Compaction Mechanism and Tablet Strength of Cellactose®

Adi I. Arida[1]✉ and Moawia M. Al-Tabakha[2]

[1] Faculty of Pharmacy, Philadelphia University, Amman, Jordan.
[2] Faculty of Pharmacy and Health Sciences, Ajman University of Science and Technology Network, Al-Fujairah, UAE.

ABSTRACT

Objective: This paper describes the differences, in relation to compaction properties, between Microcrystalline Cellulose (MCC) and α-lactose monohydrate physical mixture, and microcrystalline cellulose co-processed with α-lactose monohydrate (Cellactose®).

Methods: The different compaction parameters were not only studied on the pure materials, but also on the lubricated powders with magnesium stearate.

Results: Magnesium stearate does not facilitate the densification of either the physical mixture or Cellactose during compaction. The difference in tablet relaxation of the physical mixture and Cellactose indicates that the negative effect of the lubricant on the interparticle bonding of Cellactose particles is smaller compared to its effect on the physical mixture particles. However, a larger increase in tablet relaxation at a high compression speed was found for both Cellactose and the physical mixture at different lubricant concentrations. Accordingly, the decrease in tablet strength was larger for the physical mixture tablets than for the Cellactose tablets when lubrication was applied. The examination of the tablet strengths of tablets compressed from physical mixtures of different ratios of α-lactose monohydrate and MCC proved the positive effect of cellulose on the tensile strength of tablets.

Conclusions: Co-processing of MCC with α-lactose monohydrate showed extra contribution to the tablet strength of a physical mixture with the same mixing ratio.

Keywords: Cellactose; Microcrystalline cellulose; α-lactose monohydrate; Direct compression; magnesium stearate.

INTRODUCTION

Cellactose® is a co-processed spray dried compound consisting of 75% α-lactose monohydrate and 25% cellulose. This product was developed in particular for direct compression, as it combines filler and binder properties of its two ingredients ideally, which allows for a simplified and economical compaction.

Belda and Mielck[1] found that Cellactose exhibited enhanced crushing strength compared to the powder mixtures each containing 25% w/w Avicel PH-101 or Elcema P-100 and 75% w/w Tablettose or lactose (100#), due to co-processing. In addition to the good compactibility of Cellactose, it has good flowability. The compactibility is due to a synergetic effect of the consolidation caused by fragmentation of lactose and plastic deformation of cellulose[2].

Armstrong et al.[3], and Arida[4] found that Cellactose exhibits dual consolidation behaviour since it contains

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✉ E-mail: arida@go.com.jo

both fragmenting lactose and cellulose which consolidates primarily by plastic deformation. Gohel and Jogani[5] stated in their review paper on Cellactose that researchers found that the Cellactose exhibited better compressibility compared to Ludipress, Fast Flo lactose, Tablettose, Di-pac and anhydrous lactose[5-8].

Casalderrey et al.[9] reported that the Cellactose tablets prepared at a compression pressure that largely eliminated macro pores had better mechanical properties but much poorer disintegration than tablets of other blends having similar composition, true density, and particle size at the same punch pressure. They also reported that as compression pressure is reduced, the tensile strength and disintegration time of Cellactose tablets decreased rapidly. Ruiz et al.[10] found also that the compression characteristics of Cellactose were better than Ludipress®.

Reimerdes and Aufmuth[11], and Gohel and Jogani[5] reported that the Cellactose exhibited increased crushing strength of the compacts along with reduced friability and lower disintegration time than the dry mixture of cellulose and lactose.

With the structure of Cellactose, cellulose disintegration only begins after the lactose outer layer has dissolved; giving rise to aqueous solutions of considerable viscosity, which further hinders water access to the cellulose nucleus[12-13]. Because the lactose covers the cellulose fibers, moisture sorption is much lower than that of microcrystalline cellulose alone[5]. Reimerdes and Reimerdes[14] showed that a mixture of lactose and cellulose may combine the good flowability and solubility of the lactose with the good water absorption and disintegration properties of cellulose.

Gohel and Jogani[15] prepared and evaluated co-processed directly compressible adjuvant containing lactose and microcrystalline cellulose using starch as a binder. The Carr's index of the agglomerates, percentage fines as well as tensile strength and friability of the tablets were affected by percentage of starch in binder solution and the ratio of lactose to microcrystalline cellulose.

