Research Article

Application of Crustacean Chitin as a Co-diluent in Direct Compression of Tablets

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Abstract. A "simplex-centroid mixture design" was used to study the direct-compression properties of binary and ternary mixtures of chitin and two cellulosic direct-compression diluents. Native milled and fractioned (125–250 μm) crustacean chitin of lobster origin was blended with microcrystalline cellulose, MCC (Avicel® PH 102) and spray-dried lactose–cellulose, SDLC Cellactose® (composed of a spray-dried mixture of alpha-lactose monohydrate 75% and cellulose powder 25%). An instrumented single-punch tablet machine was used for tablet compactions. The flowability of the powder mixtures composed of a high percentage of chitin and SDLC was clearly improved. The fractioned pure chitin powder was easily compressed into tablets by using a magnesium stearate level of 0.1% (*w/w*) but, as the die lubricant level was 0.5% (*w/w*), the tablet strength collapsed dramatically. The tablets compressed from the binary mixtures of MCC and SDLC exhibited elevated mechanical strengths (>100 N) independent of the die lubricant level applied. In conclusion, fractioned chitin of crustacean origin can be used as an abundant direct-compression co-diluent with the established cellulosic excipients to modify the mechanical strength and, consequently, the disintegration of the tablets. Chitin of crustacean origin, however, is a lubrication-sensitive material, and this should be taken into account in formulating direct-compression tablets of it.

KEY WORDS: Cellactose®; chitin; direct compression; microcrystalline cellulose; simplex-centroid mixture design; tablets.

INTRODUCTION

Chitin is the second most common natural polymer on earth and the basic structural material of crustaceans and insects. It is a biocompatible and non-toxic amino polysaccharide composed of β(1-4)-linked *N*-acetyl-D-glucosamine units (1). This structure makes it also a chemically and physically very stable material (excipient).

In the literature, only few reports have been published so far on applications of chitin as an excipient in tablet compression. Chitin has been evaluated as a tablet disintegrant (2–4) and as a tablet filler-binder (5–9). Sawayanagi *et al.* studied blended powders of lactose, potato starch and mannitol with chitin and chitosan for direct compression of tablets (5,6). More recently, chitin of crustacean origin was found as an excellent diluent for direct compression resulting in, e.g. favourable disintegration properties of the tablets (7–9).

Chitin as an abundant and inexpensive material would be an interesting and potentially useful excipient to be applied as a co-diluent with the established direct-compression excipients. In the literature, mixtures of microcrystalline cellulose with other direct compression excipients have been evaluated with variable success (10,11). Mixing with two or three direct-compression excipients could provide enhanced flowing and compression properties of the mass and, consequently, significant improvements in, e.g. weight variation, mechanical strength, friability and disintegration of the tablets.

The aim of the present study was to investigate the direct compression properties of binary and ternary mixtures of a native chitin of crustacean origin and two cellulosic direct-compression excipients. A modified "simplex-centroid mixture design" was used as an experimental design for studying the effects of material components on tablet properties and for optimising the compositions of the respective binary and ternary mixtures.

MATERIALS AND METHODS

Materials

The materials studied were milled and fractioned native chitin (125–250 μm; extracted from lobster shell; Cuban Industry, Cuba), microcrystalline cellulose, MCC (Avicel® PH 102, FMC International, Cork, Ireland) and spray-dried lactose–cellulose, SDLC (Cellactose®, Meggle, Germany). Magnesium stearate (Ph.Eur.) was used as a lubricant for

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Table I. Experimental Matrix of the Modified Simplex-Centroid Mixture Design

Exp.	Mixture component proportions (%w/w)		
	Chitin (X_1)	MCC (X_2)	SDLC (X_3)
1	100	0	0
2	0	100	0
3	0	0	100
4	75	25	0
5	50	50	0
6	25	75	0
7	75	0	25
8	50	0	50
9	25	0	75
10	0	75	25
11	0	50	50
12	0	25	75
13	33.3	33.3	33.3
14	66.7	16.7	16.7
15	16.7	66.7	16.7
16	16.7	16.7	66.7

direct compression. The materials were stored under controlled conditions for at least 48 h (at 21°C and 50% RH) before testing.

Experimental Design

A modified "simplex-centroid mixture design" was used for studying the direct compression properties of binary and ternary powder mixtures of chitin and two cellulosic excipients, with two different amounts of magnesium stearate (0.1% and 0.5%, w/w). Table I presents the composition of the powder mixture. The total number of experiments (performed in a randomised order) was 36, and the centre point (experiment 13) was made in duplicate in both blocks.

