Identification of the Consolidation Mechanisms of Emcompress ®

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ABSTRACT

This work is an attempt to elucidate the consolidation mechanisms of the powder Emcompress® under compression. Consolidation mechanisms play an important role in the forces of attraction between different particles, and this has extensively earned the interest of scientists due to the many newly and continuous findings in this area.

Emcompress® is a directly compressible excipient that undergoes extensive fragmentation under compression as demonstrated by large increase in its specific surface area under pressure, which is measured by gas adsorption technique, or other ones. Its different physical properties have been compared to that when adding povidone powder to it which is known to be used as a plastisizing material that decreases fragmentation of powder.

After the attempt to extract the pure forces which are responsible for the consolidation mechanisms of Emcompress®, many forces were involved in such consolidation. It was also noted that there is an indirectly proportional qualitative relationship between the specific surface area of Emcompress® and its average pore radius.

It has been shown that Emcompress® consolidates only by weak distance forces and mechanical interlocking.

Keywords: Consolidation mechanisms; Emcompress®; Gas adsorption; Specific surface area; Average pore radius; Wet granulation; Povidone.

INTRODUCTION

Emcompress® is used as a tablet and capsule diluent. It has an empirical formula expressed as: $CaHPO_4$ $2H_2O$ and its molecular weight is 172.09 (gm/mol). Dibasic calcium phosphate dihydrate (Emcompress®) has good compression characteristics, compaction taking place primarily by brittle fracture [1]. Emcompress® is prepared by precipitation from dilute slurry of hydrated lime with phosphoric acid. It consists of aggregates of very small crystals and not of individual particles [(2)]. Dibasic calcium phosphate dihydrate is a white, odourless, tasteless powder or crystalline solid [(1)].

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For production of tablets by direct compression, the unmilled dibasic calcium phosphate dihydrate is generally used, since it combines low hygroscopicity and considerable physical and chemical stability with good compression and flow properties and relatively low cost[(3-5)].

Emcompress® undergoes extensive fragmentation during compression as demonstrated by the large increase of the surface area after compression[(6-9)], a high strength isotropy ratio[(8)], a very small effect of lubricants on tablets strength[(6,8,10-12)] and absence of time-dependent effects[(13-16)]. Duberg and Nyström[(9)], using a scanning electron microscope, showed that the aggregates of Emcompress® crystals shatter during compression such that it is impossible to distinguish the original particles.

Povidone is readily soluble in water and is used in pharmaceutical industry as a tablet binder and also as a

plasticising agent. As a polymer, it is expected to undergo plastic deformation under pressure with slight stiffness and low yield pressure value [1]. Povidone has a high softening point (~150ºC) so the effect of heat build up during compression would be minimal, and hence, a negligible contribution from melting asperities as bonding mechanisms will be expected.

As Emcompress® is a water insoluble powder, a 5.0% (w/v) solution of povidone in water was chosen to induce plasticity in an extensively fragmenting material like Emcompress® and to see the changes, if any, on the consolidation mechanism of Emcompress®.

2. MATERIALS AND METHODS

Manesty F3 (Manesty Machines Ltd, Liverpool) press was used to prepare tablets of Emcompress® (Mendell, Reigate) at range of pressures. Compression pressure was measured by fitting strain gauges (Welwyn Strain Measurement, Basingstoke) to the upper part of the press, and their amplified output was recorded on light sensitive paper (Eastman Kodak Ltd, Rochester, New York, USA). Powders were used as received from the manufacturer. A wet granulation process was carried out using povidone (M.W. 44000, BDH, Poole) 5.0% (w/v) solution in water. 500 grams dry Emcompress® powder of particle size range 350-420 µm was mixed with povidone solution in a Sigma blade mixer (Copley Instruments Ltd, Nottingham) for 10 minutes. A rough way of determining the end point of mixing is to press a portion of the mass in the palm of the hand; if the ball crumbles under moderate pressure, the mixture is ready for the next stage in processing, which is wet screening. The wet screening process involved converting the moist mass into coarse, granular aggregates by passing through an oscillating granulator (Type FGS, Copley Instruments Ltd, Nottingham), equipped with screens having large perforations; 12-mesh screen (1.405 mm). The purpose is to increase surface area to facilitate drying. After that the granule was dried for 20 minutes at 40ºC using a fluidised bed drier (Type FBD/L72, P.R.L. Engineering Ltd, Mostyn). After drying, the granules were screened again through a 22-mesh screen (0.699 mm) and powder under 0.353 mm (44-mesh screen) was removed. Finally, the lubricant was added to the powder and mixed together in an Erweka UG cube mixer (Copley Instruments Ltd, Nottingham) for 5 minutes. Concentrations of 0.5% and 1.0% of magnesium stearate were used as lubricant.

