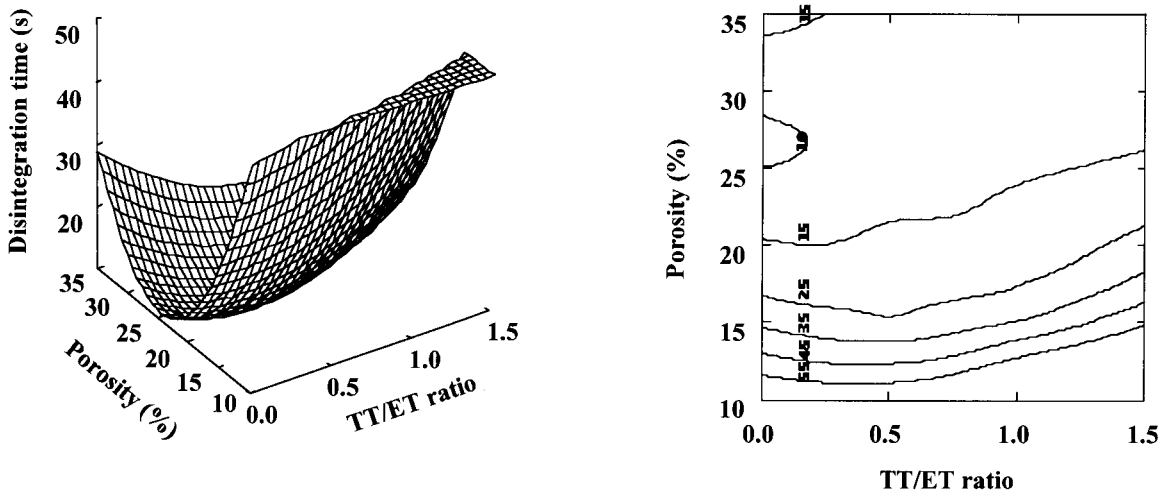

Figure 6. Response surface and contour plots of disintegration time of tablets containing TT, ET, and 40% MCC.

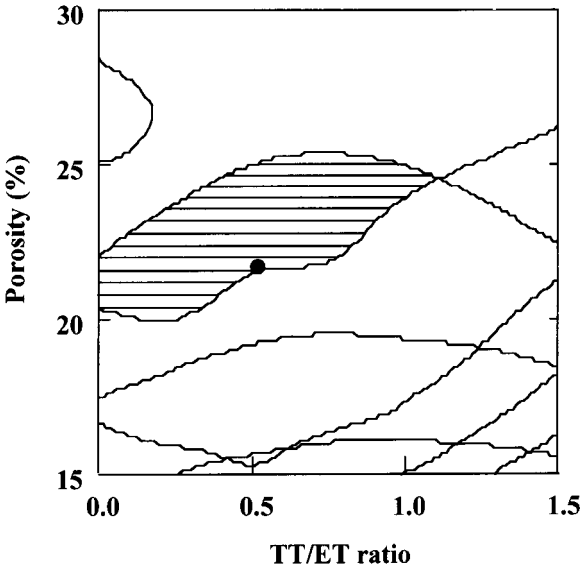

Figure 7. Optimum region of tensile strength and disintegration time as a function of TT/ET ratio and porosity for tablets in which MCC content was 40%. ●, TT/MCC 0.5; porosity 22%.

in Fig. 7, in which tablet tensile strength is more than 5 kg/cm^2 and tablet disintegration occurs within 15 sec. The taste of tablets with the features described in this area was much improved.

The point at which the MCC content was 40%, the TT/MCC ratio was 0.5 (B2 formulation), and the tablet porosity was 22% is indicated in Fig. 7. Tensile strength and disintegration time of these tablets were 8 kg/cm^2 and 15 sec, respectively. When the contents of excipients in this formulation were reduced to 80% and the remaining 20% was replaced by the model drug ETZ (B7), tablets with a porosity of 22% were prepared. The tensile strength of these tablets was 6 kg/cm^2, and disintegration time was 14 sec, both of which were within the acceptable range. Thus, this optimization method can be applied to tablets containing model drugs.

