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Influence of fill factor variation in high shear granulation on the post granulation processes: compression and tablet properties.

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Abstract

This paper describes an investigation of the effect of fill factor; on the compaction behaviour of the granules during tableting and hence mechanical properties of tablets formed. The fill factor; which is the ratio of volume of wet powder material to vessel volume of the granulator, was used as an indicator of batch size. It has been established previously that in high shear granulation the batch size influences the size distribution and granule mechanical properties [1]. The work reported in this paper is an extension to the work presented in [1], hence granules from the same batches were used in production of tablets. The same tabletting conditions were employed during tabletting to allow a comparison of their properties. The compaction properties of the granules are inferred from the data generated during the tabletting process. The tablet strength and dissolution properties of the tablets were also measured. The results obtained show that the granule batch size affects the strength and dissolution of the tablets formed. The tablets produced from large batches were found to be weaker and had a faster dissolution rate. The fill factor was also found to affect the tablet to tablet variation of a non-functional active pharmaceutical ingredient included in the feed powder. Tablets produced from larger batches show greater variation compared to those from smaller batches.

Keywords: fill factor, compression, granules strength, compaction energy, batch size

1. Introduction

High shear wet granulation has been used extensively in the pharmaceutical industrial as a size enlargement process for granulating feed powders in order to improve their flow characteristics. Moreover, it has been used in a number industries for the manufacture of different products, e.g. fertilisers in agro-based industries [2-4], and for the granulation and mixing of metal or powder oxides such as iron , silica and aluminium in the metal processing industry [5, 6]. The quality of the granules formed during this process is sensitive to the process conditions as well as the formulation [1, 7-11]. Several studies have been undertaken to investigate the importance of process variables on the granule size and size distribution [8, 12-15]. Research on scale-up has focused particularly on the influence of the size distribution of the product [7, 12, 16-20]. Hassapour et al. [21] and Rahmanian et al. [22] examined scale-up rules based on constant speed, shear stress and the Froude number to achieve a target granule strength. It was concluded that a constant tip speed was the most effective. However, even when using the same granulator, small variations in the size of the batch can lead to significant differences in the properties of the granules [10, 12, 20, 23-25].

The fill factor is defined as the ratio of the volume of wet powder material to the vessel volume of the granulator. Recent work has shown that not only is the granules size affected by the variations in the fill factor but also the mechanical properties of the granules formed [1]. The total mass of the granulate material was varied (from 2113 to 2875 g corresponding to fill factors of 0.21 to 0.42 respectively) without changing the other variables such as impeller speed, granulation time and liquid to solid ratio. The resulting mechanical properties, such as strength, yield stress and Young's modulus, of the granules were measured. The granule strength, Young's modulus and yield stress of the granules were shown to increase with increasing batch size as represented by the fill factor.

The implications of batch size variation on the downstream processes due to changes in the material properties have not been investigated and this is the objective of the current work. The main aim was to establish the effects of the fill factor on the compression behaviour of the granules and the consequent effect on the tablet properties. The fill factor was varied by changing the total mass of the feed powder and binder liquid without changing other variables (impeller speed, liquid-to-solid ratio and granulation time) as described in previous work by the current authors [1]. It was found out that changing the fill factor of the granulator resulted in changes in the size distribution and mechanical properties of the granules produced.

The behaviour of granular solids under compression depends on the mechanical properties of the granules and this in turn has an effect on the mechanical properties of the tablets formed. A number of parameters that characterise the compression behaviour were determined (efficacy coefficient, net compression work and degree of compression), which will be described in the next section. The objective of this paper was to study the effect of fill factor on the mechanical, dissolution, and homogeneity of tablets formed from high shear granules. The effects of the fill factor on the strength and mean dissolution times of tablets formed from the granules were also measured. Although previous studies have considered the compositional uniformity of tablets [26-30], the effect of granulation process variables on tablet homogeneity has not been addressed.

2. Materials and Methods

2.1 Production of the granules and tablets

Granules were produced in a 10 L high shear granulator (RomatoRoto Junior) from a mixture of lactose monohydrate powder (Granulac 230, MolkerelMeggelGmBH, German) and potato starch (Solani, Pharma, Quality Avebe) using an aqueous solution of hydroxypropyl cellulose (HPC) as the binder. Sodium chloride was added to the powder mixture (1% w/w) as non-functional active

ingredient. In all the experiments, the feed powder was pre-mixed at an impeller speed of 250 rpm for 2 min. The subsequent inclusion of the binder involved pouring for a period of about 1 min with an additional granulation period of 6 min [1]. The granules were dried in a fluidised bed at a temperature of 50°C to a moisture content of approximately 4% w/w, which required a drying time of about 25 min. The fill factor was calculated from the following expression [1]:

$$\psi = \frac{m_w}{\rho_w \pi R_B^2 H} \qquad \textbf{Eq (1)}$$

where m_w and ρ_w are the mass and bulk density of the wet powder, and R_B and H are the radius and height of the cylindrical granulator vessel. The bulk densities of the dried granules, ρ_b , in the size range 0.5 to 0.6 mm, from the different batches, were determined by measuring the mass, m , of a known volume of granules, V :

$$\rho_b = \frac{m}{V} \qquad \textbf{Eq (2)}$$

2.1.1 Production of tablets

100 mg tablets were also produced from the granules in the size range 0.5 - 0.6 mm at a maximum compression force of 5 kN using a universal material tester (Instron model 3555); the loading and unloading data were stored in a computer. The loading and unloading speeds were both 10 mm/min and the internal diameter of the die was 6.35 mm. The tablets were stored in sealed plastic bags before their strength and dissolution characteristics were measured. The force – displacement data was recorded during compression of bed of granules into tablet and was used to determine the strength of the granules as described in section 2.1.2.

