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Research Article

Evaluation of Citrus Fibers as a Tablet Excipient

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Abstract. The consumption of fibers is associated with many health benefits, such as a reduction of cardiovascular and gastrointestinal diseases, control of body weight, and prevention of diabetes. Despite the widespread use of fiber supplements such as capsules or tablets, there is an almost complete lack of information concerning the technological properties of functional fibers used in nutraceutical formulations. The aim of this work was to characterize the technological properties of citrus fibers necessary for their use as a processing aid in tableting. The results obtained showed that citrus fibers share many properties of other polysaccharides used as tableting excipients, such as thermal behavior and compaction mechanism, together with an appreciable tabletability. However, the most interesting properties resulted from their disintegration power. Citrus fibers behaved in a similar manner to the well-known super disintegrant croscarmellose sodium and resulted to be little susceptible to their concentration, to lubricant type, and lubricant concentration. Thus, this work supports the idea of a potential use of citrus fibers as "active" substances and processing aid in the tableting of nutraceutical products and also as functional excipient in pharmaceutical tablets formulation.

KEY WORDS: citrus fibers; disintegration; Heckel analysis; tabletability; thermal analysis.

INTRODUCTION

Dietary fibers are a heterogeneous complex of components originally defined by Trowell as "that portion of food which is derived from cellular walls of plants which are digested very poorly by human beings" (1). Initially, dietary fibers were considered only as substances such as cellulose, hemicellulose, and lignin. Afterwards, the class of materials was broadened to include all indigestible polysaccharides (2). In 2002, the Institute of Medicine of the National Academies decided to further modify the definition of dietary fibers. Thus, the term dietary fibers now describe the non-digestible carbohydrates and lignin that are intrinsic and intact in plants, whereas the name functional fibers is used to define the isolated, non-digestible carbohydrates. Total fibers are the sum of dietary fibers and functional fibers (3,4).

A diet rich in fiber is associated with many health benefits. According to the American Dietetic Association and many other researchers, there is strong evidence that the consumption of fibers is useful to reduce the cardiovascular and gastrointestinal diseases, to control body weight and diabetes (4–6). Several studies have also highlighted a beneficial relationship between the consumption of fibers and the prevention of some types of cancer (7–9).

Although an adequate amount of fibers could be taken from food, consumers are often turning to supplements such as enriched fiber food or dietary supplements (nutraceutical products) as additional fiber sources.

The market of nutraceutical products has exhibited a steady growth in the last decade; moreover, a shift from single-ingredient to multiple-ingredient based products has been observed (10). Despite the large diffusion of fiber supplements such as capsules or tablets, at the moment, there is a lack of information concerning the technological properties of functional fibers used in nutraceutical formulations. Particularly, at the moment, it is unknown if these products are suitable for the preparation of the final dosage forms or if the addition of specific excipients is required. Such concerns are still more important in multiple-ingredient based products. The knowledge of the technological properties of substances can allow an easier and more rational formulation. In fact, some specific ingredients may show interesting technological properties and can act both as "active" substances and as processing aids in tableting or encapsulation procedures.

The aim of this work is to characterize the tableting technological properties of citrus fibers. Herbacel AQ Plus was selected as a model product for citrus fibers, since it is a well-standardized supplement of fiber material, derived from the albedo (inner part of the peel) of citrus fruit and composed of 92% fibers (of which 17% is soluble), and less than 1% of polysaccharides and fats

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(11,12). Another important feature of Herbacel AQ Plus is the high water retention capacity, up to 17 g/g fiber (11). Both the fiber content and water retention capacity are higher than many other commercially available products.

In this work, citrus fibers were characterized in terms of their powder properties, such as particle size and flowability, thermal properties, and tableting features, such as tabletability and compaction mechanism. Moreover, due to the high water retention capacity, the disintegration power of the material was also tested. The results obtained were compared with those found in the literature or derived from analyzing standard pharmaceutical tableting excipients.