Gohel et al.[16] prepared and evaluated co-processed diluents containing microcrystalline cellulose and lactose. Ratio of MCC to lactose (25:75 and 15:85), binder concentration (1 or 1.5%) and type of binder (dextrin or hydroxypropyl methylcellulose) were studied as independent factors. The results showed that the microcrystalline cellulose: lactose ratio (25:75) and dextrin as a binder are better than the ratio of (15:85) and hydroxypropyl methylcellulose as a binder. The tableting properties of the developed adjuvant were studied using diltiazem HCl as a model drug [5].

Gohel et al.[17] also demonstrated the use of factorial design in developing directly compressible adjuvant of desired characteristics consisting of microcrystalline cellulose, lactose, and dicalcium phosphate. Gohel and Jogani [18] prepared co-processed directly compressible adjuvant containing lactose and microcrystalline cellulose using melt granulation technique.

FMC Pharmaceutical Division [19] states clearly that the compactibility and flow properties of Cellactose are superior to those of physical blends of agglomerated lactose (Tablettose®), with either cellulose powder (Elcema® P100) or Avicel® PH-102. The goal of this paper is to quantify this superiority through the evaluation of the effect of co-processing α-lactose monohydrate with MCC on different compaction parameters and tablet strength. Alterations in tablet strength of Cellactose by addition of magnesium stearate are compared also with those of physical mixtures containing α-lactose monohydrate and MCC. Part of the protocol in this work has been inspired by the work of van Veen et al. [20] who studied silicified microcrystalline cellulose.

MATERIALS AND METHODS

The materials used were Cellactose® 80 (Meggle G.m.b.H., Wasserburg, Germany), α-lactose monohydrate (Tablettose® 80, Meggle G.m.b.H., Wasserburg, Germany), microcrystalline cellulose (Avicel® PH102, FMC International, Cork), magnesium stearate Ph. Eur. (Centrachemie, Etten-Leur, the Netherlands).

Before use, all powders were conditioned at 20 °C and 60% Relative Humidity (RH) for a week at least. The true densities of Cellactose, Tablettose, and Avicel PH102 measured by helium pycnometry were 1.542, 1.560, and 1.546 g cm^{-3}, respectively.

Physical mixtures were prepared using a Turbula mixer model 2P (W.A. Bachofen, Basle, Switzerland) at 90 rev min^{-1} for a period of 15 min. For the production of tablets containing magnesium stearate, mixing with magnesium stearate was performed for 5 min.

Compaction of 500 mg powder into tablets was carried out using an instrumented Manesty F3 eccentric tablet machine fitted with 12.5 mm diameter flat-faced punches (Manesty Machines Ltd, Liverpool) at 20 °C and 60% RH. The upper punch displacement profiles were sine waves with different amplitudes in order to vary the maximum compression pressures. The average compression rates were 0.83 and 1.5 cycle s^{-1}, reflecting slow and high compaction speeds, respectively. The lower punch was stationary during compression. To secure equal frictions between die wall and powder bed for compacts, the die was always prelubricated with magnesium stearate with a brush before each compression. Yield pressures and tap densities were calculated according to Heckel(21). However, the authors believe that as long as Heckel plots are still subjected to controversy in compaction studies, there was no need to concentrate onto Heckel plots in detail, but rather; in this work they were considered preliminary indicators and, instead, further studies were used such as the densification and tablet relaxation.

Tablets were stored for at least 14 h in a controlled climate chamber (Heraeus, Hanau, Germany) at 20 °C and 60% RH. Tablet dimensions were measured with an electronic micrometer (Miutoyo, Tokyo, Japan) and weights were determined on an analytical balance (Sartorius G.m.b.H., Gottingen, Germany). Tablet porosity was calculated from tablet dimensions and tablet weight. Crushing strengths of the tablets were measured using a CT40 strength tester (Engineering Systems, Nottingham). Tensile strength was calculated according to Fell and Newton(22). Subsequently, the tensile strength of 20 or more compacts with different porosities was related to the porosity and fitted by the Ryskewitch–Duckworth equation(23). Using this fit, the tensile strengths at different porosities were obtained.

