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Research paper

Tableting and tablet properties of alginates: Characterisation and potential for Soft Tableting

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ABSTRACT

The aim of the study was to evaluate the suitability of alginates for Soft Tableting. For this purpose the compaction properties of alginates, varying in molecular weight, guluronic acid/mannuronic acid ratio and salt, were investigated and compared to MCC. Based on the mechanical properties, the suitability of the tested excipients for Soft Tableting was predicted. In order to test the prediction the tested materials were used to tablet enteric coated pellets, which served as a pressure sensitive material. The tableting behaviour was analysed by the 3-D modeling technique. The tablet properties were analysed by determining the elastic recovery and the compactibility. Alginates in general deformed elastically. The compression behaviour depended on the chemical composition of the alginates with sodium alginates being more elastic than potassium alginates. Tablets containing alginates with low guluronic acid content exhibited higher elasticity than tablets with alginates having a low mannuronic acid content. The plasticity of potassium alginates was higher than for sodium alginates. However, the plasticity of all tested alginates was lower than the plasticity of MCC. The compactibility of the tested alginates was sufficient. The proposed prediction, which states that tableting excipients with higher elasticity are more suitable for tableting sensitive materials than plastic excipients, was valid for the tested materials. The elastic alginates inflicted less damage on the pellets than the plastic MCC. Thus, all alginates were more appropriate for tableting pressure sensitive materials than MCC.

1. Introduction

Alginates are natural polysaccharide polymers extracted from brown seaweed. Due to different manufacturing procedures they can be obtained either as alginic acid or as salts of alginic acid. Alginic acid is a polysaccharide composed of D-mannuronic and L-guluronic acid, whereas chemical composition can vary due to the utilized resource [1].

Alginates in general are widely used in pharmaceutical compositions. For example, alginic acid is applied as a disintegrant [1,2]. Furthermore, alginates are used as a thickening agent [1,3] and for the preparation of modified release beads [4–6]. Most recently different studies evaluated sodium alginates as a matrix material for modified release [7–11]. In this context, it is remarkable that only little information can be found in the literature about compression properties of alginates. Most of the studies dealing with matrix tablets analyse tensile strength of the tablets. Also the fact that alginates in general show a high elastic recovery after compression seems to be well known [8,12]. Takeuchi et al. [13] analysed the compaction properties of tablets containing spray-dried composite particles of alginate and lactose. The release properties of alginate-containing matrix tablets are affected by chemical composition and particle size [14] and by compaction pressure [12]. However up to now no study has been performed analysing the tableting behaviour of alginates. However, the matrix-forming excipient plays a dominant role in the compaction characteristics of the whole composition because in matrix tablets it is required in a relatively high content.

Alginates are natural polysaccharides and in this context they can be compared with carrageenans and chitosans. Like alginates, carrageenans and chitosans are used for similar purposes. The tablet formation behaviour of carrageenans and chitosans has been explored most recently and besides being useful for solid dosage form design, they exhibited special deformation properties [15–18]. This predominantly elastic deformation behaviour made them suitable for Soft Tableting [18,19]. Soft Tableting is a concept to predict the ability of excipients to reduce damages to tableted materials.

The tableting process is associated with relatively high pressure in order to form suitable compacts. However, not only the tableting excipients are deformed during the process of tablet formation, but also the tableted product deforms. This can lead to total or partial

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damage to such materials. For example, biologically active proteins, such as enzymes, can lose their activity, e.g. [20]. Polymorphic transformation can occur [21,22], and the coating of pellets may be damaged and lose its function [23–29].

Most recently, different excipients were tested in order to prevent such damages [18,26,27,30]. Amongst others, polysaccharides like chitosans and carrageenans have shown to be advantageous because of their elastic tableting behaviour [18,30].

Thus, the first aim of this study was to evaluate the potential of alginates for their use in Soft Tableting and to test whether they obtain the same functionality like carrageenans and chitosans. For this purpose the compaction behaviour of different alginates varying in their chemical composition was analysed with special regard to their elasticity.

Based on these data, the suitability of the tested alginates for Soft Tableting was predicted. In order to prove the prediction, enteric coated pellets were tableted using the alginates as tableting excipient. Afterwards, the tablets were analysed for damages in the enteric coating of the pellets.

2. Materials and methods

2.1. Materials

Seven different alginates were used (FMC Biopolymer, Brussels, Belgium). Two potassium salts varying in guluronic acid ratio were used. Furthermore, five sodium alginates which vary in the guluronic acid ratio and the molecular weight were tested. An overview of the used materials is given in Table 1.

MCC (Avicel PH 101, FMC Biopolymer, Brussels, Belgium) was used for comparison.

For the production of the pellets, Bisacodyl (Fagron, Barsbuettel, Germany), Granulac 200 (Meggle, Wasserburg, Germany) and Avicel PH 101 (FMC Biopolymer, Belgium) were used. The enteric coating contained Eudragit L 30 D (Röhm GmbH & Co. KG, Darmstadt, Germany), glycerol monostearate, Polysorbate 80 and propylene glycol (Carl Roth GmbH & Co. KG, Karlsruhe, Germany).

2.2. X-ray powder diffraction

The X-ray diffraction pattern was recorded with Co-Kα_1 X-ray radiation (STOE STADI-MP diffractometer, STOE & Cie GmbH, Darmstadt, Germany). The diffraction angle (2θ) was varied from 5° to 50°.

