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RESEARCH PAPER

Evaluation of Era-Tab as a Direct Compression Excipient

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ABSTRACT

The physical and compressional properties of a modified rice starch, Era-Tab, were evaluated and compared with those of 4 commercially available direct compression excipients, namely, microcrystalline cellulose (Avicel PH-101), partially pregelatinized starch, spray-dried lactose (Super-Tab Lactose), and granular dicalcium phosphate dihydrate (Emcompress). It was found that Era-Tab possessed high flowability and adequate compressibility. The compacted material made with Era-Tab has a higher crushing strength and a lower friability than 3 other direct compression excipients, except microcrystalline cellulose. Tablets containing terfenadine of the same degree of hardness (≈10 kg) were also prepared using different direct compression excipients. The disintegration time of the tablets made with Era-Tab was approximately 2.5 min. The maximum of the accumulated percentage of terfenadine released from the tablet reached 90%, and 63.2% of it was released within 20 min. Both the powder characteristics and tablet properties show that the modified rice starch, Era-Tab, is a useful product as a direct compression tablet excipient.

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INTRODUCTION

The direct compression method for the production of tablets offers many advantages such as simplicity, reduction of labor costs, fewer manufacturing steps and pieces of equipments, and increasing product stability (1–3). Mainly, 4 types of direct compression excipients are currently used in the pharmaceutical industry: (i) inorganic compounds (e.g., dibasic calcium phosphate), (ii) lactose (e.g., spray-dried lactose), (iii) microcrystalline cellulose, and (iv) partially pregelatinized starches. Each of them has its own merits when used in direct compression tablet formulation (4).

Due to its sensitivity to hydrophobic lubricants, such as magnesium stearate, in the tablet formulation process, partially pregelatinized starch did not gain popularity in the direct compression excipient market (4). Recently, it was reported that Proflo cornstarches and Preflo potato starches could be a potential for direct compression of sustained-release tablets (5).

Era-Tab is an agglomerated form of modified rice starch. It is primarily used in processed food and food products. Era-Tab is intended to be used as a direct compression excipient and has been claimed to be compatible with a wide range of pharmaceutical materials (6). Recently, the modified rice starch (also marketed as Primotab ET) had been reported to be suitable for direct compression tablet formulations containing oxazepam (7).

The purpose of this investigation was to evaluate Era-Tab further as a direct compression excipient with respect to its physical and tableting properties, and to compare it with those of the 4 types of direct compression excipients.

MATERIALS

Microcrystalline cellulose N.F. (Avicel PH-101) (Asahi Chemical Industry Co., Ltd., Japan), partially pregelatinized starch (PPS) (Hui Ming Pharm. Co., Ltd., ROC), spray-dried lactose (Super-Tab Lactose) (The Lactose Company of New Zealand Co., Ltd., New Zealand), dicalcium phosphate dihydrate (Emcompress) (Edward Mendell Co., Ltd., USA), and modified rice starch (Era-Tab), (Erawan Pharmaceutical Research and Laboratory Co., Ltd., Thailand) were used as supplied. Terfenadine (Synsefarm, Co., Ltd.,8/0392010, Italy) was chosen as the model drug. Magnesium stearate (Wako Co., Ltd., Japan) and Primojel (AVEBE b.a., The Netherlands) were used as lubricant and disintegrant, respectively. The excipients were stored under controlled temperature (25° ± 1°C) and humidity condition (RH = 45 ± 1%) prior to study for at least 2 weeks.

METHODS

Powder Characterization of Excipients

Particle size distributions of excipients were determined in triplicate by sieve analysis on an Alpine Air Jet Sieve (Alpine, Augsburg, Germany). The results were plotted on log-probability axes, and the geometric mean diameters (d_g) were calculated. The flowability (angle of repose) of the excipients was measured according to the fixed-funnel and free-standing-cone method. The results of angle of repose are the mean of 5 measurements.

The true densities of the powders were determined by gas pycnometry (Multi-Pycnometer, Quantachrome Co., USA) using helium. By placing a powder carefully into a 100-ml measuring cylinder using a spatula until the 100-ml volume mark was reached, the weight of the powder could be determined. The bulk density (g/cm^3) of each of the excipients was computed. Subsequently, the cylinder was fixed onto the Vanderdamp Tap Density Tester (VanKel Industries, Inc., USA), and the tapping procedure was performed. The volume readings were taken at intervals of 500 taps. Then the tapped bulk densities of the excipients were determined. The results of the density determinations are the mean of 3 determinations, with which the percentage porosity and percentage compressibility (8) were calculated.

