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RESEARCH PAPER

Functionalized Calcium Carbonate as a Novel Pharmaceutical Excipient for the Preparation of Orally Dispersible Tablets

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ABSTRACT

Purpose To overcome the limitation of insufficient hardness during the production of rapidly disintegrating orally dispersible tablets (ODTs). Furthermore, we investigated the properties and usefulness of functionalized calcium carbonate (FCC) as a new pharmaceutical excipient for the production of ODTs.

Methods A highly sensitive tensiometer-based method was developed to measure kinetics of weight loss during tablet disintegration. With this method we were able to determine the residence time of tablets placed on a basket immersed into a test medium. The shapes of tensiometer plots allowed us to categorize substances into four different types of disintegration.

Results At the same volume and hardness, the tablet formulations with FCC showed a significantly higher porosity (over 60%) than all other formulations. Residence time depended mainly on the tablet composition rather than on porosity. When combined with disintegrants, FCC formulations exhibited favorable disintegration properties, comparable to those of the marketed drug risperidone oro (disintegration time ca. 10 s).

Conclusions Oral dosage forms - based on the new pharmaceutical excipient FCC - can be designed to have a short disintegration time combined with good mechanical strength. Due to these properties, FCC can be used for the preparation of ODTs.

KEY WORDS disintegration · ODT · porosity · residence time · tensiometer

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INTRODUCTION

Orally dispersible/disintegrating tablets (ODTs) constitute a solid, single-unit dosage form which instantaneously disperses/dissolves in the saliva (1). ODTs can be prepared by different techniques, such as freeze drying (2,3), moulding (4), spray drying (5), and mass extrusion (6). Depending on the technique, the final form dissolves very rapidly (5–15 s), but may be associated with low mechanical strength, high production costs, low drug content, or limited stability (7). The easiest technique to prepare ODTs is by direct compression. With conventional equipment, a limited number of process steps, and commonly available excipients, ODTs containing large amount of active ingredients can be produced at low costs. However, disintegration capacity of ODTs produced by this technique is limited by the size and hardness of the tablets (8,9). Increased compression force applied during tableting leads to harder tablets thus increasing disintegration time (10). Consequently, ODTs with optimal disintegration properties are often small and/or have a low hardness and higher friability (8).

In accordance with the European Pharmacopeia, ODTs should disintegrate within 3 min when tested with the conventional disintegration apparatus (11). The American Food and Drug Administration (FDA) requires an *in-vitro* disintegration time of approximately 30 s or less (12,13). The disadvantage of the conventional disintegration apparatus is poor discrimination among rapidly disintegrating tablets (14). Furthermore, the volume of the test medium (900 ml) is relatively large, compared with the volume of saliva in the mouth cavity (less than 6 ml) (15). Several techniques have been proposed to measure the disintegration time of ODTs (14,16–23). For example, one research group used the force measurement detection to analyze the forces developed during the disintegration process due to water absorption (24). In our current work, we adapted the standard liquid

absorption measurement by means of a tensiometer (25) to accurately determine tablet disintegration time and mimic disintegration in the patient's mouth cavity. This method employs the microbalance of the tensiometer to detect kinetics of weight loss during tablet disintegration. In addition, the proposed method provides quantitative information on dispersion kinetics, i.e., speed; ability to readily disperse in small volumes of liquid (e.g., teaspoon); and to detect formation of big swollen lumps.

Disintegration time of an ODT depends on the porosity of the tablet. The rate of water uptake increases with higher porosity of the ODT. Thus, disintegration rate increases because of faster wetting of the tablet (26). On the other hand, higher porosity of the ODT affects the hardness of the resulting tablets hence compromising further processing of formulations. Consequently, an ideal ODT combines two controversial properties, i.e., higher porosity and higher hardness. An excipient with combined functionality (highly porous and providing strong grip between particles) has been identified in paper industry.

Ridgway *et al.* modified a natural ground calcium carbonate to enhance porosity up to 60% (*v*/*v*) and enlarge the surface area. This functionalized calcium carbonate (FCC) absorbs water at a faster rate and is able to absorb 10 times more fluid than conventional calcium carbonate (27).

The manufacturing process of FCC shows some similarities to the production of precipitated calcium carbonate, an established pharmaceutical excipient. Both substances are produced by decomposition, once in aqueous solution (precipitated calcium carbonate) and once under acidic conditions (FCC). The different conditions and different concentrations lead to different shapes and different particle size distributions of the particles (28,29).

The aim of the current work was to investigate the properties and usefulness of FCC as a new pharmaceutical excipient in the production of ODTs. Performance of FCC was compared to that of other commonly used excipients such as microcrystalline cellulose (MCC 102 and MCC burst), and FlowLac (fillers) and AcDiSol, VivaStar, and Kollidon CL as disintegrants.

MATERIALS AND METHODS

Materials

FCC (VP-220976 S02, Omya, Switzerland), directly compressible calcium carbonate (Barcroft™ CS90, SPI Pharma, Germany), calcium carbonate (PharMagnesia CC Type Natur 120, Lehmann & Voss & Co., Germany), microcrystalline cellulose (MCC SANAQ® 102, Pharmatrans Sanaq AG, Switzerland), and lactose monohydrate (FlowLac® 100, Meggle, Germany) were used as fillers. As disintegrating agents, modified cellulose gum (Ac-Di-Sol®, FMC, USA), insoluble, cross-linked polyvinylpyrrolidone (Kollidon® CL, BASF, Germany) and sodium starch glycolate (Vivastar®, JRS, Germany) were selected. A special kind of microcrystalline cellulose (MCC SANAQ® burst, Pharmatrans Sanaq AG, Switzerland) was used both as filler and disintegrant. The market ODT formulation, Risperidone-Mepha® 0.5 oro tablets, was used as a reference of a market.

Isopropyl myristate (Hänseler AG, Switzerland) was chosen as a dispersant for particle size distribution measurements.

Methods

Characterization of FCC

The true density of FCC was determined by helium pycnometry (Micromeritics AccuPyc 1,330, USA).