2.3. Glass transition temperature

The glass transition temperature (T_g) of the equilibrated materials was measured with a DSC 200 (Netzsch Gerätebau GmbH, Selb, Germany) in the range from −40 °C to 140 °C at a heating rate of 20 K/min. The T_g was calculated of the half step height during the first heating. Each substance was measured in triplicate, and means and standard deviations were calculated.

2.4. Sorption isotherms

Three samples per substance were equilibrated over saturated salt solutions at specific RH for 7 days. After equilibration, the powders were weighed and transferred to the next higher RH. The water content was calculated on the basis of the weight of the dry powder at 0% RH (phosphorous pentoxide).

2.5. Particle size determination

Particle size distribution was measured using a laser light diffractometer equipped with a dry feeder (Malvern 2600C, Malvern Instruments, Worcestershire, UK). The feeder was set at a pressure of 2 bar, and the focal distance was 300 mm. The mean volume particle size distribution was calculated, and the median particle size was determined. Determinations were done in quadruplicate, and results are given as mean and standard deviation.

2.6. Apparent particle density

Helium pycnometry (Accupyc 1330; Micromeritics, Norcross, GA, USA) was used to determine the apparent particle density of all equilibrated substances [31]. Determinations were performed in triplicate.

2.7. Bulk and tap density

Bulk and tap density were determined in a 250 ml cylinder using a volumeter (Stampfvolumeter STAV 2003, J. Engelsmann AG, Germany). According to the European Pharmacopoeia, determinations were performed in triplicate. The Carr Index was calculated and used for expressing flowability [32].

2.8. Tableting

Tableting was performed using an instrumented eccentric tableting machine (EK0/DMS, No. 1.0083.92; Korsch GmbH, Germany) in a climate controlled room at 22 ± 1 °C and 42 ± 2% RH. The tableting machine was equipped with 11 mm diameter flat faced punches (Ritter GmbH, Germany). Equal volumes of the substances based on apparent particle density were tableted to different graded maximum relative densities ($\rho_{rel,max}$) of the tablets between 0.75 and 0.95 (precision 0.001). The minimum height of the tablets under load was 3 mm for all tablets. Displacement of the punches was measured using an inductive transducer (W20 TK; Hottinger Baldwin Messtechnik, Germany) and corrected for elastic deformation of the punches and machine. The depth of filling was held constant at 13 mm. The production speed was 10 tablets per min. The amount of material necessary for each tablet with a given $\rho_{rel,max}$ was calculated. The powder was manually filled into the die, and one compaction cycle was performed without using any lubricant.

At least 10 single tablets were produced at each condition, and data were recorded by a DMC-plus system (Hottinger Baldwin

Table 1
Material properties of tested alginates (Protanal®).

	Abbreviation	LOT	Salt	M_w (1000 g/mol)	G (%)/M (%)
Protanal LF 240 D	LF 240 D	S18867	Na	180–250	30–35/65–70
Protanal LF 120 M	LF 120 M	S17664	Na	180–250	35–45/55–65
Protanal LF 200 M	LF 200 M	S16855	Na	270–325	35–45/55–65
Protanal LF 200 S	LF 200 S	S18867	Na	270–325	65–75/25–35
Protanal HF 120 RBS	HF 120 RBS	S16589	Na	340–400	45–55/45–55
Protanal KF 200	KF 200	S15727	K	270–325	65–75/25–35
Protanal KF 200 RBS	KF 200 RBS	S15888	K	270–325	45–55/45–55

Messtechnik). Force, time and displacement of the upper punch were recorded for each compaction cycle.

2.9. Data analysis

For analysing tableting data, only data >1 MPa were used. For all compaction cycles of each material, normalized time, pressure and $\ln(1/(1-D_{rel}))$ according to Heckel [33] were calculated.

2.10. 3-D model

For applying the 3-D modeling technique, the three parameters were presented in a 3-D data plot, to which a twisted plane was fitted by the least-squares method according to Levenberg–Marquardt (Matlab) [34].

$$Z = \ln\left(\frac{1}{1-D_{rel}}\right) = (t - t_{max}) \cdot (d + \omega \cdot (p_{max} - p)) + (e \cdot p) \cdot (f + d \cdot t_{max}) \quad (1)$$

where D_{rel} = relative density, t = normalized time, p = pressure,

$$d = \frac{\delta \ln(1/(1-D_{rel}))}{\delta t},\ e = \frac{\delta \ln(1/(1-D_{rel}))}{\delta p},\ f = \ln\left(\frac{1}{1-D_{rel}}\right)$$

t_{max} = normalized time at maximum pressure, p_{max} = maximum pressure, ω = twisting angle at t_{max}.

The plane is twisted at $t = t_{max}$. Time plasticity (d), pressure plasticity (e), and fast elastic decompression, the inverse of ω, for each tablet (material and a given $\rho_{rel,max}$) were averaged, and means and standard deviations were calculated.

2.11. Tablet properties

After 10 days the height of the tablets was determined, and the elastic recovery of the tablets was calculated using the equation of Armstrong and Haines-Hutt [35]:

$$ER\ (\%) = 100 \cdot \frac{H_1 - H_0}{H_0} \quad (2)$$

where ER = elastic recovery, H_1 = height of the tablet after 10 days, H_0 = minimal height of the tablet under load.