Tablets Containing 50% Erythritol

To improve tablet taste further, the ET content was increased to 50%. Twenty kinds of tablet with various TT/MCC ratios and porosity values were prepared, and their tensile strengths and disintegration times were determined (tablet formulations B3, B4, B5, B6; compression force 0.98, 1.96, 2.94, 3.92, and 4.90 kN).

The polynomial equations expressing tensile strength and disintegration time of these tablets are Eq. 9 and Eq. 10, respectively, and the corresponding response surface plots and contour plots are shown in Figs. 8 and 9, respectively.

$$\begin{aligned} Ts &= -3.351x - 4.078y + 2.555x^2 \\ &\quad + 2.960xy + 1.712 \\ N &= 20 \quad R = .973 \quad T(15) < 0.05 \\ \mathrm{SD} &= 1.229 \quad F(4,15) = 66.718 \end{aligned} \tag{9}$$

$$\begin{aligned} Dis &= 2.688x + 8.933x^2 + 5.385y^2 \\ &\quad + 7.488xy + 7.869 \\ N &= 20 \quad R = .874 \quad T(15) < 0.05 \\ \mathrm{SD} &= 2.891 \quad F(4,15) = 12.133 \end{aligned} \tag{10}$$

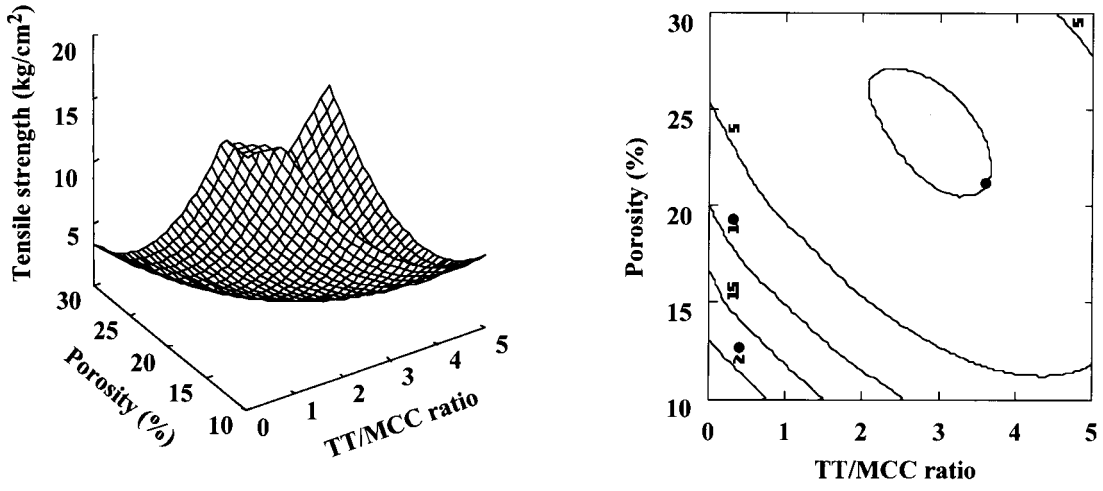

Figure 8. Response surface and contour plots of tensile strength of tablets containing MCC, TT, and 50% ET.