Scanning electron microscopy (SEM) images were obtained using the FEI/Philips XL30 FEG apparatus (Philips, Netherlands). Before measurements, the samples were sputtered with a 40 nm gold layer by a sputter coating machine (MED 020, BalTec, Liechtenstein).

Pore size distribution of FCC was determined with a mercury porosimeter (AutoPore IV 9,500, Micromeritics Instrument, USA). Low-pressure mercury intrusion ranged from 3.59 kPa to 206.64 kPa. During high-pressure mercury intrusion, the pressure ranged from 206.64 kPa to 206.78 MPa. For both high- and low-pressure intrusion, equilibration time was 10 s.

To measure the specific surface area, Nova 2000e (Quantachrome Instruments, USA) was used with the five-point BET (Brunauer, Emmett, Teller) method. After degassing the samples for 12 h at room temperature, the samples were measured with nitrogen at constant temperature (77.4 K). The measurement was performed in duplicate.

Particle size distribution was determined with the Mastersizer X long bed (Malvern Instruments, UK). For MCC 102, MCC burst, FlowLac, Barcroft, AcDiSol and VivaStar, the dry powder feeder (Malvern) was used. These measurements were performed in triplicate. Kollidon and FCC were dispersed in isopropyl myristate and then analyzed (in duplicate) by using the small volume sample presentation unit (Malvern). The medians of the particle diameter and their standard deviations are shown.

Tablet Preparation

All powders and formulations were mixed by using a tumbling mixer (Turbula T2C, Switzerland) for 10 min at 32 rpm. The tablets were compressed by a single punch press (Korsch EK0, Berlin) with 11 mm round flat tooling. The punch gap was adjusted to compact 500 mg of FCC powder into a tablet with a hardness of 100 N. The resulting tablet had a height of

5.30 mm. This setting for the punch gap was kept constant for all other mixtures. The target hardness of 100 N was obtained by changing the mass of the compacts. The powder was introduced manually into the die. After compacting, the tablets were stored in closed glass bottles in the room at 24±2°C and at 40±5% relative humidity (measured values) for 30 days to allow enough time for expansion.

We did not use any lubricant in order to avoid potential influence of the lubricant distribution on the properties of FCC in combination with a disintegrant. Due to manual tableting, the speed of compaction was slower than with an automated process, i.e. using hopper. The lower compression speed caused less friction; hence the tablets were not damaged during ejection.

We could obtain the same tablet hardness with 0.5% magnesium stearate. In order to exclude potential influence of lubricants, we compressed 300 mg S02 powder at 4 kN. For the tablets without magnesium stearate, we obtained a hardness of 124±8 N, whereas the tablets with magnesium stearate showed a hardness of 126±5 N.

The concentration of the disintegrant was kept constant and comprises of 3% w/w in accordance to general recommendations (30). Our focus was set on the comparison of different filler excipients (e.g. FCC) on the disintegration behavior in presence of different disintegrants. In addition, our earlier experience in application of the percolation theory to the tablet disintegration and water uptake has revealed that the percolation threshold is located at 3% *v/v* for AcDiSol (31). This value could be corroborated by computer-based simulations of the percolation thresholds carried out by Garboczi *et al.* (32). In accordance with these results the optimal theoretical value lays in the area of 3% *v/v* for elongated particles with aspect ratio approx. 20.

Tablet Characterization

To determine the mean tablet weight, tablets (n=13) were weighted on an electronic balance (Mettler Toledo, type XS204 DeltaRange, Switzerland). Tablet diameter (n=13) was measured with a micrometer screw (Mitutoyo Model CD-15CPX, Japan), and tablet thickness (n=13) was determined with a dial indicator (Compac type 532G, Switzerland). Friability was measured by an ERWEKA (type TA200, Germany). The hardness of the tablets (n=3) was checked with a hardness tester (Tablet tester 8 M, Switzerland). To determine the true densities, a helium pycnometer was used (Micromeritics AccuPyc 1,330, USA). Porosity ε (%) of the tablets was calculated with the Eq. 1, as follows:

$$\varepsilon = \left(1 - \frac{\frac{\mathrm{m}}{\rho}}{\pi \cdot \mathrm{r}^2 \cdot \mathrm{h}}\right) \cdot 100 \qquad (1)$$

where m is the tablet weight (g), ρ the true density of the powder mixture (g/cm^3), r the radius of the tablet (cm), and h the height of the tablet (cm).

Method for Characterization of Disintegration and Dispersion Kinetics

To characterize disintegration and dispersion kinetics of the tablets (n=3, for FCC without disintegrants n=2) a tensiometer (Krüss Processor Tensiometer K100MK2, Germany) was used. The experimental setup was composed of a special metal-wire basket (Fig. 1a) which was attached to the microbalance of the tensiometer with four nickel wires. For the measurement of small tablets (such as risperidone oro tablets), the mesh size was reduced by a nickel wire to a size of 4 mm × 4.5 mm. As shown in Fig. 1b, the basket was immersed to a defined depth (12 mm) into a beaker. The beaker was filled up to the edge with distilled water. The beaker was heated (37°C ±1°C) by the surrounding thermostatic water bath.

Weight loss *versus* time was recorded by the tensiometer software. Figure 1c shows a schematic representation of this plot. The tablet was placed manually on the basket immersed in the water. With the aid of the tensiometer software, the mass was plotted against the time. The time point at which the tablet reached the basket and disintegration induced by water absorption started was indicated as t_0. At this stage, the weight was increased due to water uptake. This was reflected as weight increase on the profiles. The weight decrease was explained as tablet disintegration upon water uptake. The end of tablet disintegration was indicated by the leveling off of the profile. This event was referenced as t_1. The difference between t_1 and t_0 (t_1-t_0) was the tablet residence time on the basket. Residence time is a measure of disintegration time and is a good indicator of the time needed to disperse the tablet in the mouth cavity or on a spoon. To determine t_0 and t_1, the two linear equations were fitted with OriginPro version 8.5 (OriginLab Corporation, USA). A user-defined double linear curve fit was programmed with Eq. 2.

$$m_{\text{absorption}} = m_0 + k_0 \cdot \mathrm{t} \qquad t < t_c$$

$$m_{\text{elimination}} = m_0 + k_0 \cdot t_c + k_1(\mathrm{t} - \mathrm{t_c})t \geq t_c \qquad (2)$$

where m is the weight (g) and t is the time (s).

