ELSEVIER

International Journal of Pharmaceutics 171 (1998) 195–206

international journal of pharmaceutics

# Reducing dust and improving granule and tablet quality in the roller compaction process

Sabine Inghelbrecht, Jean Paul Remon *

*Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium*

Received 5 February 1998; received in revised form 5 June 1998; accepted 6 June 1998

**Abstract**

The dramatic reduction of non-compacted material during roller compaction and an important improvement of the granule and tablet qualities were obtained by a controlled wetting process before the roller compaction. The continuity of the roller compaction process was maintained by using a continuous fluid bed system. Due to a controlled water addition, a better binder distribution was obtained than when using micronised dry binders. When dry compacting poorly water soluble hydrochlorothiazide mixtures, the resultant dissolution rate was not influenced by the HPMC binder viscosity. When moistened blends were compacted, the resultant dissolution rate decreased with increasing HPMC binder viscosity. The roller compaction pressure had almost no influence on the drug dissolution rate. The addition of disintegrants did not improve the dissolution rate. When a fraction of the filler $\alpha$-lactose monohydrate was replaced by microcrystalline cellulose, the dissolution rate increased with an increasing microcrystalline cellulose fraction. With the addition of 0.5% Tween® 80 to a formulation containing 25% microcrystalline cellulose and 50% $\alpha$-lactose monohydrate, the dissolution rate increased and an immediate release tablet formulation was obtained. The presence of microcrystalline cellulose also improved the processing and avoided lump formation.


*Keywords:* Roller compaction; Granule; Dust reduction; Moisture content

## 1. Introduction

Roller compaction is a dry granulation process by which material is densified between two counter rotating rolls. By a subsequent milling process, the obtained compacts are milled to granules of the desired particle size. The method can be used for materials sensitive to heat and water or solvents. The main merit of roller compaction is the continuity of the granule production reducing costs (Miller, 1994). The main disadvantages of roller compaction are the production of non-compacted material, defined as 'fines' and sometimes

* Corresponding author. Tel.: + 32 9 2648054; fax: + 32 9 2228236; e-mail: jeanpaul.remon@rug.ac.be

0378-5173/98/$ - see front matter 
PII: S0378-5173(98)00195-1

the production of compacts and granules of poor quality. In industry, recycling systems are integrated into the process to recuperate the fines and to improve the yield. However, negative influences of recycling fines on drug uniformity were reported by Sheskey et al. (1994).

The aim of this study was to improve the granule and tablet quality while using lower binder concentrations and to reduce the production of fines during the roller compaction process by improving the binder distribution. Two approaches were evaluated: the use of micronised dry binders and the addition of a controlled amount of water to the dry powder mix containing the binder. The water addition, by spraying on a continuously moving and fluidizing powder bed, was used in order to keep the advantage of the continuity of the roller compaction process and to avoid lump formation. An immediate release hydrochlorothiazide tablet with HPMC as binder was formulated in a pilot study using the controlled water addition process.

## 2. Materials and methods

### 2.1. Materials

The three hydroxypropylmethylcellulose products used were Pharmacoat® 606 (HPMC 2910, viscosity of 6 mPa.s for a 2% aqueous solution), Metolose® 60SH50 (HPMC 2910, viscosity of 50 mPa.s for a 2% aqueous solution) and Metolose® 90SH100 (HPMC 2208, viscosity of 100 mPa.s for a 2% aqueous solution); all supplied by Shin-Etsu (Tokyo, Japan). Pharmacoat® 606 and Metolose® 60SH50 were also micronised by the company UCIB (Usines Chimique d'Ivry la Bataille, Anet, France) with 95% of the particles showing a particle size below 50 $\mu$m. The other materials used were: $\alpha$-lactose monohydrate 200 M (Pharmatose® 200M, DMV, Veghel, The Netherlands) and hydrochlorothiazide (HCT), polysorbate 80 (Tween® 80) and magnesium stearate, all supplied by Ludeco (Brussels, Belgium). Sodium croscarmellose (Ac-Di-Sol®) and microcrystalline cellulose (Avicel® PH-101), both were supplied by the F.M.C. Corporation (Philadelphia, PA), sodium starch glycolate (Explotab®, Mendell, New York, NY) and crospovidone NF (Polyplasdone® XL, ISP Technologies, New York, NY).

### 2.2. Formulations

The evaluation of micronised binders was performed on mixtures containing 10% (w/w) micronised or non-micronised Pharmacoat® 606, micronised or non-micronised Metolose® 60SH50 and 90% (w/w) Pharmatose® 200M for the dry and moisture controlled productions, respectively. To determine the effect of the water addition on the drug release profile, formulations containing 10% HCT (w/w), 10% Pharmacoat® 606, Metolose® 60SH50 or Metolose® 90SH100 (w/w) and 75.5% Pharmatose® 200M (w/w) were prepared. Before tableting, 4% (w/w) Ac-Di-Sol® and 0.5% (w/w) magnesium stearate were added. The influence of adding a wetting agent (polysorbate 80) on the drug release profile was studied on powder blends containing 10% HCT, 10% Metolose® 60SH50, 2% Ac-Di-Sol®, 0.1 or 0.5% (w/w) polysorbate 80 with increasing concentrations of Avicel® PH-101 (0, 10, 25, 50 and 75% w/w). Before tableting, 2% Ac-Di-Sol® and 0.5% magnesium stearate were added to the granules. The rest of the formulation consisted of Pharmatose® 200M. When polysorbate 80 was used it was added to the water. The blends were moistened with 20% (w/w) water calculated on a dry basis except for the blends containing Avicel® PH-101 where 30% (w/w) water was incorporated.

