Drug Development and Industrial Pharmacy, 25(8), 869–878 (1999)

RESEARCH PAPER

Pharmaceutical Evaluation of Multipurpose Excipients for Direct Compressed Tablet Manufacture: Comparisons of the Capabilities of Multipurpose Excipients with Those in General Use

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ABSTRACT

Recently, a novel type of multipurpose excipient (MPE) with high binding characteristics and high fluidity has been developed. In this study, the capabilities of MPEs (Ludipress and Microcelac) were compared with those of excipients in general use. Also, the effects on powder and tableting characteristics of the physical properties and contents of active ingredients were examined in tablets prepared with these MPEs by the direct compression method. Multipurpose excipients mixed with adjuvants such as fillers, binders, lubricants, disintegrants, and the like show superior fluidity and compressibility. Tablets containing very small amounts of highly active ingredients with little dispersion were prepared. However, with increases in active ingredient content, each of the physical properties was affected strongly by the properties of the active ingredient. Tablets with appropriate hardness and disintegration characteristics could be prepared by mixing of different types of MPEs.

Key Words: *Appropriate hardness; Direct compression; Multipurpose excipient; Optimal disintegrant property.*

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INTRODUCTION

Several types of additives for direct compressed tablet manufacture (direct compression) have been developed recently (1–6) to overcome the economic disadvantages of the inclusion of granulation procedures and to simplify the process. Direct compression is also more suitable for active ingredients that are sensitive to moisture or unstable at high temperatures (7), and there are no differences in quality of the products.

However, the utilization of the additives for direct compression of tablets is not yet common in Japan because of the heterogeneous distribution of the active components in each tablet, which is a problem for very potent drugs administered in small doses (8–14). For components with high activity, there are limitations on the amounts of additives to improve the fluidity and to prevent compressibility so that the segregation of the components cannot be prevented.

Moreover, novel types of additives, including mixtures of adjuvants such as fillers, binders, lubricants, and disintegrants, have been studied. The representative multipurpose excipients (MPEs) Ludipress (15) and Microcelac are prepared by spray-drying methods with spherical granules and are commercially available.

In this study, first we evaluated the complex type of excipients in comparison with excipients generally used for direct compression. Next, to investigate the effects of the physical properties and content of active ingredient, the characteristics of mixing powder and tablet were examined. Various active ingredients with different physical properties were used to establish the properties of mixing and tableting.

EXPERIMENTAL

Samples

The excipients are listed in Table 1 with their ingredients. Ludipress (BASF Japan, Tokyo, Japan) and Microcelac 100 (Meggle Japan, Tokyo, Japan) were used as complex types of excipients for direct compression. Tablettose 80 (Meggle Japan) and Avicel PH101 (Asahi Chemical Industry, Tokyo, Japan) were employed as references. Magnesium stearate (Yoneyama Reagent, Osaka, Japan) was used as a lubricant, and Primojel (CS; Matsuya Chemical, Hyougo, Japan) and Ac-di-sol (SCS; Asahi Chemical Industry) were used as disintegrants for addition to samples that showed poor disintegration. Formulations used in this study are listed in Table 2. These formulations were introduced for comparison of the effects of excipients with those generally used for direct compression. Glibenclamide (GC), acetaminophen (AC), ascorbic acid (VC), and ethenzamide (EZ) were used as active ingredients. The basic properties of each active ingredients are listed in Table 3, and the formulations are listed in Table 4. All samples were stored in an air-conditioned room at 25°C with relative humidity of 35% for 24 hr prior to use.

Mixing Properties of Excipient with Active Ingredients

Samples were taken from the three parts of the V-type mixer (VM-5, Fuji Powdal, Osaka, Japan) during mixing of the active ingredient and excipient. The quantity of each active ingredient was measured by high-performance liquid chromatography (HPLC). The HPLC conditions are listed in Table 5. The excipient, passed through 355-μm sieves, was mixed with active ingredient. Following sieving for 3 min with 355-μm sieves, the active ingredient on the sieves (i.e., active ingredient adhering to the excipient) was measured, and the ratio of active ingredient, that is, the index of mixing, was measured.