A 12.5 mm diameter flat faced punch and die system were used to prepare tablets from the different mixtures using the instrumented tablet press. Each type of powder was fed manually into the feed hopper and tablets were prepared at wide range of compaction pressures to give tablets of different thickness (porosity). Force transducers were fitted to the upper punch and signals were displayed on a cathode ray oscillograph (Micromovements Ltd, Eversley). The pressure exerted by the upper punch was calculated by dividing the compaction force (kN) by the cross-sectional area of the punch. Thirty tablets were collected at each compaction pressure, the first six tablets being discarded. Tablets from each compaction pressure were appropriately labelled and stored in airtight containers under ambient conditions (18ºC ± 2ºC and 45% ± 5% relative humidity) for at least one week before testing.

After storage at least for a week, ten tablets of each batch were weighed (± 1 mg) and their dimensions were measured (± 0.01 mm). The porosity, or the volume fraction, of the compacts was calculated using equation 1:

$$\varepsilon = 1 - \frac{W}{\pi r^2 t \rho} \qquad (1)$$

where,

ε = Porosity
W = Tablet weight (kg)
r = Tablet radius (m)
t = Tablet thickness (m)
ρ = True density of the powder granules ($kg.m^{-3}$)

True density values were taken from Armstrong et al.[17] and Wade and Weller[1]. Each tablet was then subjected to a crushing strength test using the CT40 tester

(Engineering Systems, Nottingham). The tensile strength was calculated using Den Hartog equation [8]. Den Hartog suggested that under conditions of ideal line loading, i.e. point loading of the cylinder across its diameter, the diametral tensile stress is constant and can be calculated using equation 2:

$$\sigma = \frac{2P}{\pi D t} \qquad (2)$$

where,

σ	=	Tensile strength (Pa).
P	=	Applied load (N).
D	=	Tablet diameter (m).
t	=	Tablet thickness (m).

For determination of surface area by gas adsorption, it is essential that the surface of the solid is free from films of moisture and other contaminants, and that the surface area is accessible to the adsorbing gas. Therefore, a further conditioning process is necessary via a process called "degassing" or "outgassing", which is a process involving in removing the moisture or contaminants from the surface of the solid to be examined. NOVA-1000 (Quantachrome Corporation, New York, USA) is an instrument, which measures surface area by gas adsorption. In this experiment, one gram of powder was inserted into a NOVA-1000's Pyrex-glass cell, the cell was placed in the degassing station in the NOVA-1000 and the degassing was loaded. Powder was degassed at 20ºC, 40ºC and 60ºC in vacuo (10^{-3} torr) for 3 hours, 6 hours and 18 hours, and analyzed 5 times each using 5 points BET method of relative pressure of Nitrogen range 0.05-0.35. 1.00 being the saturation pressure for nitrogen. The conditions giving the smallest coefficient of variation with a correlation coefficient higher than 0.9999 were chosen to degas that powder. From these experiments, 18 hours at 20°C was selected as a condition to degas the powder. However, it must be mentioned that the surface area measurements reflect only surface area that is accessible to the adsorbing gas, which excludes surface area of pores that are no longer open to the surrounding porosity, i.e. their pore cross sectional area is less than the cross-sectional area of nitrogen molecule that is 16.2×10^{-20} m^2.

The Brunauer-Emmett-Teller (BET) method [18] is the most widely used procedure for the determination of the surface area of solid materials, and involves the use of the BET equation. However, it must be remembered that the adsorption isotherm and desorption isotherm branches of the 6 types of isotherms in general do joint at approximately just about the relative pressure of 0.35. Therefore, all tablets were degassed at 20ºC for 18 hours, before measuring their specific surface area and average pore radius. The BJH method, which measures the average pore radius, is measured using a much higher initial relative pressure and close to unity. The BJH method is proposed by Barrett, Joyner and Halenda [19]. Assuming that the initial relative pressure $(P/P_o)_1$ is close to unity, all pores are filled with liquid. The largest pore with their radius being r_{P1} has a physically adsorbed layer of nitrogen molecules with their thickness being t_1. Inside this thickness is an inner capillary with Kelvin radius r_K from which evaporation takes place as P/P_o is lowered. When the relative pressure is lowered from $(P/P_o)_1$ to $(P/P_o)_2$ a volume V_1 will desorb from the surface. This liquid volume V_1 represents not only emptying of the largest pore of its condensate but also a reduction in the thickness of its physically adsorbed layer by an amount Δt_1. Across this relative pressure decrement, the average change in thickness is $\Delta t_1/2$. The highest experimental adsorption P/P_o measured in this study was equal to 0.985, therefore, nitrogen will be forced inside the pores and all pores are expected to be filled with liquid nitrogen.

3. RESULTS

When povidone is incorporated with Emcompress® and pressure is applied, there is an increase in the specific surface area of the powder up to a certain extent (~100 MPa) after which the line has levelled off (Figure 1); indicating no more fragmentation in the powder but rather a combined behaviour between fragmentation and

plastic deformation which has been induced by the effect of povidone, this was contradictory to the behaviour of Emcompress® alone under pressure were the specific surface area kept rising up in the studied scale of pressure.