2.1.2 Determination of granule strength

During compression of the bed of granules to form tablets the force displacement data was recorded The force-displacement data were analysed using a method described previously [31] to obtain the single granule strength:

$$\ln P = \ln\left(\frac{\tau}{\alpha}\right) + \alpha\varepsilon_n + \ln\left(1 - e^{(-\alpha\varepsilon_n)}\right) \quad \textbf{Eq (3)}$$

where P is the applied pressure, ε_n is the natural strain, α is a pressure coefficient and τ is the strength parameter which is a measure of the single granule strength. The values of τ and α were obtained by fitting Eq. (3) to the measured values of $\ln P$ as a function of ε_n using non-linear regression.

2.1.3 Analysis of the granule compaction data

The stored elastic energy per unit mass of granules during compression of granules into tablets, W_e , was calculated from the integral of the unloading force data:

$$W_e = \frac{1}{m_b}\int_{\Delta_m}^{\Delta_0} F_{unl}(\Delta)\mathrm{d}\Delta \quad \textbf{Eq (4)}$$

where $F_{unl}(\Delta)$ is the force during unloading, m_b is the mass of the bed of granules in the die; Δ_0 and Δ_m correspond to the displacement at zero and maximum loading respectively. The net compaction work, W_{net} , which represents the energy dissipated, corresponds to the difference between the integrals of the loading and unloading curves:

$$W_{net} = \frac{1}{m_b}\left(\int_0^{\Delta_{\max}} F_l(\Delta)\mathrm{d}\Delta - W_e\right) \quad \textbf{Eq (5)}$$

where $F_l(\Delta)$ is the force during loading.

The degree of compression was determined from the initial bed height, h_0, and bed height at maximum compression pressure, $h_{\max}$ using [32]:

$$C_p = \left(\frac{h_0 - h_{\max}}{h_0} \right) \times 100\% \qquad \textbf{Eq(6)}$$

This parameter corresponds to the maximum percent engineering compressive strain.

2.1.4 Tablet tensile strength

The tablets were compressed diametrically at a speed of 2 mm/min, until fracture occurred and the force-displacement data were automatically logged. A minimum of 10 tablets were measured for each experimental condition and compact type. The strength of the tablets, σ_t , was calculated from the maximum load, $F_{\max}$ and the dimensions of the tablet, i.e. the tablet diameter D_t and thickness, x *[33, 34]*:

$$\sigma_t = 2 \frac{F_{\max}}{\pi x D_t} \qquad \textbf{Eq (7)}$$

The specific fracture energy required to fracture the tablets, W_t , was determined from the integral of the force-displacement curve:

$$W_t = \frac{1}{m_t} \int_0^{\delta_{\max}} F(\delta) \mathrm{d}\delta \qquad \textbf{Eq (8)}$$

where $F(\delta)$ is the current compressive force, δ is the current displacement, $\delta_{\max}$ is the displacement corresponding to fracture of the tablet, and m_t is the mass of the tablet. The fracture energy was normalised by the mass.

2.1.5 Efficacy of compression coefficient

The efficacy of compression coefficient, C_{eff}, which expresses the ability of the granules to convert the net compression energy into cohesion energy, was determined [35, 36]. The cohesion energy is that required to form bonds between the granules during compression:

$$C_{eff} = \frac{W_t}{W_{net}} \times 100\% \qquad \textbf{Eq (9)}$$

Values > 0.1% are characteristic of an effective conversion of net compression work into cohesion [36-39]. The strength of the tablets formed during compression is linked to amount of cohesion between the constituents of the tablet; higher cohesion would result in formation of stronger tablets whereas lower cohesion would be linked to formation of weaker tablets. Hence efficacy of compression is of particular interest to this study.

2.2 Tablet dissolution

The dissolution of 100 mg tablets in 250 ml distilled water was measured at a temperature of 37°C. This involved stirring with a paddle at 250 rpm and monitoring the conductivity of the solution as a function of time using a conductivity meter (Hanna 9000, Hanna Instruments, USA). The conductivity and temperature data were recorded automatically at 10 s intervals using a computer. Five repeat measurements were made.

The fraction of the non-functional active ingredient (sodium chloride) dissolved, *Y*, after a time, *t*, was determined as follows:

$$Y = \left(\frac{\chi - \chi_o}{\chi_\infty - \chi_o} \right) \times 100\,\% \qquad \textbf{Eq (10)}$$

where χ is the conductivity of the solution at a time *t*, and χ_o and χ_∞ are the initial and final conductivities (μS/cm). The Weibull distribution function was used to describe the data [9, 40].

$$Y = 1 - \exp\left(-\left(\frac{t - t_0}{\tau_d}\right)^{\xi}\right) \quad \textbf{Eq (11)}$$

where τ_d is the time taken to dissolve 63.2% of the non-functional active ingredient, ξ is a shape factor of the curve and t_0 is the lag-time, which is zero in the current work. The amount of the non-functional active ingredient in each tablet, m_a (mg), was determined from:

$$m_a = \Delta\chi\,\lambda V_s = \left(\chi_\infty - \chi_o\right)\lambda V_s \quad \text{Eq (12)}$$

where λ is a constant obtained from a calibration curve of the amount of NaCl as a function of $\Delta\chi$, which is the change in conductivity of the solution caused by presence of a known mass active of ingredient, and V_s is the volume of the dissolution medium (ml). The mean of 10 measurements was determined for each fill factor and the coefficient of variation of the non-functional active ingredient in the tablets was determined using:

$$n_t = \frac{\overline{\sigma}}{\overline{m}_a} \times 100\% \quad \text{Eq(13)}$$

where $\overline{m}_a$ is the mean value of active ingredient composition in the tablets and $\overline{\sigma}$ is the standard deviation of the non-functional active ingredient compositions.

2.2.1 Determination of acceptance values

The European Pharmacopea recommends assessing the content uniformity of tablets by computing Acceptance Values (AV) from the concentrations of the active ingredient and their standard deviations and comparing them with previously established ranges [41]. The AV is calculated from:

$$AV = \left|M - X\right| + k\overline{\sigma} \quad \text{Eq (14)}$$

where M is the reference value, X is the average value for individual tablets, k is a constant equal to 2.4 for n = 10 (n = number of repeat measurements) and $\bar{\sigma}$ is the standard deviation. The content of uniformity requirement is assumed to be met if the AV of the first set of 10 tablets is ≤ 15. The acceptance values of the tablet from the different batches are reported in Table 1. According to this table the granulation batches with fill factors of only 0.31 and 0.34 would pass acceptance.