The shape and surface characteristics of the powders were examined in a scanning electron microscopy (SEM) (S-2300, Hitachi, Japan). The specific surface areas of the excipients were determined by the BET method using the Micromeritics Flowsorb II 2300 (Micromeritics Co., Ltd., USA). Thermal analyses of the powders were performed using a Perkin–Elmer differential scanning calorimeter (DSC) (DSC7, Perkin–Elmer Co., USA), and the possible interactions between terfenadine and the respective excipient were estimated from the DSC thermograms.

Preparation and Characterization of Tablets

Flat-faced placebo tablets each weighing 550 ± 5 mg were individually prepared by compressing the powder in a single-punch hydraulic press (Model-C, Freds. Carver Inc., USA). The tablet diameter was 1.25 mm

and the compression pressures used were 30, 50, 70, 100, 120, 150, 200, 250, and 300 kg/cm^2, respectively. The tablets were weighed accurately and tested for thickness, crushing strength (CT-5 engineering system hardness tester, Nottm. Co., Ltd., England), and friability (Erweka Instruments Inc., Germany) after storage for 24 hr in a desiccator. The tensile strength of the tablets was then determined (9).

Tablets containing terfenadine (Table 1) as the model drug were prepared at predetermined compression pressure for the same degree of hardness (≈10 kg). After ejection, the tablets were stored in a desiccator for 24 hr prior to disintegration and dissolution testing. The disintegration time of the tablets was determined with a disintegration apparatus (Ming-pen Machine Co., ROC) adopting the method described in USP XXIII for uncoated tablets without the guide disk in place. The disintegration medium was distilled water maintained at 37° ± 0.5°C. The mean of 6 determinations was taken for each batch.

Dissolution tests were carried out with the USP XXIII dissolution apparatus, (DT-610 JASCO Co., Ltd., Japan) in 900 ml 0.1 N HCl maintained at 37° ± 0.5°C as dissolution medium, and the paddle speed was 100 rpm. Samples of the drug solution passed through a 30–50 μm filter at 1, 2, 3, 5, 7, 10, 15, 20, 30, 40, 60, 90, 120, and 180 min were collected, then the amounts of the dissolved drug were determined spectrophotometrically (UV-700, JASCO Co., Ltd., Japan) at 256 nm. For each sampling point, 6 tablets were tested for each formulation.

RESULTS AND DISCUSSION

Powder Characteristics of 5 Direct Compression Excipients

The physical characteristics of the 5 excipients are listed in Table 2. The geometric mean diameter of Era-Tab is 72 μm. It has an angle of repose of 34° and percentage compressibility of 14%, both indicating good flowability (8). The SEM examination has shown that Era-Tab particles are aggregates of a more spherical shape with a main size range between 50 and 100 μm, similar to those reported by Bos et al. (7). It also explains why Era-Tab has a good flowability, which coincides with the results of geometric mean diameter. The geometric mean diameters and flowability of Avicel PH-101, Emcompress, and PPS are similar to those reported previously (10,11).

Differential scanning calorimetry (DSC) was used to predict a possible incompatibility of terfenadine–excipient binary mixtures from the DSC profile. The results illustrate that the DSC thermogram of terfenadine shows

Table 1

Formulations, Disintegration Time, and Weibull Equation Parameters of Terfenadine Tablets

	Formulation				
Ingredient	1	2	3	4	5
Terfenadine	60mg	60mg	60mg	60mg	60mg
Era-Tab	450mg				
Emcompress		450mg			
Avicel PH-101			450mg		
Super-Tab Lactose				450mg	
PPS					450mg
Magnesium stearate	5mg	5mg	5mg	5mg	5mg
Premojel	35mg	35mg	35mg	35mg	35mg
Disintegration time (sec)	139.00	21.25	18.50	19.00	74.00
(± *SD*)	(± 4.95)	(± 1.92)	(± 2.69)	(± 1.22)	(± 3.16)
Parameters[a]					
T_{lag}	-0.2544	0.4512	-0.0728	0.7978	-0.2269
k	0.8162	0.5085	0.4996	0.4063	0.5050
T_d	20.3055	7.3170	17.9411	15.6287	4.2957
M	90.0090	83.6665	78.7047	65.4983	81.8400

[a]T_{lag}: the lag time; k: the shape parameter; T_d: the time (min) when 63.2% of drug was released; M: the accumulated percentage released.