Five tablets were analysed, and the means and standard deviations were calculated.

2.12. Crushing force

The crushing force of the tablets was determined using a crushing force tester (TBH 30; Erweka GmbH, Germany). Five tablets were analysed 10 days after tableting, and the means and standard deviations were calculated.

Table 2
Composition of pellets.

Pellets	
Bisacodyl	133
MCC	300
α-Lactose monohydrate	300
Water	410
Enteric coating	
Eudragit L 30 D	315
Glycerol monostearate	4.725
Polysorbate 80	2.363
Propylene glycol	9.425
Water	112.1

2.13. Production of pellets

After mixing the substances for the pellet core (Table 2), the pellets were produced by extrusion/spheronisation on a twin screw extruder (Fuji-Paudal, Japan) which was equipped with dies of 0.6 mm diameter. The extrudate was spheronised for 4 min in a 250-mm radial plate spheronizer (Fuji-Paudal, Japan) using a cross-hatch frictional plate of 3×3 mm^2 pitch and 1.2 mm depth. The resulting pellets were dried in an circular air oven at 40 °C. The loss on drying was 2.3% (Moisture Analyzer HR 73, Mettler-Toledo). After drying the pellets were classified, and the fraction between 425 μm and 630 μm was used for the coating process. The pellets were coated using Eudragit L 30 D as a coating dispersion and 10% (m/m) (related to polymer) propylene glycol as plasticiser. The polymer content of the coated pellets was 36% (m/m). After coating the pellets were sieved, and the fraction between 500 μm and 630 μm was used for tableting. The apparent density of the pellets was determined in triplicate using helium pycnometry (ρ = 1.265g/ml ± 0.001g/ml).

2.14. Production of pellet tablets

Each alginate sample was mixed with the enteric coated pellets. It was found that a pellet content of higher than 42% (v/v) leads to pellet–pellet interaction during compression [24]. In order to avoid pellet damage by pellet contact, the concentration of the pellets in the mixtures was held constant at 40% (v/v).

The mixtures were manually filled into the die and tableted to $\rho_{rel,max}$ of 0.90.

Assuming that the pellets do not undergo marked densification during tableting, $\rho_{rel,max}$ of the excipient reaches 0.84 for these tablets. With each alginate six pellet containing tablets were produced.

2.15. Release

The release of the pellet containing tablets was tested in a dissolution tester PTW II (Pharmatest, Hainburg). Five tablets of each alginate were analysed. Before analysis, the alginate tablets were carefully cleaved in order to separate the pellets from the matrix and to exclude the matrix effects caused by the alginate matrix. The dissolution medium was 500 ml 0.1 N HCl. After 2 h, a sample of 5 ml was taken, centrifuged, diluted with NaOH and immediately spectrophotometrically analysed at 246 nm.

2.16. Scanning electron microscopy

The pellet containing tablets were broken diametrically. The breaking surfaces were analysed using scanning electron microscopy (ESEM 30, Philips, Kassel, Germany) at an accelerating voltage of 12 keV. For each excipient one tablet was analysed. The complete breaking surface of the tablet was screened under the microscope. Afterwards, a representative picture was taken. The magnification was adjusted to enable a good overview but also to give a close look to eventual pellet damages.

3. Results and discussion

3.1. Powder properties

First the physico-chemical properties of the materials were determined. X-ray diffraction patterns show a relatively broad peak with an underlying halo. This is in accordance with the literature [36]. Thus, all tested alginates are relatively amorphous. The T_g seems to be influenced by the guluronate content. Alginates

Table 3
Powder properties of tested alginates (Protanal®) (mean ± SD).

	Apparent particle density (g/cm^3)	Median particle size (μm)	Water content (%)	Glass transition temperature (°C)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr Index (%)
LF 240 D	1.722 ± 0.002	47 ± 4.9	15.9 ± 0.0	−2.0 ± 4.5	0.634 ± 0.010	0.898 ± 0.009	29.4 ± 1.8
LF 120 M	1.706 ± 0.001	41 ± 0.3	17.8 ± 0.1	−1.6 ± 1.7	0.629 ± 0.017	0.873 ± 0.034	27.9 ± 1.0
LF 200 M	1.711 ± 0.003	42 ± 0.3	16.2 ± 0.1	−0.5 ± 5.4	0.619 ± 0.014	0.872 ± 0.022	29.1 ± 0.3
LF 200 S	1.713 ± 0.003	41 ± 0.3	16.7 ± 0.0	−6.4 ± 2.7	0.544 ± 0.012	0.734 ± 0.003	25.9 ± 1.4
HF 120 RBS	1.724 ± 0.005	48 ± 0.2	16.6 ± 0.0	−5.5 ± 2.0	0.616 ± 0.015	0.845 ± 0.023	27.1 ± 1.5
KF 200	1.749 ± 0.002	45 ± 0.2	16.5 ± 0.0	−6.6 ± 2.9	0.583 ± 0.017	0.796 ± 0.013	26.7 ± 3.4
KF 200 RBS	1.736 ± 0.005	38 ± 0.4	15.8 ± 0.1	−5.4 ± 3.8	0.610 ± 0.022	0.848 ± 0.025	28.0 ± 1.4

