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

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14

15 **Abstract**

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

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

31

32

## 33 **1. Introduction**

34 High shear wet granulation has been used extensively in the pharmaceutical industrial as a  
35 size enlargement process for granulating feed powders in order to improve their flow characteristics.  
36 Moreover, it has been used in a number industries for the manufacture of different products, e.g.  
37 fertilisers in agro-based industries [2-4], and for the granulation and mixing of metal or powder  
38 oxides such as iron , silica and aluminium in the metal processing industry [5, 6]. The quality of the  
39 granules formed during this process is sensitive to the process conditions as well as the formulation  
40 [1, 7-11]. Several studies have been undertaken to investigate the importance of process variables on  
41 the granule size and size distribution [8, 12-15]. Research on scale-up has focused particularly on  
42 the influence of the size distribution of the product [7, 12, 16-20]. Hassapour et al. [21] and  
43 Rahmanian et al. [22] examined scale-up rules based on constant speed, shear stress and the Froude  
44 number to achieve a target granule strength. It was concluded that a constant tip speed was the most  
45 effective. However, even when using the same granulator, small variations in the size of the batch  
46 can lead to significant differences in the properties of the granules [10, 12, 20, 23-25].

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

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

64           The behaviour of granular solids under compression depends on the mechanical properties of  
65 the granules and this in turn has an effect on the mechanical properties of the tablets formed. A  
66 number of parameters that characterise the compression behaviour were determined (efficacy  
67 coefficient, net compression work and degree of compression), which will be described in the next  
68 section. The objective of this paper was to study the effect of fill factor on the mechanical,  
69 dissolution, and homogeneity of tablets formed from high shear granules. The effects of the fill  
70 factor on the strength and mean dissolution times of tablets formed from the granules were also  
71 measured. Although previous studies have considered the compositional uniformity of tablets [26-  
72 30], the effect of granulation process variables on tablet homogeneity has not been addressed.

## 73   **2.    Materials and Methods**

### 74   **2.1   Production of the granules and tablets**

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

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

$$84 \quad \psi = \frac{m_w}{\rho_w \pi R_B^2 H} \quad \text{Eq (1)}$$

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

$$90 \quad \rho_b = \frac{m}{V} \quad \text{Eq (2)}$$

### 91 **2.1.1 Production of tablets**

92 100 mg tablets were also produced from the granules in the size range 0.5 - 0.6 mm at a  
93 maximum compression force of 5 kN using a universal material tester (Instron model 3555); the  
94 loading and unloading data were stored in a computer. The loading and unloading speeds were both  
95 10 mm/min and the internal diameter of the die was 6.35 mm. The tablets were stored in sealed  
96 plastic bags before their strength and dissolution characteristics were measured. The force –  
97 displacement data was recorded during compression of bed of granules into tablet and was used to  
98 determine the strength of the granules as described in section 2.1.2.

99

100

### 101 **2.1.2 Determination of granule strength**

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

$$105 \quad \ln P = \ln\left(\frac{\tau}{\alpha}\right) + \alpha\varepsilon_n + \ln(1 - e^{-\alpha\varepsilon_n}) \quad \text{Eq (3)}$$

106 where  $P$  is the applied pressure,  $\varepsilon_n$  is the natural strain,  $\alpha$  is a pressure coefficient and  $\tau$  is the  
107 strength parameter which is a measure of the single granule strength. The values of  $\tau$  and  $\alpha$  were  
108 obtained by fitting Eq. (3) to the measured values of  $\ln P$  as a function of  $\varepsilon_n$  using non-linear  
109 regression.  
110

### 111 **2.1.3 Analysis of the granule compaction data**

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

$$114 \quad W_e = \frac{1}{m_b} \int_{\Delta_m}^{\Delta_0} F_{unl}(\Delta) d\Delta \quad \text{Eq (4)}$$

115 where  $F_{unl}(\Delta)$  is the force during unloading,  $m_b$  is the mass of the bed of granules in the die;  $\Delta_0$  and  
116  $\Delta_m$  correspond to the displacement at zero and maximum loading respectively. The net compaction  
117 work,  $W_{net}$ , which represents the energy dissipated, corresponds to the difference between the  
118 integrals of the loading and unloading curves:

$$119 \quad W_{net} = \frac{1}{m_b} \left( \int_0^{\Delta_{max}} F_l(\Delta) d\Delta - W_e \right) \quad \text{Eq (5)}$$

120 where  $F_l(\Delta)$  is the force during loading.  
121

122  
123 The degree of compression was determined from the initial bed height,  $h_0$ , and bed height at  
124 maximum compression pressure,  $h_{\max}$  using [32]:

$$125 \quad C_p = \left( \frac{h_0 - h_{\max}}{h_0} \right) \times 100\% \quad \text{Eq(6)}$$

126  
127 This parameter corresponds to the maximum percent engineering compressive strain.

