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Research paper

# Crushing strength, disintegration time and weight variation of tablets compressed from three Avicel® PH grades and their mixtures

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**Abstract**

Tablets compressed from 16 different mixtures of Avicel® grades PH-101, PH-102 and PH-200 were studied using a mixture design. The crushing strength, disintegration time and weight variation of tablets were determined after compressing with an upper punch force up to 30 kN. The particle size and density parameters of the powders were the most important factors influencing the tablet properties. The higher the amount of Avicel® PH-101 in the mixture, the stronger and more resistant to disintegration were the tablets. A high proportion of Avicel® PH-101 also resulted in greater weight variation. Increasing the proportion of granular Avicel® PH-102 and, especially Avicel® PH-200, in the mixture resulted in tablets with a lower crushing strength, shorter disintegration time and smaller weight variation. Increasing the compression force resulted in stronger and more slowly disintegrating tablets. Mixing with Avicel® PH grades was found to be worth trying in optimization of weight variation, strength and disintegration properties of tablets. © 1997 Elsevier Science B.V.

*Keywords:* Avicel® PH grades; Compression force; Crushing strength; Disintegration time; Mixture design; Optimization; Particle size; Weight variation

## 1. Introduction

Microcrystalline cellulose is often regarded as one of the best excipients for direct compression of tablets. The first commercially available product, Avicel®, was introduced by the American Viscose Corporation. Today Avicel® microcrystalline cellulose is a widely used excipient and it appears in many different grades. According to the manufacturer, Avicel® grades suitable for dry applications like direct compression are designated Avicel® PH. They differ from each other by their particle size, particle shape and moisture content [1].

As early as the 1960s it was reported that extremely strong tablets could be formed of Avicel® microcrystalline cellulose. However, such tablets disintegrated fast when placed in water as a result of the destruction of cohesive forces between the microcrystalline particles [2,3]. The tabletting properties of Avicel® PH grades have been investigated extensively ever since. Different Avicel® PH grades and other excipients for direct compression have been compared [4–6]. Also mixtures of Avicel® PH grades with other direct compression excipients have been evaluated [7–9]. Since the 1980s, comparison has been made also with generic microcrystalline cellulose products [10].

In a recent paper, Doelker et al. [11] studied Avicel® grades, including both the classical PH-101, PH-102, PH-103 and PH-105 as well as the new grades PH-112 and PH-200. Compared with the standard-grade Avicel® PH-101, PH-102 was very similar in performance, except that a lower weight variation of the tablets and a higher sensitivity to lubricant (0.5% magnesium stearate) were detected. The large-particle-size-

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Table 1
Compositions of the Avicel® PH mixtures

| Mixture | PH-101 proportion (%) | PH-102 proportion (%) | PH-200 proportion (%) |
|---|---|---|---|
| 1 | 100 | 0 | 0 |
| 2 | 0 | 100 | 0 |
| 3 | 0 | 0 | 100 |
| 4 | 75 | 25 | 0 |
| 5 | 50 | 50 | 0 |
| 6 | 25 | 75 | 0 |
| 7 | 75 | 0 | 25 |
| 8 | 50 | 0 | 50 |
| 9 | 25 | 0 | 75 |
| 10 | 0 | 75 | 25 |
| 11 | 0 | 50 | 50 |
| 12 | 0 | 25 | 75 |
| 13 | 33.3 | 33.3 | 33.3 |
| 14 | 66.7 | 16.7 | 16.7 |
| 15 | 16.7 | 66.7 | 16.7 |
| 16 | 16.7 | 16.7 | 66.7 |

grade PH-200 displayed a compactibility close to that of all the other Avicel® grades (except PH-105), but the highest sensitivity to lubricant. Tablets made of Avicel® PH-200 exhibited the lowest weight variability because of its good flowability. The disintegration properties of the tablets were similar to those made of PH-101, PH-102 and PH-103.

In our previous study, we studied Avicel® grades PH-101, PH-102 and PH-200 as well as their mixtures [12]. After storage in controlled conditions of temperature and humidity, the basic powder properties (appearance, particle size, bulk density, tapped density and flowability) were investigated. It was concluded that it might be beneficial to study whether certain mixtures of these different Avicel® PH grades could be used to achieve better flowing and packing properties when tabletted.

