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THE USE OF STRESS RELAXATION TRIALS TO CHARACTERIZE TABLET CAPPING

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SUMMARY

A new method is described for estimating capping risks due to the entrapment of air during compression.

For this, the curves obtained during a stress relaxation test were analysed using a WISCHERT model.

Two processing modes of computation from experimental data made it possible to characterize the stress relaxation of each product or mixture of products by a sum of two or three exponentials.

The first exponential represents a more or less rapid structure relaxation. When the quantity of fines particles is too great, the structure relaxation is slowed down by the entrapped air as soon as constant deformation is applied.

INTRODUCTION

The aim of the tabletting process is to reduce the powder bed volume under the influence of an applied deformation and to press the particles close enough together for bonding to occur.

Several different mechanisms have been suggested to explain the consolidation stage. The most important are packing of particles,

elastic and plastic deformation of the material, cold working and fragmentation (1).

Plastic deformation is time dependent (2), i.e. it depends on the time during which the particular material is held under deformation , and during which the moving upper punch (U.P.) receives a detectable force from the die contents during the compression and decompression stages.

It is now known that the U.P. displacement in relation to time is a parabola flattened at the top (3).

During the time of the "plateau" curve and after the last Pmax value, it may be considered that the tablet undergoes stress relaxation: according to the material, it may be observed that the force decreases to zero during the plateau curve or when the U.P. begins to move upwards in the die.

Thus, the tablet undergoes true stress relaxation for a very short time (about 15 to 30 ms). This characteristic has been studied by DAVID and AUGSBUCHER (4) and WIEDERKEHR (5) who defined a viscoelastic constant when decompression begins; according to these investigators, materials with a high constant undergo more plastic flow and often form strong tablets at relatively low compaction forces.

Likewise, DAVID and AUGSBURGER (4) have analysed stress relaxation data using the MAXWELL model of visco-elastic behaviour in a attempt to quantify the rate of plastic deformation of some direct compression agents.As discussed in this paper, this model limits

their usefulness in assessing the tabletting characteristics of pharmaceutical materials.

These results were confirmed by REES & RUES (2) who studied stress relaxation behaviour for 360 sec. and observed that data plots behave as a true Maxwell model 30 sec. after application of the maximal force .

If we take into account the time of compression (which is about 0.15 to 0.4 sec whatever the machine), it is likely that only the phenomena which take place during the first section of the stress relaxation curve have a significance on the compressional behaviour of most formulations.

This section of the curve depends on the chemical nature, particle size and size distribution of powders, moisture content (2)...etc.

For a given deformation, solids presenting a sufficient degree and rate of relaxation have a great area of contact, and consequently, a greater degree of bonding. This makes it possible to reduce the risk of structural failure of tablets, which may result from elastic recovery or from the forces required to eject the tablet from the die.

A preliminary study (6) suggests that the shapes of stress relaxation curves can be affected by air entrapped in the powder bed when a constant deformation is applied.

During compression and particularly when the U.P. moves upwards, the compressed air in such formulations expands and leads to tablet fracture if the bonds are not strong .This mechanism may cause capping with formulations containing too great a rate of fine powders (7).

The purpose of this work is to propose a new method for predicting whether active ingredients and/or compression additives present a risk of capping or splitting due to the entrapped air during the consolidation stage.

EXPERIMENTAL

1) APPARATUS AND OPERATING MODE

Stress relaxation experiments were performed using an instrumented reciprocating tablet machine FROGERAIS TYPE OA, equipped with two 12 mm diameter punches.

Data recorded in a MAURER transitory memory were then restored in a microcomputer.

After manually filling the die (10 mm deep) with a fixed weight of powders, the tablet machine fly-wheel was turned by hand until the U.P. closed the die. The U.P. was then held at this fixed position by blocking the gears.

Deformation of the powder or mixture was caused by means of the adjusting wedge of the lower punch block, which was equipped with a crank.

The selected deformation was fixed by the number of revolutions of the crank at 2 r.p. s.

The evolution of the force in relation to time caused by the lower punch displacement was then recorded during 40 sec.

This time was long enough for monitoring the relaxation of the material, the latter slighly varying about 20 sec. after maximal deformation.