Manufacture of Direct Compressed Excipient Tablets

Each excipient was mixed with 0.5% magnesium stearate in a V-type mixer for 5 min at 42 rpm. The mixed powder was compressed in a rotary tablet machine (Cleanpress Correct HUK12, Kikusui, Kyoto, Japan) to prepare uniform 180-mg flat-face, beveled edge, and 6.5R tablets 8 mm in diameter.

Physical Characterization of the Compressed Excipient Tablets

The hardness of the tablets was determined with a tablet hardness tester (Speed Checker TS-50N, Okada Seiko, Tokyo, Japan), and disintegration times of the tablets were determined with a disintegration tester (JS-2, Kayagaki Rika Kougyou, Tokyo, Japan), also according to the JP XII disintegration test without a supporting board.

RESULTS AND DISCUSSION

Physical Characteristics of the Excipients

Table 6 summarizes the physical characteristics of the excipients studied. There were no significant differences

Table 1

Samples Used in This Experiment

Samples	Symbol	Constituents	Ratio (%)	Attributes	Maker
Direct compression					
Ludipress	LP	α-Lactose monohydrate	93	Filler, binder	BASF
		Kollidon 30	3.5	Binder	
		Kollidon CL	3.5	Disintegrant	
Microcelac	MC	α-Lactose-monohydrate	75	Filler, binder	Meggle
		Microcrystalline cellulose	25	Binder	
Tablettose	TT	α-Lactose-monohydrate	100	Filler, binder	Meggle
Avicel PH101	AP	Microcrystalline cellulose	100	Binder	Asahi Chemical Industry
Additive					
Primojel	CS	Carmellose sodium	100	Disintegrant	Matsutani Chemical Industry
Ac-di-sol	SCS	Sodium carboxy-methyl starch	100	Disintegrent	Asahi Chemical Industry
MG-stearate	Mg-St			Lubricant	Yoneyama Reagent

Table 2

Formulations (%)

Formulation	LP	MC	TT	AP	CS	SCS	K30	KCL
L-0	100	—	—	—	—	—	—	—
M-0	—	100	—	—	—	—	—	—
M-1	—	97	—	—	3	—	—	—
M-2	—	90	—	—	10	—	—	—
M-3	—	97	—	—	—	3	—	—
M-4	—	90	—	—	—	10	—	—
LM-1	75	25	—	—	—	—	—	—
LM-2	50	50	—	—	—	—	—	—
LM-3	25	75	—	—	—	—	—	—
T-0	—	—	100	—	—	—	—	—
T-1	—	—	93	—	—	—	3.5	3.5
A-0	—	—	—	100	—	—	—	—
TA-1	—	—	75	25	—	—	—	—

K30, Kollidon 30 (Povidone); KCL, Kollidon CL (Crospovidone).

Table 3

Model Drugs Used in This Study

Drug	Symbol	Mean Particle Diameter[a] (μm)	Particle Density[b] (g cm^{-3})	Maker
Glibenclamide	GL	16.3	1.65	Secifarma
Ascorbic acid	VC	12.6	1.79	Takeda Chemical Industry
Acetaminophen	AC	17.3	1.40	Yoshitomi Pharmaceuticals
Ethenzamide	EZ	26.0	1.26	Yoshitomi Pharmaceuticals

[a] Image analyzer (Luzex, Nireco, Tokyo, Japan).
[b] Helium-air pycnometer (Shimadzu, Kyoto, Japan).

Table 4

Formulations (%) with Drug

Formulation	LP	MC	TT	AP	GL	VC	AC
L-GL	95	—	—	—	5	—	—
M-GL	—	95	—	—	5	—	—
T-GL	—	—	71.3	23.8	5	—	—
L-VC	95	—	—	—	—	5	—
M-VC	—	95	—	—	—	5	—
T-VC	—	—	71.3	23.8	—	5	—
L-AC	95	—	—	—	—	—	5
M-AC	—	95	—	—	—	—	5
T-AC	—	—	71.3	23.8	—	—	5

GL, glibenclamide; VC, ascorbic acid; AC, acetaminophen.

