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# Effect of different excipients on the tableting of coated particles

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**Abstract**

Drug release data were used as an indirect method to study the possible protective effect of different excipients on the tableting of theophylline granules coated with Eudragit RS. Under our experimental conditions the order of least damage to the coating was: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate. These results are in good agreement with the yield values of these materials. It seems that the tablet matrix has a lower yield pressure than the pellet/pellet coating, such that the energy of compaction is absorbed by the matrix, and that the matrix is preferentially deformed. Under our experimental conditions, and even at very low compressional pressure there is always damage of the coating membranes. Nevertheless, by appropriate selection of the excipients, it is possible to achieve a formulation to ensure minimum damage to this coating. To this end, a combination of the following excipients with low yield pressure values is proposed as a suitable excipient mixture for coated particles: microcrystalline cellulose 50%, polyethylene glycol 3350 25% and crospovidone 25%.

*Key words:* Drug release; Coating; Tablet; Theophylline; Release rate; Compressional pressure

## 1. Introduction

Interest in oral controlled release dosage forms has brought about increasing attention to multiparticulate systems usually consisting of barrier coated particles, like pellets, coated microgranules and microcapsules. In recent years, a great deal of interest has developed in finding ways to incorporate such particles into compressed tablets. The advantages of tableting are: (i) reduced cost; (ii) reduced liability to tampering and (iii) tablets are less prone to difficulties in oesophageal transport than are capsules.

Unfortunately, compression of coated particles, such as microcapsules, can lead to damage of the coating membranes with a subsequent increase in the dissolution rates of the tablets (Ruiz et al., 1990; Béchard and Leroux, 1992). On the other hand, decreased dissolution rates have been reported when microcapsules were compressed without any excipient to ensure the disintegration of the tablets (Jalsenjak et al., 1980; Chemtob et al., 1986; Akbuga, 1992; Baykara and Karatas, 1993). Other studies show contrasting results. Abdel and Price (1986) found that tablets containing 40% matrix microcapsules, 55% microcrystalline

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cellulose and 5% carboxymethyl starch did not exhibit a change in the dissolution characteristics compared to the microcapsules before compression.

In the present work, granules of theophylline coated with Eudragit RS were used as a model to study the effect of different excipients on the compressibility of the coated particles. To this end, tablets were made at different compression pressures with microcrystalline cellulose, crospovidone, polyethylene glycol 3350 (PEG 3350), dicalcium phosphate and lactose.

## 2. Material and methods

### 2.1. Materials

Crospovidone NF (Polyplasdone XL-10, GAF), povidone NF (K 29/32, GAF), microcrystalline cellulose NF (Avicel PH 101, FMC), lactose NF (80 M, Sheffield), polyethylene glycol 3350 (Union Carbide), dicalcium phosphate (Di-Tab, Rhone Poulenc) and Eudragit RS (Rhöm Pharma GmbH) were obtained from the indicated sources. All the other materials were reagent grade from Sigma.

### 2.2. Methods

#### 2.2.1. Granulation and coating of theophylline

100 g of theophylline were granulated in a conventional coating pan with a mixture of 100 g of maize starch and 200 g of saccharose. 200 ml of saccharose syrup (50% w/v) was used as a binder solution. Once dried, the granules were coated in a coating pan with 800 ml of a solution of Eudragit RS 12.5% w/v containing triacetin as a plasticizer (10% of Eudragit RS). The granules were then dried and sieved to obtain a fraction between 410 and 590 $\mu$m.

#### 2.2.2. Preparation of excipients

500 g of crospovidone, Avicel and lactose were granulated separately in a planetary mixer with water. The system was mixed for 3 min and then sieved and dried overnight in a conventional oven at 65°C. The final product was sieved to collect the granules with a size between 710 and 850 $\mu$m. When Di-Tab was granulated in this way, excessively fragile granules were obtained, and for this reason it was granulated using a 3% w/v solution of povidone as a binder solution, instead of just distilled water. Flakes of PEG 3350 were milled in a morter and separated into size fractions by sieving, a size fraction between 710 and 850 $\mu$m being selected.

