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GRANULE STRESS RELAXATION STUDIES AS A FUNCTION OF DIFFERENT LUBRICANTS

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تم إختيار تأثير خواص اللزوجة والمرونة للمشحمات المختلفة مثل ستيارات الماغنسيوم وبدرة التلك والبريسيرول على الخواص الإنضغاطية للحبيبات بإستخدام جهاز محلل الملمس (Texture analyser TA-XT21). كما تم دراسة منحنيات ضغط الإرتخاء للمضغوطات وعلاقتها بكل من المسامية واللزوجة والمرونة وحجم الجزيئات للمشحمات. وقد كشفت الدراسات أن الترابط بين الحبيبات المضغوطة المشحمة بإستخدام ستيارات الماغنسيوم كان عاليا عن المضغوطات المشحمة بإستخدام المشحمات الأخرى. ويرجع السبب فى ذلك أن ضغط الإرتخاء فى حالة إستخدام ستيارات الماغنسيوم كان نتيجة التشوه التطويعى للمشحم بدون تجزئة ، بينما الضغط الإرتخائى نتيجة إستخدام بدرة التلك أو البريسيرول كان نتيجة أن هذه المواد تتشوه بالتجزئة. وهكذا تتميز ستيارات الماغنسيوم كمشحم للأقراص بتقليل تراكم الضغط فى المضغوط الذى يتسبب فى مشكلة تقشير الأقراص مما يؤدى إلى المثالية فى صناعة الأقراص.

Effect of the visco-elastic properties of different lubricants, namely magnesium stearate, talc and precirol, on granule compaction properties was examined using texture analyser TA-XT21®. Stress relaxation curves of the compacts have been discussed in relation with three parameters (porosity, visco-elasticity as well as particle size). The study revealed that bonding in compacted granules lubricated with magnesium stearate was higher than those in compacts with other lubricants in study. It is reasonable that, the large stress relaxation due to magnesium stearate was plastic deformation dependent with no evidence of fragmentation. While, small stress relaxation due to talc or precirol suggested that, these materials deformed principally by fragmentation. However, magnesium stearate as tablet lubricant, could be characterized by minimizing the accumulation of stress in the compact, which cause problem of capping, leading to the optimization of tablet manufacturing.

INTRODUCTION

During tableting process, pharmaceutical powders are not subjected to an increasing force but undergo a mechanical deformation.[1] However, the force observed is a direct consequence of the resistance offered by the material under compaction, which intern depends on the physical properties of substances which undergo a time dependent volumetric change.[2] Thereby, the tendency of tablets to cap has been related to many factors including the storage of elastic energy during compaction, with subsequent elastic recovery after the removal of axial pressure.[3] Several mechanisms have been suggested to explain the consolidation stage. Hence, the compaction process can be summarized as packing of particles by diffusion into void spaces, elastic and plastic deformation of the material and characteristic compaction profiles can be expected.[4] Velasco *et al.*[5] have stated that, the formation of intact compact by compression results due to forces present at the particle-particle contact area. As the compression

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pressure was increased, large true contact areas between particles are established. Plastic materials will permanently deform and create extensive areas of true contact between particles; elastic materials will store energy under compression. Whereas, during decompression, the stored elastic energy may disrupt and separate the true contact area that was established by compression forces resulting in poor bonding.

Shlanta and Milosovich[6] have studied the stress relaxation characteristic of various pharmaceutical materials, they concluded that, materials possessing satisfactory compaction properties exhibited an intermediate stress relaxation and a decrease in the applied force occurs. This phenomenon results from deformation of the compressed material into interstitial space. When the stress relaxation was either high or lows a suitable compact was not formed under static compression.[7] However, stress relaxation curves have been employed to quantitate the energy required for elastic and plastic deformation, hence, interprets the consolidation of different pharmaceutical compacts. In other words, for a given plastic deformation, solids presenting a sufficient degree of relaxation have a great area of contact and consequently, a greater degree of bonding. This deformation mechanism makes possible to reduce the risk of structure failure of compact, which may result from elastic recovery.[8] In contrast, during relaxation of elastic compacts, the compressed air in such formulations expands and leads to fracture of compacts due to bonds' weakness. A risk of capping or splitting with formulations containing fragmented particles dHx to entrapped air during the consolidation stage has been discussed.[9]

