

1 **Comparative study on the rheological properties and tablettability of various APIs**  
2 **and their composites with titatane nanotubes**

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## 18 **1. Introduction**

19 Titanate nanotubes (TNT) are newly explored and promising nanomaterials for a wide  
20 range of medical applications. Among others, they show aptness to be used as  
21 radiosensitizer agents in radiotherapy [1], biocompatible biosensors [2] or cell viability  
22 and proliferation enhancing materials for orthopaedic and periodontal use [3, 4].  
23 Besides, TNTs proved their capacity of being loaded with various active pharmaceutical  
24 ingredients (API) and therefore came into focus of pharmaceutical research as carrier  
25 materials [5, 6].  
26 Based on the experimental results, drug loaded TNTs may provide development in  
27 many issues of pharmaceutical sciences. On the one hand, TNTs carrying nano-sized  
28 APIs may overcome fundamental difficulties related to the formulation and  
29 manufacturing of nanocrystalline active substances, which may show an unavoidable  
30 tendency to autoaggregation, thereby worsening their physicochemical properties and  
31 setting a limit to their commercialization. On the other hand, TNTs show an ability to  
32 achieve targeted drug delivery and controlled drug release, offering to put new and  
33 modern medical therapies into practice [7, 8]. From this aspect, the outstanding  
34 mechanical properties of TNTs may help to overcome formulation problems of other  
35 nanocarriers such as dendrimers, micelles, liposomes, etc., which are available on the  
36 market, but their large-scale manufacturing, stabilization as well as their processing into  
37 solid dosage forms require great efforts [9]. The present study aims to investigate the  
38 suitability of hydrothermally synthesized TNTs for the improvement of the processing  
39 of nano-sized APIs into solid dosage forms with direct compression method.  
40 The structure of a tablet is influenced by many parameters, such as the physicochemical  
41 properties of the compressed materials, the type of the tablet press, the applied

42 compression force, etc. [10]. When focusing on the materials, the understanding of the  
43 behaviour of the compressed substances is essential for the commercial scale  
44 manufacturing of tablets. In order to reveal the tablettability of hydrothermally  
45 synthesized TNTs and estimate their influence on the rheological properties of APIs,  
46 which is a completely new field in pharmaceutical research, a competitive study was  
47 performed involving four APIs and their 1:1 ratio composites formed with TNTs. By  
48 using an instrumented tableting machine, the monitoring of the compression cycle is  
49 feasible and with the help of statistical models flowability, particle rearrangement and  
50 compressibility of the compressed materials are possible to be determined [11, 12]. In  
51 the present study the Kawakita-Lüdde and Walker compression models were applied to  
52 estimate the compressibility characteristics and the deformation mechanism of the API  
53 and API-TNT composite containing powder mixtures. The widely used Kawakita-  
54 Lüdde model [13] describes the volume reduction of the powder at a given compression  
55 pressure as a function of the pressure and therefore makes the analysis of particle  
56 rearrangement and compactibility possible. However, it does not give much information  
57 about the deformation mechanism of the powders, thus it is necessary to complement  
58 the analysis with another model. The Walker model [14], which expresses the volume  
59 reduction corresponding to a one-decade change in pressure, allows the characterisation  
60 of powder compressibility and therefore completes the Kawakita equation perfectly.  
61 Although the calculated parameters can serve to predict the post-compressional  
62 properties, tablets were investigated thoroughly in order to better understand the effects  
63 of TNT composite formation on tablet properties.

64

## 65 **2. Materials and methods**

### 66 2.1. Materials

67 Diltiazem hydrochloride (DiltHCl), diclofenac sodium (DicNa), atenolol (ATN) and  
68 hydrochlorothiazide (HCT) were kindly supported by Sanofi-Aventis PLC, Egis  
69 Pharmaceuticals PLC, TEVA Pharmaceuticals PLC and Gedeon Richter PLC,  
70 respectively. The following 1:1 ratio of active pharmaceutical ingredient (API)-  
71 hydrothermally synthesized titanate nanotube (TNT) composites were produced by the  
72 University of Szeged, Department of Applied and Environmental Chemistry: diltiazem  
73 hydrochloride-TNT (DiltTi), diclofenac sodium-TNT (DicTi), atenolol-TNT (ATNTi),  
74 hydrochlorothiazide-TNT (HCTTi). Excipients for tableting were Avicel PH 112 (FMC  
75 Biopolymer Inc., USA), Tablettose 70 (Meggle Pharma GbbH, Germany), talc and  
76 magnesium stearate.

77

## 78 2.2. Preformulation study

79 The flowing properties of the APIs and the API-TNT composites were examined by a  
80 software-controlled PTG-1 (Pharma Test Apparatebau AG, Germany) powder  
81 rheological tester. A stainless-steel funnel with a 10-mm-diameter outlet nozzle was  
82 filled with 100 ml of bulk powder and the powder flow was detected by IR sensors. The  
83 equipment measured the flow time and calculated the angle of repose of the powder  
84 heap.

85 Densification studies were performed for the APIs and the composites with a STAV  
86 2003 Stampfvolumeter (Engelsmann AG., Germany). 250 ml of powder was put into a  
87 graduated cylinder taking care that the powder does not pack. This volume served to  
88 calculate the bulk density. The powder in the cylinder was mechanically tapped by the  
89 apparatus at a speed of 1/sec until no further decrease in volume could be observed or  
90 until tap number 1250 was reached. The volume of the densified powder was used to

91 calculate the tap density. The Hausner Ratio (Eq. (1)) and Compressibility Index (Eq.  
92 (2)) values of the samples were determined as follows:

$$93 \text{ Hausner Ratio} = \frac{\rho T}{\rho B} \quad (1)$$

$$94 \text{ Compressibility Index} = [(\rho T - \rho B) / \rho T] * 100(\%) \quad (2)$$

95 where  $\rho T$  is the tap density and  $\rho B$  is the bulk density of the powder in  $\text{g/cm}^3$ . The

96 evaluation of the results was based on the USP scale of flowability [15].

97 **In order to determine the porosity of the APIs and the composites, the pycnometric**  
98 **volume of the powders was measured with a Quantachrome Helium**  
99 **Multipycnometer (Quantachrome GmbH, Germany). The porosity was calculated**  
100 **by applying Eq. (3):**

$$101 \epsilon = [1 - (\rho B / \rho P)] * 100 \quad (3)$$

102 where  $\epsilon$  is the porosity (%),  $\rho T$  is the bulk density and  $\rho P$  is the pycnometric  
103 density of the powder in  $\text{g/cm}^3$ .

104

### 105 2.3. Tableting

106 Tablets containing APIs and API-TNT composites were formulated. The compositions  
107 of the tablets **displayed in Table 1. were designed for constant tablet weight (300**  
108 **mg) and quantity of API (50 mg) in order to respect the therapeutic goals and be**  
109 **able to compare the API and API-TNT tablets according to the pharmaceutical**  
110 **requirements.**

111 The powders were mixed with a Turbula (Willy A. Bachofen Maschienenfabrik,

112 Switzerland) mixer at 50 rpm for 8 minutes without magnesium-stearate and for 2

113 minutes more with it. The weight of the tablets was designed to be about 300 mg. The  
114 tablets were produced by the direct compression method with a Korsch EK0 (E. Korsch  
115 Maschinenfabrik GmbH, Germany) eccentric tablet press, instrumented with strain  
116 gauges and a displacement transducer. 10-mm-diameter flat punches were applied with  
117 a compression force of 5.0, 7.5, 10.0, 12.5 and 15.0 kN for all the compositions.

118

#### 119 2.4. Compaction properties

120 The compaction properties of the powder mixtures (Table 1.) were estimated according  
121 to the out-of-the-die method using the Kawakita and Walker models.

122 The Kawakita equation (Eq. (4)) was used to study the particle rearrangement of the  
123 powder mixtures during the compression:

$$124 \quad P/C = P/a + 1/ab \quad (4)$$

125 where  $P$  is the applied pressure **in MPa**,  $C$  is the degree of the volume reduction and  $a$   
126 and  $b$  are constants. The degree of volume reduction is expressed by Eq. (5):

$$127 \quad C = (V_0 - V)/V_0 \quad (5)$$

128 where  $V_0$  is the initial volume of the powder bed and  $V$  is the volume of the powder bed  
129 at the applied pressure **in mm<sup>3</sup>**.

130 Constant  $a$  gives an indication of the initial porosity of the sample. Its higher value

131 presumes the loose packing of the powder in the die before compression. Constant  $1/b$

132 describes the pressure which is needed to reduce the powder bed volume by 50%.

133 Higher coefficient  $1/b$  implies higher cohesive energy of interaction, which shows up as  
134 a hindered particle rearrangement.