MATERIALS AND METHODS

Materials

Citrus fibers (Herbacel AQ Plus; Herbafood, Germany), dibasic calcium phosphate (Emcompress; JRS Pharma LP, Germany), microcrystalline cellulose (Avicel PH-101; FMC BioPolymer, Belgium), croscarmellose sodium (Ac-Di-Sol; FMC BioPolymer, Belgium), α-lactose monohydrate (Pharmatose 200; DMV, The Netherlands), magnesium stearate (ACEF, Italy), hydrogenated vegetable oil, type 1 (Lubritab; JRS Pharma, Germany), and sodium stearyl fumarate (PRUV; JRS Pharma, Germany) were all used as received.

Throughout the text, the material names will be reported with the following abbreviations: CFIB for the Citrus fibers, MCC for microcrystalline cellulose, LAC for α-lactose monohydrate, DCP for dibasic calcium phosphate, MgSt for magnesium stearate, ACDI for croscarmellose sodium, LUB for hydrogenated vegetable oil, type 1, and PRUV for sodium stearyl fumarate.

Methods

Powder Characterizations

Particle size analysis. A sample of CFIB was analyzed using optical microscopy (MT9000 Polarizing Microscope, Meiji Techno Co., Ltd., Japan) equipped with three megapixels CMOS camera (Invenio 3S, DeltaPix). The acquired images (2,048×1,536 pixel) were analyzed through the use of an image analysis software (Image Pro Plus, Media Cinernetics Inc.), previously calibrated using a specific glass slide with a 5-mm graticule (S2-StageMic, Graticules Ltd., UK). One hundred particles, randomly selected, were analyzed in terms of projected area equivalent diameter and elongation ratio. The results were reported as the median value (D50) and interquartile range of the obtained particle size distribution.

Density and flowability. The true density of CFIB was measured using a helium pycnometer (AccuPyc 1330, Micromeritics). For every sample, the analysis was performed by carrying out 10 measurements after 30 purging cycles.

The bulk (ρ_b) and tapped (ρ_t) densities of the samples were determined by pouring a pre-weighted amount of sample in a cylinder and measuring the volume occupied initially and after 700 taps, respectively (after 600 taps, the powder volume remained constant).

Carr's index (13) was estimated from the bulk and tap densities according to equation 1.

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \cdot 100 \quad (1)$$

Bulk and tapped densities were determined in triplicate.

Thermal analysis. Thermal analysis was carried out using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

TGA analysis was performed by thermogravimetric balance (STA 6000, PerkinElmer, USA). Approximately 5–20 mg of sample was placed in aluminum crucibles and the weight variation monitored from 25 to 450°C at a rate of 10°C/min under a nitrogen atmosphere.

DSC analysis was performed using a DSC 8500 (PerkinElmer, Norwalk, USA) equipped with an intracooler (intracooler 2, PerkinElmer, Norwalk, USA) and analyzed in an inert nitrogen atmosphere. A small amount (2–4 mg) of the sample was placed in non-hermetically closed aluminum pans and analyzed, using an empty closed pan as reference, from −10 to 250°C at a scan rate of 10°C/min in a cyclic test, composed of three runs as follows: first heating, first cooling, and second heating. The final temperature of the test was selected at a value of 25°C lower than the degradation temperature, as determined by TGA.

Evaluation of citrus fibers compaction behavior. CFIB were compacted using a ten-station rotary tablet press (Ronchi, Cinisello Balsamo, Italy) instrumented to measure both the force and the displacement of the upper and lower punches (14,15). The tableting machine was equipped with 6-mm diameter, round, flat-faced punches, and the rotation speed of the turret was set at 25 rpm. One hundred milligram tablets were prepared setting the punch penetrations in order to obtain a pressure of 200 MPa.

The force and punch penetration data acquired during each single-compression cycle were processed in order to perform the Heckel (16,17) and energy analysis (18). Details of data processing for Heckel analysis was previously reported by the authors (14,15); while for the energy analysis, the procedure based on the punch separation determination was followed (19,20).

Tabletability. The tabletability of CFIB was evaluated by preparing 4 batches of 100-mg tablets at different pressures, 100, 150, 200, and 250 MPa. The tableting conditions were the same of those described in the previous section. For each batch, ten tablets were analyzed using a hardness tester (TBH30, Erweka) and the obtained crushing forces (H) were converted into tensile strength using Eq. 2 proposed by Fell and Newton (21).

$$TS = \frac{2 \cdot H}{\pi \cdot D \cdot t} \quad (2)$$

Where D is the tablet diameter (in millimeters) and t the tablet thickness (in millimeters), measured using a micrometer (103–137, Mitutoyo, Japan).

