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Research Article

The Influence of the API Properties on the ODTs Manufacturing from Co-processed Excipient Systems

Anna Krupa,[1,3] Renata Jachowicz,[1] Zbigniew Pędzich,[2] and Krystyna Wodnicka[2]

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Abstract. Directly compressible co-processed excipient systems facilitate orodispersible tablets (ODTs) manufacturing. Despite several excipient systems available, it is reported that the incorporation of high drug dose into the tablet mass may negatively affect both disintegration and mechanical properties. Therefore the influence of drug properties on the quality of orodispersible tablets was investigated. Fast dissolving tablet matrix was made of a co-processed excipient system F-Melt. Two grades of F-Melt that differed in composition, particle shape, and specific surface area were used to form tablet matrix. Ibuprofen, diclofenac sodium, and diltiazem hydrochloride were chosen as model drugs of different physicochemical properties such as solubility, particle size, and shape. Ninety formulations containing 12.5, 25, or 50 wt% of the model drug and F-Melt type C or M were prepared by direct compression. The quality of tablets was examined on the base of disintegration time, wetting time, mechanical resistance and texture analysis. The results showed that F-Melt grade, drug solubility, and its dose had an influence on the quality of tablets. From ninety formulations prepared, only four batches containing F-Melt type C and 12.5 wt% of ibuprofen, diclofenac sodium, or diltiazem hydrochloride could be classified as ODTs. Their disintegration time ranged from 41 to 144 s. In the case of F-Melt type M, tablets disintegrating within 101 s of friability below 1% could be prepared only if 12.5 wt% of diclofenac sodium was incorporated into the tablet mass.

KEY WORDS: diclofenac sodium; diltiazem hydrochloride; direct compression; F-Melt; ibuprofen; ODTs.

INTRODUCTION

Orodispersible tablets (ODTs) are convenient solution for patients with difficulties in swallowing solid dosage forms. This disorder concerns in particular pediatric, geriatric, bedridden, travelling patients, as well as patients undergoing chemotherapy, or antipsychotic treatment (1,2). According to the pharmacopoeial definition, orodispersible tablets consist of uncoated tablets destined to be placed in the mouth where they disintegrate rapidly in the saliva. The *in vitro* disintegration time should not be longer than 3 min. This kind of tablets can be taken without any liquid.

Several methods, such as freeze-drying, moulding, and direct compression have been proposed to prepare orodispersible tablets (3–5). Co-processed excipient systems have been developed with the aim to facilitate ODTs manufacturing (6,7). During co-processing, two or more known excipients are combined together in a technological process to form a material of new properties (8–10). The chemical structure of the components is not altered. Thus, there is no need for toxicological studies of the new material. An important advantage of co-processed excipient systems is a fixed and homogeneous distribution of the components in the mixture that prevents their segregation. Furthermore, the application of spray-drying process results in the formation of highly porous granules, which assures immediate disintegration of the tablet in the saliva (6).

Among co-processed excipient systems, F-Melt (Fuji Chemical Industry, Japan), Pharmaburst (SPI Polyols, USA), Ludiflash (BASF, Germany), Pearlitol Flash (Roquette, France), and Prosolv ODT (JRS, Germany) are destined to form ODTs by direct compression. In general, they are composed of polyols, disintegrants, and inorganic compounds. The drug is simply dry blended with the excipient and lubricant, then the tablet mass can be compressed directly.

A co-spray-dried excipient system F-Melt (Fuji Chemical Industry Ltd., Japan) is a proprietary formulation composed of microcrystalline cellulose, superdisintegrant, carbohydrates, and inorganic compounds. F-Melt is available in two grades such as Type C and Type M. They differ in the inorganic compound. Grade C contains anhydrous dibasic calcium phosphate, whereas grade M has porous magnesium aluminometasilicate in its composition.

[1] Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Jagiellonian University, Medical College, Cracow, Poland.
[2] Faculty of Materials Science and Ceramics, AGH—University of Science and Technology, Cracow, Poland.
[3] To whom correspondence should be addressed. (e-mail: akrupa@cm-uj.krakow.pl)

The data given by the manufacturer indicate that F-Melt type C is recommended for faster disintegration needs in both pharmaceutical and nutraceutical formulations, whereas Type M has better flow properties and it can be used for pharmaceutical formulations.

There is no report on the influence of the API on the quality of the tablets made of F-Melt to our best knowledge. Therefore, the aim of the present work was to evaluate the application of a new co-processed excipient system F-Melt to form orodispersible tablets by direct compression. To understand and control the manufacturing process according to Process Analytical Technology (PAT) recommendations, the properties of raw materials as well as process and formulation variables were analyzed.

Three active principle ingredients (APIs) of different solubility were chosen as models for this study. Ibuprofen represented the API practically insoluble in water, diclofenac sodium was used as a sparingly soluble compound and diltiazem hydrochloride was chosen as a freely soluble API. Their specific water solubility was 0.070, 1,110, and 486.4 mg/ml, respectively. The morphology, particle size, and specific surface area of the raw materials were also investigated. Tablets were prepared within a defined range of the compression force. Due to the fact that the manufacturing of orodispersible tablets with high drug dose is still a challenge, the study focused also on the application of F-Melt to form tablets with different drug doses. Therefore, tablets containing from 50 to 200 mg of the API were prepared. The influence of the API on the quality of the final tablets was evaluated taking into account the results from disintegration time measurements, mechanical resistance, and texture analysis.

MATERIALS AND METHODS

Materials

Ibuprofen was purchased from Shasun Chemicals & Drugs Ltd., India. Diclofenac sodium was kindly donated by Polpharma S.A., Poland. Diltiazem hydrochloride was obtained from Nicolas Piramal India Ltd., India.

