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Compression behaviour of κ-carrageenan pellets

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ABSTRACT

The compression behavior of high- and low drug strength pellets containing κ-carrageenan as pelletisation aid was investigated. Model drugs and fillers with different compression mechanisms were used and the effects of compression force and turret speed were examined. Regardless of the compression behavior of their starting components, all pellet formulations exhibited minimal to absent fragmentation and underwent compression by deformation, confirmed by increased equivalent diameter and aspect ratio and decreased roundness factor of the pellets retrieved after de-aggregation of tablets prepared from lubricated pellets. The retrieved pellets showed also higher fracture resistance in three of the tested formulations and no statistically significant difference in the remaining one thus excluding significant crack formation. A densification mechanism was suggested by decreased total porosity and reduced median pore radius of the compressed pellets. No effect of the process parameters on the degree of pellet deformation was reported. The tensile strength of the tablets prepared from unlubricated pellets increased slightly with increased compression force. Compression of pellets with high density silicified microcrystalline cellulose (SMCC HD 90) as embedding powder protected them from severe deformation and resulted in tablets with sufficient tensile strength, minimal friability, negligible elastic recovery and short disintegration time. The percentage of the pellets and the compression force affected the tensile strength of the prepared tablets whereas no influence of the turret speed and the pre-compression force was observed.

1. Introduction

Microcrystalline cellulose MCC has been the number one pelletisation excipient used to prepare pellets for pharmaceutical applications by the extrusion/spheronisation technique (Gehbre-Sellassie, 1989; Dukic'-Ott et al., 2009). The lack of disintegration (Kleinebudde, 1994) leading to a slow matrix-like drug release from MCC pellets (Zimm et al., 1996) as well as the adsorption of some active pharmaceutical ingredients onto MCC fibres (Okada et al., 1987; Rivera and Ghodbane, 1994; Al-Nimry et al., 1997) emphasize the need for pelletisation aids which can overcome these problems. κ-Carrageenan has shown to be a promising alternative to microcrystalline cellulose. Recent studies indicate that pellets prepared using κ-carrageenan are of high quality (Bornhöft et al., 2005) and exhibit lower tensile strength, faster disintegration and faster drug release compared to MCC pellets (Thommes and Kleinebudde, 2006a). Moreover, the influence of drug solubility on its release profile from κ-carrageenan pellets is much less pronounced than that from MCC pellets (Thommes and Kleinebudde, 2006b). κ-Carrageenan pellets also possess a considerably high formulation robustness allowing the use of a wide spectrum of fillers and active ingredients at largely variable fractions (Thommes and Kleinebudde, 2006b). Therefore κ-carrageenan seems to be particularly advantageous for the formulation of enteric coated pellets containing poorly water soluble drugs which, after leaving the stomach, release the active ingredient quickly in the small intestine.

Pellets for oral use are generally presented in the form of capsules or tablets. The development of multiparticulate dosage formulations in the form of tablets is more cost-effective (Celik, 1994) and allows higher drug content compared to encapsulated forms of pellets, which are limited by the packing properties of the pellets and the capsule size (Lundqvist et al., 1997), given also the higher compliance to big tablets compared to big capsules (Bodmeier, 1997). The divisibility of multiparticulate tablets (Beckert et al., 1996) as well as the reduced liability to tampering and the less problems encountered during oesophageal transport (Bodmeier, 1997) are other advantages of this dosage form in comparison to capsules.

The compression of κ-carrageenan powder has been the subject of a few studies (Picker, 1999). However, pellets show different consolidation and deformation mechanisms during tabletting to those of powders, due to the significantly lower surface to volume ratio of the former which results in a smaller contact area between the particles upon compression. Different compaction

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properties and tensile strengths of tablets prepared from microcrystalline cellulose powder and pellets were reported (Maganti and Celick, 1993). Thus, further work should be done to assess the compression behaviour and the properties of tablets prepared from κ-carrageenan pellets.

The great majority of compression studies on pellets were carried out using eccentric compression machines. A better approach would be to use rotary tabletting machines, which ultimately mimic the work conditions encountered in the pharmaceutical industry. The aim of this study is to investigate the compression behaviour and tablet forming ability of κ-carrageenan pellets in a rotary tabletting machine.

Compression of pellets in a powder bed helps protecting them from severe deformation and prevents the formation of a matrix tablet upon contact with water. The embedding powder should possess, in addition to the properties of directly compressible excipients, a high deformability and an excellent ability to form homogeneous mixtures with the pellets in order to ensure the uniformity of content of the prepared tablets. It should also exhibit a high dilution potential leading to a higher amount of pellets within the tablet while maintaining sufficient mechanical properties. Most importantly the powder bed should ensure fast disintegration of the tablet into pellets (Bodmeier, 1997). In this study the use of high density silicified microcrystalline cellulose SMCC HD 90 was investigated as a potential embedding medium for κ-carrageenan pellets.

2. Materials and methods

2.1. Materials

Theophylline monohydrate (BASF, Ludwigshafen, Germany), paracetamol BP/PH EUR/USP PowderAPC 178 (Atabay, Turkey), hydrochlorothiazide (Unichem, Mumbai, India), κ-carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, PA, USA), α-lactose monohydrate (Granulac® 200, Meggle, Wasserburg, Germany), dicalcium phosphate dihydrate C 92-14 (Chemical fabric Budenheim, Germany), high density silicified MCC SMCC HD 90 (Prosolv® HD90, J.R.S. Pharma Rosenberg, Germany), crospovidon (Kollidon® CL, BASF, Ludwigshafen, Germany), magnesium stearate pharma VER (Baerlocher, Unterschleissheim, Germany), deionised water.

2.2. Methods

2.2.1. Preparation of pellets by extrusion–spheronisation

Four pellet formulations A, B, C and D (Table 1) were prepared by the extrusion–spheronisation technique.

The weighed powders were transferred into a laboratory-scale blender (LM40, Bohle, Ennigerloh, Germany) and blended for 30 min at 35 rpm. The dry powders were then wetted with deionised water using a high shear mixer (Mini-MGT, Bayer, Leverkusen, Germany) for 5 min at 420 rpm. The wetted mass was supplied to a flat die press 14-175 (Amandus kahl, Germany) at a feeding screw rate of 100 rpm and extruded at a roller speed of 30 rpm through a flat screen with dies of 0.6 mm diameter. The distance between the screen and knife was adjusted to 3 mm.

Table 1
Studied pellets formulations and amount of water used for extrusion/spheronisation.

	A	B	C	D
Theophylline (%)	80			
Paracetamol (%)		80		
Hydrochlorothiazide (%)			10	10
Dicalcium phosphate dihydrate (%)			70	
Lactose (%)				70
κ-Carrageenan (%)	20	20	20	20
Deionised water (%)	52	50	56	46

Collected extrudate batches of approximately 300 g were transferred into a spheroniser (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a cross-hatched rotor plate of 300 mm diameter and were spheronised for 6 min at a spheronisation speed of 1500 rpm and a temperature of 25 °C. The resulting pellets were then transferred to a fluid bed drier (GPCG 1.1, Glatt, Dresden, Germany) and dried for 20 min at 60 °C.

The prepared pellets were stored at 20 °C and 40% relative humidity at least three days before characterisation.