RESULTS AND DISCUSSION

Densification of a microcrystalline cellulose and α-lactose monohydrate mixture, and cellactose powders

The densification behaviours of Microcrystalline Cellulose (MCC) and α–lactose monohydrate mixture, and Cellactose powders can be represented by the porosity under pressure. Figure (1) shows the porosity under pressure as a function of the compaction load for Cellactose tablets and the physical mixture with, and without, magnesium stearate; namely 0.0% and 1.0%. The porosities under pressure of the lubricated materials were very near to those of the non-lubricated materials. This means that the presence of magnesium stearate has small influence on the consolidation of Cellactose and the physical mixture.

This observation is due to the fact that Cellactose has high percentage of the fragmenting component than the plastically deforming one, and thus the fragmenting behaviour predominates as many new surfaces of lactose are generated under compression, therefore, the effect of the lubricant would be at its minimum. This is consistent with previous work on MCC and sorbitol(24), and the suggestions of Armstrong et al.(3) which say that Cellactose exhibits dual consolidation behaviour, also with the findings of Duberg and Nyström(25) which states that alpha-lactose monohydrate is lubricant insensitive.

Nitrogen gas adsorption technique was used to measure changes in a specific surface area of Cellactose and the physical mixture under pressure, and to see the effect of the lubricant on the specific surface area of the powder. In this work, Cellactose tablets were degassed at 40ºC for 18 hours. Figure (2) shows that the specific surface area of Cellactose increases up to ~180 MPa of compression pressure. After this pressure, the specific surface area starts to decrease indicating that plastic deforming behaviour starts to predominate. This would agree with the finding of

Armstrong et al. that Cellactose exhibits dual consolidation behaviour[3].

However, in both cases of lubricant usage (at 0.0% and 1.0%), there were slight differences in the specific surface areas of Cellactose. As pressure increases, it was expected that as long as Cellactose contains some amount of powdered cellulose, then more surfaces will shear in case of using more lubricant, and they will eventually come closer to each other. Therefore, the surface area will be expected to be lower than the case of using no lubricant. On the contrary, the lubricant did not make a significant difference among the surface area readings in the concentrations being used. Same occurred with the physical mixture as the difference in lubricant concentration was not accompanied by a significant difference in surface area changes. Fracturing of the physical mixture was not as that of Cellactose. However, it even did not show any fragmentation as the specific surface area did not change indicating that cellulose entity is physically lubricating the surfaces of lactose particles, hence reducing the fragmentation of the lactose particles. Effect of plastic deforming behaviour dominates at pressures above 180 MPa of both lubricated and non-lubricated physical mixture. This can be seen by the declination of the curve in Figure (2).

Commonly parameters derived to reflect powder densification and particle deformation are the yield pressure and tap density. Table (1) gives the yield pressures and tap densities for Cellactose powder and the physical mixture of 75% α-lactose monohydrate and 25% MCC.

The difference in yield pressure shows that the particle deformation of both Cellatose and the physical mixture is slightly affected. This observation is confirmed by the tap densities differences at both compaction speeds (Table 1). Physical mixture minimally enhances the particle rearrangement at the initial stage of the powder bed densification. Nevertheless, no discriminating differences were found between the densification behaviours of physical powder mixture and Cellactose, resulting in minor differences in porosities under pressure (Figure 1).

Tablet relaxation

In this study, tablet relaxation is depicted as porosity expansion, which is defined as the difference between the porosity under pressure and the final tablet porosity. The measured porosity expansions are given in Table (2). The table shows that there is a small difference in porosity expansion between Cellactose powder and the physical mixture of cellulose and lactose tablets with different lubricant concentrations. Tablet relaxation is normally considered a fine balance between stored elastic energy as a driving force for expansion and particle bonding as a counteracting force [26]. Stored energy is mostly controlled by the yield pressure of the material. Since the yield pressures of both materials were nearly the same (Table 1) and physical mixture does not change the chemical properties of the pure materials and the Cellactose [8], the stored elastic energy is considered to be almost the same for both materials. Therefore, it can be assumed from the slightly higher tablet relaxations of Cellactose compacts in comparison to those of the physical mixture tablets (Table 2) that a surface - located free lactose in the physical mixture has more a positive than a negative effect on interparticle bonding.

This would also confirm the finding of Al-Aghbar [27] that the consolidation mechanism of cellulose is time-dependent. This can be seen at different speeds of the machine, where at low compression speed of 0.83 cycle s^{-1}, both Cellactose and the physical mixture had lower tablet relaxation (Table 2) and lower yield pressures (Table 1).