3. Results

3.1 Bulk density

Before compression of the granules into tablets, the bulk densities of the dried granules were determined as outlined previously. Fig.1 shows that there is a reduction in the bulk density of the granules as the fill factor is increased. This can be attributed to the changes in the degree of consolidation and compaction of the granules when the batch size is changed whilst maintaining the other granulation conditions.

3.2 Compression data

Fig. 2 (a) shows the loading and unloading curves for the fill factors investigated and Fig. 2 (b) shows the same data expressed as the pressure as a function of the strain, which was calculated from Δ / h_0 where h_0 is the initial height of the granular bed and Δ is displacement. It is clear from Fig. 2 (b) that the maximum strain increases (54 to 59%) as the fill factor decreases.

The increase in strain required to achieve a given compression force as the fill factor decreases (Fig. 2b) is consistent with data published previously that showed an increase in the strength, Young's modulus and yield stress with increasing fill factor [1]. This is exemplified in Fig. 3 for the strength, which shows that the strength of the granules approximately doubles for the range of fill factors examined.

Fig. 4 shows that efficacy coefficient decreases as the fill factor increases with the values being less than the lower ideal limit of 0.1% for the three largest fill factors. The trend is consistent with the increase in granule strength since the propensity of granules to deform is important in the development of a cohesive tablet.

3.3 Mechanical properties of the tablets

Results in Fig. 5 (a) shows that the tablet strength is reduced by ~ 25% when the fill factor is increased from 0.31 to 0.42. Since the tablets were formed by the compression of granules of the same mass, maximum pressure and compression speed, the differences in the tablet strength cannot be attributed to the tabletting conditions. Consequently, they must arise from the differences in the mechanical properties of the granules as exemplified in Fig. 3 and the trend is reflected in the reduction of the efficacy coefficient. Fig. 5(b) also shows that there is a clear correlation between the tablet strength and that of the granules. Moreover, the reduction of the tensile strength of the tablets corresponds to a similar reduction of ~ 30% in the specific fracture energy (Fig. 6).

3.4 Effect of fill factor on tablet dissolution

Since it has been shown that the fill factor or size of the batch affects the strength of the tablets it is reasonable to expect that they should also have different dissolution rates and this is evident from the data Fig. 7 (a). The symbols show the measured data points (an average of 5 measurements) and the error bars are the standard deviation. The continuous line through the data points are fits to Eq. (11). The dissolution profiles shift to the left with increasing fill factor, implying an increase in the dissolution rate. The parameter τ_d; which is the length of time it takes to release 63.2 % of the drug was obtained from non-linear regression of Eq. (11) to the dissolution data.

In our previous work similar procedure was done using granules in same size range to those used for tableting in current study to obtain dissolution characteristics of the granules [3]. The granule dissolution tests were performed using granules of the same mass as the tablets (100 mg). The results that were obtained showed that the dissolution time, τ_g of the granules increased with increasing fill factor (~4 to ~12s). The correlation between the dissolution time of the tablets and that of granules is shown in Fig 7 (b). This result is consistent with the decrease in tablet strength with increasing fill factor since it is generally the case that there is a correlation of the rate dissolution and the tablet strength [1]. The correlation between the mean tablet dissolution time and the tablet strength is shown in Fig. 8. The data demonstrate that stronger tablets require a longer time to dissolve compared to those that are weaker. On the other hand, there is a minimum strength is required for packing and handling purposes, therefore a trade-off has to be made in producing tablets sufficient strength to survive handling processes without compromising the dissolution kinetics.

3.5 Effect of batch size on tablet drug homogeneity

The relative standard deviation of the non-functional active ingredient composition in different tablets produced from granules made with different fill factors is presented in Fig. 9 (a). The coefficient of variation of the tablet non-functional active ingredient increases with the batch size, which would result in a similar variation in the active pharmaceutical ingredient (API) composition for a real pharmaceutical tablet. A similar trend has been found for the dissolution characteristics of granules [1]. In our previous work [1] the coefficient of variation of the non-functional active ingredient of samples of granules (η_g) obtained from different fill factors was determined using the same procedure described in section 2.5. The coefficient of variation of non-functional ingredient in the granules data from [3] was then plotted Fig. 9 (b). Please note that the masses of granules used

254 in these measurements were the same as tablet masses used in the current study. The results show
255 that there is a linear correlation of the coefficient of variations of the tablets and corresponding
256 granules. This is an interesting point to note since it implies that information about the content
257 homogeneity of the tablets can be inferred from tests performed on the granules even before the
258 tablets are produced.

259 ## 4. Discussion

260 In the current work it was found that increasing the granulator fill factor results in an
261 increase in the strength of the granules and a decrease in their degree of compression. It has also
262 been observed previously that the compressibility of granules decreased with their strength [42].
263 Similarly it was reported that the degree of compression of microcrystalline cellulose pellets
264 decreased with increasing values of their crushing strength [32]. Recent work by Chan et al. [43]
265 showed that increasing the bed load (which is equivalent to increasing fill factor) results in an
266 increase in granule-blade bed stress and the effect was more pronounced at high impeller speeds.
267 The granules from larger batches are then more likely to be more consolidated than those from
268 smaller batches. Such strong granules would be less compressible compared to those that are weaker
269 as observed in the current work. Thus it may be concluded that the ability of granules to convert net
270 compaction energy to cohesion decreases with increasing fill factor. This is consistent with the
271 tablet strength data, which showed a reduction with increasing fill factor.
272

5. Conclusion

The granulator fill factor has a profound effect on the compaction properties of the granules. Those produced from smaller batch sizes have superior compaction properties than those from larger batches. The degree of compression of the granules decreases with increasing fill factor. This may be due structural changes in the granules as a result of the different batch sizes. Further work is recommended to analyse the changes in the internal and surface properties of the granules. An important novel finding of the current work is that the variation of the non-functional active ingredient in tablets are significantly affected by the value of the fill factor.