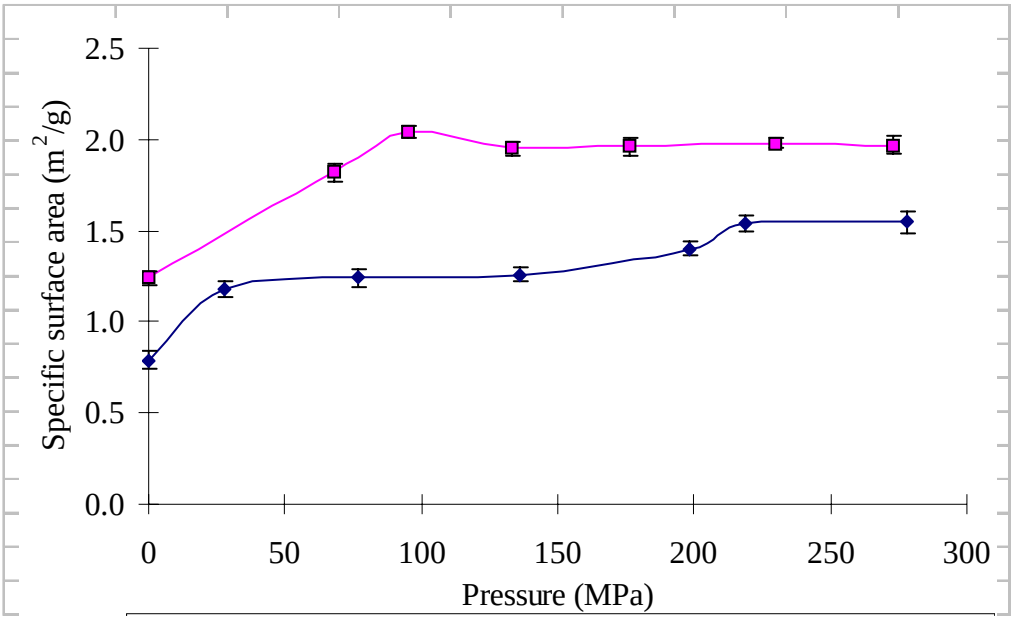

Figure 1. The variation of specific surface area (m^2/g) with change in compression pressure (MPa) for tablets made from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

As pressure increases, the porosity decreases (Figure 2). Heckel plots were used as simple method to see and check if there is any induced plasticity in the powder being used, however, consistent means must be found for determining the slope of Heckel plots, and this was done according to equations 3 [20-21] and 4 [22], which calculate the mean or pseudo-yield pressure of the material, P_y, for the different powders used in this study (where P_y is the reciprocal of the slope K of relevant Heckel plots).

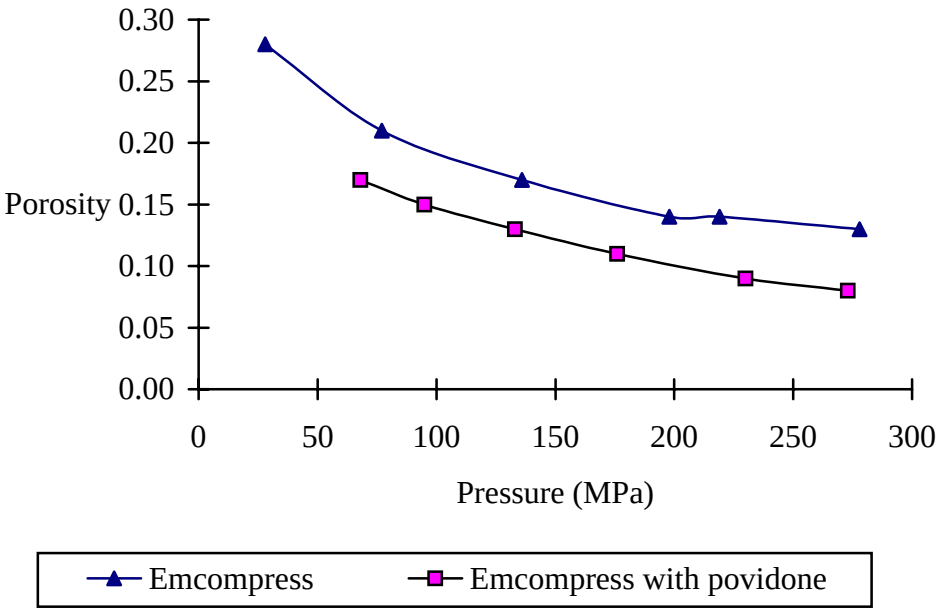

Figure 2. A plot of porosity versus compression pressure (MPa) for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

$$\ln \frac{1}{(1 - D)} = KP + A \quad (3)$$

Where, D, the relative density of the compact, (1–D), pore fraction (porosity), P, the applied pressure, K and A are constants.

$$K = \frac{1}{P_y} \quad (4)$$

Two points were chosen from the X axis (100 MPa and 200 MPa) for all the powders, then two points (from the Y axis) relevant to those in X axis, were chosen and the slope was calculated.