Blaey and Polderman have suggested that, in tablet manufacturing, the addition of lubricant implies a decrease in friction together with an increase of the expansion work, which is consistent with the concept that, lubricants increase visco-elastic nature of the materials and therefore avoid the accumulation of stress in the compact that cause problem of capping.[10] However, lubricant particles coat granules particles and interrupt interparticulate bonding with plastic deformation. While, fragmentation of brittle particles results in large areas of new surfaces reducing the detrimental effect of a lubricant.[11]

As physical and chemical characteristics of lubricants are the causes of their behavior.[5] The objective of this study was to assess and critically evaluate the effect of different lubricants namely magnesium stearate, talc and precirol, on the consolidation and stress relaxation of different granules using texture analyser TA-XT21, and to relate their compression to the properties of lubricants and granules utilized, aiming in optimizing compaction technique.

MATERIALS AND METHODS

Materials

Corn starch (Roquette, France), fine lactose powder (100 mesh, Holland), monohydrate theophylline (Cooper Meulun-France), calipharm BP (dicalcium phosphate dihydrate, Albright & Wilson Ltd, West Midlands), Natrosol (Hydroxyethylcellulose, Hercules, Netherlands). All ingredients were used as received. Talc P3 (St. Denis-France)., Magnesium stearate (Cooper, Meulun-France) and Precirol Ato 2155 wl (glycerol palmito-stearic ester, Gattefosse, St. Priest-France), were classified through 32 mesh (500 nm) fractions using Analysensieb Retsch, 5657 Haan Germany.

Procedure

Wet granulation technique

Two formulae were prepared for this study, mixture A: lactose fine powder and corn starch (80 and 15% respectively), mixture B: lactose fine powder, natrosol and calipharm (45, 40 and 10% respectively). Theophylline monohydrate in 5% was taken as tracer. Techniques adopted for wet granulation was illustrated in Table 1. The prepared granules were mixed with different lubricants namely talc, magnesium stearate and precirol in different concentrations (0.5, 1, 1.5, 2, 2.5 and 3% w/w). Granules were mixed with lubricants using Turbula type T2C mixer at 42 rpm for 5 minutes.

Table 1: Wet granulation parameters.

Granulation parameters	Apparatus used	Mixture A	Mixture B
Water volume	Loading: 250 rpm (TM 20)	500 ml	1000 ml
Wetting time	Loading: 250 rpm (TM 20)	10 min	15 min
Drying (60°)	Ventilated Oven	5 hr 30 min	4 hr 50 min
Calibration	Oscillating grandulator-erweka FGS	1000 μm	1000 μm
Percent relative humidity (120°, 15 min)	Infra-Red Balance (Mettler LP 16)	1.5 %	2.8 %

Stress relaxation analysis

The compression characteristics of the prepared granules (mixtures A&B) in absence and presence of different lubricants were studied. The instrumental method was developed to measure stress relaxation of compacted granules under constant deformation. Texture analyzer TA-XT2i, as a well controlled compaction device (RHEO Champlan-France, Figure 1), was installed. It was supplied with aluminum probe adapted at speed of 1mm/sec. A weight of granules equivalent to a volume of 30 cm^3 was mounted and subjected to a maximum compression pressure of 49 N. The texture analyzer has been calibrated by fixing the probe displacement speed at 1 mm/sec, and maintained time for 60 sec. When the compression pressure reached a fixed value of 49 N, the probe cylinder displacement was kept stationary and the decay of the probe force was measured. Stress relaxation in the compact was monitored for 60 seconds and the deformation was measured through probe displacement recording. Three compacts being repeated for each measurement. The stiffness of granules (Young's modulus E) was determined as a function of the ratio between the recorded maximum stress (σ_{max}) that granules have been exposed and the maximum deformation of granules after compression which could be recorded by the texture analyser (δ_{max}).[12]

$$E = \frac{\sigma_{max}}{\delta_{max}}$$

Peleg M. (1979) has previously presented Relaxation stress parameter in term of percent relaxation (%R), as the ratio between the monitoring force (F) (force atthe end of each experiment) and the maximum compaction force (F_0).[13]

$$\% \text{ Relaxation} = (F_0 - F) / F_0 \times 100$$

As consolidation mechanisms may be predicted by the interdependence between the mechanical strength of compacts and compaction variables, such as plastic and elastic deformation, particle size of compressed granules as well as porosity, fundamental studies of these properties have been proposed.