Zuurman et al. [24] demonstrated that the larger tablet relaxation of lubricated MCC tablets, as compared with unlubricated MCC tablets, can be ascribed to a reduction of interparticle bonding by the presence of a lubricant film upon the MCC particles. Because a strong interparticle bonding counteracts tablet relaxation[26, 28], tablets produced from materials with low interparticle attraction tend to suffer from more relaxation than tablets made from materials where interparticle attractions are large[29-30]. Realizing that magnesium stearate negatively affects interparticle bonding, it was expected that the relaxation of lubricated tablets is higher than that of unlubricated tablets. Table (2) shows increased tablet relaxations for all lubricated tablets. Remarkable is the higher increase found for lubricated mixture tablets at a high compaction speed. In contrast, the change in tablet relaxation of Cellactose tablets by an increased tablet speed was hardly affected by the presence of 1.0% magnesium stearate. This implies that the negative effect of the lubricant on the interparticle bonding of Cellactose particles is smaller compared to its effect on the physical mixture particles. It must be mentioned that this phenomenon was not observed for tablets compacted at low speed. As the only difference between Cellactose and the physical mixture is the processing of the powder, the difference in interparticle bonding points to an interaction between magnesium stearate and the physical mixture. Although the densification of the unlubricated Cellactose and the physical mixture were comparable, after ejection and relaxation of the tablets, Cellactose tablets contained marginally higher tablet porosities than the physical mixture tablets at equal compaction pressures.

Tablet strength of tablets compressed from cellactose and the physical mixture

Figure (3) (a) and (b) show the tensile strength of Cellactose and the mixture of cellulose and lactose tablets, both unlubricated and lubricated with 1.0% magnesium stearate. The average compression speeds were 0.83 cycle s^{-1}, Figure (3/a) and 1.50 cycle s^{-1}, Figure (3/b), respectively. The tensile strengths of the unlubricated Cellactose and the mixture of cellulose and lactose tablets are comparable in both figures. Only at higher compaction pressures, the tensile strength of unlubricated physical mixture tablets is a little higher than lubricated mixture. At compaction pressures higher than 180 MPa, the apparent porosity under pressure reaches values below 0%. This indicates intraparticle changes combined with material density increase under compaction pressure. These processes are obviously to some extent altered by the physical mixture.

Although the presence of magnesium stearate decreases the tensile strength of tablets compressed from both materials, the effect is larger for the mixture tablets than for Cellactose tablets, Figure (3/b). Since the higher tensile strength of Cellactose tablets in comparison with the mixture tablets cannot be explained by a high increase in tablet porosity, this may be a consequence of interfacial interaction of the particles rather than the co-processed excipient. This confirms the finding of Arida[4] that the only dominating consolidation mechanism of Cellactose would be the distance forces (intermolecular forces). Moreover, Edge et al.[31] and van Veen et al.[20] found that the strength enhancement by silicification of microcrystalline cellulose tablets properties may be a consequence of interfacial interaction rather than modification of bulk MCC properties.

In order to elucidate the effect of both mixing ratios and magnesium stearate concentration and their possible interactions on the binding properties comparably to that of Cellactose, the tensile strength of tablets compressed from different physical mixtures of lactose and cellulose, with and without magnesium stearate, was compared with that of the unlubricated Cellactose.

Figure (4/a) depicts the tensile strength of unlubricated tablets compressed from MCC, Cellactose, physical mixtures of MCC and lactose in different concentrations, and lactose. The three different tablet porosities (10, 20 and 30%) reflect high, medium and low densificated tablets, respectively. An increase in the MCC powder concentration in the mixtures enhances the tablet strength, especially for high densificated tablets. However, it can be generally stated that increasing amounts of lactose in the mixture decrease the tablet strength, most probably by lowering the interparticle bonding strength between MCC particles. There was a difference in tensile strength between the physical mixture of lactose:cellulose (75:25%) and its co-processed equivalent; Cellactose. This would agree with the finding of Reimerdes and Aufmuth [11] that Cellactose exhibited increased crushing strength of the compacts along with reduced friability and lower disintegration time than the dry blend of lactose and cellulose.