In order to evaluate the CFIB tabletability, the same procedure was applied to some common tablet excipients, such as MCC, LAC, and DCP.

Evaluation of disintegration power. In order to evaluate the disintegration power of CFIB, DCP was selected as the model substance to prepare tablets with poor disintegration behavior. Preliminary tests showed that the blends of DCP and MgSt (in concentrations of 0.5 to 1.5% w/w) compacted at 200 MPa produced tablets with disintegration times greater than 1 h.

To study the disintegration ability of CFIB, several formulations were prepared varying both CFIB and MgSt amounts (between 2.5 and 20% w/w for CFIB and 0.5–1.5% w/w for MgSt). All the formulations were compressed setting the punches penetration to obtain tablets with the same hardness (in the range 20–25 N) of those prepared using only DCP, to avoid any effects due to the different hardness of the compared tablets.

The same set of formulations was also prepared by substituting CFIB with MCC and ACDI, two well known disintegration agents (22). Further tests were also performed substituting MgSt with two other pharmaceutical lubricants; LUB and PRUV. All formulations prepared and analyzed in terms of disintegration power are summarized in table ST1 of the supplementary materials.

All disintegration experiments were performed at 37°C in a European Pharmacopeia apparatus A (TecnoGalenica, Cernusco s/N, Italy), using distilled water as a medium. The disintegration time was considered as the time necessary to obtain a complete disintegration of the tablets, i.e., the time after which no tablet residue was visible on the screen of the test tubes of the instrument.

RESULTS AND DISCUSSION

Powder Characterization

CFIB appeared as a brownish powder composed of elongated particles with small size and irregular shape (Table I and Fig. 1). They exhibited a high value of Carr's index typical of particles with a flowability defined as "poor" according to Carr (13) and the USP 36. The obtained values are comparable with those of other polysaccharides with similar particle size commonly used as tableting excipients, such as MCC (23) and several types of starches (24).

Table I. Density, Particle Size, and Moisture Content of Citrus Fibers

Parameter	Units	
Particles diameter (median/IQR)	μm	25.62/13.00
Elongation ratio(median/IQR)	–	1.6/0.78
Bulk density (mean ± SD)	g ml^{-1}	0.40±0.01
Tapped density (mean ± SD)	g ml^{-1}	0.54±0.02
True density (mean ± SD)	g ml^{-1}	1.50±0.00
Carr's index(mean ± SD)	%	27.21±2.43
Absorbed moisture (mean ± SD)	%	10.31±0.44

When analyzed using a thermogravimetric balance, the sample displayed two different transitions associated with a weight variation; the water evaporation from ambient to around 130°C, and the material degradation starting from around 215°C (Fig. 2b). The moisture content of the sample resulted around 10% (Table I), slightly higher than microcrystalline cellulose (25,26) and comparable with starch (26). CFIB started degrading at around 215°C similar to many others polysaccharides (27–29). Moreover, the first derivative trace exhibited the presence of two peaks at temperature above 215°C, suggesting a multistep degradation mechanism or the presence of more components with different degradation temperatures. A similar degradation pattern has been observed for Sisal (27) and Hemp fibers (30) and had been attributed to the presence of hemicellulose, pectin, and cellulose inside the sample. Degradation temperatures of pure hemicelluloses, pectin, and cellulose reported in literature (31,32) match with those found in this work (Fig. 2b). This result is also in agreement with the composition of CFIB reported in the literature (33).

CFIB were also analyzed using DSC in the temperature range below the degradation temperature. Samples were analyzed using a thermal cycle of two heating scans divided by a cooling phase. This program was selected to remove the moisture from the samples (endothermic peak in the first heating in Fig. 2a), which would hide any other transition in the range 25–125°C. The analysis of the three DSC traces did not show any other thermal transition except the water loss in the first heating scan. The results are in agreement with previous studies on pure polysaccharides, although performed only with a single scanning step (31,34).