Table 5

Condition of High-Performance Liquid Chromatography

Drug	GL	VC	AC	EZ
Monitoring wavelength (nm)	300	251	244	293
Flow rate (ml min^{-1})	1.5	1.0	1.0	1.0

Column: Cosmosil 5C18AR (4.6 mm i.d. × 150 mm); mobile phase: MeOH:water:phosphoric acid = 600:396:4.

Table 6

Physical Characteristics of the Excipients

Physical Parameter	L-0	M-0	T-0	A-0	TA-1
Mean particle diameter (μm)	148.0	135.8	158.6	28.8	—
Geometric standard deviation (σg)	2.07	1.67	1.84	2.85	—
Angle of repose (degrees)	35.9	34.8	43.4	46.7	39.0
Particle density (g cm^{-3})[a]	1.61	1.48	1.70	1.84	1.74
Granule strength (g cm^{-2})[b]	3.15	1.03	2.45	—	—
Shape index (ψ)[c]	1.49	1.81	1.49	2.66	—
Pore volume (cc g^{-1})[d]	1.004	0.924	0.775	—	—
Mean pore diameter (μm)[d]	50.0	46.9	30.1	—	—
Crystallinity (%)[e]	49.4	54.6	83.5	—	—

[a] Helium-air pycnometer (Shimadzu, Kyoto, Japan).
[b] Grano (Okada Seiko, Tokyo, Japan).
[c] Image analyzer (Luzex, Nireco, Tokyo, Japan).
[d] Pore-Sizer 9305 (Shimadzu, Kyoto, Japan).
[e] Differential scanning calorimetry method.

in the physical properties among L-0, M-0, and T-0, all of which were comprised of round granules with good fluidity. The complex type of excipients for direct compression, L-0 and M-0, had more pores than T-0. According to the theory of ordered mixing of Johnson and Hersey (8–14), micronized drugs with high cohesive properties might adhere to coarser carrier granule surfaces by van der Waals and electrostatic forces, increasing the mixing properties.

According to Peter and Claus (16,17), all excipients (L-0, M-0, T-0) showed typical α-lactose monohydrate thermograms. Dehydration of crystalline-water takes place between 100°C and 150°C, followed by an exothermic transition at 160°C, indicating recrystallization of amorphous (glass) lactose for L-0 and M-0. The lactose melts at approximately 220°C, and these results indicate that the whole excipient does not become a glass, but one part becomes a glass for Ludipress and Microcelac.

Physical Characteristics of the Excipient-Containing Compressed Tablets

The relationship between tablet hardness and compression (Fig. 1) was proportional. Large values of L-0 and M-0 were related to good fluidity and a high level of amorphous lactose compared with TA-1 and T-1; therefore, these tablets easily underwent plastic deformation during compression, increasing the binding capacity of lactose (1), resulting in hard tablets. Also, L-0 and M-0 were less crystalline than T-0. In addition, L-0 and M-0 granules have large numbers of pores on the surface. Thus, plastic deformation of L-0 and M-0, which are porous and have low crystallinity, during compression might be responsible for increased interparticle bonding in the tablets (18).

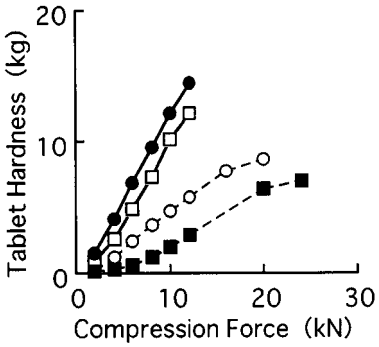

Figure 1. Relationship between compression force and tablet hardness: □, L-0; ●, M-0; ○, TA-1; ■, T-1.