Figure (4/b) shows the tensile strength of tablets compressed from Cellactose, physical mixtures of MCC with lactose in different concentrations, and lactose, all of which were lubricated with 1.0% magnesium stearate at three different porosities. Capping of MCC tablets is observed with 0.5% and 1.0% magnesium stearate, therefore it was eliminated from this comparison. Figure 4 (a) and (b) show that the different concentrations of magnesium stearate have a very small effect on the tensile strength of lubricated tablets. Combining figures 4 (a and b) shows that there are different results between Cellactose and different physical mixtures of lactose and cellulose. Comparing the results of Cellactose and a physical mixture of lactose (75%) and cellulose (25%) shows that they are somewhat near to each other, however, it was of interest to see that as the percentage of lactose decreases, then the results become near to Cellactose. This is obvious with the tensile strength results of a physical mixture comprised of lactose (25%) and cellulose (75%).

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Table 1. Yield pressure and tap density obtained from Heckel plots of Cellactose powder and the mixture of cellulose and lactose at compression speeds of 0.83 and 1.5 cycle s^{-1}

	Yield Pressure (MPa)		Tap density (g cm^{-3})	
	0.83 cycle s^{-1}	**1.5 cycle s^{-1}**	**0.83 cycle s^{-1}**	**1.5 cycle s^{-1}**
Cellactose	51.2 ± 0.8	58.9 ± 0.5	0.551 ± 0.005	0.521 ± 0.004
Physical Mixture	46.9 ± 0.9	54.7 ± 0.7	0.529 ± 0.003	0.495 ± 0.004

Table 2. Tablet relaxation, given as porosity expansion, of tablets lubricated with different concentrations and compressed from Cellactose powder and the mixture of cellulose and lactose at compression speeds of 0.83 and 1.5 cycle s^{-1}

	Unlubricated tablets	1.0% Lubricated tablets	Change in tablet relaxation (%)
0.83 cycle s^{-1}			
Cellactose	3.6	4.1	0.5
Physical Mixture	3.4	4.0	0.6
1.5 cycle s^{-1}			
Cellactose	4.3	4.9	0.6
Physical Mixture	3.9	5.0	1.1

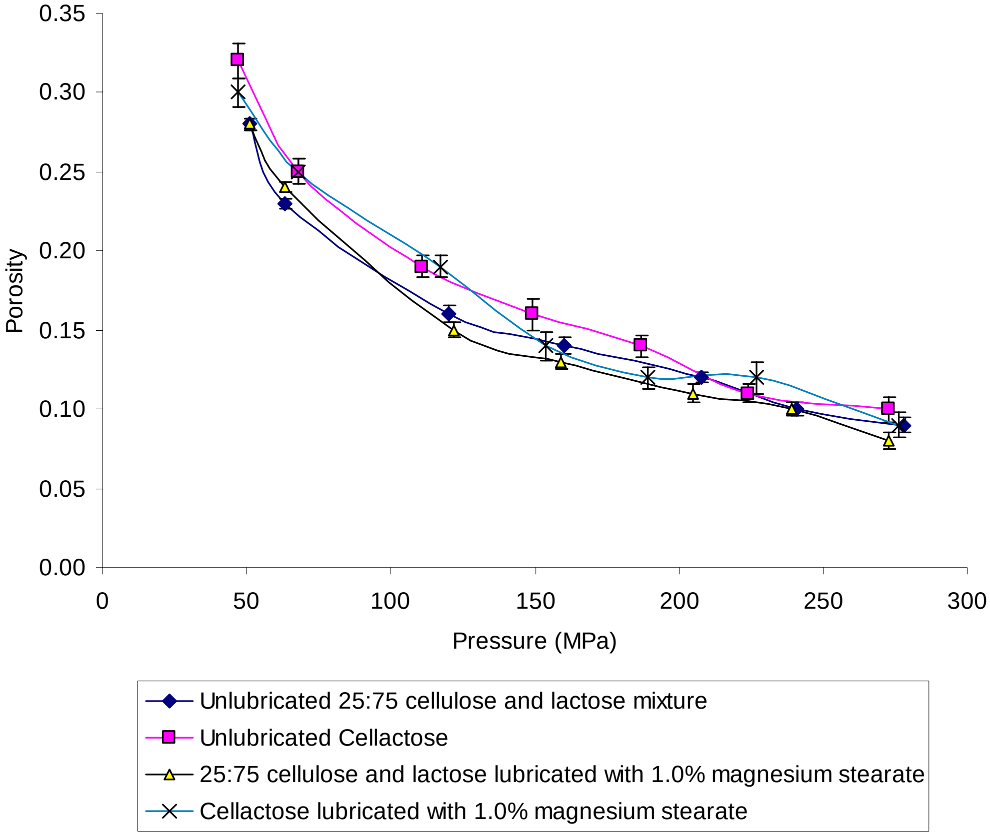

Figure 1. Porosity under pressure of Cellactose tablets and the physical mixture lubricated with 0.0% and 1.0% magnesium stearate at compression speed 0.83 cycle s^{-1}.