Two grades of a co-processed excipient system F-Melt such as Type C and Type M obtained from Fuji Chemical Industry Ltd., Japan were used to form fast disintegrating tablet matrix in direct compression process. Stearate fumarate sodium (Pruv, JRS Pharma, Germany) was used as a lubricant in the present study.

Preparation of Tablets

The composition of the tablet mass was listed in Table I. API, F-Melt, and the lubricant were gently dry blended in mortar for 5 min. The mixture was compressed directly to form tablets of total weight 400 mg. Single-punch press Korsch-type EK0 with flat-faced punches 12.1 mm in diameter equipped in tensometers was used. The measurement of the compression force was carried out by Electronic Signal Acquisition Module Type 0508-S (Meßtechnik GmbH, Germany) with the software ESAM for Windows. The compression force (F) ranged from 10 to 30 kN.

To find out the interaction between the pure drug and F-Melt during the direct compression process, no taste masking was used.

Table I. Composition [%] of the Tablet Mass

		Amount in the formulation [%]		
			F-Melt	
			type C	type M
	Drug dose per tablet [mg]	Drug	+ 2% Pruv	
Placebo	0	0	100.0	0
	0	0	0	100.0
Ibuprofen	50	12.5	87.5	0
		12.5	0	87.5
	100	25.0	75.0	0
		25.0	0	75.0
	200	50.0	50.0	0
		50.0	0	50.0
Diclofenac sodium	50	12.5	87.5	0
		12.5	0	87.5
	100	25.0	75.0	0
		25.0	0	75.0
	200	50.0	50.0	0
		50.0	0	50.0
Diltiazem hydrochloride	50	12.5	87.5	0
		12.5	0	87.5
	100	25.0	75.0	0
		25.0	0	75.0
	200	50.0	50.0	0
		50.0	0	50.0

Methods

The properties of the raw materials were evaluated on the base of surface morphology analysis and specific surface area measurements. The quality of the final tablets was studied taking into account: surface morphology, specific surface area, mechanical resistance, texture, disintegration, and wetting time.

Surface Morphology

The surface of drug particles, F-Melt particles, and *placebo* tablets prepared at 10 kN was examined using scanning microscope Hitachi S-4700 (Japan). Powder particles or tablets were adhered to the sample holder by a double-sided copper tape. The tablet surface was coated with carbon using 208 HR carbon sputter coater (Cressington, USA). The pictures of tablets were taken at ×50, ×250, and ×400 magnification.

Specific Surface Area

Specific surface area (S_{BET}) measurements of F-Melt particles were made using the ASAP 2010 multi-station gas sorption surface area analyzer (Micromeritics, USA) using nitrogen as the adsorbate and applying the Brunauer–Emmett–Teller (BET) equation (Eq. 1), where V was the volume adsorbed, V_m was the volume of the monolayer, p was the sample pressure, p_0 saturation pressure and c a constant related to the enthalpy of adsorption.

$$\frac{p}{V(p_0 - p)} = \frac{1}{V_m c} + \frac{c-1}{V_m c}\frac{p}{p_0} \tag{1}$$

The BET surface area (S_{BET}) was then calculated from Eq. 2, where n_a was Avogadro's number, a_m was the cross-sectional area occupied by each adsorbate molecule and m_V was the gram-molecule volume. Surface area measurements were carried out in triplicate.

$$S_{BET} = \frac{V_m \cdot n_a \cdot a_m}{m_V} \tag{2}$$

Mechanical Properties

Hardness tester Vanderkamp Benchsaver Series type VK200 (VanKel, USA), was used to determine the crushing force (F) of the tablets. The mean crushing force (n=5) was expressed in kilopond (kp). Specific crushing strength (SCS) of tablets (n=5) was calculated on the base of crushing force (F), diameter (D), and height (h) according to the Eq. (3). Diameter and height were expressed in mm.

$$SCS = \frac{F}{D \cdot h} \tag{3}$$

Friability (n=10) was determined using tablet tester Erweka with 12 paddles because tablets wedged on the blade when the pharmacopoeial apparatus was used.

Texture Analysis

The texture of tablets obtained by applying the compression force of 10 kN was analyzed by the mercury porosimeter PoreMaster 60 (Quantachrome, USA). Prior to the measurement, the tablet was half cut, weighed, and desorbed under vacuum below 10 mbar. The contact angle (Θ) between mercury and the sample was 130° and the surface tension of the mercury (δ) was 0.486 N/m. The measurement range of the pore size was from 3.5 nm to 300 μm. The pore size (D) and the pore size distribution was calculated from the ratio of the volume of mercury entering the tablets at a particular pressure relative (p) to the total volume of mercury (Eq. 4).

$$D = -\frac{4 \cdot \delta}{p}\cos\theta \tag{4}$$

The true density of the samples was determined by helium picnometry (AccuPyc 1330, Micromeritics, USA).

Disintegration Time

In Vitro Disintegration Time

The test was carried out using the pharmacopoeial apparatus. The tests were performed at 37°C. Distilled water was used as a solvent. The mean disintegration time was calculated from six measurements.

In Vivo Disintegration Time

The study was performed on six healthy volunteers. Prior to the test, the volunteers were asked to rinse the mouth with a glass of water. The measurements were performed at least 1 h after a meal. One *placebo* tablet was placed on a tongue. The time of complete disintegration when there was no tablet core on a tongue was measured by stop-watch.

