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Summary of PhD thesis

**Investigation of physicochemical characteristics and tablettability
of titanate nanotube-active drug composites**

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1. INTRODUCTION

One of the key challenges of pharmaceutical industry is to find suitable methods to improve the processing, solubility and bioavailability of the available active substances. From this aspect, the rapidly developing nanotechnology captivated the attention of many medical scientists in recent years. Among others, organic and inorganic nanotubes got into the focus of their curiosity due to their promising properties presented in various scientific fields like physics, chemistry and electronics. However, the strict safety requirements of medical application shortly decreased the number of potential nanotube types for adaptation to medical use. Despite the limiting factors, some inorganic nanotubes such as titanate nanotubes (TNTs) proved to be feasible for therapeutic use. Thereafter several research works were engaged in the investigation of TNTs from the diagnostic to the active therapeutic fields. Considering that the term titanate nanotube covers TNTs with extremely diverse physicochemical properties (different tubular structure, length, drug carrying capacity, etc.), the unexplored medical aspects of TNTs is endless.

Regarding the pharmaceutical goals, the most essential and informative research topics over the safety questions are the capacity of TNTs to carry nano-sized active pharmaceutical ingredients (APIs), including the capability of TNTs to be loaded with active substances and the association methods stabilizing the API-TNT composites, as well as the processability and manufacturing of API-TNT composites.

2. AIMS

The purpose of the present research is to define the potential pharma-industrial benefits of the utilization of hydrothermally synthesized TNT carriers in the manufacturing and stabilization of nano-sized active substances. Within the confines of this purpose, the present study aims to thoroughly investigate and determine the physicochemical properties of API-TNT composites as well as to reveal the utility of composite formation in tableting with direct compression method.

Abbreviations: API: active pharmaceutical ingredient, API-TNT: active pharmaceutical ingredient-titanate nanotube composite, ATN: atenolol, ATN+TNT: physical mixture of atenolol and titanate nanotubes, ATNTi: atenolol- titanate nanotube composite, DiltHCl: diltiazem hydrochloride, DiltHCl+TNT: physical mixture of diltiazem hydrochloride and titanate nanotubes, DiltTi: diltiazem hydrochloride-titanate nanotube composite, DicNa: diclofenac sodium, DicNa+TNT: physical mixture of diclofenac sodium and titanate nanotubes, DicTi: diclofenac sodium- titanate nanotube composite, DSC: differential scanning calorimetry, FT-IR: fourier-transform infrared, HCT: hydrochlorothiazide, HCT+TNT: physical mixture of hydrochlorothiazide and titanate nanotubes, HCTTi: hydrochlorothiazide-titanate nanotube composite, MS: mass spectroscopy, SEM: scanning electron microscopy, TEM: transmission electron microscopy, TGA: thermogravimetric analysis, TNT: titanate nanotube

The main endpoints of my research work are the followings:

- to determine the suitability of the API-TNT composite formation method
- to reveal the type(s) and strength of interactions inside the API-TNT composites
- to define the influence of composite formation on the physicochemical properties and behaviour of the API
- to estimate the effect of the composite formation on the formulation of tablets with direct compression and on the tablet properties
- to propose potential industrial utilization of TNTs

3. MATERIALS AND METHODS

3.1. Materials

A representative API of each Biopharmaceutical Classification System (BCS) classes was chosen for examination. Diltiazem hydrochloride (DiltHCl), diclofenac sodium (DicNa), atenolol (ATN) and hydrochlorothiazide (HCT) were supported by Sanofi-Aventis PLC, Hungary, Egis Pharmaceuticals PLC, Hungary, TEVA Pharmaceuticals PLC, Hungary and Gedeon Richter PLC, Hungary, respectively.

Hydrothermally synthesized titanate nanotubes (TNTs) were produced by the University of Szeged, Department of Applied and Environmental Chemistry.

1:1 ratio of diltiazem hydrochloride-TNT (DiltTi), diclofenac sodium-TNT (DicTi), atenolol-TNT (ATNTi) and hydrochlorothiazide-TNT (HCTTi) composites were provided by the University of Szeged, Department of Applied and Environmental Chemistry.

Tableting was carried out with the use of the following excipients: Avicel PH 112 (FMC Biopolymer Inc., USA), Tablettose 70 (Meggler Pharma GmbH, Germany), Talc (Ph.Eur., Molar Chemicals Ltd., Hungary), Magnesium stearate (Ph.Eur., Molar Chemicals Ltd., Hungary).

3.2. Methods

Morphological characterization: The morphology of the APIs, TNTs and API-TNT composites was investigated with a HITACHI S-4700 (Hitachi, Tokyo, Japan) scanning electron microscope. TNTs were also analysed with a FEI Tecnai G2 20 X-TWIN (FEI, Hillsboro, OR, USA) transmission electron microscope. The particle size of the TNTs was estimated by using Image J 1.47t (National Institute of Health, Bethesda, MD, USA) software.