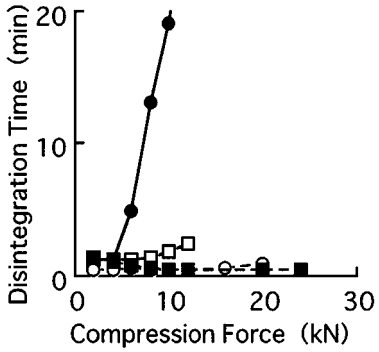

Figure 2. Relationship between compression force and disintegration time: □, L-0; ●, M-0; ○, TA-1; ■, T-1.

Tablets other than M-0 disintegrated immediately (Fig. 2), which was considered to be due to the disintegrants Kollidon CL or Avicel PH 101 in L-0, T-1, and TA-1. However, M-0 also contained microcrystalline cellulose, which was granulated by the spray-drying method and easily underwent plastic deformation to produce dense compact tablets. Therefore, disintegration occurred later than in TA-1, which contained the same components as M-0. Formulations M-1-1,2 and M-2-1,2, to which were added the disintegrants CS and SCS to improve the disintegrant property of Microcelac (which has the good molding properties) were examined (Fig. 3). As hardness and friability of tablets were little changed and disintegration time was shortened only with a disintegrant content of 3%, it was necessary to add the disintegrant to M-0.

The L-0 and M-0 were stable on exposure to high temperatures and humidity. However, the shape of L-0 tablets changed with moisture absorption (1,19–26), and compressed M-0 tablets hardly disintegrated. Mixtures of L-0 and M-0 (LM-1, LM-2, LM-3) were examined to compensate for both of these problems. As shown in Fig. 4, these mixtures showed no differences in tablet hardness, but the increment in Ludipress ratio indicated a decrease in disintegration time. Thus, M-0 tablets to which disintegrants were added at 10% became brittle, while for mixtures of these MPEs (Ludipress and Microcelac), this problem was resolved, and MPE that had optional disintegrant properties was prepared.

Mixing Properties with Active Ingredients

The mixing properties of GL and AC with each excipient are shown in Figs. 5 and 6, respectively. These results indicated that the content of active ingredient was more fixed on the surface of Microcelac and Ludipress by the

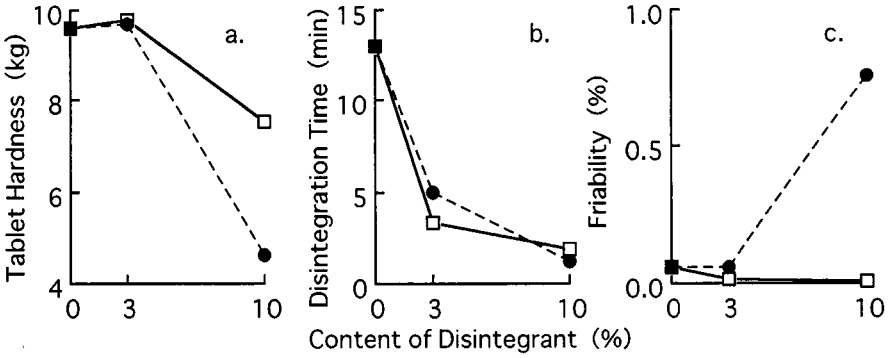

Figure 3. Effect of disintegrants on the properties of tablets for Microcelac: (a) tablet hardness; (b) disintegration time; □, SCS; ●, CS.

GL and AC series than from the mixture of Tablettose and Avicel, and dispersion became small. However, the content of active ingredient did not become fixed even if they were mixed in GL series of a mixture of Tablettose-Avicel for 30 min.

The rates of adherence of GL AND EZ to Microcelac as an MPE and the mixture of Tablettose and Avicel as an excipient in general use for direct compression are shown in Fig. 7a. For both M-GL and T-GL, GL showed little adhesion to the excipient before mixing. However, following mixing for 30 min, GL showed good adherence to the excipient M-GL and adhered little to T-GL. As shown in Fig. 7b, types L and M multipurpose excipients had superior mixing properties at all EZ contents examined to type T excipient in general use. Moreover, types L and M MPEs showed almost the theoretical value until a content of 20%, indicating that EZ strongly adhered to the excipient. Thus, Ludipress and Microcelac had superior mixing properties to the mixture of Tablettose and Avicel, as shown in Figs. 5 and 6.