### 2.3. Methods

#### 2.3.1. Roller compaction of dry and moistened formulations

The different powder components were mixed for 30 min in a Hobart mixer A200 (Hobart, London, UK). One part of the powder formulation was roller compacted dry by a Fitzpatrick L-83 Chilonsator® (The Fitzpatrick Company, Elmhurst, USA), the other part was moistened in an Anhydro Fluid Bed Agglomerator Unit 38 (APV Anhydro A/S, Copenhagen, Denmark). Nozzles sprayed water, eventually containing polysorbate 80, on a vibrating powder bed that

was continuously moving on a band conveyer. Via three cold air inlets, the powder was fluidized on the band conveyer. The spray rate was 100 ml/min. The water content of the mixtures was determined by Karl Fisher titration. Next, the mixture was roller compacted by an instrumented (Inghelbrecht et al., 1997) Fitzpatrick L-83 Chilsonator® consisting of two counter rotating, flat shapened rolls. A hydraulic pressure system was applied to the movable roll. With the hydraulic system an air pressure ($P_{air}$) was converted to a 25-times higher hydraulic pressure ($P_{oil}$) acting on the movable roll. The adjustable parameters of the Fitzpatrick L-83 Chilsonator were the air pressure ($P_{air}$), the roll speed (RS), the vertical (VS) and horizontal (HS) screw speeds. The roller compactor was not fitted with vacuum deaeration. The two following roller compactor setting combinations were used: RS = 7 rpm, VS = 1000 rpm, HS = 7 rpm and a $P_{air}$ so chosen that a hydraulic pressure between the rolls ($P_{oil}$) of 2.3 or 6.9 MPa was reached. The amount fines produced during the roller compaction process was determined by weighing the amount of the compacted and non-compacted material. After drying the compacts to their original moisture content, the compacts without the dust formed during compaction, were milled by a Frewitt granulator (MGI 624, Frewitt, Fribourg, Switzerland) equipped with a 1-mm sieve with squared wiring and set at a rotor speed of 130 rpm. The distance between rotor and sieve was kept minimal. In this way, the amount of fines, produced during the roller compaction process and during the milling process, were separately determined. The particle size distribution of the granules, determined by sieve analysis (90, 180, 250, 500, 710 and 1000 $\mu$m sieves) and the granule friability was evaluated (Inghelbrecht et al., 1997). The process yield for the different powder mixtures was evaluated using the 250–1000 $\mu$m sieve fraction. The fraction below 250 $\mu$m defined the amount of fines produced during milling.

### 2.3.2. Tablet production

The granule fraction 250–1000 $\mu$m was selected for tablet production. Some formulations contained intra- and extragranular disintegrants while other formulations contained only extragranular disintegrant. When the disintegrant Ac-Di-Sol® was extragranularly added, it was mixed with the granules for 10 min in a Turbula mixer (Type T2A, W.A. Bachafen, Basel, Switzerland). Next, 0.5% magnesium stearate was added to all formulations and mixed additionally for 1 min. Tablets with a total weight of 250 mg and 9 mm diameter were compressed on an eccentric press (Korsch Type EKO, Frankfurt, Germany) at a compression force of 18.6 kN. The tablet strength was determined by a Pharma Test strength tester (PTB311, Pharma Test, Hainburg, Germany) and the friability by a friabilator (Erweka GmbH, Frankfurt am Main, Germany). Dissolution tests (VanKel, Edison, CA) were performed on the tablets following the USP XXIII specifications (USP XXIII, 1995): dissolution medium was 900 ml HCl 0.1 M buffer, temperature was 37°C and the paddle speed 100 rpm. Hydrochlorothiazide concentrations were determined at 272 nm using UV spectrophotometer (Beckmann DU 65, Fullerton, CA). The influence of the roller compaction pressure on the mean tablet strength was examined by the two-tailed unpaired $t$-test. Differences in tablet strength for the different formulations were evaluated using the parametric one-way ANOVA test.

### 2.3.3. Reproducibility of the roller compaction process with controlled moisture addition

The reproducibility of the whole process was studied on 6 different days. The formulation used for the reproducibility test contained 10% (w/w) Pharmacoat® 606 and 90% (w/w) Pharmatose® 200M. The procedure consisted of spraying 20% water onto the powder during a 20-min time period. The moistened mixture was then roller compacted using the following combination: $P_{oil} = 6.9$ MPa, RS = 7 rpm, VS = 1000 rpm and HS = 7 rpm. The amount of non-compacted material and the moisture content were determined during roller compaction. The granule quality was evaluated by the granule friability tests and sieve analysis.

Table 1
Reproducibility of the continuous fluid bed-roller compaction process on 6 different days for a mixture containing 10% (w/w) Pharmacoat® 606 and 90% (w/w) Pharmatose® 200M. The parameters evaluated were the water content of the blend (%), the amount of fines produced during roller compaction (%), granule friability (%) and the granule fraction $<250$ $\mu$m (%).

| Parameters roller compactor | Water content (%) | Fines (%) | Friability (%) | Fraction $<250$ $\mu$m (%) |
|---|---|---|---|---|
| $P_{oil} = 6.9$ MPa | 11.2 | 2.9 | 24.4 | 18.0 |
| RS = 7 rpm | 8.8 | 3.4 | 27.4 | 20.4 |
| VS = 1000 rpm | 8.2 | 6.1 | 26.5 | 25.5 |
| HS = 7 rpm | 7.8 | 8.4 | 23.7 | 17.2 |
| | 7.7 | 11.4 | 23.1 | 21.8 |
| | 7.7 | 8.4 | 24.6 | 17.9 |
| Mean | 8.6 | 6.8 | 24.9 | 20.1 |
| S.D. | 1.36 | 3.27 | 1.66 | 3.16 |