Plasticity values determination

The difference between maximum compaction force (F_0) and monitoring force (F) has been taken as a representative of plasticity.[8]

$$\text{Plasticity} = F_0 - F$$

Particle size analysis

Average particle size of both lubricants and granules together with their mixtures were analyzed before and after compaction using Laser diffractory Mastersizer (Type S long bed Ver. 2.15 Malvem Instruments, UK).

Granule partial porosity

Castle empirical formula was utilized for the determination of granule partial porosity $\epsilon(\%)$.[14]

$\epsilon(\%)$ = (Partial void volume/granule volume) x 100

However, partial void volume could be evaluated as a function of maximum probe displacement when relaxation took place.

RESULTS AND DISCUSSION

Several different mechanisms have been suggested to explain the consolidation stage.[15] The use of texture analyser TA-XT21 (Figure 1) was considered to be a good technique for the evaluation of the stress relaxation of solid particles in compression process. Figure 2, represents stress relaxation curves of compacted granules, which characterizes the visco-elastic behavior of the compacts in presence of different lubricants. During the first section of the curves, the maximum force is relatively high (F_0). Then, when deformation is constant, the monitoring force recorded (F) in relation to time decreases more or less quickly and tends toward an asymptotic value.[8] As, (F) represents the resistance opposed by the elastic part of the compacted material.[2] It may be noticed that structure relaxation of compacts lubricated with magnesium stearate slowed down more quickly than that of talc and precirol. This can be explained as a result of the low resistance (F) opposed by the plastic compacted granules lubricated with magnesium stearate, as compared with the higher resistance opposed by elastic granules lubricated with either talc or precirol.

Table 2 illustrates that, a material with high elasticity and deformation rate has the lowest Young's modulus (granules stiffness) as indicated by talc and precirol.[12] In contrast, magnesium stearate showed the highest Young's modulus indicating high plasticity.

Figure 3 demonstrates that granules lubricated with magnesium stearate displayed higher plasticity values than those lubricated with talc and precirol. These results indicated different consolidation mechanisms. Granules lubricated with magnesium stearate have consolidated initially by particles slippage and then subsequently by plastic deformation.[7] For proper bonding force, plasticity is necessary to sufficiently reduce the distance between adjacent particles,[16] and play the dominant roles during densification.[7] The evidence is changed for both talc and precirol. They have high elasticity and consolidate fragmentation and small amount of stress relaxation. Whereas, the interparticle bonding of compacted granules decreases quite drastically. The influence of moisture content on the degree of plasticity of different granules was previously studied.[8] The authors have reported that degree of plasticity is increased with moisture content. Accordingly Figure 3 illustrates that, granules of mixture B with high moisture content have highest plasticity values than those proposed by mixture A.

Cole *et al.*[17] previously explained the phenomenon of stress relaxation. Accordingly, when a particulate system having high percent relaxation is compacted and held under load, stress relaxation in the compressing device occurs as a result of reduction in the compact volume. The phenomenon can be explained as a result of the plastic deformation of compacted material into void spaces causing increased bonding between particles. However, the compact behaves as a set of spring and shock absorber.[18] Recently, it has been demonstrated that compact relaxation depends to a large extent, on the amount of energy stored in the compact during compression, as well as on the interparticle bonding.[19]

Figure 4 shows the effect of different lubricants on percent relaxation [$(F_0 - F) / F_0$ x 100], of the prepared granules (Mixture A and B). The consolidate profiles show that, granules lubricated with magnesium stearate exhibited the greatest stress relaxation followed by talc and precirol. Hiestand and co-workers have demonstrated that, materials that tend to cap, exhibit slowly stress relaxation.[20] As shown in Figure 4, the stress relaxation of compacts increased with magnesium stearate concentration, due to high bonding between particles. While, in case of compacts lubricated with talc or precirol the order is reversed. As the stress relaxation of compacts is inversely proportional with lubricant concentrations. In case of precirol the order is reversed at

Table 2: Effect of different lubricants on the young's modulus and partial porosity of prepared granules.

