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# Influence of lubricant properties on compression behaviour and drug dissolution rate of scleroglucan hydrophilic matrix

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**Abstract**

The present work was undertaken to investigate the effect of lubricant hydrophobicity level on the pharmacotechnical and dissolution behaviour of a scleroglucan hydrophilic matrix.

Sodium stearyl fumarate *Pruv*® was compared to magnesium stearate. The influence of the amount of lubricant on the compression behaviour of the matrix was considered. The relationship between an increase in the polymer concentration and lubricant on dissolution rate was also studied. A statistical approach was made to evaluate the significant level of lubricant influence on drug dissolution.

It was found that even at a level of 0.5%, the lubricant can influence both the compression ability and drug dissolution rate of scleroglucan hydrophilic matrix.

*Keywords:* Hydrophilic matrix; Scleroglucan; Lubricant; Compression; Dissolution

## 1. Introduction

The effect of additives on the dissolution behaviour of a hydrophilic matrix is of interest to many researchers. It also noteworthy that the influence of the nature of the lubricant has not been studied.

In its simplest form, a hydrophilic matrix device is a compressed powder mix of a drug with a water-swelling viscous polymer. A variety of other excipients may optionally be included to aid tableting properties.

When a hydrophilic matrix comes into contact with water, the pores near the surface of the matrix are filled with water and drug release is initially controlled by the dissolution of the drug in the water-filled pores and by its diffusion in water (Gurny et al., 1982; Korsmeyer et al., 1983). The high viscosity of the polymer solution in the pores slows down the drug transport by forming a gel-layer. The drug is released by a combination

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of diffusion through the gel-layer and erosion of the outer gel surface. The resistance of this barrier also depends on matrix additive properties (Rizk et al., 1993a), for example, the presence of lactose as a diluent will increase drug liberation from the matrix, due to the solubility of the lactose (Rizk et al., 1994a).

In previous works (Rizk et al., 1993a; Rizk et al., 1994a), the ability of scleroglucan to form sustained-release tablets prepared by the direct compression process: 20 and 30% of scleroglucan (Actigum CS11®) were required to form a resistant hydrophilic matrix. It was found that increasing the polymer concentration required increasing compression energy to obtain tablets of the same crushing strength; 0.5% of magnesium stearate was quite sufficient to prepare tablets, but we did not evaluate if it might affect compression ability of the formulations and decrease the wettability of the matrix and, thus, increase the dissolution time.

In this work, the effects on the lubricants, magnesium stearate and sodium stearyl fumarate (Pruv), on the pharmacotechnical and dissolution behaviour of a scleroglucan hydrophilic matrix were compared. The influence of lubricant concentration on matrix behaviour was also considered.

## 2. Materials and methods

### 2.1. Raw materials

Scleroglucan, Actigum CS11® (Sanofi Bio Industries, France): Scleroglucan is a $\beta$ (1-6)-D-Glucan with a single, pendant glucose group attached through a $\beta$ (1-3) linkage (Yanaki et al., 1983). Scleroglucan is a natural exocellular polysaccharide secreted by a fungus Sclerotium rolfsii (Rodgers et al., 1973). This water soluble polymer has been used as a suspending, coating and gelling agent. It exhibits a gel-like structure in aqueous solution at low temperature (Bluhm et al., 1982; Crescenzi et al., 1988). Dibasic calcium phosphate dihydrate, Emcompress®: Edward Mendell Co. Inc. via SPCI, France. Theophylline (anhydrous): Boehringer, Ingelheim, Germany. Magnesium stearate: Cooper, Melun, France. Sodium stearyl Fumarate, Pruv®: Edward Mendell Co. Inc. via SPCI, France.

### 2.2. Formulations

Initially, two separate 1.6 Kg mixtures containing Emcompress, theophylline 20% w/w and two different concentrations polymer (20 and 30%) were prepared and coded A20 and A30 (Table 1).

Powder mixing was carried out in a Turbula mixer (W.A. Bachafen Switzerland) at a speed of 90 rpm for 5 min.

In a second step, the specified lubricant was added to 400g of the initial mixture just before compression, and mixed for 5 min.

### 2.3. Tablet preparation and evaluations

Tablets of $500 \pm 50$ mg were made by direct compression of mixtures (20% relative humidity at 20°C) on a Frogerais OA (Frogerais, France) instrumented (Bleuse et al., 1982) single punch press (punch diameter = 11.28 mm). The upper punch displacement X, the force measured on the upper punch Y1 and the force on the lower punch Y2 were noted. The ejection force was also registered during compression (Delacourte et al., 1983; Delacourte et al., 1993).