2.2.2. Characterization of the prepared pellets

2.2.2.1. Yield of the pelletisation process. The yield of the pelletisation process (the fraction of pellets with a diameter between 400 and 1000 μm) was determined using a sieving system (Retsch, Haan, Germany) coupled with a vibration apparatus (AS200 control, Haan, Germany) at an amplitude of 1.5 over 3 min.

Additionally, pellets of the size fraction 500–800 μm were collected and used for characterisation and throughout the compression studies.

2.2.2.2. Image analysis. The particle size distribution (median of mean Feret diameters, median equivalent diameter and 10% interval) and shape factors (aspect ratio and roundness factor) were determined with the help of an image analysis system consisting of a stereo microscope (Leica MZ 75, Cambridge, UK), a ring light with cold light source (Leica KL 1500, Cambridge, UK), a digital camera (Leica CS 300 F, Cambridge, UK), and an image-analysing software (Qwin, Leica, Cambridge, UK). 500 pellets of the chosen size fraction of each pellet formulation were analysed at a suitable magnification (1 pixel = 5.47 μm). For each pellet 64 Feret diameters and the projected area (A) were measured. The equivalent diameter was quoted as $d_{eq} = \sqrt{4A/\pi}$ and the 10% interval was calculated as the percentage of pellets with a dimensionless diameter $d_d = d_{eq}/d_{eq50}$ between 0.9 and 1.1 (Thommes and Kleinebudde, 2006a).

The aspect ratio was calculated as the ratio between the maximum Feret diameter and the Feret diameter perpendicular to it. The roundness factor was quoted as the ratio of the particle area A to the area of a sphere with a diameter equal to the maximum Feret diameter d_{max} of the measured particle: Roundness $= A/[\pi(d_{max}/2)^2]$.

2.2.2.3. Poured bulk density, tapped density. The poured bulk density and the tapped density of the pellets ($n = 3$, sample mass = 150 g) were determined using a tap volumeter (J. Englsmann A.G., Ludwigshafen, Germany) equipped with a 250 ml cylinder as described in the European Pharmacopeia 6th edition (2009).

2.2.2.4. Particle density. The particle density (helium density) of the prepared pellets was determined using helium pycnometry (AccuPyc 1330, Micromeritrics, Mönchengladbach, Germany) ($n = 3$).

2.2.2.5. Mercury porosimetry and voidage. The apparent bulk density (mercury density) and the median pore radius of the prepared pellets were determined using mercury porosimetry (Pascal 140, Pascal 440, Thermo Finnigan Milano, Italy) ($n = 2$). The total porosity was calculated as: porosity (%) = [1 − (mercury density/helium density)] × 100.

The voidage of each bed of pellets was calculated from the tapped density and the mercury density.

2.2.2.6. Disintegration time. The disintegration time of the pellets was determined using a tablet disintegration tester (DT2, Sotax, Basel, Switzerland). 6 samples of 50 mg of each pellet formulation were filled into special sample holders equipped with 350 μm

Table 2
Design of tabletting experiments for lubricated (all formulations) and unlubricated pellets (formulation B).

Factor	−1	0	+1
Compression force (kN)	15	20	25
Turret speed (rpm)	10	25	40

sieves on the upper and lower faces. The compartments were then placed in the disintegration apparatus and tested in deionised water at 37 °C and 30 shakes per minute.

2.2.2.7. Resistance to fracture. The mechanical properties of pellets were characterized using a texture analyzer (TA.XT2i, Stable Micro Systems, Godalming, UK) at a loading rate of 0.01 mm/s. The fracture force (F) of 55 pellets per formulation was determined as the first peak of the recorded force displacement curve.

2.2.3. Compression of pellets without an embedding powder

Pellets of the chosen size fraction (500–800 μm) were compressed using a rotary tabletting machine (Pressima, Kilian, Cologne, Germany) equipped with a single convex punch with a diameter of 12 mm and a curvature radius of 15 mm, to give tablets of 550 mg weight.

Two sets of pellet formulations were used for compression studies: (I) lubricated pellets (all pellet formulations), prepared by mixing the pellets with 0.5% magnesium stearate for 5 min at 42 rpm in a turbula mixer (T2C, Willy A. Bachofen, Basel, Switzerland) and (II) unlubricated pellets (formulation B).

In case of unlubricated pellets, the upper punch and lower punch as well as the die walls were lubricated with a suspension of 1% magnesium stearate in ethanol 96%.

Compression of both lubricated and unlubricated pellets took place according to a 2^2 full factorial design with three replicates of the central point (Table 2).

The prepared tablets were then stored at 20 °C and 40% relative humidity for 7 days before characterization.

2.2.4. Retrieval and characterization of compressed lubricated pellets

Tablets prepared starting from lubricated pellets were gently shaken in Petri dishes to de-aggregate them and retrieve the original pellets.

Retrieved pellets were then subjected to further tests (image analysis, texture analysis and porosity measurements) as previously described.

2.2.5. Characterisation of the tablets prepared from sole unlubricated pellets

2.2.5.1. Tensile strength. The tensile strength of the tablets was determined using a tablet hardness tester (Sotax HT1, Basel, Switzerland) in the mode constant speed of 1 mm/s. The diametrical force needed to crush the tablets was measured and the tensile strength was calculated using the following equation for convex tablets according to Pitt et al. (1988):

$$\sigma_t = \frac{10P}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1}$$

where P is the fracture force, D is the tablet diameter, t is the thickness of the cylindrical part of the tablet and W is the curvature radius.

2.2.5.2. Elastic recovery. The thickness of the produced tablets was measured immediately and 10 days after compression. The post-compressional elastic recovery was calculated as the percentage increase in tablet thickness.

Table 3
Design of compression experiments for pellet formulation D with SMCC HD 90 as embedding powder.

Factor	−1	0	+1
Percentage of pellets (%)	50	60	70
Pre-compression force (kN)	0	2.5	5
Compression force (kN)	15	20	25
Turret speed (rpm)	10	25	40

2.2.6. Compression of pellets with SMCC HD 90 as an embedding powder

Pellets of the chosen size fraction 500–800 μm from formulation D were mixed with 1% Kollidon® CL and SMCC HD 90 at different ratios for 20 min and the resulting mixtures were lubricated with 0.05% magnesium stearate in a turbula mixer for 5 min at 42 rpm. The prepared mixtures were compressed to give tablets of 600 mg weight according to a 2^{4-1} fractional factorial design (Table 3) with three replicates of the central point.

Additionally a highly lubricated pellet–powder mixture was prepared by separate lubrication of the pellets and SMCC HD 90 with magnesium stearate (0.5% for 5 min for the pellets and 2% for 24 h for SMCC HD 90 in a turbula mixer at 42 rpm), followed by mixing of the two components for 20 min (percentage of pellets 60%).

The highly lubricated mixture was then compressed under the compression conditions for the central point (Table 3).

The prepared tablets were then stored at 20°C and 40% relative humidity for 7 days before characterization.

2.2.7. Retrieval and characterisation of compressed pellets from the tablets prepared from a highly lubricated pellets/SMCC HD 90 mixture

Tablets prepared from the highly lubricated pellets–powder mixture were gently shaken in Petri dishes to de-aggregate them, followed by sieving through a 500 μm sieve to remove the powder rests.

The particle size and shape factors of the retrieved pellets were then determined as described above.