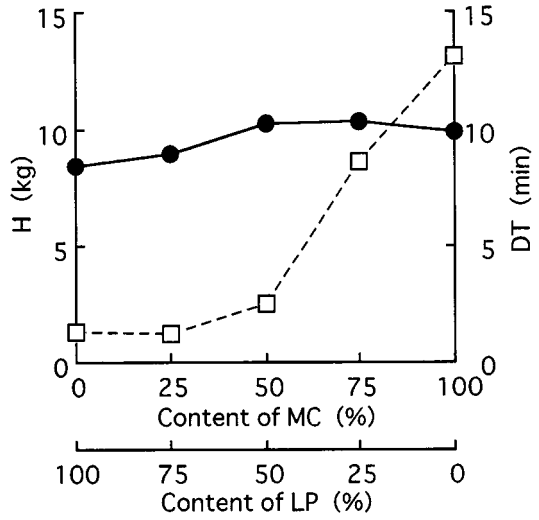

Figure 4. Changes in the hardness and disintegration time of tablets of the mixture of MPEs: ●, hardness; □, disintegration time of tablet.

Physical Properties of Tablets Containing Active Ingredients

The disintegration times of each tablet are shown in Table 7. Due to the inclusion of disintegrants in types L and T, disintegration time was fastest in these tablets and slowest in type M, and there was no influence of type of active ingredient. Disintegration time appeared to be affected by the solubility of the active ingredient in water. Because of physical characteristics, VC was very soluble, AC was soluble, and GL was practically insoluble, therefore, tablets containing VC showed the fastest disintegration, while those containing GL showed the slowest disintegration. In M-GL, disintegration time was over 30 min, which requires improvement for clinical use.

Moreover, in the case of types L and T, disintegration time was not affected by EZ until it reached a content of 30%. However, in the case of L, no effect was seen until there was an EZ content of 50%. In the case of type M, increases in EZ content were accompanied by increases in disintegration time; at contents of 20%, disintegration times were more than 30 min. This was because of the lack of solubility of EZ in water. At EZ contents over 50%, disintegration time showed a marked increase. This was thought to be because the properties of the tablets were affected strongly by those of the active ingredient when they were included in such high concentrations.

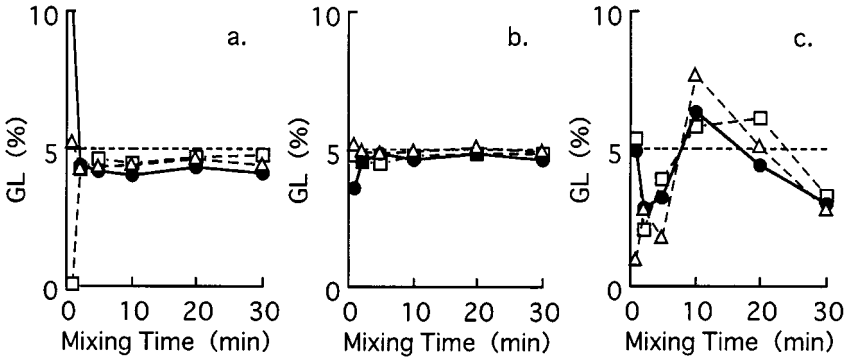

Figure 5. Effect of mixing time on mixing property of GL: (a) L-GL; (b) M-GL; (c) T-GL; . . . theoretical line. Sampling point: □, right; ●, center; △, left of the V-type mixer.