The modelling was performed using Modde for Windows (Version 7.0, Umetrics, Umeå, Sweden). The best fitting mathematical model was selected on the basis of statistical testing and using Scheffé's (MLR) model with a level of significance $\alpha=0.05$. The model evaluation tools were goodness of fit (R^2), goodness of prediction (Q^2), analysis of variance, in terms of lack of fit test and the third tool was the evaluation of the model residuals using a normal probability plot (N plot) for detecting deviating experiments (12). The model was reduced to get as high Q^2 values as possible. The

values for R^2 and Q^2 as well as the mathematical models are shown in Table II.

Preparation and Characterization of Powder Mixtures

Physical mixtures of chitin and celluloses were prepared by blending the powder mixtures for 3 min in a glass jar with a laboratory-scale Turbula mixer (Turbula T10B, Willy A. Bachhofen AG Maschinenfabrik, Basel, Switzerland). Each batch prepared comprised 300.0 g of powder mixture. The mixtures were evaluated for particle size, shape, bulk and tapped densities and flowability. The particle size and shape of the excipients were studied by scanning electron microscopy (SEM; DSM 962, Zeiss, Oberkochen, Germany). Bulk and tap densities were determined by the established method of the European Pharmacopoeia (Ph.Eur.; 13). For determination of tap density, a standardised tapped density tester (Erweka SVM12, Heusenstamm, Germany) was employed. The Carr index and Hausner ratio were calculated from the tapped and bulk densities (14). Flow rate and static angle of repose were measured with an Erweka flowmeter (Pharmatest PTG, Heusenstamm, Germany).

A novel non-commercial apparatus was applied to study the flow properties of the powder mixtures. The present system was constructed by a glass funnel (with a wall angle of 60° and a round orifice of 25 mm in diameter) over a standardised tapped density tester (Erweka SVM12, Heusenstamm, Germany; Fig. 1). A glass plate equipped with an opened glass cube ($a=$ 25 mm) in the centre of it was adapted over the Erweka tester. The system included also a CCD camera (IAI CV-M50, Copenhagen, Denmark) and a personal computer.

For measuring the flowability, the fixed amount of a powder sample (30.0 ml) was allowed to flow from the filled funnel onto the glass cube. As the glass cube was full of powder, it began to flow over. A powder cone with a regular base was thus achieved. After this the powder cone was tapped a total of 16 times, the cone was imaged by a CCD camera and the height of the cone was calculated from the digital image using Matlab software (v. 7.0, MathWorks Inc., Natick, Massachusetts, USA).

Tablet Compression

Before the compression, the lubricant (magnesium stearate) was added to the previously prepared powder mixture of chitin and celluloses, and the mixture was blended

Table II. Summary of Fitted Models and Values of Goodness of Fit (R^2) and Goodness of Prediction (Q^2)

| Fitted model	R^2	Q^2
Bulk density, $0.50X_1+0.38X_2+0.46X_3-0.08X_1X_2-0.07X_1X_3$	0.987	0.946
Tap density, $0.44X_1+0.31X_2+0.39X_3+0.06X_1X_2-0.08X_1X_3$	0.972	0.941
Height of cone, $4.09X_1+6.66X_2+4.76X_3$	0.862	0.824
Crushing strength (at a lubricant loading level of 0.5%), $2.61X_1+358.04X_2+143.14X_3+66.11X_1X_2-37.05X_1X_3-42.73X_2X_3$	0.988	0.975
Friability (0.5%), $24.43X_1+0.50X_2+0.52X_3-35.38X_1X_2-32.98X_1X_3$	0.930	0.543
Crushing strength (0.1%), $2.48X_1+266.64X_2+145.01X_3-376.49X_1X_2-152.09X_1X_3-41.76X_2X_3$	0.985	0.943
Friability (0.1%), $3.76X_1+0.37X_2+0.04X_3-7.86X_1X_2$	0.852	0.586
R value (0.1%), $0.91X_1+0.92X_2+0.81X_3+0.19X_1X_3$	0.890	0.700
Ejection force (0.1%), $153.61X_1+47.92X_2+507.53X_3-785.22X_1X_3$	0.681	0.508
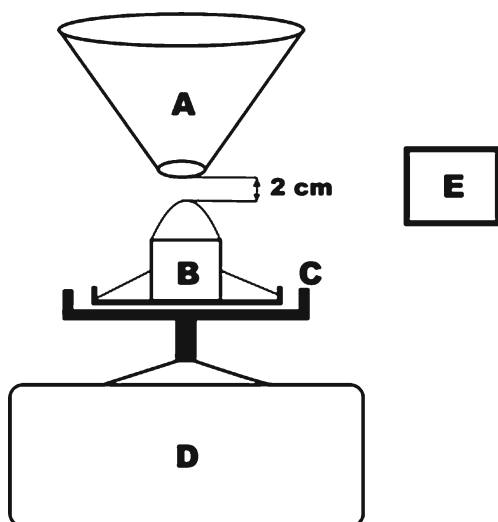
Fig. 1. Schematic diagram of an apparatus for determination of flowability of powders. Key: (*A*) glass funnel, (*B*) opened glass cube, (*C*) glass plate (Petri dish), (*D*) Erweka tapped density tester and CCD camera (*E*)