The aim of the present paper was to study tablets made of powder mixtures consisting of one to three Avicel® PH grades using a mixture design. In addition to the effect of different formulations, the effect of compression force on the crushing strength, disintegration time and weight variation of the tablets was evaluated.

## 2. Materials and methods

### 2.1. Materials

Three grades of Avicel® microcrystalline cellulose (PH-101, PH-102 and PH-200; FMC International, Cork, Ireland) were used. Magnesium stearate (0.5%; Ph. Eur. grade) was added to the powders as a lubricant. The powders were mixed for 5 min in glass jars using a laboratory-size mixer (Turbula T10B, Willy A. Bachofen AG Maschinenfabrik, Basle, Switzerland) at 14 rpm.

### 2.2. Methods

#### 2.2.1. Study design

Sixteen different mixtures were made from the three Avicel® PH grades studied. The compositions of the powder mixtures tabletted are presented in Table 1.

In our previous study, the mixture design was considered to be suitable for studying the properties of the Avicel® PH-grade mixtures. With a mixture design, it is possible to make estimates of the chosen responses through response surface methodology. The mixture design has been described in our previous paper [12]. The numerical data obtained were treated with Design-Expert® software (V. 3.0, Stat-Ease, Inc., Minneapolis, Minnesota, USA). Bolhuis et al. [13,14] have recently reported on the use of the mixture design and the same Design-Expert® software in tablet formulation.

In our present study, the best fitting mathematical model was selected on the basis of statistical testing. Suitable models for mixture designs consisting of three

Table 2
Mathematical models for mixture designs consisting of three components [15]

| | |
|---|---|
| Linear model | $\eta = \beta_i x_i + \beta_j x_j + \beta_k x_k$ |
| Quadratic model | $\eta = \beta_i x_i + \beta_j x_j + \beta_k x_k + \beta_{ij} x_i x_j + \beta_{ik} x_i x_k + \beta_{jk} x_j x_k$ |
| Special cubic model | $\eta = \beta_i x_i + \beta_j x_j + \beta_k x_k + \beta_{ij} x_i x_j + \beta_{ik} x_i x_k + \beta_{jk} x_j x_k + \beta_{ijk} x_i x_j x_k$ |

$\eta$, dependent variable (response).
$x_i$, $x_j$, $x_k$, fractions of components $i$, $j$ and $k$ in the mixture.
$\beta_i$, $\beta_j$, $\beta_k$, $\beta_{ij}$ etc., regression coefficients.