Heckel plots (Figure 3) and table (1) show that the yield pressure value of Emcompress® with povidone is much lower than that of Emcompress® itself and that it has decreased from 323 MPa to 263 MPa. This would be an indicator of the induced plasticity in Emcompress® regardless of the concentration of the lubricant being used.

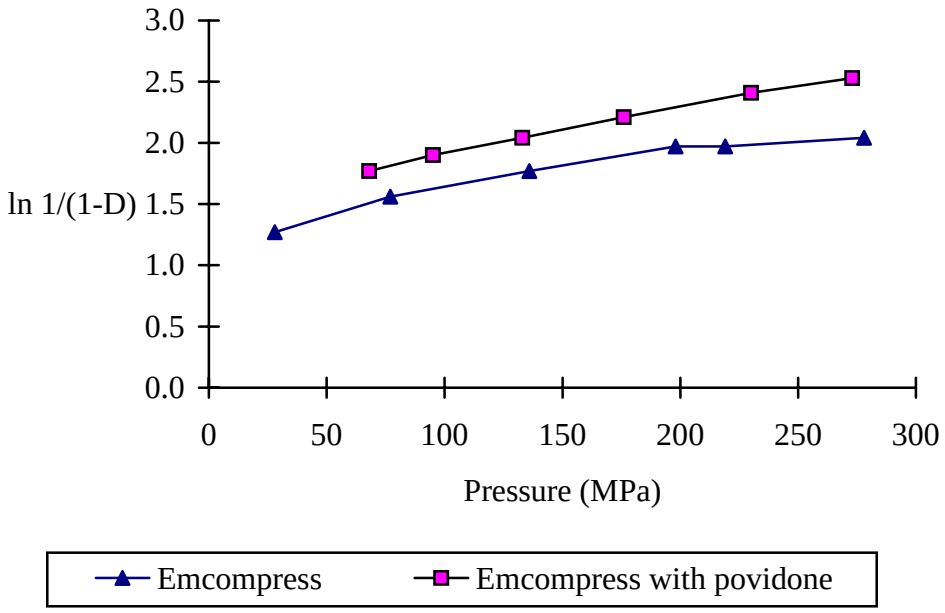

Figure 3. Heckel plot for Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

Table 1. Mean yield pressure (MPa) of powders.

Powder	Y2‡	Y1‡	X2† (MPa)	X1† (MPa)	K (MPa^{-1})	Py (MPa)
* Emcompress®	1.97	1.66	200	100	0.0031	**323**
* Emcompress® and 5.0% povidone	2.30	1.92	200	100	0.0038	**263**
** Emcompress®	1.91	1.60	200	100	0.0031	**323**
** Emcompress® and 5.0% povidone	2.18	1.80	200	100	0.0038	**263**

† X1 and X2 are two points, chosen from the pressure axis (MPa).

‡ Y1 and Y2 are the values of ln 1/(1-D) corresponding to X1 and X2.

* lubricated with 0.5% magnesium stearate.

** lubricated with 1.0% magnesium stearate.

It was expected that as long as there is a slight increase in the specific surface area of a powder at the beginning of the curve, this means that the material is fragmenting and that there is no plastic deformation. Hence the pores are in filling conditions during fragmentation with their own debris, and their pore radii are expected to decrease. This was the case with Emcompress®. After a certain pressure (~125 MPa), there were no changes in the specific surface area of Emcompress® with povidone which coincided also with no change in the average pore radii (Figure 4). This is mostly due to the counteracting effect of fragmentation and plastic deforming behaviours, thus establishing almost a horizontal line. Plotting a curve representing the average pore radius versus specific surface area (Figure 5) shows that there is no relationship between these two parameters. This low or poor correlation coefficient can be explained by the fact that the BET method, which measures the specific surface area, is measured in the relative pressure range of 0.05 to 0.35, while the BJH method, which measures the average pore radius, is measured using much higher initial relative pressure and close to unity (the highest adsorption P/P_o in this study was equal to 0.985). Therefore, nitrogen will be forced inside the pores and all pores are expected to be filled with liquid nitrogen. Thus, in the case of measuring the surface area, the surface area available for the gas molecules will be dependent upon the penetration capacity of the nitrogen, while in the BJH method more nitrogen is forced and more spaces are measured.