Structure analysis: Thermogravimetric analysis (TGA) and Differential scanning calorimetry (DSC) tests of APIs, TNTs, API-TNT composites 1:1 ratio physical mixtures of TNTs and

APIs were performed with a Mettler Toledo TGA/DSC1 simultaneous analyser (Mettler-Toledo GmbH, Switzerland). The results were evaluated with STARe Thermal Analysis Software. Connected to the Mettler Toledo TGA/DSC1 simultaneous analyser, mass spectroscopy (MS) measurements were carried out by using a ThermoStar™ GSD 320 (Pfeiffer Vacuum GmbH, Asslar, Germany) quadrupole MS. A Thermo Nicolet Avatar 330 (Thermo Fisher Scientific Ltd., Waltham, MA, USA) Fourier transform infrared (FT-IR) spectrometer with a Transmission E. S. P. accessory was used to record FT-IR spectra of the APIs, TNTs and API-TNT composites.

Physical properties: The surface free energy of the APIs, TNTs and API-TNT composites was studied with a DataPhysics OCA 20 (DataPhysics Instruments GmbH, Filderstadt, Germany) optical contact angle tester. A software-controlled PTG-1 (PharmaTest Apparatebau AG, Germany) powder rheological tester was used to investigate the flowing properties of the APIs and API-TNT composites. Densification of the APIs and the API-TNT composites were tested with a STAV 2003 Stampfvolumeter (Engelsmann AG., Germany). The defined bulk density and tap density values were used to calculate the Hausner Ratio and Compressibility Index of the samples.

Direct compression with excipients: Tablets of constant weight (300 mg) and quantity of API (50 mg) were compressed with a Korsch EK0 (E. Korsch Maschinenfabrik GmbH, Berlin, Germany) eccentric tablet press instrumented with strain gauges and a displacement transducer. Compression forces of 5.0, 7.5, 10.0, 12.5 and 15.0 kN were used for all compositions (Table 1) The powders were mixed with a Turbula mixer (Willy A. Bachofen Maschinenfabrik, Switzerland).

Table 1. Composition of API and API-TNT tablets

<i>Component</i>	<i>API tablets (300 mg)</i>	<i>API-TNT tablets (300 mg)</i>
API (DiltHCl/DicNa/ATN/HCT)	16.7 %	-
API-TNT composite (DiltTi/DicTi/ATNTi/HCTTi)	-	33.3 %
Avicel PH 112	50.0 %	39.5 %
Tabletose 70	29.3 %	23.2 %
Talc	3.0 %	3.0 %
Magnesium-stearate	1.0 %	1.0 %

Direct compression without excipients: TNTs, APIs and API-TNT composites were compressed with a Lloyd 6000R uniaxial press (Ametek SAS Lloyd Inst, Elancourt, France), instrumented with a force gauge and a linear variable differential transformer

extensometer. The compacts were prepared using 50, 100, 150, 200 and 250 MPa pressures for each material. Force and displacement data were recorded by a computer (R-Control software, Version 2.0, Lloyds Inst LTD, Fareham, UK) connected to the equipment. The retrieved data set was evaluated with Origin 7.5 software (OriginLab Corporation, Northampton, MA, USA) in order to determine the energy utilisation of the raw materials during the compression cycle. The energy analysis was expanded with the determination of R_i (R_1 , R_2 and R_3) values which serve to describe pressure related transformation of energies: mechanical energy (MCW) into theoretical energy (ThCW) (R_1), ThCW into total energy (TCW) (R_2) and TCW into net energy (NCW) (R_3).

Post-formulation methods: The compaction properties of the powder mixtures (Table 1.) were estimated with Kawakita and Walker out-of-the die models. Geometry of the tablets produced with excipients was measured with Kraemer UTS-50 tablet tester (Charles Ischi AG, Switzerland) right after the production and one week later. Weight, height and diameter of tablets produced without excipients were measured 24 hours after production with an analytical scale, a calliper and a Lloyd 6000R uniaxial press (Ametek SAS Lloyd Inst, Elancourt, France), respectively. Geometrical parameters served to calculate the compaction ratio. The breaking force of the tablets fabricated with excipients were studied by a Heberlein 2E/205 tablet hardness tester (HeberleinAG, Switzerland), while that of the tablets compressed without excipients was tested with a Lloyd 6000R uniaxial press (Ametek SAS Lloyd Inst, Elancourt, France). The breaking force results were also used to calculate the tensile strengths. The texture of the breaking surface of the tablets fabricated with excipients was investigated with a Hitachi S4700 (Hitachi Ltd., Japan) scanning electron microscope. Disintegration was determined for tablets fabricated with excipients with an Erweka ZT71 (Erweka GmbH, Germany) disintegration tester apparatus. Drug dissolution from tablets compressed with excipients was examined in pH 1.2 and pH 6.8 dissolution media by using an Erweka DT700 (Erweka GmbH, Heusenstamm, Germany) dissolution tester, applying paddle method. Results were evaluated a ThermoScientific GENESYS 10S UV-VIS spectrophotometer (Thermo Fisher Scientific Ltd., Waltham, MA, USA).