#### 2.2.3. Characterization of the granules

*2.2.3.1. Moisture content.* Moisture content of the different particles was measured using a Karl-Fisher apparatus (Fisher).

*2.2.3.2. True density.* True density was determined using a multivolume pycnometer (Micromeritics).

*2.2.3.3. Bulk density measurements.* Approx. 30 g of granules were allowed to flow freely into a measuring cylinder. Tapping was carried out with a Stav 2003 machine (J. Engelsman A-G). The initial bulk density and the bulk density after tapping 500 times were calculated by dividing the weight by the original volume or the final volume.

*2.2.3.4. Hausner factor and percentage compressibility.* The powder flow properties of the granules were studied according to two indirect methods: the Hausner factor (H.F.) and the percentage compressibility (P.C.):

$$\text{H.F.} = d_{500}/d_0$$

$$\text{P.C.} = [(d_{500} - d_0)/d_{500}] \times 500$$

*2.2.3.5. Tableting.* The experimental powders were tableted at different pressures using an instrumented rotary tablet press (Stokes B-2, Key). Tablets of 11.1 mm diameter, weighing approx. 250 mg were prepared. Each sample was subjected to a single motor-driven compression cycle. Inmediately after ejection, compact weight and dimensions were measured with a dial micrometer (25 $\mu$m resolution). The data from these compacts were used for 'out of die' Heckel analysis in order to calculate the yield pressure (Heckel, 1961a,b).

*2.2.4. Evaluation of tablets*

*2.2.4.1. Crushing strength.* The crushing strength of at least six tablets was measured with a mechanical strength tester (Hardnesstester HT-300,Key).

*2.2.4.2. Disintegration.* The disintegration was measured according to the USP XXI.

*2.2.4.3. Dissolution.* The dissolution study was performed according to Apparatus I of the USP XXII at 50 rpm. Distilled water at 37°C was used as dissolution medium. Samples were taken at different times (5, 10, 15, 20, 30, 40, 50 and 60 min) filtered and analyzed for drug content spectrophotometricaly at 272 nm.

*2.2.4.4. Overall dissolution rate (O.D.R.).* The overall dissolution rate at 30 min was calculated according to the following equation:

O.D.R. = (% theophylline dissolved/30 min)

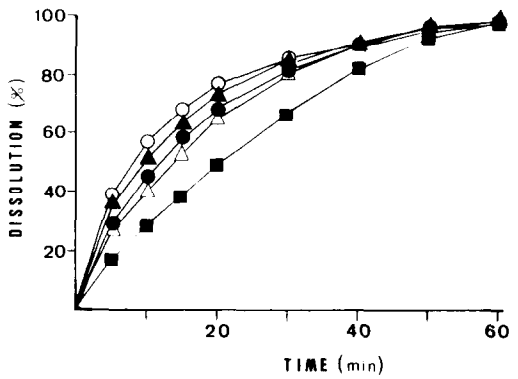


Fig. 1. Drug dissolution from non-compressed theophylline granules and tables of 70% Polyplasdone XL, 25% coated theophylline granules and 5% of non-granulated Polyplasdone XL. (■) Non-compressed theophylline granules, (△) tablets compressed at 2.3 MPa, (●) tablets compressed at 4.9 MPa, (▲) tablets compressed at 17.8 MPa and (○) tablets compressed at 33.3 MPa.

## 3. Results and discussion

Table 1 lists the characteristics of the different materials used in this study.

In order to study the possible protective effect of different fillers on the compression of the coated granules, formulations with 70% of different fillers, 25% of coated theophylline granules and 5% Polyplasdone XL were tableted at different compression pressures.

Figs. 1–5 show drug dissolution from tablets made with Polyplasdone XL, Avicel, PEG 3350, lactose and Di-Tab. Table 2 lists the characteristics of these tablets.

Tablets made with coated granules using Polyplasdone XL and Avicel (Figs. 1 and 2) clearly show that when the tableting pressure is increased, the drug release and dissolution profile from the tablet are also increased, and are faster than the non-compressed coated theophylline granules. Hence, damage of the coating membranes occurs when the coated particles are tableted. The good tableting properties of Avicel for tableting microcapsules has been pointed out by Prapaitrakul and Whitworth (1990).