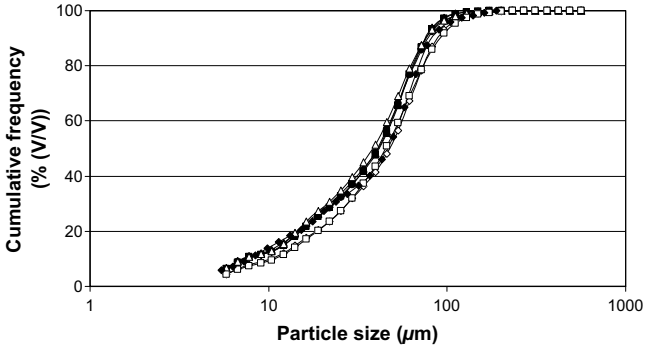

Fig. 1. Particle size of the tested alginates (■ LF 200 M, ▲ LF 120 M, ♦ LF 240 D, ● LF 200 S, □ KF 200, △ KF 200 RBS, △ HF 120 RBS).

with a higher guluronate ratio exhibit a lower T_g (Table 3). The T_g of all alginates is below room temperature. Therefore, similar to carrageenans these materials are in the rubbery state when tableted [17].

The particle size distributions of the powders are given in Fig. 1. All tested substances have similar particle size distributions. Hence, effects of different particle sizes on compression properties can be excluded. The median particle diameters lie between 38 μm and 48 μm for all tested substances (Table 3). Thus, the particle size is comparable to that of Avicel PH 101 and carrageenans [15], and is smaller than that of the chitosans [37]. Ninety percentage of the particles are smaller than 100 μm. The fairly small particles lead to poor flowability and low bulk densities, which are both problematic for tableting especially on high speed rotary tableting machines.

Water content of the sodium alginates increases with increasing RH (Fig. 2). Hence, tableting is needed to be performed under controlled climatic conditions. The high molecular weight substance contains the highest level of water. The water content of the potassium salts is lower compared to that of the sodium salts. Water content at 43% RH for all alginates is between 15% and 18%. Thus, the sorption behaviour of the alginates is comparable to that of the carrageenans with the exception that the total sorption of the alginates is slightly higher [15]. The apparent particle density of the potassium salts is slightly higher than for sodium salts (Table 3). Overall it can also be compared to that of the carrageenans [15].

3.2. Tableting properties

The tableting properties of the alginates were analysed by the 3-D modeling technique which allows the simultaneous evaluation of the three most important tableting process variables force, time and displacement which are presented as pressure, normalized time, and density. Using this technique, the tableting process can be fully characterized through the observed changes in the derived parameters pressure plasticity *d*, time plasticity *e*, and fast elastic decompression, the inverse of ω. By analysing these three parameters in 3-D parameter plots even materials with similar tableting properties can be uniquely characterized. The 3-D parameter plots for the alginates are given in Fig. 3, while the parameters and their standard deviations are shown in Table 4. For the sake of clarity, 3-D data of MCC are only given in Table 4. The 3-D-parameter plots show for all substances an increase in the *d* value with increasing powder densification. Higher *d* values indicate a faster densification. The potassium salts exhibit a strong decrease in ω combined with a decrease of the *e* values. This indicates brittle compression

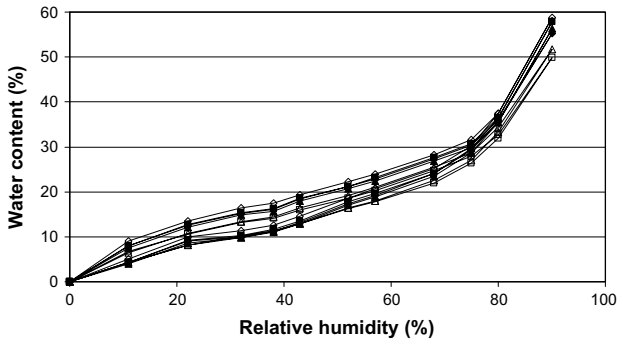

Fig. 2. Sorption isotherms (■ LF 200 M, △ LF 120 M, ♦ LF 240 D, ● LF 200 S, □ KF 200, △ KF 200 RBS, ◇ HF 120 RBS).

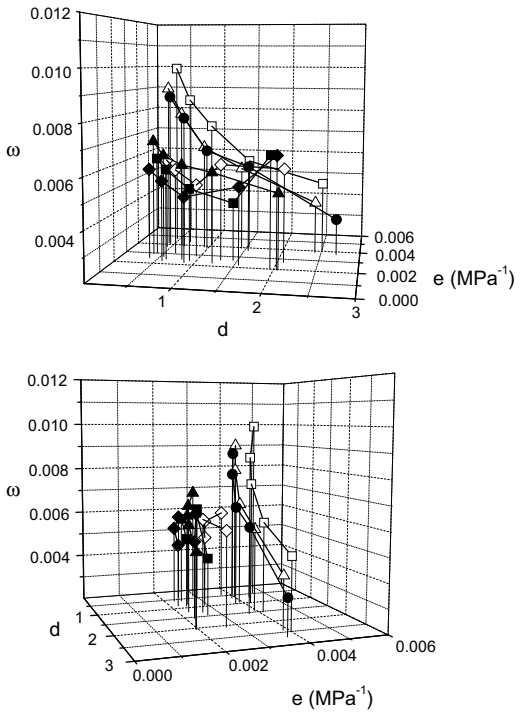

Fig. 3. 3-D parameter plots of the different alginates (■ LF 200 M, ▲ LF 120 M, ♦ LF 240 D, ● LF 200 S, □ KF 200, △ KF 200 RBS, ◇ HF 120 RBS).