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399

400

List of Tables.

List of figures

425

426 **Table 1:** Summary of non-functional active ingredient composition, acceptance values for tablets from
427 different batch sizes.

Fill factor (-)	Average composition $\overline{m}_{ai,tab}$ (mg)	Reference composition M (%)	Percentage Average composition fX (%)	Acceptance value AV (-)
0.31	1.83	100	91.6	8.7
0.34	1.88	100	94.0	6.4
0.38	1.59	100	79.5	21.1
0.41	1.78	100	89.0	11.7

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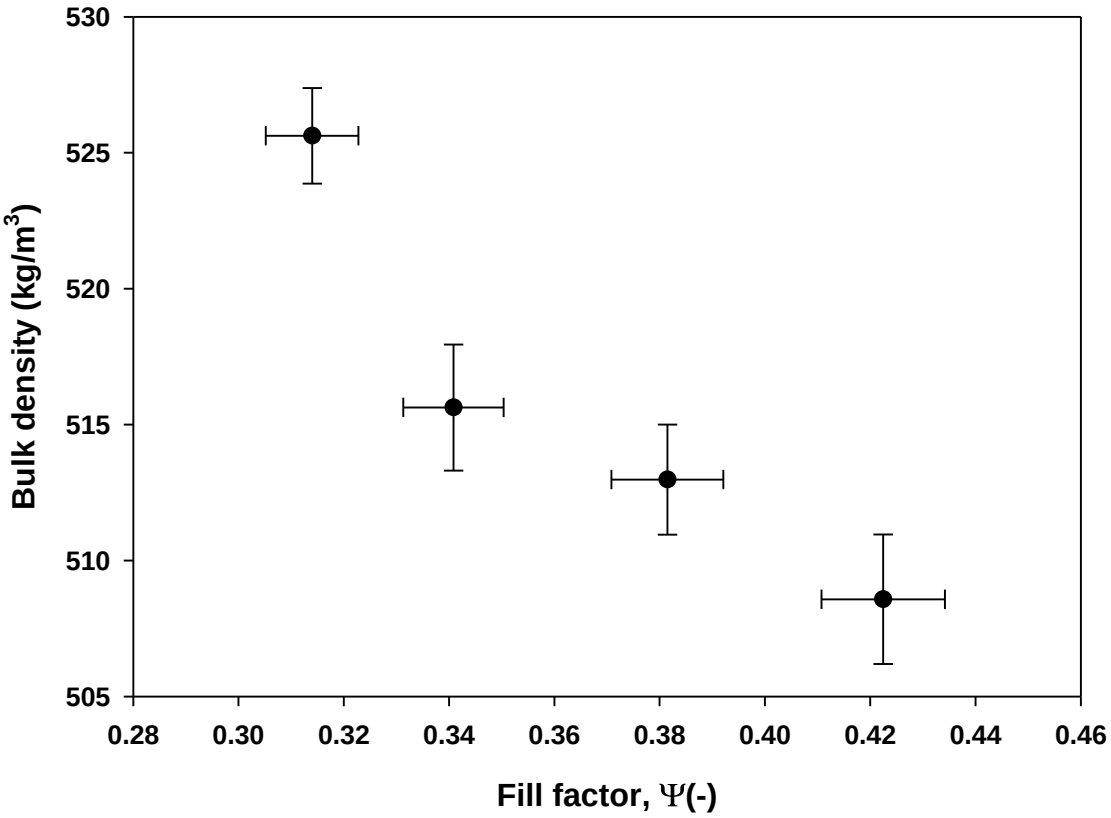
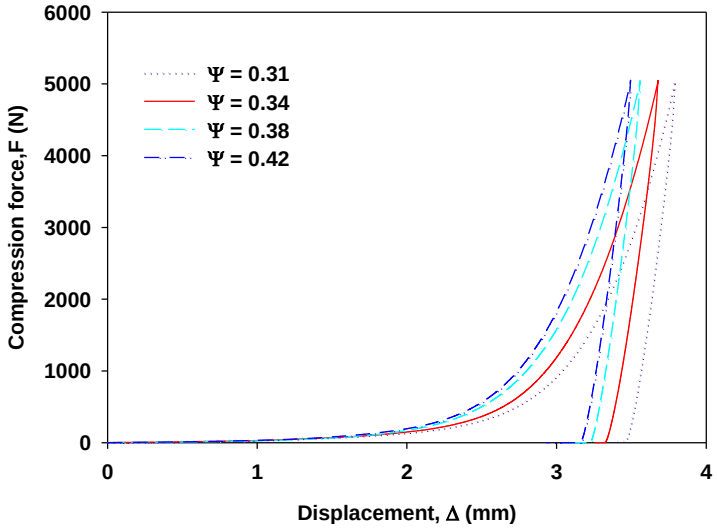
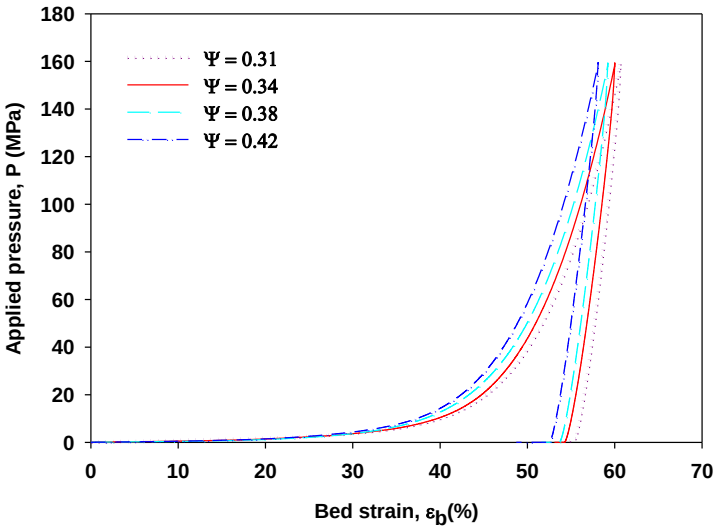


Fig. 1: Bulk density of the granules in the size range 0.5 - 0.6 mm.