#### 128 **2.1.4 Tablet tensile strength**

129 The tablets were compressed diametrically at a speed of 2 mm/min, until fracture occurred and  
130 the force-displacement data were automatically logged. A minimum of 10 tablets were measured for  
131 each experimental condition and compact type. The strength of the tablets,  $\sigma_t$ , was calculated from  
132 the maximum load,  $F_{\max}$  and the dimensions of the tablet, i.e. the tablet diameter  $D_t$  and thickness,  $x$   
133 [33, 34]:

$$134 \quad \sigma_t = 2 \frac{F_{\max}}{\pi x D_t} \quad \text{Eq (7)}$$

135  
136 The specific fracture energy required to fracture the tablets,  $W_t$ , was determined from the integral  
137 of the force-displacement curve:

$$138 \quad W_t = \frac{1}{m_t} \int_0^{\delta_{\max}} F(\delta) d\delta \quad \text{Eq (8)}$$

139  
140 where  $F(\delta)$  is the current compressive force,  $\delta$  is the current displacement,  $\delta_{\max}$  is the  
141 displacement corresponding to fracture of the tablet, and  $m_t$  is the mass of the tablet. The fracture  
142 energy was normalised by the mass.

143



### 144 **2.1.5 Efficacy of compression coefficient**

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

$$148 \quad C_{eff} = \frac{W_t}{W_{net}} \times 100\% \quad \text{Eq (9)}$$

149 Values  $> 0.1\%$  are characteristic of an effective conversion of net compression work into cohesion  
150 [36-39]. The strength of the tablets formed during compression is linked to amount of cohesion  
151 between the constituents of the tablet; higher cohesion would result in formation of stronger tablets  
152 whereas lower cohesion would be linked to formation of weaker tablets. Hence efficacy of  
153 compression is of particular interest to this study.

## 155 **2.2 Tablet dissolution**

156 The dissolution of 100 mg tablets in 250 ml distilled water was measured at a temperature of  
157  $37^\circ\text{C}$ . This involved stirring with a paddle at 250 rpm and monitoring the conductivity of the  
158 solution as a function of time using a conductivity meter (Hanna 9000, Hanna Instruments, USA).  
159 The conductivity and temperature data were recorded automatically at 10 s intervals using a  
160 computer. Five repeat measurements were made.

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

$$163 \quad Y = \left( \frac{\chi - \chi_o}{\chi_\infty - \chi_o} \right) \times 100\% \quad \text{Eq (10)}$$

164 where  $\chi$  is the conductivity of the solution at a time  $t$ , and  $\chi_o$  and  $\chi_\infty$  are the initial and final  
165 conductivities ( $\mu\text{S/cm}$ ). The Weibull distribution function was used to describe the data [9, 40].

166

$$167 \quad Y = 1 - \exp \left( - \left( \frac{t - t_0}{\tau_d} \right)^\xi \right) \quad \text{Eq (11)}$$

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

$$171 \quad m_a = \Delta\chi \lambda V_s = (\chi_\infty - \chi_o) \lambda V_s \quad \text{Eq (12)}$$

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

$$177 \quad n_t = \frac{\bar{\sigma}}{\bar{m}_a} \times 100\% \quad \text{Eq( 13)}$$

178 where  $\bar{m}_a$  is the mean value of active ingredient composition in the tablets and  $\bar{\sigma}$  is the standard  
179 deviation of the non-functional active ingredient compositions.  
180

### 181 **2.2.1 Determination of acceptance values**

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

$$186 \quad AV = |M - X| + k\bar{\sigma} \quad \text{Eq ( 14)}$$

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

## 192 **3. Results**

### 193 **3.1 Bulk density**

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

### 199 **3.2 Compression data**

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

204 The increase in strain required to achieve a given compression force as the fill factor  
205 decreases (Fig. 2b) is consistent with data published previously that showed an increase in the  
206 strength, Young's modulus and yield stress with increasing fill factor [1]. This is exemplified in Fig.  
207 3 for the strength, which shows that the strength of the granules approximately doubles for the range  
208 of fill factors examined.

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

### 213 **3.3 Mechanical properties of the tablets**

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

### 222 **3.4 Effect of fill factor on tablet dissolution**

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

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

### 244 **3.5 Effect of batch size on tablet drug homogeneity**

245 The relative standard deviation of the non-functional active ingredient composition in different  
246 tablets produced from granules made with different fill factors is presented in Fig. 9 (a). The  
247 coefficient of variation of the tablet non-functional active ingredient increases with the batch size,  
248 which would result in a similar variation in the active pharmaceutical ingredient (API) composition  
249 for a real pharmaceutical tablet. A similar trend has been found for the dissolution characteristics of  
250 granules [1]. In our previous work [1] the coefficient of variation of the non-functional active  
251 ingredient of samples of granules ( $\eta_g$ ) obtained from different fill factors was determined using the  
252 same procedure described in section 2.5. The coefficient of variation of non-functional ingredient in  
253 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

273

## 274 **5. Conclusion**

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

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400

401 **List of Tables.**

402

403 Table 1: Summary of non-functional active ingredient composition, acceptance values for tablets from  
404 different batch sizes

405

406 **List of figures**

407

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

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

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

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

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

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

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

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

419 **Fig. 9:** (a) Coefficient of variation of the tablet non-functional active ingredient content as a  
420 function of fill factor and (b) correlation between  $\eta_t$  and  $\eta_g$ .