		Partial porosity ε (%)	Young's modulus E (N/mm)
Mg. Stearate (% w/w)	Mixture A		
	0	25.14 ± 1.37	55.46 ± 2.1
	0.5	18.26 ± 0.2	92.2 ± 1.04
	1	17.5 ± 0.21	94.73± 2.9
	1.5	16.59 ± 0.3	100.7 ± 2.97
	2	16.04 ± 0.96	89.98 ± 1.7
	2.5	15.67 ± 0.75	93.31 ± 2.5
	3	13.12 ± 0.84	83.30 ± 2.02
	Mixture B		
	0	20.07 ± 0.25	72.12 ± 5.03
	0.05	19.23 ± 0.27	103. ± 2.65
	1	19.8 ± 0.57	101.39 ± 1.95
	1.5	18.77 ± 0.25	99.87 ±2.85
	2	17.75 ± 0.32	105.32 ± 6.1
	2.5	17.87 ± 0.37	96.35 ± 2.048
	3	17.44 ± 0.152	100.94 ± 3.95
Talc (% w/w)	Mixture A		
	0	25.14 ± 1.37	55.46 ± 2.1
	0.5	31.72 ± 0.6	60.75 ± 1.9
	1	31.31 ± 0.01	61.66 ± 3.2
	1.5	32.94 ± 0.07	56.98 ± 5.29
	2	32.62 ± 0.156	60.23 ± 3.52
	2.5	32.30 ± 1.82	61.18 ± 1.93
	3	31.22 ± 1.67	63.01 ± 2.97
	Mixture B		
	0	20.07 ± 0.25	72.12 ± 5.03
	0.05	20.19 ± 0.39	75.34 ± 1.98
	1	19.94 ± 0.25	78.69 ± 2.53
	1.5	20.34 ±0.11	77.21 ± 2.85
	2	21.13 ±0.51	74.01 ± 0.99
	2.5	21.97 ± 0.2	70.85 ± 4.56
	3	20.80 ± 0.81	74.14 ± 7.21
Precirol (% w/w)	Mixture A		
	0	25.14 ± 1.37	55.46 ± 2.1
	0.5	33.64 ± 0.75	59.83 ± 1.90
	1	39.10 ± 0.17	68.19 ± 2.58
	1.5	26.06 ± 1.23	74.40 ± 4.21
	2	26.91 ±1.03	72.58 ± 2.03
	2.5	28.44 ± 0.4	68.96 ± 1.42
	3	28.23 ± 0.24	96.16 ± 0.98
	Mixture B		
	0	20.07 ± 0.25	72.12 ± 5.03
	0.05	19.29 ± 1.58	85.32 ± 3.95
	1	21.35 ± 0.07	80.27 ± 5.32
	1.5	23.72 ± 0.74	88.26 ± 7.21
	2	20.19 ± 0.11	83.45 ± 5.89
	2.5	19.94 ± 0.63	76.40 ± 4.25
	3	20.34 ± 1.38	70.04 ± 3.95

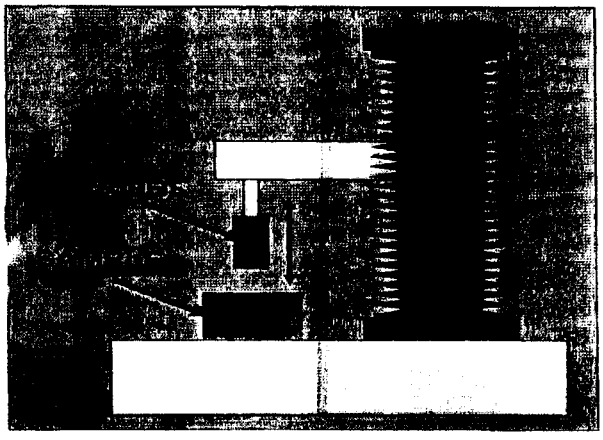

Fig. 1: Texture analyser apparatus (simplified model).