2.2.8. Characterization of the tablets prepared from unlubricated pellets using SMCC HD 90 as embedding powder

2.2.8.1. Tensile strength. The tensile strength of the tablets was determined as described above.

2.2.8.2. Elastic recovery. The post-compressional elastic recovery of the tablets after 10 days was determined as previously described.

2.2.8.3. Disintegration time. The disintegration time of 6 tablets per formulation was determined using a tablet disintegration tester (DT2, Sotax, Basel, Switzerland) in deionised water at 37 °C and 30 shakes per minute. Disks of appropriate size were used to prevent the tablets from floating during the test.

2.2.8.4. Friability. The friability was determined using a friability tester (Erweka, Heusenstamm kr. Offenbach, Main, Germany) as described in the European Pharmacopeia 6th edition (2008a). Samples of whole tablets corresponding to approximately 6.5 g were de-dusted prior to testing, weighed and placed in the drum, which was rotated 100 times. The tablets were then removed, de-dusted again and weighed. Friability was calculated as the percentage loss of weight.

2.2.8.5. Homogeneity of content. The homogeneity of content of the prepared tables was evaluated using the acceptance criteria described by the European Pharmacopeia 6th edition (2008b). 10 tablets were separately dissolved each in 1 l of deionised water in

an Ultrasound bath for 30 min at room temperature. The resulting solutions were then filtered and diluted. The hydrochlorothiazide content was determined using UV spectroscopy at a wavelength of 272.

2.2.9. Scanning electron microscopy

The morphology of the uncompressed and retrieved pellets of all pellet formulations as well as the fracture surfaces of the tablets after the crushing strength test were examined using scanning electron microscopy (LEO VP 1430, Carl Zeiss, Jena, Germany). Before scanning, the dried samples were sputter-coated with gold for 180 s under Argon (Agar Manual Sputter Coater B7340, Agar Scientific, Stansted, UK).

3. Results and discussion

3.1. Characterisation of the prepared pellets

Table 4 shows the yield of the pelletisation process, the size and shape factors and the disintegration times of the four prepared pellet formulations. All pellet formulations met the required specifications in terms of roundness, aspect ratio (median aspect ratio around 1.1) and particle size distribution (10% interval of the dimensionless diameter above 50%, Thommes and Kleinebudde, 2006a). The prepared pellets exhibited also short disintegration times of few minutes as expected with pellets made using κ-carrageenan as pelletising agent.

3.2. Compression behaviour of the studied pellet formulation

3.2.1. Model

In order to provide a realistic and comprehensive approach the prepared pellet formulations were chosen to represent both cases of high drug strength (formulations A and B) and low drug strength (formulations C and D) as well as pellet components with different compression mechanisms in each category: 80% of the highly plastically deforming theophylline in formulation A against 80% of the highly fragmenting paracetamol known for its capping tendency in formulation B and 70% of the granular lactose, deforming by fragmentation but also to a certain extent by plastic deformation in formulation D against 70% of the highly fragmenting aggregates of dicalcium phosphate dihydrate in formulation C.

3.2.2. Scanning electron microscopy

SEM micrographs of the uncompressed pellets and the pellets retrieved by de-aggregation of the tablets prepared of lubricated pellet from the four pellets formulations (Fig. 1) indicate that, regardless of the compression behaviour of the original pellet components, the pellets remained as coherent units after compression and did not fragment. Moreover, cracks on the surfaces of retrieved pellets are almost absent. It can be then suggested, that deformation is the dominating mechanism of compression for the studied pellets and that their fragmentation under load is minimal.

The retrieved pellets were readily obtained by gentle shaking of tablets in Petri dishes and only a small difficulty was encountered in the retrieval of compressed pellets D. The ability to easily de-aggregate the tablets prepared from lubricated pellets or in other words the low compactibility of lubricated pellets is an indirect indication of the domination of deformation and the absence of fragmentation and attrition which would otherwise rupture the magnesium stearate film surrounding the pellets thus creating new lubricant-free surfaces which is accompanied by increased bonding resulting in stronger tablets that are difficult to de-aggregate (Johansson et al., 1995). It should be also noticed, that the amount of magnesium strearate used to lubricate the pellets (0.5%) as well as the mixing time (5 min) were lower than those mentioned in the literature for MCC pellets (2% for 100 min, Nicklasson et al., 1999a; 0.5% for 100 min, Johansson et al., 1995) but still sufficient to deaggregate the κ-carrageenan pellets used in this study.

SEM micrographs of the fracture surface of the tablets prepared from unlubricated pellets of formulation B support the previous findings (Fig. 2) whereby the fragmentation of pellets is negligible and the deformation at the surfaces and sides of the tablets is greater than that in the centre of the tablets, due to the convex shape of the used punches.

3.2.3. Image analysis

The data acquired from image analysis (Fig. 3) confirm the statements made above. For all pellet formulations there was no reduction of the pellet size upon compression, thus eliminating the occurrence of significant fragmentation. On the opposite an increase in the equivalent diameter was noticed in all cases (Fig. 3I), thus confirming the flattening of pellets after compression since this size parameter is calculated based on the measured projected area of the particles. The minimal reduction in the equivalent diameter of pellet formulation D (in less than 10% of the measured particles) suggests a limited fragmentation. The flattening of pellets after compression was further confirmed by the increase in the aspect ratio (Fig. 3II) and the decrease of roundness (Fig. 3III), two shape factors which are commonly used to assess the sphericity of pellets. In this work the roundness was quoted to provide another assessment tool in addition to the aspect ratio, since the latter is rather suitable for the description of roundness of cylindrical to round particles and the retrieved pellets being examined exhibit an irregular shape. The worsening of these two shape factors in the retrieved pellets in comparison to the original pellets indicates the deformation of particles after being subjected to the applied load. Furthermore, all three measured parameters showed a considerably wider distribution in case of the retrieved pellets in comparison to the uncompressed pellets, caused by the different deformation patterns undergone by the pellets due to the different stress distribution in the different areas of the tablets, i.e.

Table 4
Yield of the pelletisation process, size and shape factors, poured bulk density, tapped density, voidage and disintegration time of the chosen size fraction (500–800 μm) of the studied pellet formulations.

Pellets formulation	A	B	C	D
Yield (400–1000 μm) (%)	96.3	97.3	87.0	86.5
Median of mean Feret diameters (μm)	680	697	647	710
10% interval	60.8	65.4	58.6	65.8
Median aspect ratio	1.11	1.10	1.11	1.11
Median roundness	0.86	0.87	0.86	0.86
Bulk density (g/ml)	0.77 ± 0.005	0.67 ± 0.012	0.92 ± 0.005	0.75 ± 0.003
Tapped density (g/ml)	0.83 ± 0.007	0.75 ± 0.018	1.02 ± 0.011	0.85 ± 0.006
Tapped voidage of pellets masses (%)	37.6	32.1	36.0	31.5
Disintegration time (s)	219 ± 19	208 ± 18	301 ± 23	218 ± 17