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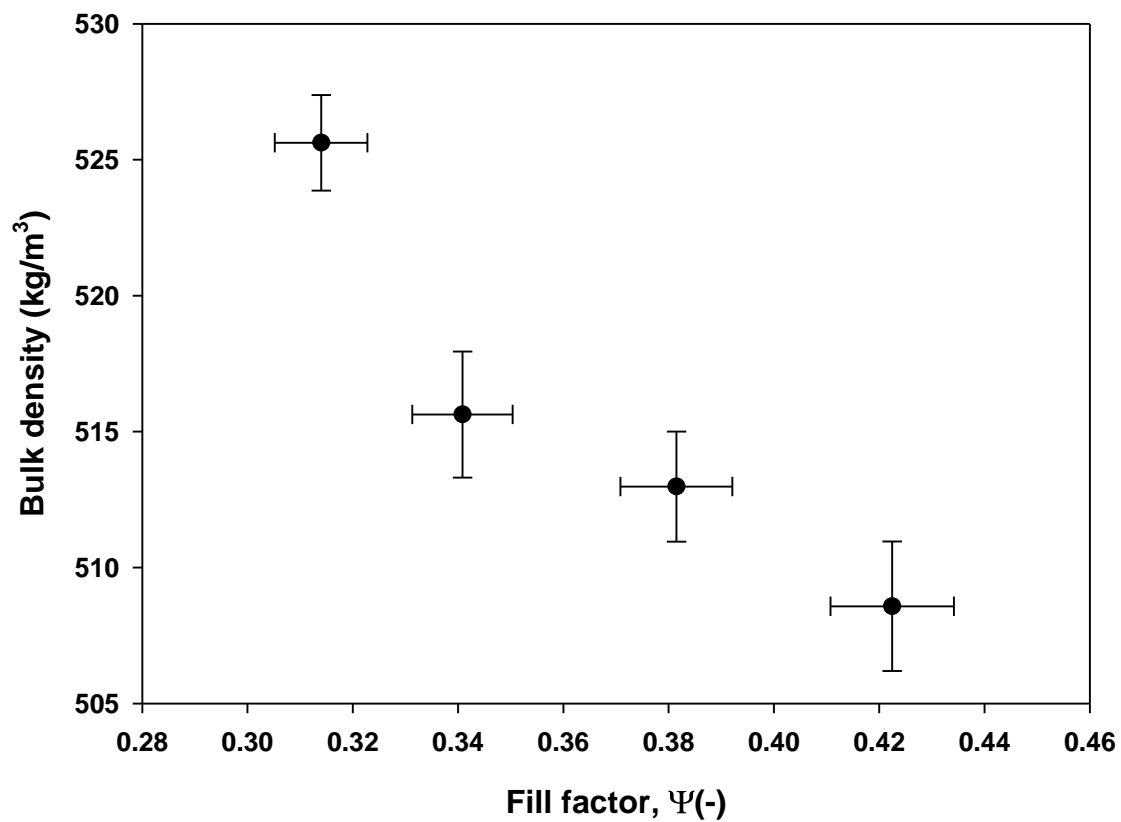
426 **Table 1:** Summary of non-functional active ingredient composition, acceptance values for tablets from  
427 different batch sizes.

Fill factor (-)	Average composition $\bar{m}_{ai,tab}$ (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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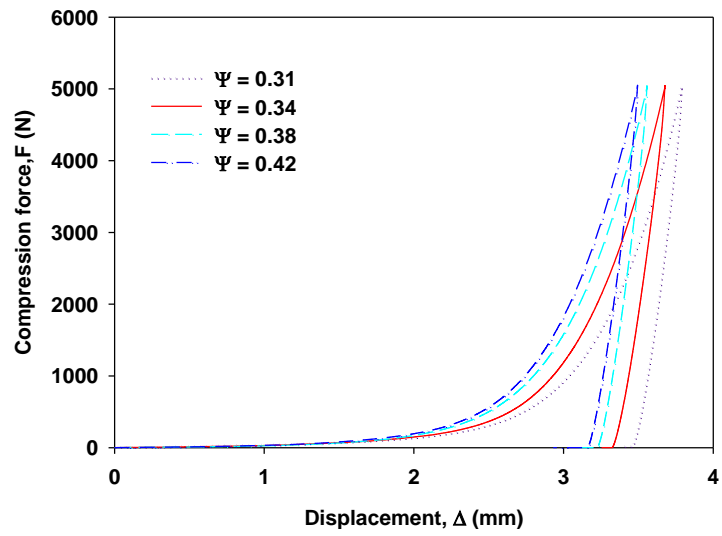
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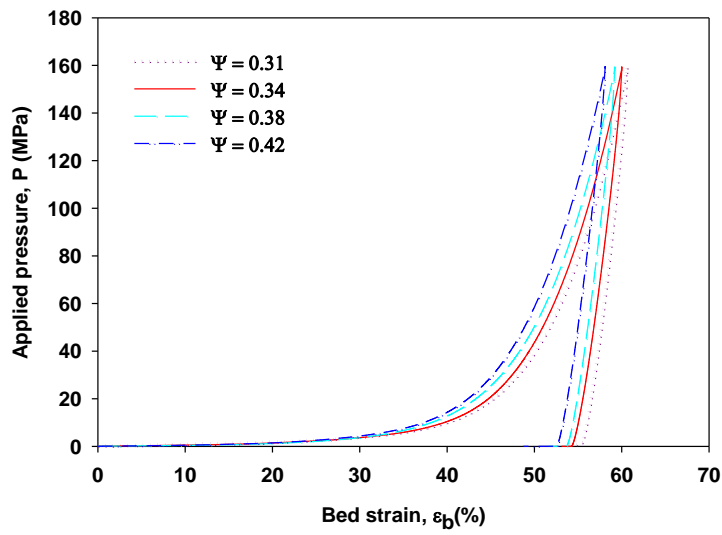
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432 **Fig. 1:** Bulk density of the granules in the size range 0.5 - 0.6 mm.