## 3. Results

### 3.1. Reproducibility of the roller compaction process with controlled moisture addition

Table 1 shows the roller compactor parameter settings with the corresponding blend water content, the amount of fines produced during roller compaction, the granule friability and the granule fraction below 250 $\mu$m after milling during the 6 different day evaluations. For each production, 20% water dry weight basis, was sprayed over a 20-min period onto the fluidized and conveyed powder bed resulting in a powder-water content between 7.7 and 11.2%. For each batch, a close relationship was found between the water content of the powder and the amount of fines produced during roller compaction. The higher the moisture content the smaller the amount of fines. This relationship was not observed for the granule friability and granule fraction below 250 $\mu$m. The amount of water that could be sprayed onto the powder bed was limited to water levels not above 11%. Lumps were formed and compaction became difficult due to stickiness on the rolls at higher moisture levels. At water levels below 7%, the production of fines increased. The optimal water level range was situated between 8 and 10%.

### 3.2. Micronised binders

When roller compacting the following dry mixtures, a granule friability of 43.3%, 32.4%, 30.6%, 38.4% and 39.9% was obtained for the formulations containing no binder, 10% micronised or non-micronised Pharmacoat® 606, micronised or non-micronised Metolose® 60SH50 with 90% Pharmatose® 200M, respectively. By spraying 20% water onto the mixtures before roller compaction, a granule friability of 25.4%, 20.4%, 24.4% and 19.0% was obtained for the formulations containing 10% micronised or non-micronised Pharmacoat® 606, micronised or non-micronised Metolose® 60SH50 and 90% Pharmatose® 200M, respectively.

### 3.3. Effects of controlled water addition on hydrochlorothiazide tablets containing HPMC's of different viscosity as a binder

Table 2 shows that the influence of the roller compaction pressure ($P_{oil} = 2.3$ and 6.9 MPa) during the compaction of the dry blends was an important parameter. The highest hydraulic pressure of 6.9 MPa reduced the production of fines. The granule friability and the granule fraction below 250 $\mu$m, a measurement of the amount of fines produced by the milling process, improved at this pressure setting and the fraction 250–1000 $\mu$m, defined as the process yield increased. However, the amount of fines produced during the roller compaction process was still high while the granule quality remained low. At the pressure of 6.9 MPa, no difference in granule size distribution and amount of fines was seen for the three different HPMC grades. For the dry compacted formu-

Table 2
Evaluation of formulations containing 10% (w/w) Pharmacoat® 606, Metolose® 60SH50 or Metolose® 90SH100 when the formulation was dry and wet roller compacted at a hydraulic pressure ($P_{oil}$) of 2.3 and 6.9 MPa

| | Pharmacoat® 606 Type 2910, 6 mPa.s | | | | Metolose® 60SH50 Type 2910, 50 mPa.s | | | | Metolose® 90SH100 Type 2208, 100 mPa.s | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dry | | Wet | | Dry | | Wet | | Dry | | Wet | |
| | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa |
| Water content wet mix (%) | 4.3 | 4.3 | 9.8 | 9.8 | 4.4 | 4.4 | 9.0 | 9.0 | 3.2 | 3.2 | 9.6 | 9.6 |
| Fines during compaction (%) | 49.1 | 28.6 | 4.6 | 3.7 | 42.5 | 24.0 | 3.6 | 2.7 | 54.8 | 28.1 | 10.6 | 5.0 |
| Granule friability (%) | 80.4 | 41.4 | 22.3 | 23.3 | 84.0 | 40.2 | 16.5 | 17.6 | 60.0 | 33.8 | 16.2 | 15.3 |
| Fraction $<250$ $\mu$m (%) | 41.0 | 32.0 | 19.8 | 18.2 | 51.0 | 31.3 | 24.5 | 16.7 | 39.0 | 29.0 | 13.7 | 17.3 |
| Fraction 250–1000 $\mu$m (%) | 58.2 | 66.4 | 76.9 | 75.5 | 47.4 | 67.2 | 71.0 | 77.0 | 59.1 | 67.4 | 62.6 | 60.7 |
| Fraction $>1000$ $\mu$m (%) | 1.1 | 1.2 | 3.2 | 6.3 | 0.8 | 1.5 | 4.5 | 6.3 | 1.5 | 3.2 | 23.7 | 22.0 |
| Tablet strength (N) | 33.6 | 32.0 | 54.5[b] | 53.6[b] | 27.3 | 30.5 | 56.5[b] | 53.4[b] | 47.7 | 38.1[a,c] | 65.3[b] | 67.7[b,d] |
| Tablet friability (%) | 1.7 | 1.0 | 0.9 | 1.0 | 0.5 | 0.5 | 1.0 | 1.2 | 1.8 | 1.9 | 1.0 | 1.0 |

[a] Significant influence of the roller compactior hydraulic pressure (two-tailed unpaired $t$-test, $p<0.0001$).
[b] Significant influence of the wet process at 2.3 or 6.9 MPa (two-tailed unpaired $t$-test, $p<0.0001$).
[c] Significant influence of binder type at 6.9 MPa for the dry process (one-way ANOVA, $p<0.01$).
[d] Significant influence of binder type at 6.9 MPa for the wet process (one-way ANOVA, $p<0.001$).