Wetting Time and Water Absorption Ratio

The measurements were carried out according to the method described by Bi *et al.* (3). The tablet was put on twice folded filter paper (12×10,75 cm) placed in the middle of a Petri dish (7 cm in diameter) containing 7 ml of 0.05% red dye aqueous solution. The time necessary to the complete wetting of the outer surface of the tablet was detected by stop-watch. The measurements (n=3) were performed at the room temperature. The water absorption ratio (R) was calculated on the base of the tablet weight before (W_b) and after wetting (W_a) as showed in Eq. 5. After weighing the tablet was half-cut to see if the tablet core was wetted. The value of the water absorption ratio (n=3) was expressed in percentage (Eq. 5).

$$R = \left[\frac{(W_b - W_a)}{W_a}\right] \cdot 100\% \tag{5}$$

RESULTS AND DISCUSSION

The analysis of technological process and formulation variables is essential to develop orodispersible tablets by direct compression. Despite many patented technologies,

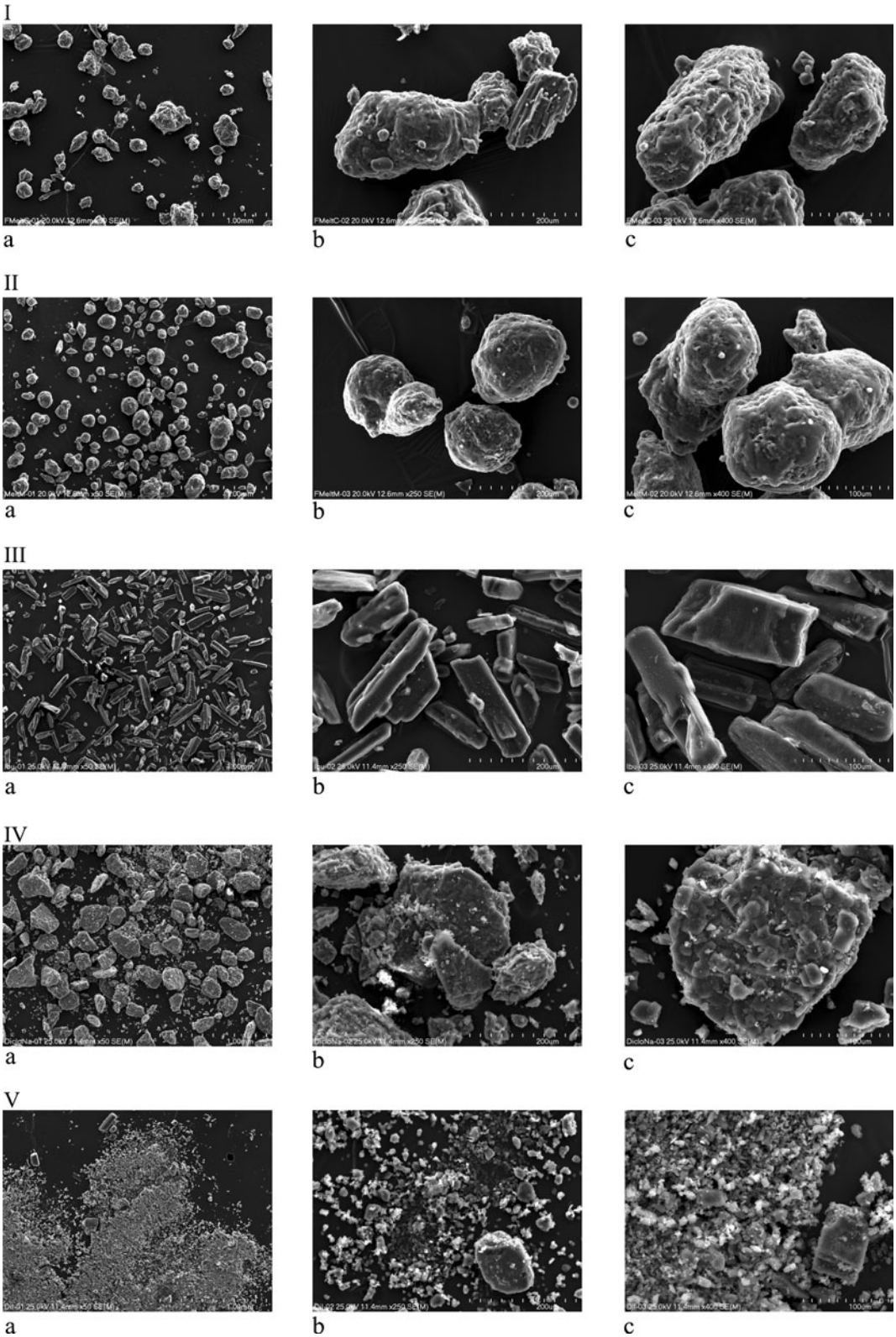

Fig. 1. SEM pictures of excipients and APIs: *I* F-Melt type C, *II* F-Melt type M, *III* ibuprofen, *IV* diclofenac sodium, *V* diltiazem hydrochloride. Magnification **a** x50, **b** x250, and **c** x400

the efforts are made to prepare tablets of opposite characteristics such as fast disintegration and sufficient mechanical resistance. During pre-formulation studies, it should be taken into account that to assure a fast disintegration, the tablet weight should preferably not exceed 500 mg (11).

Recent developments in directly compressible co-processed excipient systems facilitate ODTs manufacturing by

direct compression (1,7–9). Although Fu *et al.* (4), reported that during ODTs manufacturing, the incorporation of high drug dose into the tablet mass may negatively affect both disintegration and mechanical properties. It may be due to various interactions between the API and a composed excipient, which may occur in the solid state. Therefore the present study focused on the identification of critical factors that determine the quality of ODTs.

Influence of Powder Characteristics on Tablets Properties

Among powder characteristics particle size, surface morphology, specific surface area, or solubility may influence the quality of orodispersible tablets (4,10,12–14).