for another 3 minutes in a glass jar with a laboratory-scale Turbula mixer. Tablets (target weight 250 mg) were compressed by direct compression in an instrumented single-punch tablet machine (Korsch EK-O, Berlin, Germany) equipped with 9-mm flat-faced punches and a mass feeding device. The press was operated at a fixed speed of 60 rpm. The direct compression tablets were prepared aiming at a fixed compression force (maximum upper punch force) of 10.5 kN. All tablet compressions were made under controlled room conditions at 21°C and 50% RH.

Evaluation of Tablet Properties

The tablet properties were studied 5 days after the tabletting. The weight, crushing strength, thickness and diameter of the tablets were measured ($n=50$, Erweka Multicheck tablet tester, Erweka GmbH, Heusenstamm, Germany). The friability of the tablets was determined according to the European Pharmacopoeia (Ph.Eur.) using a double-drum friabilator (Sotax AG, Basel, Switzerland). The disintegration time of the tablets ($n=6$) was determined using the method described in Ph.Eur. (Sotax DT 3, Sotax AG, Basel, Switzerland)(13).
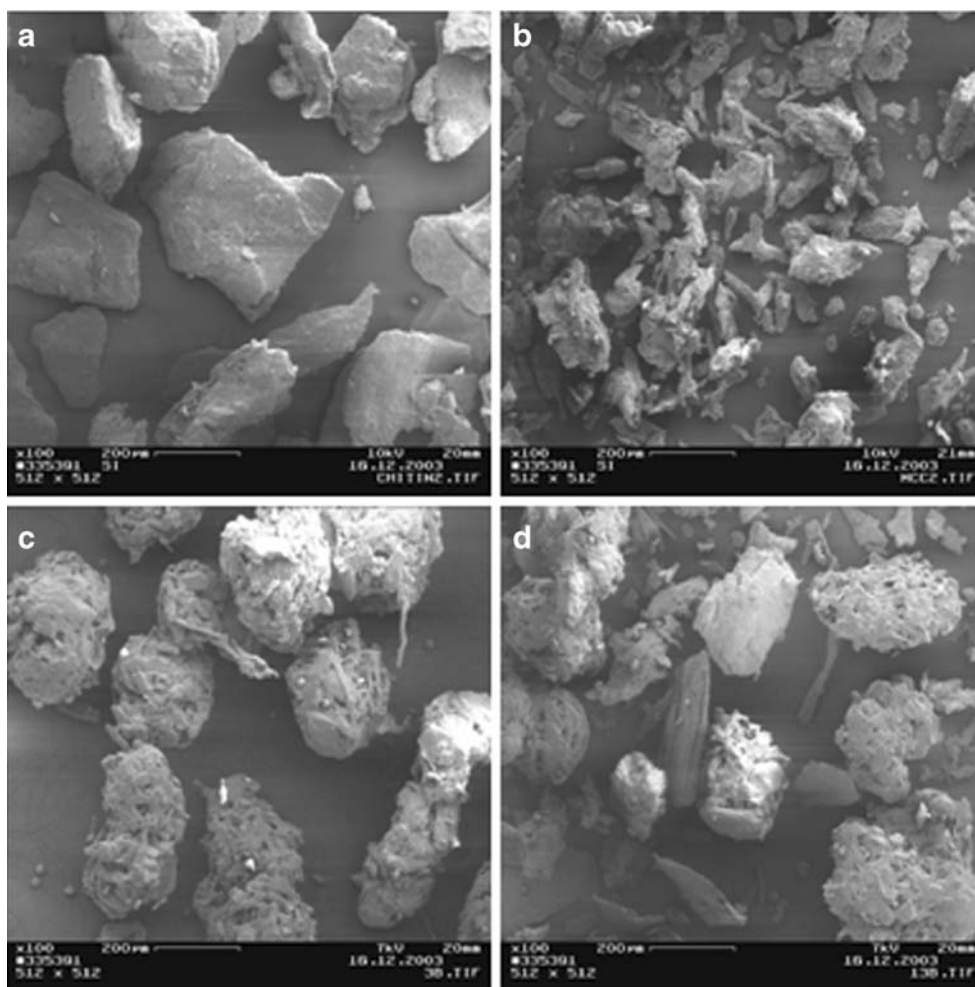