Evaluation of Compaction Behavior

The compaction behavior of CFIB was determined through Heckel and energy analysis. Heckel analysis is commonly used to determine the main compaction behavior, through the building of plots (as shown in Fig. 3a) showing the variation of the logarithm of powder bed porosity (-lnϕ) against the applied pressure (P). The reciprocal of the slope of such a plot is defined as the yield pressure (Py) and is related to the ductility of the material. Low values of Py are typical of highly deformable materials while high values of Py are related to materials that densify through other mechanisms such as fragmentation (35,36). The calculated yield pressure value of the CFIB was 89.9 ±3.2 MPa, which is a value typical of a material that shows a predominantly plastic deformation mechanism when subjected to a compression process inside a confined space. This behavior has been observed for many other polysaccharides such as MCC (37–40), several types of starch (39–41), or pectin (40).

Compaction data were also used to perform energy analysis. The measurement of the energy involved during the

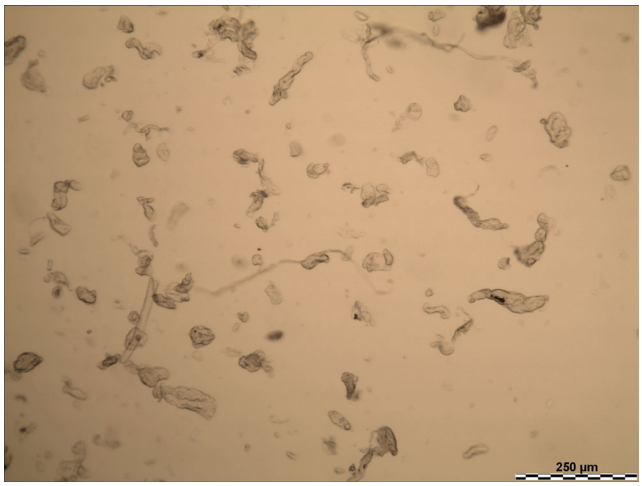

Fig. 1. Optical microscope image of CFIB

compression and the decompression phase was determined through integration of the force–punch separation plots (Fig. 3b). The energy measured during the compaction phase represents the work performed by the two punches on the powder bed and is called total energy or gross energy, while the energy obtained from the decompaction phase represents the work performed by the powder on the two punches and represents the material elasticity (called elastic energy). The difference between compaction and decompaction work is the energy effectively employed by the tableting machine to reduce the porosity of the powder bed and to form bonds between particles and is usually referred as net energy. CFIB required a total compaction energy of 43.9±2.8 J/g composed of 5.1±0.3 J/g of elastic energy and 38.8±2.6 J/g of net energy. The results of the energy analysis are difficult to compare with literature data since they are very sensitive to experimental parameters such as the maximum compaction pressure, the velocity of the tableting machine, and the shape and diameter of the punches. However, in a previous study (37), the authors reported the energy data of different excipients acquired at the same experimental conditions and are thus comparable with those measured for CFIB. According to those results, CFIB appear to possess similar energetic indices to MCC, while they show a better energy utilization with respect to other pharmaceutical excipients such as dicalcium phosphate dihydrate, poly ethylene oxide 600,000 Da, and Eudragit® RS.

Tabletability

Tabletability represents the most important parameter concerning the ability of an excipient to work as a diluent in tablet formulations. Materials with low tabletability are unsuitable to be added in high amounts within a formulation intended for a direct compression process. To better evaluate the tabletability of CFIB, it was compared to three different commonly used tableting diluents, namely MCC, DCP, and LAC. CFIB showed a much lower tabletability compared to MCC, while it appeared more similar with respect to LAC and DCP. This result is not surprising since MCC is probably the most tabletable pharmaceutical excipient. From the zoom section in Fig 4, differences can be highlighted also between CFIB and LAC or DCP. Specifically, CFIB demonstrated improved performance compared to LAC and DCP only when the applied pressure was higher than 150 MPa, while the materials showed a similar tabletability at lower pressures.