For this reason, the time required to reach the various applied deformation had little or no influence on relaxation results.

2) MATERIALS TESTED

* Avicel PH 101 (microcristalline cellulose)
* Commercial red rubber
* Micronized sodium Chlorure (NaCl)
* NaCl Crystals
* Non tablet-able agar-agar mixture
* Celutab (glucose)
* Non tablet-able F.C. Paracetamol (French COOPER -micronized product)
* F.C. Paracetamol granulated with potato starch (1%) and lubricated with 0.5% magnesium stearate.

3) RESULTS AND DISCUSSION

1) VISCOELASTIC OR PLASTO-VISCOELASTIC BEHAVIOUR OF SOME PHARMACEUTICAL POWDERS.

The method used was first validated; particularly it was verified that the measurements were not affected by the way the

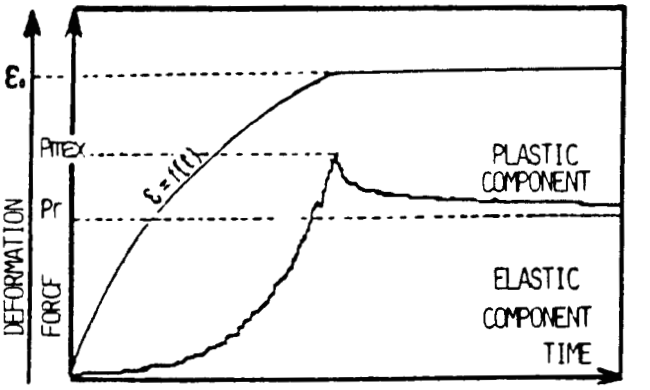

FIG. 1: STRESS RELAXATION CURVE OF AVICEL

gears were blocked. Moreover, each test was repeated 5 times to confirm the results obtained.

Figure 1 represents a stress relaxation curve for Avicel PH 101, obtained with the above operating mode. During the first section of the curve, i.e. the time required to apply the predetermined deformation, the force increases. Then, when deformation is constant, the force recorded in relation to time decreases more or less quickly and tends toward an asymptotic value.

This type of curve characterizes the visco-elastic behaviour of pharmaceutical powders.

Let Pmax be the maximal force measured and Pr be the residual force at the end of each test.

Pr represents the elastic component of the material for the applied deformation. Then, the difference, (Pmax-Pr), represents its degree of plasticity.

The visco-elasticity of the various materials expressed here by the ratio Pr/Pmax was studied in relation to Pmax (Figure 2).

It may be noted that the non tablet-able mixture (6) containing 70 % of agar-agar has a degree of plasticity as great as Sodium Chloride crystals.