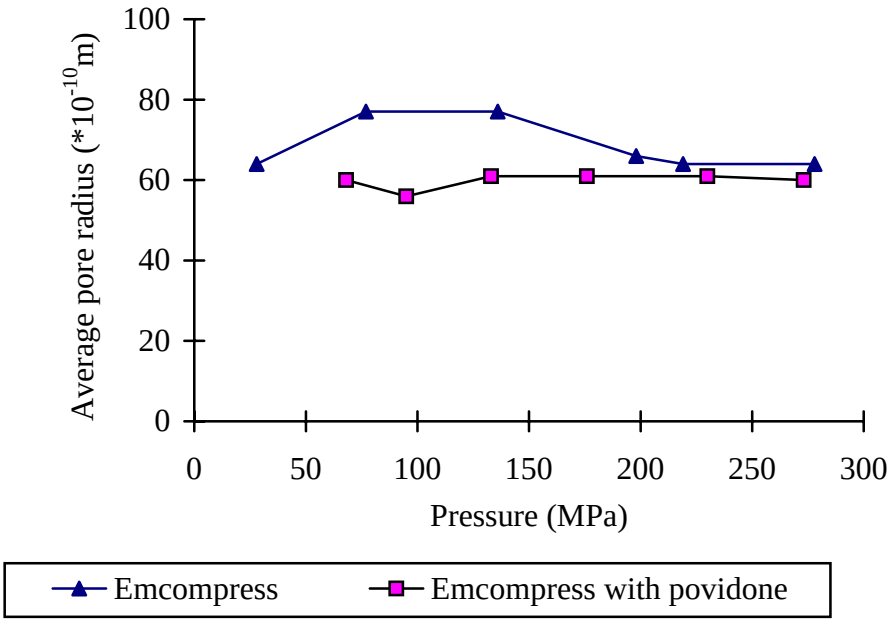

Figure 4. The relationship between average pore radius (×10^{-10}m) and compression pressure (MPa) for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

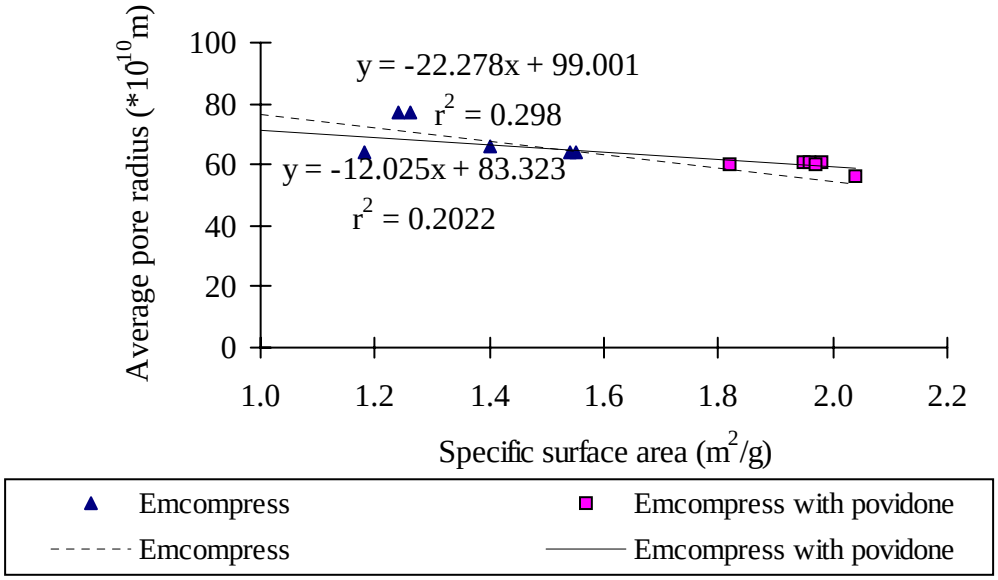

Figure 5. A plot of average pore radius (×10^{-10}m) versus specific surface area (m^2/g) for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

Figure (6) illustrates the inversely proportional qualitative relationship between specific surface area and average pore radius. However, figure (7) shows a directly proportional relationship between pressure applied and tensile strength of Emcompress® with povidone, and it also shows that there is slight effect for the lubricant concentration on the tensile strength values.

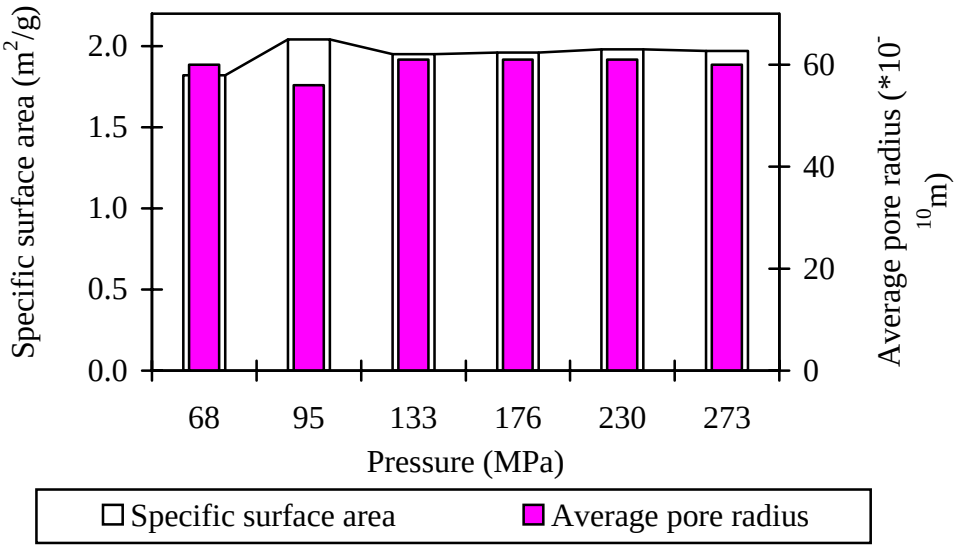

Figure 6. A plot of specific surface area (m^2/g) and average pore radius (×10^{-10}m) versus compression pressure (MPa) for tablets compressed from Emcompress® powder granulated with 5.0% povidone in water and lubricated with 0.5% magnesium stearate.