Fig. 2. Scanning electron micrographs of **a** chitin, **b** microcrystalline cellulose, MCC (Avicel® PH 102), **c** spray-dried lactose–cellulose, SDLC (Cellactose®), **d** overall centre mixture
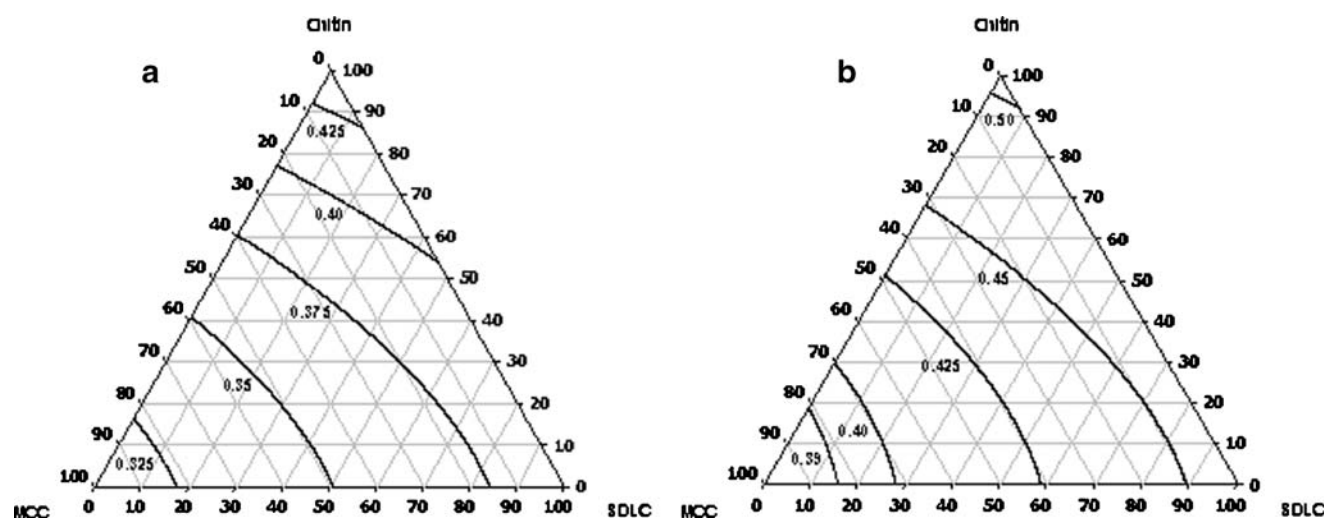
Fig. 3. Contour plots for **a** bulk and **b** tapped densities (g/cm^3) of powder mixtures of chitin, microcrystalline cellulose, MCC (Avicel® PH 102) and spray-dried lactose–cellulose, SDLC (Cellactose®)

RESULTS AND DISCUSSION

Particle and Powder Properties

The appearance of chitin, MCC and SDLC powders was assessed from scanning electron micrographs taken at a magnification of ×100. As seen in Fig. 2, chitin and SDLC presented a particle size of approximately 200 μm in diameter while the particle size of MCC was approximately 50–100 μm. The shape of chitin particles was clearly flaky and sharp-edged while SDLC exhibited almost round and porous granular particles. The shape of the MCC particles was more elongated (fibre-like) and different from the chitin and SDLC particles. Differences between particles can be seen in the SEM photograph (Fig. 2d) taken from the powder mixture representing the overall centroid point of the design (Exp. 13). Each material in the mixture kept its typical particle characteristics. For this reason, the amount of each component in the present mixtures could affect the flow and packing properties of the final powder mixture.