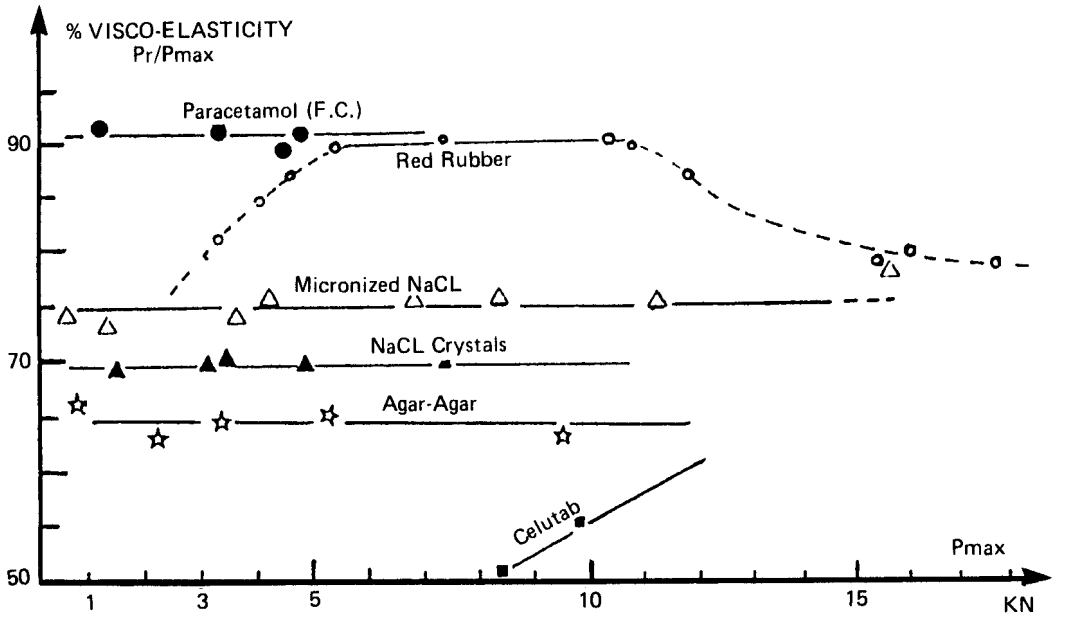

FIG 2 : VISCO-ELASTICITY IN RELATION TO Pmax.

Thus, the plasticity of a material cannot alone explain the tabletability of a formulation.

Likewise, in Figure 2, it may be observed that the viscoelasticity of red rubber is almost constant for a Pmax between 5 and 10 kN.; it then decreases for a greater deformation. This phenomenon characterizes the plasto-visco-elastic behaviour of this material.

Figure 3 shows that the curve during the first stage of relaxation in Avicel is more concave and its rate is faster than that observed with the agar-agar mixture.

An analogic model was therefore used to explain the behaviour of the various materials.

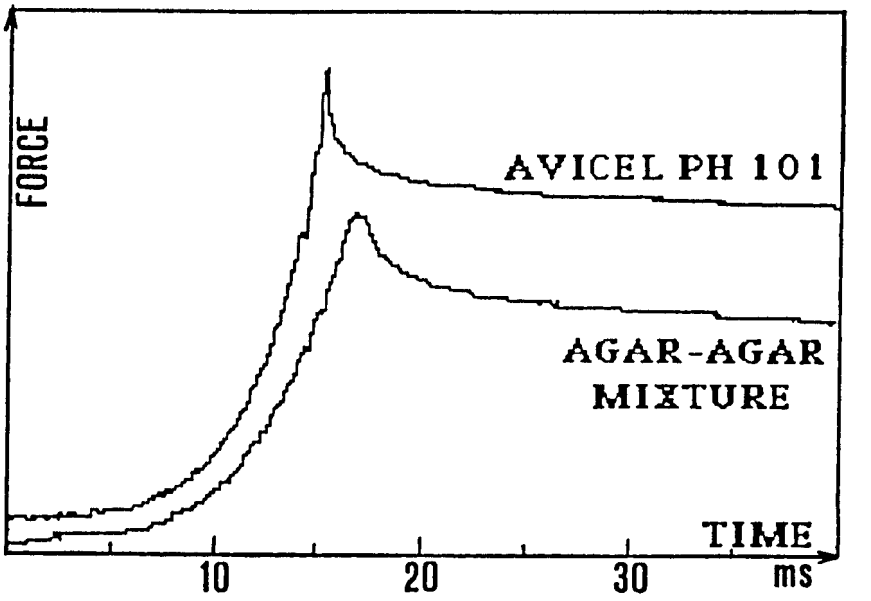

FIG.3 : STRESS RELAXATION CURVE OF AVICEL PH 101 AND AGAR-AGAR MIXTURE.

2) ANALOGIC STUDY OF VISCO-ELASTIC BEHAVIOUR OF PHARMACEUTICAL POWDERS.

In previous work (6), we proposed a mechanical model for representing the viscoelastic behaviour of some powders. This used the MAXWELL model as a basis.

2-1) THE MAXWELL MODEL

This model was already chosen by DAVID and AUGSBUCHER (4). It is composed of a spring and a shock absorber grouped in series, the spring translating the linear elasticity E of the material, and the shock absorber its viscosity η.

If force and displacement may be considered representative of stress and applied deformation respectively, the behaviour of such a model is as follows:

$$P(t) = Pmax * \exp(- t/to) \qquad \text{(eq. 1)}$$

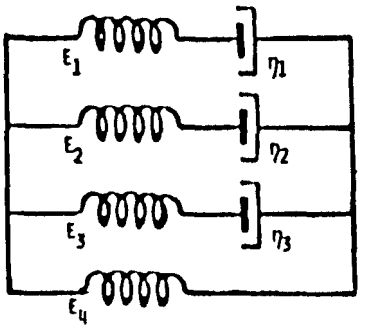

FIG. 4 : THE WISHERT MODEL.

to, being the relaxation constant and P(t) the force measured at time t.

