University of Szeged

Faculty of Pharmacy

Institute of Pharmaceutical Technology and Regulatory Affairs

Summary of the Ph.D. Thesis

EVALUATION OF DRUG-MATRIX INTERACTIONS IN DIRECTLY COMPRESSED DRUG DELIVERY SYSTEMS AND MODELLING OF DRUG-RELEASE RATE

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1 INTRODUCTION

Individual differences among patients have considerable importance in the effectiveness of the therapy of different chronic diseases. Co-morbidities, genetical differences or various life-events may cause changes in important physiological parameters affecting the absorption, elimination or effectiveness of drugs and influence treatment efficacy. Personalized medicine is a recently emerging trend meant to overcome these difficulties. Therefore, pharmaceutical industry faces a new challenge on providing solid dosage forms, which as still the most favourable medicines, with tailorable properties.

Tailored release of drugs has even higher importance in the long-term therapy of chronic diseases, when ensuring a stable plasma level is a key question regarding to the treatment effectiveness. Patient compliance is advised if medicines needed to be administered multiple times throughout long therapies but may be problematic in case of psychiatric or neurodegenerative diseases, or if the administration interval is long, such in case of osteoporosis. Implantable drug delivery devices may provide controlled release for months, which may be very advantageous in those cases, especially if the active pharmaceutical ingredient (API) has poor bioavailability in the gastrointestinal (GI) tract, such as the antiosteoporotic bisphosphonates.

The present work aims the better understanding of the mechanism and kinetics of drug release from directly compressed, biodegradable and non-degradable implantable matrices designed for bisphosphonate delivery, in order to utilize a novel approach on the use of drug-polymer interactions in the tailoring of sustained-release solid delivery matrices.

The use of the principles of Quality by Design (QbD) is essential nowadays in applied drug development but its tools such as Design of Experiments (DoE) or artificial neural networks (ANNs) may be well utilized also in fundamental research. In present work they were used to reveal the role of drug-polymer interactions on the Critical Quality Attributes (CQA), such as diametral breaking hardness, porosity and drug dissolution rate of implantable matrices. Therefor a line of chemically similar drugs with increasing acidic strength were formulated in accordance with a mixed 2 and 3 level full factorial DoE. The presence of solid-state drug-polymer interactions based on the formation of H-bonds were confirmed by FT-IR spectroscopy, while their effect on dissolution was estimated by an ANN based predictive model.

2 AIMS

2.1 Primary aim

The primary aim of present research work was the development of a directly compressed polymer-based implantable monolithic matrix system for the delivery of risedronate sodium by the comparison of the potential of biodegradable (chitosan) and non-degradable (PVC) polymers for such purposes, based on the evaluation of mechanical properties, mechanism and rate of the drug release. The desired QTPP consisted affordable tablet hardness, sustained drug liberation for minimum 3, but preferable for 6 months, without considerable initial burst release of the drug. Biodegradable nature of the applied matrix is also preferred from the aspect of patient compliance.

2.2 Secondary aims of the research

During the implementation of the primary objective an unexpected occurrence of in-situ formed chemical interactions were observed, which required the revision of the results of the original risk assessment and the better understanding and detailed investigation of that phenomenon, which became the secondary objective of the study. The modified objective was to confirm the hypothesis, that the strength of drug-excipient interactions may be predicted based on acidic strength of the drugs, and the gathered data may help to achieve tailored drug-release from implantable drug delivery systems, which have emerging interest in pharmaceutical sciences, to ensure safe and long-term therapy of patients with chronic diseases. For this fundamental investigation we applied a QbD approach, therefore introduced several model API with varying acidic strength but similar chemical structures and more matrix forming polymers as well.

The main points of the present dissertation are the following:

1. Determination of the applicability of polymers as solid matrix system forming agents – comparison and evaluation of release rate and mechanism.
2. Confirmation the hypothesis, that the strength of drug-excipient interactions may be predicted based on acidic strength of the drugs.
3. A consequential objective of the present work is to compare the effectiveness of various modelling approaches to enable generalized prediction of drug dissolution rates from different matrices. Our hypothesis is that kinetic-based modelling allows for a simplified network structure and faster generalization.

3 MATERIALS AND METHODS

3.1 Materials

Risedronate sodium (RIS), aceclofenac (Ace), diclofenac sodium (DiS) and paracetamol (PAR) were used as active agents while the non-biodegradable polyvinyl chloride (MW: 60-150) (PVC), the biodegradable chitosan (MW: 400-600 kDa, average viscosity: 1000 cP deacetylation degree: 80%) (CHIT), and a powder form of Eudragit E100, Eudragit EPO (EE) and Eudragit L100-55 (EL) were used as matrix forming agents (Table 1).

Table 1. Physicochemical properties of raw materials

	RIS	PAR	DiS	ACE	EE	EL	PVC	CHIT
Solubility (water)	10,4 mg/ml	14g/l	15.9 mg/l	Not soluble	<10 µg/ml (> pH 5)	< 0,03 mg/ml (> pH 6)	<10 µg/ml	Not soluble
logP	-0.75	0.34	3.10	4.16	-	-	-	-
pKa	0.68	9.46	4.00	3.44	-	-	-	-
H^+ acceptor	3	3	3	4	3/n*	3/n*	-	variing
H^+ donor	3	1	1	2	1/n*	1/n*	-	variing
Rotatable bonds	8	3	3	5	-	-	-	2

*x/n: represents the number of H+ acceptor/donor groups per monomer

** predicted value by ChemAxon via https://foodb.ca/compounds/FDB019541 (available on 22.06.2020.)

3.2 Methods

3.2.1 Preformulation studies

During the research and development of the bisphosphonate carrier system preformulation studies were conducted on RiS, CHIT and PVC.

The flow properties (flow time, angle of repose, bulk density) of the powders were studied with a Pharmatest PTG-1 (Pharmatest GmbH, Germany) powder rheological tester.