If m_a and m_e are set equal to 0 and Eq. 2 is solved for t, the following equations are obtained:

$$t_0 = \frac{-m_0}{k_0}$$

$$t_1 = t_c - \frac{m_0 + k_0 . t_c}{k_1}$$

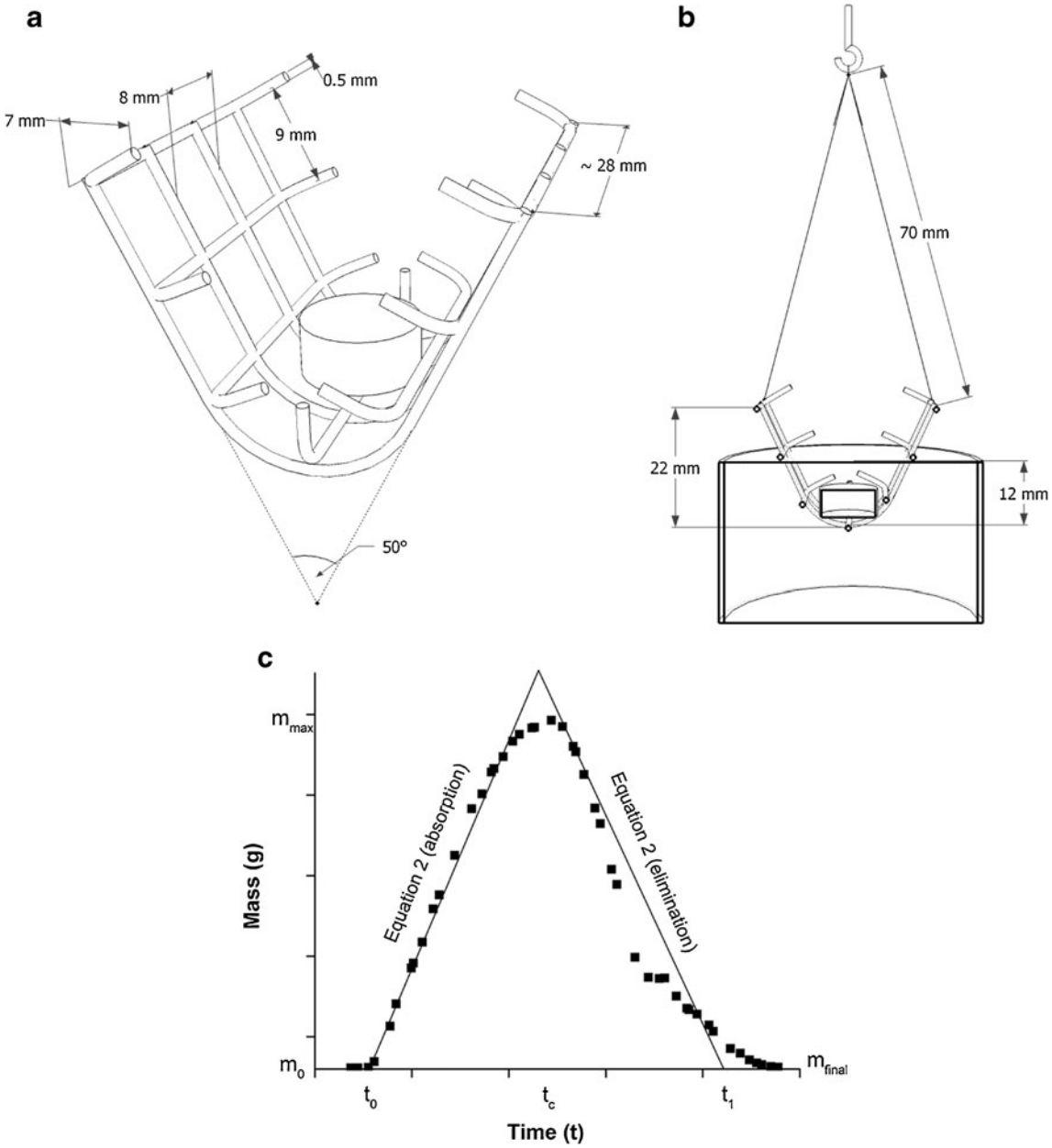

Fig. 1 (**a**) Schematic representation of the basket. (**b**) Schematic representation of the experimental setup for measuring the residence time. (**c**) Schematic representation of the mass *versus* time plot from the tensiometer software.

To calculate the residence time, Eq. 3 was used.

$$\Delta t = t_1 - t_0 = t_c - \frac{m_{0+}k_0.t_c}{k_1} - \frac{-m_0}{k_0} \quad (3)$$

In addition to the residence time, the disintegration degree was calculated with Eq. 4:

$$n = \left(1 - \frac{m_{final}}{m_{max}}\right) \cdot 100 \quad (4)$$

where n is the disintegration degree (%) and m is the weight (g). For m_{max} the weight at time point t_c was used, and m_{final} is the weight at leveling off of the profile (Fig. 1c).

Kinetics of Water Absorption (Tensiometer)

Water absorption capacity of the tablets ($n=3$) for each lot was measured with a tensiometer (Krüss Processor Tensiometer K100MK2, Germany) in a water bath (37°C ± 1°C). The tablet was placed in a glass tablet holder with a ceramic filter bottom. With the help of the software, time was plotted against mass gain. The slope of this function indicated the speed of water absorption, and the saturation level corresponded to the relative amount of absorbed water. To calculate the slope, the values for the time points between 6 and 9 s were taken into account. OriginPro version 8.5

(OriginLab Corporation, USA) was used for curve fitting and the evaluation of tensiometer plots.