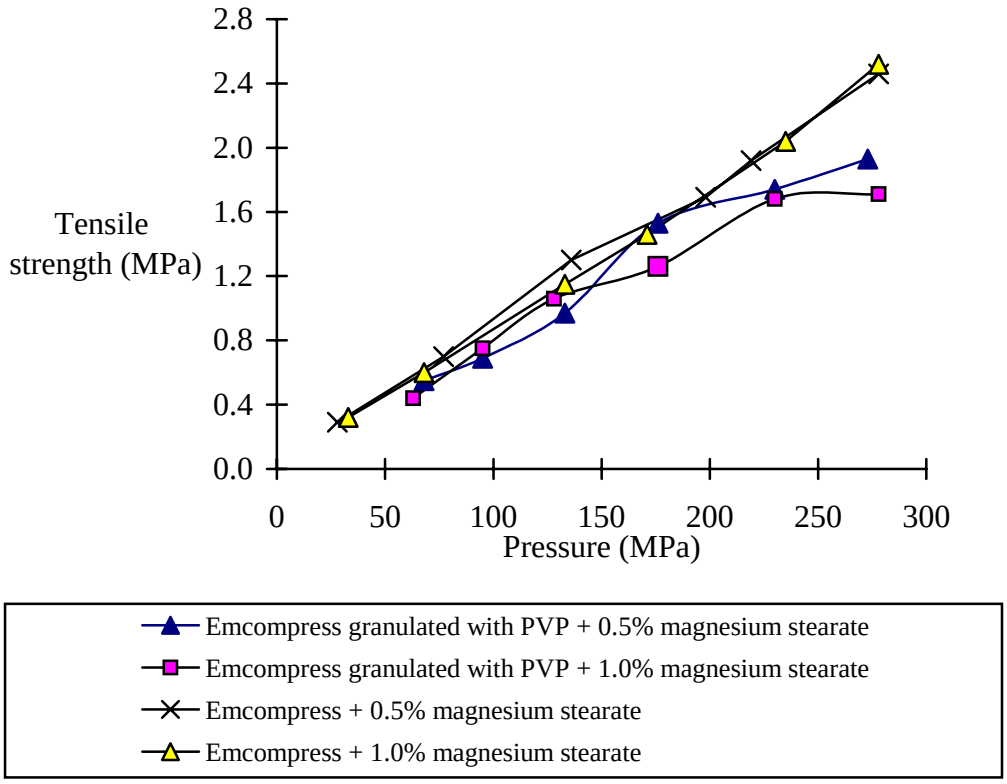

Figure 7. A plot of tensile strength (MPa) versus compression pressure (MPa) for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water.

Correlating tablet tensile strength to porosity shows a good correlation with $r^2 = 0.9671$ (Figure 8). Trying to correlate the tablet tensile strength to the specific surface area, shows that there was no relationship between them (Figure 9) indicating that the surface area does not play a role in the consolidation mechanism of an extensively fragmenting powder like Emcompress® with induced plasticity. Due to the finding that tensile strength was slightly affected upon increasing the lubricant indicate that this mixture bonds by weak distance interparticulate bonds. Also, due to the plastically deforming behaviour, bonding by solid bridges is to be included too. Dibasic calcium phosphate dihydrate consists of granulated primary particles. These agglomerates are expected to have a rough surface texture. Therefore, mechanical interlocking cannot be excluded.