2-2) THE WISCHERT MODEL

According to the product, a spring and two or three MAXWELL bodies are grouped in parallel (Fig. 4) and used as an analogic model.

The mathematical solution of such a system is as follows (7) :

$$P(t) = Pr + \sum_{i=1}^{n} Pi * \exp(-t / \tau i) \qquad \text{(eq. 2)}$$

with

- Pi and Pr, representing respectively the stiffness Ei of spring n°i, and of the system 's residual stiffness
- $\tau i = \eta i / Ei$, ηi representing the viscosity of shock absorber n°i

and

$$Pmax = Pr + \sum_{i=1}^{n} Pi$$

To our knowledge, no accurate method exists for solving this problem.

Experimental Data were analysed with two new processing computer programs developed in our laboratory. The latter used in a previous work (6) does not make it possible to differentiate non tablet able and tablet able products presenting a low degree of plasticity . These two data processing programs calculate the various constants and exponents of two or three different exponentials by successive approximations, and automatically optimize the correlation coefficient of the system. Moreover, they compare the data of the plotted force and the calculated force curve at each stage of calculation.

It may be verified that the recorded force obtained with all materials tested behaves like the sum of 3 exponentials; with some of them, two of them are merged and the system behaves like the sum of two exponentials.

However, it must be noticed that although the 3 exponentials may be easily calculated for materials with a high degree of plasticity , the lack of accuracy (our memory can store only 8 bit words for measurements) makes it difficult to calculate the exponentials of highly elastic products.

Moreover, in purely mathematical terms, it should be realized that this system of 3 exponentials gives several solutions of which one is better than the others. In these conditions, the lack of accuracy of the measurements does not allow the optimal solution to be obtained.

For this reason with highly elastic materials, results are given by the sum of two or three exponentials.

This sum of the 3 exponentials may be written as follows:

$$P(t) = A1 * EXP(B1 * T) + A2 * EXP(B2 * T) + A3 * EXP(B3 * T)$$

TABLE I : SODIUM CHLORIDE : B3 VALUES IN RELATION TO PMAX

MATERIALS	NACL CRYSTALS					MICRONIZED NACL					
P_{MAX} NEWTONS	1435	2627	3333	4862	7450	2509	3960	4196	6392	11137	16078
-10^{-6} B3 ms^{-1}	3.09	3.28	3.25	2.98	3.19	2.89	3.20	3.59	3.30	3.02	2.79
CORRELATION COEFFICIENT $R^{2(*)}$	0.96	0.92	0.94	0.98	0.967	0.91	0.90	0.84	0.93	0.92	0.98
AVERAGE B3 ± SD	3.15 ± 0.32					-3.13 ± 0.73					

* N POINTS (N > 150)

the 3 terms respectively representing the relaxation at the beginning, middle and end of the stress relaxation curve.

Constants A being the constants at time = 0, i.e. at the beginning when constant deformation is applied,

Exponents B are here time constants (ms-1)

2.1-1) Significance of the different exponentials

1) Third exponential representing the end of the relaxation curve

Whatever the applied deformation, Table 1 shows that the time constants B3 of the third exponential given by NaCl crystals are very similar, and their average value is not different ($p < 0.5$) from that observed with micronized Sodium Chloride.

Thus, with this material, B3 is irrespective of particle size .

As no significant change in particle size may be observed during compression of Sodium Chloride (6 & 7), the end of the stress relaxation curve represents the relaxation of the so-called material.

This phenomenon is visualized by the calculated curves 1 of Figures 5.