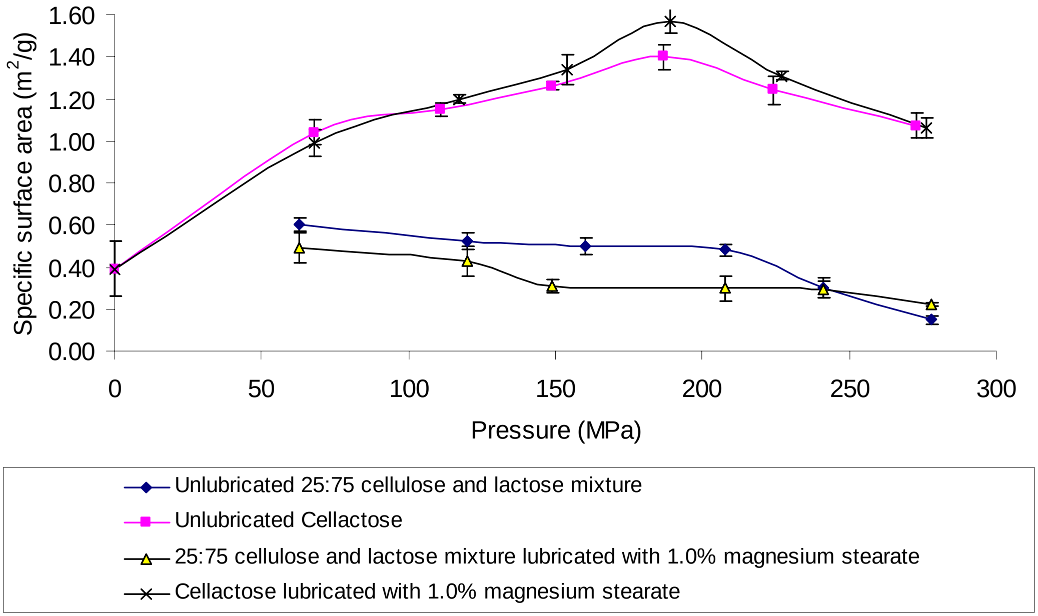

Figure 2. Comparative plots of specific surface area (m^2/g) versus pressure (MPa) for tablets compressed from Cellactose and a mixture of 25:75 (w/w%) cellulose and lactose, lubricated with different magnesium stearate concentrations.

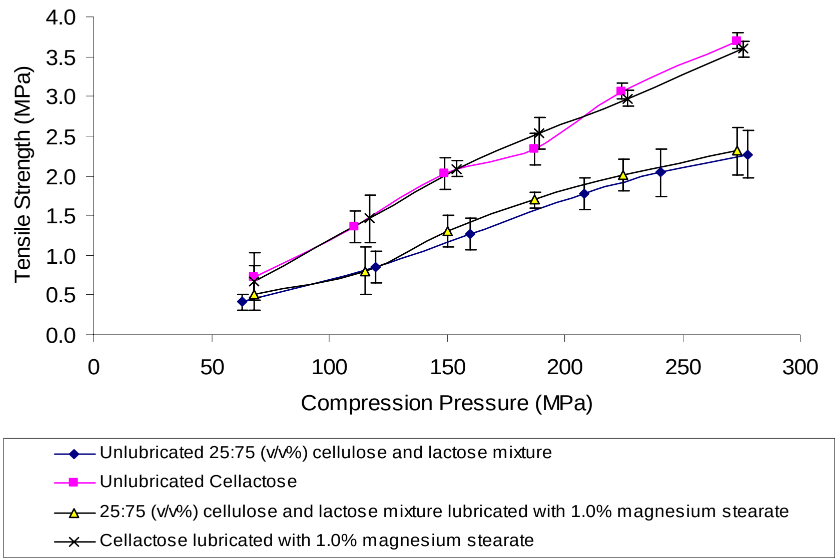

Figure 3. (a). Tensile strength of unlubricated and lubricated tablets compressed from Cellactose and a mixture of cellulose and lactose. Compression speed is 0.83 cycle s^{-1}.