Table 3
Statistics of mixture design models fit

| Response | Model | C.V.% | $R^2$ | Adjusted $R^2$ | Press |
|---|---|---|---|---|---|
| Crushing strength ($F$ 4 kN) | Linear | 4.06 | 0.86 | 0.84 | 741 |
| | Quadratic | 4.43 | 0.87 | 0.81 | 909 |
| | Special cubic | 4.65 | 0.87 | 0.79 | 1272 |
| Crushing strength ($F$ 8 kN) | Linear | 3.34 | 0.88 | 0.86 | 1632 |
| | Quadratic | 3.29 | 0.91 | 0.86 | 1560 |
| | Special cubic | 3.46 | 0.91 | 0.85 | 2156 |
| Crushing strength ($F$ 15 kN) | Linear | 3.22 | 0.91 | 0.90 | 2325 |
| | Quadratic | 3.14 | 0.94 | 0.90 | 2357 |
| | Special cubic | 3.20 | 0.94 | 0.90 | 2750 |
| Crushing strength ($F$ 30 kN) | Linear | 3.01 | 0.93 | 0.92 | 2365 |
| | Quadratic | 2.64 | 0.96 | 0.94 | 2762 |
| | Special cubic | 2.70 | 0.96 | 0.94 | 3203 |
| Disintegration time ($F$ 4 kN) | Linear | 24.6 | 0.73 | 0.68 | $1.37 \times 10^3$ |
| | Quadratic | 25.1 | 0.78 | 0.67 | $2.26 \times 10^3$ |
| | Special cubic | 26.3 | 0.78 | 0.64 | $2.71 \times 10^3$ |
| Disintegration time ($F$ 8 kN) | Linear | 24.7 | 0.61 | 0.55 | $2.41 \times 10^4$ |
| | Quadratic | 25.0 | 0.69 | 0.54 | $4.17 \times 10^4$ |
| | Special cubic | 26.2 | 0.70 | 0.50 | $5.19 \times 10^4$ |
| Disintegration time ($F$ 15 kN) | Linear | 22.1 | 0.72 | 0.68 | $2.15 \times 10^5$ |
| | Quadratic | 22.3 | 0.79 | 0.68 | $2.58 \times 10^5$ |
| | Special cubic | 23.5 | 0.79 | 0.64 | $3.83 \times 10^5$ |
| Disintegration time ($F$ 30 kN) | Linear | 35.2 | 0.56 | 0.50 | $1.38 \times 10^6$ |
| | Quadratic | 35.7 | 0.65 | 0.48 | $2.17 \times 10^6$ |
| | Special cubic | 31.5 | 0.76 | 0.60 | $1.85 \times 10^6$ |
| Weight C.V. ($F$ 4 kN) | Linear | 29.8 | 0.37 | 0.28 | 0.60 |
| | Quadratic | 22.3 | 0.65 | 0.48 | 0.49 |
| | Special cubic | 26.6 | 0.74 | 0.56 | 0.56 |
| Weight C.V. ($F$ 8 kN) | Linear | 33.1 | 0.33 | 0.22 | 0.79 |
| | Quadratic | 25.0 | 0.75 | 0.63 | 0.70 |
| | Special cubic | 26.7 | 0.76 | 0.59 | 0.83 |
| Weight C.V. ($F$ 15 kN) | Linear | 28.2 | 0.35 | 0.25 | 0.45 |
| | Quadratic | 22.4 | 0.69 | 0.54 | 0.41 |
| | Special cubic | 27.0 | 0.71 | 0.51 | 0.47 |
| Weight C.V. ($F$ 30 kN) | Linear | 36.4 | 0.39 | 0.30 | 1.01 |
| | Quadratic | 27.6 | 0.73 | 0.59 | 0.91 |
| | Special cubic | 26.4 | 0.78 | 0.63 | 1.04 |

components are listed in Table 2. The coefficient of variation (C.V.), the multiple correlation coefficient ($R^2$) and the adjusted multiple correlation coefficient (adjusted $R^2$) for each response and mathematical model are listed in Table 3. The same table shows also the predicted residual sum of squares (PRESS) for each model. The PRESS indicates how well the model fits to the data, and for the chosen model it should be small in relation to the other models under consideration [15].

### 2.2.2. Preparation of tablets

Before tabletting, the powders were stored for 7 days in controlled conditions of temperature ($25.6 \pm 0.3$°C) and relative humidity ($51.6 \pm 4.5$%). After storage, the moisture content of the powders was $6.2 \pm 0.1$%, as determined by Karl-Fischer titration. The powders were compressed into round, flat tablets with a diameter of 9 mm and a weight of 230 mg using an instrumented single-punch press (Korsch EK-0, Erweka Apparatenbau GmbH, Berlin, Germany). The compression speed was 34 tablets $min^{-1}$. Four levels of compression force (upper punch force, F) were used: 4, 8, 15 and 30 kN.

### 2.2.3. Tablet properties

The tablet properties were studied 7 days after the tabletting. The diametral crushing force of the tablets (here referred to as crushing strength) was measured using a Schleuniger tester (model 6D, Dr K. Schleuniger & Co., Zürich, Switzerland). The measurement was made from 20 tablets. The disintegration time of