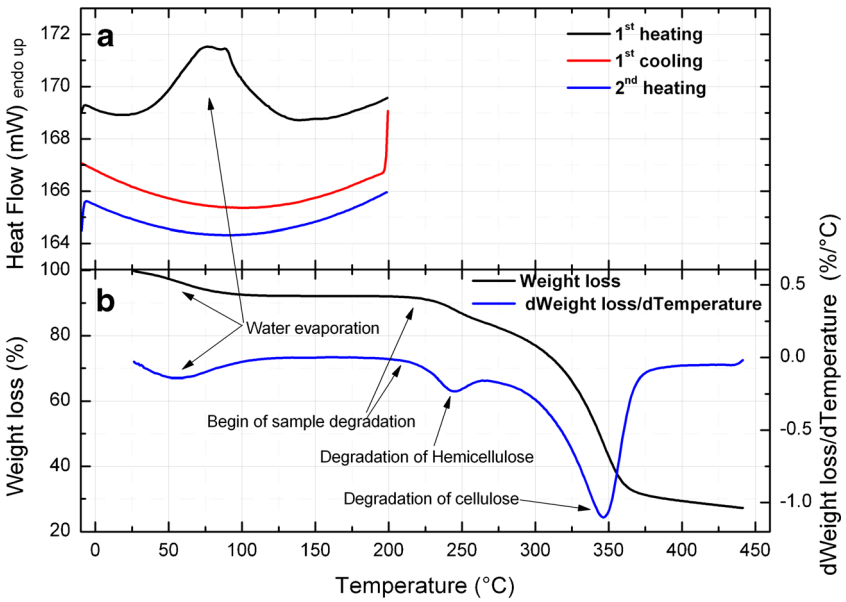

Fig. 2. DSC (**a**) and TGA (**b**) traces of CFIB

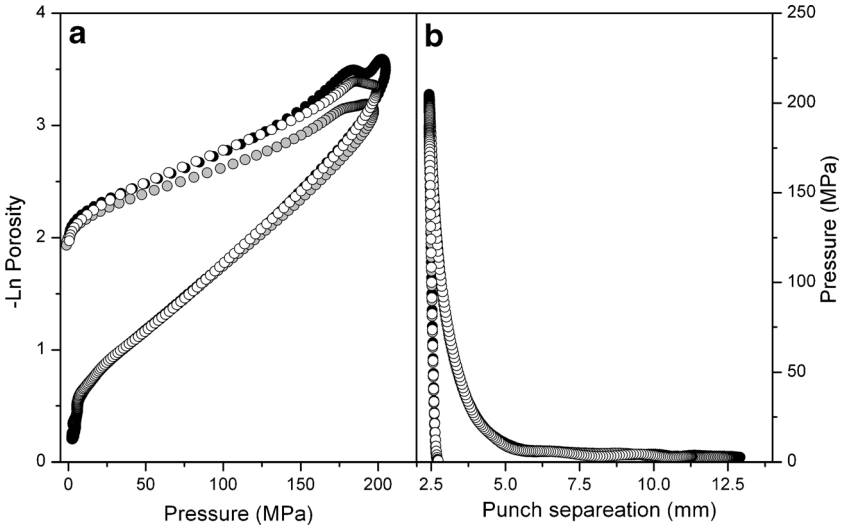

Fig. 3. Examples of the Heckel plots (**a**) and punch separation curves (**b**) used to derive yield pressure and the energetic indices

Evaluation of Disintegration Power

Disintegration is a fundamental prerequisite for all oral dosage forms intended for rapid release of active compounds in the gastrointestinal tract. In the pharmaceutical field, substances added to improve tablet dispersion or breakup when they are exposed to gastrointestinal fluids are defined as disintegrants. Cellulose and starch are the most widely used disintegrants due to their high versatility, being able to work also as diluents and binders. Their main disadvantage is the relatively low disintegration power, which sometimes oblige formulators to use the so-called super-disintegrants, such as modified starch or chemically cross-linked cellulose. These substances show excellent performance in terms of disintegration power, although such behavior is observed only in a narrow concentration window, usually 1–5%; moreover, they