135 The compressibility of the powder mixtures was investigated using the Walker (1923)  
136 equations (Eq. (6) and (7)):

$$137 \quad \log P = -LV + C_1 \quad (6)$$

138  $100V = -W \log P + C$  (7)

139 where  $P$  is the applied pressure **in MPa**,  $L$  is the pressing modulus which reflects the  
140 volume reduction at a given pressure,  $V$  is the relative volume,  $W$  is the Walker  
141 coefficient which gives information about the volume reduction corresponding to one-  
142 decade change in the pressure, and  $C$  and  $C_1$  are constants. The relative volume is  
143 expressed by Eq. (8):

144  $V'/V_0$  (8)

145 where  $V'$  is the volume at the applied pressure and  $V_0$  is the initial volume of the powder  
146 bed **in mm<sup>3</sup>**.

147

#### 148 2.5. Post-compressional properties

149 The mass, the thickness and the diameter of the prepared tablets were investigated with  
150 a Kraemer UTS-50 (Charles Ischi AG, Switzerland) tablet testing system right after the  
151 production and one week later in order to follow the changes in the geometrical  
152 parameters. 20 numbered tablets of each composition and compression force were  
153 characterized. The parameters above served to calculate the apparent density of the  
154 tablets. **In addition to the apparent density, the study was completed with**  
155 **pycnometric density measurements allowing the determination of tablet porosity**  
156 **(see the applied method under Section 2.2.)**

157 The breaking strength of the tablets was studied with a Heberlein 2E/205 tablet hardness  
158 tester (Heberlein AG, Switzerland), measuring 10 tablets per composition per  
159 compression pressure. In addition, the tensile strength of the tablets was calculated  
160 using the following equation (Eq. (9)):

161  $\sigma = 2F/(\pi * d * h)$  (9)

162 where  $\sigma$  is the tensile strength in N,  $F$  is the breaking force in N,  $d$  is the diameter and  $h$   
163 is the height of the tablet in mm.

164 **The texture of the prepared tablets was studied by taking Scanning Electron**  
165 **Micrographs of the surface, while their breaking surface was examined with a**  
166 **Hitachi S4700 (Hitachi Ltd., Japan) scanning electron microscope. The tablets**  
167 **were stuck to a double-sided carbon adhesive tape and a conductive golden layer**  
168 **was deployed with the use a sputter apparatus (Polaron Ltd., UK). The**  
169 **measurements were performed at a magnification of 100-500, applying 10.0 kV of**  
170 **electron energy and 1.3-13 MPa of air pressure.**

171 The disintegration of the prepared tablets was investigated in distilled water with an  
172 Erweka ZT71 (Erweka GmbH, Germany) disintegration tester apparatus according to  
173 the criteria of the Eur. Pharmacopoeia [16].

174 **The drug release from the tablets was determined by an Erweka DT700 (Erweka**  
175 **GmbH, Germany) dissolution tester, using the USP II method [17]. The dissolution**  
176 **was tested at 37 °C, with pH 6.8 phosphate buffer as a dissolution medium. The 5-**  
177 **ml aliquots were taken after 3, 5, 10, 15, 30, 60, 90, 120 minutes. The dissolved**  
178 **drug ( $\mu\text{g/ml}$ ) was defined with a ThermoScientific GENESYS 10S UV-VIS**  
179 **spectrophotometer (Thermo Fisher Scientific Ltd., USA).**

180

### 181 **3. Results and discussion**

#### 182 3.1. Preformulational properties of the APIs and the API-TNT composites

183 Within the preformulation studies, the determination of the flow properties, the Hausner  
184 Ratio and Compressibility Index values **and the porosity** of the samples was put into  
185 focus (Table 2.). The results showed uniformity in that the composites displayed



186 preferable flow properties compared to the pure APIs, irrespective of the incorporated  
187 API.

188 The measurements revealed that the APIs have extremely poor flow properties. In  
189 contrast, favourable flowability was observed for the pure TNTs. As concerns the  
190 composites, the results are not consonant, the incorporation of DiltHCl and DicNa  
191 induced better (measurable) flow time, while the composite formation of ATN and HCT  
192 did not result in measurable flow time. This can be explained by the partially feasible  
193 incorporation of ATN and HCT into TNTs [18]. Therefore, as ATNTi and HCTTi  
194 products contain individual API crystals, the flowability improving effect of TNTs  
195 decreases or completely lags behind.

196 The investigation of the particle rearrangement revealed an exponential-type  
197 rearrangement profile for all the samples (**Fig.1**). Regarding the calculated Hausner  
198 Ratio and Compressibility Index values, it is clearly visible that all the APIs reached an  
199 upper range of the USP scale of flowability [15] by the incorporation. The flowability of  
200 the composites varies between those of the component materials, which was expected  
201 based on the fact that the APIs are located not only in the inner parts of TNTs but on  
202 their surface as well [18]. The rate of the flowability improvement probably depends on  
203 the ratio of the surface coverage.

204 **The results of the pycnometric volume measurements confirmed that TNTs possess**  
205 **notably high pycnometric density and high porosity, which was expected due to the**  
206 **tubular structure and the great number of interparticular pores between the**  
207 **nanosized particles. Accordingly, the porosity of the composites is also greater than**  
208 **that of the pure APIs: this phenomenon was more expressed for DiltTi and DicTi,**  
209 **where the drug incorporation was complete, and less (or not) expressed for the**  
210 **partially incorporated ATNTi and HCTTi products. It is also notable that HCTTi,**

211 **where TNTs are attached to the surface of the HCT particles [18], exhibits slightly**  
212 **decreased porosity, which may be due to the decreasing number of interparticular**  
213 **pores.**

214

215 3.2. Compaction properties of the API and API-TNT containing powder mixtures

216 **The tablettability of the powder mixtures was thoroughly investigated by using an**  
217 **instrumented tablet press.**

218 **Knowing the degree of volume reduction under pressure, the** particle rearrangement  
219 of the powder mixtures was studied by using the Kawakita model. The results of the  
220 analysis were plotted; the graphs of the DiltHCl and DiltTi tablets are presented in Fig.  
221 2. The data fit the Kawakita model well with a  $R^2$  being at least 0.998. Constants  $a$  and  
222  $1/b$ , which were obtained from the graphs, are displayed in Table 3.

223 The values of constant  $a$ , which give information about the rearrangement of the  
224 powders, are very similar for all the samples. Although the preformulation studies  
225 presumed lower constant  $a$  values for the composite containing compositions, no  
226 remarkable differences could be noticed either between the four API tablet  
227 compositions or between the API and the related API-TNT tablet compositions. This  
228 result confirms the selection of an appropriate excipient profile for the tablets, resulting  
229 in powder mixtures with nearly the same flow properties. However, the fact that the  
230 compositions of the composites contain proportionally less excipient than those of the  
231 APIs implies the better flowability of the composites.

232 The values of constant  $1/b$ , which correlate with the cohesiveness, showed important  
233 differences between the API and API-TNT tablet compositions. Based on the several  
234 times higher  $1/b$  values of the composite containing powders, it is clear that the  
235 composite content requires much higher energy to reduce the volume of the powder to

236 half of the original. The low  $l/b$  values can be explained by the fast collapse of the  
237 powders in the die, supporting our visual observations made during the preformulation  
238 studies. In contrast, powders with a high  $l/b$  value exhibit continuous densification  
239 under increasing load. It can be seen that the relation between the value of constant  $a$  of  
240 the HCT and the HCTTi tablet compositions is different, and the HCTTi containing  
241 powder mixtures have a lower  $l/b$  value than the HCT tablet composition. In order to  
242 make this exceptional behaviour clear, the structural properties of the HCTTi product  
243 have to be taken into consideration. As it was already mentioned, the incorporation of  
244 HCT into TNTs was not completely successful, resulting in a product which, besides the  
245 aggregated composites, contains HCT crystals covered with TNTs [18]. Owing to the  
246 surface coverage, the HCTTi product displays higher surface free energy than the pure  
247 HCT, therefore it shows superior adhesivity as well. For this reason, instead of  
248 improving compactibility, the HCTTi product generates an unfavourable particle  
249 rearrangement, showing an even worse compactibility profile than the pure API itself.  
250 The compressibility of the compositions was examined by applying the Walker model.  
251 From the plotted graphs (the graphs of DiltHCl and DiltTi tablets are shown in Fig. 3  
252 and 4) coefficients  $L$  and  $W$  were defined. The data are presented in Table 3.  
253 According to the results, coefficient  $L$ , also called pressing modulus, appeared to be  
254 lower for the composite containing compositions, reflecting their higher volume  
255 reduction at a given pressure compared to the tablet compositions containing pure API.  
256 This behaviour is supported by the preformulation studies, during which the composites  
257 revealed higher density than the APIs, and also by the fact that the composite formation  
258 results in smaller surface free energy [18]. The results of HCT and HCTTi tablet  
259 powder mixtures showed up again oppositely, thus the HCTTi containing composition

260 displayed a higher coefficient  $L$  value. This result is in perfect accordance with our  
261 conception described above.