The plasticity of materials and mixtures was determined with a computer-connected Korsch EK0 eccentric tablet press (E. Korsch Machienenfabrik, Berlin, Germany), instrumented with strain gauges on both punches and a displacement transducer (Micropulse, BTL5-A11-M0050-P-532, Balluff, Germany)

A DataPhysics OCA 20 (DataPhysics Instruments GmbH, Fielderstadt, Germany) optical contact angle tester was used for the determination of the surface free energies and wettability of the materials using sessile drop method. Water and diiodomethane were dropped onto the surface of solid comprimates with 13 mm diameter, prepared with a Specac hydraulic press (Specac Inc, Orpington, UK) at a pressure of 4 tons.

3.2.2 Tablet preparation

The tablet preparation was based on a factorial design. The results of the Design of Experiments (DoE) were evaluated with the help of Statistica for Windows v12 software package (Statsoft Inc., Tulsa, OK, USA).

3.2.2.1 Matrices for bisphosphonate delivery

The composition of the bisphosphonate carrying matrix tablets were determined according to a mixed 2 and 3 level full factorial design. The general QTTP was high drug load, preferably more than 40%, which later may enable the decreasing of the device size, appropriate mechanical hardness ensuring proper handling and implantation procedure (min. 50 N, with an optimal range of 80-120 N), and sustained drug release for at least 3 months, without considerable burst release (less than 10%-of drug content liberated within the first 24 hrs. Therefore the effect of the polymer (biodegradable/non-biodegradable) as a 2 level, qualitative, the amount of the API (10% or 40%) as 2 level, quantitative and the applied compression force (1, 3 or 5 tons equal with 58, 174 or 290 MPa compression pressure, respectively) as a 3 level, quantitative factor was studied (Table 2.)

Table 2: Bisphosphonate containing matrix compositions

Materials	Biodegradable		Non-biodegradable	
	CA-1 (%)	CA-2 (%)	CA-3 (%)	CA-4 (%)
RIS	10	40	10	40
PVC	-	-	89	59
CHIT	89	59	-	-
Ca-stearate	1	1	1	1

3.2.2.2 Matrices for the investigation of the role of chemical interactions

Tablet preparation for the investigation of API-excipient interactions also based on a mixed 2- and 3-level factorial design, where the nature of excipients was studied as 2-level, while the acidic strength of API, the weight ratio of excipients and the applied compression force as 3-level factors.

Powder mixing was made with a Paul Schatz principle based 1,5L mixer (Inversina, BioEngineering, Wald, Switzerland) then the mixtures were compressed with an instrumented Kilian SP 300 hydraulic press (IMA Kilian GmbH & Co., KG, Cologne, Germany) with the application of 2.9, 8.7, or 14.4 kN compression force (75, 225 and 375 MPa compression pressure, respectively)

3.2.3 Tablet testing

3.2.3.1 Physical properties

The physical characterisation of tablets was made with a Kraemer UTS tablet tester (Kraemer Elektronik GmbH, Germany). Porosity calculations were based on the physical parameters and the true density of matrices, which was determined with a helium gas pycnometer (AccuPyc 1330, Micromeritics, Norcross, GA, USA),

3.2.3.2 Physico-chemical characterization

For the specific identification and characterization of interactions FT-IR spectra were acquired. ZeSe HATR accessory was used, and measurements were taken on 4 cm^{-1} resolution, 128 scan numbers, with CO_2 and H_2O correction.

3.2.3.3 Dissolution tests

A special apparatus was developed for the testing of the dissolution rate of APIs from the implantable matrix tablets. The tablets were placed into Erlenmeyer flasks containing 50 ml of pH 7.4 phosphate buffered saline solution. The continuous closed-loop flow of the dissolution medium was ensured with an Alitea-XV (Alitea, Sweden) peristaltic pump. The dissolution medium was periodically renewed to maintain the concentration gradient, considering a time-dependent manner.

In case of the matrices prepared for the investigation of chemical interactions only a 24-hour dissolution tests were conducted for all compositions to obtain the most important kinetic parameters, and only few samples were selected afterwards for a one-week. From each

composition three parallel measurements were taken. Quantitative analysis was made with a ThermoGenesys UV-spectrometer.

3.2.3.4 Design of Experiments and Artificial Neural Networks

DoE analysis and ANN modeling was performed with Statistica v.13.5.0.17 (Tibco Software Inc., Palo Alto, CA, USA). Compression pressure (x_1), amount of excipient (x_2), API (x_3) and excipient used (x_4) were examined as independent factors, while hardness (y_1), porosity (y_2) and release rate (y_3) were used as optimization parameters in the DoE analysis.

One of the objectives of the present study was to compare the effectiveness of various modeling approaches to enable generalized prediction of drug dissolution rates from different matrices. In kinetic-based modelling, the release rate and release exponent were used as the output of the ANN model, while in point-to-point modeling the dissolved amount of drug at the various sampling times was applied according to Galata et al., which included 7 data points. Our hypothesis is that kinetic-based modelling allows for a simplified network structure and faster generalization.

Feed-forward, back-propagation Multilayer Perceptron networks were developed in all cases. A multistart method including 10.000 networks was applied using the Automated Neural Networks module of Statistica, for each network layout. The training was stopped, when the root mean square error (RMSE) of test dataset reached its minimum. The 5 best preforming networks from each multistart run were retained for further analysis.

4 RESULTS AND DISCUSSION

4.1 Matrices for bisphosphonate delivery

4.1.1 Preformulation studies

The results of the powder rheological test revealed that the micronized risedronate sodium exhibited no measurable flow properties, while chitosan platelets also exhibited the poor flow properties and extremely low bulk density, low surface free energy and low polarity. The PVC resulted in moderate flow properties, bulk density and excellent arrangement profile.