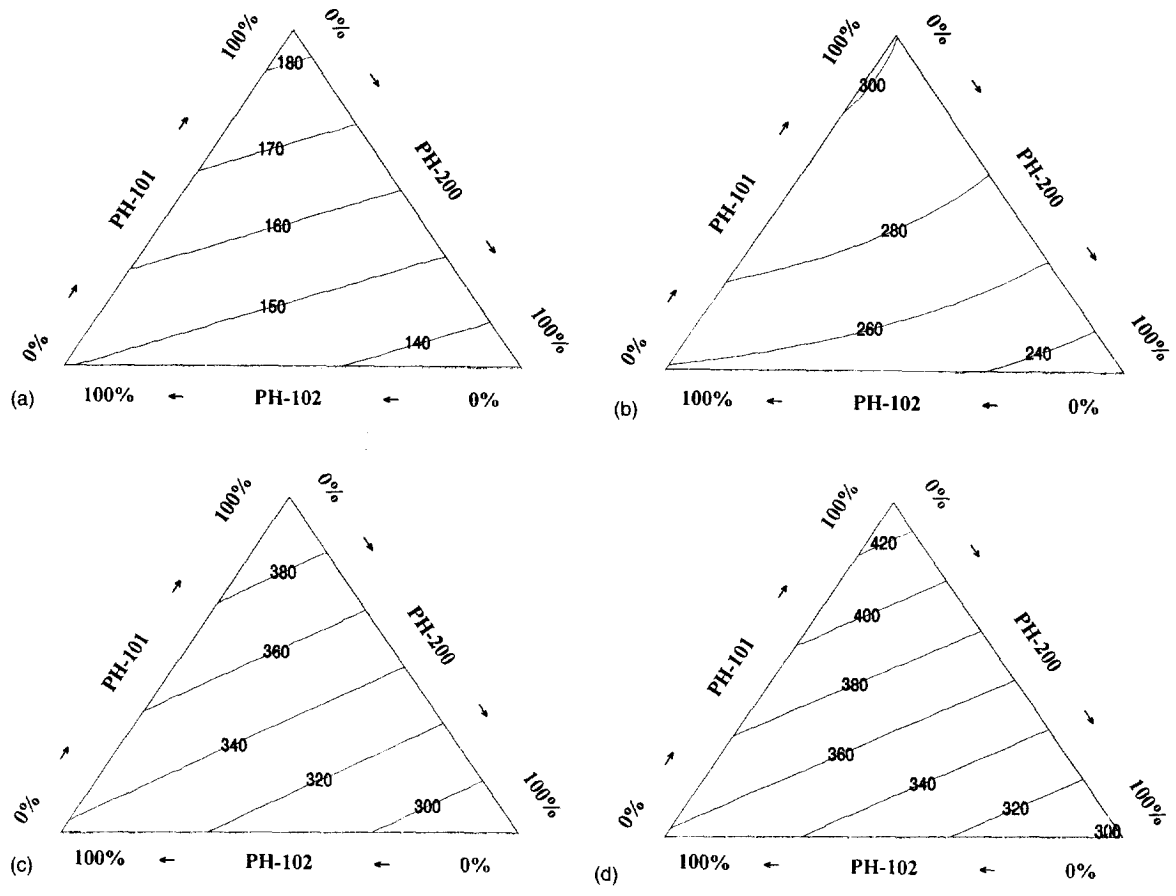


Fig. 1. Contour plots for the crushing strength (N) of tablets compressed with an upper punch force of (a) 4 kN, (b) 8 kN, (c) 15 kN, (d) 30 kN. The models chosen are linear (a, c, d) and quadratic (b).

the tablets was determined at 37°C in water using a Ph.Eur./USP apparatus (Erweka ZT 3-4, Erweka Apparatenbau GmbH, Heusenstamm, Germany) with discs. The disintegration time was determined from six tablets. The weight variation, diameter and thickness of the tablets were determined from 100 tablets with a large-scale tablet tester (Fette Checkmaster 3, Wilhelm Fette GmbH, Schwartzenbek, Germany). Determination of the diametral crushing force could have been done with the same tester, but some of the tablets were too strong for it. The determination could be done from all the tablets with the Schleuniger tester. The density of tablets was calculated from their weight and geometrical dimensions using the mean values of the sixteen tablet compositions studied.