Figure 3a, b shows the contour plot describing bulk and tapped densities of unlubricated ternary mixtures. In general, the bulk and tapped densities increased with increasing amount of chitin in the powder mixtures. Powder mixtures containing MCC had the lowest bulk and tapped densities as well as the poorest flowing properties (Fig. 3 and Table III). The minimum values for Carr's index were obtained with chitin powder (100%), indicating the best flow properties. The values for flow rate and angle of repose were in accordance with the results based on Carr's index of pure materials (Table III). The flowability of powder mixtures comprising a high percentage of MCC could not be measured by standard methods since they were cohesive and, consequently, did not flow through the test funnel (Table II; Exp. 2, 5, 6, 10, 11 and 15). The treatment of the flowability responses led to an invalid model, and the assumed Scheffé (MLR) regression model did not explain the variation of the responses obtained.

Figure 4 presents the contour plots for the height of the powder cone obtained with the unlubricated powder mixtures with a novel flow measuring equipment after 16 taps. The highest cone height (6.6 mm) was obtained with a pure MCC, thus indicating the poorest flow properties among the samples tested. As the amount of chitin and SDLC increased in the powder mixtures, the cone height was diminished, evidencing clear improvement in the flowability of the samples. The lowest value for the cone height (4.1 mm) was measured for chitin as a pure material, thus showing the best flowability of the powder samples tested.

The relative standard deviation (RSD) of the tablet weights was also studied as a potential indicator of flow behaviour of the powder mixtures but the responses led to an unsatisfactory model, and consequently, the Scheffé (MLR) regression model did not explain the variation of the responses obtained. Variations (RSD) in tablet weights and compression forces were only 0.2–1.0% and 0.9–6.3%, respectively.

Table III. Flow and Packing Properties of Powder Mixtures ($n=3$)

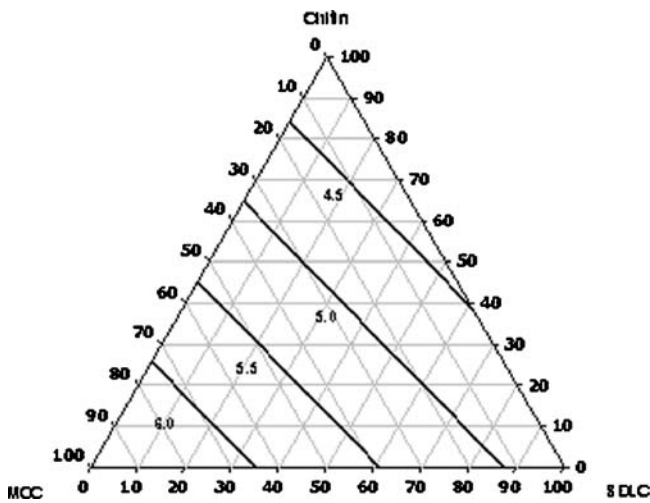| Exp.	Carr's index (%)	Flow rate (g/cm^2 s)	Angle of repose (°)
1	13.1±0.5	5.48±0.04	31.8±0.5
2	18.8±0.3	–	–
3	16.0±0.8	4.42±0.19	33.5±0.5
4	14.1±0.7	4.46±0.09	32.3±0.4
5	14.8±0.8	–	–
6	14.1±0.6	–	–
7	14.7±0.8	5.13±0.04	30.7±0.3
8	14.4±0.7	5.09±0.03	30.6±0.2
9	13.7±0.5	4.73±0.03	30.7±0.3
10	16.6±1.0	–	–
11	15.2±0.1	–	–
12	17.1±0.5	4.12±0.04	32.8±0.5
13	15.7±1.1	4.48±0.05	32.3±0.3
14	15.1±0.8	4.83±0.05	30.8±0.5
15	14.9±0.7	–	–
16	15.8±0.7	4.51±0.06	30.5±0.1

– not possible to measure

Fig. 4. Contour plots for height of powder cone in flow measurements of powder mixtures of chitin, microcrystalline cellulose, MCC (Avicel® PH 102) and spray-dried lactose–cellulose, SDLC (Cellactose®)

Mechanical Strength of Tablets

The compression experiments were carried out at two different magnesium stearate concentrations (0.1% w/w and 0.5% w/w of the powder mass). Figure 5 shows the contour plots describing the crushing strength and friability of the tablets at a magnesium stearate concentration of 0.5% (w/w). The mechanical strength and hardness of tablets obtained with MCC and SDLC and with their binary mixtures were very good. Inclusion of chitin in the MCC and SDLC mixtures (lubricated with magnesium stearate at a concentration of 0.5% w/w) resulted in tablets with impaired mechanical properties (Fig. 5). With the powder mixtures consisting of chitin at a concentration less that 40% (w/w); however, the values for the friability of the tablets were less than 1% (Fig. 5b). With chitin powder alone (Exp. 1) it was not possible to obtain any satisfactory tablets at a magnesium stearate concentration of 0.5% (w/w).