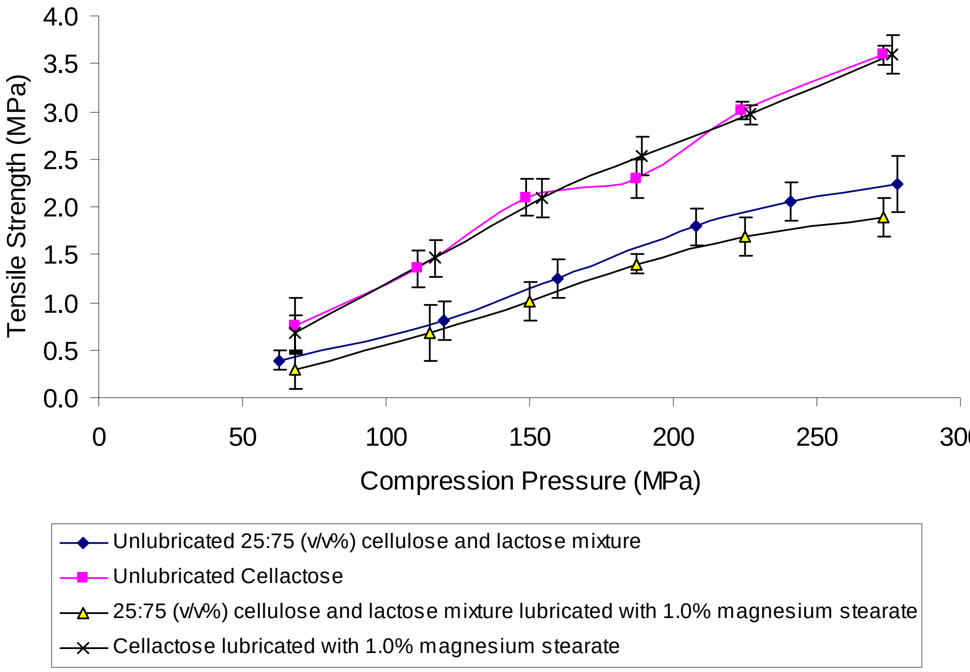

Figure 3. (b). Tensile strength of unlubricated and lubricated tablets compressed from Cellactose powder and a mixture of cellulose and lactose. Compression speed is 1.5 cycle s^{-1}.

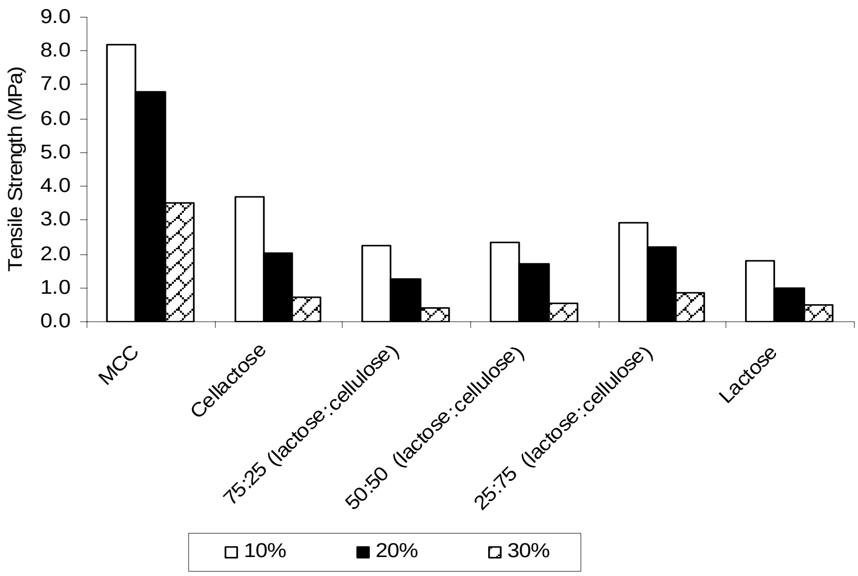

Figure 4. (a). Tensile strength of unlubricated tablets compressed from MCC, Cellactose, physical mixtures of MCC and lactose in different concentrations, and lactose at 10% (white bars), 20% (black bars) and 30% (layered bars) porosity.