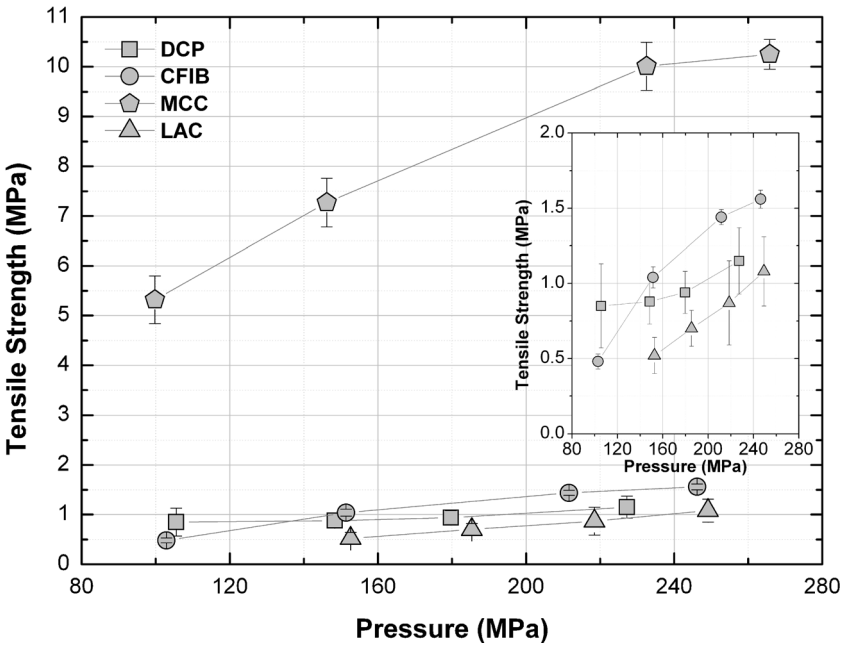

Fig. 4. Tabletability of CFIB compared with DCP, MCC, and LAC. The inset show CFIB, DCP, and LAC traces with a higher zoom (mean ± SD $n=10$)

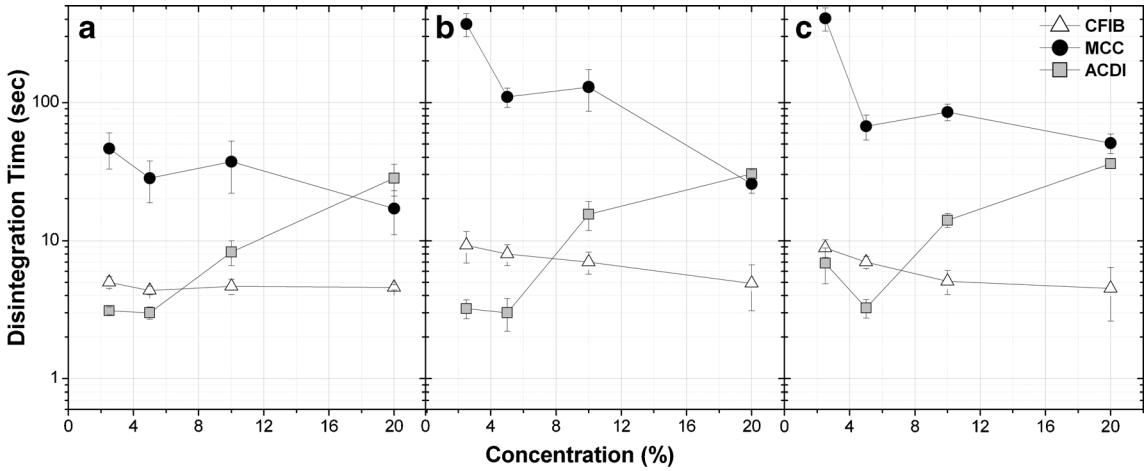

Fig. 5. Effect of CFIB and other disintegrant concentrations on the disintegration time of model tablets at MgSt concentrations of 0.5 (**a**), 1 (**b**), and 1.5% (**c**) (mean ± SD n=5)

also show poor tabletability (42). According to the manufacturer, CFIB possess a high water retention capacity which is a fundamental property for disintegration ability. The effect adding CFIB and other disintegrants on the disintegration time of model tablets are reported in Fig. 5. All the tested substances were able to reduce the disintegration time from a value higher than 1 h of the pure DCP to values lower than 7 min. However, marked differences can be observed. Particularly, at low concentrations, CFIB showed a similar performance to the superdisintegrant, ACDI, with only slightly higher disintegration times (differences in the range of a few seconds). For both these two materials, it was possible to obtain tablet breakage within 10 s. However, for concentrations equal to or higher than 10%, ACDI showed a reduction in disintegration power while CFIB showed a moderate increase in its efficiency. The concentration-dependent efficiency of ACTI has previously been reported in the literature (43,44), although it was found to be dependent on the solubility of the model substances (43). On the other hand, MCC exhibited much higher disintegration times, in the range of 20–400 s. In this case, the increase of MCC concentration lead to an improvement in its disintegration ability. Another important aspect is the effect of lubricant concentration. In fact, ACDI and CFIB were not particularly sensitive to these two parameters, while MCC was affected by the lubricant concentration.