Figure 6 presents the contour plots describing the crushing strength and friability of the tablets compressed with a lower magnesium stearate level of 0.1% (w/w). Interestingly, the amount of magnesium stearate appeared to affect greatly the mechanical strength of all the chitin-containing tablets tested here. The chitin-containing tablets with a magnesium stearate concentration of 0.1% (w/w) exhibited a clearly higher crushing strength and lower friability values than those compressed with a higher magnesium stearate concentration of 0.5% (w/w). The negative effect of magnesium stearate on tablet strength is widely known, especially with materials which deform plastically under compression (15,16). However, this lubricant effect on the mechanical properties of chitin-containing direct-compression tablets was exceptionally strong and critical. This effect is probably a result of reduction of interparticle bonding associated with chitin or a result of physical and chemical interaction between chitin and magnesium stearate.

As far as mechanical strength and hardness of the tablets (Fig. 6) are concerned, combination of chitin with MCC seems to be more beneficial than with SDLC. The tablets compressed from binary mixtures of chitin and SDLC were less hard than the tablets obtained from the mixtures of chitin and MCC. According to the literature, MCC exhibits a superior bonding capacity, and with SDLC the binding between the majority of the lactose particles is mediated by cellulose in spite of the low cellulose proportion (17).

Effect of Die Lubricant on Tablet Compression

The compression R value representing the ratio of the maximum lower punch force to the maximum upper punch force has been applied as a measure of efficiency of a die lubricant (18, 19). The present parameter is dependent on the compression force applied, and for the most effectively lubricated formulations the R values are close to unity (19). In the present study, at a magnesium stearate concentration of 0.5% (w/w), the R values for all direct compressions ranged from 0.920 to 0.930, thus indicating the efficiency of magnesium stearate as a tablet lubricant at this loading level.
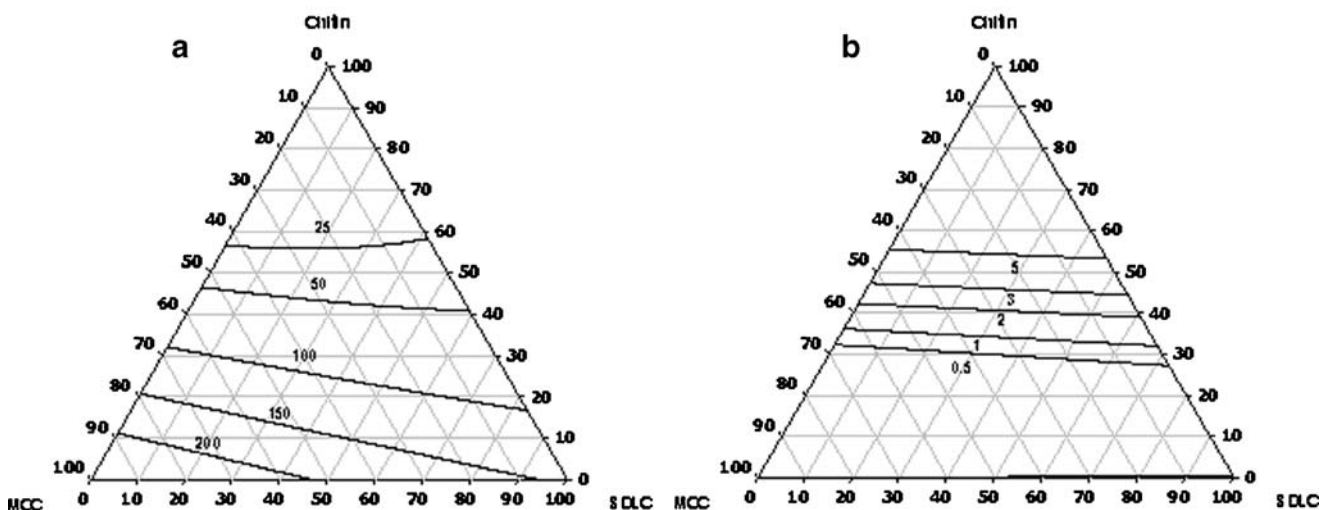