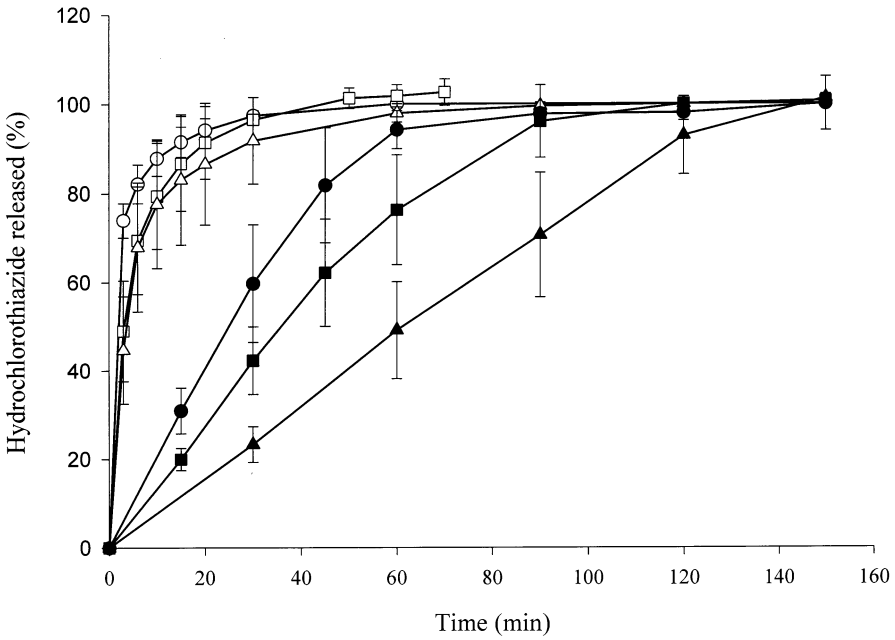


Fig. 1. Amount hydrochlorothiazide released (%) in function of time (min) for the formulation containing 10% (w/w) Pharmacoat® 606 (○), Metolose® 60SH50 (□) and Metolose® 90SH100 (△), dry (open symbols) or wet (closed symbols) roller compacted at a high hydraulic pressure of 6.9 MPa.

lations, a significant influence of the roller compaction pressure on the mean tablet strength was seen only when Metolose® 90SH100 was used (two-tailed unpaired $t$-test, $p < 0.0001$). At the highest roller compaction pressure, a significant difference in mean tablet strength was seen between the formulations containing Metolose® 90SH100 and Metolose® 60SH50 ($p < 0.001$), or Pharmacoat® 606 ($p < 0.01$), but not between Metolose® 60SH50 and Pharmacoat® 606 ($p > 0.05$, one-way ANOVA).

The formulation containing 10% Metolose® 90SH100 started to show lump formation at a water content level above 11%. For each HPMC formulation, a dramatic improvement of the roller compaction process was seen if the powder was moistened before roller compaction. By moistening the mixture the amount of non-compacted material nearly disappeared. In fact, in contrast with the compaction of a dry blend, the hydraulic pressure had no influence on the granule quality. When comparing the roller compaction process of the dry and wetted blends at a $P_{oil}$ of 6.9 MPa, the granule friability decreased by 44, 56 and 55% for the blends containing Pharmacoat® 606, Metolose® 60SH50 and Metolose® 90SH100, respectively. The granule size was larger for the wetted mixtures. The amount of granules below 250 $\mu$m was reduced while the amount of overs ($> 1000$ $\mu$m) increased. A significant increase in tablet strength was seen for the tablets made of the moistened mixture at both roller compactor pressures ($P_{oil} = 2.3$ and 6.9 MPa) compared to those made of the dry mixtures ($p < 0.0001$, two-tailed unpaired $t$-test). Fig. 1 shows the dissolution profiles of the tablets made of dry and wet roller compacted blends at a high roller compaction hydraulic pressure of 6.9 MPa. An immediate release was observed for the three dry compacted formulations containing only the filler $\alpha$-lactose monohydrate, while a dramatic decrease in dissolution rate was seen for all moistened mixtures. At 60 min (USPXXIII specification), 93%, 76% and 49% HCT was released from the Pharmacoat® 606, Metolose® 60SH50 and Metolose® 90SH100 formulations, respectively.

Table 3
Evaluation of formulations containing 10% (w/w) Metolose® 60SH50, 2% (w/w) intra- and extragranular Ac-Di-Sol® and different Avicel® PH-101 concentrations. All formulations were wet roller compacted at a hydraulic pressure ($P_{oil}$) of 2.3 and 6.9 MPa.

| Avicel® PH-101 | 0% | 0% | 10% | 10% | 25% | 25% | 50% | 50% |
|---|---|---|---|---|---|---|---|---|
| $P_{oil}$ | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa |
| Water content wet mix (%) | 9.3 | 9.3 | 11.6 | 11.6 | 9.2 | 9.2 | 6.3 | 6.3 |
| Fines during compaction (%) | 5.8 | 2.5 | 1.9 | 2.1 | 4.6 | 2.7 | 8.2 | 9.6 |
| Granule friability (%) | 13.3 | 16.4 | 11.9 | 10.2 | 14.2 | 13.5 | 14.4 | 10.8 |
| Fraction $<250$ $\mu$m (%) | 13.9 | 16.9 | 16.5 | 12.2 | 15.6 | 16.9 | 20.8 | 16.6 |
| Fraction 250–1000 $\mu$m (%) | 67.0 | 63.3 | 63.4 | 64.2 | 44.6 | 58.3 | 57.4 | 57.3 |
| Fraction $>1000$ $\mu$m (%) | 19.2 | 19.8 | 20.1 | 23.6 | 39.9 | 24.8 | 21.9 | 26.2 |
| Tablet strength (N) | 62.4 | 76.0[a] | 68.6 | 67.0[c] | 68.1 | 75.2[a,c] | 59.3[b] | 60.5[c] |
| Tablet friability (%) | 0.9 | 0.6 | 0.9 | 0.5 | 0.2 | 0.3 | 0.5 | 0.5 |

[a] Significant influence of the roller compactior hydraulic pressure (two-tailed unpaired $t$-test, $p<0.0001$).
[b] Significant influence of the Avicel® PH-101 concentration (10, 25 and 50%) at a $P_{oil}=2.3$ MPa (one-way ANOVA, $p<0.001$).
[c] Significant influence of the Avicel® PH-101 concentration (10, 25 and 50%) at a $P_{oil}=6.9$ MPa (one-way ANOVA, $p<0.001$).