## 3. Results and discussion

### 3.1. Crushing strength

On the basis of the contour plots obtained, the crushing strength of tablets was sensitive to changes in the proportions of Avicel® PH-101 and PH-200 (Fig. 1a–d). The proportion of Avicel® PH-102 did not have any great effect. The contour plots describing the crushing strength of tablets behaved in the same way as the contour plots of particle sizes and densities in our previous powder study [12]. Granular Avicel® PH-200 powder had the highest bulk density, but in order to achieve a maximum tapped density, PH-101 and/or PH-102 had to be added. When compressed, the weakest tablets were formed of Avicel® PH-200, but addition of the above mentioned grades, especially PH-101, resulted in significantly stronger tablets. The highest values of crushing strength were determined for tablets that were compressed from powder mixtures containing a major proportion (80% or more) of Avicel® PH-101; about 10–20% Avicel® PH-102 and/or PH-200 could be included. The phenomenon was the same with all the compression forces used.

The overall tablettability of the Avicel® PH mixtures studied was good. The tablets compressed with the compression force as low as 4 kN were quite strong: even the weakest ones which were made of pure Avicel® PH-200 had a crushing strength of over 135 N (Fig.

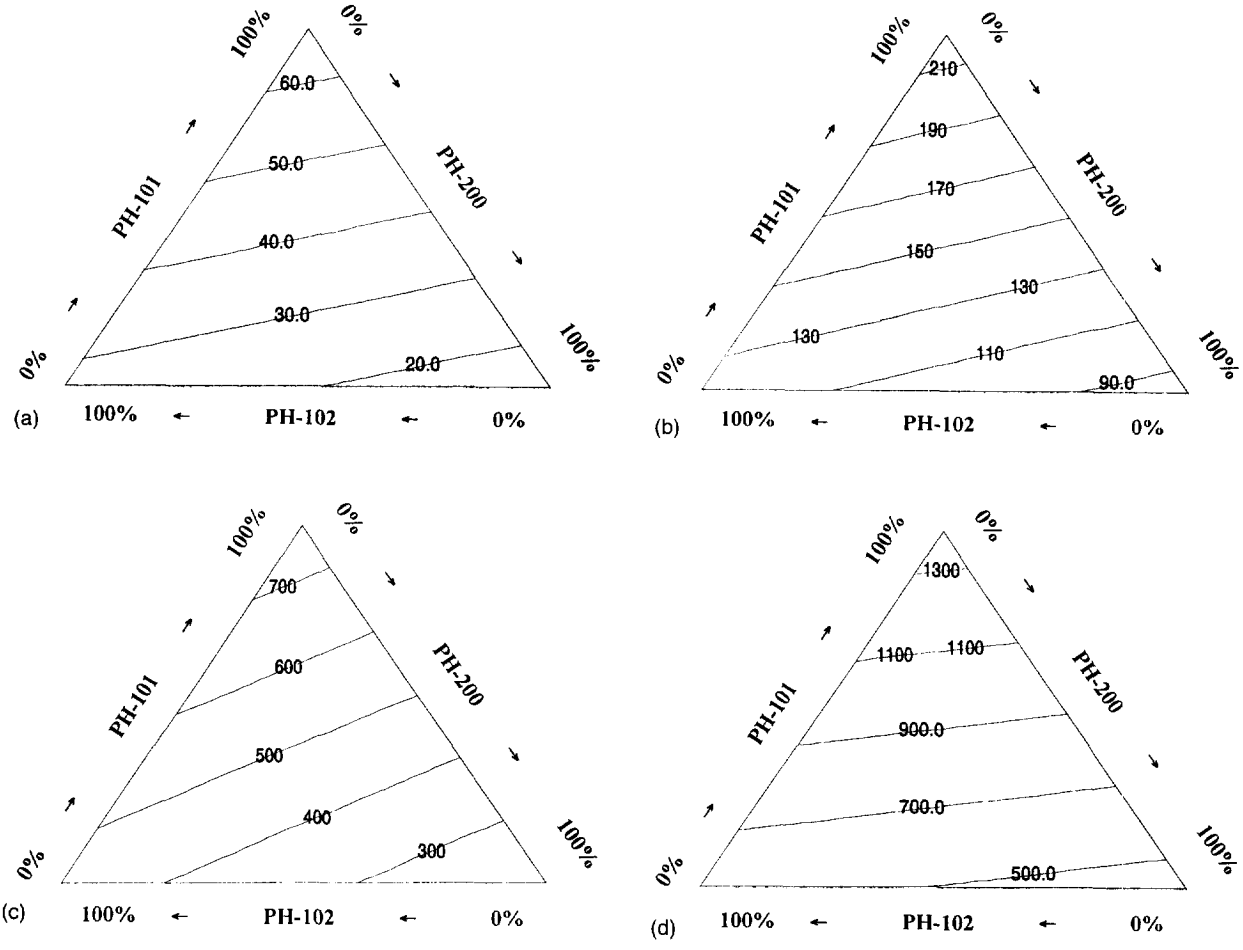


Fig. 2. Contour plots for the disintegration time (s) of tablets compressed with an upper punch force of (a) 4 kN, (b) 8 kN, (c) 15 kN, (d) 30 kN. The models chosen are linear.

1a). When the maximum compression force of 30 kN was used, the tablets formed were very strong irrespective of the composition used (Fig. 1d). Tablets with a crushing strength of over 300 N are rarely needed, however.

In order to produce strong tablets, the powder particles have to be packed densely, close to each other. In these experimental tabletting conditions the maximum bonding between the Avicel® PH particles was achieved with mixtures where the proportion of small, fibrous particles was high. Using large amounts of granular Avicel® grades PH-102 and especially PH-200 resulted in weaker tablets. Doelker et al. [11] have reported that Avicel® PH-101, PH-102 and PH-200 have similar compactibilities, particularly when taking into account the interbatch variability. This similarity of deformation under pressure and the results of our experiments demonstrate that the particle size and density parameters of the powder were the most important factors influencing the tablet strength.