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(a)



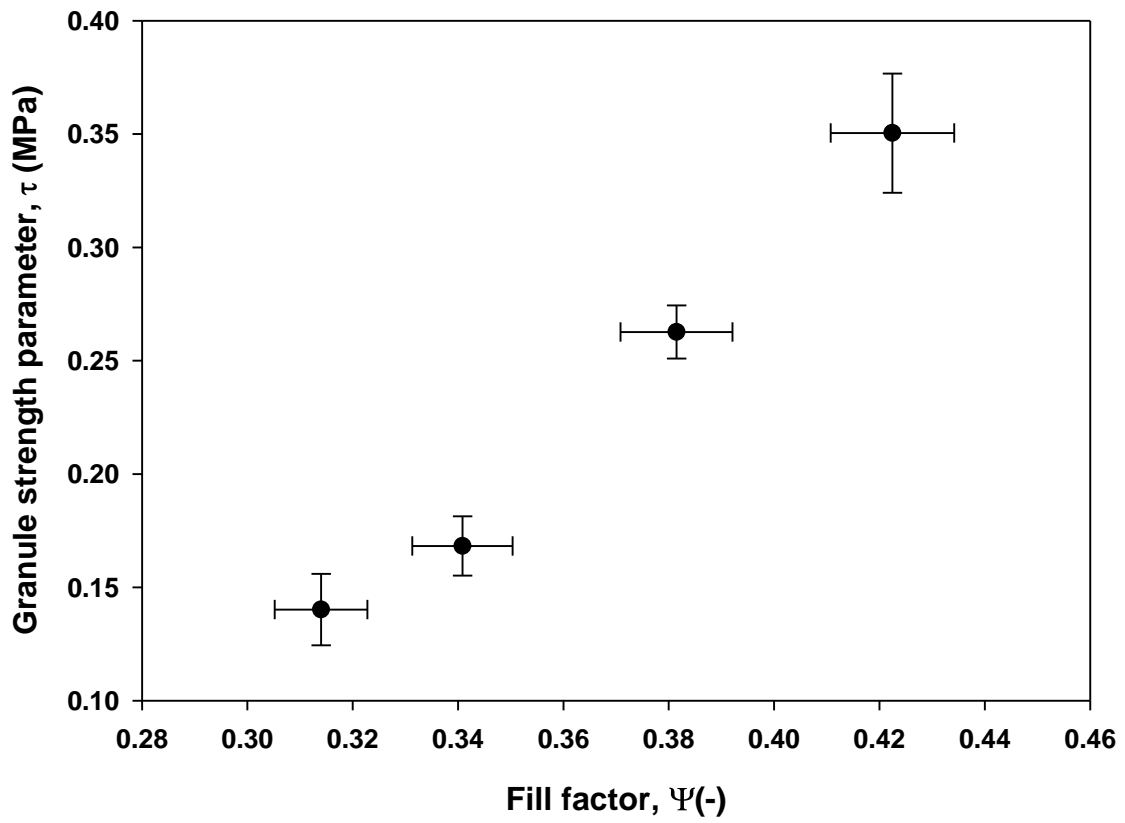
(b)