An increase in the binder viscosity reduced the dissolution rate. The roller compaction pressure ($P_{oil}=2.3$ and 6.9 MPa) did not influence the dissolution rates of the tablets made from the dry and moistened mixtures (data not shown).

### *3.4. Formulation of a HCT immediate release tablet containing 10% Metolose® 60SH50 and using the roller compaction process with controlled water addition*

As an immediate drug release from the tablets made of dry compacted granules was lost with the controlled wetting technique, in the next part of the study an immediate release formulation using the controlled water addition process was developed using Metolose® 60SH50 (viscosity of 50 mPa.s) as binder. Table 3 shows the water content of the moistened mixture, the amount of fines produced during roller compaction, the granule and tablet quality for the formulations with intra- and extragranular disintegrant addition, and different Avicel® PH-101/Pharmatose® 200M ratio's (0/75.5; 10/65.5; 25/50.5; 50/25.5). Addition of Avicel® PH-101 to the formulation improved processing as the water was more uniformly distributed without lump formation. Moistened blend mixtures showed the amount of fines and granule friability were comparable for the formulation containing intra- and extragranular 2% Ac-Di-Sol® (Table 3) and the formulation containing 4% Ac-Di-Sol® extragranular and both containing only Pharmatose® 200M as a filler (Table 2). For the formulation containing intra- and extragranular 2% Ac-Di-Sol®, the mean tablet strength was significantly higher at a hydraulic pressure of 2.3 and 6.9 MPa ($p<0.001$, two-tailed unpaired $t$-test). The intra- and extragranular presence of 2% Ac-Di-Sol® did not modify the dissolution rate compared to the formulation containing 4% extragranular Ac-Di-Sol® (Fig. 1).

No important difference in granule strength and granule particle size distribution was observed for the formulations containing different Avicel® PH-101 concentrations. The presence of Avicel® PH-101 reduced tablet friability in comparison to tablets made with the filler $\alpha$-lactose monohydrate. For the formulations containing 0% and 25% microcrystalline cellulose, a significant influence of the roller compaction pressure was observed ($p<0.0001$, two-tailed unpaired $t$-test). Only for the formulation containing 50% Avicel® PH-101, a significantly lower mean tablet strength was seen at a hydraulic pressure of 2.3 or 6.9 MPa ($p<0.001$, one-way ANOVA). The dissolution profiles of the tablets made with the granules containing different Avicel® PH-101/Pharmatose® 200M ratio's and roller compacted at a hydraulic pressure of 2.3 and 6.9 MPa are shown in Fig. 2. The roller compaction pressure did not influence the dissolution profile. At 60 min, 50.9%, 97.8% and 98.6% HCT was released

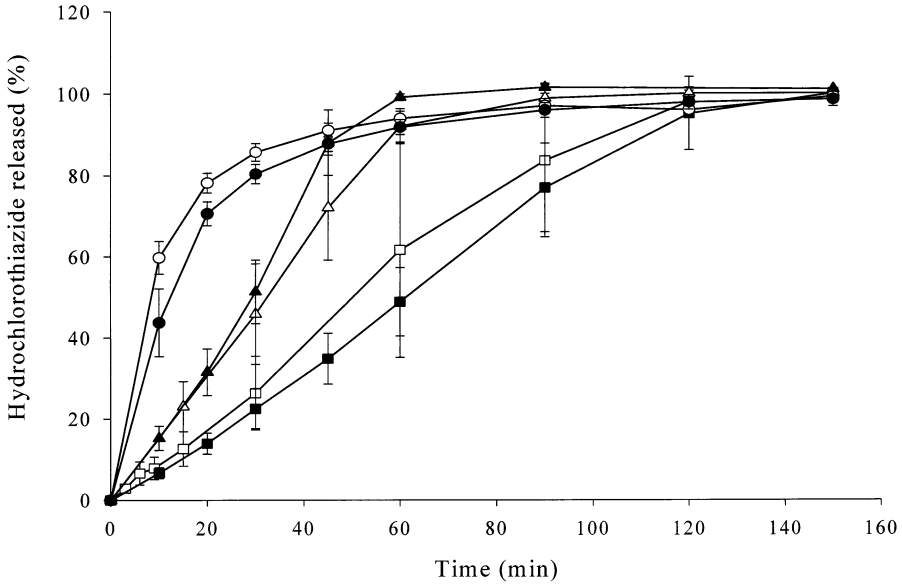


Fig. 2. Amount hydrochlorothiazide released (%) in function of time (min) for the formulation containing 10% (w/w) Metolose® 60SH50 and 10% (□), 25% (△) or 50% (○) Avicel® PH-101, roller compacted after controlled water addition at a hydraulic pressure of 2.3 MPa (open symbols) or 6.9 MPa (closed symbols).

from the formulations compressed at a high roller compaction pressure and containing 10%, 25% and 50% Avicel® PH-101, respectively. A higher Avicel® PH-101 concentration further decreased the disintegration time of the tablet into the granules but the release rate of HCT from the granules remained slow.