4. RESULTS

4.1. Material properties: APIs, TNTs, API-TNT composites

4.1.1. Morphology

Based on the TEM pictures, the average diameter of the TNTs was determined to be 7.01 nm (SD \pm 1.08 nm) while the length, which is a matter of the synthesis parameters, was found to

be 164.25 nm (SD \pm 50.38 nm). The SEM pictures allowed concluding that TNTs are not present individually but in form of aggregates (Fig. 1).

The SEM images of the composites (Fig. 2) revealed that the efficacy of drug incorporation was not equal for all 4 APIs. While the composite formation of DiltHCl and DicNa seemed to be ideal and resulted in homogenous composite products, that of ATN and HCT was only partially effective and left several individual API crystals in the final products, as shown by yellow arrows on Fig. 2. Based on the pictures, the ATNTi product seems like the physical mixture of the source materials, while in case of the HCTTi product, a kind of reverse mechanism of the composite formation could be recognized inducing that approx. 60% of the API crystals are covered with TNTs.

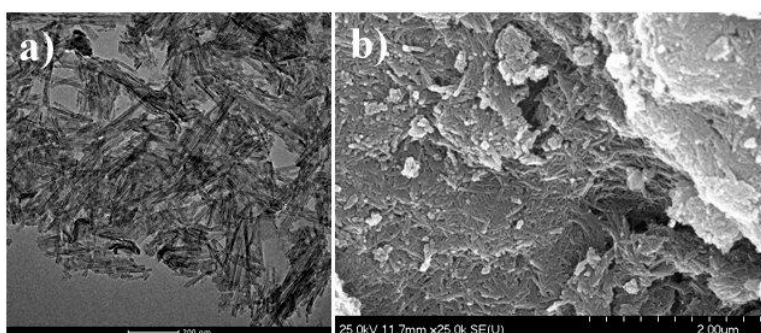


Figure 1. TEM micrograph (a) and SEM micrograph (b) of titanate nanotubes

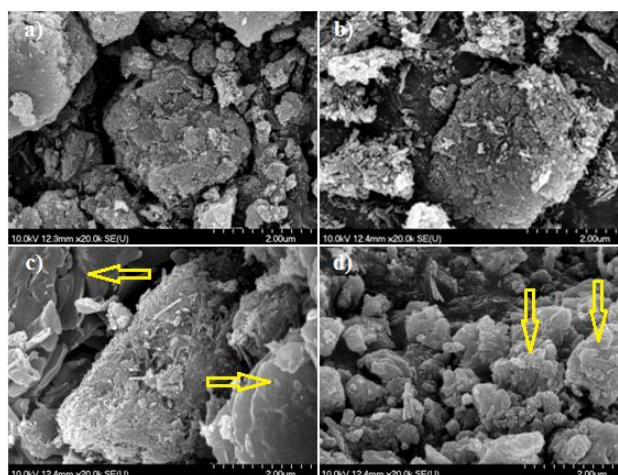


Figure 2. SEM images of the DiltTi (a), DicTi (b), ATNTi (c) and HCTTi (d)

4.1.2. Surface free energy

TNTs have high surface free energy confirming their expected hydrophilic nature. This character of the TNTs is reflected in the γ^{TOT} values of the ATNTi and HCTTi composites which showed increment in this value in comparison with the pure ATN and HCT, respectively. The increment in γ^{TOT} may be attributable to the incomplete composite formation which resulted in the surface coverage of the API crystals with TNTs. The extent

of increment is considered as an indicative of the ratio of the surface coverage. As regards the DiltTi and DicTi composites, a decrease of γ^{TOT} value and polarity could be noticed in comparison with both the TNTs and the pure APIs (DiltHCl and DicNa, respectively). This finding confirms the successful incorporation of DiltHCl and DicNa and that the APIs are not only located in the internal part of the nanotubes but are also bonded to the surface. The decrease of γ^{TOT} and polarity indicates hydrophilic intermolecular interactions on the surface of the TNTs inducing the enrichment of the hydrophobic molecular parts on the particle surface. The higher decrease in surface free energy suggests a greater bonding ratio on the surface of the TNTs.

4.1.3. Thermal properties

The resume of the thermoanalytical measurements shows a clear tendency. Fig. 3. serves as an example to support the statements. TNTs shift the fusion of an API to lower temperatures which may be due to the decreased particle size and/or to the interactions of the API and TNTs. The decreased relative enthalpy of the peaks indicates that the composite formation puts the system into an energy minimum.