Morphological analysis of APIs and co-processed excipients was presented in Fig. 1. The APIs particles differed in size and shape. The mean particle size of ibuprofen was about 100 μm. The particles of diclofenac sodium and diltiazem hydrochloride were smaller: 60 or 30 μm, respectively. Ibuprofen particles were in the shape of needles. Both diclofenac sodium and diltiazem hydrochloride were plates in shape.

The analysis of F-Melt showed that co-processed excipients were porous agglomerates. Their particle size was about 100 μm. F-Melt type M granules were more spherical than F-Melt type C agglomerates. It may be due to the presence of spherical magnesium aluminometasilicate (Fig. 1). The value of the specific surface area depended also on the presence of the porous silicate. In the case of F-Melt type M, the value of the parameter was 3.3 m^2/g, and it was more than three times higher than F-Melt type C (0.9 m^2/g).

The results revealed that powder particle size, shape as well as specific surface area and solubility influenced ODTs properties. The preparation of ODTs was possible, if the drug content was 50 mg (Table II). Since the drug dose of 50 mg corresponded to 12.5 wt% of the drug incorporated into the tablet mass, the impact of the co-processed excipient on the quality of tablets cannot be neglected. The application of F-Melt type M of high specific surface area resulted in the decrease in the mechanical resistance. Despite porous texture, spherical silicate particles might not be plastic enough to form coherent compacts during compression. Therefore only one formulation containing F-Melt type M could be classified as ODTs. In such a case, the compression force was 15 kN and friability 0.9%. The increase in the compression force from 15 to 20 kN or 30 kN caused a decrease in friability to 0.4% but the disintegration time was up to 3 min (Fig. 2, Table II). It was found that the application of less spherical F-Melt type C containing anhydrous dibasic calcium phosphate as an inorganic component, could facilitate the ODTs manufacturing, especially if low compression forces are used *i.e.* 10 kN.

Effect of Technological Process on the Quality of *Placebo* Tablets

The microscopic analysis revealed that all tablets made of either F-Melt type C or F-Melt type M had uniform, smooth surface. To determine the effect of the compression force on the mechanical resistance, specific crushing strength and friability were examined (Tables III and IV). It was shown that *placebo* tablets had better mechanical properties than tablets containing API. Their friability ranged from 0.2% to 0.9%. It was also shown that F-Melt type C tablets were less friable than F-Melt type M tablets (Table IV).

Disintegration time of *placebo* tablets depended mainly on the compression force and the excipient grade. Tablets containing F-Melt type C disintegrated more rapidly than tablets with F-Melt type M (Fig. 2). The disintegration time of *placebo* tablets containing F-Melt type C prepared at 10 kN was 24 s, whereas tablets made of F-Melt type M disintegrated within 30 s (Table V). Dobetti (12) reported that the incorporation of insoluble inorganic salts such as dibasic calcium phosphate and superdisintegrants into the tablet mass may not only shorten the disintegration time, but it also improved their mechanical resistance. This may explain why tablets made of F-Melt type C containing insoluble inorganic salt had shorter disintegration time and better mechanical resistance as compared to tablets made of F-Melt type M.

These findings were confirmed by *in vivo* studies and wetting time measurements. After placing into the mouth, tablets composed of F-Melt type C disintegrated in 39 s. The mean disintegration time of tablets containing F-Melt type M was 1 min 16 s. Their wetting time ranged from 1 to 2 min 3 s depending on the F-Melt grade. Tablets prepared of F-Melt type C had also shorter wetting time as compared to tablets made of F-Melt type M. Despite the water absorbing ability was about 83–84% regardless F-Melt grade (Table V).

Taking into account the results of both disintegration time and friability, it was found that only four of ten formulations *placebo* met pharmacopoeial requirements (Table II). The best tablets were prepared using the compression force of 10 or 15 kN. While using higher compression force, the disintegration time was over 3 min.

Influence of Drug and its Dose on Disintegration and Wetting Time

The relationship between drug solubility, drug dose and disintegration time was found. In case of the APIs soluble in

Table II. Optimal Process and Formulation Parameters to Form Orodispersible Tablets with F-Melt

F-Melt grade	Drug	Drug dose [mg]	Compression force [kN]	Disintegration time [min s]	Friability [%]
C	*placebo*		10–15	0'24"–0'39"	0.4–0.7
	Ibu	50	10	2'03"	0.8
	Diclo	50	10–15	1'18"; 2'24"	0.5–0.9
	Dil	50	15	0'41"	0.9
M	*placebo*		10–15	0'30"–0'34"	0.7–0.9
	Diclo	50	15	1'41"	0.9