In the study by Doelker et al. [11], a reduction of the tensile strength of tablets was observed when magnesium stearate was added, the extent of which depended on the Avicel® PH grade. The sequence of susceptibility was PH-200 $\gg$ PH-102 > PH-101. The amount of lubricant and the mixing time of powders were the same as in our study. The larger the particles in the powder mixture, the larger are the shearing forces during mixing. Shearing forces form a magnesium stearate film on the particles, producing weaker tablets when compressed. Van der Watt [16] reached the same conclusion after studying fractions of Avicel® PH-102. It is evident that this is one explanation why the high proportions of granular Avicel® PH grades, especially PH-200, resulted in weaker tablets in our study.

### 3.2. Disintegration time

The tablets made from Avicel® PH grades disintegrated rapidly in water. When compression forces up to 15 kN were used, all the tablets disintegrated in 12 min. The tablet disintegration time showed a similar dependence on the mixture composition as the tablet crushing strength. According to the contour plots (Fig. 2a–c),

Table 4
Weight, dimensions and density of tablets prepared of Avicel® PH mixtures ($n = 16$)

| Upper punch force (kN) | Weight (g) | C.V. (%) | Thickness (cm) | C.V. (%) | Diameter (cm) | C.V. (%) | Density (g cm$^{-3}$) | C.V. (%) |
|---|---|---|---|---|---|---|---|---|
| 4 | 0.230 | 0.50 | 0.291 | 0.86 | 0.911 | 0.49 | 1.22 | 0.94 |
| 8 | 0.230 | 0.55 | 0.258 | 1.74 | 0.909 | 0.27 | 1.38 | 1.84 |
| 15 | 0.230 | 0.47 | 0.245 | 2.11 | 0.909 | 0.27 | 1.44 | 1.85 |
| 30 | 0.230 | 0.46 | 0.248 | 1.62 | 0.909 | 0.38 | 1.43 | 1.66 |

only the amounts of Avicel® PH-101 and PH-200 had significance; the effect of Avicel® PH-102 was marginal. The higher the amount of PH-200 in the mixture, the faster the tablets disintegrated; the higher the amount of PH-101 in the mixture, the slower was the disintegration. The shortest disintegration time of tablets was achieved when only Avicel® PH-200 was used. The tablets with the longest disintegration time were made of pure Avicel® PH-101 or of a mixture where Avicel® PH-101 was mixed with about 0–10% PH-102 and/or PH-200.