RESULTS

Properties of Fillers (F) and Disintegrants (D)

Figure 2a-c shows SEM pictures of FCC at different magnifications. The size of the FCC particles was around 7 µm. The particles showed a multitude of thin lamellae that formed a porous meshwork. Figure 2d illustrates the mercury porosimetry plot of FCC.

Table I shows the true densities and medians of the particle diameter of the used substances. With the BET method a specific surface area of 62.14 ± 0.19 m^2/g was measured for the FCC particles.

Evaluation of Tablet Properties

Table II lists the properties of the tablets. At the same volume and hardness (100 N), the tablets with FCC and MCC 102 were the lightest (around 500 mg). By comparison, CS90 tablets were approx. 1.7 times heavier (approx. 840 mg) than the tablets consisting of FCC and MCC 102. Friability was 1.0% to 1.7% for all tablets except the formulations with MCC 102, where a friability of approx. 0.5% was reached. Although volume and hardness of the tablets were kept constant, porosity of the tablets varied strongly between the different tablet formulations. Tablet formulations with FCC had a porosity of over 60% whereas the MCC 102-based tablets exhibited a porosity of only 40% at the same weight. With porosities of about 25% and 35%, the tablets consisting of FlowLac and MCC burst were less porous than MCC 102 tablets. Formulations with CS90 had a porosity of approx. 35% and weighed approx. 840 mg.

Calcium carbonate Natur 120 was not suitable for the preparation of tablets with the desired properties. The target hardness (100 N) was not reached due to capping of the tablets.

Table III shows the residence times and disintegration degrees obtained after a double linear curve fit of tensiometer weight *versus* time plots (Fig. 1).

In addition, Table III indicates the speed of water absorption and amount of absorbed water after 90 s. Some formulations with FCC, MCC 102, and MCC burst reached a water absorption speed of more than 50 mg/s. Only MCC 102 and MCC burst formulations absorbed water at a speed of more than 100 mg/s. The formulations with MCC burst showed the highest absolute amount of absorbed water.

As pointed out above, an ODT should disintegrate within 3 min if tested with the standard disintegration test according to the European Pharmacopeia (11). Figure 3 illustrates the influence of tablet composition on residence time. The horizontal line indicates a residence time of 3 min. With the fillers FCC and FlowLac, three formulations in each case had a residence time of less than 3 min. In comparison with FlowLac, the FCC formulations had a significantly shorter residence time. FCC formulations showed

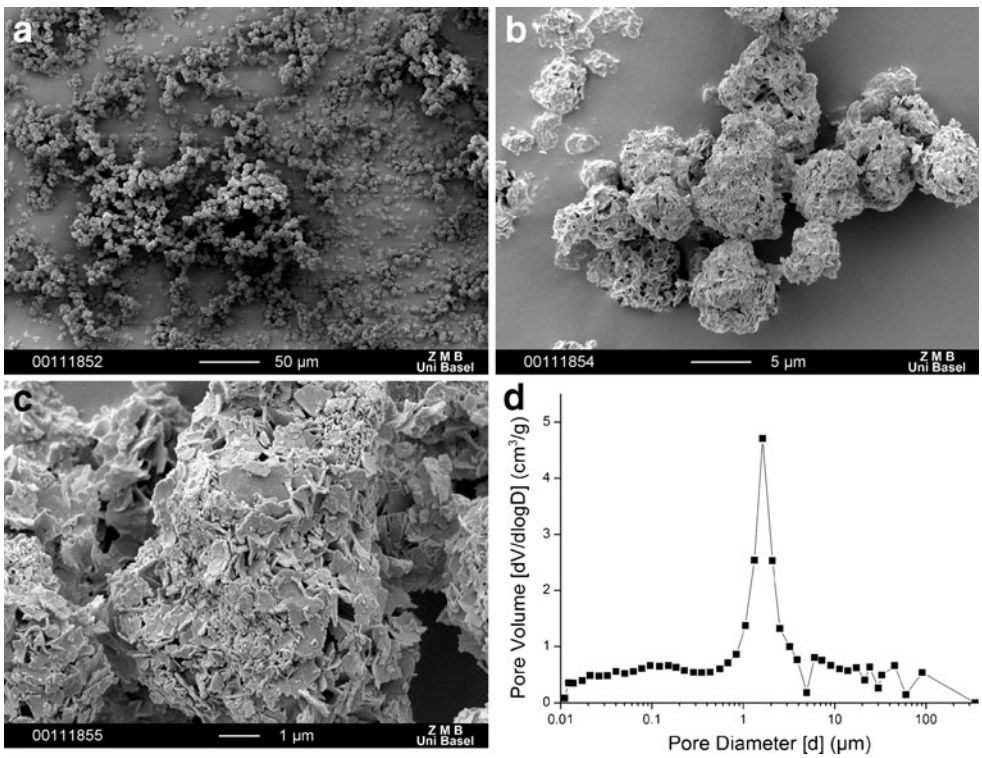

Fig. 2 (**a-c**) SEM pictures of FCC (magnifications: (**a**) x 300, (**b**) x 3,000, and (**c**) x 10,000). (**d**) Mercury porosimetry plot of FCC.

Table I True Density and Median Particle Diameter of the Substances (Where F Stands for Function as Filler and D Stands for Disintegrant)

Substance	Function in a formulation	True density (g/cm^3)	Median particle diameter (μm) ± SD
FCC	F	2.7382	7.28 ± 0.05
Barcroft CS90	F	2.5233	163.52 ± 10.00
MCC 102	F	1.5583	120.65 ± 1.31
FlowLac	F	1.5412	150.37 ± 2.19
MCC burst	F + D	1.5337	64.04 ± 0.14
AcDiSol	D	1.5996	43.74 ± 0.06
VivaStar	D	1.4778	41.20 ± 0.12
Kollidon CL	D	1.2374	91.64 ± 0.81

fast disintegration comparable to that of MCC burst and MCC 102 formulations. It is important to note that FCC formulations compared well with the reference tablets, risperidone oro. On the other hand, it has to be kept in mind that FCC had to be used in combination with a disintegrant to trigger the fast dispersion. For all tablets with a residence time below 3 min, a disintegration degree between 85% and 100% was calculated. Nevertheless, Table III shows that not all of the tablet formulations had residence times below 3 min. We marked the residence time values as ∞ if calculated residence time (Δt) indicated that water absorption was not followed by tablet disintegration.