262 The obtained Walker coefficient values, which refer to the irreversible compressibility  
263 of the powders, correspond with the results discussed so far. The higher values of  
264 coefficient  $W$  shown by the composite containing compositions hint at plastic  
265 deformation and better tableting properties. In contrast, the smaller  $W$  values of tablet  
266 compositions containing pure API mark an extended densification maximum due to the  
267 high elastic recovery of the crystalline APIs. In this case again, the HCTTi composite  
268 containing powder mixture showed opposing behaviour as compared to the other API-  
269 TNT tablet compositions, confirming the above-mentioned negative effect of the  
270 unsuccessful composite formation.

271 Overall, it can be concluded that the incorporation of drugs into TNTs is advantageous  
272 and results in more ideal compaction behaviour. However, it is also important to remark  
273 that a partially successful composite formation may affect the compaction properties  
274 negatively, therefore the appropriate incorporation process plays a key role in this issue.

275

### 276 3.3. Post-compressional properties of the API and API-TNT tablets

277 The measurements of the geometric parameters allowed us to define the apparent  
278 density of the tablets right after the compression and one week later as well. The results  
279 are summarized in Table 4.

280 Based on the data, it can be stated that the tablet density generally increases with the  
281 compression force. The only exception was shown by the ATN tablets, where the  
282 density measured right after compression decreased with the increase of the  
283 compression force. This phenomenon can be explained by the strong elasticity of ATN,  
284 which results in a rising elastic recovery with the increase of the compression force.

285 This conception is supported by the low value of coefficient  $W$  received from the  
286 Walker analysis (Table 3.). **Nevertheless, the density values measured after one-**  
287 **week storage show that the bonds in the ATN containing tablets undergo a**  
288 **considerably high consolidation during the first period of storage, which may also**  
289 **be observed in the case of other elastic systems [19].** It is also noteworthy that this  
290 phenomenon did not appear for the ATNTi tablets, which shows the positive effect of  
291 TNTs on elastic recovery.

292 It can also be established from the data that the apparent density of the API-TNT tablets  
293 is higher than that of the API tablets for all the investigated compression forces.  
294 However, in the case of DicNa and DicTi tablets this statement is relevant only at higher  
295 compression forces, which supports the good rearrangement and compressibility  
296 properties of DicNa seen in Table 3. Nevertheless, it can be concluded that the presence  
297 of TNTs generally increases the apparent tablet density.

298 It is also necessary to consider the post-compressional apparent density changes as they  
299 can provide further information about the processability of the APIs and their  
300 composites. The density of the DiltHCl tablets decreased in time at each compression  
301 force, while the density of the DicNa, ATN and HCT tablets increased during the one-  
302 week storage. The decrease in density is probably due to the release of the stored stress  
303 by the tablet by increasing its volume, while the increase of tablet density is probably  
304 the result of the consolidating bonding forces. Regarding the API-TNT tablets, in the  
305 case of DiltTi and DicTi the density did not change at lower compression forces and  
306 only barely decreased beyond 10.0kN in time. These results support the plastic  
307 deformation of these composite containing compositions inducing stable tablet density  
308 at low compression forces and only slight changes in density at high compression  
309 pressure. On the other hand, the apparent density of the ATNTi and HCTTi tablets was

310 noticed to increase during the one-week storage at all compression forces. These results  
311 showing similarity to those of the ATN and HCT tablets certainly originate in the  
312 incomplete incorporation of these materials into TNTs. Furthermore, in the case of the  
313 HCTTi tablets it was also predictable based on the compaction studies.

314 **As regards the true density and the porosity of the tablets (Table 5.), those**  
315 **containing composites showed higher true density than API tablets, which is in**  
316 **accordance with the presented apparent densities as well as with the expectations**  
317 **built on the powder porosities shown in Table 2. The porosity of the tablets, which**  
318 **constantly decreased with the increase of the compression pressure, exhibits**  
319 **considerable differences with regard to the compressibility and the texture of the**  
320 **compositions. According to the preformulation results, all the composites have**  
321 **higher porosity than the pure APIs, due to the tubular structure of TNTs. This**  
322 **difference is clearly visible also for tablets prepared from composites which exhibit**  
323 **poorer compressibility (DicTi and ATNTi), while tablets prepared from DiltTi,**  
324 **which showed superior compressibility, have lower porosity than the**  
325 **corresponding DiltHCl tablets at all compression forces. A slight decrease of**  
326 **porosity may also be observed for the HCTTi tablets, but this can be due to the**  
327 **unique structure of the composite and not to the good compressibility of the**  
328 **composition.**

329 The forces required to break the tablets and the calculated tensile strength values are  
330 displayed in Table 6.

331 As expected, the breaking strength increases with the compression force in all the cases.  
332 Based on the results, it is outstanding that the breaking strength of the API-TNT tablets  
333 is much superior to that of the API tablets at all compression forces. Moreover, in  
334 consonance with the results of the compaction measurements, the API-TNT tablets

335 display a greater increase in breaking strength between 5.0 and 15.0 kN compression  
336 force than the API tablets. According to the data, the less influence of the incorporation  
337 on the breaking strength was observed for DicNa, where a difference of 3.0 N could  
338 only be detected in the breaking strength of DicNa and DicTi tablets at 5.0 kN  
339 compression force. Although this difference slightly increased with the compression  
340 force, it was not remarkable at 15.0 kN either. This observation is in agreement with the  
341 results of the apparent density measurements. Comparing the four APIs, HCT (and  
342 therefore HCTTi) tablets showed the biggest breaking strengths at each compression  
343 force. In accordance with the high apparent density values displayed in Table 4., these  
344 results prove their greater hardness compared to the other samples.

345 The disintegration time of the API and API-TNT tablets was investigated in order to  
346 reveal the effect of the composite formation on the disintegration and therefore its  
347 impact on drug dissolution. The results of the measurements are shown in Table 6.

348 As expected, the disintegration time rose with the compression pressure in all the cases.  
349 When comparing the API and API-TNT tablets, it can be stated that the disintegration  
350 of the composite containing tablets is slower at each investigated compression pressure.

351 The superior disintegration times of the API-TNT tablets refer to their greater hardness,  
352 confirming the findings of the above post-compression studies.

353 The most considerable effect of the incorporation on the disintegration time was seen  
354 for the ATN tablets as a result of the important difference in strength observed between  
355 the ATN and ATNTi tablets. It is noteworthy that the partial incorporation of HCT is  
356 clearly reflected in the results: the HCT and HCTTi tablets show similar disintegration  
357 time values. It is also interesting to note that despite their high hardness and apparent  
358 density, the HCT and HCTTi tablets disintegrate very quickly and, in contrast with the  
359 other compositions, their disintegration is less dependent on the compression pressure.

360 The scanning electron micrographs of the tablets (Fig. 5.) support the results of the  
361 compressibility studies, according to which the HCT and HCTTi tablets go through a  
362 considerably higher densification already at lower compression forces, resulting in  
363 smaller porosity. The SEM pictures also reveal that the irregular densification may be  
364 due to the fragmentation of the HCT particles, which may also be an explanation for the  
365 fast disintegration process. The water penetrating into the microfractures (marked with  
366 white arrows) of the HCT particles disrupts the fractures and the released energy  
367 enhances the disintegration process.

368 **The results of the dissolution tests are presented in Fig. 6. In general, slower drug**  
369 **release may be observed from the API-TNT tablets than from the related API**  
370 **tablets in all the cases. This may be explained by the slower disintegration, due to**  
371 **the higher breaking strength and density of these tablets, independently from their**  
372 **porosity. This may support the conclusion that the observed porosity differences**  
373 **between the APIs and the composites are due to the tubular structure of TNTs and**  
374 **not to the looser tablet skeleton. It is important to note that the occurrence of**  
375 **strong interactions may also change the kinetics of the drug release, as observed in**  
376 **the case of DicNa, where the first order drug dissolution from the DicNa tablets**  
377 **changed to prolonged dissolution based on Korsmeyer-Peppas kinetics from the**  
378 **DicTi tablets. In accordance with the expectations, the speed of dissolution**  
379 **decreased with the increase of the compression force in the case of the API and**  
380 **API-TNT tablets as well. However, it could be seen that this slowing down of**  
381 **dissolution was more intense for the API-TNT tablets, confirming the especially**  
382 **good compressibility and compactibility of the composites.**

383

384 **4. Conclusion**



385 The present study aimed to determine the effect of 1:1 ratio API-TNT composite  
386 formation on the tablettability of the incorporated API. Four different composite  
387 products were used to obtain reliable results.

388 The preformulation measurements revealed that the composite formation with TNTs  
389 highly improved the extremely poor flowability of the APIs. This positive effect of  
390 TNTs on powder rheology was proved for all the investigated APIs, indicating  
391 promising opportunities for developing drug processability with the use of TNTs.

392 However, the rate of flowability improvement was seen to be dependent on the  
393 efficiency of the incorporation process; ATNTi and HCTTi showed slighter flowability  
394 improvement.

395 When comparing the compaction properties of the API and API-TNT tablets, it was  
396 seen that the composite formation resulted in better compactibility, showing higher  
397 volume reduction at a given compression pressure. Furthermore, drug incorporation into  
398 TNTs hindered the elastic recovery of the APIs and led to plastic deformation. These  
399 results confirmed the great advantage of composite formation for manufacturing tablets  
400 with direct compression. On the other hand, the measurements also revealed that  
401 inappropriate incorporation may also affect the compaction behaviour of the API  
402 negatively, as observed for HCT. Accordingly, the successfulness of the incorporation  
403 is considered to be the key factor of the tablettability improving effect of TNTs.