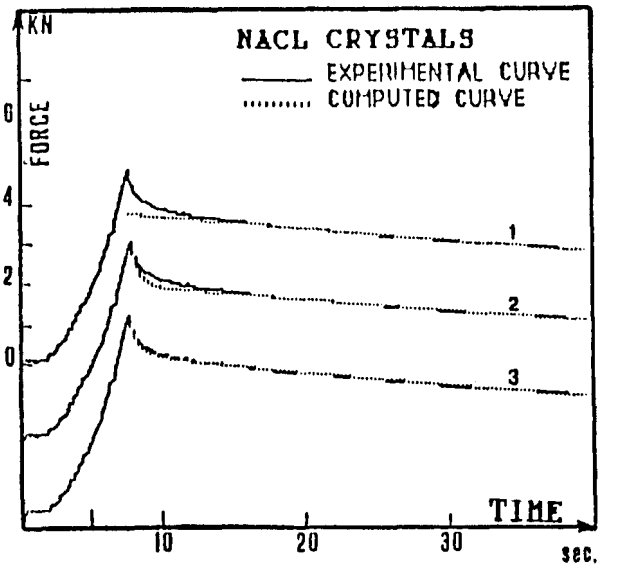

FIG.5-1: STRESS RELAXATION CURVE
OF NaCL CRYSTALS.

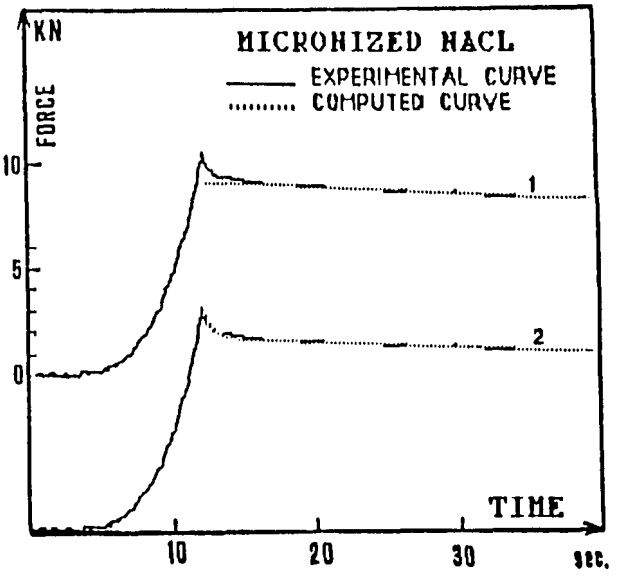

FIG.5-2: STRESS RELAXATION CURVE
OF MICRONIZED NaCL.
(Curves 2 and 3 are merged.)

TABLE II : EXPONENTS AND CONSTANTS OBTAINED WITH THE FIRST TWO EXPONENTIALS GIVEN BY SODIUM CHLORIDE CRYSTALS.

PRODUCT	SODIUM CHLORIDE CRYSTALS				
P_{MAX} NEWTONS	1435	2627	3333	4862	7450
(-) 10^{-3} B1 ms^{-1}	1.82	1.93	1.69	2.85	3.83
/A1/ (P_{MAX} - P_R)	0.48	0.53	0.58	0.51	0.47
R^2 (*)	0.98	0.98	0.97	0.97	0.97
(-) 10^{-4} B2 ms^{-1}	3.01	5.8	3.9	2.45	2.98
/A2/ (P_{MAX} - P_R)	0.25	0.158	0.161	0.24	0.26
R^2 (**)	0.90	0.65	0.53	0.92	0.90

(*) N_1 DATA ($N_1 > 10$)
(**) N_2 DATA ($N_2 > 100$)

Generally, for all the products tested, B3 values are about 1E-06 ms-1.

2) first exponential representing the beginning of the relaxation curve.

In Figures 5, it is established that NaCl crystals show greater relaxation than microsize NaCl.

During this phase, relaxation depends upon particle size.

For this reason, we have previously called this phenomenon "structure relaxation of the material".

As mentioned in Table 2, values B1 (about 1E-03 ms-1) of the first exponential are one thousand times greater than B3 values .

The calculated curves 2 in Figs 5 represent both the relaxation of the material and the structure relaxation.

For NaCL crystals, the first section of the calculated curve is quite different from the experimental force curve. Likewise, it may be seen that the end of structure relaxation is slowed down by a third phenomenon.