DISCUSSION

Tensiometer Method

The present work describes a novel strategy for the design of orally dispersible tablets (ODT). Functionalized calcium carbonate (FCC) was used as the main pharmaceutical excipient for ODTs, which are characterized by a very short disintegration time (i.e. <10 s). This rapid process is a challenge, in that conventional disintegration protocols according to the European Pharmacopeia cannot be used. This standard method relies on a vertically moving sample holder. This leads to forced disintegration of tablets due to mechanical stress. For example, formulations containing spray dried calcium carbonate (i.e. the Barcroft formulations), did not disintegrate in an unstirred solution. Upon agitation only, tablet fragments are dislocated from the tablet surface. FlowLac based formulations

Table II Tablet Properties

Tablet formulation	Diameter (mm) ($n = 13$)	Thickness (mm) ($n = 13$)	Weight (mg) ± SD ($n = 13$)	Hardness (N) ± SD ($n = 3$)	Friability (%) ($n = 1$)	Porosity (%)
FCC	11.02 ± 0.01	5.30 ± 0.02	499.4 ± 2.9	117.3 ± 15.0	1.06	64
FCC + 3% AcDiSol®	11.03 ± 0.01	5.41 ± 0.01	498.9 ± 1.9	99.7 ± 9.6	1.32	64
FCC + 3% Viva Star®	11.01 ± 0.01	5.36 ± 0.05	502.3 ± 0.8	107.0 ± 3.5	1.67	64
FCC + 3% Kollidon® CL	11.02 ± 0.01	5.14 ± 0.01	499.2 ± 1.0	116.7 ± 19.2	1.18	62
FCC + 3% MCC burst	11.03 ± 0.01	5.20 ± 0.09	500.8 ± 1.6	111.7 ± 21.1	1.10	63
Barcroft™ CS90	11.07 ± 0.00	5.47 ± 0.01	851.7 ± 1.4	95.3 ± 1.2	1.12	36
Barcroft™ CS90 + 3% AcDiSol®	11.08 ± 0.00	5.58 ± 0.01	845.3 ± 1.2	88.3 ± 2.5	1.25	37
Barcroft™ CS90 + 3% Viva Star®	11.08 ± 0.01	5.50 ± 0.01	845.9 ± 1.3	94.7 ± 2.9	1.14	36
Barcroft™ CS90 + 3% Kollidon® CL	11.07 ± 0.00	5.51 ± 0.01	833.0 ± 1.5	98.3 ± 3.8	1.12	37
Barcroft™ CS90 + 3% MCC burst	11.06 ± 0.00	5.49 ± 0.01	836.9 ± 1.1	95.7 ± 0.6	1.20	36
FlowLac®	11.05 ± 0.01	5.32 ± 0.01	594.4 ± 2.7	88.3 ± 3.2	1.46	24
FlowLac® + 3% AcDiSol®	11.06 ± 0.01	5.33 ± 0.01	593.3 ± 1.3	86.3 ± 2.1	1.28	25
FlowLac® + 3% Viva Star®	11.06 ± 0.00	5.34 ± 0.01	598.7 ± 0.8	88.3 ± 5.0	1.40	24
FlowLac® + 3% Kollidon® CL	11.06 ± 0.00	5.35 ± 0.02	595.0 ± 1.2	89.3 ± 3.2	1.50	24
FlowLac® + 3% MCC burst	11.06 ± 0.01	5.34 ± 0.01	605.4 ± 2.7	97.3 ± 7.8	1.16	23
MCC 102	11.06 ± 0.01	5.53 ± 0.02	489.0 ± 3.6	93.0 ± 7.5	0.54	41
MCC 102 + 3% AcDiSol®	11.06 ± 0.01	5.55 ± 0.02	494.0 ± 2.8	93.3 ± 2.1	0.38	41
MCC 102 + 3% Viva Star®	11.07 ± 0.01	5.54 ± 0.03	498.3 ± 2.3	96.0 ± 1.0	0.51	40
MCC 102 + 3% Kollidon® CL	11.06 ± 0.01	5.55 ± 0.02	487.9 ± 1.8	98.3 ± 3.5	0.48	41
MCC 102 + 3% MCC burst	11.07 ± 0.01	5.54 ± 0.02	493.6 ± 2.0	92.3 ± 3.5	0.59	41
MCC burst	11.10 ± 0.01	5.83 ± 0.03	566.6 ± 2.9	88.7 ± 3.8	1.52	34
MCC burst + 3% AcDiSol®	11.09 ± 0.01	5.75 ± 0.03	563.3 ± 1.9	94.0 ± 3.5	1.38	34
MCC burst + 3% Viva Star®	11.08 ± 0.01	5.84 ± 0.02	573.8 ± 1.8	90.0 ± 0.0	1.64	33
MCC burst + 3% Kollidon® CL	11.10 ± 0.01	5.82 ± 0.02	566.5 ± 1.3	86.7 ± 3.8	1.53	34

Table III Calculated Parameters for Residence Time, Disintegration Degree, and Kinetic of Water Absorption