Evaluations were performed during and after tableting to collect maximum information. Y2/Y1 ratio, indicative of transmission forces through the powder in the die was calculated. Tablet crushing strength was measured using a Schleuniger 6D hardness tester. Different adjustments of the upper punch displacements X were made to obtain different compression forces (Y1). Y1 values corresponding to a defined crushing strength were determined from linear regression between

Table 1
Formula compositions

| Formula (*) | Actigum | Emcompress | Theophylline |
|---|---|---|---|
| A20 | 20 | 60 | 20 |
| A30 | 30 | 50 | 20 |

(*)A: Actigum, 20 and 30: Actigum %.

tablet crushing strength and upper compression force Y1 (Guyot et al., 1989). As an indication of the ability of particles to cohere during the compression process, we calculated the Cohesion index C.I. (Crushing strength/Y1 ratio multiplied by $10^5$): the higher this cohesion index, the better the ability of the formulation to form tablets (Guyot et al., 1992); Uniformity of mass was determined by weighing 10 tablets on an analytical balance (Mettler Viroflay, France).

### 2.4. Dissolution test

The dissolution rates of the theophylline from the matrices were measured using the paddle device of the European Pharmacopoeia. The test was carried out at 50 rpm and 37 ± 0.5°C.

The dissolution medium was 800 ml of hydrochloric acid pH 1.0 (0–2h) and then adjusted with the addition of defined quantities of phosphate buffer to pH 6.0 (2–4h) and pH 7.0 (4–6h). After 5, 10, 15, 30, 45, 60, 120, 180, 240, 300 and 360 min, samples were taken. The drug concentration in each filtered sample was determined by measuring the absorbance at 264 nm using a spectrophotometer (Shimadzu UV1205).

Dissolution release tests were carried out on six tablets and mean values were recorded. Dissolution efficiency was determined according to the method of Khan (1975).

### 2.5. Statistical analysis

Variance analysis and the Newman Keuls test (Gouet and Philippeau, 1986) were carried out using the Stat-itcf software package on an IBM PC AT.

## 3. Results and discussions

### 3.1. Compression studies

A preliminary study was carried out to determine the quantity of lubricant necessary to obtain tablets from the A30 formula. 0.5 and 1% of magnesium stearate and Pruv were compared. The resulting formulas were coded respectively

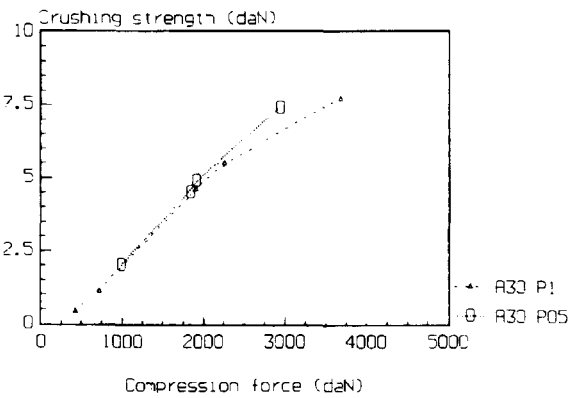


Fig. 1. Ability to form tablets (crushing strength versus upper punch force Y1) of the 30% Scleroglucan formulations with Pruv at 1% (A30 P1) and 0.5% (A30 P05).

A30 S05, A30 P05, A30 S1 and A30 P1 (S for magnesium stearate, P for Pruv, 05 for 0.5% and 1 for 1%).

The ability of the formulations to produce tablets was then studied. Fig. 1 and Fig. 2 show the variation of crushing strength values with compression force for the four formulations. These figures show that higher concentration of magnesium stearate and particularly of Pruv does not improve particle cohesion.

0.5% of magnesium stearate or Pruv was considered sufficient to ensure lubrication during compression.

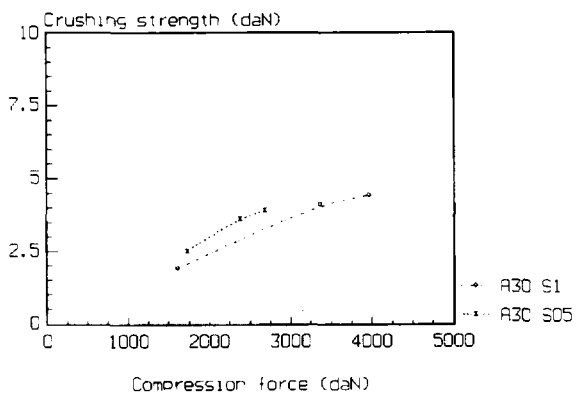


Fig. 2. Ability to form tablets of the 30% scleroglucan formulations containing magnesium stearate at 1% (A30 S1) and 0.5% (A30 S05).