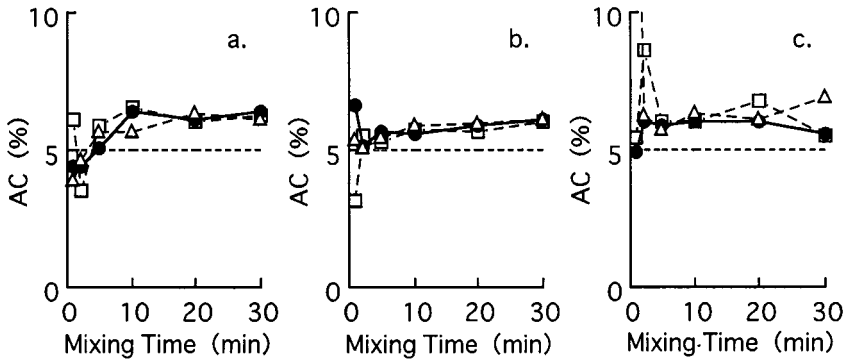

Figure 6. Effect of mixing time on mixing property of AC: (a) L-AC; (b) M-AC; (c) T-AC; . . . theoretical line. Sampling point: □, right; ●, center, △, left of the V-type mixer.

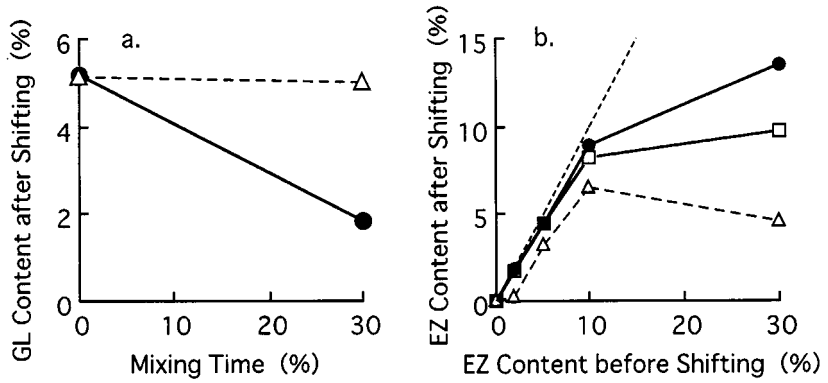

Figure 7. Ratio of adhered drugs to the excipients: (a) GL; (b) EZ; □, type L; ●, type M; △, type T; . . . theoretical line.

Table 7

Disintegration Times of Model Drugs

Compression Force (kN)	L-GL	M-GL	T-GL
6	1 min 9 sec	>30 min	0 min 20 sec
8	1 min 45 sec	>30 min	0 min 29 sec
10	2 min 49 sec	>30 min	0 min 30 sec
12	3 min 45 sec	>30 min	0 min 50 sec
Compression Force (kN)	L-VC	M-VC	T-VC
6	1 min 42 sec	8 min 57 sec	0 min 19 sec
8	2 min 30 sec	18 min 19 sec	0 min 21 sec
10	3 min 35 sec	26 min 0 sec	0 min 37 sec
12	4 min 3 sec	>30 min	0 min 57 sec
Compression Force (kN)	L-AC	M-AC	T-AC
6	0 min 53 sec	13 min 13 sec	0 min 28 sec
8	1 min 29 sec	22 min 36 sec	0 min 23 sec
10	2 min 4 sec	>30 min	0 min 24 sec
12	2 min 49 sec	>30 min	0 min 35 sec
EZ (%)	LP	MC	TA
0	1 min 19 sec	13 min 4 sec	0 min 31 sec
0.5	1 min 14 sec	12 min 41 sec	0 min 24 sec
10	0 min 39 sec	20 min 30 sec	—
20	0 min 38 sec	>30 min	—
30	0 min 44 sec	>30 min	0 min 50 sec
50	2 min 4 sec	>30 min	—