Table 4
3-D parameters and ER values of the tested alginates and MCC (mean ± SD).

		d	e	ω
LF 240 D	0.75	0.3834 ± 0.0032	0.0025 ± 0.0001	0.0058 ± 0.0001
	0.8	0.5774 ± 0.0071	0.0023 ± 0.0000	0.0053 ± 0.0001
	0.85	0.8677 ± 0.0117	0.0022 ± 0.0000	0.0047 ± 0.0001
	0.9	1.5520 ± 0.1802	0.0022 ± 0.0000	0.0052 ± 0.0007
	0.95	2.0360 ± 0.2807	0.0020 ± 0.0001	0.0066 ± 0.0006
LF 120 M	0.75	0.3780 ± 0.0070	0.0029 ± 0.0000	0.0069 ± 0.0001
	0.8	0.5426 ± 0.0116	0.0027 ± 0.0000	0.0063 ± 0.0002
	0.85	0.8043 ± 0.0154	0.0025 ± 0.0001	0.0060 ± 0.0002
	0.9	1.2141 ± 0.0209	0.0023 ± 0.0000	0.0058 ± 0.0003
	0.95	2.0557 ± 0.0404	0.0019 ± 0.0001	0.0051 ± 0.0004
LF 200 M	0.75	0.4078 ± 0.0075	0.0030 ± 0.0002	0.0061 ± 0.0002
	0.8	0.6053 ± 0.0116	0.0025 ± 0.0001	0.0058 ± 0.0002
	0.85	0.9116 ± 0.0160	0.0024 ± 0.0000	0.0050 ± 0.0001
	0.9	1.4441 ± 0.1120	0.0027 ± 0.0003	0.0044 ± 0.0004
	0.95	1.9548 ± 0.0528	0.0020 ± 0.0001	0.0066 ± 0.0005
LF 200 S	0.75	0.4455 ± 0.0058	0.0041 ± 0.0000	0.0087 ± 0.0001
	0.8	0.6595 ± 0.0078	0.0039 ± 0.0001	0.0078 ± 0.0001
	0.85	0.9868 ± 0.0126	0.0038 ± 0.0001	0.0064 ± 0.0002
	0.9	1.5511 ± 0.0410	0.0037 ± 0.0000	0.0057 ± 0.0002
	0.95	2.6967 ± 0.0956	0.0037 ± 0.0001	0.0035 ± 0.0003
HF 120 RBS	0.75	0.4451 ± 0.0060	0.0037 ± 0.0001	0.0059 ± 0.0003
	0.8	0.6434 ± 0.0058	0.0031 ± 0.0001	0.0056 ± 0.0002
	0.85	0.9449 ± 0.0119	0.0029 ± 0.0000	0.0051 ± 0.0003
	0.9	1.2904 ± 0.0574	0.0026 ± 0.0001	0.0060 ± 0.0007
	0.95	2.0796 ± 0.1015	0.0027 ± 0.0002	0.0059 ± 0.0012
KF 200	0.75	0.4603 ± 0.0061	0.0047 ± 0.0001	0.0099 ± 0.0002
	0.8	0.6849 ± 0.0069	0.0044 ± 0.0000	0.0085 ± 0.0003
	0.85	1.0068 ± 0.0040	0.0042 ± 0.0000	0.0074 ± 0.0001
	0.9	1.5273 ± 0.0080	0.0041 ± 0.0000	0.0059 ± 0.0001
	0.95	2.5067 ± 0.0271	0.0040 ± 0.0000	0.0050 ± 0.0004
KF 200 RBS	0.75	0.4124 ± 0.0059	0.0042 ± 0.0001	0.0090 ± 0.0001
	0.8	0.6136 ± 0.0054	0.0040 ± 0.0001	0.0079 ± 0.0001
	0.85	0.9367 ± 0.0091	0.0039 ± 0.0000	0.0065 ± 0.0001
	0.9	1.4399 ± 0.0079	0.0039 ± 0.0000	0.0056 ± 0.0001
	0.95	2.4198 ± 0.0313	0.0039 ± 0.0000	0.0042 ± 0.0005
MCC	0.75	0.6622 ± 0.0034	0.0054 ± 0.0001	0.0145 ± 0.0001
	0.8	0.8842 ± 0.0047	0.0046 ± 0.0001	0.0139 ± 0.0001
	0.85	1.1852 ± 0.0093	0.0041 ± 0.0001	0.0131 ± 0.0002
	0.9	1.6565 ± 0.0156	0.0037 ± 0.0001	0.0125 ± 0.0002
	0.95	2.6062 ± 0.0327	0.0032 ± 0.0001	0.0119 ± 0.0002

