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A METHOD FOR QUANTITATIVE EVALUATION OF THE EFFECTIVENESS OF THE LUBRICANTS USED IN TABLET TECHNOLOGY

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1. INTRODUCTION

Modern formulation bases the appropriate selection of excipients on technological determinations. Due to negative effects on mechanical and biopharmaceutical properties of tablets, the amount of lubricant to be used requires optimization. Lubricants are difficult to evaluate in terms of effectiveness. The number of references existing in literature on this topic substantiates the necessity still remaining in pharmaceutics for lubricant testing (1, 2, 3, 4, 5).

In previous papers (6, 7), the signal obtained during tablet ejection in a single punch machine equipped for force measuring was studied. Following this, the machine was implemented with an inductive transducer, in order to measure the displacement of the lower punch during the ejection phase (8). The analysis of the signals obtained with various substances made it possible to

relate each part of the recorded signal to the corresponding phase of tablet ejection.
However, some difficulty still exists in carrying out a quantitative evaluation of the ejection phenomenon. A lot of parameters, such as tool quality, room conditioning, powder mixture preparation, operative procedures,had considerable influence on the measurements. Consequently, the need to develop a rigorous methodology for measuring lubricant effectiveness, in relation to amounts in formulation and interaction with excipients arises.
The aim of this paper is to propose a new procedure for lubricant studying, based on the determination of the value of upper punch force that could produce the "jamming" of tabletting machines.
The required standardization of each procedure step is carefully described.

2. MATERIALS AND METHODS

Excipients:

Lactose Fast Flo	SEPPIC	Paris (F)
Emcompress	SPCI	La Plaine St Denis (F)

Lubricants:

Magnesium stearate	Cooper	Melun (F)
Compritol 888	Gattefossé	Saint Priest (F)
Precirol atomisé	Gattefossé	Saint Priest (F)
Lubritab	SPCI	La Plaine St Denis (F)
PEG4000	Hoechst-F	Paris (F)
Talc	Cooper	Melun(F))

Raw materials, preserved in a thin layer in an air conditioned room the day before experimenting, were sieved, weighed and mixed according to the technique described below.

Standard Mixture:
After sieving through a 1.250 mm sieve, 495 g of Lactose and 5 g of magnesium stearate are weighed. One third of the lactose is put in the container of a Turbula mixer with the total amount of lubricant. The mixing is achieved during 5 minutes at a speed of 54 rpm. After this time, another third of lactose is added and mixed for 5 minutes, followed by the last portion and 5 more minutes of mixing.

All the compression experiments were made on a single punch machine Frogerais OA, equipped with a 11.28 mm diameter flat punches. Upper and lower punches are

instrumented with strain gauges calibrated against a reference device in a hydraulic press. A variable linear differencial transducer (LVDT) measures the displacement of the upper punch with an accuracy of 1/100 mm. A second LVDT measures the displacement of the lower punch during the ejection phase. Strain gauges and displacement transducers are connected to computers by means of measuring bridges. The computer following the compression phase is an APPLE II E, adapted and programmed in our laboratory (9).
The data on the ejection phase were collected by a MINC DIGITAL computer connected to a X/Y recorder (8)

For each tablet the signal, of the upper and lower forces against time and punch displacement are visualised and the maximum upper and lower forces (in daN) are measured.
The data on the ejection phase were collected by a MINC DIGITAL computer connected to a X/Y recorder (8)
For each tablet the signal of the lower punch force against time is visualised and the different part of this signal are mesured, residual force and ejection forces (in daN).
The crushing strength of the tablet is measured (in daN) with an Heberlein hardness tester.