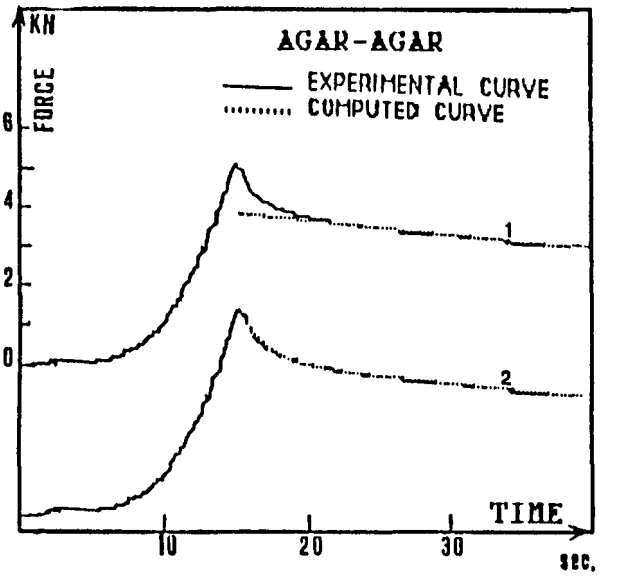

FIG. 6: STRESS RELAXATION CURVE OF AGAR-AGAR MIXTURE.

3) Significance of the second exponential.

With non tablet-able agar-agar mixture which gives capping during compression on a reciprocating tablet machine (8), it may be noticed that structure relaxation is slowed down more quickly than with NaCl crystals (Figure 6) and that calculated curve may be represented by the sum of two exponentials.

Table III shows results obtained with this mixture. Whatever Pmax value, it may be seen that A1 and A3 constants, and B1 and B3 values calculated with the two data processing programs are not different.

Moreover, constant A2 calculated with the one of the data processing programs is much lower.

If we refer now to the time constant B2 (about 1E-04 ms-1) obtained with the highly plastic Celutab (Table IV) or NaCl crystals (Table 2), it is possible to establish that the magnitude of the

TABLE III : AGAR-AGAR MIXTURE : CONSTANTS AND EXPONENTS VALUES OBTAINED WITH THE TWO PROCESSING DATA COMPUTER PROGRAMS.

	3 EXPONENTIALS						2 EXPONENTIALS			
P_{MAX} NEWTONS	A1/P [a]	A2/P [a]	A3/P [a]	(-) B1 10^{-4} MS^{-1}	(-) B2 10^{-4} MS^{-1}	(-) B3 10^{-6} MS^{-1}	A1/P [a]	A3/P [a]	(-) B1 10^{-4} MS^{-1}	(-) B3 10^{-6} MS^{-1}
2447	0.776	2.38 x 10^{-4}	0.21	9.24 (0.976)	2.38 (0.11) [c]	5.19 (0.95)	0.78	0.22	9.17 (0.986)	5.37 (0.95)
5098	0.715	1.4 x 10^{-5}	0.28	5.84 (0.975)	13 (0.26) [c]	5.88 (0.937)	0.72	0.27	5.71 (0.974)	5.74 (0.959)

(A) WITH P=(PMAX - PR)
(B) THE CORRELATION COEF. ARE IN BRACKETS
(C) CORRELATION COEF. NO SIGNIFICANT

TABLE IV : TIME CONSTANTS B1, B2 AND B3 OBSERVED WITH CELUTAB.

CELUTAB \ P_{MAX} NEWTONS	2274	2941	7882	10117
(-) 10^{-3} B1 MS^{-1}	3,52 (0,97)	3,82 (0,98)	2,76 (0,98)	3,43 (0,98)
(-) 10^{-4} B2 MS^{-1}	4,5 (0,59)	3,15 (0,92)	2,63 (0,98)	3,54 (0,93)
(-) 10^{-6} B3 MS^{-1}	5,28 (0,93)	5,96 (0,93)	4,39 (0,98)	5,45 (0,97)

agar-agar time constant B1 is about that of the B2 values of the two other products.

This phenomenon shows that the structure relaxation of agar-agar is slowed down by the entrapped air as soon as constant deformation is applied.

Thus, B1 time constants of about 1E-04 ms-1 characterize a capping tendency which may be observed when residual air cannot freely leave the powder bed during the consolidation phase.