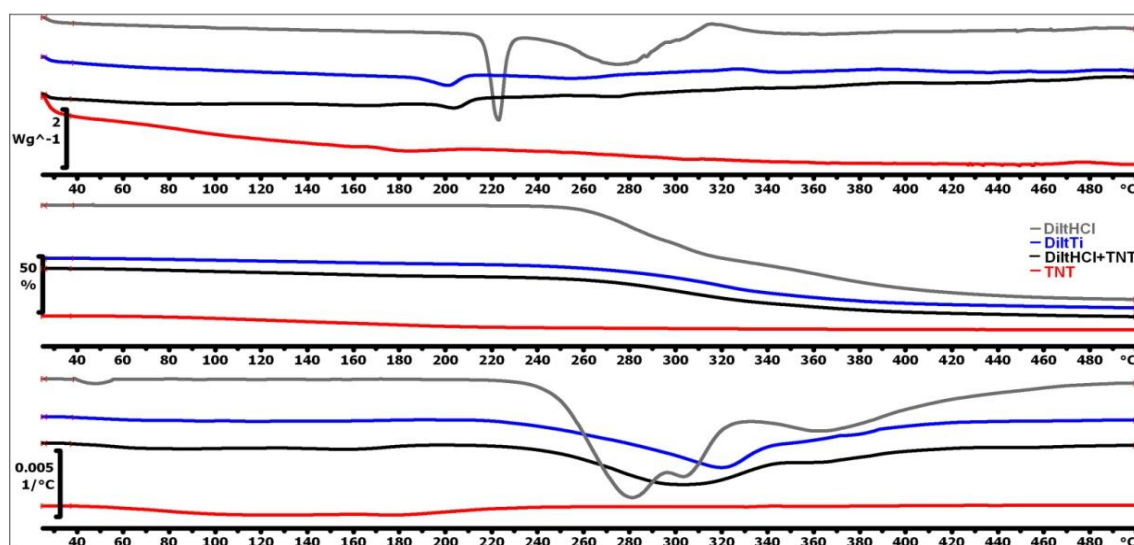


Figure 3. DSC, TG and DTG curves of DiltHCl, DiltTi, DiltHCl+TNT and TNT

The long-lasting decomposition is probably due to the TNT-API interactions on the interfacial surface, which may be observed both for physical mixtures and composites, but increased rate of extension was noticed in latter case. This may be due to the certainly stronger interactions inside the composites, or can be explained by the location which results immediate decomposition of the surface-attached API, while the drug locked inside the nanotubes decomposes with a time lag.

Overall, it can be established that DicNa and HCT are perfectly suitable to form stable API-TNT composites, while DiltHCl and ATN are less capable to form strong interactions with the TNTs.

4.1.4. FT-IR

The results of the FT-IR examination confirmed the thermoanalytical findings and also provided new essential information about the structure of the API-TNT composites. The assessment of the results pointed out that the strength of the association inside the composites is based on the hydrogen donor strength of the incorporated API. The hydrogen acceptor groups of the API play only a minor role in the association which can be explained by the high quantity of OH groups (having poor hydrogen donating capacity) on the titanate surface (Fig. 4).

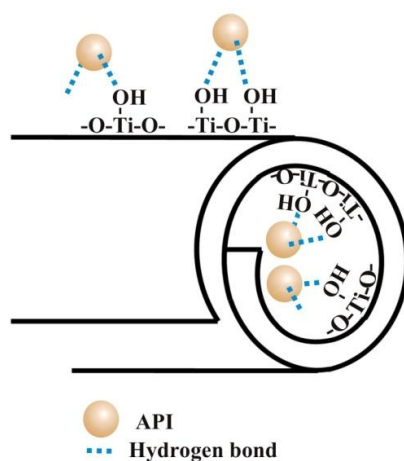


Figure 4. Association mechanism of APIs (DiltHCl, DicNa, ATN, HCT) with TNTs

4.1.5. Powder rheology

Based on the powder rheological properties (Table 10) it can be established that TNTs have good flowability and this affects the flow properties of the incorporated APIs in a positive way; a great improvement of flowability is shown by DiltTi and DicTi compared to DiltHCl and DicNa, but the flowability improvement of ATNTi and HCTTi was less defined since these composites contain individual API crystals. By evaluating the results as per the United States Pharmacopeia (USP) scale, it is clear that the flowability of the composites varies between those of the component materials. This can be explained by the fact that the APIs are located not only in the internal parts of the TNTs but on their surface as well. The rate of improvement may depend on the ratio of the surface coverage.

4.1.6. Compressibility and compactibility

The post-compressional properties of tablets are summarized in Fig. 5, providing a complex image of the tablettability of the investigated materials.

Tablets prepared from pure APIs may be characterized by high (approx. 75–90 %) compaction ratio at low pressure which shows slight increase with the increment of compression pressure. Despite of the high compressibility, API tablets display very low tensile strengths indicating their poor compactibility. In contrast, TNTs show poor (approx. 55 %) compaction ratio at low compression force, but still result in tablets of high tensile strength in the whole compression force range and can be considered adequate for tableting. The results of the composite tablets need to be assessed one by one due to the unique characteristics. However, a clear tendency of improved tablettability can be established based on Fig. 5. It can be stated in general, that the composite tablets have higher tensile strength induced at lower compaction ratios compared to the API tablets, which indicates that hard tablets can be produced with relatively high porosity, providing considerable benefits in drug release.