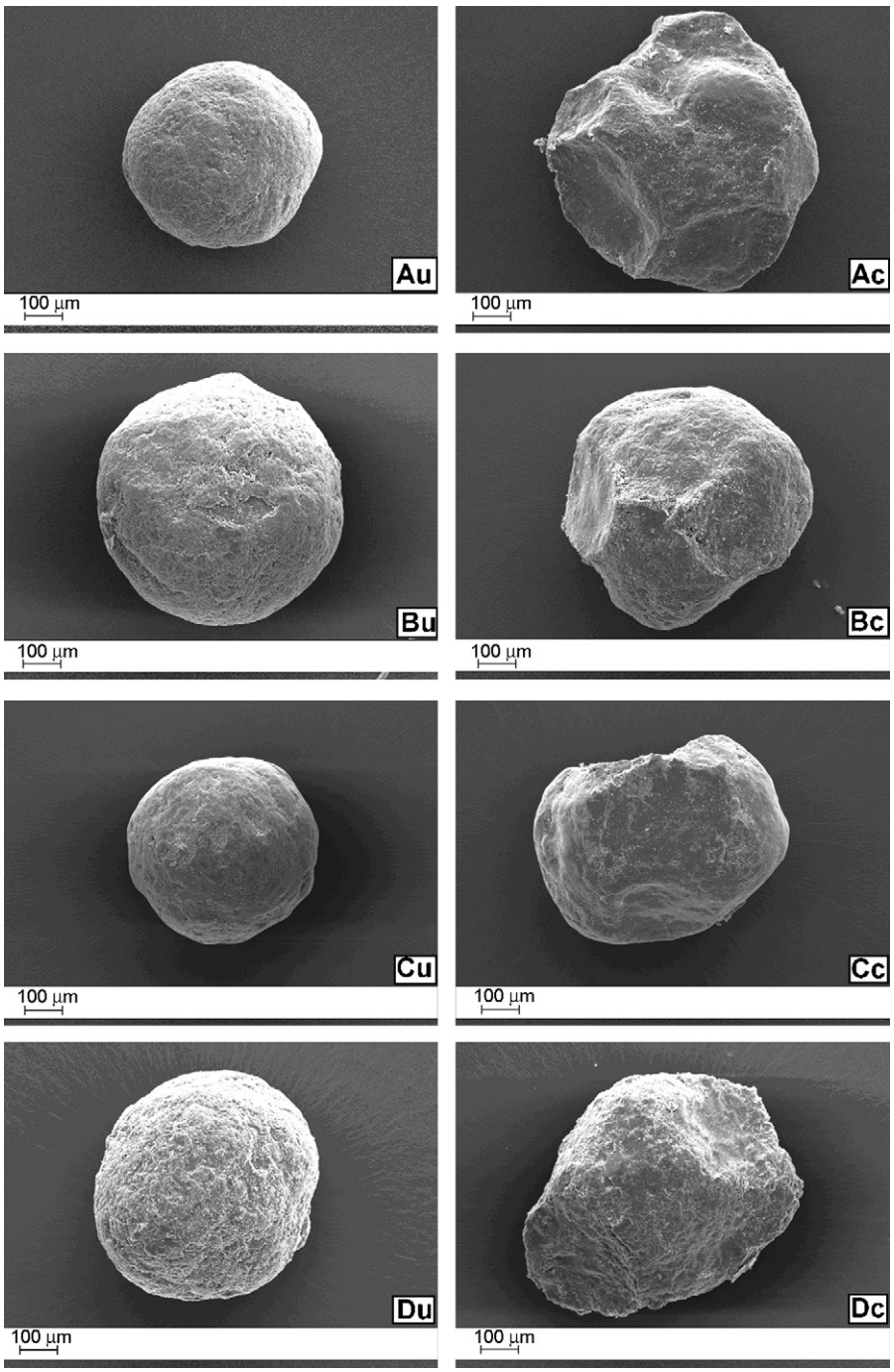

Fig. 1. SEM micrographs of uncompressed pellets (A_u, B_u, C_u, D_u) and pellets retrieved after compression (A_c, B_c, C_c, D_c) of the lubricated pellet formulations (20 kN, 25 rpm).

in the centre or closer to the surfaces or to the periphery of the tablets.

3.2.4. Fracture force and porosity measurements

The fracture forces of the uncompressed pellets and those of the pellets retrieved after compression were compared (Fig. 4). A one-tailed *t*-test assuming unequal variances showed, at a confidence level of 95%, that the average fracture force of the retrieved pellets was significantly higher than that of the original pellets in case of pellet formulations A, B and D whereas no statistically significant difference was found in case of formulation C. These findings support the fact that the pellets remained as intact units and exclude the formation of significant cracks upon compression. The unchanged fracture resistance in case of formulation C may be caused by the rigid character of dicalcium phosphate. Nicklasson et al. (1999a) suggested that DCP/MCC pellets with a ratio of 4:1 exhibit lower densification when compared to MCC pellets and attributed the difference in the degree of densification to the properties of the primary particles and their readiness to reposition under load, which are limited in case of the rigid and non-deformable DCP. The same authors reported a different mode of deformation between the two studied pellet formulations whereby the DCP/MCC pellets exhibited a high surface deformation due to the concentration of stress at the contact areas between the pellets rather than across the pellets whereas MCC pellets underwent a bulk deformation under stress. The increase in the equivalent diam-

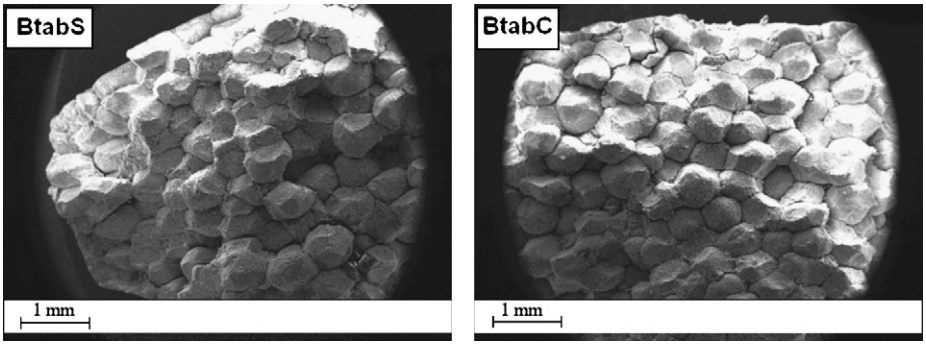

Fig. 2. SEM micrographs of the fracture surface of tablets prepared by compression of unlubricated pellet formulation B: (BtabS) side of the tablet and (BtabC) centre of the tablet (20 kN, 25 rpm).