behaviour. Similar curve progression can also be seen for dicalcium phosphate dihydrate [38]. The broken particles exhibit a higher elasticity indicated by lower ω values. The higher amount of guluronic acid of KF 200 compared to that of KF 200 RBS leads to lower elasticity ($p < 0.001$) and higher pressure plasticity ($p < 0.001$). However, pressure plasticity of all alginates is relatively low. On the other hand, elastic decompression is high especially for sodium alginates with lower guluronic acid content. Similar to the potassium salts, deformation of the sodium alginates also is dependent on guluronic acid ratio. The high guluronic acid ratio of LF 200 S leads to significantly higher pressure plasticity ($p < 0.001$) compared to LF 200 M. Additionally, for $\rho_{rel,max} < 0.95$ fast elastic decompression is lower ($p < 0.001$). Furthermore, the curve progression of the high guluronic acid alginate indicates brittle fracture because of the decreasing ω and e values. The other tested sodium alginates show fairly flat curves with low pressure plasticity but high fast elastic decompression. LF 200 M shows a strong increase of ω and a decrease in e at the highest $\rho_{rel,max}$. HF 120 RBS and LF 240 D have a minimum of ω at $\rho_{rel,max} = 0.85$. Additionally, a slight browning at the upper edges of the tablets at $\rho_{rel,max} > 0.9$ was visible. This indicates a change in deformation properties possibly due to the changes in the material. Recently, Odeku et al. reported similar results for some starches, where the browning was attributed to the changes in the material [39].

The different M_w slightly influences the compaction properties. Except for the highest densification, the sodium alginate with the higher M_w (LF 200 M) exhibits lower ω values compared to LF 120 M ($p < 0.001$). Thus, for lower densifications the sodium alginate with a higher degree of polymerisation (DP) deforms more elastically than the sodium alginate with lower DP.

Altogether sodium alginates deform very elastically, whereas plasticity is relatively low. Potassium alginates are less elastic and somewhat brittle. Compared to carrageenans [16] and chitosans [37], most of the tested sodium alginates deform more elastically.

3.3. Tablet properties

Elastic recovery after ten days storage is shown in Fig. 4. The potassium alginate tablets exhibit the highest elastic recovery. KF 200 tablets show more than 20% ER at all densification levels. Except for the highest $\rho_{rel,max}$, the potassium alginate tablets with higher guluronic acid ratio exhibit a lower elastic recovery. Similar to this the sodium alginate tablets with a high guluronic acid content (LF 200 S) also show a high elastic recovery after storage compared with the other sodium alginate tablets. Except for HF 120 RBS tablets, all sodium alginate tablets exhibit lower ER values than LF 200 S tablets. In addition to the higher molecular weight, HF 120 RBS also has a higher guluronic acid content than the other three sodium alginates which exhibit lower ER values.

Thus, the guluronic acid ratio not only influences the tableting properties but also the tablet behaviour after storage. Additionally, tablets made of potassium alginates show higher elastic recovery after storage than tablets made of sodium alginates.

Overall, the extent of elastic recovery of the alginate tablets is comparable to that of the chitosan tablets with the exception that the ER values are not decreasing with increasing densification [37]. In this respect, the alginate tablets behave more similar to the carrageenan tablets [16].

The compactibility plot is given in Fig. 5. The alginates which deform more plastically produce tablets with higher crushing forces than the alginates deforming less plastically. LF 200 M does not follow this order. Although pressure plasticity of LF 200 M is low, tablet strength is higher than for most of the other sodium alginates.

Compared to carrageenans and chitosans, compactibility of alginates is lower [16,37].

3.4. Prediction

By only knowing the mechanical properties of the polysaccharides, it is possible to predict the ability of an excipient to reduce damage to the tableted materials [18].

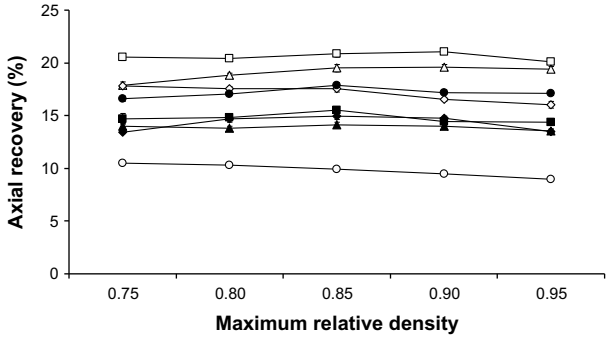

Fig. 4. Elastic recovery of tablets after 10 days storage (■ LF 200 M, ▲ LF 120 M, ♦ LF 240 D, ● LF 200 S, □ KF 200, △ KF 200 RBS, ◇ HF 120 RBS, O MCC).

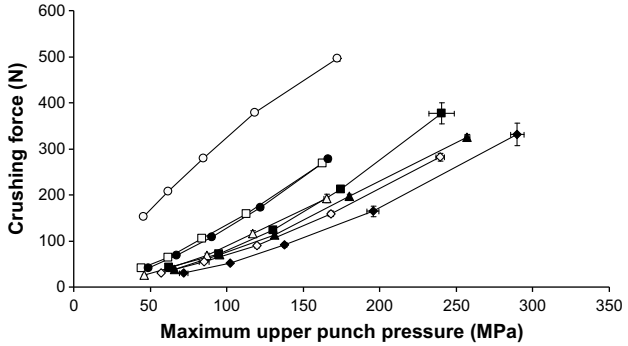

Fig. 5. Crushing force of tablets after 10 days storage (■ LF 200 M, ▲ LF 120 M, ♦ LF 240 D, ● LF 200 S, □ KF 200, △ KF 200 RBS, ◇ HF 120 RBS, O MCC).