3. OPERATIVE PROCEDURE FOR LUBRICANT EVALUATION

In view of obtaining reproducible data, the following operative steps are strictly adopted (Table 1):

1st step: Preliminary adjustments
Before each series of experiments, all the parameters are controlled:

- zero adjustment, calibration and linearity of the measuring devices of forces and displacement
- depth of the compression chamber (10 +/- 0.01 mm)
- speed of the machine (1 tablet each second)
- relative humidity (20 %) and temperature (20°C) of the air conditioned compression room

2nd step:Tool cleaning
Tool cleaning is a critical operation for the reproducibility of measurements. This procedure consist of four minutes compression of a mixture of microcristalline cellulose with 1 % of magnesium stearate. In order to polish the tools effectively, the maximum displacement of the upper punch is adjusted to 8.00 mm during the operation.

Table 1: Method for quantitative evaluation of the effectiveness of tablet lubricants

1. PRELIMINARY ADJUSTMENTS

Room air conditionning
Speed of the machine

2. TOOL CLEANING

Compression of a cleaning mixture for 4 minutes in standardised conditions

3. STANDARDIZATION

Compression of a standard mixture and comparison of the answer obtained with stadardized values.

If the values obtained are not inside the standardized values, go to point 2 for a new tool cleaning

4. MEASUREMENT

Compression of 30 tablets in standardized conditions under a low upper punch displacement

If no ejection problems occur, increasing of the upper punch displacement in order to determine the "limit of industrial workability", that is the maximum upper punch force that makes it possible to compress for 3 minutes without ejection problems

3rd step: Measurement standardisation

To assure that the experimental conditions remain the same, the results obtained by compressing the Standard Mixture were statistically compared before each trial.
Maximum upper punch displacement in the die is adjusted to 5.40 +/- 0.05 mm.
Under these conditions, mean values and confidence limits at 95% level are:

- tablet crushing strength = 20 +/- 0.2 daN
- residual force = 25 +/- 3.2 daN
- ejection force = 69 +/- 3.2 daN

4th step:powder compression

After cleaning the compression chamber as previously described, the powder mixture is loaded in the hopper.
Maximum upper punch displacement is adjusted to 4.50mm. After the compression of 30 tablets, the data relative to 10 successive tablets are measured and stored in the computer. Following these measurements, ejection forces are recorded.
We noted that residual force was lower than 60 daN with only a small ejection peak and that no ejection problems occurred. Ejection problems (a tendency to jamming) are clearly identified when the lower punch has difficulty in ejecting the tablet. Consequently,a typical grinding noise occurs in ejection, and the tablet appears with vertical scratched edges, often fractured. The electric signal from the lower punch force is disturbed, with a residual force higher than 80 daN. The shape of the signal is that of a saw-tooth line. Moroever the punch finds some resistance to recover the lowest position. Sometimes a negative peak in the signal appears at this point.
If no ejection problems occur, upper punch displacement is increased to 4.75 mm, and measurements are repeated as before. Then, measurements at 5 different displacements (4.50, 4.75, 5.00, 5.25 and 5.40 mm)are taken.
After the last trial at 5.40 mm, the punch displacement is adjusted in order to obtain upper punch maximum force of 2.000 daN and the machine is run for 2 minutes. The aim of this trial is to verify if ejection problems develop with time.
On the contrary, in the case of ejection problems, the machine is stopped, the tools are cleaned again and the upper punch displacement of the machine is slightly decreased.
An upper punch force that allows for compression without ejection problems for 3 minutes is iteratively required and defined as the "limit of industrial practicability".
For each tablet the forces measured on the upper and

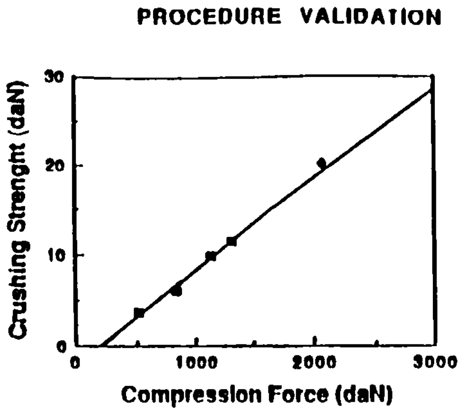

Figure 1: procedure of the validation: overlay fit of Standard Mixture mean value of 20 trials (•) to compression force/crushing strenght relationship (95% confidence interval is lower than symbol size)

lower punches, the displacement of the upper punch during the compression phase and of the lower punch during the ejection phase, were recorded. The tablets of each displacement batch were checked for weight, thickness, diameter and crushing strength.