Table 1
Characteristics of the different materials used in this work

| Materials | Y.P. (MPa) | M.C. (%) | Tr.D. (g/cm$^3$) | B.D. (g/cm$^3$) | T.D. (g/cm$^3$) | H.F. (%) | P.C. |
|---|---|---|---|---|---|---|---|
| Lactose | 179.4 | 4.9 | 1.54 | 0.5 | 0.55 | 1.1 | 9.1 |
| Avicel | 98.8 | 3.6 | 1.64 | 0.21 | 0.26 | 1.25 | 19.2 |
| Di-Tab | 406.3 | 1.8 | 2.78 | 0.52 | 0.62 | 1.19 | 16.1 |
| Polyplasdone XL-10 | 159.1 | 9.7 | 1.23 | 0.21 | 0.23 | 1.08 | 8.7 |
| PEG 3350 | 24.2 | 0.3 | 1.18 | 0.54 | 0.61 | 1.13 | 11.2 |
| Coated theophylline granules | 90.2 | 2.8 | 1.41 | 0.69 | 0.72 | 1.05 | 4.7 |

Y.P., yield pressure; M.C., moisture content; Tr.D., true density; B.D., bulk density; T.D., tapped density; H.F., Hausner factor; P.C., percentage compressibility.

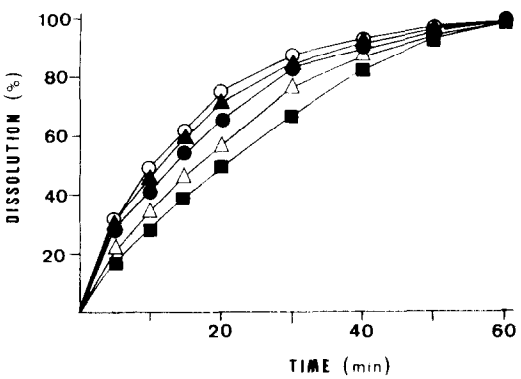


Fig. 2. Drug dissolution from non-compressed theophylline granules and tables of 70% Avicel, 25% coated theophylline granules and 5% of non-granulated Polyplasdone XL. (■) Non-compressed theophylline granules, (△) tablets compressed at 3 MPa, (●) tablets compressed at 7.9 MPa, (▲) tablets compressed at 13.6 MPa and (○) tablets compressed at 21.9 MPa.

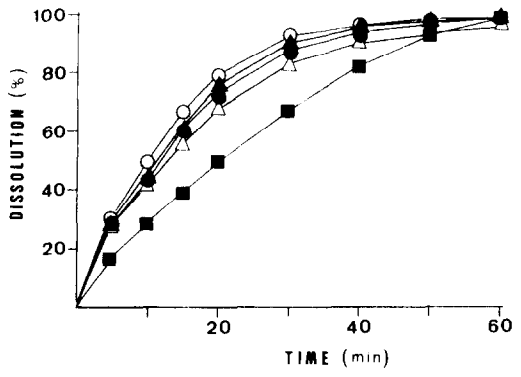


Fig. 4. Drug dissolution from non-compressed theophylline granules and tables of 70% lactose, 25% coated theophylline granules and 5% of non-granulated Polyplasdone XL. (■) Non-compressed theophylline granules, (△) tablets compressed at 12 MPa, (●) tablets compressed at 21.9 MPa, (▲) tablets compressed at 49.9 MPa and (○) tablets compressed at 105.8 MPa.

Results from PEG 3350, lactose and Di-Tab are no as clear, since these fillers are capable of making matrix tablets with high disintegration characteristics (see Table 2). If matrix tablets are produced drug relese is also slower, and cannot be considered exclusively as dependent on the coating membranes. For this reason, and in order to avoid this undesirable interference only values of tablets with short disintegration times can be considered and compared.