The ratio of the plastic/elastic properties (plasticity) of the materials is in negative correlation with the applied compression force.

It was detected that PVC basically deforms plastically but this value highly depends on the compression force. Chitosan and risedronate sodium exhibit higher elasticity but their behaviour is less dependent on compression force.

4.1.2 Physical parameters

In case of the RIS containing matrices the response surface of the best fitting model regarding diametric tablet hardness, as one the CQAs, can be described with the following equation (Eq. 1):

$$y=70.71+\mathbf{42.37x_1}+\mathbf{14.76x_3}+\mathbf{5.57x_3^2}-\mathbf{12.72x_1x_2}+2.56x_1x_3+3.52x_2x_3 \quad (1)$$

where the significant factors are highlighted in boldface. The value of the MS residual was 38.93, R^2 was 0.9935 and the adjR^2 value was 0.9867, indicating the excellent fit of the applied model. The predefined acceptance range for this parameter was min 50 N, with an optimal range of 80-120 N.

It can be seen that the hardness of the tablets mostly depends on the properties of the matrix former polymers, and the amount of the API plays a negligible role in this aspect.

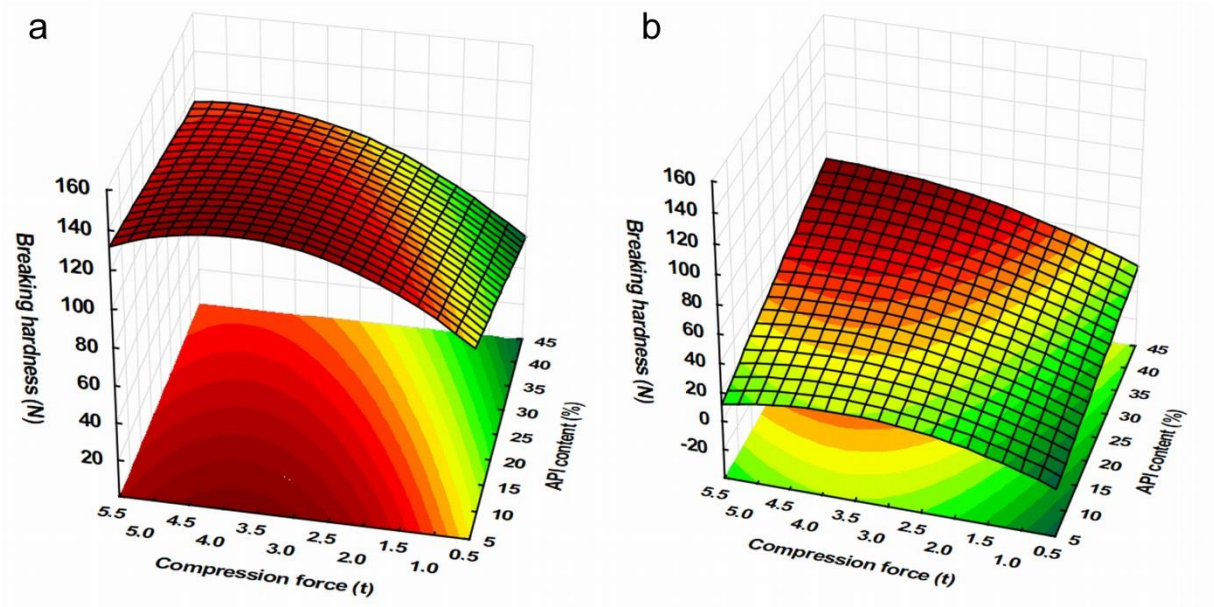

Figure 1: Breaking hardness of RIS containing PVC (a) and chitosan (b) tablets

The change in the porosity of the systems can be described with Eq. 2.

$$y=0.175-\mathbf{0.057x_1}-\mathbf{0.016x_2}-\mathbf{0.047x_3}-\mathbf{0.019x_3^2}+\mathbf{0.023x_1x_2}+\mathbf{0.021\ x_1x_3} \quad (2)$$

The MS residual value of the model is 0.0002, R^2=0.9856 and adjR^2=0.9682.

In contrast with hardness, the API content has a significant effect on porosity, especially in the case of chitosan-based tablets. However, the decreasing porosity does not result in a significant change of the drug release rate for chitosan matrices (Fig. 2).