Tablet formulation	Residence time (s)	Disintegration degree (%)	Disintegration type (I-IV)	Amount of absorbed water after 90 s (g)	Speed of water absorption (mg/s)
FCC	∞	0	II	0.189 ± 0.011	4.5 ± 0.33
FCC + 3% AcDiSol®	8.92	100	I	1.232 ± 0.018	80.4 ± 2.69
FCC + 3% Viva Star®	11.94	100	I	1.599 ± 0.055	86.8 ± 3.95
FCC + 3% Kollidon® CL	9.53	100	I	0.816 ± 0.007	37.9 ± 0.92
FCC + 3% MCC burst	4858.26	2	II	0.229 ± 0.008	4.9 ± 0.54
Barcroft™ CS90	∞	0	II	0.115 ± 0.013	0.7 ± 0.09
Barcroft™ CS90 + 3% AcDiSol®	7703.4	4.7	II	0.080 ± 0.033	1.9 ± 0.05
Barcroft™ CS90 + 3% Viva Star®	197.68	100	III	0.263 ± 0.015	5.9 ± 0.29
Barcroft™ CS90 + 3% Kollidon® CL	∞	0	II	0.074 ± 0.037	1.6 ± 0.24
Barcroft™ CS90 + 3% MCC burst	∞	0	II	0.113 ± 0.021	1.1 ± 0.19
FlowLac®	61.92	100	III	0.311 ± 0.044	5.4 ± 2.06
FlowLac® + 3% AcDiSol®	127.85	100	III	0.322 ± 0.016	5.5 ± 0.29
FlowLac® + 3% Viva Star®	194.2	100	III	0.667 ± 0.026	16.2 ± 1.64
FlowLac® + 3% Kollidon® CL	65.09	100	III	0.375 ± 0.017	9.8 ± 0.33
FlowLac® + 3% MCC burst	64.57	85	III	0.344 ± 0.045	9.1 ± 0.95
MCC 102	∞	0	II	0.807 ± 0.040	79.2 ± 17.95
MCC 102 + 3% AcDiSol®	1681.78	47.2	IV	1.306 ± 0.017	82.3 ± 13.61
MCC 102 + 3% Viva Star®	9.65	99.1	I	1.840 ± 0.050	152.9 ± 27.09
MCC 102 + 3% Kollidon® CL	∞	0	IV	0.877 ± 0.016	70.1 ± 15.83
MCC 102 + 3% MCC burst	∞	0	II	0.847 ± 0.044	71.0 ± 12.97
MCC burst	∞	0	IV	1.741 ± 0.059	96.6 ± 5.63
MCC burst + 3% AcDiSol®	5.92	96.3	I	1.864 ± 0.052	70.9 ± 3.22
MCC burst + 3% Viva Star®	10.4	100	I	2.347 ± 0.034	98.1 ± 4.64
MCC burst + 3% Kollidon® CL	∞	0	IV	1.826 ± 0.054	104.9 ± 13.24
Risperidone oro	17.26	100	I	-	-

have a similar behavior in that tablets are fractured by agitation. However, this "accelerated" or "forced" disintegration does not reflect the intended use of our ODT formulations. Here, disintegration in unstirred liquid (i.e. in a spoon prior to oral administration) is needed. We were therefore forced to develop our own disintegration method. As expected, the disintegration time for most formulations was shorter for the standard method as compared to our tensiometer method. In particular, MCC based formulations swell only and do not disintegrate if not agitated. An additional advantage of our tensiometer based method is its ability to monitor rapid disintegration processes with very high precision. In addition, a slight modification of the experimental setup allows for quantification of the absorbed amount of water. Thereby, the type, volume, and temperature of fluid can be varied.

FCC as a New Pharmaceutical Excipient for the Production of ODTs

Comparison between FCC and Barcroft showed considerable differences in the porosity. FCC-containing formulations (with disintegrants) showed the best results. Formulations combining FCC with a disintegrant disintegrated/dispersed within a few seconds. Thereby, the mode of action of the different disintegrants had no significant influence on the residence time. Furthermore, all formulations of FCC combined with disintegrants belonged to the disintegration type I and showed a disintegration degree of 100%. We successfully produced tablets with marked porosity and high hardness.

Properties of FCC

Several studies have demonstrated that porosity has a surprisingly low impact on the disintegration behavior of FCC. Figure 4 correlates speed of water absorption and the absorbed amount of water after 90 s for FCC combined with different excipients. Speed of water absorption and absorbed amount of water after 90 s for each formulation were influenced by the disintegrants only.

For FCC as well as all other excipients, no correlation could be shown between the tablet weight and disintegration degree (Table II and III). Disintegration degree was only dependent on the composition of the tablet formulations. Residence time also depended on the tablet composition and

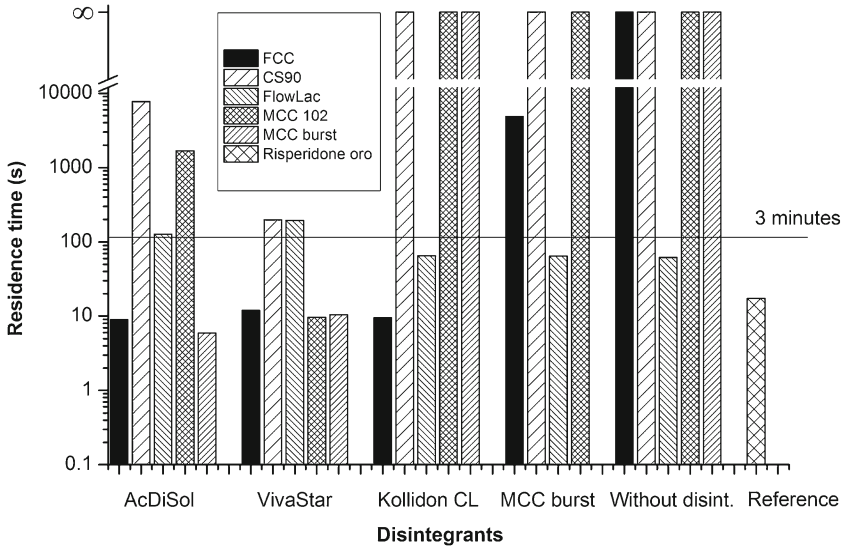

Fig. 3 Influence of tablet composition on residence time.

was not affected by the porosity or weight of the tablets. This latter finding was surprising since it has been suggested recently that porosity might be an important property of ODTs (26). Again, the combination of filler and disintegrants seems to be the decisive factor, which appears to be a unique property of FCC. All other excipients studied did not show such a linear correlation (data not shown). This result suggests that the speed of water absorption is modulated by disintegrants. In the case of FCC, water absorption is a prerequisite for disintegration since pure FCC neither absorbs water nor disintegrates. Thus, the choice of a specific disintegrant is not a critical factor.