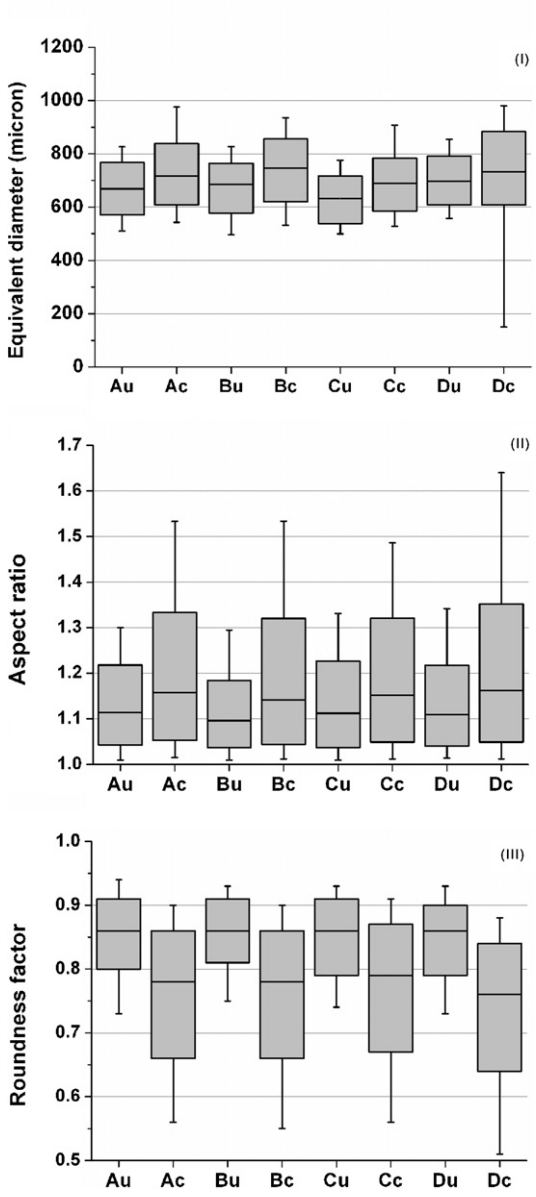

Fig. 3. (I) Equivalent diameter, (II) aspect ratio and (III) roundness factor (x_1, x_{10}, x_{50}, x_{90}, x_{99}) of the uncompressed pellets (A_u, B_u, C_u, D_u) and the pellets retrieved after compression (A_c, B_c, C_c, D_c) (20 kN, 25 rpm).

eter and aspect ratio of retrieved pellets C without a significant change in the fracture force in comparison with the uncompressed pellets agrees with the statements made by Nicklasson.

The few low values of fracture force for the retrieved pellets in all pellet formulations (Fig. 4) may be explained by the position of pellets under the texture analyser probe during the analysis. When the edge of a deformed particle comes under the probe or oppositely lies in contact with the test plate the pellet can reorient itself during the measurement leading to a fall in the measured force, which is falsely interpreted by the system as a fracture force.

The higher fracture resistance of the retrieved pellets may be attributed to the lower porosity of the retrieved pellets in comparison to the original pellets (Fig. 5I) thus indicating a densification of pellets under load. A decrease in the total porosity was also reported for pellet formulation C but the decrease was less pronounced compared to the other formulations, which is in accordance with the assumptions made above. Moreover, the decrease of porosity was also accompanied by a decrease of the median pore radius (Fig. 5II), which supports the deformation of pellets by flow of primary particles in the free pores area as described by Johansson et al. (1995). The unchanged median pore radius in case of pellet formulation A can be attributed to the poor reproducibility of porosity measurements performed on the retrieved pellets of this formulation, probably caused by the very small pore size which lies close to the limits of sensitivity of the mercury porosimeter. Due to the high deviation in the results obtained with this formulation, a third measurement was carried out on these retrieved pellets. Two of the measured samples showed significantly smaller median pore radius (0.004 and 0.005 μm) in comparison to the uncompressed pellets (0.007 μm) whereas the remaining sample had a higher median pore radius (0.013 μm). Another possible reason for the increased resistance to fracture of the studied pellets after compression is the flattening of pellets upon compression leading to a higher stress distribution during the test for fracture resistance.

Key factors in the compression mechanics of aggregates is the porosity as well as the physical and mechanical properties of the primary particles contained in the compressed entities. The extent of fragmentation during volume reduction of porous aggregates reported in the literature varies from a considerable level to very limited or non-existent based on the formulation used. Dominating deformation, some densification and limited fragmentation during compression was reported for Xanthan gum pellets (Santos et al., 2004), MCC pellets (Johansson et al., 1995; Johansson and Alderborn, 1996, 2001) and DCP/MCC pellets (Nicklasson et al., 1999b) having different levels of porosity together with increased degree of deformation leading to a higher compactibility upon increasing the original porosity of the pellets. On the other hand, fracture of soft pellets containing MCC, barium sulphate and glycerol monostearate under low pressure and formation of cracks and flaws after a compression threshold of 9 MPa in hard pellets con-

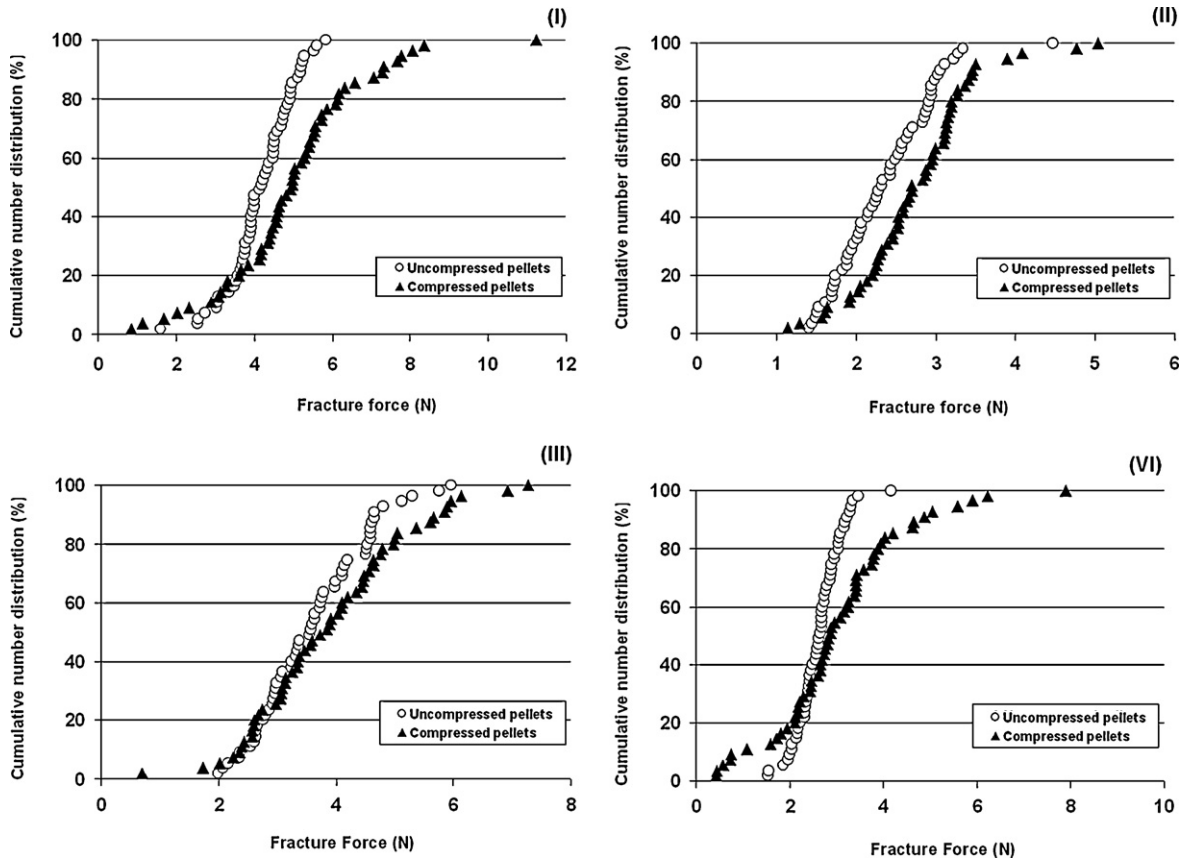

Fig. 4. Cumulative number distribution of the fracture force of the uncompressed pellets and the pellets retrieved after compression: (I) pellets formulation A, (II) pellet formulation B, (III) pellet formulation C and (VI) pellet formulation D (20 kN, 25 rpm).

taining riboflavin, hydrous lactose and microcrystalline cellulose were reported by Salako et al. (1998). Elastic deformation and some fragmentation of pellets containing MCC, propranolol, and lactose or dicalcium phosphate dihydrate as fillers were mentioned by Maganti and Celick (1993).