404 In accordance with the more ideal compaction behaviour, the API-TNT tablets showed  
405 better post-compressional properties than the tablets containing pure APIs, displaying  
406 higher apparent density, superior breaking strength and slower disintegration at all the  
407 applied compression forces. The greater strength of the API-TNT tablets compared to  
408 that of the pure APIs was observed for all the APIs without reference to the efficacy of  
409 the incorporation.

410 Overall, the present work revealed that the appropriate incorporation of APIs into TNTs  
411 highly improves their tablettability and results in tablets with favourable mechanical  
412 properties. Accordingly, it can be concluded that hydrothermally synthesized TNTs can  
413 advantageously be used as drug carriers in the manufacturing of tablets with direct  
414 compression.

415

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418

#### 419 **Conflict of Interest**

420 The authors declare that there is no conflict of interest regarding the publication of this  
421 paper.

422

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492 **Figure captions**

493 **Figure 1: Particle rearrangement profile of TNTs, APIs and API-TNT composites**

494 **Figure 2: Kawakita-Lüdde plot of DiltHCl and DiltTi containing powder mixtures**

495 **Figure 3: Walker W plot of DiltHCl and DiltTi containing powder mixtures**

496 **Figure 4: Walker L plot of DiltHCl and DiltTi containing powder mixtures**

497 **Figure 5: SEM micrographs of tablets (DicTi 5kN tablet surface (a) and breaking**

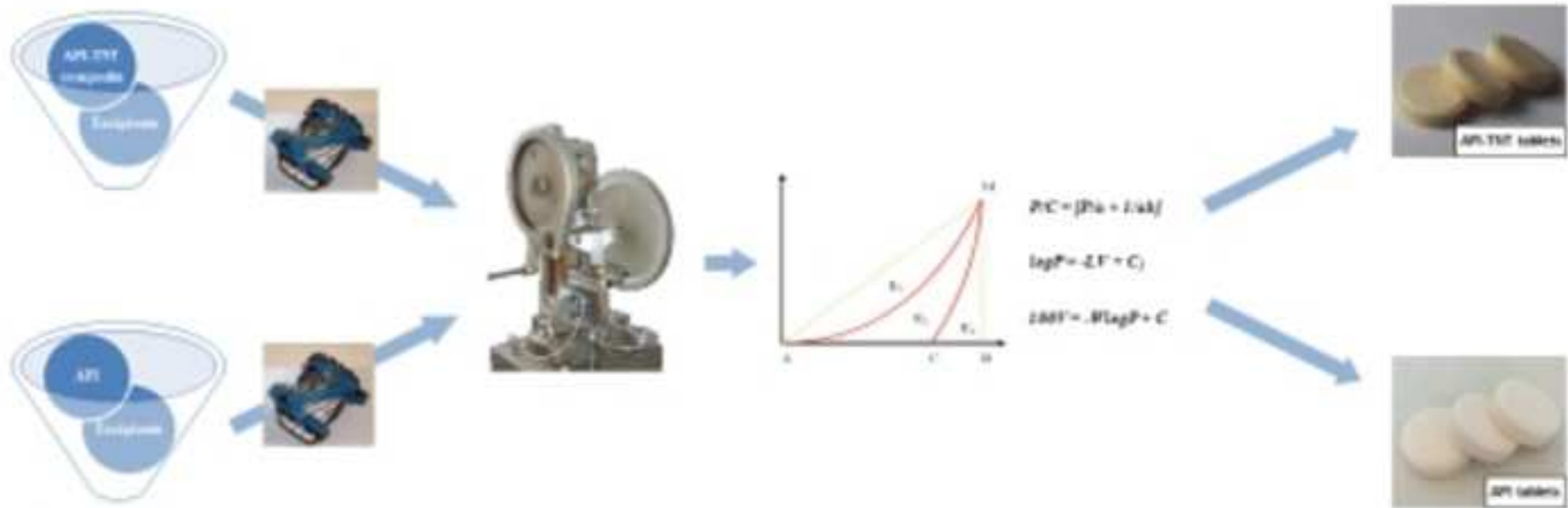
498 **surface (b); DicTi 15kN tablet surface (c), breaking surface (d); HCTTi 5 kN tablet**

499 **surface (e), breaking surface (f); HCTTi 15 kN tablet surface (g), breaking surface**

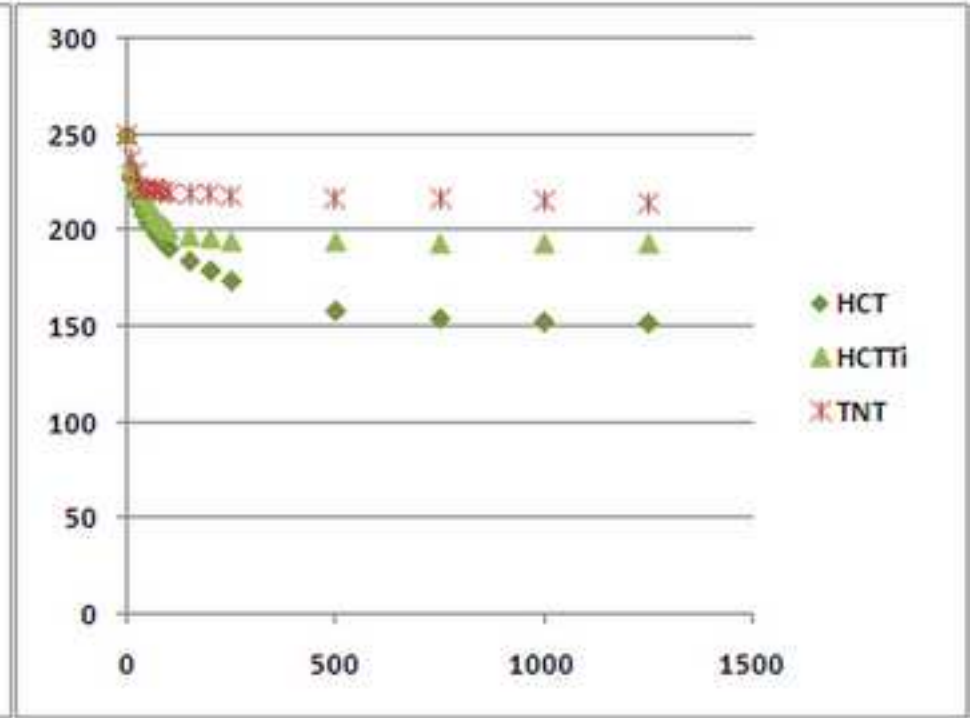
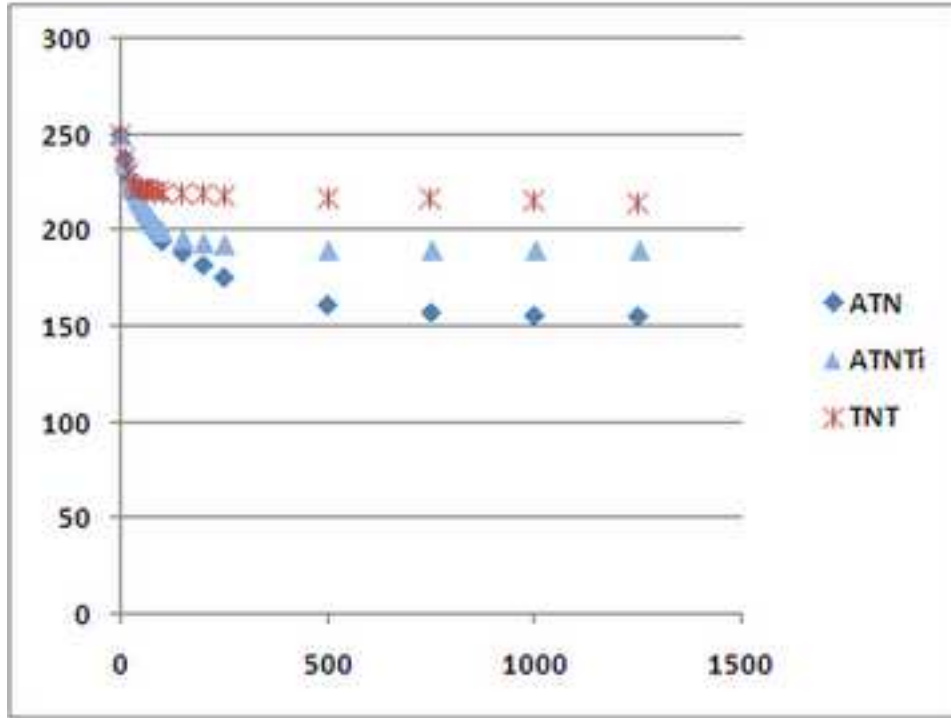
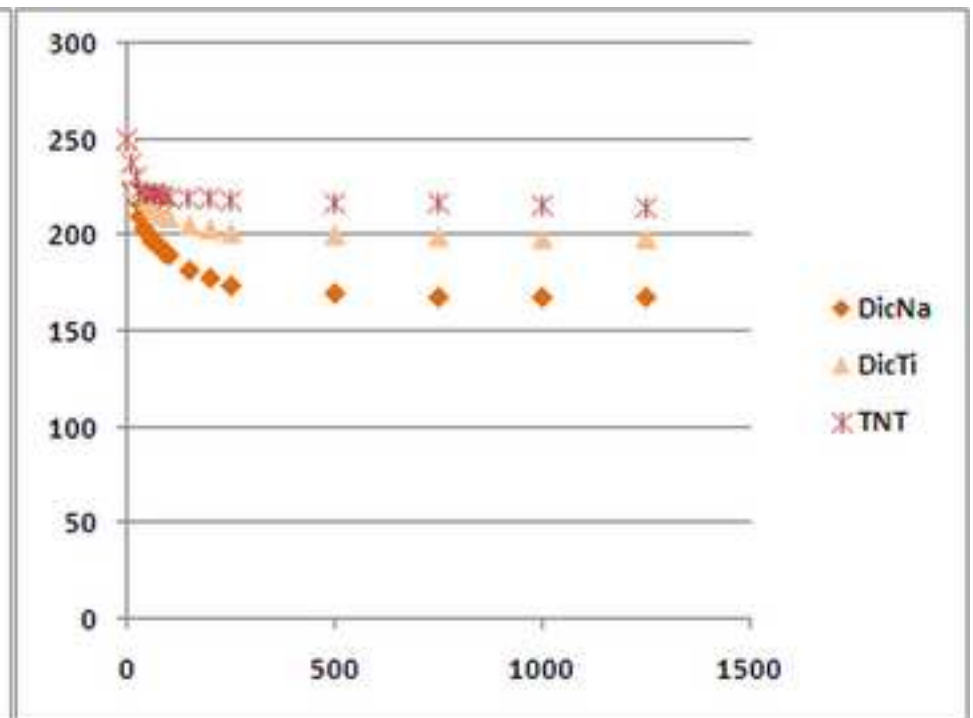
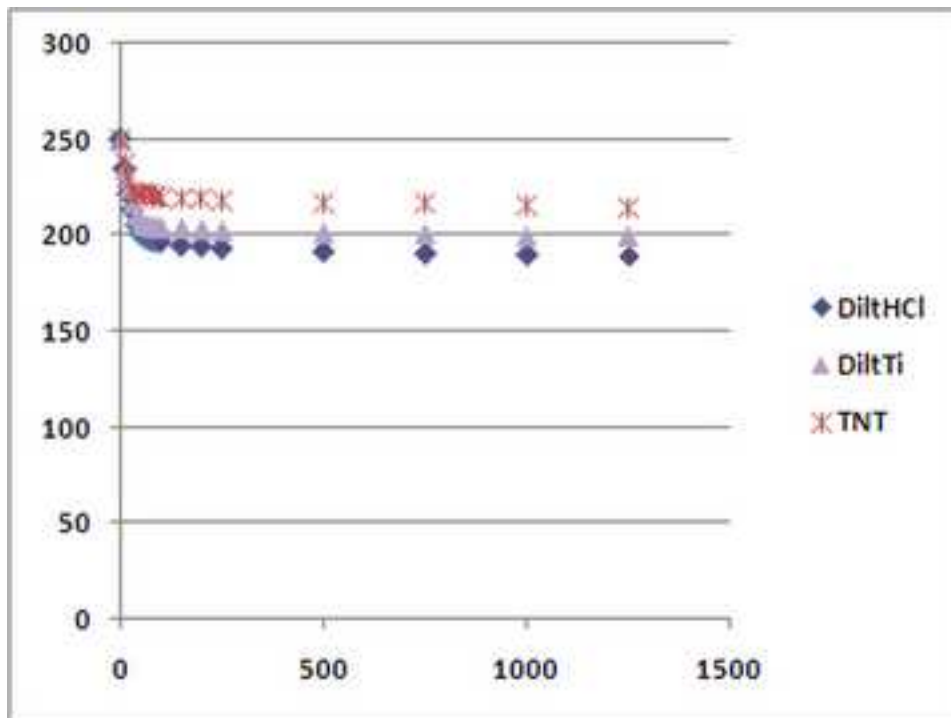
500 **(h))**