Under our experimental conditions, the order of least damage to the coatings was: PEG 3350 < Avicel < Polyplasdone XL < lactose < Di-Tab. These results are in good agreement with the yield values of the materials. It appears that the tablet matrix has a lower yield pressure than the

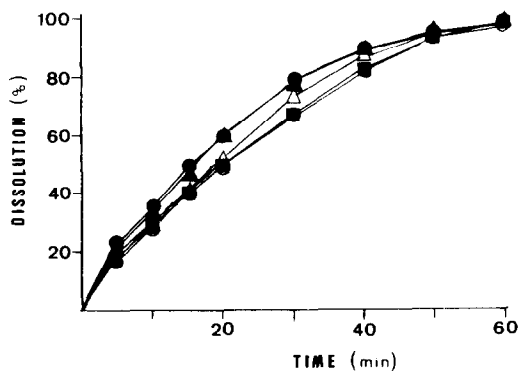


Fig. 3. Drug dissolution from non-compressed theophylline granules and tables of 70% PEG 3350, 25% coated theophylline granules and 5% of non-granulated Polyplasdone XL. (■) Non-compressed theophylline granules, (△) tablets compressed at 3 MPa, (●) tablets compressed at 7.5 MPa, (▲) tablets compressed at 11.4 MPa and (○) tablets compressed at 45.4 MPa.

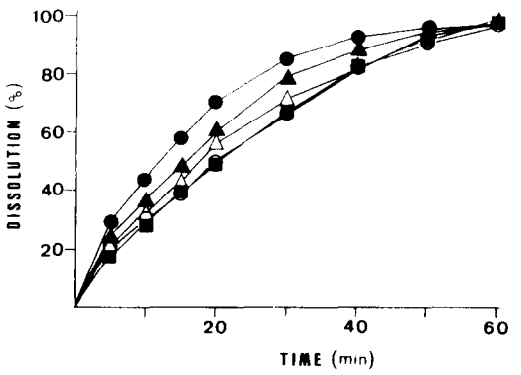


Fig. 5. Drug dissolution from non-compressed theophylline granules and tables of 70% Di-Tab, 25% coated theophylline granules and 5% of non-granulated Polyplasdone XL. (■) Non-compressed theophylline granules, (△) tablets compressed at 12.9 MPa, (●) tablets compressed at 25.7 MPa, (▲) tablets compressed at 60.5 MPa and (○) tablets compressed at 96.8 MPa.

pellet/pellet coating, such that the energy of compaction is absorbed by the matrix, and that the matrix is preferentially deformed.

The effect of compression force on the rate of dissolution of theophylline from tablets made with different excipients is shown in Fig. 6. If compressional pressure does not affect the rate of dissolution a constant release rate equal to that of non-compressed coated granules should be expected. The effect of increasing pressure on a tablet has been summarized by Finholt (1974) for two extreme possibilities:

(i) Particle bonding is affected: if particle bonding is the predominant phenomenon, then dissolution rates will diminish with increasing pressure.

(ii) Particle cleavage or crushing is affected: if this is the predominant effect, dissolution rates will increase with increasing pressure.

Depending on which of these two effects is affected most, different response curves may result. Fig. 6 shows that crushing and damage of the coating granules are the predominant effects on tablets made with Avicel and Polyplasdone. On the other hand, Fig. 6 shows that particle bonding is the predominant effect on tablets made with PEG 3350 and Di-Tab. This observation is consistent with the long disintegration times of these tablets (see Table 3). Tablets made with lactose show intermediate behavior.

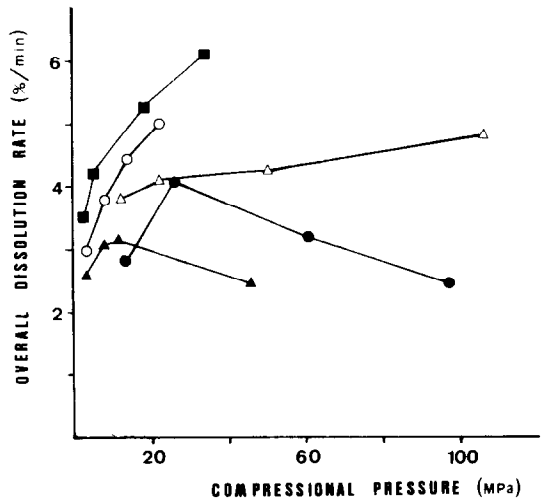


Fig. 6. Effect of different compressional pressure on the overall dissolution rate of the following materials. (■) Polyplasdone, (○) Avicel, (▲) PEG 3350, (△) lactose and (●) Di-Tab.