The fact that despite the low tensile strength of the studied pellet formulations (as with pellets made with κ-carrageenan in general) the fragmentation of pellets under load was minimal to absent may disagree with the statements made by Wickberg and Alderborn (1992) who reported that a low mechanical strength of the aggregates leads to high degree of fragmentation under compression and correlated the fragmentation of different lactose granule formulations to their lower tensile strength (varying between less than 1 and 4 N) compared to that of dipentium granules (fracture force between 3 and 4 N) which mainly deformed during tabletting. It may be however argued that the round homogenous shape and the smooth surface of the examined pellets are quite different from the irregular rough surface of granules which were used in these studies. MCC pellet formulations with different levels of fracture forces varying from 2 N to around 13 N were all found to deform upon compression with no fragmentation (Johansson et al., 1995). In the same study it was suggested that the resistance to fracture of the individual pellets used in the study is not a key factor in their behaviour under load but may be of primary importance for pellets and granules exhibiting considerable fragmentation upon compression. Johansson attributed the minute fragmentation of the examined MCC pellets and the domination of deformation upon compression to the lower energy needed to cause particle repositioning within the pellets by a shearing process compared to that required to fragment the pellets and assigned this energy gap to the special pressure conditions of the sole pellets in the die whereby the pellets are simultaneously stressed from all directions and are thus not easily fractured. However, the same author did not exclude the role of the round shape and smooth surface of the compressed pellets as well as the plastic nature of the forming material. On the other hand, both MCC granules having irregular shape and MCC pellets with low, intermediate and high porosity deformed under load and did not fragment with only some attrition of the high porosity granules i.e. the aggregate shape did not influence the compression mechanisms for the pellets made from this substance although it influenced their degree of deformation (Johansson and Alderborn, 2001). It seems therefore that also the role of the mechanical properties of the primary particles forming the pellets cannot be omitted and is most probably of significant relevance. Compression studies on κ-carrageenan powder reported a Heckel function of 0.0175 MPa^{-1}, high elasticity (elastic recovery up to 28% after 10 days) with mechanical interlocking of the particles (Picker, 1999). Unlubricated pure κ-carrageenan pellets were compressed in the preliminary experiments of this work and no tablets could be obtained indicating that the high elasticity of this substance was maintained after wet extrusion/spheronisation and subsequent drying. The low or absent fragmentation of the studied pellet could be hence possibly partially related to this elastic behaviour of κ-carrageenan. Force–displacement curves obtained from texture analysis of all studied pellets (data not shown) exhibit an initial curvature indicating an elastic component followed by plastic linear phase before the first drop of force corresponding to breakage. An elasto-plastic deformation pattern (initial non-linear part followed by a linear section in the pressure–strain curves of the individual granules) for different types of MCC pellets with different degrees of deformation propensity including high and low porosity pure MCC pellets as well as MCC pellets with lactose as

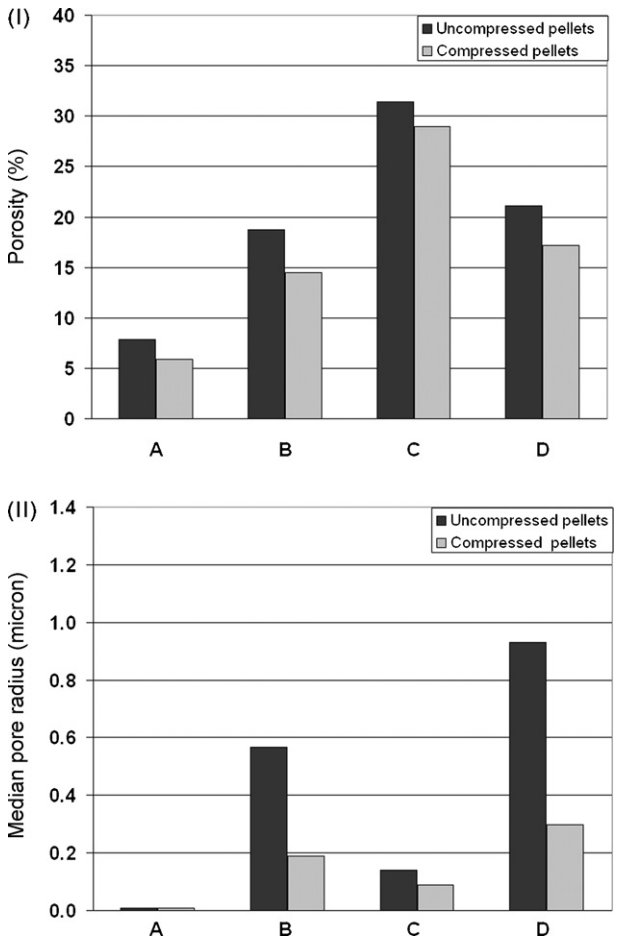

Fig. 5. (I) Total porosity and (II) median pore radius of the uncompressed pellets (A_u, B_u, C_u, D_u) and the pellets retrieved after compression (A_c, B_c, C_c, D_c), (20 kN, 25 rpm).

a brittle material or polyethylene glycol as a soft component was also reported by Nordström et al. (2008). The same authors related the compression properties of pellets to the mechanical behavior of their single granules.

The limited fragmentation observed in the retrieved pellets in case of formulation D may be explained as suggested by Santos et al. (2004) by the recrystallisation of the water soluble lactose during drying on the wet pellets leading to increased interparticulate bonds within the pellets and resulting in less elastic and more brittle structure. Pellet formulation D exhibited also lower original porosity than that of pellet formulation C which is coherent with the suggested more closed structure. Limited fragmentation upon compression (small fragments in the voids between the pellets seen at the tablet fracture surface) and a more brittle nature for MCC lactose pellets compare to other types of MCC pellets were also observed by Nordström et al. (2008) along with the dominating deformation mechanisms for these granules. It is also to

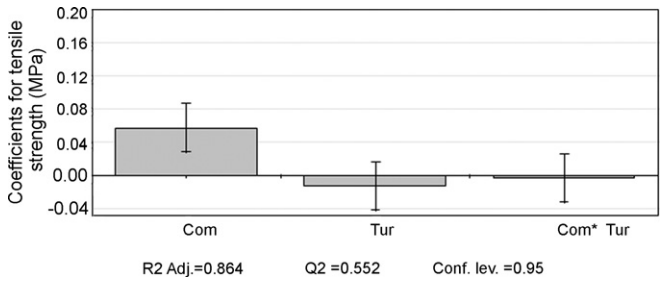

Fig. 6. Coefficients plot for the tensile strength of tablets prepared from unlubricated pellet formulation B: (com) compression force, (tur) turret speed.

be mentioned, that the tablets prepared from lubricated pellets of this formulation were more difficult to deaggregate than those prepared from the other three formulations, which suggests some fragmentation or probably an extensive degree of deformation leading to increased lubricant-free bonding surfaces. It is also possible that this minute fragmentation occurred during the retrieval process. However, whether this limited fragmentation occurred during compression or during retrieval of compressed pellets its extent is minimal and can be therefore neglected.