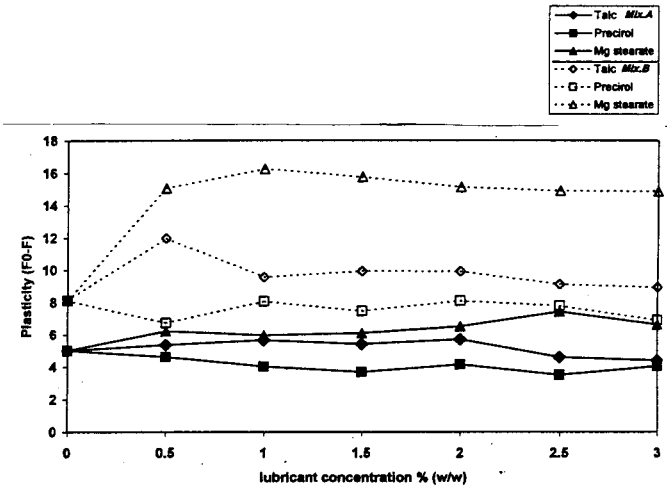

Fig. 3: Plasticity of prepared granules as a function of different lubricants.

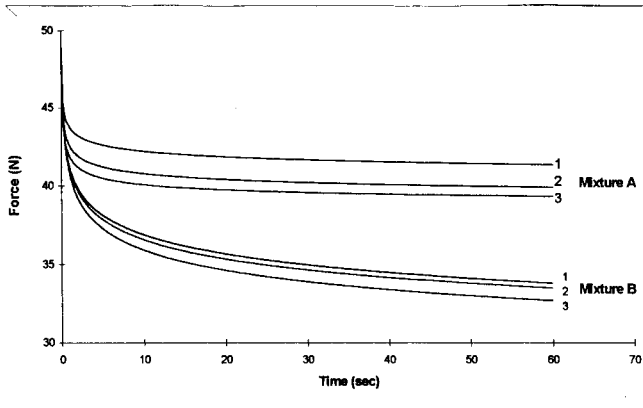

Fig. 2: Effect of different lubricants (%) on the stress relaxation curves of prepared granules (mix. A and B).
1: Precirol; 2: Talc; 3: Mg. stearate.

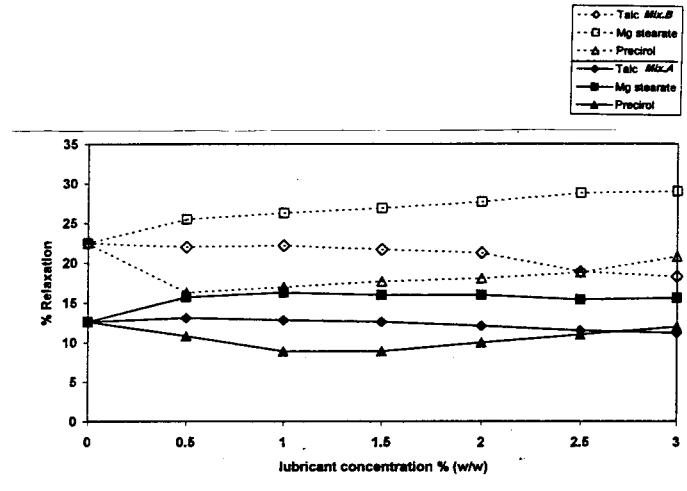

Fig. 4: Relaxation percentage characterisation of prepared granules as a function of different lubricants.