4. VALIDATION OF THE TECHNIQUE

For procedure validation, the data obtained by daily compressing Standard Mixture to control operative onditions were analysed. With an average of all the measurements collected at 2000 daN, an evaluation of the precision of the measurement can be obtained. By comparing mean values with regression line obtained by plotting respectively crushing strength, ejection force or residual force versus upper punch force, an indication of the accuracy can be established. Figure 1 shows mean value relative to crushing strength obtained from 20 successive trials, plotted in the graph showing crushing strength versus upper punch force. The correspondance to previously found relationships is quite good and the variability among the values notably reduced. Figures 2 and 3 show the same comparison concerning residual and ejection forces. In the case of residual force, less accuracy can be noted in relation to the measurement technique.

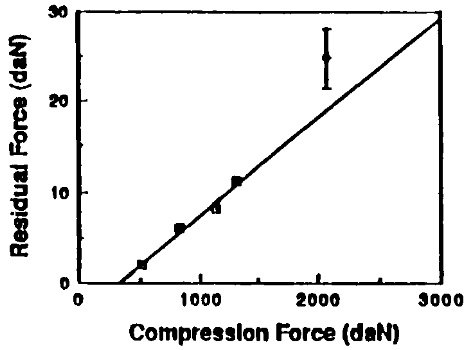

Figure 2: procedure of the validation: overlay fit of Standard Mixture mean value of 20 trials to compression force/residual force relationship.

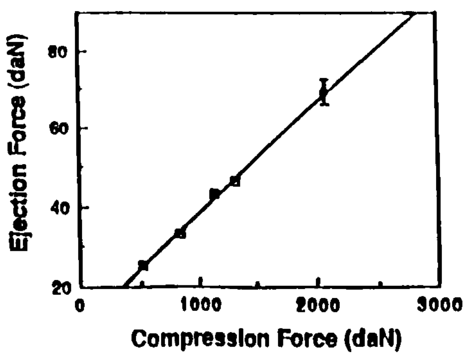

Figure 3: procedure of the validation: overlay fit of Standard Mixture mean value of 20 trials to compression force/ejection force relationship.

5. RESULTS AND DISCUSSION

For this study, Lactose FF and Emcompress were chosen because they cannot be compressed without lubricant:lactose gives a signal of lower punch ejection force versus time with an evident saw-tooth profile and Emcompress shows a tendancy to jamming. Some lubricants make it possible to compare the two products, but others are incapable of reducing friction level sufficiently.
Results obtained with Lactose FF and Emcompress mixtures with different lubricants are presented in Tables 2 and 3. The data measured for the upper punch maximum force which allows, under our experimental conditions, for 3 minutes production time, without ejection problems, are recorded in the following sequence:

Table 2: Limits of Industrial Practicability with Lactose Fast Flo

Lubricant	%	Y1	R	Re	Ej	D	
Magnesium stearate	0.25	592	.85				
	0.5	2017	.90	27	63	19.3	957
	1	2042	.87	21	64	17.3	847
Compritol	1	598	.81	48	67	6.2	1037
	1.5	1455	.86	56	66	15.1	1037
	2	2089	.86	52	70	19.9	952
Précirol	1	565	.89	17	31	7.1	1256
	1.5	1550	.91	22	42	9.5	613
	2	1943	.92	24	48	19.2	988
PEG 4000	7	479	.82				
Talc	5	636	.54				
Lubritab	1	593	.88	21	27	4.7	792
	2	1475	.88	24	45	13.4	908

- the upper punch force in daN (Y1)
- the transmission ratio R (lower force / upper force)
- the residual force in daN (Re)
- the ejection force in daN (Ej)
- the crushing strength of tablets in daN (D)
- the cohesion index (CI) which is the ratio of tablet hardness (in daN), on the maximum upper punch force (in daN) X 100.000. The higher the CI, the better the compressibility is.