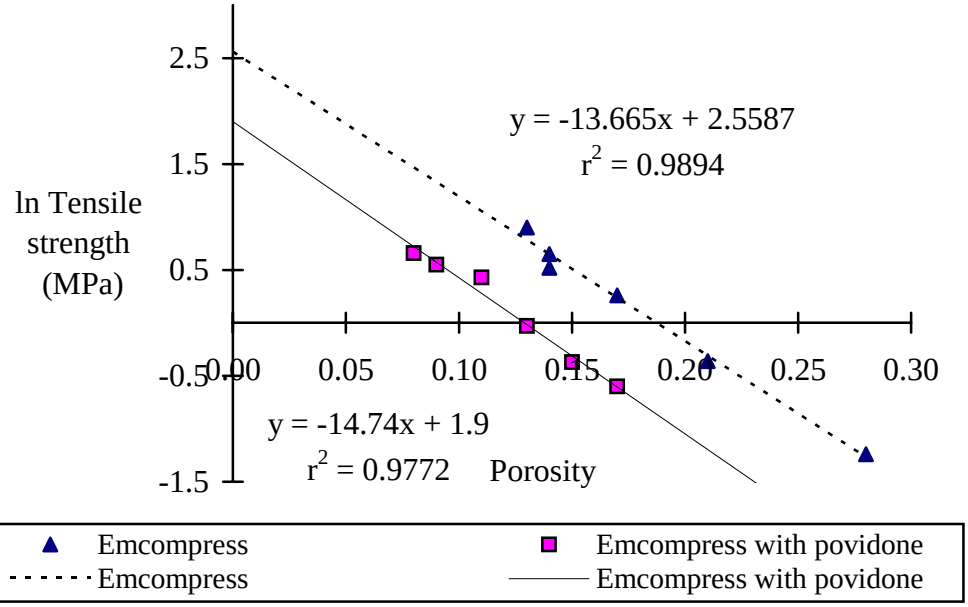

Figure 8. The relationship between tablet tensile strength (MPa) and porosity for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

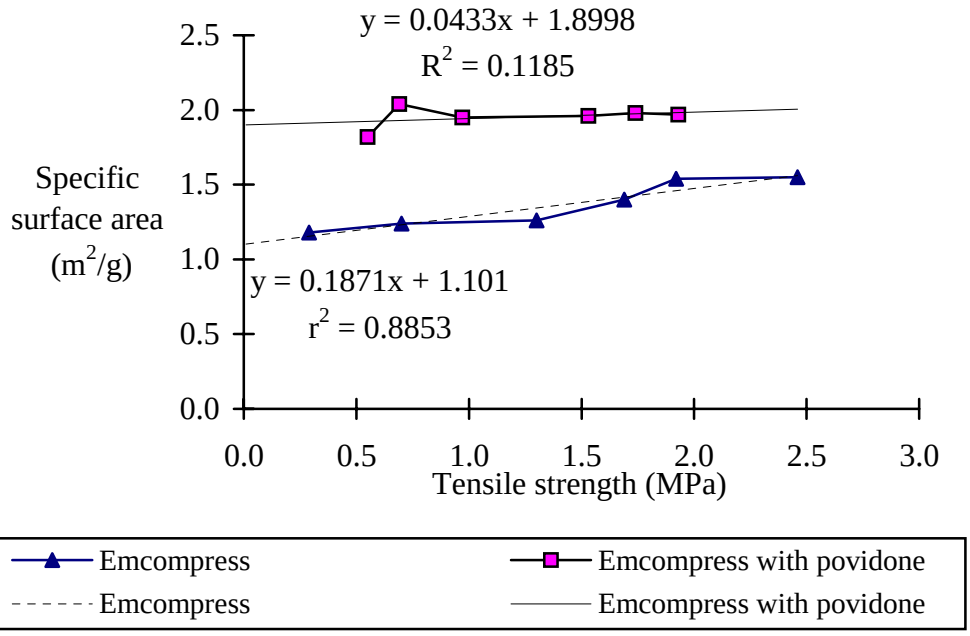

Figure 9. A plot of specific surface area (m^2/g) versus tensile strength (MPa) for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

DISCUSSION

The readings for Emcompress® alone that is used in the comparison can be found in the work of Arida [6]. Comparing the specific surface areas between Emcompress®, and Emcompress® with 5.0% povidone (Figure 1) shows that the granules of Emcompress® with povidone have increased in their specific surface area compared to that of Emcompress® powder itself. This is due to the effect of the binding agent (povidone) which has bound the particles of Emcompress® together. This enlarges the particle size and hence the specific surface area. This agrees with the finding of D'Alonzo et al. [23] who found that the concentration of binder used and its method of addition as a dry powder or as a granulating fluid, can significantly affect granule size. Therefore, the readings of Emcompress® with povidone are larger than those without povidone.

Higuchi et al.[24] found that as the lactose granules, which were granulated by adding 10% starch paste, are compressed into a tablet, the specific surface area is increased to a maximal value (four times that of the initial granules), indicating the formation of new surfaces due to fragmentation of the granules. Further increases in compressional force produce a progressive decrease in specific surface area as the particles bond.

Due to the induced plasticity, there is a slight difference on the porosity (Figure 2) in which the surfaces, with the addition of povidone, are capable of slithering on each other and the compact will be more compressed and the porosity will be eventually lower than that without povidone. Figure (3) and table (1) show that due to the induced plasticity effect of povidone, the yield pressure value has decreased upon adding povidone from 323 MPa to 263 MPa. Moreover, it can be noted that there was no effect of lubricant concentration on the values of yield pressures.

Figure (4) shows that as long as there is a slight increase in the specific surface area of Emcompress® at the beginning of the curve, this means that the material is fragmenting and that there is no plastic deformation. Hence the pores within a tablet are in filling conditions during fragmentation and their pore radii are expected to decrease. With povidone, there have been no changes in the specific surface area which coincided with no change in the average pore radii. This is mostly due to the counteracting effect of fragmentation and plastic deforming behaviours, thus establishing almost a horizontal line (Figure 4). Plotting a curve representing the average pore radius versus specific surface area (Figure 5) shows that there is no relationship between these two parameters.