concentrations above 1%. The morphological characteristics of the used lubricants (magnesium stearate, talc and precirol) justified the obtained results. Whereas, magnesium stearate has the highest projected specific surface area (16 m^2/g) as measured by gas adsorption using Nova 2000 (RHEO, France) and the lowest particle size diameter (5.66 μm). Those for talc and precirol were 12 and 1.02 m^2/g, and 18.68 and 46.41 μm, respectively. The small particle of magnesium stearate can occupy the spaces between granules, forming a lubricant film on the particle surface showing a significantly high cohesive index,[11] which increased with lubricant concentration. Precirol, due to its morphological properties, has small flakes with high cohesion forming agglomerates, which may not delaminate.[5] This hypothesis can explain the consolidation behavior of granules lubricated with precirol at different concentrations. At low concentration, precirol particles will distributed between granules during consolidation, resulting in low relaxation of the compact. At concentrations higher than 1% however, precirol particles agglomerate with an increment in the compact relaxation. Talc is not an anti-friction lubricant,[21] and presents a high elastic behavior.[8] Beside, the film formation is unlikely to become complete when dealing with poorly flowing powder like talc.[23]

Since particle size is known to affect compact properties, where the degree of relaxation depends upon particle size.[6] Figure 5 implies that, granules lubricated with talc have the highest fragmentation propensity during compaction, followed by those lubricated with precirol. In case of granules lubricated with magnesium stearate, the lack of fragments in the compact cause a more or less coherent lubricant matrix to be formed.[23]

Figure 6 shows that, average particle size distribution of granules lubricated with magnesium stearate after compaction was higher than that of original granules before compaction (592.19 and 423.04 μm, respectively). This could be returned to the lubricant film formed around granule particles.[24] Unfortunately, it has been pointed out that, particle size of granules lubricated with talc as well as precirol was reduced after compaction to 122.5 and 141.5 μm, respectively. This reduction intern reduced the possibility of forming strong bonding.[25] As preliminary relaxation data obtained previously indicated correlation with physical properties of the compact. It has been verified that the preliminary relaxation curves obtained with tested lubricated granules could be the sum of three exponentials, particle size, and porosity as well as plasticity of particles in compacts.[8]

The consolidation behavior of different granules (Mixtures A and B) have been demonstrated in Figure 4, where mixture B with the highest moisture content exhibited an increment in percent relaxation values than those proposed by mixture A. Li and Peck have stated that, method of granulation had an influence on the physical properties of granules and that moisture content of material exerted an effect on its compaction behavior.[26]

With a view to optimizing compact formation, attention would therefore be paid to porosity. Porosity of different compacts has been depicted in Table 2. Statistically significant differences existed between porosity values of compacted granules lubricated with magnesium stearate and those lubricated with talc or precirol ($p < 0.01$). The obtained order of porosity values (magnesium stearate < precirol < talc) together with stored energy imply that, the amount of stored energy was found to be the driving force for porosity expansion.[12] Thus, the final tablet porosity depends on powder consolidation during compression and compact relaxation after punch release.[16] However, for a predominantly plastic material, a direct relationship appears to be existed between the small amount of elastically stored energy and the minimum porosity that can be reached.[16] Table 2 realized that, porosity expansion is counteracted by bonding due to magnesium stearate particles. This circumstance could be explained as a result of the attraction between particles which causes resistance against porosity expansion.[12]