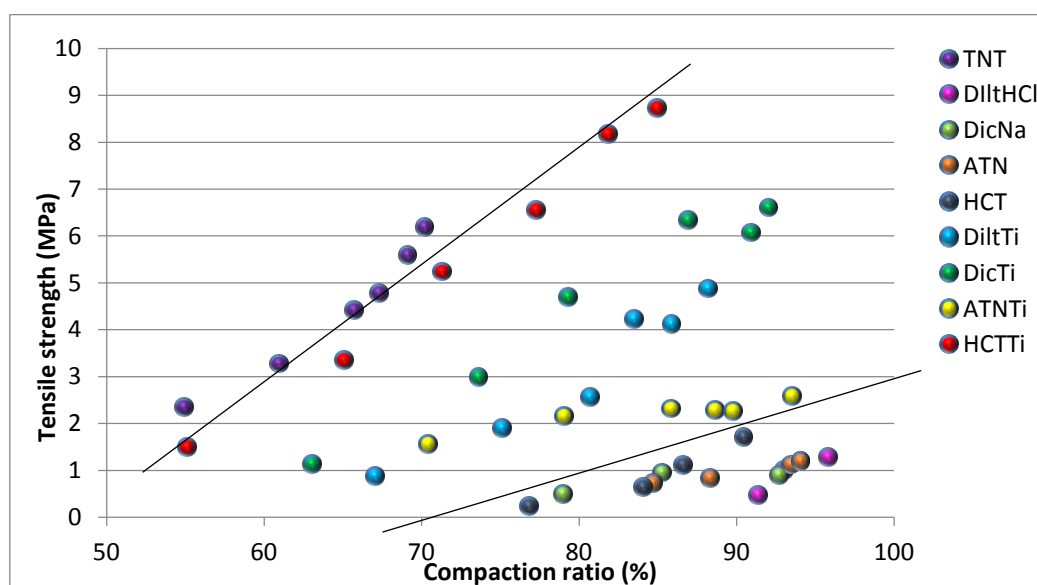


Figure 5. Evaluation of the tensile strength vs. the compaction ratio of the investigated materials compressed with 50, 100, 150, 200 and 250 MPa compression pressure

Based on the results, DiltTi and DicTi tablets (where the APIs are well incorporated into the TNTs) have morefold higher tensile strengths compared to the DiltHCl and DicNa tablets at same compaction ratios. Furthermore, an immense improvement in tablettability could be recognized for DicNa/DicTi as the strong lamination of the DicNa tablets completely disappeared due to the composite formation. In case of the incompletely incorporated APIs (ATN and HCT), the properties of the composite tablets reflect a special mixture of the

characteristics of the source materials. As regards the ATNTi, this resulted in relatively bad tablet properties which again prove the physical-mixture-like character of the ATNTi product. As concerns the HCTTi composite, the deficient incorporation of HCT induced more beneficial properties to the composite product than expected. The HCTTi tablets display not only far better tablet properties than all the other composites, but show even more favourable ones than the pure TNTs. This interesting phenomenon is probably due to the positive consonance of the reverse interaction between the HCT and the TNTs, and the good compactibility of both source materials.

4.2. Powder mixtures: APIs, API-TNT composites with excipients

4.2.1. Compressibility and compactibility

The constant values calculated by applying Kawakita-Lüdde and Walker models are summarized in Table 2.

Table 2. Parameters calculated from Kawakita and Walker plots

Tablet	a	$1/b$	L	W
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

The constant a values (Table 2), which demonstrate the rearrangement of the particles, are very similar for all the samples. Despite the fact that the results obtained for the raw materials presumed lower constant a values for the API-TNT tablet compositions, no considerable differences occurred neither within the API tablet compositions nor between the API and the related API-TNT tablet compositions. This allows concluding that the excipients were appropriately selected and could compensate the poor flow properties of APIs during packaging. However, it is notable that API-TNT powder mixtures contain proportionally less excipient than those of the APIs which means that TNTs could replace the function of the excipients.

The calculated $1/b$ values correlate with the cohesiveness (Table 2). The high $1/b$ values of the API-TNT tablet compositions are in accordance with the smaller compaction ratios of the API-TNT composites (Fig. 5). The low $1/b$ values of the API tablet compositions is due to the

fast collapse of the powder bed in the die resulting limited compressibility as it was observed for the pure API powders (Fig. 5.). It is clear from the results that the behaviour of the HCT and HCTTi tablet compositions is exceptional since the HCT tablet composition has a quite high l/b value, while the HCTTi tablet composition displays an unexpectedly low l/b value. This phenomenon is probably due to the inverse composite formation mechanism which results in higher surface free energy and adhesivity of HCTTi compared to the pure HCT, which is resulted in decreased compactibility.