The highest compression force of 30 kN resulted in great variation in the tablet disintegration time. The contour plot (Fig. 2d) shows that the effects of Avicel® PH-102 and PH-200 were now quite similar: increasing their amount in the mixture resulted in shorter tablet disintegration. The effect of Avicel® PH-101 was the opposite: with increasing amount the disintegration time of the tablets was prolonged. The longest disintegration time, 25 min, was determined from tablets made of Avicel® PH-101.

Disintegration of microcrystalline cellulose tablets has been attributed to the penetration of hydrophillic liquid (water) into the tablet matrix by means of capillary pores and the subsequent breaking of the hydrogen bonding between cellulose microcrystals [3]. In our study, the influence of mixture composition and compression force on the disintegration time of Avicel® PH tablets may also be explained by the porosity, hydrogen bonds and their disappearing. Small, fibrous particles of Avicel® PH-101 packed densely and had a large bonding area with relatively small interparticular pores. Possible magnesium stearate film formed on the surface of the particles may have resulted in even more delayed penetration of water into tablets. Adding of large, granular particles of PH-102 and especially Avicel® PH-200, resulted in large interparticular pores that may have been enhanced by elastic recovery after tablet compression. Water reached easily the hydrogen bonds between cellulose microcrystals and caused their breaking and thus rapid disintegration of tablets. The tablets that resisted the disintegrating effect of water over the shortest period of time were made of quite the same mixtures that resulted in mechanically weak tablets.

When the compression force is increased, the capillary porosity decreases, and this results in a slower disintegration of Avicel® tablets [3]. In our study, increasing the compression force up to 15 kN resulted in thinner and denser tablets no matter what the composition was (Table 4). When the compression force was increased to 30 kN, the thickness and density parameters did not change any more. In this study, the porous structure of the tablets was not determined; only the apparent tablet response, disintegration time. According to Table 4, the geometrical dimensions and densities of the tablets compressed with upper punch forces of 15 and 30 kN were similar. However, the disintegration times of the latter were longer. Analysing the porous structure of the tablets could have given an explanation to that.

### 3.3. Weight variation

In general, the weight variation of the Avicel® PH tablets was small. According to the contour plots (Fig. 3a–d), almost all the Avicel® PH mixtures resulted in tablets with a weight C.V. under 1%. When the proportion of Avicel® PH-101 in the powder mixture was over 80%, the tablet weight tended to vary more, but even the highest values of the weight C.V. were slightly over 1%. Different levels of the compression force did not have a noticeable effect on the weight variation of tablets (Fig. 3a–d; Table 4).

These observations of the effect of mixture composition on tablet weight variation were logical when compared with our previous study with powders [12]. As a powder, Avicel® PH-101 exhibited the poorest flow properties, but when mixed with PH-102 and PH-200, a significantly better flowability was achieved. Relatively high proportions of Avicel® PH-101 resulted in increased tablet weight variation. Rod-shaped particles of Avicel® PH-101 flowed better in the tabletting machine if some larger and more granular particles of PH-102 and PH-200 were mixed with them. The amount of these 'ball-bearings' needed for a better tablet weight uniformity was about 20% of the powder mixture, or even less. According to Doelker [10], Avicel® PH-200 will probably remedy the main drawback attributed to microcrystalline cellulose, i.e., tablet weight variation.