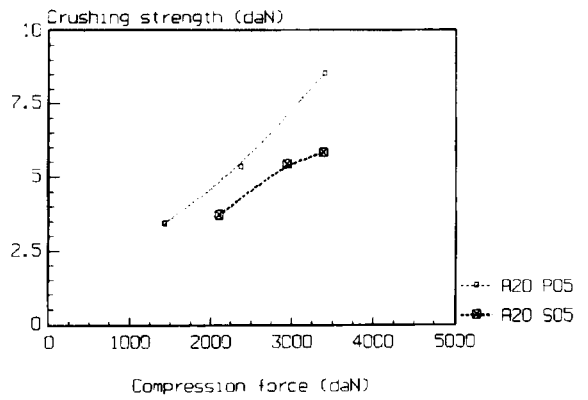


Fig. 3. Ability to form tablets of the 20% scleroglucan formulations containing 0.5% of Pruv (A20 P05) or 0.5% magnesium stearate (A20 S05).

For this reason, the A20 formula was mixed with 0.5% of each lubricant respectively. The codes of the resulting formulas were: A20 S05, A20 P05. The ability of the mixtures was then studied.

Fig. 3 and Fig. 4 show the crushing strength versus compression force for the A20 and A30 formulas mixed with 0.5% of each lubricant. With magnesium stearate, it can be observed that for the same level of compression energy, increasing tablet crushing strength proved difficult with the A20 formula and practically impossible in the case of A30, due to the weak particle cohesion

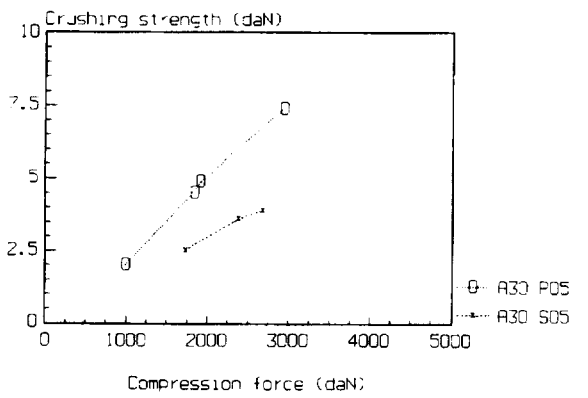


Fig. 4. Ability to form tablets of the 30% scleroglucan formulations containing 0.5% of Pruv (A30 P05) or 0.5% magnesium stearate (A30 S05).

induced by this lubricant. On the other hand, the presence of Pruv made it possible to increase the tablet crushing strength of both formulas, but especially of the A30.

In Table 2, the compression parameters of the above-mentioned formulas are presented for a 4 $\pm$ 0.5 daN tablet crushing strength value.

The Y2/Y1 ratio was satisfactory for all the formulas, showing improved energy transmission through the powder. The ejection force was lower with Pruv than with magnesium stearate for A20 formulas and higher for A30 formulas. No significant differences were found between 0.5 and 1% for the A30 formula.

In Table 3, Y1 force and Cohesion index (C.I.) values were calculated for a 4 daN tablet crushing strength value, from the linear regression equation established between tablet crushing strength and compression force. The C.I. was higher with Pruv than with magnesium stearate and for the A30 formula compared to the A20 formula using Pruv at 0.5% in both cases. C.I. decreased from A20 to A30 with magnesium stearate and with A30 formulas when lubricant was increased from 0.5 to 1% with either lubricant.

It can be seen that increasing either lubricant does not improve the compression either the A20 or A30 formula. Thus, 0.5% of lubricant is the optimum concentration. For this reason dissolution tests were carried out only on 0.5% lubricant formulations.

### 3.2. Dissolution study

Theophylline release profiles of A20 P05, A20 S05, A30 P05 and A30 S05 tablets are presented in Fig. 5. It can be noted that: (i) the increase in scleroglucan concentration used slows down drug transport by increasing both the viscosity of the gel around the tablet and the reducing erosion [3,4]; (ii) whatever the polymer concentration used (20% or 30%), the theophylline release was prolonged with formulas containing magnesium stearate; (iii) the presence of Pruv, a less hydrophobic lubricant, at a concentration of 0.5% accelerated drug release by increasing matrix wettability.