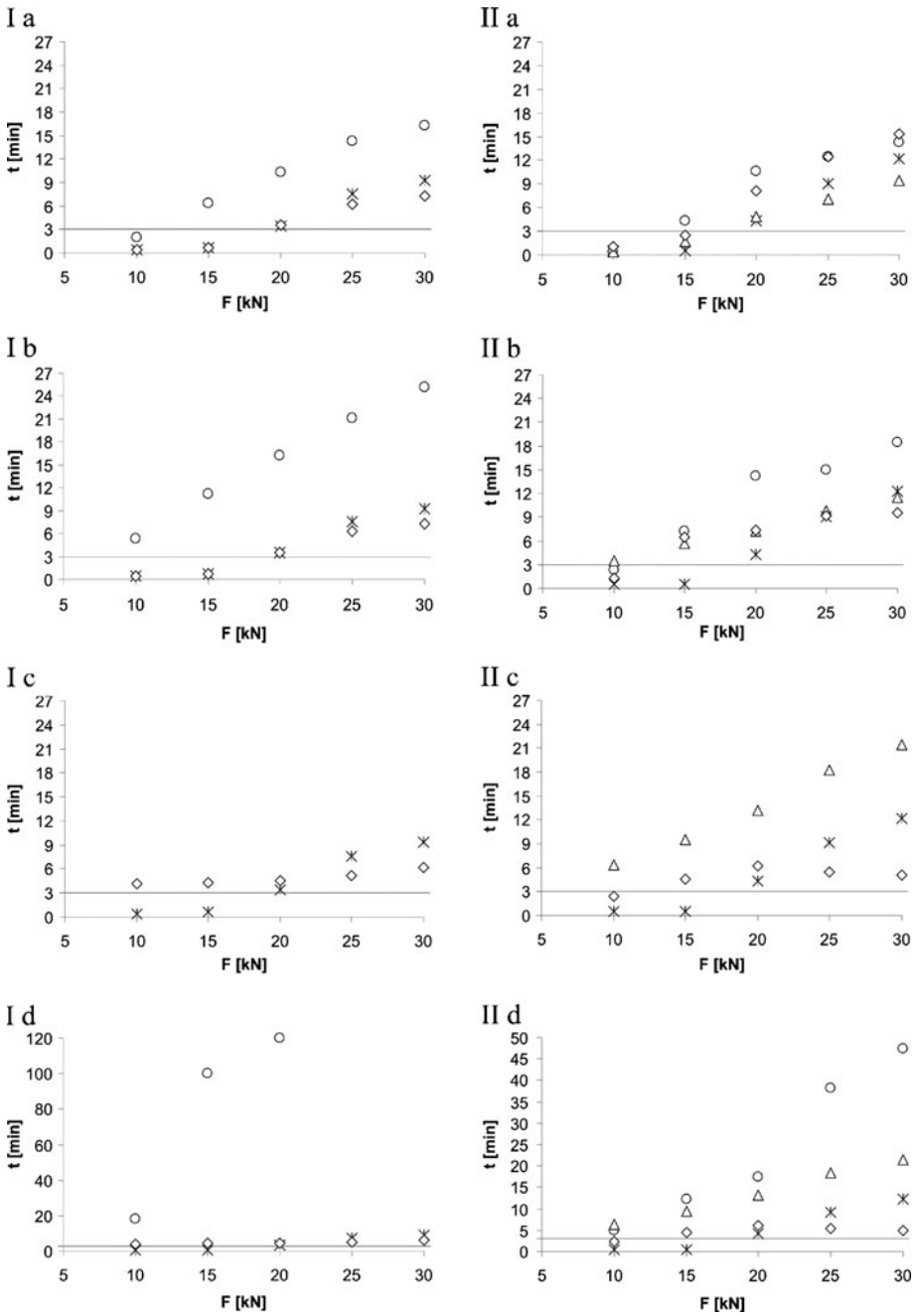

Fig. 2. Disintegration time (t) of tablets containing F-Melt type C (*I*), or F-Melt type M (*II*) in function of the compression force (F). *Placebo* tablets (*asterisk*), tablets with ibuprofen (*circle*), diclofenac sodium (*triangle*), and diltiazem hydrochloride (*diamond*). Drug dose per tablet **a** 50, **b** 100, and **c**, **d** 200 mg

water such as diclofenac sodium and diltiazem hydrochloride, used in the dose of 50 mg per tablet, ODTs could be formed regardless F-Melt grade. The disintegration time of tablets containing insoluble ibuprofen was longer (Fig. 2).

Generally the disintegration time of tablets composed F-Melt type C was shorter than the disintegration time of F-Melt type M tablets.

The disintegration time of tablets containing 50 mg of soluble drugs and F-Melt type C ranged from 25 s to 2 min 3 s. Similar results were obtained for tablets with 100 mg of diltiazem hydrochloride. When 100 mg of ibuprofen or diclofenac sodium was incorporated into the tablet mass, the disintegration time was longer and it ranged from 4 to 25 min 39 s (Fig. 2).

It was surprising that the disintegration time of tablets containing F-Melt type C and ibuprofen in 1:1 ratio, which corresponded to 200 mg of the API per tablet, could be over 120 min. The disintegration time of similar tablets with F-Melt type M was about 15 min (Fig. 2). This phenomenon might be due to a chemical interaction between calcium ions coming from F-Melt type C and carboxylic group of uncoated ibuprofen particles since there is no calcium ions in grade M. Due to

Table III. Specific Crushing Strength (SCS) of Tablets with F-Melt

			SCS [kp/mm^2]				
			Compression force [kN]				
F-Melt type	Drug	Drug dose [mg]	10	15	20	25	30
C	*Placebo*	0	0.12	0.20	0.28	0.35	0.40
	Ibu	50	0.11	0.20	0.26	0.29	0.32
		100	0.08	0.16	0.20	0.24	0.27
		200	0.09	0.15	0.18	–	–
	Diclo	50	0.10	0.20	0.27	0.33	0.38
		100	0.09	0.15	0.22	0.29	0.35
		200	0.08	0.13	0.18	0.24	0.32
	Dil	50	0.06	0.14	0.24	0.30	0.35
		100	0.06	0.14	0.24	0.29	0.37
		200	0.06	0.14	0.24	0.30	0.35
M	*Placebo*	0	0.12	0.16	0.24	0.30	0.38
	Ibu	50	0.06	0.13	0.23	0.24	0.29
		100	0.09	0.16	0.22	0.25	0.27
		200	0.09	0.14	0.17	0.20	0.21
	Diclo	50	0.06	0.13	0.21	0.27	0.37
		100	0.07	0.13	0.22	0.29	0.34
		200	0.09	0.15	0.24	0.28	0.30
	Dil	50	0.05	0.11	0.18	0.24	0.32
		100	0.09	0.16	0.23	0.32	0.38
		200	0.06	0.13	0.20	0.24	0.29

the fact that F-Melt represents co-processed excipient system, the interaction may be more complex and its understanding needs further studies.