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

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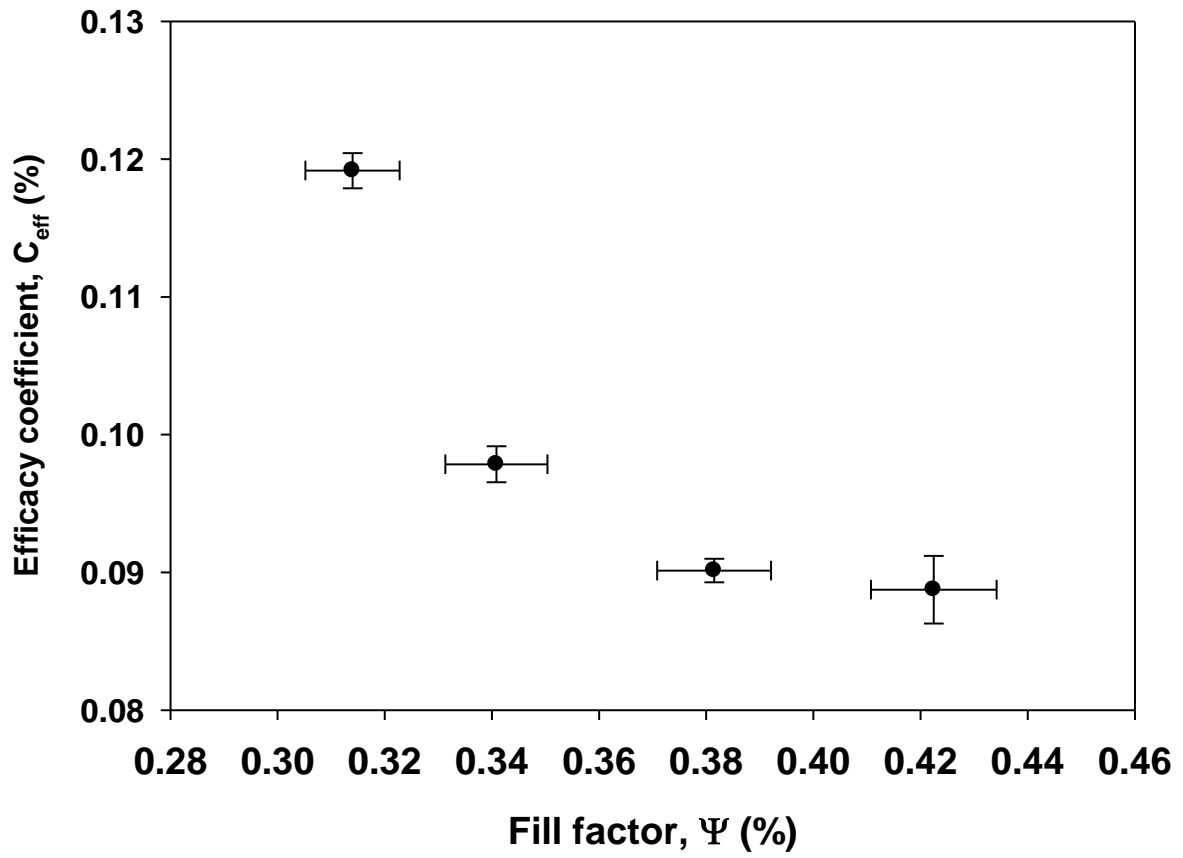
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440 **Fig. 3:** Effect of fill factor on granule strength parameter.

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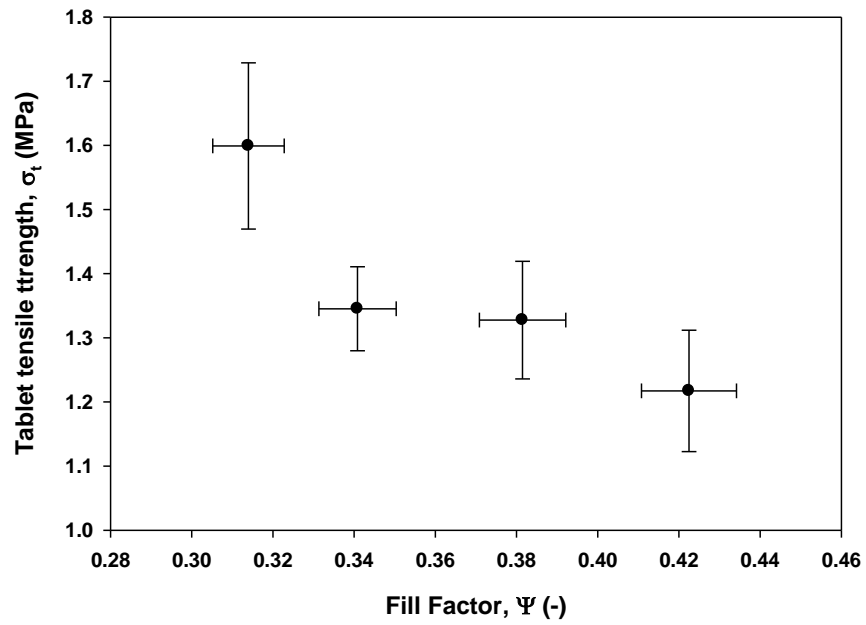
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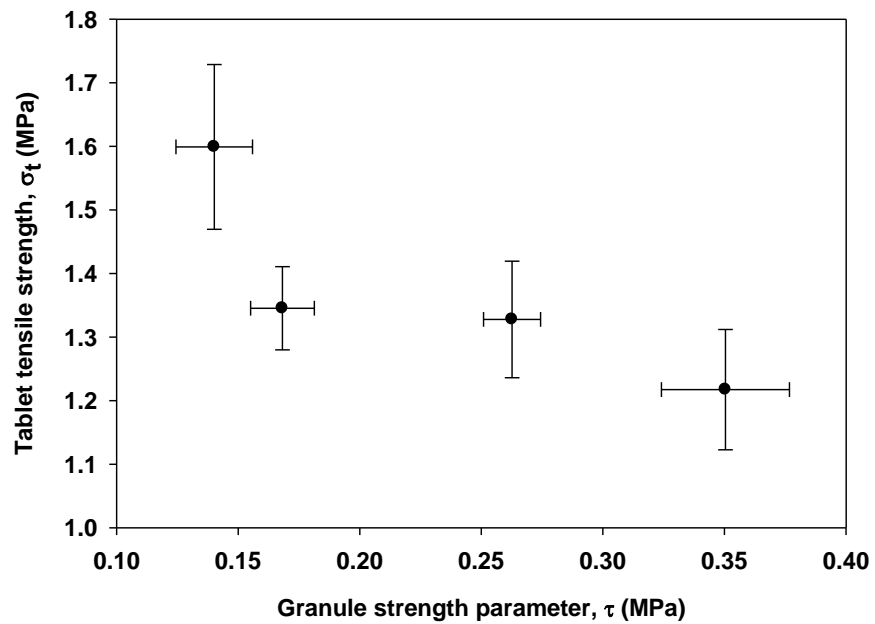
444 **Fig. 4:** Efficacy coefficient as a function of fill factor.