501 **Figure 6: Drug dissolution from API and API-TNT tablets compressed with 5.0,**

502 **7.5, 10.0, 12.5 and 15.0 kN in pH 6.8 phosphate buffer**

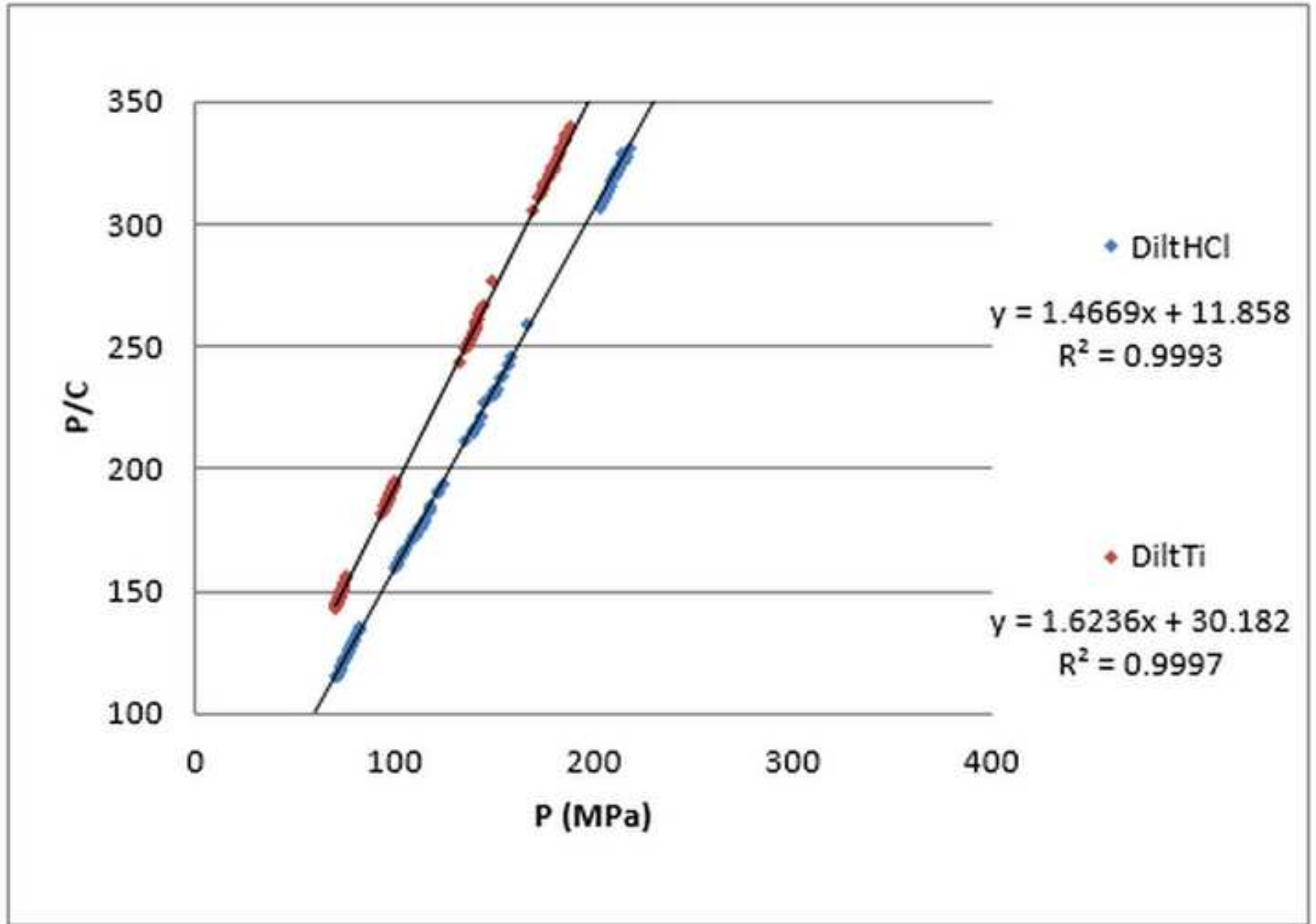