Table 4 shows the evaluation of the formulations containing 25/50, 50/25 and 75/0% Avicel® PH-101/Pharmatose® 200M as filler and 0.5% polysorbate 80 as wetting agent. Also, 0.1% polysorbate 80 was used for the formulation containing 25/50% Avicel® PH-101/Pharmatose® 200M. The granule friability values and the particle size distributions were comparable for all formulations at both pressures. Very low tablet strength was obtained when no $\alpha$-lactose monohydrate was present in the formulation. The roller compaction pressure had a significant influence on the mean tablet strength for the formulations with 0.5% ($p < 0.0001$) but not for the one with 0.1% solubilizer ($p > 0.05$, two-tailed unpaired $t$-test). No influence of the polysorbate concentrations 0.1 and 0.5% on tablet strength was seen at high pressure ($p > 0.05$) while the tablet strength of both formulations differed from the formulation without solubilizer ($p < 0.01$, one-way ANOVA). A significant influence ($p < 0.05$) between the formulations of 50/25% Avicel® PH-101/Pharmatose® 200M with and without 0.5% polysorbate 80 and the formulation containing 25/50% Avicel® PH-101/Pharmatose® 200M and 0.5% polysorbate was observed ($p < 0.05$, two-tailed unpaired $t$-test). Fig. 3 shows the dissolution profiles of the formulations containing increasing Avicel® PH-101 concentrations, and 0, 0.1 and 0.5% polysorbate 80, roller compacted at a high pressure. An important decrease in dissolution rate was observed with increasing polysorbate 80 concentrations for the formulation containing 25/50% Avicel® PH-101/Pharmatose® 200M. Only with the presence of 0.5% wetting agent in the formulation containing 25/50% Avicel® PH-101/Pharmatose® 200M an immediate-release formulation was obtained as all HCT was released within 40 min. For the formulations containing 25/50, 50/25, 100/0 Avicel® PH-101/Pharmatose® 200M and 0.5% polysorbate 80, the dissolution rate decreased with increasing Avicel® PH-101 concentration (Fig. 3) while for the same

Table 4
Evaluation of the formulations containing 10% Metolose® 60SH50, different ratio's of Avicel® PH-101/Pharmatose® 200M and different Tween® 80 concentrations. All formulations were wet roller compacted at a hydraulic pressure ($P_{oil}$) of 2.3 and 6.9 MPa.

| Tween ® 80 | 0.1% | 0.1% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% |
|---|---|---|---|---|---|---|---|---|
| Avicel® PH-101 | 25% | 25% | 25% | 25% | 50% | 50% | 75% | 75% |
| $P_{oil}$ | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa | 2.3 MPa | 6.9 MPa |
| Water content wet mix (%) | 8.91 | 8.91 | 10.7 | 10.7 | 7.6 | 7.6 | 7.8 | 7.8 |
| Fines during compaction (%) | 11.7 | 10.6 | 6.7 | 5.1 | 10.5 | 10.8 | 12.8 | 10.5 |
| Granule friability (%) | 11.52 | 9.0 | 9.3 | 11.4 | 10.2 | 9.0 | 10.6 | 9.8 |
| Fraction $<250$ $\mu$m (%) | 18.3 | 16.6 | 18.8 | 15.7 | 16.9 | 12.7 | 13.3 | 12.0 |
| Fraction 250–1000 $\mu$m (%) | 56.5 | 59.2 | 62.6 | 61.5 | 57.4 | 52.4 | 56.4 | 55.5 |
| Fraction $>1000$ $\mu$m (%) | 25.2 | 24.2 | 18.6 | 22.8 | 25.7 | 34.9 | 30.3 | 32.5 |
| Tablet strength (N) | 71.9 | 68.4 | 56.8[b,d] | 64.7[a,c] | 63.1[b] | 58.5[a,c] | 32.6[b] | 25.9[a,c] |
| Tablet friability (%) | 0.5 | 0.6 | 0.5 | 0.5 | 0.5 | 0.5 | 1.4 | 2.0 |

[a] Significant influence of the roller compactior hydraulic pressure (two-tailed unpaired $t$-test, $p<0.0001$).
[b] Significant influence of the Avicel® PH-101 and 0.5% Tween® 80 containing formulations at a $P_{oil}=2.3$ MPa (one-way ANOVA, $p<0.001$).
[c] Significant influence of the Avicel® PH-101 and 0.5% Tween® 80 containing formulations at a $P_{oil}=6.9$ MPa (one-way ANOVA, $p<0.05$).
[d] Significant influence of the amount Tween® 80 (one-way ANOVA, $p<0.0001$).

formulations without polysorbate 80 an increase in dissolution rate with increasing Avicel® PH-101 was observed (Fig. 2).

## 4. Discussion

Air, occupying the voids between the particles is the main source of the production of fines (Johanson and Cox, 1987; Johanson, 1989). It can cause an inadequate powder supply in the gripping zone, the zone in which powder is conveyed by the rolls, so that powder does not fully convey into the narrowest part of the roller gap and that a non-uniformly distribution of the compaction pressure over the whole roller-gripped powder mass is observed (Funakoshi et al., 1977). An attempt for reducing the amount of fines was made by Funakoshi et al. (1977) who used a rectangular feed chute and flaps to avoid side seal effects and a concave-convex 65° rimmed shape roller pair. The use of vacuum deaeration systems on twin horizontal auger feed screws or vertical screws, just before the rolls does reduce the production of fines, especially for low bulk density mixtures (Miller, 1997). Binders are widely used in wet granulation for their adhesive and cohesive characteristics that improve the strength and friability of the granules and tablets (Symecko and Rhodes, 1995). Sheskey and Dasbach (1995) already studied the behaviour of different dry binders in the roller compaction process. High binder levels (20%) were necessary for improving tablet strength but no data were presented on the reduction of the amount of fines. These high binder levels were probably necessary because of a poor binder distribution during roller compaction. Seager et al. (1979) visually proved the importance of the binder distribution in the granules. The binder distribution was dependent on the production method. They showed that using a low shear mixer and a fluidized bed for the wet granulation a binder network and a binder outer shell were formed resulting in a good binder action. On the contrary, the roller compacted granules showed individual flattened binder molecules resulting in a poor granule and tablet quality. In literature a 'moisture-activated dry granulation' technique (MADG) was described (Ullah et al., 1987; Chen et al., 1990; Christensen et al., 1994) where the drying step in a conventional discontinued wet granulation process was eliminated by reducing the amount of granulation liquid and by absorbing the liquid via a final addition of a water