(a)

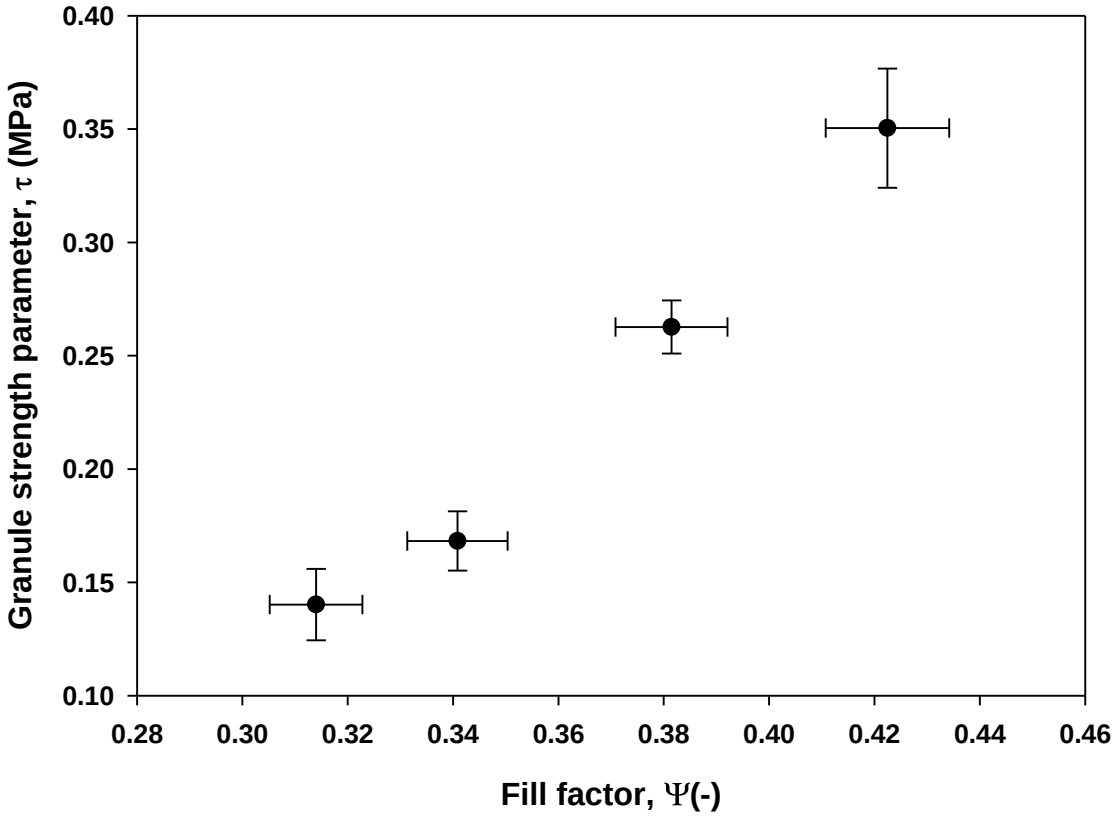


(b)

434

435 **Fig. 2**: a) Force-displacement profiles for the four different fill factors and (b) applied bed pressure as
436 function of bed strain.

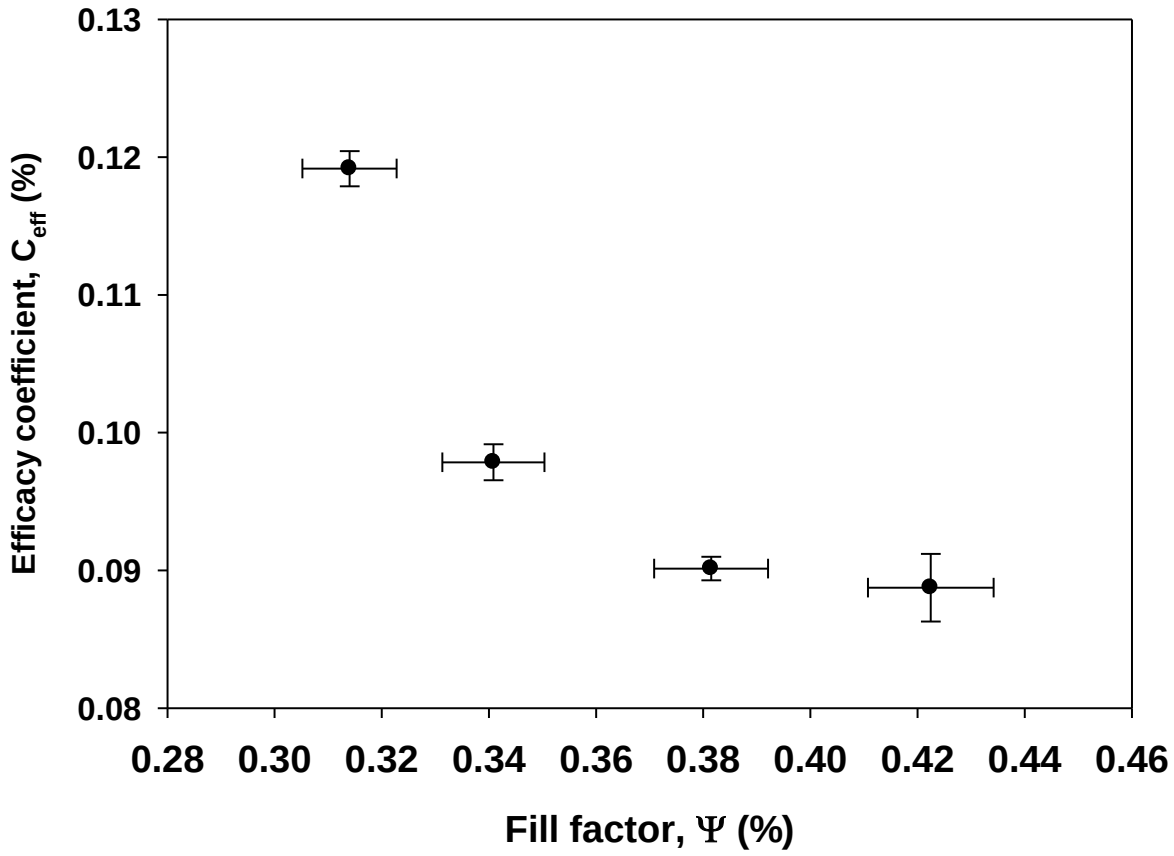
437
438



439

440 **Fig. 3:** Effect of fill factor on granule strength parameter.