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(a)

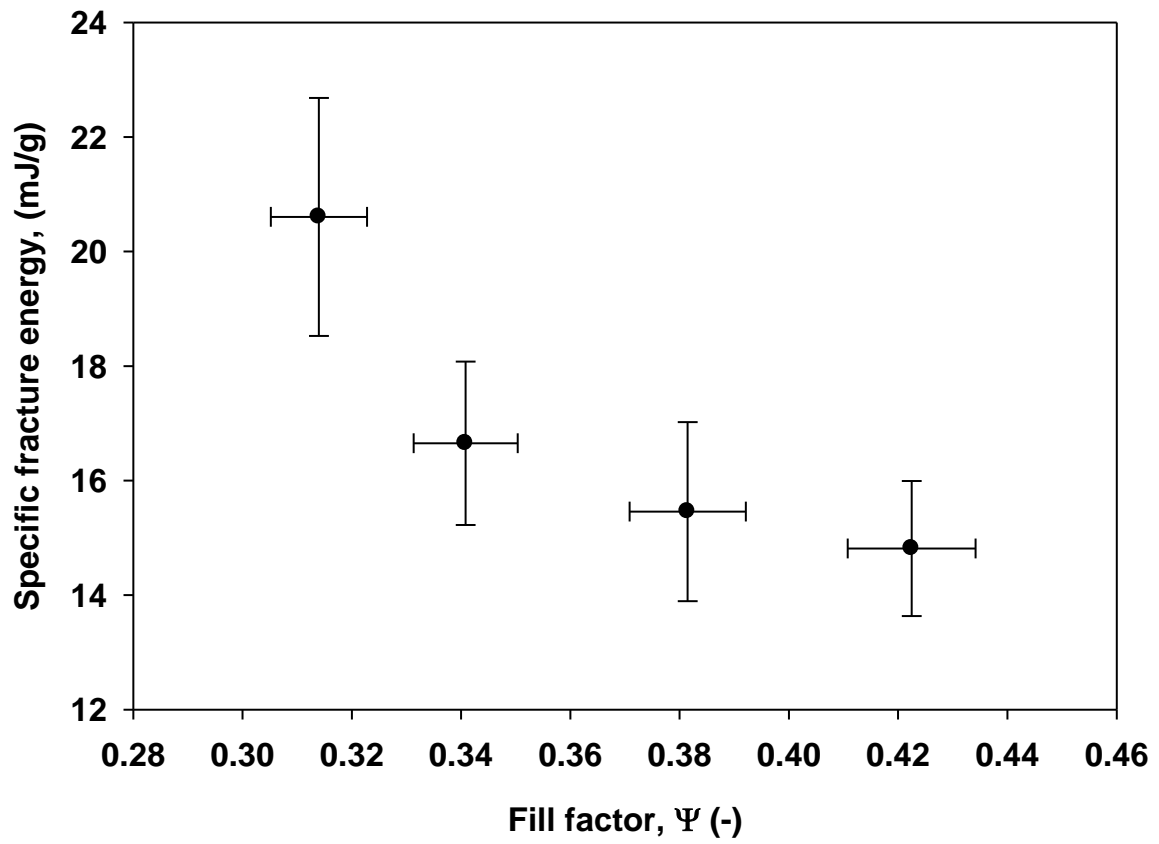


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448 **Fig. 5:** (a) Tablet tensile strength as a function of fill factor and (b) correlation between granule and tablet  
449 strength.