The analysis of tablets composed of F-Melt type M and diltiazem hydrochloride revealed that the disintegration time was below 3 min regardless the drug dose (Fig. 2). Tablets disintegrating within 2 min 27 s could also be obtained with 100 mg of ibuprofen but the compression force should be about 10 kN. Twofold increase in ibuprofen dose caused the prolongation of disintegration time to 5 min 6 s. When the compression force was over 10 kN, the disintegration time was even more than three times longer.

The results showed that the drug dose and the drug solubility influenced also the water absorption ratio as well as wetting time. In general, the higher the drug dose, the lower the water uptake. Tablets containing 50 mg of the drug had almost twice higher water absorption ratio than tablets with 200 mg of the API (Table V). If soluble drug was combined with F-Melt type M, the water absorption ratio was higher than after incorporation of the drug into F-Met type C matrix. Depending on the F-Melt grade, the value of the parameter ranged from 46% to 81% for grade M or from 37% to 68% for grade C. In contrast, tablets containing insoluble ibuprofen and F-Melt type C had higher values of the parameter as compared to F-Melt type M. The water absorption ratio was from 37% to 72% or from 32% to 70% for F-Melt type C and M, respectively (Table V).

Similar findings were reported by Fukami *et al.* (5,13) and Kuno *et al.* (14). They found that the incorporation of polar amino acids or hydrophilic lubricant such as sodium stearyl fumarate into the tablet mass can shorten the wetting time. Tablets with hydrophobic ethenzamide and hydrophilic glycine disintegrated in mouth within 30 s, which was twice shorter as compared to tablets without the amino acid.

Due to the high value of specific surface area, F-Melt type M might be able to absorb the aqueous solution of diltiazem hydrochloride into its smallest pores. In the case of insoluble ibuprofen, the solvent penetration into these pores can be more difficult since pores may be partially filled with the drug. Therefore after the incorporation of the soluble drug into F-Melt type M, the higher solvent or API solution uptake was stated than in case of the insoluble drug.

Moreover tablets containing diltiazem hydrochloride and F-Melt type C had shorter wetting time than tablets, which matrix was made of F-Melt type M. Their wetting time ranged from 4 to 6 min 25 s or from 5 min 30 s to 9 min 37 s, respectively.

Influence of Drug and Its Dose on Mechanical Resistance

The analysis of the tablets containing F-Melt type C and 50 mg of ibuprofen, diclofenac sodium, or diltiazem hydrochloride revealed that only 4 formulations of 15 had friability and disintegration time within the pharmacopoeial range.

The mechanical resistance of F-Melt type M tablets was lower than F-Melt type C tablets. The same relationship had previously been described for *placebo* tablets. Consequently, only one orodispersible formulation could be obtained in the case of F-Melt type M. It contained 50 mg of diclofenac sodium (Table II). The compression force higher than 25 kN could be necessary to prepare tablets of friability below 1% using F-Melt type M

Table IV. Friability [%] of Tablets Containing F-Melt

			Friability [%]				
			Compression force [kN]				
F-Melt type	Drug	Drug dose [mg]	10	15	20	25	30
C	*Placebo*	0	0.7	0.4	0.2	0.2	0.2
	Ibu	50	0.8	0.4	0.4	0.4	0.3
		100	1.7	0.9	0.7	0.5	0.5
		200	1.5	1.0	0.7	–	–
	Diclo	50	0.9	0.5	0.4	0.3	0.3
		100	2.0	1.1	0.8	0.5	0.3
		200	2.0	1.3	0.7	0.6	0.2
	Dil	50	1.6	0.9	0.5	0.3	0.3
		100	2.5	0.9	0.6	0.5	0.4
		200	2.1	1.0	0.8	0.6	0.5
M	*Placebo*	0	0.9	0.7	0.6	0.4	0.2
	Ibu	50	2.4	1.3	0.7	0.6	0.4
		100	1.6	0.9	0.7	0.6	0.5
		200	1.9	1.0	1.0	0.9	0.8
	Diclo	50	1.9	0.9	0.6	0.4	0.4
		100	2.3	1.1	0.8	0.5	0.5
		200	1.7	1.2	0.8	0.3	0.3
	Dil	50	3.2	1.3	0.9	0.7	0.4
		100	2.0	1.0	0.7	0.5	0.5
		200	3.1	1.5	1.1	0.9	0.6

Table V. Disintegration Time [min], Wetting Time [min], and Water Absorption Ratio [%] of Tablets Prepared Using the Compression Force 10 kN

F-Melt type	Drug	Drug dose [mg]	Disintegration time Ph. Eur. [min]	Wetting time [min]	Water absorption ratio [%]
C	*Placebo*	0	0'24±0'05	1'00	84
	Ibu	50	2'03±0'05	2'50	72
		100	5'49±0'03	5'47	60
		200	18'07±0'08	25'00	37
	Dil	50	0'25±0'03	4'00	68
		100	2'55±0'07	5'17	55
		200	4'15±0'15	6'25	37
M	*placebo*	0	0'30±0'03	2'03	83
	Ibu	50	0'27±0'07	2'30	70
		100	2'27±0'10	5'02	53
		200	5'06±0'20	10'11	32
	Dil	50	1'00±0'10	5'30	81
		100	1'34±0'04	7'00	77
		200	2'44±0'25	9'37	46

(Tables II, III and IV). However, their disintegration time was longer than 3 min (Fig. 2).

The study also showed that because of low mechanical resistance and long disintegration time, the preparation of orodispersible tablets with the model APIs in the drug doses over 100 mg was impossible (Fig. 2, Tables II, III, IV, and V). The higher the amount of the API was incorporated into the tablet mass, the lower the mechanical resistance was noticed (Tables III and IV).