441



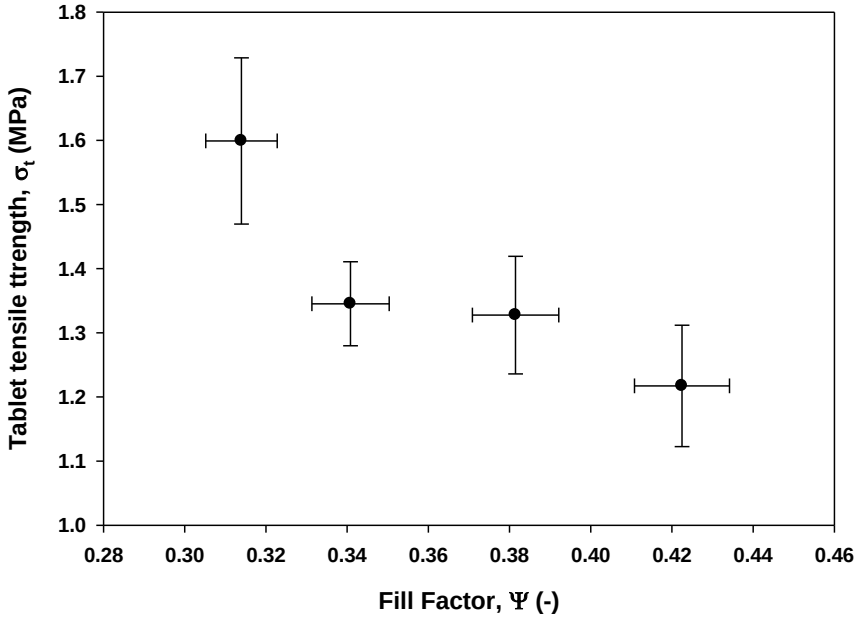
442

443

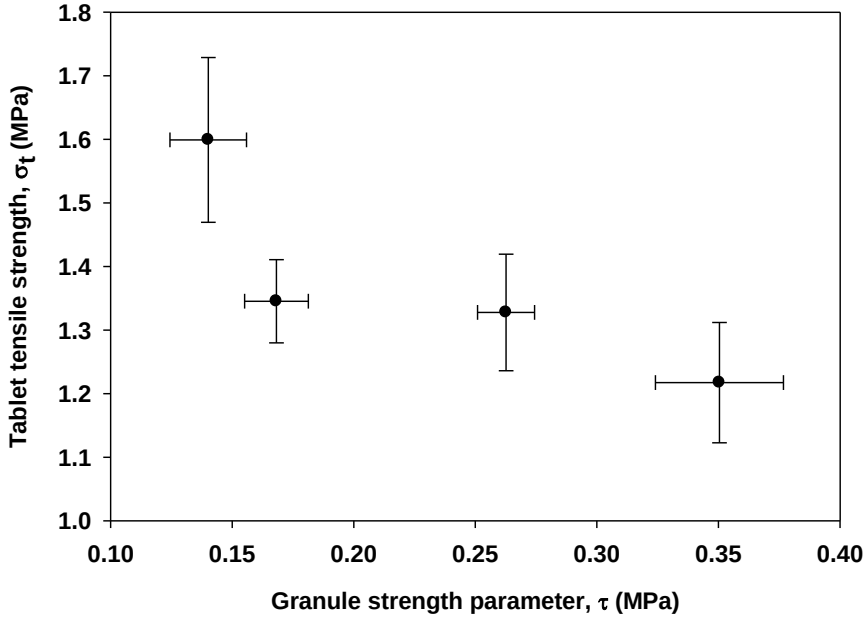
444 **Fig. 4:** Efficacy coefficient as a function of fill factor.

445

446



(a)