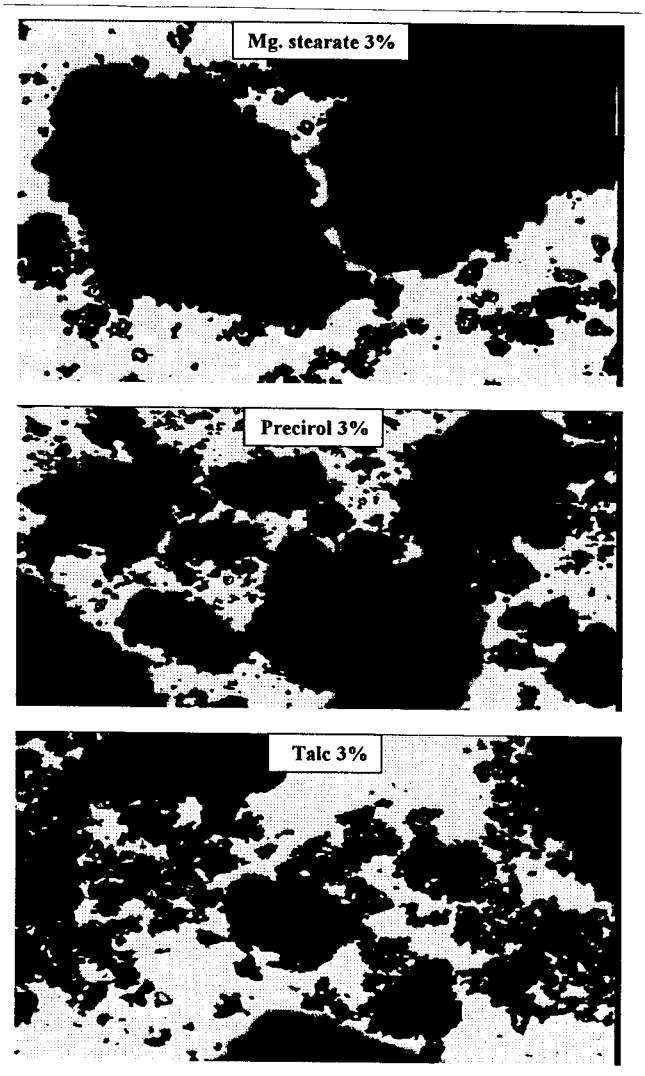

Fig. 5: Micrograph of compacted granules with different lubricants.

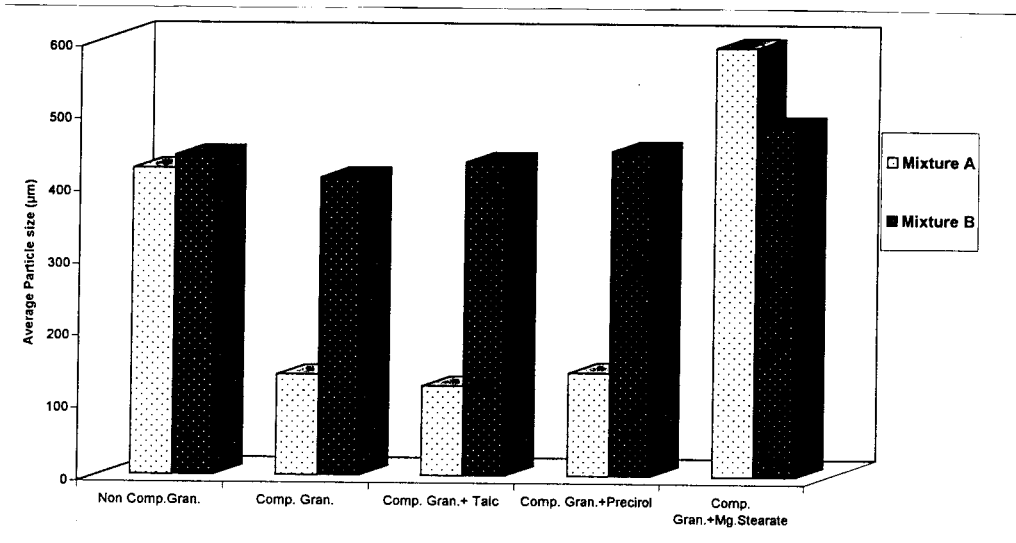

Fig. 6: Effect of 3% lubricants on the average particle size of different granules on compression under 49 N.

CONCLUSION

For characterizing the compaction behavior of materials, the effect of different lubricants on the compression properties of granules was studied. The results indicated different consolidation mechanisms for magnesium stearate, talc and precirol. Studies of the consolidation mechanisms could correlate stress relaxation behavior with lubricant particle size and plasticity as well as porosity data of compacts. The study revealed that magnesium stearate was the lubricant that exerted the highest stress relaxation followed by talc and precirol. These results could be explained based on the structure properties of lubricants under study. While, magnesium, stearate consolidates by plastic deformation, talc and precirol undergo fragmentation on consolidation. Generally, magnesium Stearate could be expected to be the lubricant of choice in the estimation of capping risks.

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