3.2.5. Effect of process parameters on the size and shape of compressed pellets

No significant effect of the process parameters (compression force and turret speed) on the size and shape of retrieved pellets could be established for all pellet formulations in the range of force and speed examined. As an example the results obtained with pellet formulation C are presented in Table 5. The variances between the measured responses were very small and lower than that between the replicate experiments of the central point. It can then be argued, that the pellets show no significant difference in their degree of deformation inside the chosen ranges of the examined parameters. The change of shape factors for MCC pellets with increased pressure reported by Johansson and Alderborn (1996) occurred in a pressure range far less than that used in this study, and probably changes in the degree of deformation of the studied pellets could be seen at lower compression pressure or upon examining a larger pressure range than the one applied. The variability of the replicate experiments of the central point could be attributed to the complicated deformation pattern of the pellets in a convex tablet due to differences in the stress distribution between the various areas of the compact.

3.2.6. Effect of the process parameters on the properties of tablets made of sole pellets

Moreover, the process parameters had a slight effect on the tensile strength of the tablets prepared from unlubricated pellets (Table 6 and Fig. 6). The tabletting of sole pellets resulted in weak compacts caused most probably by the reduced bonding area in the compressed system due to the low surface area as well as the absence of attrition which would have resulted in new bonding points. Johansson and Alderborn (2001) highlighted the effect of

Table 5
Measured responses for the compression experiments with lubricated pellet formulation C.

Exp. name	Compression force (kN)	Turret speed (rpm)	Median equivalent diameter (μm)	10% interval (%)	Median aspect ratio	Median roundness factor
N1	15	10	670	56.0	1.15	0.78
N2	25	10	675	63.6	1.15	0.78
N3	15	40	668	61.4	1.15	0.78
N4	25	40	672	64.8	1.16	0.79
N5	20	25	690	61.8	1.15	0.79
N6	20	25	671	58.4	1.14	0.79
N7	20	25	652	59.8	1.14	0.78

Table 6
Measured responses for the compression experiments with unlubricated pellet formulation B.

Exp. name	Compression force (kN)	Turret speed (rpm)	Tensile strength (MPa)	Elastic recovery (%)
N1	15	10	0.14	0.25
N2	25	10	0.26	0.31
N3	15	40	0.12	0.36
N4	25	40	0.23	0.37
N5	20	25	0.22	0.32
N6	20	25	0.18	0.34
N7	20	25	0.19	0.28

shape on the compatibility of MCC aggregates whereby a more irregular shape of MCC granules corresponding to a lower poured bulk density resulted in stronger compact than those prepared from MCC pellets having a higher poured bulk density. The poured bulk densities of the studied pellets are presented in Table 1. An increase in the compression force led to only a slight increase in the tensile strength of the prepared tablets whereas no influence of the turret speed or the combination of the two examined parameters on the tensile strength was detected in the studied range. The slight increase in the tensile strength with increased fracture force agrees with the insignificant change in the shape factors mentioned previously. However, during the preliminary experiments the compression of unlubricated pellet formulation B at 10 kN compression force did not result in coherent tablets. Hence, again, more significant changes in the tensile strength with increased compression force could be noticed at lower ranges of applied load.

The measured post-compressional elastic recovery was minimal probably due to the fact that a great part of the elastic recovery may have occurred in the tabletting machine, which could not be determined due to the absence of an accurate displacement measuring system.

3.3. Compression of pellets with SMCC HD 90 as embedding powder

The results of the compression experiments carried out on the pellet formulation D using SMCC HD 90 as an embedding powder are summarized in Table 7. A low amount of magnesium stearate (0.05% of the total tablet weight and 0.1–0.17% of the powder weight depending on the percentage of pellets in the tablets) was used to lubricate these mixtures, due to the excellent flow properties of SMCC HD 90 consisting of a high density microcrystalline cellulose enriched with 2% colloidal silicone dioxide and the low surface area of the compressed system caused by the presence of pellets. The amount used resulted in good lubrication as shown by the low ejection force (220.6 ± 14.5 N at the compression conditions for the central point, $n = 10$). Pre-experiments with higher amounts of magnesium stearate resulted in weak tablets.

The resulting tablets fall in the optimal range of tensile strength of 0.56–1.11 MPa mentioned by Muzikova and Novakova (2007) except those prepared with a high pellet content (70%) at a low compression force (15 kN) which were below the lower limit and those with 50% pellet content prepared at high compression force which were higher than the defined range. A high percentage of pellets resulted in reduced bonding forces within the tablets due to the reduced contact area between the compressed entities. An increase in the compression force led to stronger tablets whereas no influence of the pre-compression force or the turret speed (excluded from the model upon optimisation being the most insignificant) on the tensile strength could be noticed in the examined range (Fig. 7I).

All tablets showed low values of post-compressional elastic recovery and friability, thanks to the good compression properties of SMCC HD 90. Most tablets disintegrated very rapidly (less than 90 s). The disintegration time of the hard tablets containing 50% pellets and compressed at a high compression force (25 kN) was markedly higher than the rest of the prepared tablets, remained however within the acceptable limits of less than 15 min. A multiparticulate behaviour of the compressed system could be thus maintained in all studied cases. The coefficients plot for the disintegration time (Fig. 7II) suggests an increase in the disintegration time with increased compression force whereas an increased pellet percentage and the interaction of pellet percentage and compression force results in decreased disintegration time.

Tablets containing 70% pellets showed poor uniformity of content. No variation of the tablet weight was observed and can be then exempted as a reason for the variation of content. The tablets prepared with 50 and 60% pellet percentage had a uniform drug content thus excluding any analytical mistake. Therefore, it could be suggested that the poor uniformity of content of tablets with 70% pellets is due to de-mixing. The particle size, bulk and tapped densities of SMCC HD 90 and pellet formulation D are summarized in Table 8.

Table 7
Measured responses for the compression experiments carried out on pellet formulation D with SMCC HD 90 as embedding powder.

Exp. name	Percentage of pellets	Percompression force (kN)	Compression force (kN)	Turret speed (rpm)	Tensile strength (MPa)	Elastic recovery (%)	Friability (%)	Disintegration time (s)	Coefficient of variation for tablet weight (%)	Acceptance value for the uniformity of content (%)
N1	50	0	15	10	1.27	0.05	0.009	48	1.2	13.0
N2	70	0	15	40	0.31	0.14	0.012	15	0.6	**18.1**
N3	50	5	15	40	1.06	0.06	0.017	37	0.5	7.6
N4	70	5	15	10	0.39	0.09	0.007	44	0.5	12.6
N5	50	0	25	40	1.87	0.04	0.011	470	0.7	7.2
N6	70	0	25	10	0.70	0.01	0.017	94	1.3	**19.8**
N7	50	5	25	10	1.66	0.04	0.006	349	0.8	12.4
N8	70	5	25	40	0.59	0.12	0.015	59	1.1	**15.1**
N9	60	2.5	20	25	0.82	0.06	0.023	89	0.6	11.1
N10	60	2.5	20	25	0.80	0.05	0.017	95	0.4	7.1
N11	60	2.5	20	25	0.83	0.06	0.015	99	0.7	7.7

The bold values refer to the acceptance values, which are out of specification of the European Pharmacopeia.