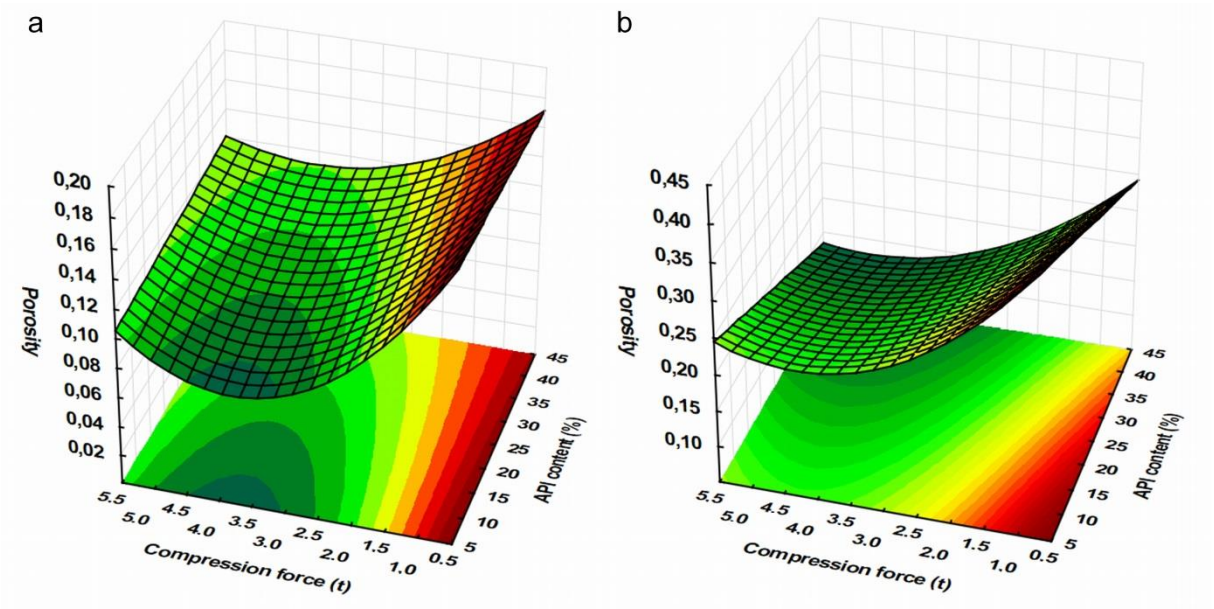

Figure 2. Porosity of RIS containing PVC (a) and chitosan (b) tablets

4.1.3 Dissolution studies

The negligible change mentioned in the previous section may be due to the complete disintegration of chitosan matrices in the first 24 hours, inducing a burst release of the drug in the initial stage of dissolution (Fig 3). However, the fast disintegration did not result in the completion of the dissolution process. After an initial burst release a much slower release of drug was detected even after the complete renewal of the dissolution medium, which indicates that the API is entrapped in the chitosan flakes due to a strong interaction. Nevertheless, chitosan-based matrices were unsuitable to achieve the targeted dissolution profile.

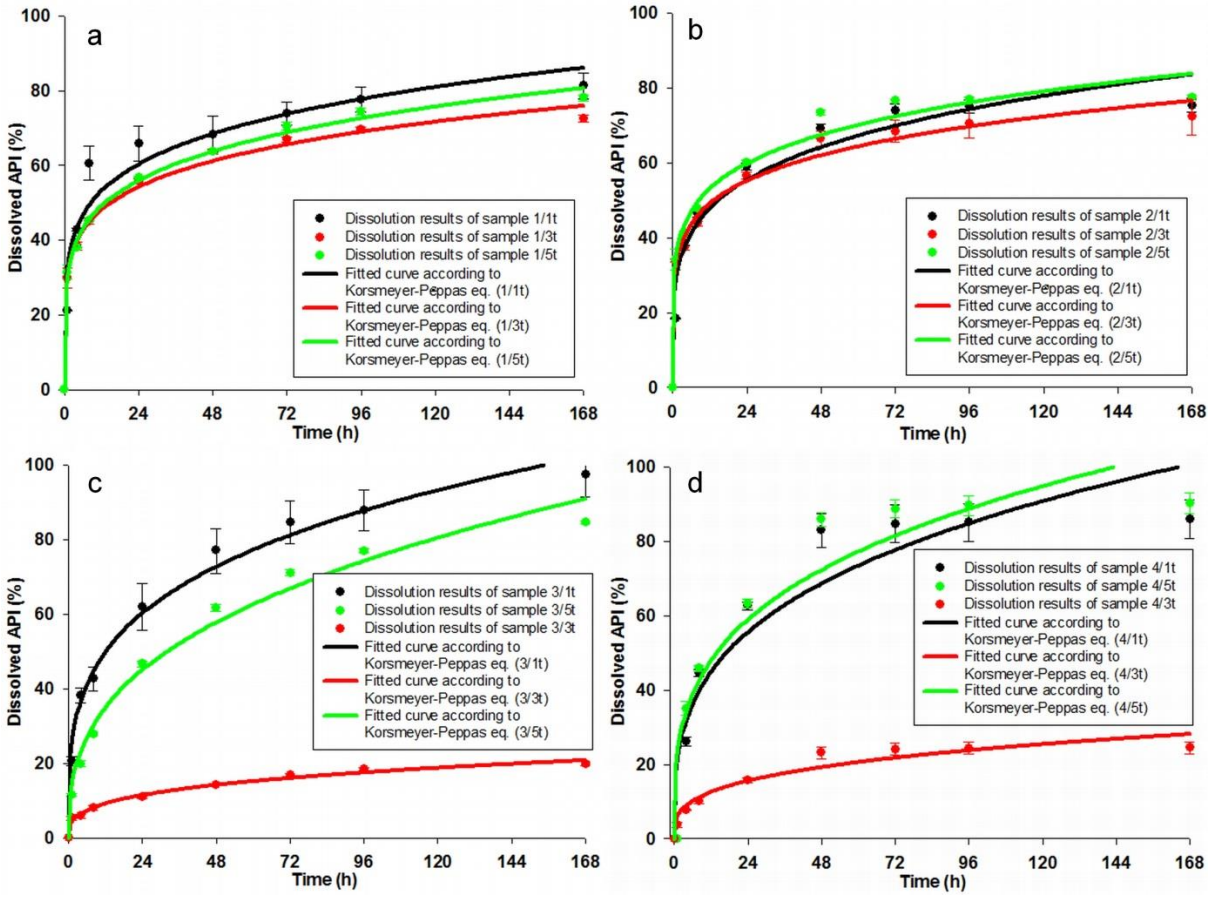

Figure 3. Drug dissolution curves of the CA-1 (a), CA-2 (b), CA-3 (c) and CA-4 (d) samples

4.1.4 Investigation of drug-carrier interactions

To reveal the mechanism of interactions the influence of the wet media was also tested. A tablet was placed into the dissolution medium until the end of the disintegration process. The remaining flakes were then filtered and dried.

The results of FT-IR measurements (Fig. 4) revealed that presence of drug-polymer interaction may be identified already in the directly compressed samples. It is well visible that the most characteristic peak of this region at 1549 cm^{-1} is separated to a peak doublet at 1540 and 1558 cm^{-1}, and the peak at 1567 cm^{-1} exhibits a partial left shift to 1575 cm^{-1}, indicating different strength association between the drug and polymer. Concurrently the peak of chitosan at 1302 cm^{-1} exhibits a left shift to 1321 cm^{-1}, which indicates that the amino groups of the polymer also take part in this interaction It may be stated that the present strong drug-polymer interaction is based on hydrogen bonds and not on the formation of a polyelectrolyte complex.