Table 2

Physical Properties of 5 Excipients

Excipients	Era-Tab	Emcom press	Avicel PH-101	Super-Tab Lactose	Starch 1500
Geometric mean diameter dg (μm)	72	118	43	106	160
Geometric standard deviation σg	1.7	1.68	1.87	2.08	3.88
Correlation coefficient of particle size distribution	0.94	0.85	0.94	0.96	0.99
Angle of repose (deg)	33.69	36.53	53.75	49.27	41.94
True density (g/cm^3)	1.47	2.29	1.51	1.66	1.50
Bulk density (g/cm^3)	0.52	0.84	0.31	0.64	0.61
Ultimate tap density (g/cm^3)	0.60	1.00	0.46	0.83	0.87
Specific surface area (m^2/g)	0.29	0.71	1.04	0.25	0.98

the melting endothermic peak at 152.1°C (Fig. 1), with no apparent decomposition up to a temperature of 250°C. Era-Tab shows a broad endotherm ranging from 70° to 120°C. The DSC thermogram of the terfenadine–Era-Tab mixture essentially reserves the parent peaks of the pure components. It implies that no interaction between terfenadine and Era-Tab was observed. Thus, Era-Tab can be used in combination with

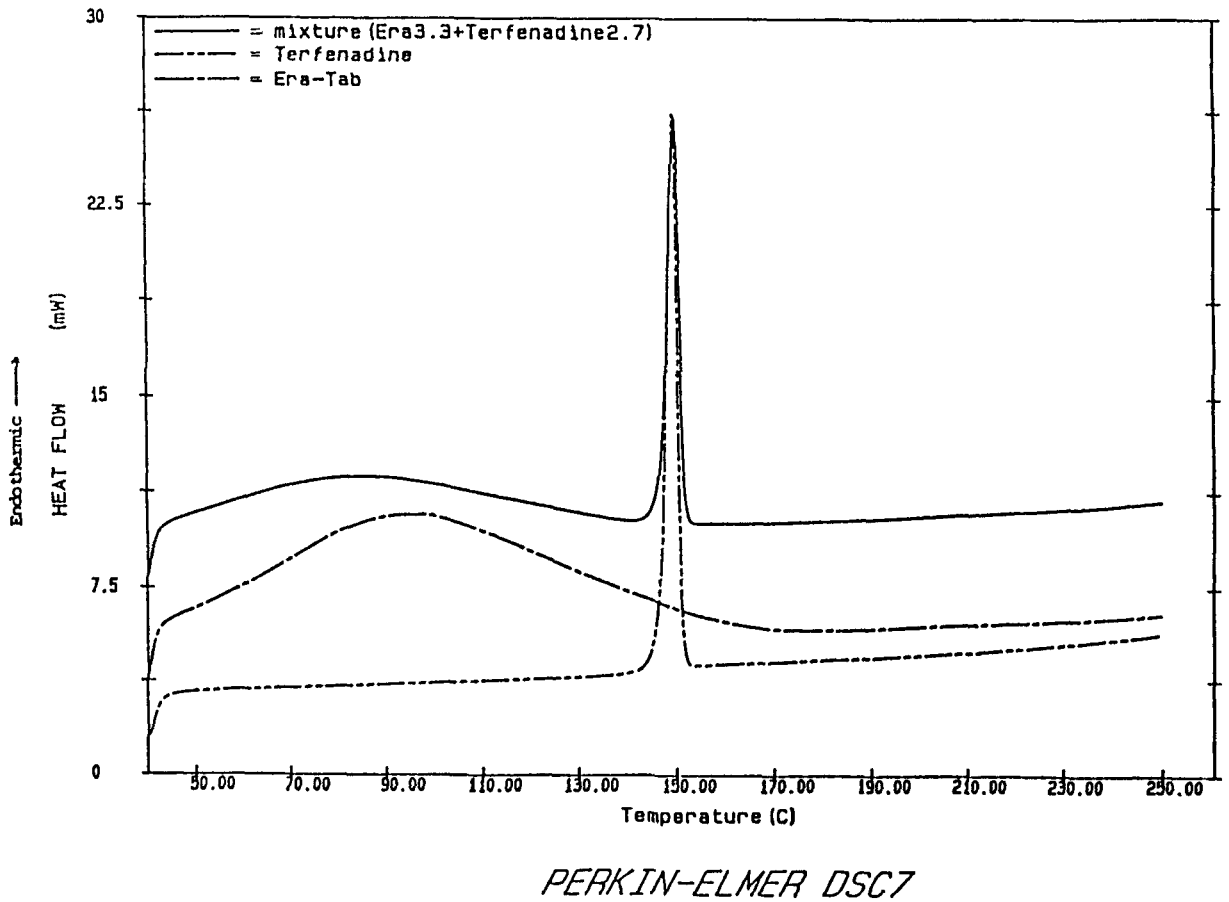

Figure 1. DSC thermograms of Era-Tab, terfenadine, and Era-Tab + terfenadine mixture.