Data listed in Table IV indicate that all the tablets with F-Melt type C and 50 mg of ibuprofen, prepared using the compression force from 10 to 30 kN, had the friability below 1%. Similar findings were reported for tablets containing 50 mg of diclofenac sodium and 50 or 100 mg of diltiazem hydrochloride. These tablets were prepared using the compression force of 10 or 15 kN. To obtain tablets of friability below 1% containing 100 or 200 mg of ibuprofen, the compression force should not exceed 15 or 20 kN (Table IV). It was also revealed that even higher compression force than 20 kN should be applied in the case of tablets with diclofenac sodium or diltiazem hydrochloride.

These findings were confirmed by values of specific crushing strength (SCS) listed in Table III. The specific crushing strength of tablets prepared using the compression force ≥15 kN was higher than 0,1 kp/mm^2. The application of F-Melt type C resulted in higher values of this parameter as compared to tablets made of F-Melt type M.

Similarly to the results of friability, the specific crushing strength depended also on the drug dose. The highest values of the SCS were characteristic to tablets containing 50 mg of ibuprofen or diclofenac sodium. SCS ranged from 0.11 to 0.32 kp/mm^2 or from 0.10 to 0.38 kp/mm^2, respectively (Table III).

The increase in the drug dose caused a decrease in SCS value, except for tablets with F-Melt type C and diltiazem hydrochloride. In such a case, the value of the parameter was constant regardless the drug dose and it depended only on the compression force. Different relationship was found for tablets made of F-Melt type M and diltiazem hydrochloride. The highest values of SCS were noticed for tablets containing 100 mg of the drug. The analysis of the tablets with ibuprofen and diclofenac sodium showed diversity of the parameter, which ranged from 0.06 to 0.37 kp/mm^2 (Table III).

Effect of Tablet Texture on Disintegration Time

The porosimetry of mercury was used to evaluate the relationship between the pore size distribution and disintegration time (Fig. 3, Table VI).

It was found that the total porosity of *placebo* tablets was about 23% regardless the F-Melt grade. However the total pore volume depended on the F-Melt type. *Placebo* tablets composed of F-Melt type M had higher pore volume than tablets made of F-Melt type C. The total pore volume was 364 mm^3/g or 317 mm^3/g. It might be due to the presence of magnesium aluminometasilicate particles and it can also be correlated with the high value of the specific surface area.

Pore size distribution was shown in Fig. 3. There were two kinds of pores in all tablets examined, indicating a bimodal pore size distribution. The size of big pores ranged from 0.5 to 5 μm. There was also small amount of pores below 0.01 μm.

The incorporation of the drug into the tablet mass had an influence on the tablet texture. Twofold increase in the dose of diltiazem hydrochloride or diclofenac sodium caused an increase in the total porosity as well as in the total pore volume. Different relationship was found in the case of ibuprofen, especially if tablet matrix was formed using F-Melt type M. The increase in ibuprofen dose from 100 to 200 mg caused not only decrease in porosity from 27% to 22% but also the reduction of the pore volume from 318 to 196 mm^3/g. This phenomenon might be due to low melting point of ibuprofen (74°C) and needle shape of its particles. When ibuprofen consisted 50 wt% of the tablet mass, the energy generated during the compression process could cause its melting. Then the drug in liquid form might fill the smallest pores in the porous matrix, which resulted in the decrease in pore volume and porosity but it also might increase the median pore size from 0.85 to 1.10 μm. In contrast to ibuprofen, particles of diltiazem hydrochloride and diclofenac sodium were in the shape of plates, which particle size ranged from 30 to 60 μm. Their melting point was 212°C and 284°C, respectively. During compression, only the finest