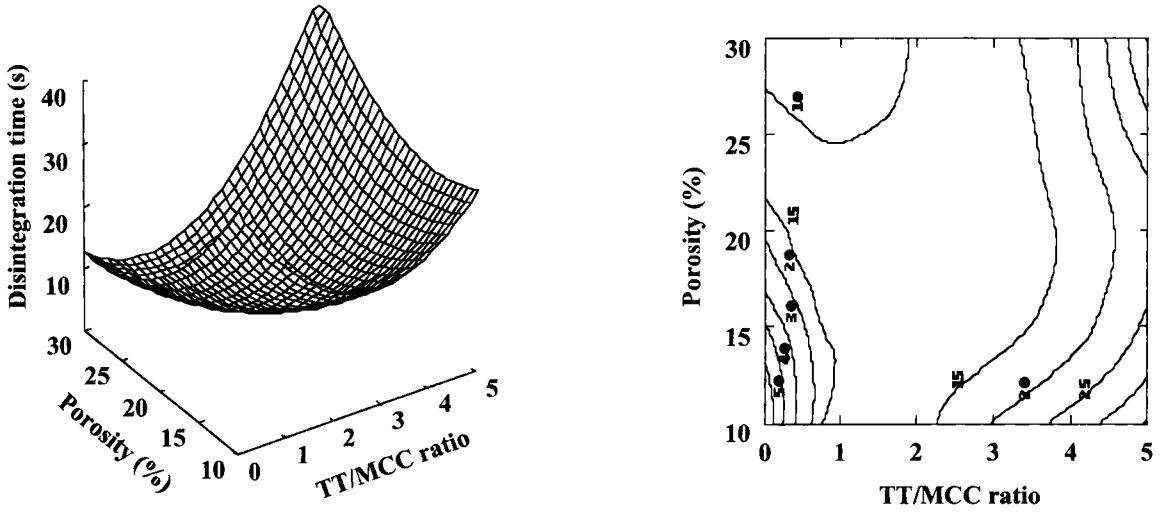

Figure 9. Response surface and contour plots of disintegration time of tablets containing MCC, TT, and 50% ET.

where x stands for the transformed TT/MCC ratio, and all other symbols are the same as for Eq. 5 and Eq. 6.

The square term x^2 in Eq. 9 suggests that there exists a curvature in the x direction in Fig. 8. However, within the region of analysis, only half of the curvature can be observed where *Ts* decreases with increasing TT/MCC ratio. The term xy suggests a synergistic effect between the TT/MCC ratio and porosity. Figure 8 indicates that, with porosity between 20% and 27% and a TT/MCC ratio between 2.1 and 3.7, tensile strength shows the minimum value.

It is clear from Fig. 9 that, at each porosity level, there is a wide TT/MCC ratio range in which disintegration time is less than 15 sec.

The optimum region of TT/MCC ratio and tablet porosity combination is shaded in Fig. 10. In this region, tablet tensile strength is greater than 5 kg/cm^2, and disintegration time is shorter than 15 sec. As these tablets contained large amounts of ET, their taste was further improved.

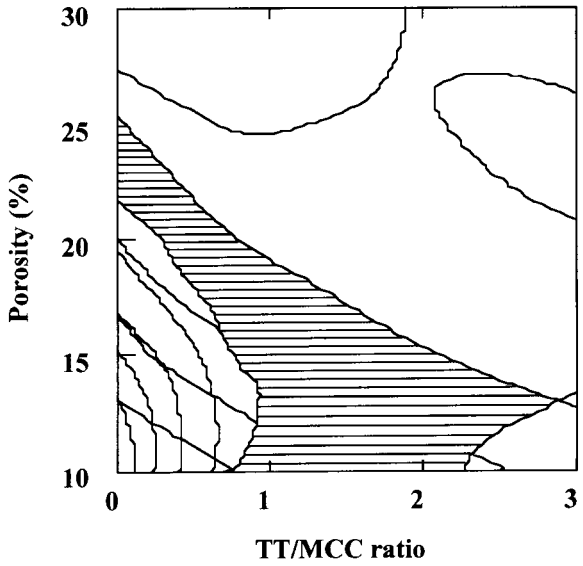

Figure 10. Optimum region of tensile strength and disintegration time as a function of TT/MCC ratio and porosity for tablets in which ET content was 50%.

CONCLUSIONS

In this study, MCC, TT, Ac-di-sol, and ET were used as excipients to prepare rapidly disintegrating tablets with good taste and sufficient tensile strength. The tensile strengths and disintegration times of these tablets were expressed as functions of tablet porosity and parameters representing tablet composition. Optimum formulation and tableting conditions (expressed by porosity) could be determined by superimposing the contour plots of tensile strength and disintegration time. Within this optimal region, the minimum tensile strength was 5 kg/cm^2, while the maximum disintegration time was 15 sec.

A point within the optimum region was selected, and tablets containing 20% ETZ as a model drug were pre-

pared under these conditions. The properties of these tablets met our design specification.

The method described here was useful for the preparation of rapidly disintegrating tablets with good taste and sufficient tensile strength.

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