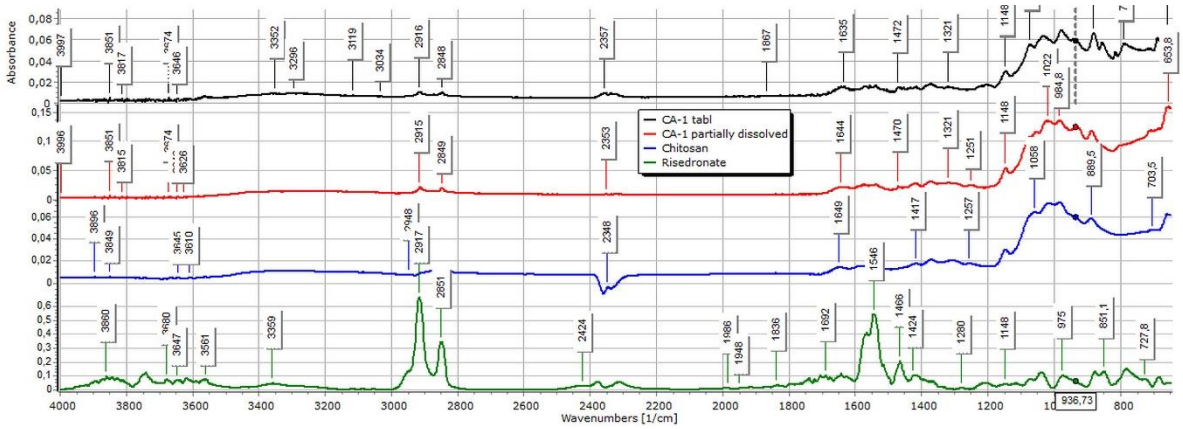

Figure 4. FT-IR spectra of CA-1 sample (CA-1 dry tablet (black), CA-1 tablet after 8h dissolution and drying (red), Chit (blue) and RIS (green)

The presence of hydrogen bond-based interaction was confirmed also with NIR spectroscopic investigations.

In the case of PVC containing samples, and despite of the expectations, major changes were identified in the FT-IR spectrum (Fig. 5) of the partially dissolved sample.

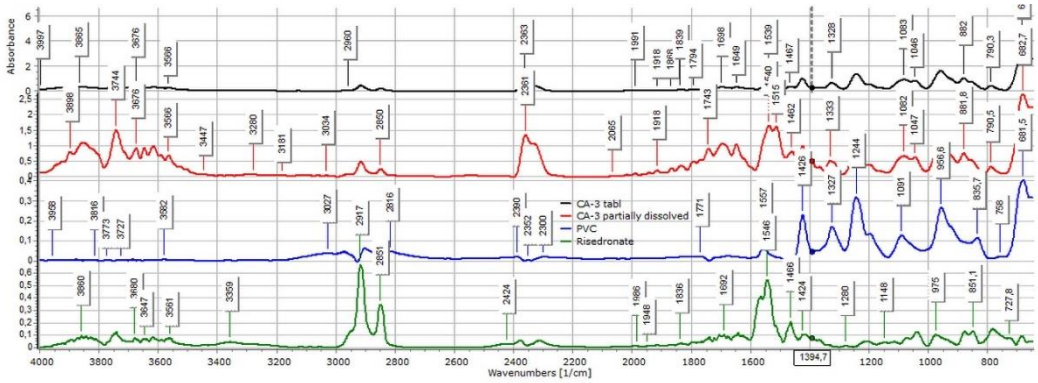

Figure 5. FT-IR spectra of CA-1 sample (CA-3 dry tablet (black), CA-3 tablet after 8h dissolution and drying (red), PVC (blue) and RIS (green)

4.1.5 Brief discussion

The results confirmed that both the chitosan and the PVC based matrix systems may be applicable for long term bisphosphonate delivery. The unexpected, in-situ emerging hydrogen bond between the drug and polymer ensuring the prolongation of drug release may have significant importance and enable a new way for modification and tailoring of drug release. Nevertheless, the PVC-based system mostly fulfilled the predefined QTTP, the hardness of matrices compressed with 3t force was within the optimum 80-120 N hardness range, while the achieved kinetic model projected more than 1 year-long dissolution time.

4.2 Matrices for the investigation of the role of chemical interactions

4.2.1 Physical parameters

The statistical evaluation of the effect of compression pressure (x_1), amount of excipient (x_2), API (x_3) and excipient used (x_4) on hardness (y_1) and porosity (y_2) of the various compositions are displayed in equations 3 and 4, respectively. The significant factors and factor interactions are highlighted in boldface in all cases.

$$y_1=110.11+\mathbf{47.02x_1}+\mathbf{9.46x_1^2}+\mathbf{19.31x_2}-\mathbf{10.04x_3}-\mathbf{29.78x_4}+2.45x_1x_2+2.45x_1^2x_2+2.29x_1^2x_2^2-\mathbf{6.31x_1x_3}-\mathbf{4.29x_1^2x_3}+\mathbf{4.96x_1x_3^2}-\mathbf{3.62x_1^2x_3^2}-3.32x_2x_3^2-\mathbf{11.48x_2x_4}-2.24x_2^2x_4-2.33x_3x_4+\mathbf{6.83x_3^2x_4} \quad (3)$$

R^2=0.9743 adj. R^2=0.9599 MS Res=123.02

$$y_2=0.133-\mathbf{0.053x_1}-\mathbf{0.023x_1^2}-\mathbf{0.046x_3}+\mathbf{0.018x_4}+\mathbf{0.024x_1x_2}-\mathbf{0.019x_1x_2^2}+0.012x_1^2x_3+0.011x_1^2x_3^2-0.014x_1x_4-\mathbf{0.033x_2x_3}-0.009x_2x_3^2+0.010x_2^2x_3^2-0.009x_2x_4+\mathbf{0.016x_2^2x_4} \quad (4)$$

R^2=0.7627 adj R^2=0.6775 MS Res=0.0023

The porosity of the system exhibited a well-established logarithmic correlation with tablet hardness, the increase of pressure resulted in stronger matrices and decrement in porosity.