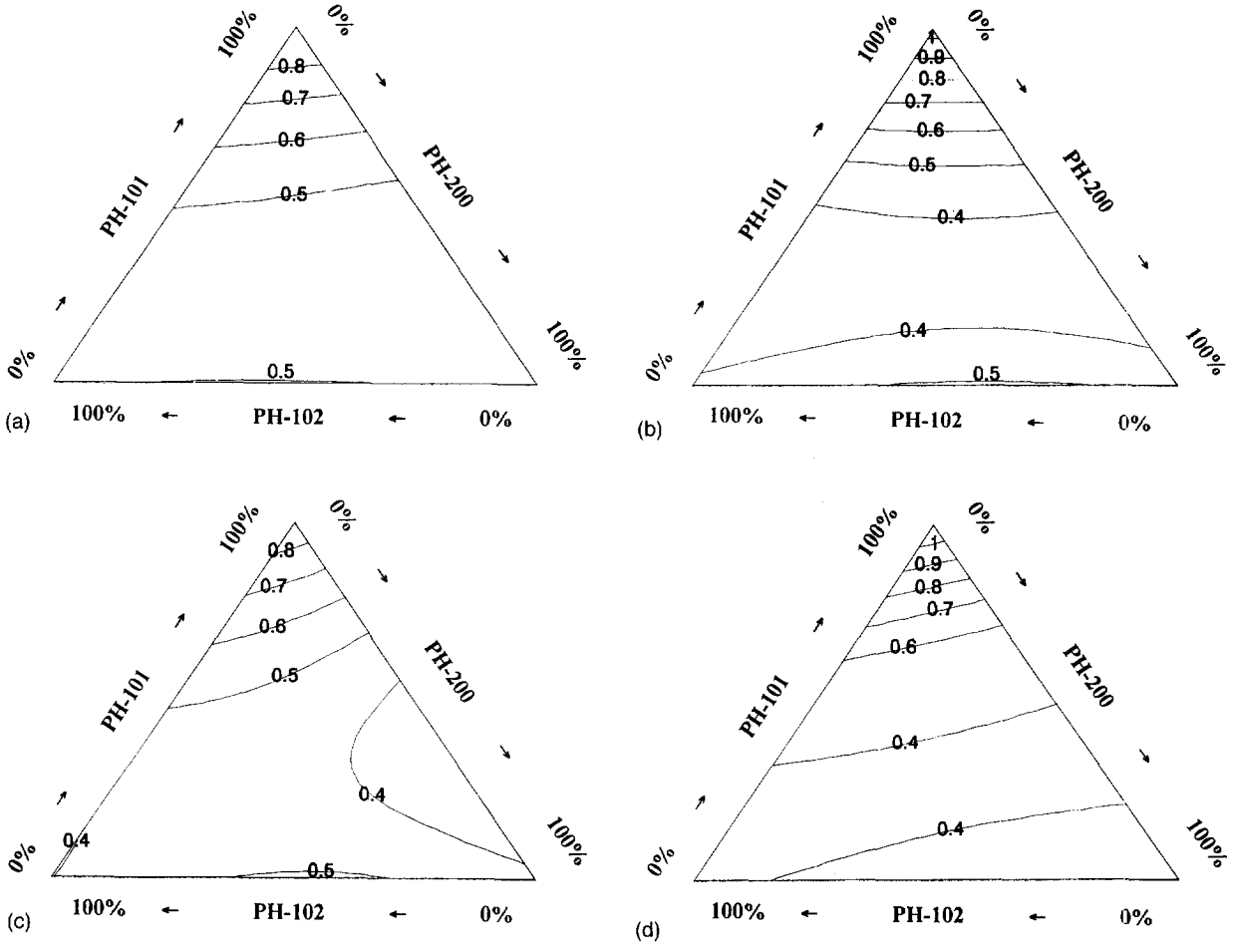


Fig. 3. Contour plots for the C.V. (%) of tablet weight; $n = 100$. The upper punch force used is (a) 4 kN, (b) 8 kN, (c) 15 kN, (d) 30 kN. The models chosen are quadratic.

In our opinion, the above mentioned mixing is one way of doing it.

## 4. Conclusion

Mixing with Avicel® PH grades could be worth trying in optimizing powder flow rates and achieving maximum productivity with high-speed direct compression formulas. Using the standard-grade Avicel® PH-101 results in strong tablets; mixing with granular PH-102 and especially PH-200 eases their disintegration. Using the granular Avicel® PH grades also remedies the main drawback attributed to microcrystalline cellulose, i.e., tablet weight variation. However, the content uniformity will not always be better because of the risks of segregation. A major proportion (60–80%) of Avicel® PH-101 mixed with granular Avicel® grade like PH-102 or PH-200 could be near the optimum composition that resulted in uniform, strong and thus well disintegrating tablets.

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