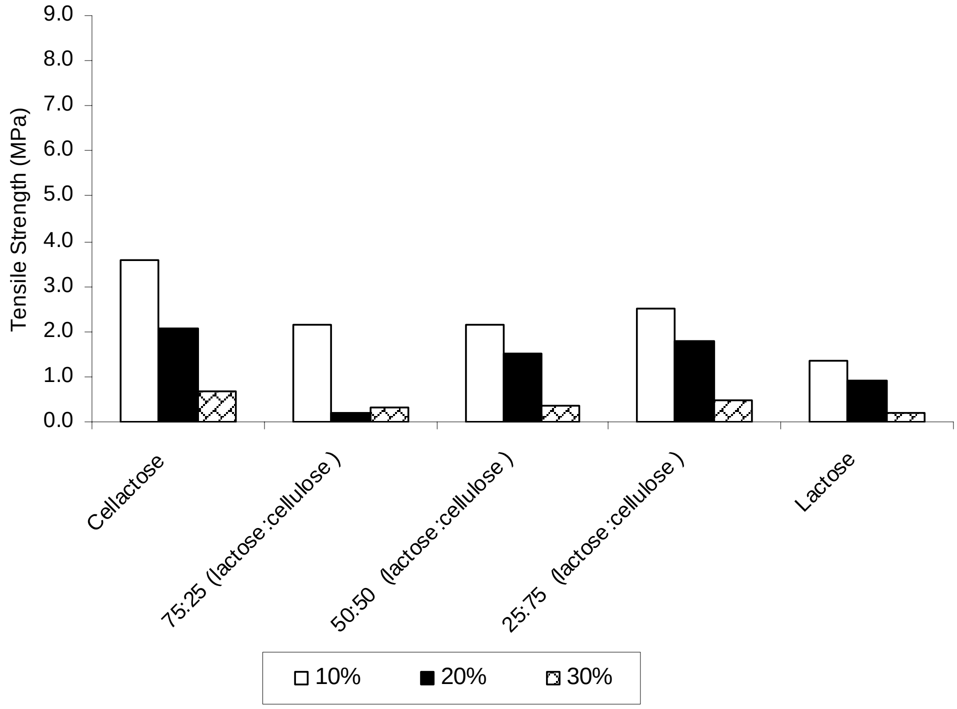

Figure 4. (b). Tensile strength of tablets lubricated with 1.0% magnesium stearate compressed from Cellactose, physical mixtures of MCC with lactose in different concentrations, and lactose at 10% (white bars), 20% (black bars), and 30% (layered bars) porosity.

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ميكانيكية انضغاط وقوة اقراص سواغ السيلاكتوز

عدي عريضه[1] ومعاويه الطباخة[2]

[1] كلية الصيدلة، جامعة فيلادلفيا، عمان، الأردن.

[2] كلية الصيدلة وعلوم الصحة، جامعة عجمان للعلوم والتكنولوجيا، الفجيرة، الإمارات العربية المتحدة.

ملخـص

الأهداف: يصف هذا البحث الاختلافات في خواص الانضغاط ما بين بودرة السليولوز و بودرة الفا لاكتوز أحادي الهدرجة وما بين المركب المكافيء لتركيبهم وهو السيلاكتوز.

الطرق: تمت دراسة هذه الخواص للمواد منفردة دون المشحم مغنيسيوم ستياريت ومعه.

النتائج: المغنيسيوم ستياريت لم يحسن انضغاط هذه المواد مفردة أو مخلوطة. وعند دراسة ارتخاء القرص بعد الضغط كان أثر المغنيسيوم ستياريت على المركب المكافيء وهو السيلاكتوز أقل منه في حالة خلط هذه المواد فيزيائياً.

الخاتمة: أثبتت هذه الدراسة أن سرعة جهاز كبس الاقراص لها علاقة بارتخاء الحبوب حتى عند استخدام تراكيز مختلفة من المشحم، وبالتالي فإن ضعف قوة القرص كان أكبر في حالة خلط المواد فيزيائياً مقارنة مع المركب المكافيء عند استخدام المشحم. فحص قوة الأقراص أثبت تأثير السليولوز على البودرة المخلوطة. ان خواص المركب المكافيء أفضل بكثير من مجرد خلط البودرة بالنسب المماثلة التي تشكل المركب المكافيء.

الكلمات الدالة: سيلاكتوز ، سليولوز، الفا لاكتوز أحادي الهدرجة، الضغط المباشر، مغنيسيوم ستياريت.

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