Thus, based on the tableting data the general plasticity (GP) was calculated using the normalized values of the 3-D model parameters and of ER [18]

$$\mathrm{GP} = e_{\mathrm{norm}} + d_{\mathrm{norm}} + \omega_{\mathrm{norm}} - \mathrm{ER}_{\mathrm{norm}} \quad (3)$$

The GP values of the tested substances are given in Fig. 6. MCC exhibits the highest GP. As indicated by the tableting data GP of sodium alginates is lower. The GP of potassium salts is higher compared to most of the sodium alginates. LF 200 S exhibits higher GP values than the other sodium alginates.

According to the concept of Soft Tableting highly plastic excipients are not appropriate for tableting pressure sensitive materials, whereas elastic excipients are more suitable. Thus, MCC is hypothesized to cause more damages to enteric coated pellets than sodium alginates.

3.5. Testing for Soft Tableting

The release profiles of the pellet containing tablets are given in Fig. 7. Tableting behaviour highly influences the release of bisacodyl out of the enteric coated pellets. LF 240 D, which was less plastic but highly elastic, shows the lowest release in HCl (21%), indicating that the pellets within the tablets are less damaged compared to the other tablets. When using MCC, which is plastic, the release is significantly higher compared to all the other tested materials ($p < 0.01$). Similar to this, the more plastic alginates show a higher release than the more elastic alginates. LF 200 S which is less elastic and more plastic than the other sodium alginates exhibits a significant ($p < 0.001$) higher release compared to the other sodium alginates.

The release of the potassium alginates is comparable to that of LF 200 S while also the tableting properties of LF 200 S were similar to those of the potassium alginates.

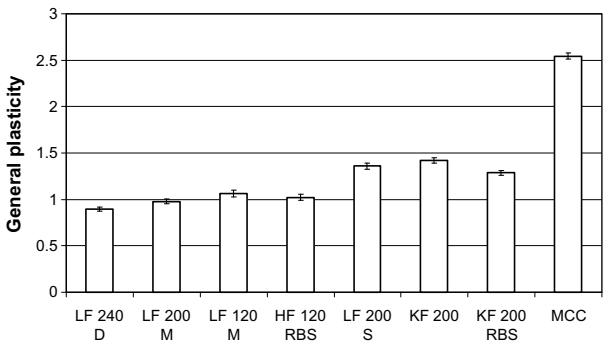

Fig. 6. General plasticity of the tested alginates and MCC ($\rho_{\mathrm{rel,max}} = 0.85$).

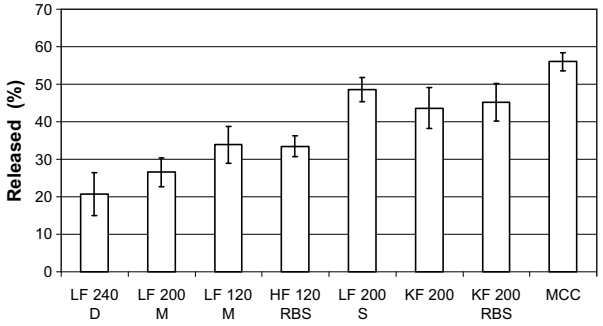

Fig. 7. Release rate of pellet tablets after 2 h in 0.1 N HCl.

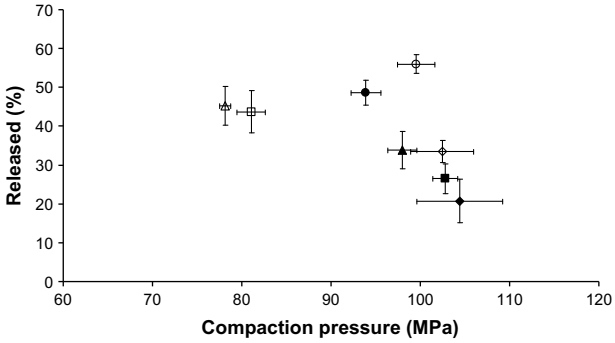

Fig. 8. Release rate of pellets tablets vs. compaction pressure (■ LF 200 M, ▲ LF 120 M, ♦ LF 240 D, ● LF 200 S, □ KF 200, △ KF 200 RBS, ◇ HF 120 RBS, O MCC).

When considering the compaction pressures which were needed to compress the tablets to a $\rho_{\mathrm{rel,max}} = 0.9$ it can be seen that low pressures do not lead to lower release (Fig. 8). Because of their plastic tableting properties, the potassium salts needed less pressure compared to the sodium alginates. However, the release of potassium salts is higher. Compaction pressure of LF 200 S tablets was lower than for all other sodium alginates, but the release was higher compared with these materials.

The SEM micrographs can be seen in Fig. 9. Especially, tablets made of MCC and potassium alginates contain noticeably damaged pellets in the centre of the tablets as well as at the edges. In contrast, no damaged pellet could be observed in the centre of the tablets made of LF 240 D and LF 200 M. Tablets containing LF 200 S and HF 120 RBS as matrix exhibit less amount of damaged pellets compared to MCC.