The values of coefficient L (Table 12) were lower for the API-TNT tablet compositions, indicating higher volume reduction of the composite containing compositions at a certain pressure in the deformation phase compared to the API tablet compositions. The opposite behaviour of the HCT/HCTTi tablet compositions appeared here as well due to the previously mentioned structural properties of the composite.

The coefficient W value correlates with the irreversible compressibility of the powders (Table 2). Accordingly, the higher W values of the API-TNT tablet compositions reflect to their plastic deformation while the lower values displayed by the API tablet compositions refer to their high elastic recovery resulting in an exceeded densification maximum. These findings are in accordance with the results obtained for the deformation mechanism of the raw materials. Here again, the behaviour of the HCT/HCTTi tablet powder mixtures occurred to be just the opposite of that of the other API/API-TNT tablet compositions for the already mentioned reason.

In general, it can be concluded that the results of the powder mixtures correlate well with the observations of the energetic analysis of the raw materials. The only exception is the case of HCT/HCTTi, where the raw materials indicate the positive effect of the composite formation, while this effect seems unfavourable in the powder mixtures.

Overall, it can be established that the incorporation of drugs into TNTs has a positive effect on the tablettability and therefore TNTs can be considered as a multifunctional excipient in tablet production. However, it is important to note that an unsuccessful composite formation can even lead to a worse tablettability profile than expected from the pure API itself.

4.2.2. Tablet properties

As expected, the tablets showed increased apparent density with the increase of the compression force. The only exception was noticed for the ATN tablets during the 0 h measurements, where the density decreased with the increase of the compression force. This indicates the strong elasticity of the ATN, which corresponds with the low coefficient W value of the ATN tablet composition (Table 2). The previously established positive effect of

TNTs on the deformation mechanism is confirmed by the fact that no such phenomenon was identified for the ATNTi tablets. API-TNT tablets have higher apparent densities at all investigated compression pressures than the corresponding API containing tablets indicating that the presence of TNTs generally increases the apparent density of the produced tablets.

When comparing the apparent density changes in time, it turned out that no remarkable density changes occurred for those API-TNT tablets where the composite formation was complete (DiltTi and DicTi tablets) while tablets containing incomplete composites (ATNTi and HCTTi tablets) showed increased apparent density after one-week storage at all compression forces.

As concerns the breaking strength of the tablets, it increases with the compression pressure for every tablet compositions, but the increment is greater for the API-TNT tablets than for the API tablets. Furthermore, the breaking strengths of the API-TNT tablets are much superior to those of the API tablets at all compression forces. These results are in agreement with the compaction properties of the powder mixtures (Table 2) and the raw materials as well (Fig. 5).

Supporting the expectations, the disintegration time appeared to be proportional with the compression pressure in all cases and the disintegration time of the API-TNT tablets is longer than that of the corresponding API tablets which correlates with their greater hardness.

The results of the dissolution tests in pH 6.8 phosphate buffer are displayed in Fig. 6. Regarding to the expectations no considerable change was observed in the dissolution profiles of the well soluble DiltHCl/DiltTi or ATN/ATNTi tablets, except of the decreased dissolution speed with the increasing compression pressure or resulted by the bigger density of the API-TNT tablets. The dissolution profiles of the HCT/HCTTi tablets were also highly similar, which may be due to the incomplete incorporation and non-considerable particle size decrease of HCT. In contrast, considerable changes in drug release profile were noted for the DicNa/DicTi tablets, due to the strong drug-carrier interactions. The dissolution from DicNa tablets follows a first order dissolution profile as per Noyes-Whitney equation, while DicTi tablets shows prolonged drug release kinetics according to Korsmeyer-Peppas equation. In this case the TNTs act as a standalone matrix system, which may be utilized as modified-release drug delivery system. Furthermore, in contrast with the other investigated API/API-TNT tablets, an improved dissolution rate was observed from DicTi tablets compared to DicNa tablets in artificial gastric juice (Fig. 7).