Table 2
Tablet characteristics of the compacts prepared using different fillers

| Filler | C.P. (MJpa) | Weight (mg) | Thickness (mm) | C.S. (N) | Disintegration (s) |
|---|---|---|---|---|---|
| Polyplasdone XL | 2.3 | 249 | 5.3 | 0 | 8 |
| | 4.9 | 253 | 5.1 | 0 | 9 |
| | 17.8 | 251 | 3.9 | 0 | 11 |
| | 33.8 | 249 | 3.5 | 37 | 14 |
| Avicel | 3 | 253 | 4.3 | 0 | 3 |
| | 7.9 | 248 | 3.5 | 5 | 4 |
| | 13.6 | 256 | 3.2 | 11 | 4 |
| | 21.9 | 254 | 2.9 | 23 | 7 |
| PEG 3350P | 3 | 256 | 3.2 | 0 | 5 |
| | 7.5 | 255 | 2.7 | 6 | 16 |
| | 11.4 | 258 | 2.5 | 9 | 29 |
| | 45.5 | 248 | 2.2. | 38 | 345 |
| Lactose | 12 | 251 | 2.8 | 0 | 20 |
| | 21.9 | 249 | 2.4 | 0 | 31 |
| | 49.9 | 251 | 2.3 | 8 | 40 |
| | 105.8 | 252 | 2.1 | 23 | 42 |
| Di-Tab | 12.9 | 252 | 2.3 | 0 | 22 |
| | 25.7 | 246 | 2.1 | 1 | 30 |
| | 60.5 | 253 | 1.8 | 18 | 38 |
| | 96.8 | 254 | 1.7 | 31 | 52 |

C.P., compressional pressure; C.S., crushing strength.

All the tested materials show overall dissolution rates which are faster than that of non-compressed teophylline granules (2.17%/min), therefore, under our experimental conditions there is always damage to the coating membranes.

Figs. 7 and 8 show drug dissolution from tablets made with mixtures of Di-Tab/Polyplasdone XL and Avicel/PEG 3350 as fillers from the tablets (see formulations I and II in Table 3).

Fig. 7 demonstrates how, when Di-Tab was used in combination with Polyplasdone XL, a dissolution profile more similar to that of Polyplasdone XL was obtained (see Fig. 1).

Fig. 8 displays the dissolution profile of tablets made with Avicel and PEG. Although the drug release of these tablets is quite similar to that of the non-compressed coated theophylline granules, formation of matrix tablets still takes place at high compressional pressures (see disintegra-

Table 3
Tablet characteristics of the compacts prepared with different formulations

| Formulation | C.P. (MPa) | Weight (mg) | Thickness (mm) | C.S. (N) | Disintegration (s) |
|---|---|---|---|---|---|
| I | 9.1 | 251 | 3.5 | 0 | 25 |
| | 15 | 253 | 3.1 | 0 | 28 |
| | 30.2 | 254 | 2.7 | 12 | 30 |
| | 52.9 | 250 | 2.5 | 28 | 30 |
| II | 4.5 | 252 | 3.4 | 0 | 20 |
| | 9.8 | 254 | 3.1 | 5 | 37 |
| | 16 | 253 | 2.9 | 13 | 40 |
| | 34.8 | 251 | 2.5 | 36 | 65 |
| III | 12.1 | 250 | 3.2 | 0 | 10 |
| IV | 12.7 | 251 | 3.3. | 9 | 11 |
| V | 12.9 | 252 | 3.5 | 13 | 10 |

C.P., compressional pressure; C.S., crushing strength. Composition of the different formulations (all the formulations contained 5% of non-granulated Polyplasdone XL as disintegrant): formulation I, Di-Tab 35%, granulated Polyplasdone XL 35% and coated theophylline granules 25%. Formulation II.: Avicel 35%, PEG 3350 35% and coated theophylline granules 25%; formulation III, coated theophylline granules 45%, Avicel 25%, PEG 3350 12.5% and Polyplasdone XL 12.5%; formulation IV, coated theophylline granules 25%, Avicel 35%, PEG 3350 17.5% and Polyplasdone XL 17.5%; formulation V, coated theophylline granules 5%, Avicel 45%, PEG 3350 22.5% and Polyplasdone XL 22.5%.

tion characteristics in Table 3). For this reason, Polyplasdone XL was included in the formulation and the effect of different proportions of excipients/coated particles on the drug release profile was studied.