If the line is empty, it means that, for this adjustment, it was not possible to make the measurements and to obtain tablets.

If no problem occurs, even if the force measured is about 2.000 daN, the results obtained for this adjustment are noted.

Table 3: Limits of Industrial Practicability
with Emcompress

Lubricant CI	%	Yl	R	Re	Ej	D
Magnesium stearate 754	0.25	2068	.90	21	49	15.6
691	0.5	2155	.90	20	54	14.9
617	1	2104	.90	19	54	13
Compritol 863	1	382	.85	34	53	3.3
766	1.5	665	.87	34	48	5.1
721	2	2106	.90	33	42	15.2
Précirol 796	1	666	.88	14	23	5.3
675	1.5	2103	.91	44	66	14.2
	2	2086	à compléter			
PEG 4000 1137	7	466	.80	20	27	5.3
Talc	5	540	.56			
Lubritab	1	465	.85			
1264	2	435	.88	19	33	5.5

LACTOSE FF:

Magnesium stearate:
Trials were made with 3 mixtures containing 0.25, 0.5 and 1.0 % of magnesium stearate.
With the lowest amount of lubricant (0.25 %), a tendancy to jamming is to be observed even at a very low upper punch force value (about 600 daN).
On increasing the content of lubricant to 0.5%, no more jamming occurs, and the residual force is notably reduced.
However, at a level of 1.0 % of lubricant, a significant decrease in tablet hardness is observed.

Compritol 888:
This lubricant is not so effective as magnesium stearate, because jamming is observed at very low upper punch force values, with 1% Compritol.
With 1.5 % of Compritol, no jamming is observed, if the upper punch force remains under 1500 daN. The problem appears over 1900 daN.
Percentages over 2% help to avoid ejection problems. Residual and ejections forces are notably reduced, but less than with magnesium stearate.

Precirol:
Low percentages of this lubricant (0.75 and 1.0 %), give rise to ejection problems.
A 1.25% level of Precirol allows for compression at an upper punch force lower than 1750 daN.

With higher percentages, all the problems are overcome. The lubricant efficiency of precirol and compritol are very close, Precirol being slightly superior,as far as its lower residual and ejection forces are concerned.The hardness of the tablets obtained are similar to those containing Compritol.
In addition, Precirol is particularly effective in packing mixtures. This can be easily seen from the maximum upper punch displacement value needed to obtain the same compression force.

PEG 4000:
This hydrosoluble lubricant does not possess an efficacy comparable to previous lubricants for percentages lower than 7 %. Even when the upper punch forces were very low, jamming was observed.

Talc:
At a level lower than 5 % of talc, residual and ejection forces remain unvaried compared with the unlubricated mixture. Moreover sticking is also a problem.
By increasing the percentage of talc in the mixture, capping problems, together with lubrication defects, appear.

Lubritab:
A percentage of 1 % gives rise to jamming if the upper punch force is higher than 600 daN.
Increasing the value to 2 % of Lubritab, no more jamming can be noted, even when the upper punch force reaches 2000 daN.

EMCOMPRESS:

Magnesium stearate:
The efficacy of this lubricant is evident from the 0.5 % level. However, also in this case, higher percentages of magnesium stearate produce an evident decrease in tablet hardness.

Compritol 888
An amount of 1 % of compritol gives rise to ejection problems at 500 daN of upper punch force.
Increasing the level to 1.5 % of Compritol, they appear over 700 daN.
2 % of Compritol is enough to eliminate all the ejection problems of Emcompress.

Precirol:
This lubricant shows an effect similar to Compritol.
Mixtures containing 1 % of Precirol are subject to jamming only over 700 daN of compression force, but 1.5 % of Precirol is enough to eliminate ejection problems.
Also Precirol shows a negative effect on tablet hardness, but its rating is just between Magnesium stearate and Compritol.