The results revealed that matrices made of EE could reach higher breaking hardness and lower porosity than the tablets made of EL. The composites containing more methacrylate copolymer and less PVC appear to be the strongest systems

4.2.2 Investigation of drug-carrier interactions

According to our primary hypothesis, the interaction potential of the studied APIs is decreasing in the order of ACE>DIS>>PAR and stronger interactions were expected with EE than with EL in all cases. The results generally confirmed this hypothesis.

The Fig. 6 displays the IR spectra of ACE-PVC-EE composition, which exhibits intensive signs of drug-polymer interactions.

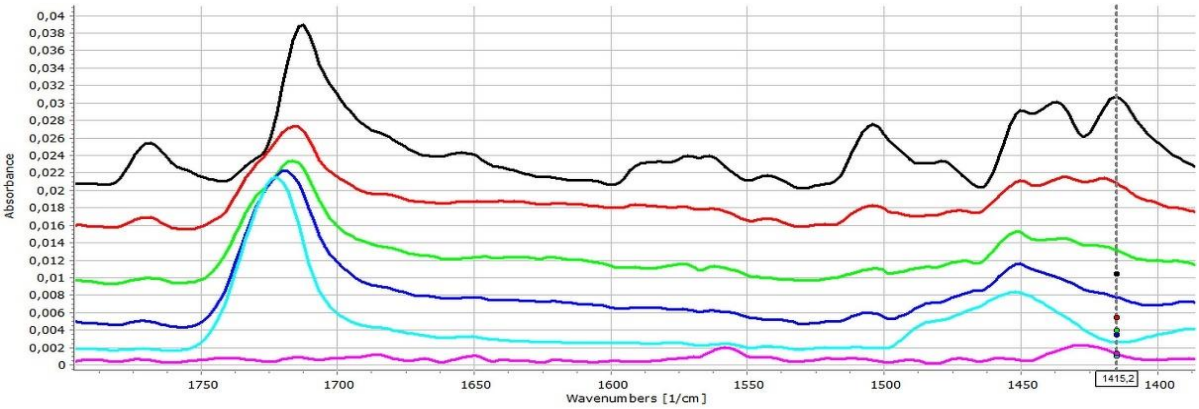

Figure 6. FT-IR spectra (1400-1800 cm^{-1} range) of the ACE (black); ACE-PVC:EE 75:25 (red); ACE-PVC:EE 50:50 (green); ACE-PVC:EE 25:75 (deep blue); EE (light blue) and PVC (purple) samples, multi cursor indicates the place of peak shift in the spectrum.

As it was expected, ACE exhibited fewer signs of interactions in relation to the acidic EL polymer.

Tablets were also dipped into pH 7.4 buffer to achieve a complete moisturization, and the samples were measured with FT-IR. The strength of intermolecular interaction has increased as effect of water absorption.

As it was expected, the matrices prepared with DIS exhibited fewer spectral changes after compression, primarily due the weaker acidity of the drug, but the higher porosity may also play a possible role in this phenomenon

In the case of PAR containing compositions exhibit no obvious signs of interaction. Nevertheless, after dipping the tablets into the dissolution medium considerable changes were observed Peak shifting suggest that the drug is connected to tertiary amino groups of the polymer.

4.2.3 Dissolution tests and kinetic study

The results of statistical analysis (Eq. 5) revealed that the main governing forces of the drug dissolution rate (y_3) are the physicochemical properties, especially the acidic strength of the drug (x_3), and the applied compression force (x_1),

$$y3=0.937-\mathbf{0.380x_1}-\mathbf{0.284x_1^2}-\mathbf{0.804x_3}+0.185x_4-0.242x_1x_2^2+\mathbf{0.403x_1x_3}+0.116x_1x_3^2+\mathbf{0.289x_1^2x_3}-0.208x_1x_4-0.181x_1^2x_4-0.241x_2x_3-0.135x_2x_3^2+0.197x_2x_4+0.116x_2^2x_4-\mathbf{0.440x_3x_4}-\mathbf{0.427x_3^2x_4} \quad (5)$$

R2=0.7669 adj R2=0.6661 MS Res=0.5176

To minimize the effect of the mechanical differences, the dissolution rates of tablets with similar porosities (0.13±0.02) were compared (Fig 7a). The results met with the expectations since EE-based compositions exhibited considerably lower dissolution rates in all cases.