Upon adding povidone to Emcompress®, tablet tensile strength did not increase, as was expected due to the binding effect, but rather slightly decreased (Figure 10).

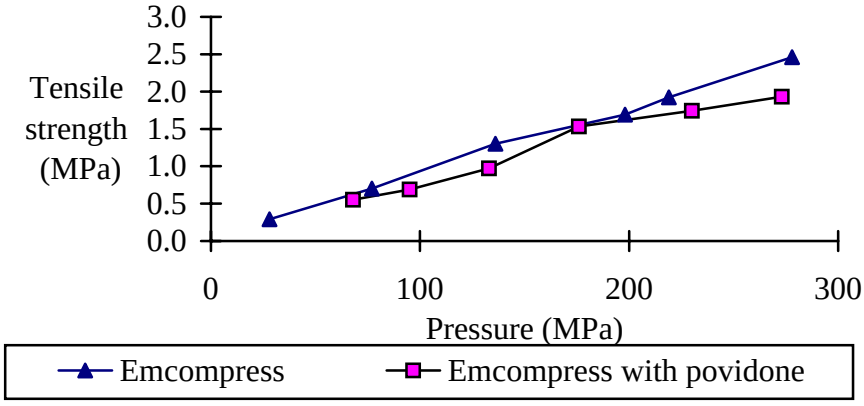

Figure 10. A plot of tensile strength (MPa) versus compression pressure (MPa) for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water, both lubricated with 0.5% magnesium stearate.

It is already known that solid bridges are stronger than distance forces [25]. Therefore, and as long as the tensile strength of Emcompress® with povidone is lower than that of Emcompress® itself, then the solid bridges binding mechanism is to be excluded from the binding mechanism of Emcompress® with povidone, as has been previously discussed and suggested in this work, and that Emcompress® with povidone binds via distance intermolecular forces and mechanical interlocking. Figure (8) shows that both Emcompress®, and Emcompress® with povidone have good correlations between the tensile strength and the porosity. This would agree with recent research on Emcompress®[26-36]. However, surface area of both does not play a role in their binding mechanism (Figure 9).

The extrapolated tensile strength at zero porosity at different lubricant concentrations (Table 2) shows that the tensile strength values of Emcompress® with povidone (6 and 7 MPa) are almost half that of Emcompress® alone (13 MPa).

Table 2. Tensile strength (MPa) at zero porosity for tablets compressed from Emcompress® powder alone, and Emcompress® powder granulated with 5.0% povidone in water.

Powder	Tensile strength (MPa) at zero porosity †	Tensile strength (MPa) at zero porosity ‡
Emcompress®	13	13
Emcompress® and 5.0% povidone	7	6

† Lubricant concentration is 0.5% (w/w%).

‡ Lubricant concentration is 1.0% (w/w%).

This could be explained by the fact that Emcompress® alone has more tough surface than that with povidone, so mechanical interlocking play an advanced role here, also povidone might have filtered some of the intermolecular forces, which is shown as a slight decrease in the tensile strength of Emcompress® with povidone (Figure 7). This concludes that the only bonds which play role in the consolidation mechanism of Emcompress® are the mechanical interlocking and the distance intermolecular forces.

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تفنيد الروابط الموجودة في سواغ الامكومبرس

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ملخـص

هذا البحث هو محاولة لتحديد روابط سواغ الامكومبرس عند الانضغاط ، حيث ان موضوع تحديد نوع الروابط داخل السواغات الدوائية أخذ حديثاً حيزاً واسعاً في البحث العلمي نتيجة الافتراضات المختلفة التي أدت الى نتائج غير مؤكدة ، وهذا البحث هو محاولة لتحديد هذه الروابط ومنع أي لبس في المعلومات الموجودة لتاريخه.
تمت دراسة هذه الخواص لسواغ الامكومبرس الشديد التكسر وتمت مقارنتها مع تلك الخواص عند إضافة سواغ البوفيدون الذي يمنع تكسر الامكومبرس وبالتالي تم فرز هذه الروابط دون أي مؤثر خارجي.
بعد فرز روابط انضغاط سواغ الامكومبرس والغاء جميع المؤثرات الخارجية المؤثرة على ميكانيكية انضغاط سواغ الامكومبرس تم توضيح علاقات مختلفة تتحكم بسواغ الامكومبرس كما تم اظهار علاقة جديدة ما بين تغير المساحة السطحية للسواغ وما بين معدل قطر مسامية السواغ المذكور.
أوضحت هذه الدراسة ان سواغ الامكومبرس يرتبط بواسطة القوى البعيدة الضعيفة فقط ، بالاضافة الى التشابك الفيزيائي وتم استثناء جميع الروابط الأخرى.

الكلمـات الدالـة: ميكانيكية الانضغاط، سواغ الامكومبرس، ادمصاص النيتروجين، المساحة السطحية النوعية، معدل قطر المسامية، الغرولة المائية، سواغ البوفيدون.

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