To better define the relationship between disintegrant and lubricant, further experiments were performed using the 1% w/w lubricant formulations substituting the MgSt with two other pharmaceutical lubricants; LUB and PRUV. The results reported in Fig. 6 confirm the previously observed behavior of the different materials. ACDI and CFIB show little sensitivity to lubricant type, with a reduction in disintegration time moving from MgSt to PRUV and LUB in the order of a few seconds.

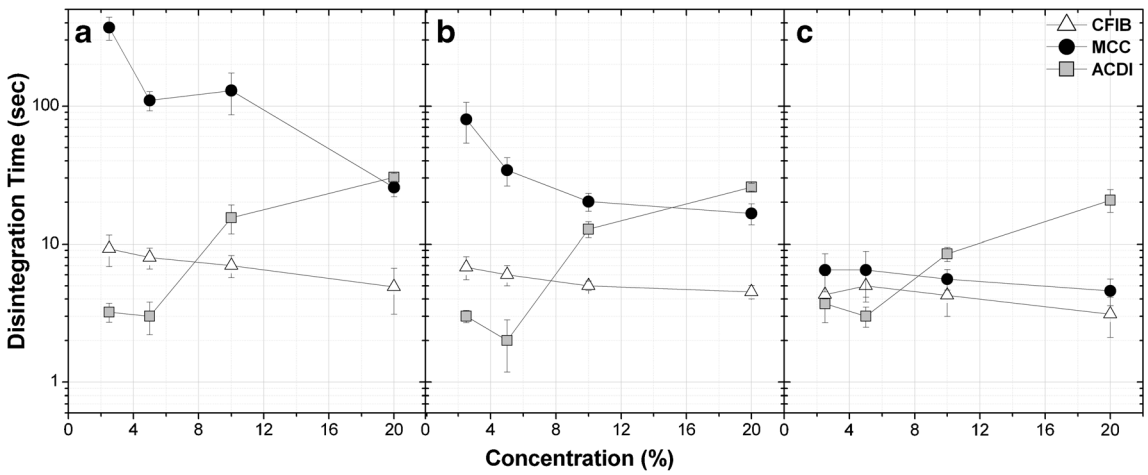

Fig. 6. Effect of the CFIB and other disintegrants on the disintegration time of model tablets in presence of 1% of MgSt (**a**), PRUV (**b**), and LUB (**c**)

Conversely, the performance of MCC was markedly influenced by the lubricant type. The MCC disintegration time was reduced by one order of magnitude in the presence of PRUV and by two orders of magnitude when LUB was used in comparison with MgSt. In the latter case, MCC showed a disintegration ability almost comparable to CFIB and ACDI. In case of the latter, MCC results were even better when the disintegrant concentration was higher than 10%. As previously observed for MCC, the effect of lubricant is much more pronounced in the formulations with the lowest concentration of disintegrant, that is when MCC is equal to or lower than 5% w/w.

CONCLUSION

Citrus fibers have been analyzed in order to verify their suitability as a pharmaceutical tableting excipient. The results obtained showed that fibers possessed a similar compaction mechanism to other well-known polysaccharides commonly used in tablet formulations. Moreover, they also exhibited acceptable tabletability, at least comparable with that of other pharmaceutical diluents. These results support the idea of their potential use as "active" substances and processing aid in the tableting of nutraceutical products.

Additionally, citrus fibers displayed promising disintegrant properties. The obtained data suggest that citrus fibers possess a disintegration power almost comparable with those substances known as super-disintegrants and much higher than microcrystalline cellulose. These results, together with the appreciable tabletability, suggest a possible use in the formulation of tablets with disintegration and tabletability concerns.

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