From the percolation theory point of view, disintegration occurs above critical concentrations (threshold) of the disintegrant (33). In our study, all formulations had disintegrant concentrations close to the theoretically predicted critical value, i.e., approx. 3% (*v*/*v*). At these concentrations, the rate of disintegration is mostly governed by the type of disintegrant rather than by tablet porosity (33).

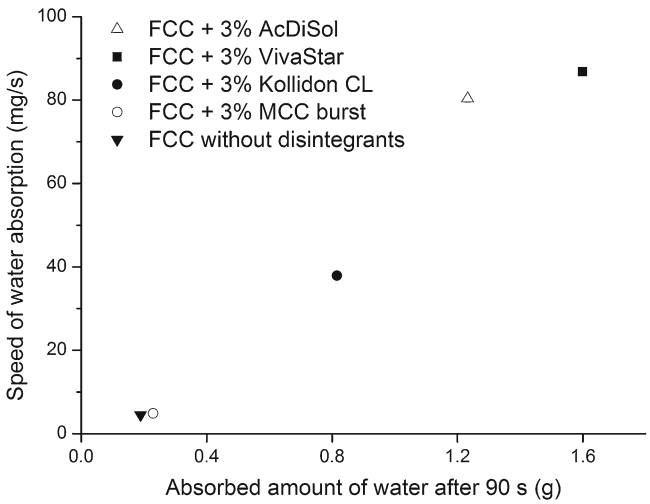

Fig. 4 Correlation plot between speed of water absorption and absorbed amount of water after 90 s.

Definition of Disintegration Patterns

We were able to distinguish four typical disintegration patterns (Table III and Fig. 5).

First, excipients such as FCC and the commercial reference, ODT formulation of risperidone oro, showed a classical disintegration pattern. Initially, absorption of water is faster than disintegration (increase in mass). After reaching a peak, the tablet continuously dispersed (decrease in mass) into very small particles. This desirable property has been termed disintegration type I. In sharp contrast, non-modified calcium carbonate particles (Barcroft) did not disintegrate. This profile was characterized by fast initial water absorption only. After saturating the pores with water, the speed of the water absorption declined continuously. Some formulations reached a plateau, whereas other formulations were still able to absorb more water, forming a large swollen lump. This profile was defined as disintegration type II. FlowLac was a typical representative of disintegration type III, which was characterized by nonuniformity in the disintegration phase caused by larger fragments falling off the tablet and then through the mesh. These parts needed some more time on the bottom of the beaker to disperse completely. We could not establish whether the fragments that had come loose were still dry on the inside. Finally, cellulose-based excipients (i.e., MCC 102 and MCC burst) combined properties of type I and type II disintegration patterns: initial phase of swelling followed by partial disintegration. This profile termed disintegration type IV.

Owing to the new and very sensitive tensiometer method, ODTs could be categorized based on their disintegration profiles (Table III).

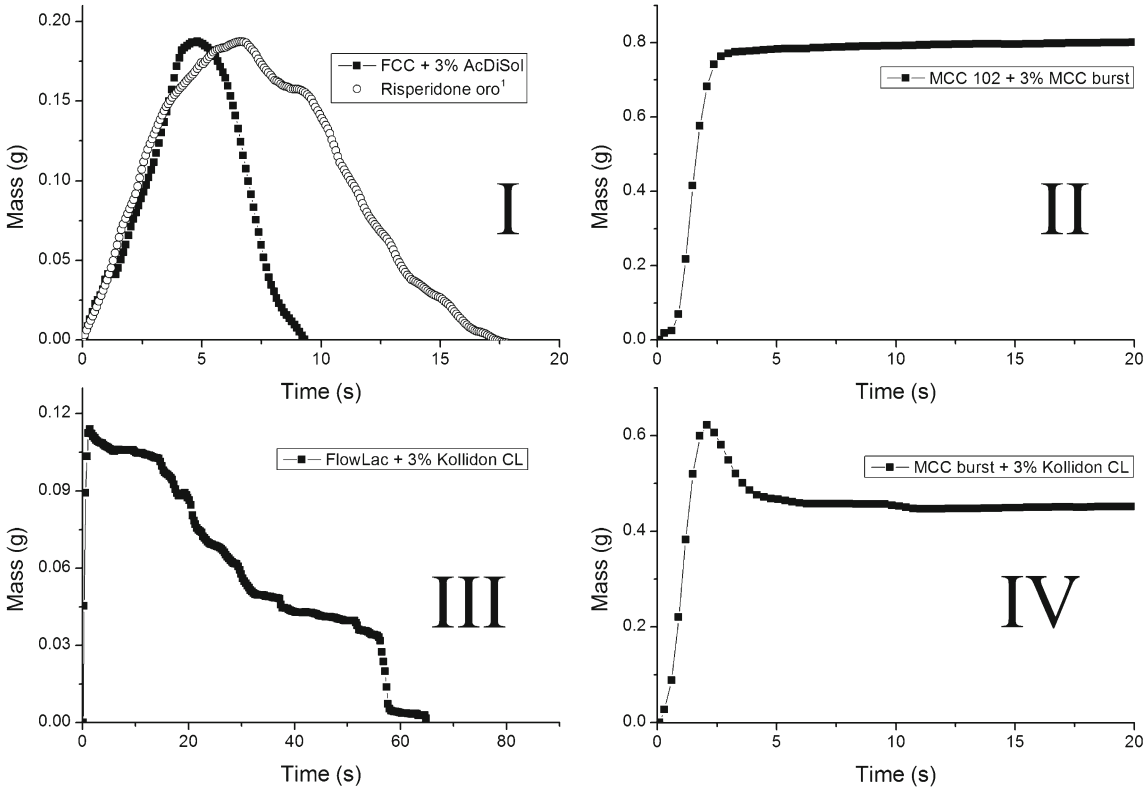

Fig. 5 Tensiometer plots for 4 types of disintegration kinetics (mass *versus* time). Re-normalized curve (with mass maximum at 0.0223 g).