These results are in a very good agreement with the hypothesis. The order of the release data correlates with the GP. However, ω exhibits the strongest correlation with the release data (correlation coefficient: 0.910). Also, pressure plasticity has an influence on the integrity of the compressed pellets (correlation coefficient: 0.838). ER shows no correlation. This is easily explainable because pellets are damaged only in the short phase during compaction. ER may play a role in long time depending processes like recrystallisation processes.

For tableting of pellets, the instantaneous release of pressure from the pellets is found to be more important. Thus, materials showing high amount of fast elastic decompression are more suitable to prevent damages in enteric coated pellets. The fast elastic decompression is indicated by the low values of the unique parameter ω. However, for developing multi unit particulate systems further excipients with high compactibility and fast disintegration are needed.

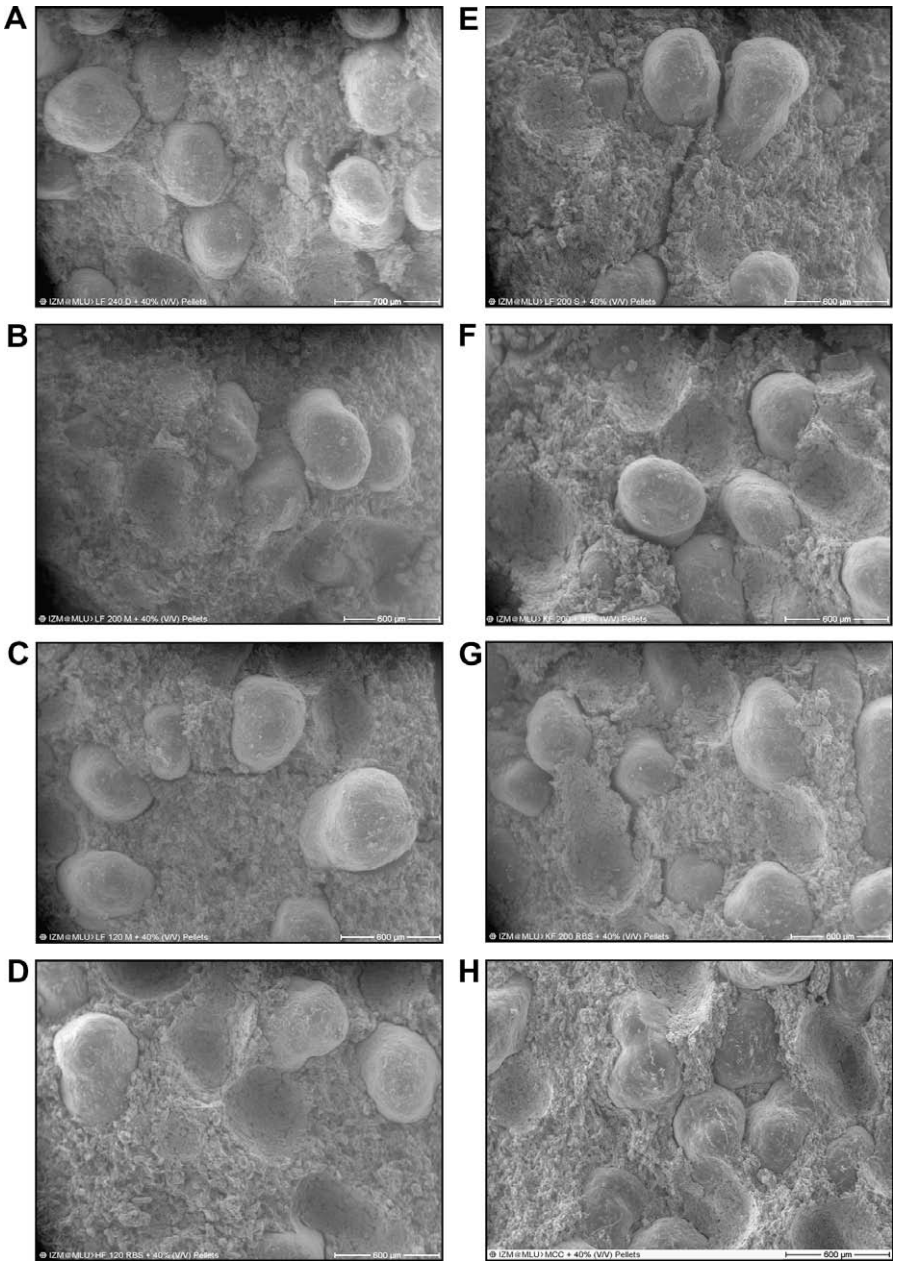

Fig. 9. SEM micrographs of pellet containing tablets. Matrix: LF 240 D (A), LF 200 M (B), LF 120 M (C), HF 120 RBS (D), LF 200 S (E), KF 200 (F), KF 200 RBS (G), MCC (H).

4. Conclusion

Alginates – especially sodium alginates with a high content of guluronic acid – deform elastically during tableting. The tableting behaviour of alginates depends on their chemical composition. As carrageenans, alginates are in the rubbery state at room temperature. This leads to a high elasticity as already shown for carrageenans. But compared with carrageenans and chitosans, alginates deform even more elastically during tableting indicated by lower ω values. However, the compactibility of alginates is lower than the compactibility of chitosans.

Furthermore, it was possible to predict the ability to reduce damages to enteric coated pellets only based on the 3-D parameters. Especially, sodium alginates show high fast elastic decompression. The high elasticity could be a reason for the laminating problem previously described in the literature [7].

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