Fig. 5. Contour plots for **a** crushing strength and **b** friability of tablets lubricated with magnesium stearate 0.5% (w/w) and compressed with a maximum upper punch force of 10.5 kN
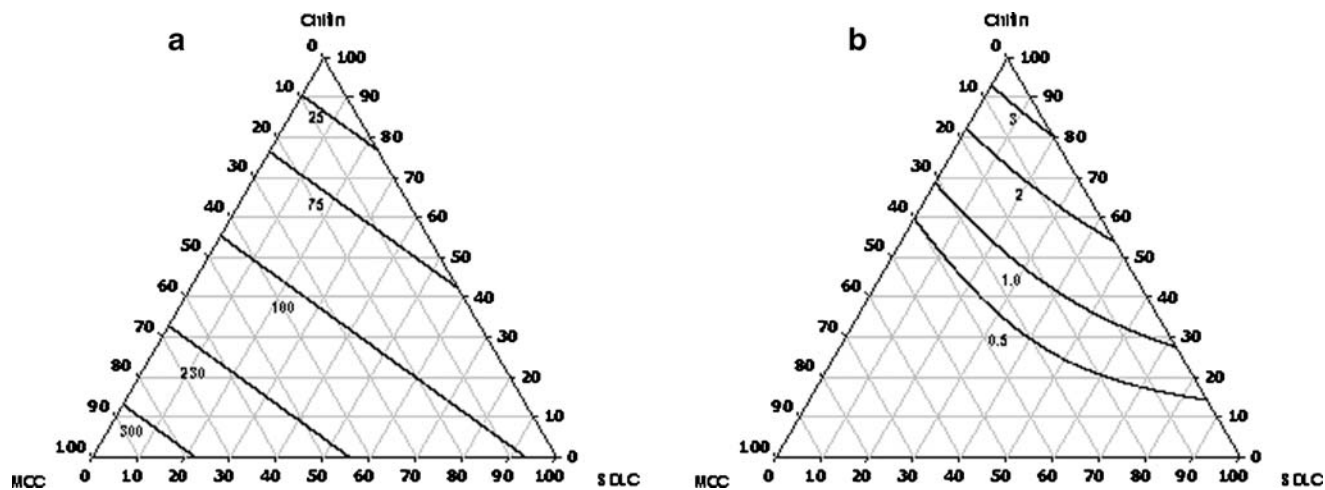
Fig. 6. Contour plots for **a** crushing strength and **b** friability of direct-compression tablets lubricated with magnesium stearate 0.1% (*w/w*) and compressed with a maximum upper punch force of 10.5 kN

As the smaller concentration level of magnesium stearate (0.1% *w/w*) was applied in the second run of the mixture design, great differences in its lubrication properties in the direct-compression masses were evident. As seen in Fig. 7, the *R* values obtained in tablet compressions of the mixtures with a high amount of chitin and MCC were close to those obtained in compressions of the first design. As the amount of SDLC in the powder mixtures was increased, the compression *R* values were clearly diminished, and the lowest *R* value (0.780) was obtained with a pure SDLC powder (Exp. 3). This is obviously due to the high amount of lactose mono-hydrate (75% *w/w*) in the composition of co-processed SDLC, thus exhibiting mainly a fragmentating behaviour of the material under compression.

According to the literature, the values for maximum ejection force during tableting can be applied as an indirect measure of friction between powder particles and the die wall as well as in estimating the efficiency of the die lubricant (20). Figure 7b shows the effects of direct-compression powder components on the maximum ejection forces during tableting. The ejection forces were great for the powder mixtures containing SDLC, and pure SDLC (Exp. 3) exhibited the

greatest maximum ejection force of 0.73 kN. This is obviously related to the presence of lactose monohydrate in the composition of co-processed SDLC. It is evident that clean, lubricant-free surfaces are created by fragmentation of particles of lactose during compression thus resulting in higher ejection force values for the powder mixtures containing SDLC. Chitin and MCC presented lower ejection force values, evidencing the low interparticulate friction of these materials. Based on the results on both *R* values and maximum ejection forces during tableting, it seems that chitin undergoes mainly plastic deformation instead of fragmentation under compression. De Boer *et al.* (1978) suggested that magnesium stearate exercised a maximum effect on the excipients that undergo complete plastic deformation without any fragmentation under compression (21). In our study, a small variation in tablet thickness probably influenced the results on ejection forces.