Quantitative Model for Residence Time

Disintegration profiles can be evaluated using a user-defined double linear curve fit model. In the majority of cases, the values of residence time determined from the tensiometer plot (Fig. 5) agreed well with the calculated values in Table III. Quantitative evaluation for profiles of type III was difficult due to the larger parts of the tablets that had fallen through the basket mesh (i.e., without dispersing/disintegrating), hence shortening the residence time. Another limitation of the model was the discrepancy between measured and calculated values for residence time for a few formulations that showed an exponential function within the tensiometer plot.

It should be emphasized, that disintegration of tablets is a complex process. Figure 1c shows a disintegration profile, which is characterized by a series of sequential events. In a first step, the tablet was wetted by the medium, followed by medium absorbance and disintegration. Thus, the tablet mass increased until equilibrium was reached between liquid sorption and mass decrease due to disintegration. Afterwards, the disintegration predominated the water sorption resulting in a net loss of mass.

In many instances (Fig. 5), the disintegration pattern is more complex. For example, some materials first soak up liquid very fast and subsequently start to disintegrate by heterogeneous fractionation. Other materials like FCC soak up water at moderate speeds, leading to continuous disintegration and loss of mass.

Several mathematical models can be used to describe these processes. For example, the concurrent effects could be modeled by the system of two differential equations (here combined into one equation):

$$\frac{d}{dt}m(t) = M_0 e^{-k_a t} - k_e m(t);$$

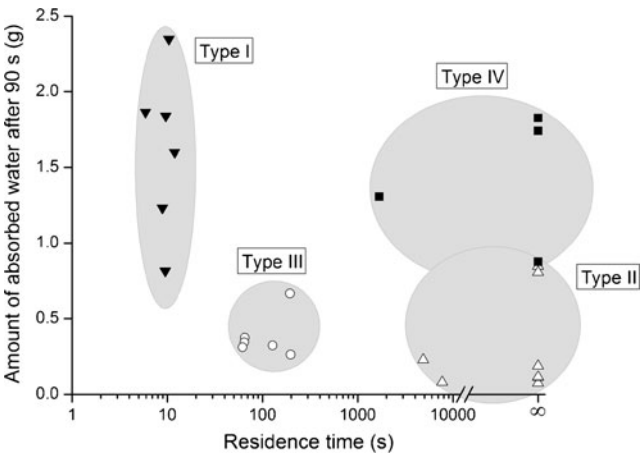

Fig. 6 Correlation plot between the amount of absorbed water after 90 s and residence time for the different disintegration types.

where m(t) is mass detected by tensiometer, t is the time, M_0 is compact mass in the test media, and K_a and K_e are the absorption and disintegration speed constants, respectively.

However, the obtained model – although it's good illustrative properties – does not produce fits of experimental data of sufficient quality. The reason for this is that the disintegration behavior is not monotonous on the whole disintegration timeline. For example, the lactose-based formulations were disintegrating by losing larger pieces of mass, hence producing "step-wise" profiles. Such profiles produce poor fitting of the exponential equations, hence we had to discard this approach. In order to take into account such inhomogeneous effects the differential model should be modified or substituted by another, – perhaps, discrete – model.

An alternative polynomial fit of the curves was not favorable due to a potential risk of over fitting.

For this publication we used a simplified linear model, which gave best results in all encountered situations. Utilizing this approach, we can determine the residence time of the pharmaceutical compact on the tensiometer sample basket.

Optimal Type I Disintegration of FCC

Figure 6 shows a correlation plot between the amount of absorbed water after 90 s and residence time for the different disintegration types. Due to very long or even unlimited residence time, disintegration type II and type IV were of no interest for the production of ODTs. Although the majority of formulations of disintegration type III had a residence time below 3 min, type III was limited by nonuniform disintegration. Disintegration type I showed the shortest residence time and was therefore the most appropriate for producing ODTs. Within type I, the formulations are better the shorter the residence time and the lower the amount of absorbed water after 90 s. The absorbed amount of water is important with respect to patient compliance in the clinical setting. We assume that a pleasant mouth feel can be achieved with tablets dispersing in small amounts of saliva. If more saliva is absorbed by the ODT, patient's mouth feels dry, and swallowing of the tablet becomes difficult. Therefore, we conclude that FCC-based formulations were the best. When combined with disintegrants, FCC formulations showed a disintegration pattern of type I, comparable to that of the market reference drug, risperidone oro.

CONCLUSION

ODTs are designed to disperse within seconds. The prerequisite for reliable classification and quantification of disintegration properties of ODTs is the availability of a fast analytical method.

In order to compare ODT tablet formulations containing FCC, we introduced a new method to characterize the disintegration/dispersion kinetics and swelling properties of ODTs. With this method we were able to detect the exact amount of absorbed water after 90 s, speed of water absorption, and residence time of a tablet placed on a basket immersed into water with a single instrument.

We conclude that FCC has the required properties to produce ODTs, such as a fast disintegration, and sufficient mechanical strength. To fulfill the requirements for a short disintegration time, the FCC formulations have to contain superdisintegrants. The FCC formulations absorbed smallest amount of water, which would enhance patient compliance in the clinical setting.

FCC is a new pharmaceutical excipient, which can be used to assist in the preparation of orally dispersible tablets. ODTs prepared using FCC as main excipient are characterized by a short disintegration time and high mechanical strength. Thus, drug delivery to the buccal cavity or upper esophageal regions can be achieved. The oral sensation after ingesting FCC particles is expected to be favorable since particles with a particle size below 15 μm are not felt in the mouth (34). Further experiments are required to study the friability and flowability of FCC particles being a prerequisite for large scale production.

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