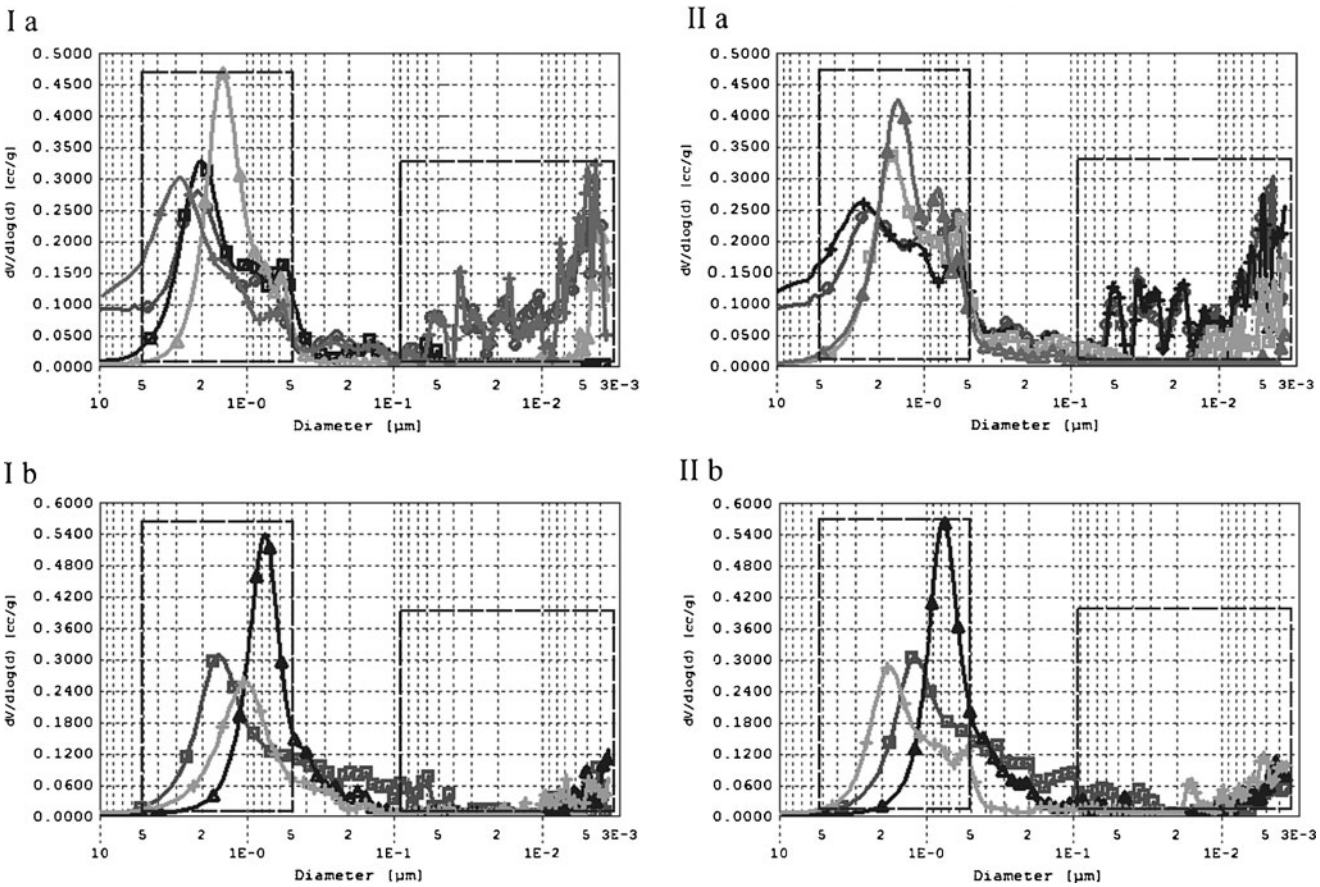

Fig. 3. Pore size [µm] distribution obtained by mercury porosimetry for tablets (10 kN) with F-Melt type C (*I*), or F-Melt type M (*II*) containing **a** 100 and **b** 200 mg of: ibuprofen (*plus sign*), diclofenac sodium (*square*), diltiazem hydrochloride (*triangle*), and *placebo* tablets (*circle*)

drug particles were able to fill the pores in the tablet matrix. This may explain the increase in the porosity and total pore volume.

Despite the porosity of tablets with F-Melt type C and 100 or 200 mg of ibuprofen, or 100 mg of diclofenac sodium was similar to *placebo* tablets, their disintegration time was different. The results of the present study showed that it might be correlated with physical chemical properties of the API such as solubility rather than tablet porosity.

Tablets containing diclofenac sodium or diltiazem hydrochloride and F-Melt type M had longer disintegration time than *placebo*, but their porosity was higher (Figs. 2 and 3, Table VI). Since the model drugs were soluble in water, saturated solution could be formed on the tablet surface. This phenomenon may be due to the prolongation of the disintegration time.

The study of pore size distribution profiles showed also that the amount of the pores, which diameter was below 0.1 µm diminished with increasing the drug dose (Fig. 3). This may explain why the disintegration time of tablets containing 200 mg of drug was the longest (Fig. 2 and 3, Table VI). The lack of the small pores on the tablet surface may inhibit the penetration of water into the tablet matrix.

Table VI. Influence of Ibuprofen (Ibu), Diclofenac Sodium (Diclo), and Diltiazem Hydrochloride (Dil) on the Texture of Tablets with F-Melt (10 kN) Analyzed by Porosimetry of Mercury

	F-Melt type C				F-Melt type M			
	Placebo	Ibu	Diclo	Dil	*Placebo*	Ibu	Diclo	Dil
Drug dose [mg]	0	100	100	100	0	100	100	100
Total pore volume [mm^3/g]	317	314	201	214	364	318	243	220
Porosity [%]	23	23	23	21	22	27	25	25
Median pore size [µm]	0.65	0.76	1.56	1.23	0.64	0.85	0.98	1.29
Drug dose [mg]	0	200	200	200	0	200	200	200
Total pore volume [mm^3/g]	dill/317	160	231	211	364	196	246	231
Porosity [%]	23	22	31	26	22	22	30	27
Median pore size [µm]	0.65	0.93	0.96	0.71	0.64	1.10	0.65	0.68

CONCLUSIONS

The results obtained in the present study showed that a co-processed excipient system F-Melt was suitable to form fast-disintegrating tablets by direct compression method, although the proper choice of F-Melt grade may be essential to form orodispersible tablets. Physical chemical properties of the drug and its dose should be taken into consideration to obtain tablets disintegrating within 3 min of friability below 1%.

The analysis of 10 formulations *placebo* and 90 formulations of tablets containing the model drugs of different solubility in 3 different doses revealed that the possibility of orodispersible tablets manufacturing was also determined by the compression force used during the direct compression process. To obtain *placebo* tablets disintegrating within 34 or 39 s of friability below 1%, the compression force ranging from 10 to 15 kN should be used. Tablets containing F-Melt type C had shorter disintegration time and better mechanical resistance than tablets composed of F-Melt type M.

The incorporation of the API into the tablet mass influenced the tablets' properties. The results revealed that the drug dose and drug solubility had an influence on mechanical resistance and disintegration time. Tablets disintegrating within 3 min of friability below 1% were prepared using F-Melt as a matrix forming agent and the API soluble in water, which was used in the lowest drug dose such as 50 mg. It corresponded to 12.5% of the API per tablet. The increase in the drug dose caused a decrease in mechanical resistance as well as a prolongation of the disintegration time. Therefore only 5 formulations of 90 analyzed could be classified as ODTs (Table II).

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