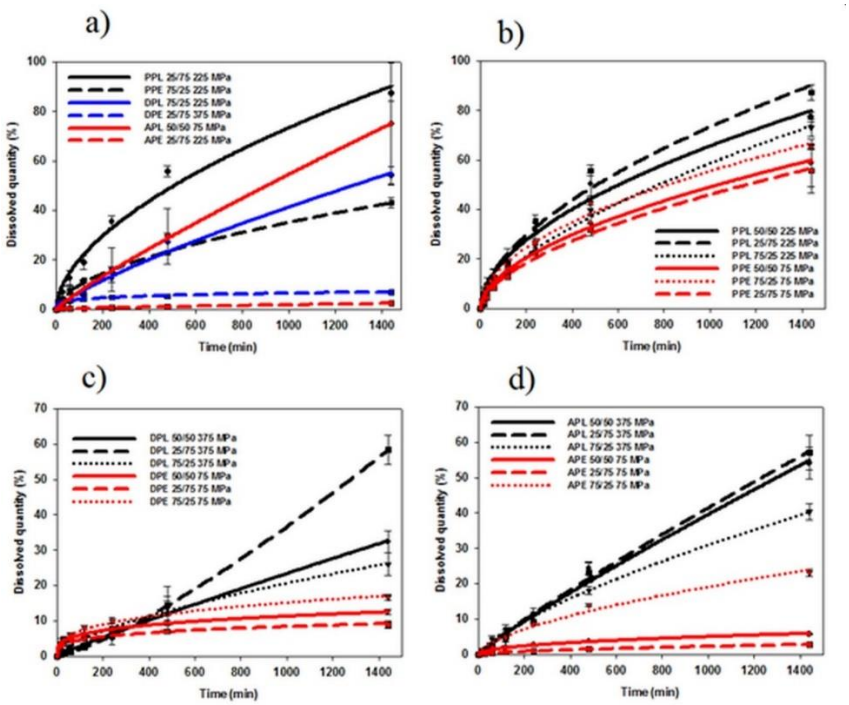

Figure 7. 24 h drug release from various non-degradable matrices: effect of the drug and polymer properties (a) and effect of the composition and compression force for PAR (b), DIS (c) and ACE (d) containing matrices

4.2.4 ANN modelling

The previous results confirmed, that the targeted QTTP may be achieved with the selected compositions, but tailored drug release requires accurate predictions. ANN modelling was performed to cross check the DoE-based results, and to compare the effectiveness of kinetic-based and point-to-point approaches in the predictability of the dissolution data.

The results revealed that the overall perfection of point-to-point modelling was significantly ($p<0.05$) better as of kinetic parameter-based models (0.92±0.02 and 0.87±0.03, respectively). The use of continuous inputs with appropriate descriptors of the tablet texture (hardness, porosity) enables the best prediction performance for both point-to-point and kinetic parameter-based approaches, despite of the fact that texture parameters exhibited relatively low importance in predictivity according to the results of the global sensitivity analysis.

The results of the global sensitivity analysis, which show the relative importance of various predictors (inputs) on the prediction outcome, are partly consistent with the results of the experimental design. The greatest effect was observed for drug solubility, but the pKa of the excipients and the peak shift indicating drug-excipient interactions exhibits similar importance than the compression pressure, tablet texture or the amount of excipient.

The best network for kinetic parameter-based modelling had 9 input, 7 hidden and 2 output neurons, with logistic activation on hidden and exponential on output neurons (training perfection: 0.9103, validation error: 0.0760). The structure of the best point-to-point network was 9 input, 16 hidden and 7 output neurons, with exponential activation on hidden and logistic on output neurons (training perfection: 0.9286, validation error: 83.06). Figure 8 shows the predicted dissolution curves of the best and worst predicted cases. It is clearly visible the point-to-point modeling approach showed more consistent accuracy, especially in cases where drug release was nearly linear (Fig. 7a, c). In other cases, the most considerable inaccuracies were observed at the 2, 4, and 8 h data points. Nevertheless, the predicted results were closer to the observed ones as for kinetic parameter-based models.

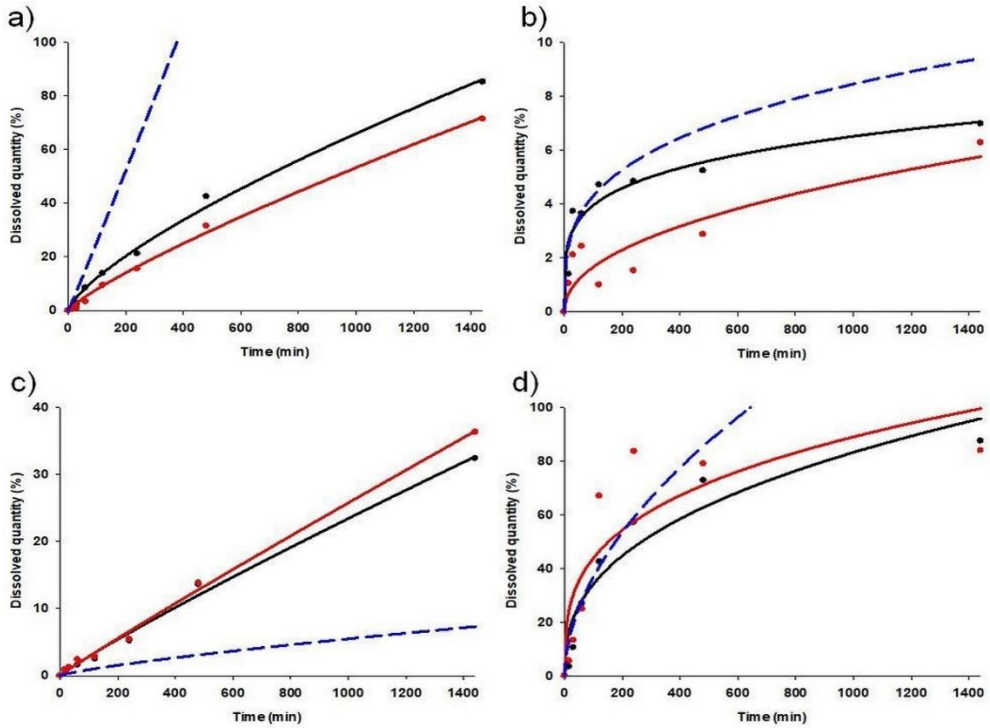

Figure 8. Observed and predicted dissolution curves of case 43 (a), case 36 (b), case 24 (c) and case 7 (d). Black dots: observed data points, black line: fitted model on observed data, red dots: predicted data points, red line: fitted model on predicted data points, blue line: predicted model.