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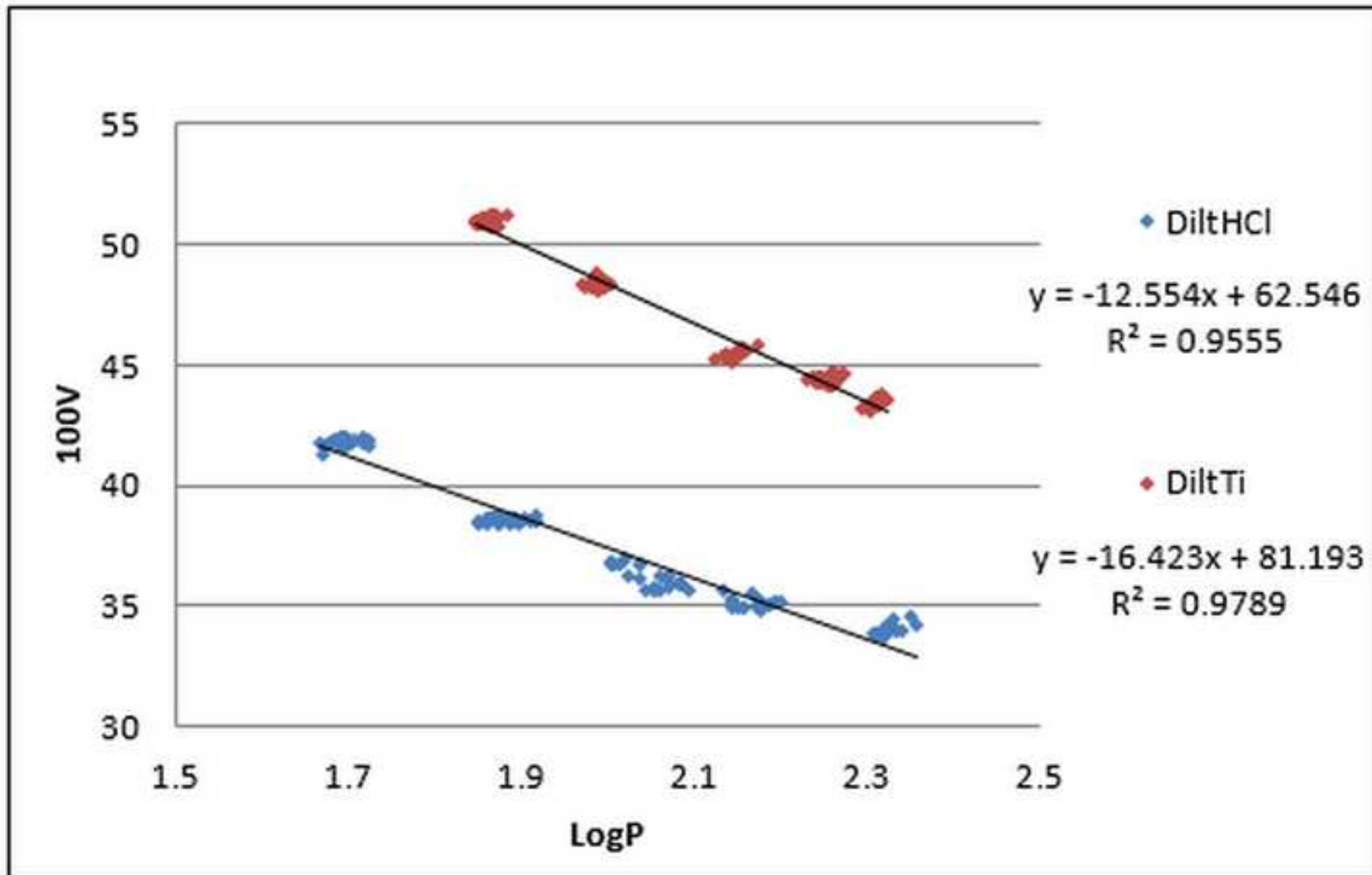




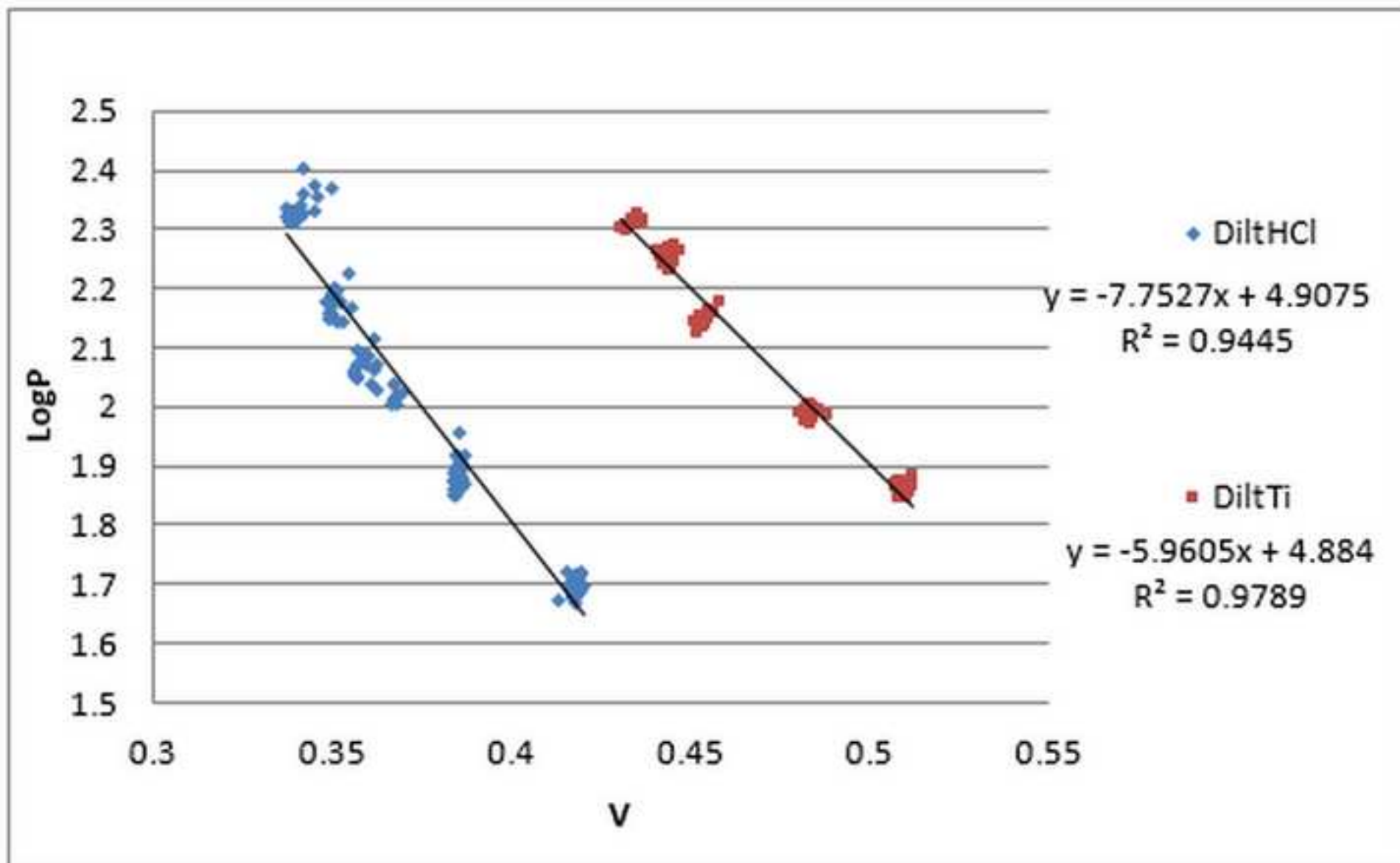
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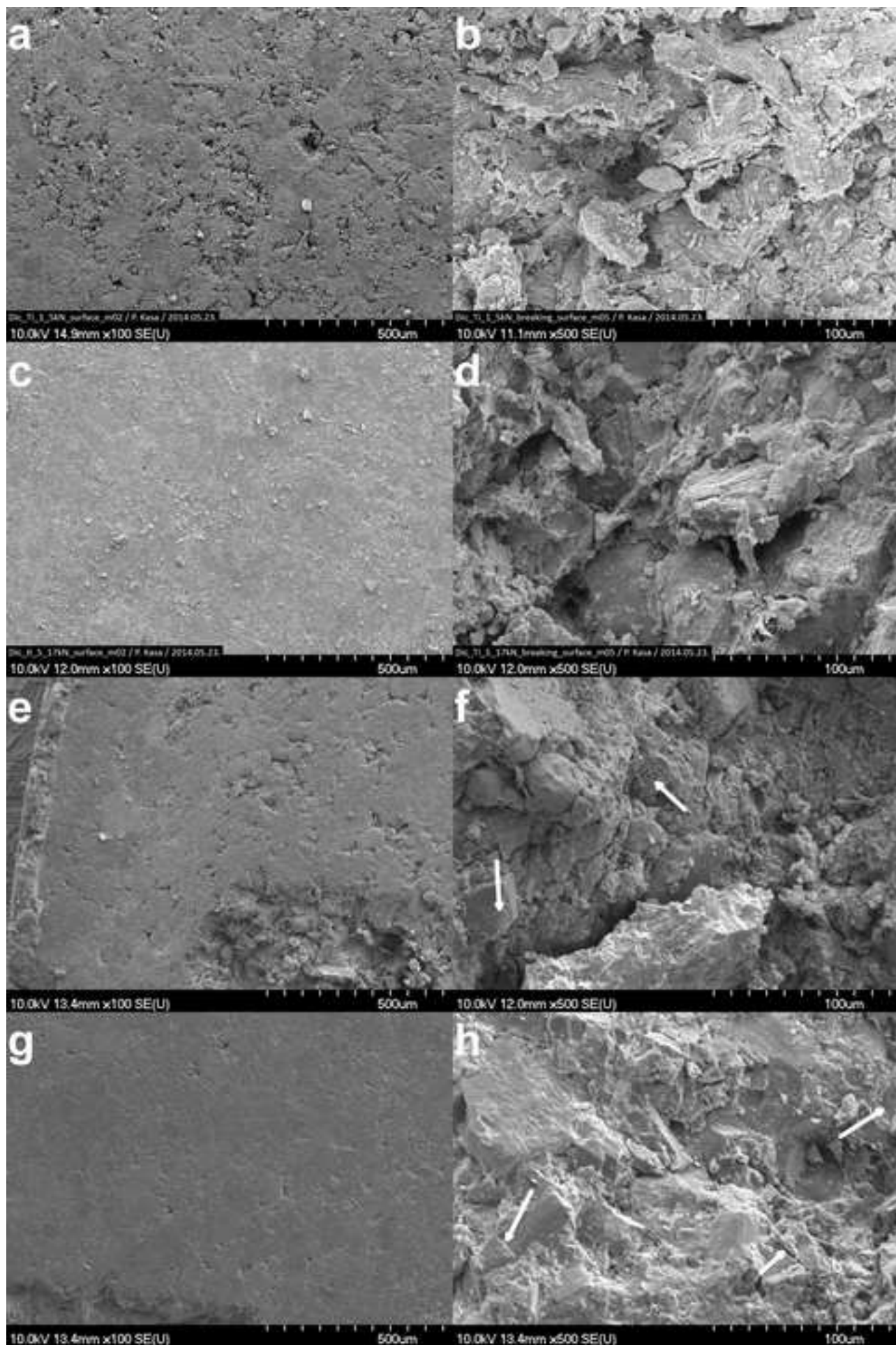