Table 2
Compression parameters of the different formulations for a 4±0.5 daN tablet crushing strength

| Formula (*) | X (mm) | Y1 (daN) | Hardness (daN) | Y2/Y1 | Ejection (daN) |
|---|---|---|---|---|---|
| A20 S05 | 2.91 | 2107 | 3.7 | 0.94 | 28 |
| A20 P05 | 2.55 | 1437 | 3.5 | 0.90 | 20 |
| A30 S05 | 3.17 | 2676 | 3.9 | 0.93 | 11 |
| A30 P05 | 2.32 | 1838 | 4.5 | 0.90 | 23 |
| A30 S1 | 2.06 | 3358 | 4.1 | 0.95 | 11 |
| A30 P1 | 2.37 | 1908 | 4.5 | 0.92 | 21 |

(*)A: Actigum, 20 and 30: Actigum %; S: Magnesium stearate; P: Pruv; 05 and 1: 0.5 and 1% of lubricant.

In Fig. 6, the percentage differences in the amount of drug dissolved versus dissolution time for A20 and A30 formulas are shown. These differences are due to the used of Pruv in place of magnesium stearate.

It was found that: (i) the A20 formulation is more affected by the presence of Pruv, an increase of 20–24% in drug liberation is noted from 0 to 30 min, this variation decreased after 30 min due to tablet surface gelation and is 12–16% at 360 min; (ii) with the A30 formula this difference is less, around 3–6% according to the dissolution time; (iii) the presence of scleroglucan at 30% induced the rapid formation of a viscous layer. The gelled matrix was less influenced by the solubility of additives. With the A20 formulation the resistance of the barrier depended on the solubility of additives creating erosion of the outer gel surface.

### 3.3. Statistical evaluation

Dissolution efficiency was calculated at 360 min and results were analysed using variance analysis

Table 3
Calculated compression force and cohesion index values corresponding to a tablet crushing strength value of 4 daN

| Formula | Y1 (daN) | C.I. |
|---|---|---|
| A20 S05 | 2252 | 178 |
| A20 P05 | 1730 | 231 |
| A30 S05 | 2702 | 148 |
| A30 P05 | 1664 | 240 |
| A30 S1 | 3462 | 116 |
| A30 P1 | 1859 | 215 |

an the Newman Keuls test at a probability threshold of 5%, based on 24 observations and 4 factors in total randomization.

The variance analysis (Table 4) shows the existence of a significant global difference between formulations ($P \ll 0.001$).

The Newman Keuls test (Table 5), allows us to classify formulations according to their ability to release the drug. Four homogeneous groups were found, which were significantly different, denoting that even at a concentration of 0.5% the lubricant can significantly influence both A20 and A30.

## 4. Conclusions

This study of the influence of lubricant hydrophobicity on the compression behaviour of scleroglucan hydrophilic matrix formulation makes it clear that the presence of Pruv improves the compressibility of the scleroglucan which is known to have poor compression properties (Rizk et al., 1993b; Rizk et al., 1994b).

There is: (i) an increase in tablet hardness, difficult to obtain with magnesium stearate was possible with Pruv for the 20% and particularly for the 30% scleroglucan formulations; and (ii) the incorporation of sodium stearyl fumarate (Pruv) rather than magnesium stearate at the same concentration can improve the compression of tablets at the same crushing strength; and (iii) 0.5% of magnesium stearate or Pruv is the necessary and sufficient level to ensure lubrication of both the 20% and 30% scleroglucan formulations.

From the dissolution study, we can deduce that the presence of Pruv at 0.5% can increase drug