4.2.5 Brief discussion

With help of FT-IR studies it was confirmed that solid-state interactions may be induced also in directly compressed matrix systems. The results also confirmed that the presence of solid-state interactions may not always presented in directly compressed systems, but their presence will definitely predict strong in-situ forming interactions during the drug dissolution process. The interactions are mostly H-bond based, but the forming of polyelectrolyte complexes cannot be excluded. With minimizing the influence of the solubility of the API and the porosity of the matrix, we have proven that interactions exert considerable influence on drug liberation by retaining the drug in the matrix. This helped to decrease the initial burst release of the drug, and to achieve the targeted QTTP with 80+N hardness, drug release for more than 3 month and less than 10% of drug release in the first 24 hrs. This study provides better understanding of the correlation of the physicochemical properties of materials with the drug liberation process, thereby promoting a more evolved formulation design.

5 CONCLUSION AND PRACTICAL RELEVANCE

The present dissertation introduces a comprehensive work on the development on implantable pharmaceutical drug delivery systems. Despite its indisputable advantage that it is completely absorbed by the body, the biodegradable chitosan was unsuitable to achieve the targeted QTTP, due to the fast disintegration and the initial burst release of the drug. In contrast, the non-biodegradable PVC-based matrix systems found to be applicable for long term bisphosphonate delivery. However, the burst release required further optimalization, but the utilization of in-situ emerging hydrogen bonds, firstly observed in case of chitosan-based systems between the drug and polymer enables further prolongation and tailoring of drug release.

To better understand the relevance of these interactions a systematic investigation was used. A Design of Experiments plan was set with the addition of varying APIs and excipients. Overall, the results confirmed that solid state drug-polymer interactions may be presented after direct compression of the materials. The weak solid-state H-bonds may further strengthen during the dissolution process and influence the drug release rate or in some cases, may even turn into the formation of polyelectrolyte complexes. According to our hypothesis, the interaction potential of the studied APIs can be predicted and is decreasing in the order of

ACE>DIS>>PAR and stronger interactions were expected with EE than with EL in all cases, which was confirmed by the results, noting that the dissolution rate is primarily determined by the physical properties of the matrix, and interactions play only secondary role in the process. Nevertheless, the utilization of the drug-carrier interactions enabled the further decrease of the initial burst release and helped to achieve the targeted QTTP.

It was also confirmed, that ANNs may provide useful complimentary tool for better understanding of the importance of various factors in the modelled processes. However, our hypothesis, that kinetic-based modelling approach, which allows a simplified network structure and faster generalization process will provide faster and more accurate predictions was not confirmed. On the contrary, according to our findings the point-to-point modelling approach proved more consistent accuracy, especially in cases where drug release was nearly linear.

Nevertheless, due to their advantageous properties, the ANN-based DDS design will soon become vast pillar of personalised medicine, overcoming individual differences among patients with chronic diseases. The fundaments of interaction-based matrix design are presented in this work and opens new ways to achieve tailored drug release.

LIST OF PUBLICATIONS AND CONFERENCE PROCEEDINGS

List of publications

I. T. Sovány, A. Csüllög, **E. Benkő**, G. Regdon, and K. Pintye-Hódi, 'Comparison of the properties of implantable matrices prepared from degradable and non-degradable polymers for bisphosphonate delivery', *International Journal of Pharmaceutics*, vol. 533, no. 2, pp. 364-372, Nov. 2017, doi: 10.1016/j.ijpharm.2017.07.023.

Q1 IF.: 4.09 (2017)

II. **E. Benkő**, I.G. Ilič, K. Kristó, G. Regdon Jr., I. Csóka, K. Pintye-Hódi, S. Srčič, T. Sovány. 'Predicting Drug Release Rate of Implantable Matrices and Better Understanding of the Underlying Mechanisms through Experimental Design and Artificial Neural Network-Based Modelling', *Pharmaceutics*, vol. 14, no. 2, pp. 228, Jan. 2022, doi: 10.3390/pharmaceutics14020228.

Q1 IF.: 6.29 (2021)

List of conference proceedings

Oral presentations

I. **E. Benkő**, API – polymer interaction studies in solid matrix systems, XIII. Clauder Ottó Emlékverseny, 22-23 November 2018, Budapest, Hungary

II. **E. Benkő**, API – excipient interaction studies within solid dosage forms, II. Ph.D. symposium on University of Szeged - Medical and Pharmaceutical Sciences, 30 November 2018, Szeged, Hungary

III. **E. Benkő**, T. Sovány, I. Csóka, API – excipient interactions in non-biodegradable solid matrix systems, I. Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science, 31 January 2019, Szeged, Hungary

IV. **E. Benkő**, T. Sovány, I. Csóka, API – excipient interactions in solid matrix systems, II. Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science, 23-24 January 2020, Szeged, Hungary

V. **E. Benkő**, T. Sovány, I. Csóka, API – excipient interaction and compressibility studies in solid matrix systems, Medical Conference for Ph.D. Students and Experts of Clinical Sciences, 17 October 2020, Online event, Hungary

VI. **E. Benkő**, I.G. Ilič, G. Regdon Jr., I. Csóka, K. Pintye-Hódi, S. Srčič, T. Sovány, Investigation of drug-matrix interaction in directly compressed matrices, III. Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science, 20-22 January 2021, Szeged, Hungary,

Poster presentations

VII. **E. Benkő**, G. Regdon jr., T. Sovány, API - excipient interaction studies in solid matrix systems, 12th Central European Symposium on Pharmaceutical Technology and Regulatory Affairs, 20-22 September 2018, Szeged, Hungary

VIII. **Benkő E.** , Ilič I.G., ifj. Regdon G., Srčič S., Sovány T., Mátrixtablettákon belüli fizikai kémiai kölcsönhatások hatóanyag-felszabadulásra gyakorolt befolyásának vizsgálata; Gyógyszertechnológiai és Ipari Gyógyszerészeti Konferencia 2019, 26-28 September 2019, Siófok, Hungary