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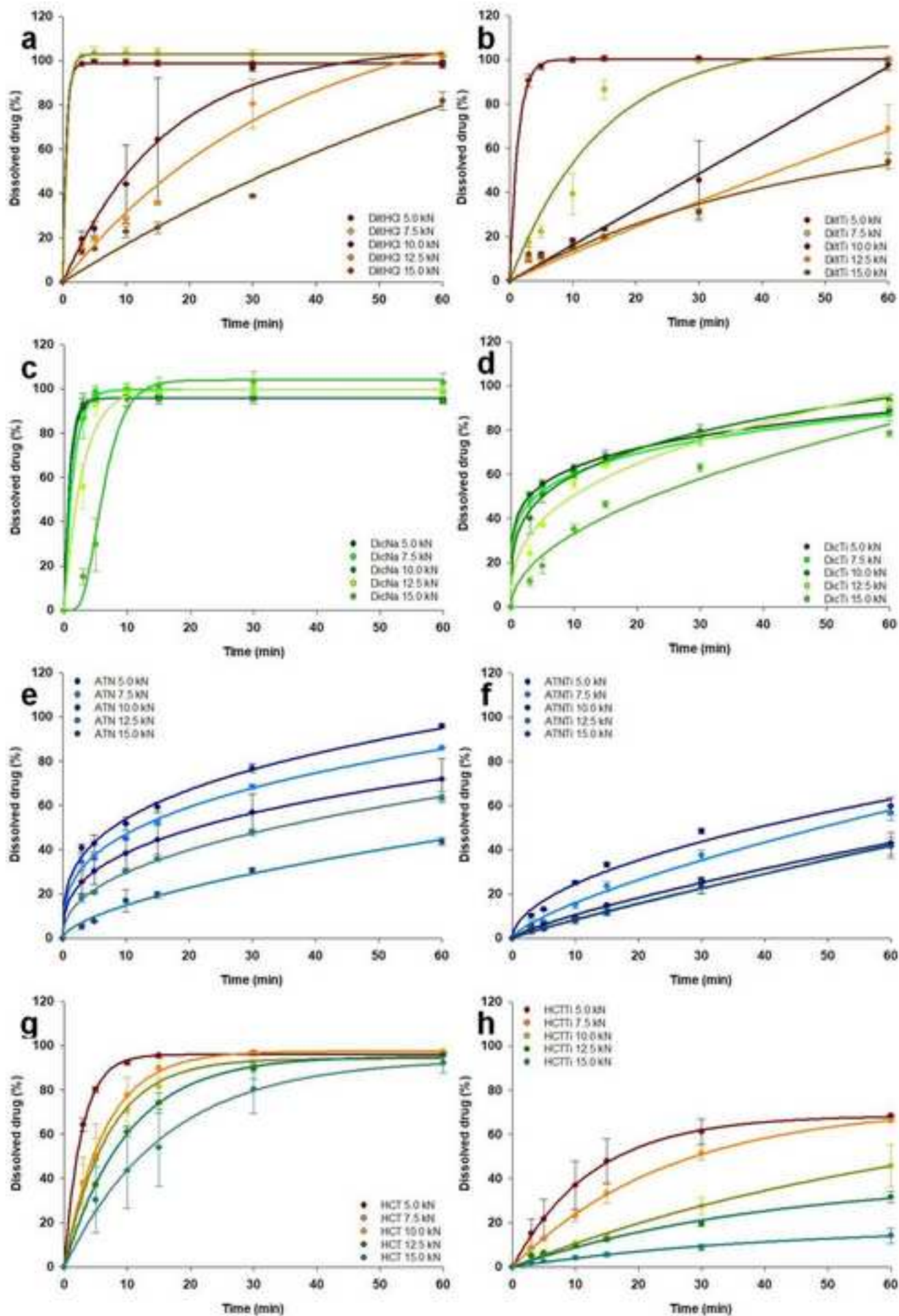


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**Table 1. Composition of API and API-TNT tablets**

<i>Materials</i>	<i>API tablets</i>	<i>API-TNT tablets</i>
<i>API</i>	16.7%	-
<i>API-TNT</i>	-	33.3%
<i>Avicel PH 112</i>	50.0%	39.5%
<i>Tabletose</i>	29.3%	23.2%
<i>Talc</i>	3.0%	3.0%
<i>Mg-stearate</i>	1.0%	1.0%

**Table 2. Preformulation results of the APIs and the API-TNT composites**

<b>Material</b>	<b>Flow time (sec)</b>	<b>Angle of repose (°)</b>	<b>Bulk density (g/cm<sup>3</sup>)</b>	<b>Tapped density (g/cm<sup>3</sup>)</b>	<b>Pycnometric density (g/cm<sup>3</sup>)</b>	<b>Porosity (%)</b>	<b>Hausner Ratio</b>	<b>Compressibility Index (%)</b>	<b>Flowability (USP scale)</b>
TNT	14.3	25.5	0.65	0.76	3.02	78.51	1.17	14.47	good
DiltHCl	n.m.	-	0.45	0.59	1.30	65.34	1.31	23.73	passable
DiltTi	16.5	28.2	0.51	0.64	1.78	71.39	1.25	20.31	fair
DicNa	n.m.	-	0.48	0.73	1.50	68.01	1.52	34.25	very poor
DicTi	6.3	28.4	0.55	0.68	1.97	72.05	1.24	19.12	fair
ATN	n.m.	-	0.3	0.48	1.21	75.16	1.6	37.5	very very poor
ATNTi	n.m.	-	0.38	0.49	1.64	76.81	1.29	22.45	passable
HCT	n.m.	-	0.46	0.76	1.69	72.72	1.65	39.47	very very poor
HCTTi	n.m.	-	0.61	0.76	2.17	71.94	1.25	19.74	fair

n.m.=not measurable

**Table 3. Parameters calculated from Kawakita and Walker plots**

<b>Tablet</b>	<b><i>a</i></b>	<b><i>1/b</i></b>	<b><i>L</i></b>	<b><i>W</i></b>
DiltHCl	0.68	8.03	7.9	11.59
DiltTi	0.62	18.63	5.93	16.49
DicNa	0.67	6.38	9.85	8.72
DicTi	0.68	13.53	6.64	14.73
ATN	0.64	5.94	13.56	4.04
ATNTi	0.65	17.61	8.47	9.43
HCT	0.61	14.32	12.89	7.01
HCTTi	0.68	6.04	17.76	2.49