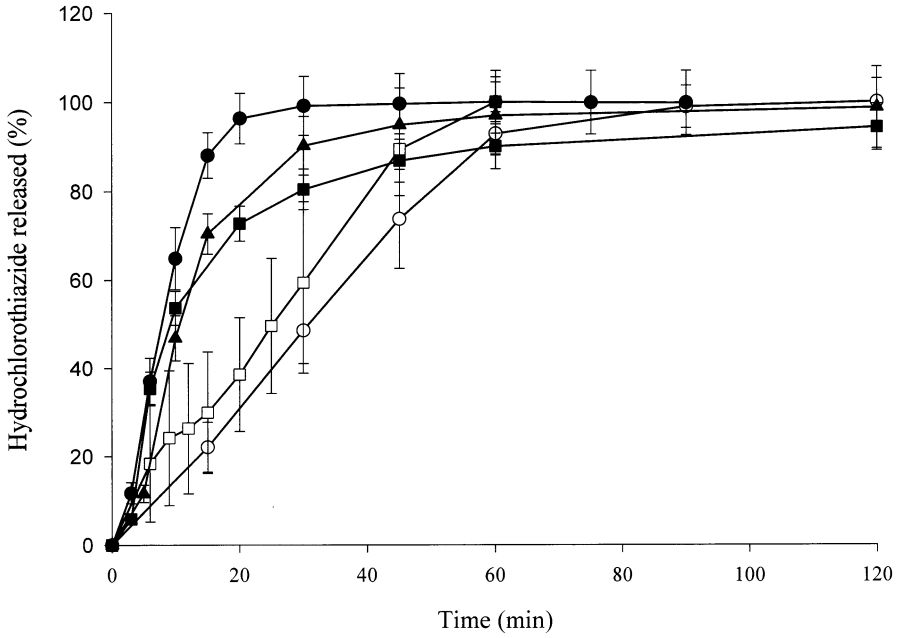


Fig. 3. Amount hydrochlorothiazide released (%) in function of time (min) for the formulations containing 10% (w/w) Metolose® 60SH50 and 25% (w/w) Avicel® PH-101 and 0% (○), 0.1% (□) and 0.5% (●) (w/w) Tween® 80 or containing 10% (w/w) Metolose® 60SH50 and 50% (▲) or 75% (■) (w/w) Avicel® PH-101 and 0.5% (w/w) Tween® 80.

absorbing material. In our study, a controlled wetting via a continuous fluid bed was integrated before the roller compaction process to improve binder distribution. During the controlled addition of an equal amount of water on the powder bed, differences in water content of the mixtures were seen within the range of 7.7–11.2% but the quality of the end product remained good and reproducible. These differences were probably due to variations in air inlet to fluidize the powder, ambient RH and temperature that were not controlled in the study. A close relationship was seen between the water content of the powder bed and the dust production during the roller compaction process. The process could therefore be improved by using an in-process control for the water addition system to the powder bed. In this way, the water content could be monitored between 8 and 10%. Within that range the amount of non-compacted material is negligible. The friability and the granule fraction below 250 $\mu$m for a same formulation dry compacted at a $P_{oil} = 6.9$ MPa, a RS = 7 rpm, a VS = 1000 rpm and a HS = 7 rpm was 41.4% and 32.0%, respectively. This means that the new process improved the granule friability by 39% and lowered the fraction below 250 $\mu$m by 37%.

Micronised binders were not able to improve the granule quality or to reduce the amount of fines produced during roller compaction. Besides, the micronisation of polymer binders remains an expensive and sometimes a hazardous process.

Pollock and Sheskey (1996) reported on the beneficial effect of micronised ethylcellulose on tablet quality produced by direct compression, although it has to be emphasised that high concentrations were used between 25 and 75%. On the contrary, moistening the powder blend containing the micronised binder improved granule friability markedly, but no advantage of using the micronised binder was seen for the moistened mixtures. This shows that a better binder distribution was obtained with the addition of a small amount of water than with the use of a micronised binder. Also, the phenomenon of a partial swelling of the polymer resulting in increased binding properties has to be taken into account.