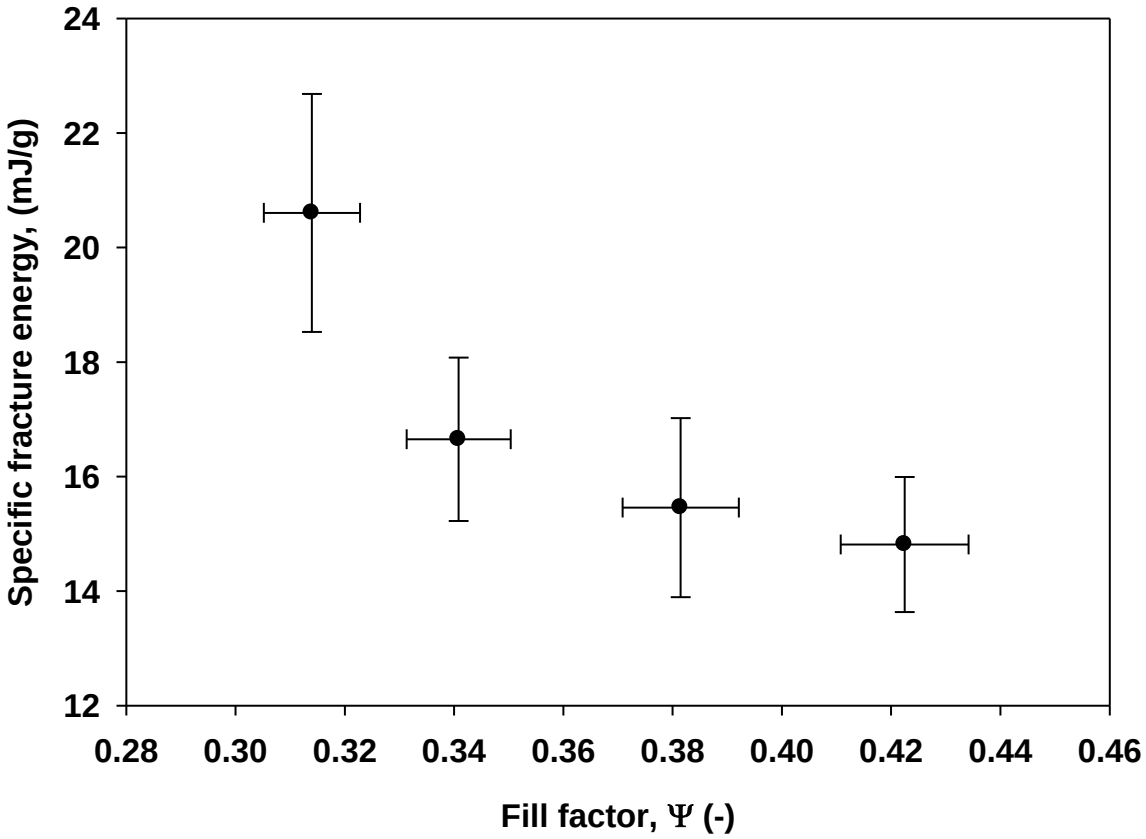


(b)

447

448 **Fig. 5:** (a) Tablet tensile strength as a function of fill factor and (b) correlation between granule and tablet
449 strength.

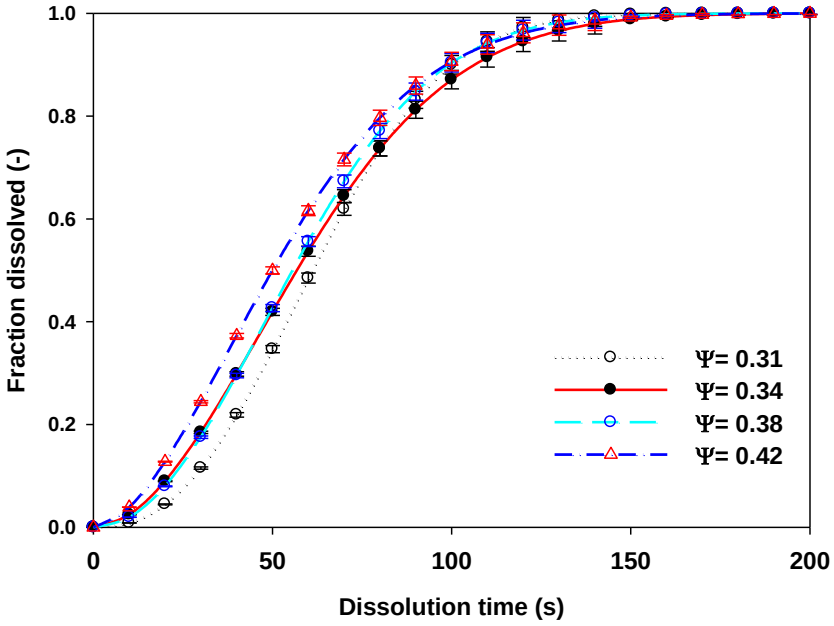
450



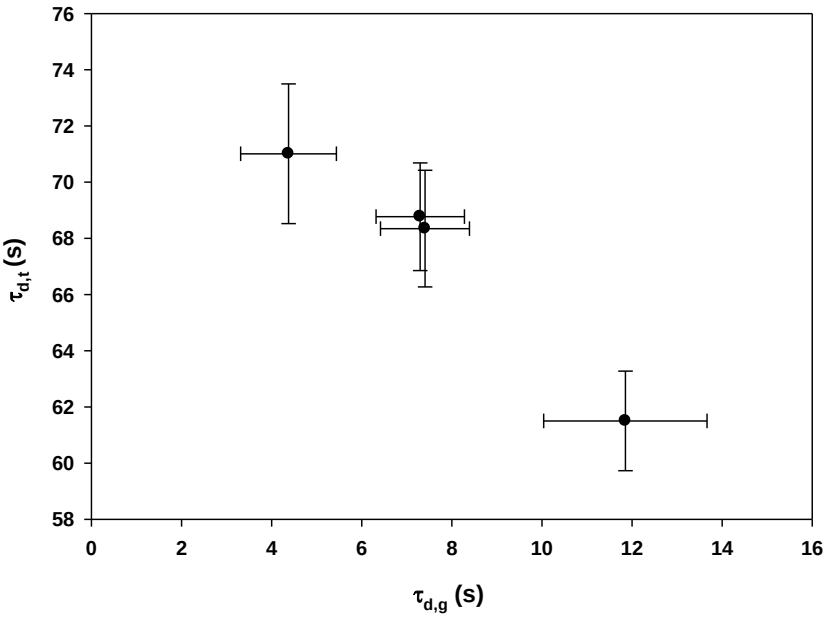
451

452 **Fig. 6:** Specific fracture energy of the tablets as a function of the fill factor

453



(a)



(b)

Fig. 7: (a) Tablet dissolution profiles for fill factor and (b) dissolution time of the tablets vs dissolution time for granules.