PEG:
This product proves ineffective even if the amount is as high as 7 %. At this percentage, the lubrication problems are just slightly reduced compared to the value of seizing force obtained with lactose FF.

Talc:
The same observations can be made as with lactose: a 5 % percentage does not significantly improve the compressibility of EMcompress. Tablets show evidence of jamming, even at an upper punch force lower than 550 daN.

The procedure proposed makes it possible to determine for each mixture the "limit of industrial suitability" in relation to the amount of lubricant used.
For example, on the basis of this value,a mixture of Lactose Fast Flo and 0.25 % of magnesium stearate is not safely lubricated. No problems occur at 0.5 % of this lubricant. This quantity can be defined as "necessary and sufficient", because we observe a decrease in CI when the lubricant is increased to 1% without any improvement in the ejection performance. On the contrary, a level of 0.25% of magnesium stearate is sufficient in the case of Emcompress.

The limit value found for Talc, often used in formulation for its anti-sticking effect, is ineffective against ejection problems.
Moreover there is no correlation between ejection problems and the ratio R = Y2/Y1. The values of R are always excellent, even if there are ejection problems (Lactose FF + 0.25 % magnesium stearate, Lactose FF + 7 % PEG 4000, Emcompress + 1 % Lubritab are examples).

Another remark can be made on CI values: generally this index decreases as the lubricant amount increases; but, in the case of Lactose + Compritol, similar CI values with 1 % (6.2 daN of hardness) and 1.5 % (15.1 daN of hardness) are to be observed. This is a typical example of the interest of CI which accounts for the effects of the lubricant on decreasing the resistance to compression, taking into account at the same time the influence on cohesion.

Comparing the values of lubricant percentage, force limit for seizing, residual and ejection forces and tablet crushing strength, lubrication is obtained differently for magnesium stearate, the group of Compritol, Precirol and Lubritab, and Talc and PEG 4000. The effectiveness of magnesium stearate at low level confirmes the capacity of this product to spread over the excipient particles, due to its crystal characteristics. Moreover its ability to mix in an orderly way is also well known. The other lubricants tested can reach comparable effectiveness, but this happens at a concentration level higher that for magnesium stearate. These observations derive from the fact that magnesium stearate even at a 0.5% concentration allows for the compression of lactose at 2000daN with an ejection force of 63 daN. If the comparison is made only on the basis of lubricant level, the superiority of this last lubricant results clear. However, extending the comparison to ejection force and mechanical quality of the tablets, Precirol, used with lactose, shows some interesting features. The substantial increase in lubricant concentration reduces the resistance to ejection, keeping the crushing strength of tablet inaltered. The same can be observed with Compritol used for lubricating Emcompress.
The deficiency of Talc and PEG is clearly revealed by the jamming method adopted.

CONCLUSION

The goal of the producer is to compress the powder without lubrication problems that can affect productivity. Among the various methods of lubricant evaluation, the one presented here has the advantage of indicating the force limit to be used according to the particularities of the formula. The force level that gives rise to machine jamming represents a new and powerful tool for tabletting optimization.Moreover the procedure makes it possible to collect data on the ejection phase of compression in a reliable manner and close to the manufacturing reality of tabletting.

The "jamming method" helps in tablet formulation as follows:

- firstly the value of "jamming force limit" immediately makes the selection of the lubricant effective for the material to be compressed. At the same time, the effective percent of lubricant to be used is indicated.
- secondly, among the selected lubricants, the final choice is made on the basis of the minimal ejection force value and satisfactory mechanical (and biopharmaceutical) properties.

The measure of compression force limit at which damage of the machine can occur, is certainly a new tool in the studies on lubricants. The force level, under which no lubrication problems arise, is a piece of knowledge that can lead to further discoveries on the mechanism of lubrication for various products.

Analysis of data in order to transform all this information into indications on lubricant mechanism is now under way.

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