Water addition to the blends containing different HPMC's viscosities eliminated the production of fines during the roller compaction process while the granule quality improved dramatically, showing a very low friability and less dust formation during the milling. Also, the tablet quality improved, showing a very low friability and a significantly increased tablet strength. The roller compaction of tablets processed dry did not affect the tablet strength and the tablets made from the dry processed formulations all showed an immediate release profile. The wet processed formulations showed a decreased release rate and a clear influence of the binder viscosity grade on the dissolution profiles. The decrease in the dissolution rate for the wet processed formulations containing HPMC can be explained by the swelling of the well distributed polymer particles during dissolution, blocking the pores partially. A higher viscosity induced a higher decrease in dissolution rate. The filler $\alpha$-lactose monohydrate was replaced by microcrystalline cellulose which has some disintegrating properties. Substituting the filler $\alpha$-lactose monohydrate for different ratio's of Avicel® PH-101/$\alpha$-lactose monohydrate, the dissolution rate increased with increasing Avicel® PH-101 concentrations, however the HCT release from the granules remained slow. Addition of Avicel® PH-101 to the formulation improved the wettability of the powder mix due to the MCC acting as a 'molecular sponge' (Fielden et al., 1988). Amidon and Houghton (1995) reported that the powder flow and the density decreased with increasing water content of Avicel® PH101. Also, the roller compactor pressure to obtain a compact of a certain strength was reduced if the moisture content increased. These findings were consistent with our observations. Nokhodchi et al. (1996) proved that the plasticity of HPMC 2208 (K4M) increased with an increasing moisture content from 0 to 14.9% (w/w). An explanation for the improved plasticity of Avicel® PH-101 and HPMC was given by Hancock and Zografi (1994) who showed that water was absorbed spontaneously by amorphous solids and acts frequently as a plasticizer.

There was a significant influence of the Avicel® PH-101/Pharmatose® 200M ratio and of the roller compaction pressure on the tablet strength for the 0.5% solubilizer containing formulations. Addition of 0.5% Tween® 80 as a wetting agent to the formulation containing 25/50% Avicel® PH-101/ Pharmatose® 200M resulted in an immediate-release profile with a total HCT release within 30 min.

## 5. Conclusions

It can be concluded, that by a controlled wetting of a formulation, a better binder distribution was obtained resulting in an improved granule and tablet quality and a dramatic reduction of non-compacted material during the roller compaction process. Another advantage of the controlled wetting before roller compaction was that differences in dissolution rates were seen for different viscosity grades of HPMC. Immediate release formulations could be developed from the lower viscosity HPMC grades, eventually by changing the filler and/or by using a wetting agent. From the dissolution profiles, it can be anticipated that the system is also usable for controlled release formulation by using high viscosity grade and higher binder concentrations.

## References

Amidon, G.E., Houghton, M.E., 1995. The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose. Pharm. Res. 12, 923–929.

Chen, C.M., Alli, D., Igga, M.R., Czeisler, J.L., 1990. Comparison of moisture-activated dry granulation process with conventional granulation methods for sematilide hydrochloride tablets. Drug Dev. Ind. Pharm. 16, 379–394.

Christensen, L.H., Johansen, H.E., Schaefer, T., 1994. Moisture-activated dry granulation in a high shear mixer. Drug Dev. Ind. Pharm. 20, 2195–2213.

Fielden, K.E., Newton, J.M., O'Brien, P., Rowe, R.C., 1988. Thermal studies on the interaction of water and microcrystalline cellulose. J. Pharm. Pharmacol. 40, 674–678.

Funakoshi, Y., Asogawa, T., Satake, E., 1977. Effects of changes in roller compactor parameters on granulations produced by compaction. Drug Dev. Ind. Pharm. 3, 555–573.

Hancock, B., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11, 471–477.

Inghelbrecht, S., Remon, J.P., Fernandes de Aguiar, P., Walczak, B., Massart, D.L., Van De Velde, F., De Baets, P., Vermeersch, H., De Backer, P., 1997. Instrumentation of a roll compactor and the evaluation of the parameter settings by neural networks. Int. J. Pharm. 148, 103–115.

Johanson, J.R., 1989. Reducing air entrainment problems in your roll press. Powder Bulk Eng. 2, 43–46.

Johanson, J.R., Cox, B.D., 1987. Fluid entrainment effects in roll press compaction. Proceedings of the 20th Biennial Conference of the Institute for Briquetting and Agglomeration, IBA. pp. 251–263.

Miller, R.W., 1994. Advances in pharmaceutical roller compactor feed system designs. Pharm. Tech. 18, 154–162.

Miller, R.W., 1997. Roller compaction technology. In: Parikh, D.M. (Ed.), Handbook of Pharmaceutical Granulation Technology. Marcel Dekker, New York, pp. 100–148.

Nokhodchi, A., Ford, J.L., Rowe, P.H., Rubinstein, M.H., 1996. The effect of moisture on the Heckel and Energy analysis of hydroxypropylmethylcellulose 2208 (HMPC K4M). J. Pharm. Pharmacol. 48, 1122–1127.

Pollock, D.K., Sheskey, P.J., 1996. Micronized ethylcellulose: opportunities in direct-compression controlled-release tablets. Pharm. Tech. 20, 120–130.

Seager, H., Burt, I., Ryder, H., Rue, P., Murray, S., Beal, N., Warrack, J., 1979. Relationship between granule structure, process of manufacture and the tableting of granulated products. Part 1. Int. J. Pharm. Technol. Prod. Manuf. 1, 2–6.

Sheskey, P.J., Dasbach, T.P., 1995. Evaluation of various polymers as dry binders in the preparation of an immediate-release tablet formulation by roller compaction. Pharm. Tech. 19, 98–112.

Sheskey, P.J., Cabelka, T.D., Robb, R.T., Boyce, B.M., 1994. Use of roller compaction in the preparation of controlled-release hydrophilic matrix tablets containing methylcellulose and hydroxypropylmethylcellulose polymers. Pharm. Tech. 18, 132–150.

Symecko, C.W., Rhodes, C.T., 1995. Binder functionality in tabletted systems. Drug Dev. Ind. Pharm. 21, 1091–1114.

Ullah, I., Corrao, R.G., Wiley, G.J., Lipper, R.A., 1987. Moisture-activated dry granulation: a general process. Pharm. Tech. 9, 48–54.

USP XXIII, 1995. US Pharmacopeial Convention, Rockvill, MD, pp. 750.