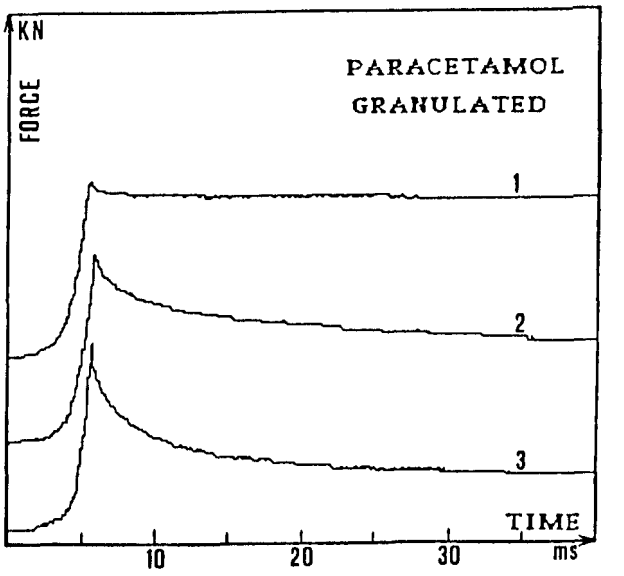

FIG 7 : STRESS RELAXATION CURVES
OBSERVED WITH GRANULES OF PARACETAMOL

Curve 1: Moisture content = 0 %
Pmax = 4980 N.

Curve 2 : Moisture content = 2 %
Pmax = 2725 N.

Curve 3 : Moisture content = 10 %
Pmax = 1105 N.

Another example of this phenomenon is given with granules of Paracetamol (granule size : 125-500 µm). Whatever the moisture content of the mass and the Pmax force used, it was not possible to obtain tablets of a good quality.

Figure 7 shows the influence of moisture content on the degree of plasticity of paracetamol granules. Although the latter is increased with the moisture of the mass, it may be seen that in all the cases, the structure relaxation is slowed down by the entrapped air.

The shape of the curve alone makes it possible to predict the poor tabletability of the mass.

TABLE V: TIME CONSTANTS AND Pmax OBTAINED WHEN PARACETAMOL GRANULES UNDERGO THE SAME DEFORMATION.
(THE CORRELATION COEFFICIENTS ARE IN BRACKETS)
(* CORRELATION COEF. NO SIGNIFICANT)

MOISTURE CONTENT	0 %	2 %	10 %
Pmax Newtons	1980	2725	1105
-10^{-4} B1 ms^{-1}	8,4 (0,78)	3,17 (0,98)	2,8 (0,984)
-10^{-4} B2 ms^{-1}	(0,78) 0,98 (0,01)*	1,91 (0,26)*	3,4 (0,65)
-10^{-6} B3 ms^{-1}	1,3 (0,77)	9,06 (0,97)	10,5 (0,96)

In table V, it may be verified that the time constants B1 calculated with the various batches of granules are unsatisfactory.

3) COULD THE TABLETABILITY OF HIGHLY ELASTIC MATERIAL BE PREDICTED?

With respect to Pmax, the value (Pmax-Pr) of highly elastic materials was much lower . For that reason, force recorded in relation to time presents a lack of accuracy. Thus, it is difficult to adjust the calculated curve and the plotted data .

Figure 8 represents stress relaxation of non tablet-able French Cooper paracetamol.

Curve 1 shows that recorded force slowly decreases and gives a curve shape by successives plateau. Although it is possible to identify the relaxation of this material (curves 2) with a bad correlation coefficient (Table VI), the time constant B1 does not allows plotted data to be to reproduced and has a 1E-03 ms-1 value like that of tablet-able products.

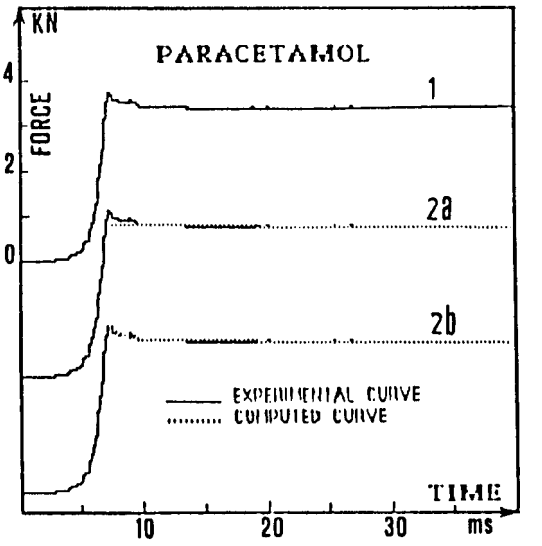

FIG. 8: STRESS RELAXATION CURVE OF PARACETAMOL (French Cooper)