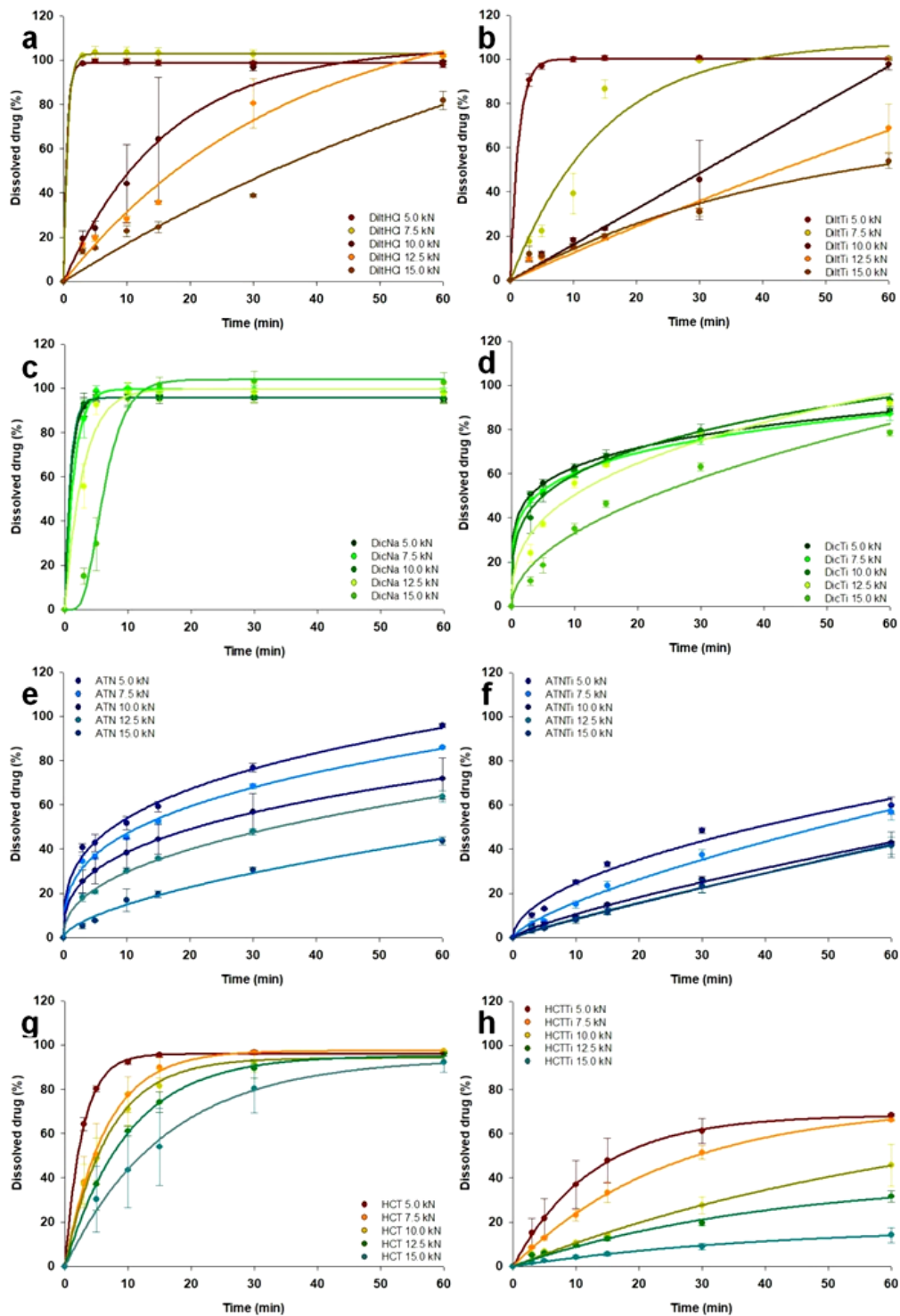


Figure 6. Dissolution study of API and API-TNT tablets in phosphate buffer

Since DicNa is poorly soluble under gastric conditions, this phenomenon may be due to the particle size decrease of DicNa which doubled the rate and the amount of the dissolved API. This observation is essential since it proves the solubility increasing capacity of TNTs.

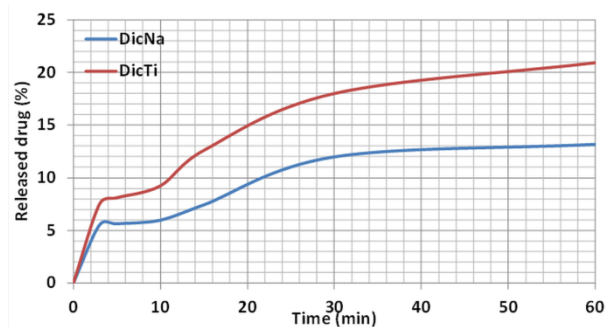


Figure 7. Dissolution from DicNa and DicTi 5kN tablets in artificial gastric juice

It can be generally stated that the first phase of dissolution is driven by the disintegration, while the slower drug dissolution in the further phases is attributed to the interactions inside the composites which retain the incorporated APIs from the quick release to different extent. Overall, the dissolution studies allowed concluding that the presence of TNTs increases the tablet strength and results prolonged drug release without reference to the success of the composite formation process. However, in case of successful drug incorporation and adequate strength of interactions inside the composite, TNTs can modify the kinetics of the drug dissolution., or in the case of an ideal composite formation process, TNTs are able to improve the solubility of the incorporated drug by decreasing its particle size.

5. CONCLUSION

The main consequences of the research may be summarized as follows.

The measurements revealed that only two (DiltHCl and DicNa) out of the four investigated APIs were successfully incorporated into the TNTs. It indicates that the applied composite formation method is only conditionally suitable since its efficacy highly depends on the physicochemical properties of the drug to be incorporated. Therefore, further optimization of the method may be required before use.