Disintegration of Tablets

All tablets tested disintegrated *in vitro* within 30 min. Most of the tablets exhibited quite a short disintegration time
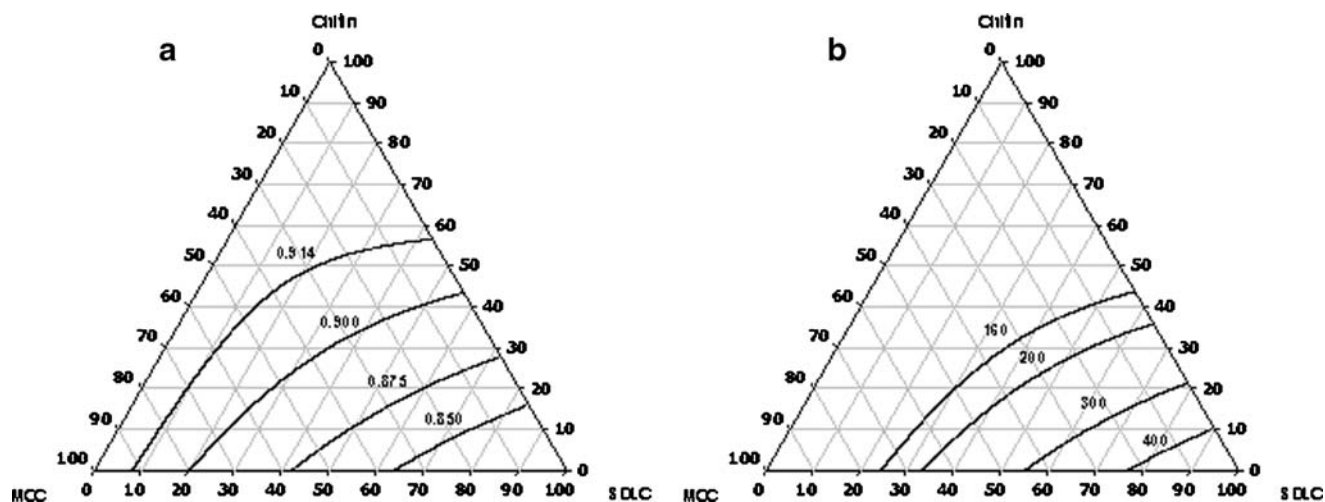

Fig. 7. Contour plots for compression **a** *R* values and **b** ejection forces of direct-compression tablets lubricated with magnesium stearate 0.1% (*w/w*) and compressed with an upper punch force of 10.5 kN

(less than 5 min), even those with a crushing strength of 150 N or more. The highest disintegration time observed was 30 min with the tablets composed of pure MCC. Due to short and equal disintegration times the treatment of the present disintegration responses led to an invalid Scheffé's (MLR) regression model.

SUMMARY AND CONCLUSIONS

Milled and fractioned native chitin of crustacean origin was studied as a co-diluent for the established direct-compression excipients, microcrystalline cellulose, MCC (Avicel® PH 102) and spray-dried lactose–cellulose, SDLC (Cellactose®). On the basis of the contour plots obtained, the mechanical strength of tablets is mainly dependent on the proportion of excipients and level of lubrication (magnesium stearate). As expected, increasing the proportion of MCC in the binary and ternary mixtures results in tablets with a higher crushing strength and lower friability. A high proportion of chitin in the powder mixtures results in tablets with a lower crushing strength and higher friability. At a low level of lubrication (0.1%), the combination of chitin with MCC (Avicel® PH 102) is more beneficial than with SDLC (Cellactose®) in terms of flowability of the powder mass and mechanical strength of the tablets. At a higher level of lubrication (0.5%), the tablets compressed are weaker and more friable irrespective the composition used. Consequently, one limitation of using chitin as a co-diluent in direct compression is its sensitivity to the presence of magnesium stearate, and this incompatibility should be taken into account in formulating chitin-based tablets. In conclusion, if tablet lubrication is properly selected, fractioned chitin of crustacean origin can be used in small proportions as a direct-compression co-diluent with MCC to improve the pharmaceutical quality of the tablets.

ACKNOWLEDGEMENTS

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