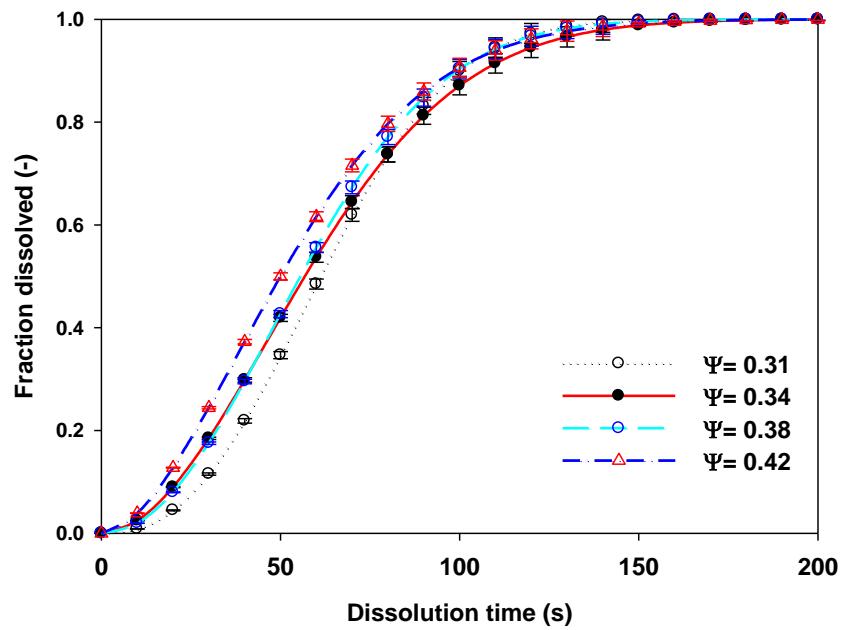




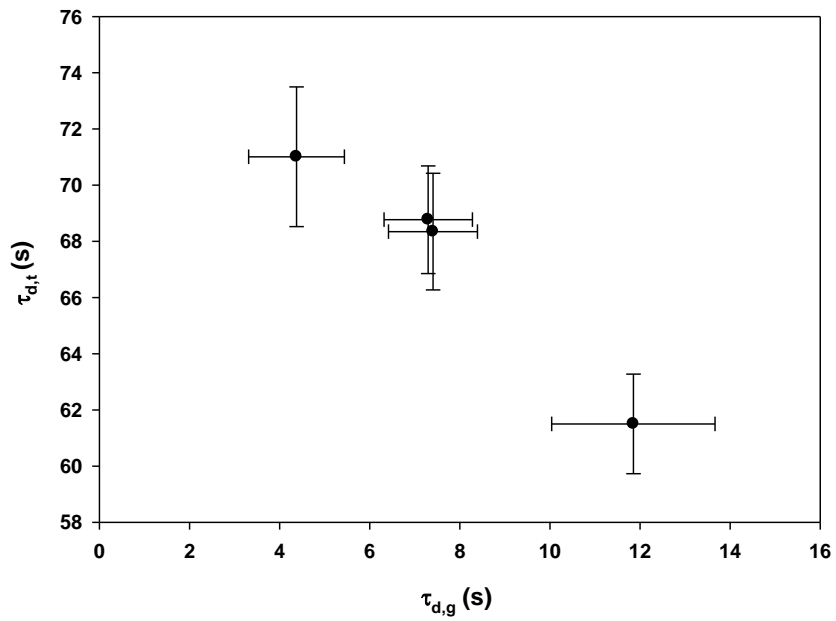
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452 **Fig. 6:** Specific fracture energy of the tablets as a function of the fill factor

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(a)