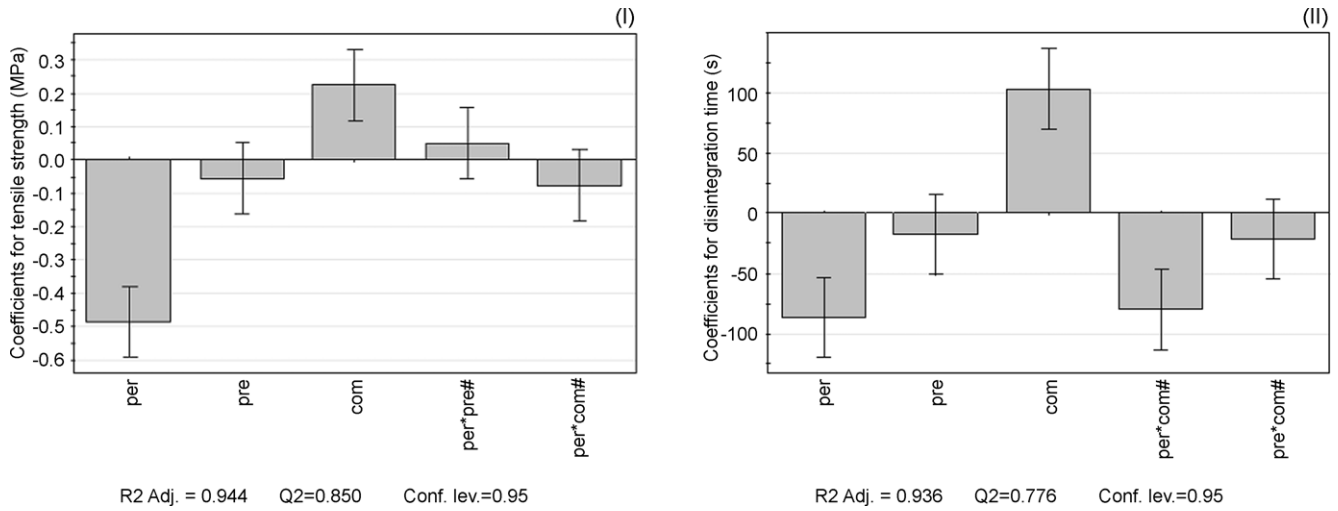

Fig. 7. Coefficients plots for (I) disintegration time and (II) tensile strength of tablets prepared from pellet formulation D with SMCC HD 90 as embedding powder: (per) percentage of pellets, (pre) pre-compression force, (com) compression force, (tur) turret speed.

Table 8
Particle size, poured bulk density and tapped density of SMCC HD 90 (according to manufacturer) and pellet formulation D.

	SMCC HD 90	Pellet formulation D
Particle size (μm)	d_{10} = 42, d_{50} = 124, d_{90} = 241 (using laser diffraction)	d_{eq10} = 608, d_{eq50} = 698; d_{eq90} = 792 (using image analysis)
Poured bulk density (g/ml)	0.46	0.75
Tapped density (g/ml)	0.59	0.85

The pellets retrieved after de-aggregation of tablets prepared from the highly lubricated pellet–powder mixture did not significantly differ in their equivalent diameter, aspect ratio and roundness (Fig. 8) from the uncompressed pellets. This may be explained by the good cushioning effect of the highly plastically deforming SMCC HD 90, which absorbs a high part of the applied load and deforms itself, thereby protecting the pellets from severe deformation.

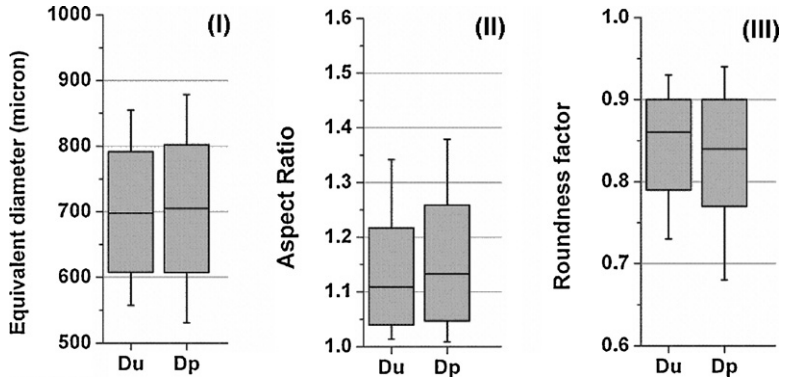

Fig. 8. (I) Equivalent diameter, (II) aspect ratio and (III) roundness factor ($x_1, x_{10}, x_{50}, x_{90}, x_{99}$) of uncompressed pellet formulation D (D_u) and pellets retrieved after compression of a highly lubricated mixture of pellet formulation D with a powder bed of SMCC HD 90 (D_p) (20 kN, 25 rpm, percentage of pellets 60%).

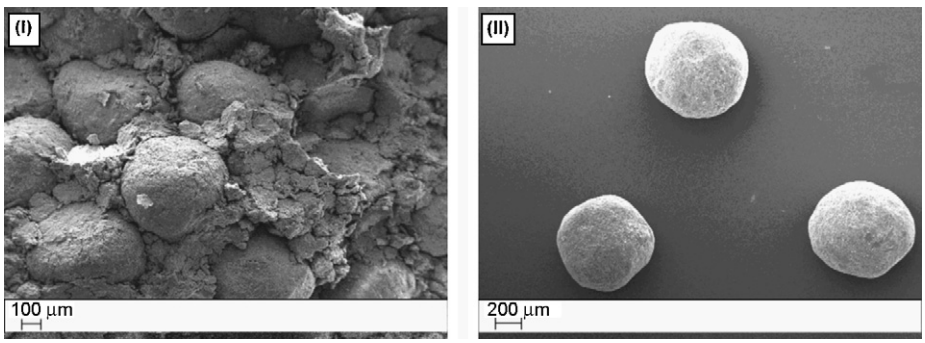

Fig. 9. SEM micrographs of: (I) the fracture surface of tablets prepared from pellet formulation D with SMCC HD 90 as embedding powder and (II) pellets retrieved after compression of a highly lubricated mixture of pellet formulation D with SMCC HD 90 (20 kN, 25 rpm, percentage of pellets 60%).

SEM micrographs of the fracture surface of the tablets prepared under the compression conditions of the central point (Fig. 9I) and the pellets retrieved after tabletting of the highly lubricated pellets–powder mixture (Fig. 9II) confirm the above findings and indicate limited deformation of the compressed pellets, which remained spherical to a considerable extent.

4. Conclusion

κ-Carrageenan pellets can be compressed into tablets with minimal fragmentation. Deformation is the dominating compression mechanisms of densification under load. Compression of the pellets with SMCC HD 90 as embedding powder can markedly minimise their deformation under stress, results in a short disintegration time and helps maintaining a multiparticulate behaviour of the tablet system. Optimisation of the properties and proportion of the powder bed are of vital importance. κ-Carrageenan pellets are promising candidates for multiparticulate tablets and may be particularly advantageous for those intended for fast drug release in the intestine.

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