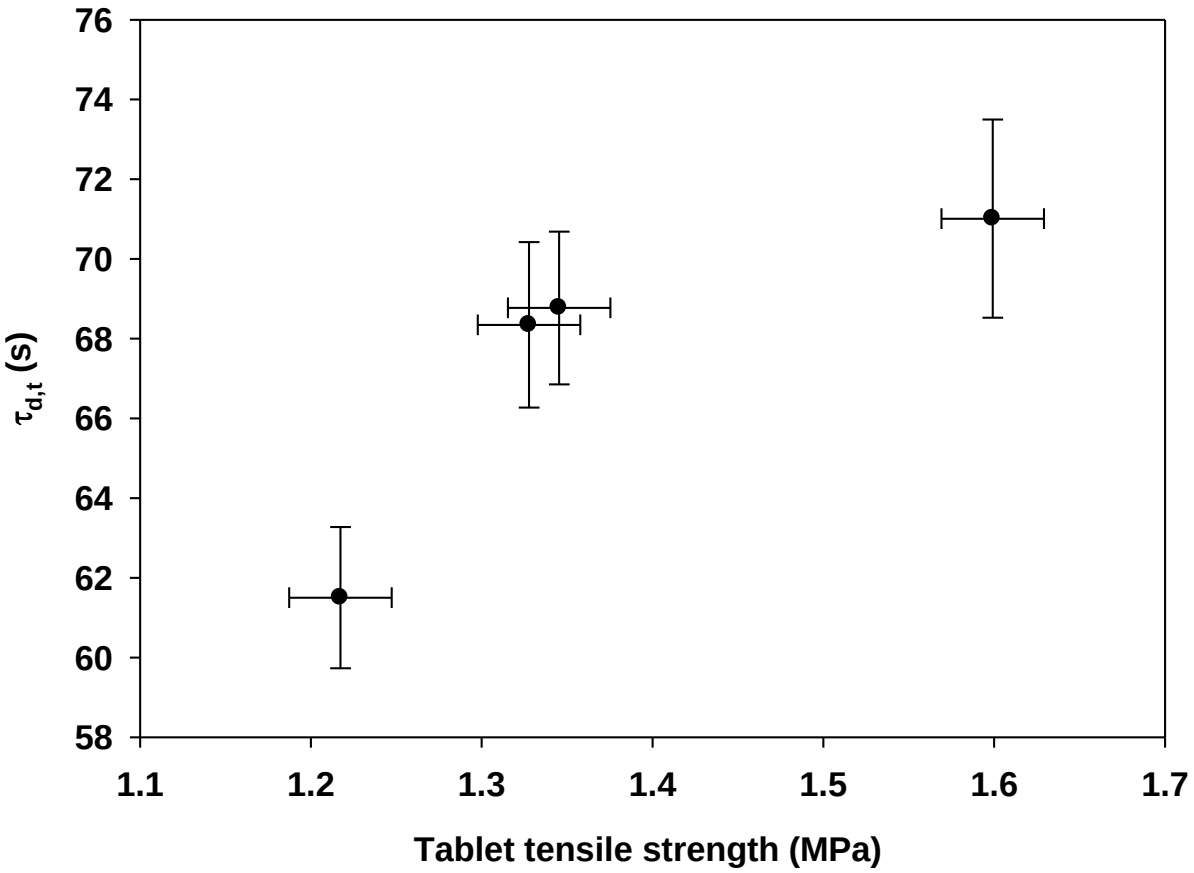
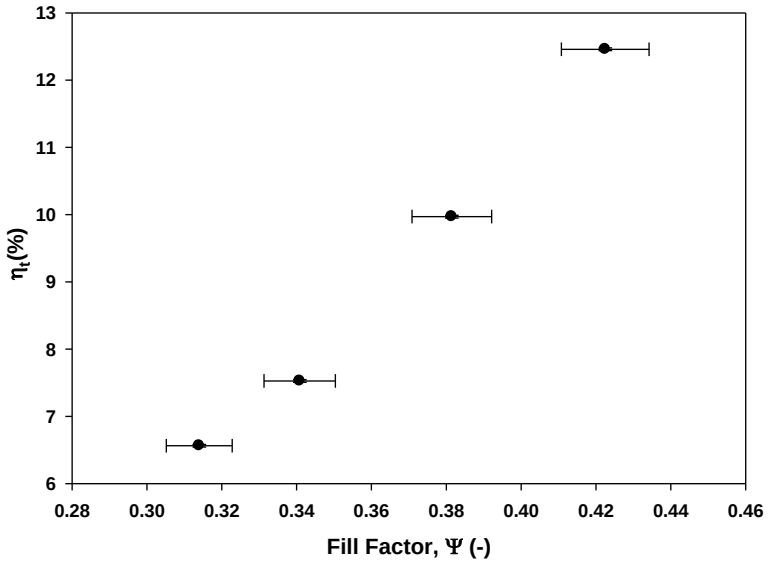
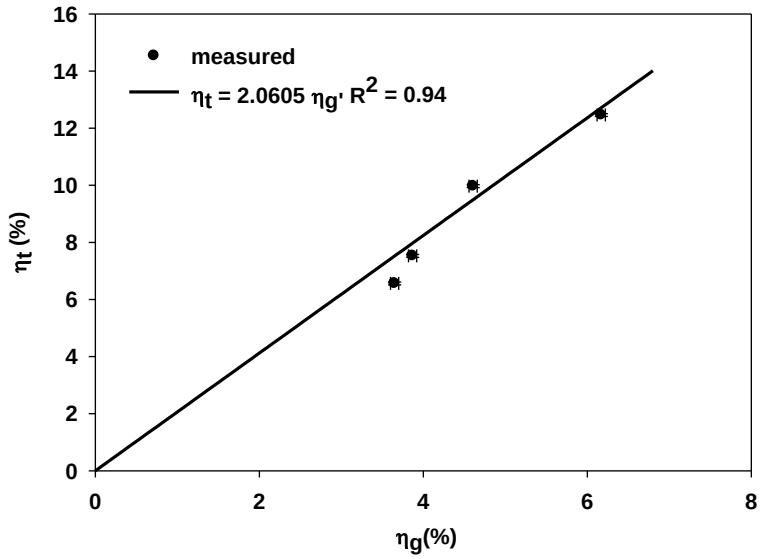


Fig. 8: Correlation between the mean dissolution time and the strength of the tablets.



(a)



(b)

Fig. 9: (a) Coefficient of variation of the tablet non-functional active ingredient content as a function of fill factor and (b) correlation between η_t and η_g.