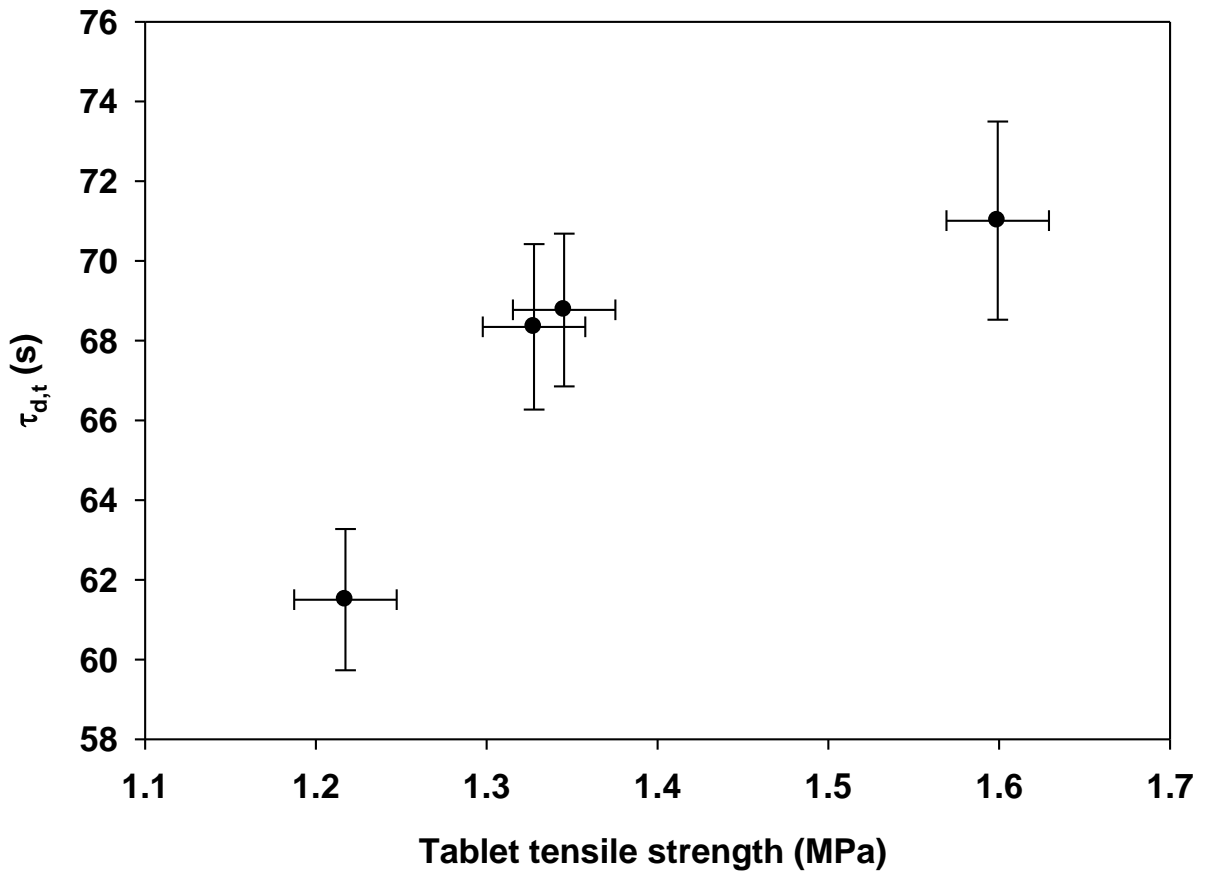


(b)

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

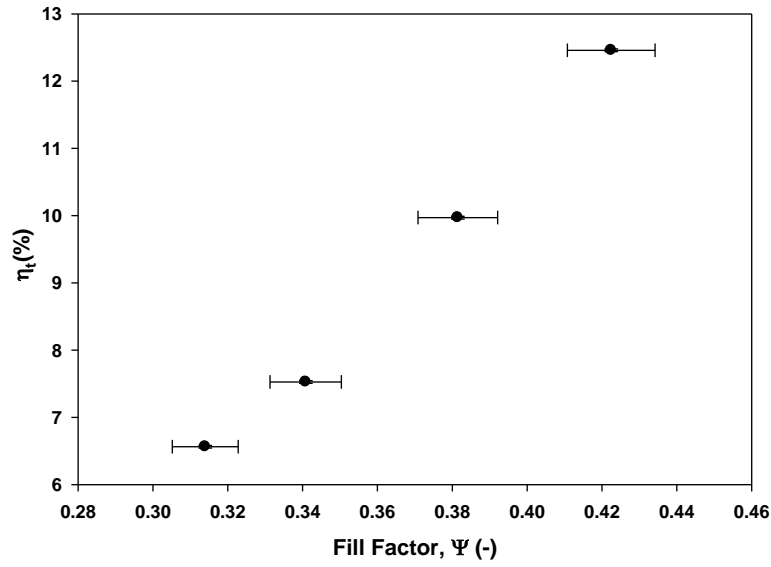
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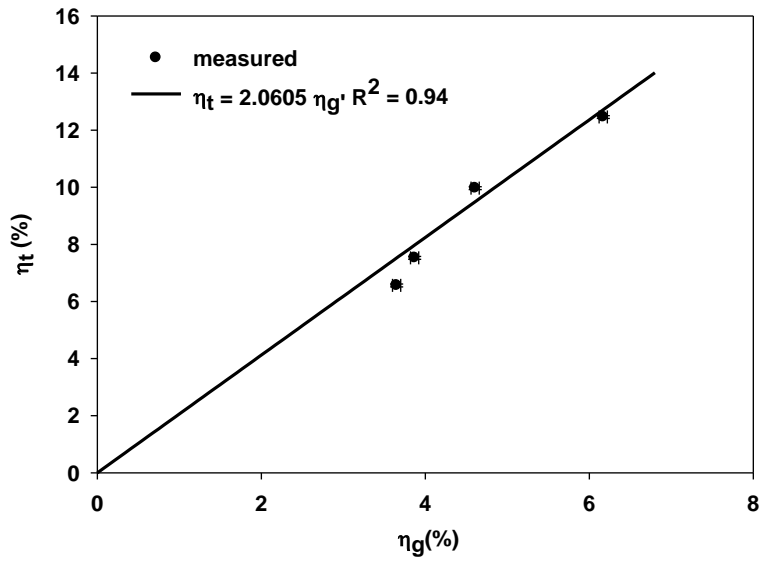
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(a)



(b)

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