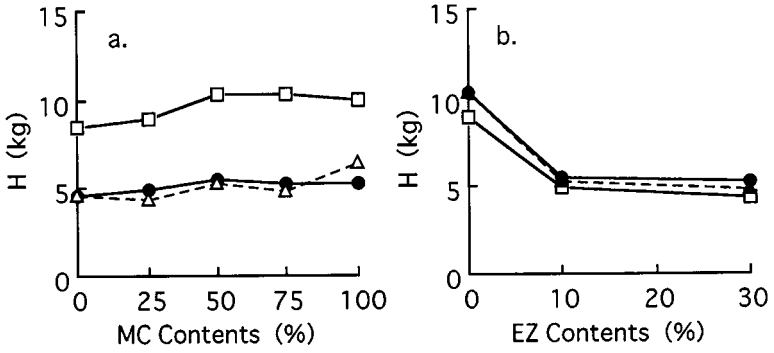

Figure 8. Effect of the ratio of LP/MC and EZ contents on the hardness of tablets: (a) □, EZ 0%; ●, EZ 10%; △, EZ 30%; (b) □, LP/MC = 75/25; ●, LP/MC = 50/50; △, LP/MC = 25/75.

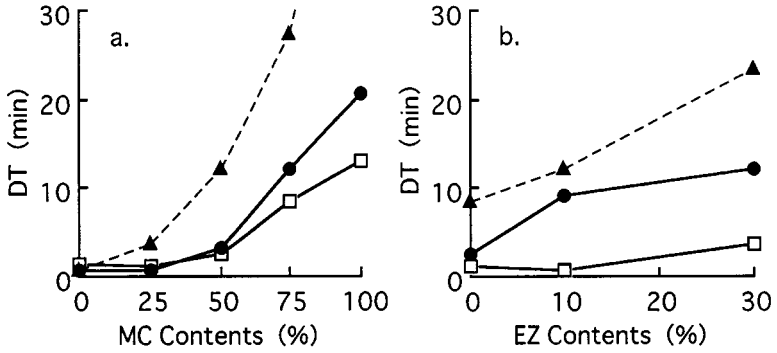

Figure 9. Effect of the ratio of LP/MC and EZ contents on the disintegration time of tablets: (a) □, EZ 0%; ●, EZ 10%; ▲, EZ 30%; (b) □, LP/MC = 75/25; ●, LP/MC = 50/50; ▲, LP/MC = 25/75.

Preparation of Mixtures of Multipurpose Excipients with Active Ingredients

Relationships between mixing ratio of MPE and EZ content with tablet hardness and disintegration time are shown in Figs. 8 and 9. Tablet hardness was almost constant, with no influence of MPE mixing ratio at any EZ content (Fig. 8). However, increases in EZ content were accompanied by decreases in tablet hardness. This was because the ratios of plastic deformation for Ludipress and Microcelac MPEs were decreased by increasing the active ingredient ratio.

As shown in Fig. 9, increases in the mixing ratio of Ludipress indicated faster disintegration. However, with increases in EZ content, the disintegration time was increased markedly due to the poor solubility of EZ in water at any mixing ratio. In this way, by changing the ratio of MPE, tablets with good disintegration characteristics could be prepared.

CONCLUSIONS

Our results indicate that Ludipress and Microcelac, complex types of excipient for direct compression, have advantages for good fluidity and compressibility compared with the excipients generally used for direct compression on mixing with similar additives (TA-1, T-1). Also, as tablets prepared from Ludipress had a short disintegration time and those prepared from Microcelac, despite good compressibility, had a long disintegration time, a mixture of these two MPEs in a suitable ratio yielded a new MPE with optional disintegrant properties.

In the case of tableting with active ingredients using an MPE, the properties of the active ingredient, especially adhesion force and solubility in water, affected the properties of powder mixtures and tablets. With active ingredients with a relatively small adhesion force, the excipient for direct compression showed good mixing properties. In the case of those with a large adhesion force, the MPEs for direct compression showed good mixing properties due to the large number of pores at the surface of the granules, while the excipient for direct compression showed poor mixing properties because the active ingredient formed agglomerates and dispersions.

Tablets with high and constant active ingredient contents with little dispersion were prepared. Each of the properties of the tablets was affected by those of the active ingredient. By changing the mixing ratio of Ludipress and Microcelac, tablets with appropriate hardness and optimal disintegrant properties were obtained even with high active ingredient content.

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