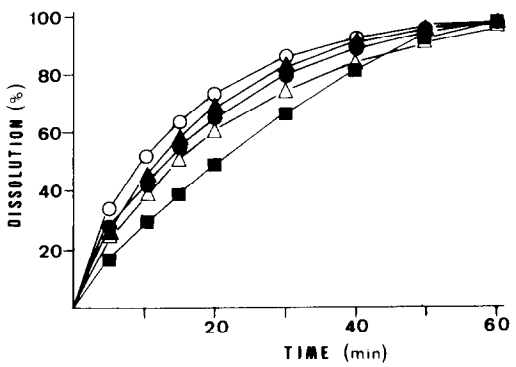


Fig. 7. Drug dissolution from non-compressed theophylline granules and tables of 35% Di-Tab, 35% granulated Polyplasdone XL, 25% coated theophylline granules and 5% of non-granulated Polyplasdone XL. (■) Non-compressed theophylline granules, (△) tablets compressed at 9.1 MPa, (●) tablets compressed at 15 MPa, (▲) tablets compressed at 30.2 MPa and (○) tablets compressed at 52.9 MPa.

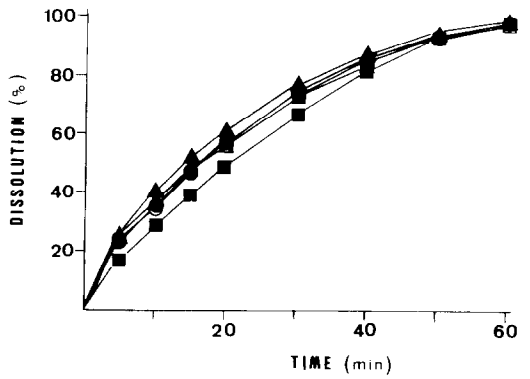


Fig. 8. Drug dissolution from non-compressed theophylline granules and tables of 35% Avicel, 35% PEG 3350, 25% coated theophylline granules and 5% of non-granulated Polyplasdone XL. (■) Non-compressed theophylline granules, (△) tablets compressed at 4.5 MPa, (●) tablets compressed at 9.8 MPa, (▲) tablets compressed at 15 MPa and (○) tablets compressed at 34.8 MPa.

Fig. 9 shows how the proportion excipient/coated theophylline granules can affect slightly the dissolution of the drug. Under our experimental conditions, few differences were observed between formulations with 5, 25 or 45% of coated granules, although a greater protective effect was noted with higher proportions of excipients.

It can be concluded from the present work that under our experimental conditions and even

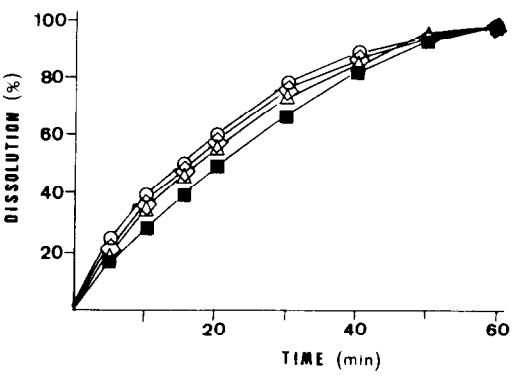


Fig. 9. Drug dissolution from: (■) non-compressed theophylline granules and tablets with different amounts of coated theophylline granules: (△) 5%, (◇) 25%, and (○) 45% (for more details see formulations III–V in Table 3).

at very low compressional pressure there is always damage of the coating membranes. Nevertheless, by the appropriate selection of the excipients, it is possible to achieve a formulation to ensure minimum damage to this coating. To this end, a combination of the following excipients with low yield pressure values is proposed as a suitable excipient mixture for coated particles: Avicel 50%, PEG 3350 25% and Polyplasdone XL 25%.

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