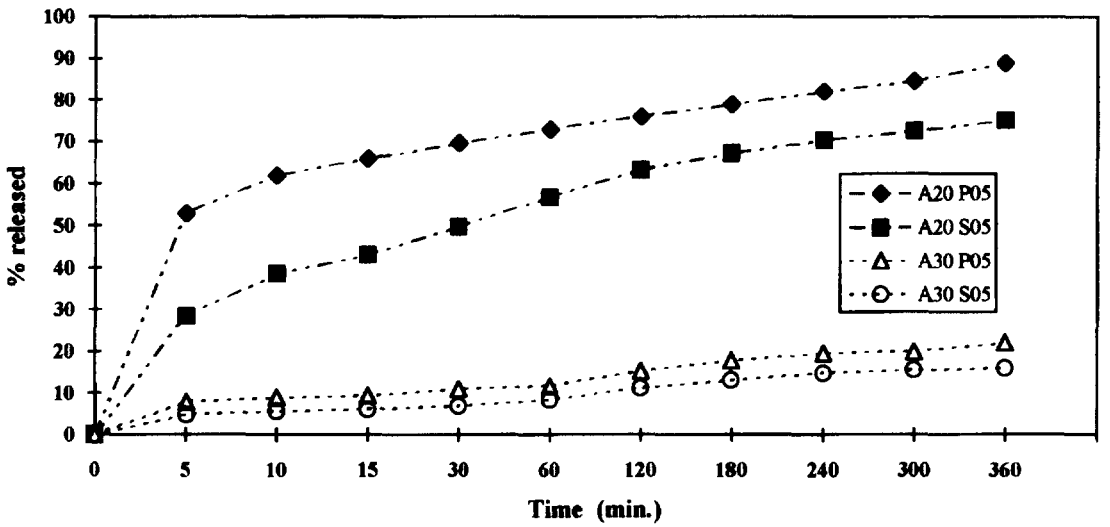


Fig. 5. Theophylline release from tablets containing 20% and 30% of scleroglucan with 0.5% of magnesium stearate (A20 S05-A30 S05) or 0.5% Pruv (A20 P05-A30 P05).

release. By comparison with magnesium stearate, it is believed that a less hydrophobic film was formed around the substrate particles. This would increase matrix wettability and accelerate dissolution. This phenomenon can explain the difference between these two lubricants in the case of the 20% scleroglucan formulations. On the other hand, with the 30% scleroglucan formulations, the quick formation of a highly viscous gel-layer attenuated lubricant influence and, therefore, less differences were found in the theophylline release.

The difference in dissolution rate between the magnesium stearate and sodium stearyl fumarate lubricated formulations was found to be statistically significant for both the 20 and 30% scleroglucan formulations.

Lubricant choice is a determining factor and cannot be neglected in hydrophilic matrix formulation studies.

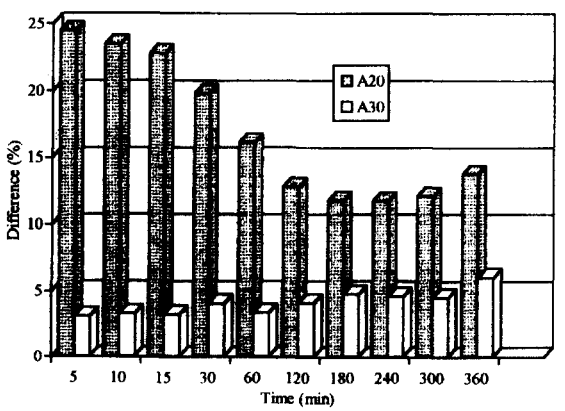


Fig. 6. Percentage differences in the amount of drug dissolved versus dissolution time resulting from using Pruv instead of magnesium stearate for the A20 and A30 formulations.

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Table 4
Variance analysis

| Source of variation | S.S. | F.D. | E | F. ratio | Prob. | S.D. | C.V. (%) |
|---|---|---|---|---|---|---|---|
| Total | 15587.85 | 23 | 677.73 | | | | |
| Factor | 15528.46 | 3 | 5176.15 | 1743.23 | 0.0000 | | |
| Residual | 59.49 | 20 | 2.97 | | | 1.72 | 4.8 |

S.S.: sum of squares; F.D.: freedom degree; E: mean of squares; S.D.: standard deviation; C.V.: coefficient of variation.

Table 5
Dissolution efficiency (E%) and Newman Keuls test (significance level = 5%)

| Formula | A20 P05 | A20 S05 | A30 P05 | A30 S05 |
|---|---|---|---|---|
| | 71.32 | 50.55 | 12.32 | 8.96 |
| | 69.66 | 58.38 | 12.86 | 9.31 |
| E% (individual values) | 68.10 | 53.17 | 14.49 | 10.08 |
| | 67.02 | 50.88 | 13.22 | 9.44 |
| | 68.83 | 51.46 | 12.25 | 8.87 |
| | 68.82 | 52.29 | 14.55 | 10.16 |
| E% (mean values) | 68.96 | 52.79 | 13.28 | 9.47 |
| S.D. | 1.46 | 2.90 | 1.02 | 0.55 |
| Homogeneous groups | A | B | C | D |

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