**Table 4. Apparent density of the API and API-TNT tablets determined right after the preparation and one week later**

Pressing force (kN)	API			Composite				
	0 h		168 h	0 h		168 h		
	Apparent density	SD	Apparent density	SD	Apparent density	SD	Apparent density	SD
	<b>DiltHCl</b>			<b>DiltTi</b>				
<b>5.0</b>	1.09	0.01	1.06	0.01	1.23	0.01	1.23	0.00
<b>7.5</b>	1.18	0.01	1.15	0.01	1.30	0.00	1.30	0.00
<b>10.0</b>	1.25	0.01	1.23	0.01	1.35	0.02	1.35	0.01
<b>12.5</b>	1.29	0.01	1.27	0.01	1.40	0.01	1.39	0.00
<b>15.0</b>	1.30	0.07	1.28	0.08	1.42	0.00	1.40	0.00
	<b>DicNa</b>			<b>DicTi</b>				
<b>5.0</b>	1.16	0.01	1.16	0.01	1.16	0.00	1.16	0.01
<b>7.5</b>	1.23	0.02	1.26	0.02	1.23	0.01	1.23	0.02
<b>10.0</b>	1.27	0.01	1.32	0.02	1.32	0.00	1.32	0.00
<b>12.5</b>	1.30	0.01	1.35	0.02	1.36	0.01	1.35	0.02
<b>15.0</b>	1.34	0.01	1.40	0.01	1.42	0.00	1.40	0.04
	<b>ATN</b>			<b>ATNTi</b>				
<b>5.0</b>	1.11	0.01	1.25	0.01	1.15	0.01	1.31	0.01
<b>7.5</b>	1.04	0.01	1.28	0.01	1.20	0.01	1.37	0.00
<b>10.0</b>	1.01	0.01	1.28	0.01	1.23	0.01	1.40	0.01
<b>12.5</b>	0.93	0.00	1.30	0.01	1.24	0.01	1.42	0.01
<b>15.0</b>	0.92	0.01	1.32	0.01	1.25	0.02	1.43	0.01
	<b>HCT</b>			<b>HCTTi</b>				
<b>5.0</b>	1.03	0.01	1.28	0.01	1.17	0.00	1.39	0.01
<b>7.5</b>	1.07	0.01	1.33	0.01	1.20	0.01	1.42	0.00
<b>10.0</b>	1.09	0.03	1.39	0.01	1.26	0.00	1.48	0.01
<b>12.5</b>	1.11	0.00	1.40	0.00	1.31	0.00	1.48	0.01
<b>15.0</b>	1.12	0.00	1.41	0.00	1.37	0.00	1.52	0.00

**Table 5. True density and porosity of the API and API-TNT tablets**

Pressing force (kN)	True density		Porosity		True density		Porosity	
	(g/cm <sup>3</sup> )	SD	(%)	SD	(g/cm <sup>3</sup> )	SD	(%)	SD
	<b>DiltHCl</b>				<b>DiltTi</b>			
<b>5.0</b>	1.0517	0.0098	29.41	0.45	1.6336	0.0080	24.70	0.36
<b>7.5</b>	1.0517	0.0098	23.42	0.49	1.6336	0.0080	20.42	0.38
<b>10.0</b>	1.0517	0.0098	18.09	0.53	1.6336	0.0080	17.35	0.40
<b>12.5</b>	1.0517	0.0098	15.43	0.54	1.6336	0.0080	14.91	0.41
<b>15.0</b>	1.0517	0.0098	14.76	0.55	1.6336	0.0080	14.29	0.41
	<b>DicNa</b>				<b>DicTi</b>			
<b>5.0</b>	1.5426	0.0065	24.80	0.31	1.6685	0.0151	30.47	0.62
<b>7.5</b>	1.5426	0.0065	18.31	0.34	1.6685	0.0151	26.27	0.66
<b>10.0</b>	1.5426	0.0065	14.42	0.36	1.6685	0.0151	20.88	0.71
<b>12.5</b>	1.5426	0.0065	12.48	0.37	1.6685	0.0151	19.08	0.73
<b>15.0</b>	1.5426	0.0065	9.243	0.38	1.6685	0.0151	16.08	0.75
	<b>ATN</b>				<b>ATNTi</b>			
<b>5.0</b>	1.4721	0.0045	15.08	0.26	1.5953	0.0043	17.88	0.21
<b>7.5</b>	1.4721	0.0045	13.04	0.26	1.5953	0.0043	14.11	0.22
<b>10.0</b>	1.4721	0.0045	13.04	0.26	1.5953	0.0043	12.23	0.23
<b>12.5</b>	1.4721	0.0045	11.68	0.27	1.5953	0.0043	10.98	0.23
<b>15.0</b>	1.4721	0.0045	10.33	0.27	1.5953	0.0043	10.35	0.23
	<b>HCT</b>				<b>HCTTi</b>			
<b>5.0</b>	1.5918	0.0038	19.55	1.87	1.6909	0.0289	17.77	1.39
<b>7.5</b>	1.5918	0.0038	16.40	1.94	1.6909	0.0289	16.00	1.42
<b>10.0</b>	1.5918	0.0038	12.63	2.03	1.6909	0.0289	12.45	1.49
<b>12.5</b>	1.5918	0.0038	12.01	2.05	1.6909	0.0289	12.45	1.49
<b>15.0</b>	1.5918	0.0038	11.38	2.06	1.6909	0.0289	10.08	1.53

**Table 6. Breaking and tensile strength of the API and API-TNT tablets**

Pressing force (kN)	Breaking strength (N)	SD	Tensile strength (N)	SD	Breaking strength (N)	SD	Tensile strength (N)	SD
	DiltHCl				DiltTi			
<b>5.0</b>	24.9	1.1	0.47	0.02	69.0	1.79	1.42	0.04
<b>7.5</b>	53.0	3.63	1.09	0.06	96.0	2.37	2.08	0.05
<b>10.0</b>	66.2	4.47	1.60	3.68	122.0	4.86	2.83	0.09
<b>12.5</b>	104.0	4.53	2.35	0.08	142.0	2.66	3.37	0.06
<b>15.0</b>	124.0	3.19	2.83	0.10	156.0	2.86	3.79	0.05
	DicNa				DicTi			
<b>5.0</b>	42.9	2.64	0.85	0.05	46.0	3.04	0.93	0.05
<b>7.5</b>	58.1	3.68	1.21	0.08	66.0	2.80	1.44	0.05
<b>10.0</b>	81.2	4.58	1.74	0.07	99.0	3.63	2.27	0.08
<b>12.5</b>	98.1	3.91	2.17	0.08	120.0	3.30	2.83	0.07
<b>15.0</b>	125.0	3.00	2.73	0.07	153.0	3.05	3.80	0.06
	ATN				ATNTi			
<b>5.0</b>	79.5	2.90	1.68	0.06	102.0	4.56	1.99	0.09
<b>7.5</b>	82.4	2.08	1.75	0.04	121.0	1.97	2.48	0.05
<b>10.0</b>	89.6	1.60	1.99	0.04	138.0	2.77	2.88	0.05
<b>12.5</b>	101.0	4.27	2.02	0.09	141.0	2.19	3.00	0.05
<b>15.0</b>	102.0	3.08	2.13	0.08	149.0	4.34	3.24	0.09
	HCT				HCTTi			
<b>5.0</b>	87.0	4.20	1.63	0.08	127.0	3.16	2.65	0.07
<b>7.5</b>	112.0	3.84	2.18	0.07	148.0	3.64	3.14	0.07
<b>10.0</b>	149.0	4.81	2.92	0.20	190.0	3.10	4.13	0.07
<b>12.5</b>	153.0	3.40	3.10	0.06	191.0	3.50	4.32	0.08
<b>15.0</b>	160.0	4.00	3.22	0.10	222.0	2.72	5.14	0.06

**Table 7. Disintegration time of the API and API-TNT tablets**

<b>Compressing force (kN)</b>	<b>Disintegration time(min)</b>	<b>SD</b>	<b>Disintegration time(min)</b>	<b>SD</b>
	<b>DiltHCl</b>		<b>DiltTi</b>	
<b>5.0</b>	0.16	0.02	0.52	0.03
<b>7.5</b>	0.41	0.17	2.44	0.29
<b>10.0</b>	8.28	0.68	9.54	0.49
<b>12.5</b>	11.07	1.34	15.49	0.27
<b>15.0</b>	18.13	0.52	18.46	0.52
	<b>DicNa</b>		<b>DicTi</b>	
<b>5.0</b>	0.20	0.01	1.34	0.09
<b>7.5</b>	0.41	0.05	2.13	0.05
<b>10.0</b>	1.05	0.13	3.21	0.41
<b>12.5</b>	1.58	0.19	4.26	0.65
<b>15.0</b>	4.23	0.05	5.27	0.37
	<b>ATN</b>		<b>ATNTi</b>	
<b>5.0</b>	1.05	0.09	4.95	0.35
<b>7.5</b>	1.56	0.28	9.56	0.17
<b>10.0</b>	3.33	0.33	13.40	0.37
<b>12.5</b>	5.40	0.48	15.30	0.46
<b>15.0</b>	6.26	0.18	18.62	0.43
	<b>HCT</b>		<b>HCTTi</b>	
<b>5.0</b>	0.12	0.02	0.31	0.06
<b>7.5</b>	0.18	0.03	0.48	0.16
<b>10.0</b>	0.23	0.06	1.18	0.13
<b>12.5</b>	0.23	0.06	1.43	0.07
<b>15.0</b>	0.28	0.03	3.19	0.30