TABLE VI : TIME CONSTANTS OBTAINED WITH PARACETAMOL (FRENCH COOPER) (THE CORRELATION COEFFICIENTS ARE IN BRACKETS)

P MAX NEWTONS	-10^{-3} B_1 MS^{-1}	-10^{-4} B_2 MS^{-1}	-10^{-6} B_3 MS^{-1}
3960	1,41 (0,81)	7,38 (0,35)	0,67 (0,28)
3803	1,09 (0,85)	4,65 (0,35)	0,47 (0,34)
4666	0,64 (0,85)	6,39 (0,12)	0,42 (0,35)

In these conditions, it is advisable to take into account the shape curve rather than constant values, when predicting tabletability of this type of material.

CONCLUSIONS

In this study, it has been shown that the capping tendency given by some formulations or materials may be predicted when stress relaxation tests are used.

Thus, it has been possible to linearize strees relaxation data using a WISCHERT model which, in mathemetical terms, may be represented by the sum of two or three exponentials.

The first one shows up the structure relaxation of the material and depends on its particle size . When the rate of this type of relaxation is greater, (with a time constant about 1E-03 ms-1) stronger bonds are formed.

The second exponential, when it appears, represents the slowing down by the entrapped air of structure relaxation. The time constant of this phenomenon is about 1E-04 ms-1.

In some cases, when this latter phenomenon is too great, the first exponential is not present and the stress relaxation curve behaves like the sum of two exponentials.

When such a phenomenon occurs, the compressed air in the powder expands and causes the tablet to fail.

The third exponential shows the same sort of material relaxation as in solids mechanic. For some products like Sodium chloride this relaxation is irrespective of particle size. The time constant here is about 1E-06 ms-1.

Thus, with respect to the compression time observed on a reciprocating tablet machine (0.15 to 0.4 sec.), the different time constants measured by means of this stress relaxation tests are much lower (at least, about 1 sec.).

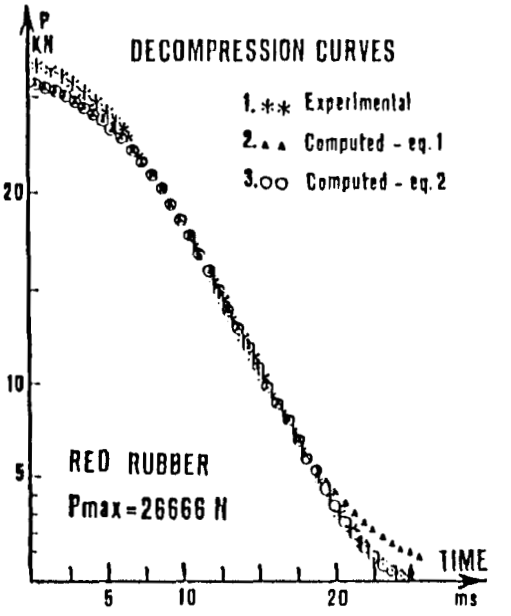

FIG. 9 : DECOMPRESSION CURVE OF RED RUBBER

These time constants indicate that during compression, the relaxation of the material could not occur and that the material behaves like a set of springs.

This assumption is not possible for the following reasons:

1) during compression, the decrease in force when Dmax (maximal displacement) is constant, and the shift with respect to time between Pmax (maximal force) and Dmax (3) could be explained if materials behaved like a set of springs and shock-absorbers (9).

2) In another work (8) the equation proposed to linearize the decompression curve showed that tablets undergo various kinds of relaxation, particularly after Pmax when the calculated curve is below the experimental curve (Fig.9); the difference may be linearized with a power law which shows that at least two mechanisms intervene during this phase.

Thus, during compression it is likely that shock-absorbers adapt to the U.P. speed and that the time constants are much greater.

This assumption must be verified in the forthcoming work.

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