We have determined that API-TNT interactions are principally based on hydrogen bonds and the strength of the association depends on the hydrogen donor strength of the incorporated API. The hydrogen acceptor groups of the API play only secondary role in the association due to the high quantity, but poor hydrogen donating capacity of OH groups on the surface of titanate nanotubes. Accordingly, the strongest association was seen for DicTi and HCTTi among the investigated composites.

The API-TNT association and the particle size reduction resulted decreased fusion temperature and enthalpy, and modified and elongated decomposition of the APIs. The

change in the thermal behaviour was affected by the strength of interactions, therefore the most important differences were observed for the DicNa/DicTi and HCT/HCTTi samples.

The image analysis and surface energy measurements revealed that the API may be located both in the inner parts and on the surface of the TNTs. The resulted decrease of the surface free energy may lead to improved flow and packaging characteristics.

The good tableting properties of the TNTs highly improved the tablettability of the incorporated APIs due to improved flowability, packaging, extended range of compressibility and better compactibility. However, these effects showed considerable dependence on the efficacy of the incorporation and therefore the best results were recorded for DilHCl and DicNa. As regards the post-compressional tablet properties, the composite formation extremely improved the tablet strength, increased the density and therefore slowed down the disintegration and prolonged the drug dissolution. The positive effect of TNTs on the tablet properties was far less influenced by the success of the incorporation than observed for other parameters.

Nevertheless, TNTs may affect the drug release from the composite product by acting as a matrix and retaining the release of the API over certain strength of interactions, as was observed in the case of DicNa. However, the decreased particle size may lead to better solubility of poorly soluble drugs, especially if the release is not disintegration-driven, as was observed in the case of 5kN DicTi tablets in artificial gastric juice.

Finally, this research proved that drug loaded TNTs can successfully and easily be formulated into tablets with direct compression method, since they are capable to improve every step of the tableting cycle and lead to favourable tablet properties even when used in small quantity and when compared to other excipients. Accordingly, TNTs have the potential to replace and over fulfil one or more excipients in a tablet composition and therefore can improve and simplify the production. Furthermore, if the API is correctly incorporated in the TNTs, these carriers can improve the drug solubility which may be promising for pharma-industry since TNTs can become alternatives of available nanocarriers with fundamental manufacturing problems such as dendrimers, liposomes, etc. In addition, by carrying nanosized drugs, TNTs may overcome the autoaggregation induced formulation difficulties of nanocrystalline APIs.

ORIGINAL PUBLICATIONS RELATED TO THE THESIS

- I. **Sipos B.**, ifj. Regdon G., Sovány T.: *Titanát nanocsövek a gyógyászatban*. Acta Pharmaceutica Hungarica 85:(2) pp. 71-79. (2015) **IF: -**
- II. **B. Sipos**, K. Pintye-Hódi, Z. Kónya, A. Kelemen, G. Regdon jr., and T. Sovány: *Physicochemical characterisation and investigation of the bonding mechanisms of API-titanate nanotube composites as new drug carrier systems*. International Journal of Pharmaceutics 518:(1-2) pp. 119-129. (2017) **IF: 3.862, Q1**
- III. **B. Sipos**, G. Regdon jr., Z. Kónya, K. Pintye-Hódi, and T. Sovány: *Comparative study on the rheological properties and tablettability of various APIs and their composites with titanate nanotubes*. Powder Technology 321: pp. 419–427. (2017) **IF: 3.230, Q1**
- IV. **B. Sipos**, K. Pintye-Hódi, G. Regdon jr., Z. Kónya, M. Viana, and T. Sovány: *Investigation of the Compressibility and Compactibility of Titanate Nanotube-API Composites*. Materials (Basel) 11:(12) p. 2582. (2018) **IF: 2.467, Q2**

PRESENTATIONS RELATED TO THE THESIS

1. Sovány T., **Sipos B.**, Kónya Z., Hódi K., ifj. Regdon G.: Titanát nanócső-hatóanyag kompozitok, mint ígéretes, új hordozó rendszerek a gyógyászatban, MKE Kristályosítási és Gyógyszerformulálási Szakosztály 7. Kerekasztal Konferenciája, Szeged, 2014 (oral presentation)
2. Sovány T., **Sipos B.**, Sápi A., Kónya Z., Hódi K., ifj. Regdon G.: Diklofenak nátrium és diklofenak nátrium-titanát nanocső kompozit tartalmú tabletták tulajdonságainak összehasonlítása, XV. Congressus Pharmaceuticus Hungaricus, Budapest, 2014 (poster presentation)
3. T. Sovány, **B. Sipos**, A. Sápi, Z. Kónya, K. Pintye-Hódi, G. Regdon jr.: Comparison of the properties of the tablets containing diclofenac sodium or diclofenac sodium-titanate nanotube composite, 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, 2014 (poster presentation)
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 9. **B. Sipos**, T. Sovány, G. Regdon jr.: Comparison of the properties of tablets containing APIs or API-titanate nanotube composites, 6th FIP Pharmaceutical Sciences World Congress, Stockholm, 2017 (poster presentation)

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