Table 3

The Physical Characteristics and Constants of the Excipients Derived from the Heckel Plots

Excipients	Slope (K)	Intercept (A)	Correlation Coefficient (r)	Yield Pressure P_y (kg/cm^2)	D_0	D_a	D_b
Era-Tab	0.017	0.75	0.98	58.8	0.35	0.53	0.12
Emcompress	0.005	1.13	0.99	200.0	0.37	0.68	0.31
Avicel PH-101	0.017	0.94	0.97	58.5	0.21	0.61	0.40
Super-Tab Lactose	0.006	1.13	0.98	178.6	0.39	0.53	0.14
PPS	0.013	0.87	0.96	75.2	0.41	0.58	0.17

terfenadine in formulations. The DSC results also indicate that there is no apparent interaction between terfenadine and the other 4 excipients (The DSC thermograms are not shown).

Tablet Characteristics of the 5 Excipients

The relationship between applied pressure and the density of the powder columns was analyzed using the Heckel plots (12–14). Using the initial linear portion of the Heckel plots, the physical characteristics and material constants of the excipients were computed and are shown in Table 3; while D_0, D_b, and D_a are the densification at zero pressure, the densification due to particle movement and rearrangement, and the densification before interparticle bonding becomes appreciable, respectively.

In general, it is obvious that the variation in D_0, D_b, and D_a is primarily a function of particle shape. Avicel PH-101, which is irregular in shape, gives a higher value for D_b; whereas Era-Tab, which is more spherical, gives the lowest D_b value. The yield pressure (P_y) values for Era-Tab and Avicel PH-101 were lower than those of Emcompress and Super-Tab Lactose, as shown in Table 3. From the results shown, Era-Tab was the most ductile material, more plastic and easily compressible even at low compression pressures.

In Fig. 2, Avicel PH-101 and Era-Tab reveal the highest tensile strength among the excipients under the same compression pressure at pressures less than 200 kg/cm^2. The friability of placebo tablets prepared from these excipients decreases with increasing pressure (Fig. 3), and it can be seen that the friability of Era-Tab tablets is relatively low over the range of pressure studied.

The bioavailability of an immediate-release orally administered tablet is most likely to be controlled by its

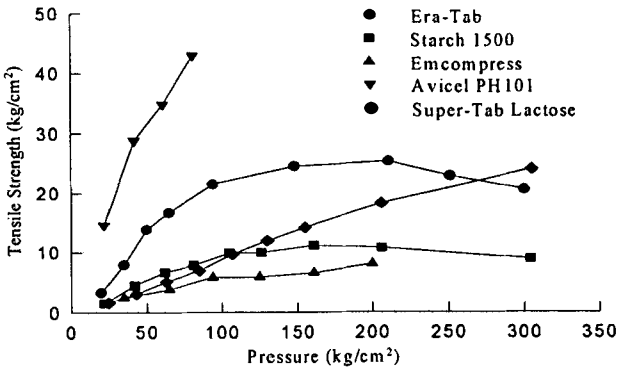

Figure 2. Tensile strength as a function of compression pressure.

rates of disintegration and dissolution. The disintegration times of the terfenadine tablets are less than 3 min (Table 1), indicating that tablets made with various excipients exhibit good disintegration property. The experimental results on the release of terfenadine from the

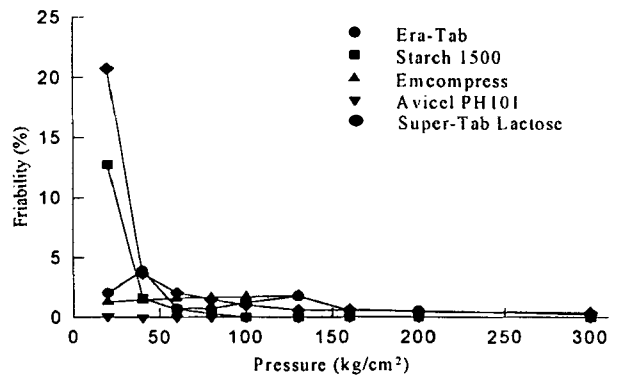

Figure 3. Friability as a function of compression pressure.

tablets were interpreted using the Weibull equation (15), and the calculated parameters are listed in Table 1 as well. From these results, the Era-Tab tablets manifested a satisfactory dissolution rate.

CONCLUSIONS

The modified rice starch, Era-Tab, exhibited good flowability and made harder and less friable tablets than Super-Tab Lactose, PPS, and Emcompress, except Avicel PH-101. It was also shown that tablets with Era-Tab as an excipient exhibited good disintegration and dissolution properties. It is believed that Era-Tab will be a possible alternative choice for direct compression excipient in tablet formulation.

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