



**University of Szeged**  
**Faculty of Pharmacy**  
**Institute of Pharmaceutical Technology and Regulatory Affairs**

Summary of Ph.D. Thesis

**Formulation of microcomposites and pastilles using spray-drying and melt  
technology**

**Dr. Gábor Katona**

Pharmacist

**Supervisor:**

**Prof. Dr. Habil. Piroska Szabó-Révész D.Sc.**

**Szeged**

**2017**

**University of Szeged**  
**Graduate School of Pharmaceutical Sciences**

Educational Program: Pharmaceutical Technology

Head: Prof. Dr. Piroska Szabó-Révész

Institute of Pharmaceutical Technology and Regulatory Affairs

*Supervisor: Prof. Dr. Piroska Szabó-Révész, D.Sc.*

**Dr. Gábor Katona**

**Formulation of microcomposites and pastilles using spray-drying and melt  
technology**

**Final Exam Committee**

**Head**

Prof. Dr. István Erős D.Sc., University of Szeged, Institute of Pharmaceutical Technology and  
Regulatory Affairs

**Members**

Dr. Ádám Dávid Ph.D., EGIS Plc.

Dr. Róbert Gáspár Ph.D., University of Szeged, Department of Pharmacodynamics and Biopharmacy

**Reviewers Committee**

**Head**

Prof. Dr. György Dombi D.Sc., University of Szeged, Institute of Pharmaceutical Analysis

**Reviewers**

Dr. Ildikó Bácskay Ph.D., University of Debrecen, Department of Pharmaceutical Technology

Dr. Anikó Szepes Ph.D., F. Hoffmann- La Roche Ltd.

Szeged

2017

## 1. INTRODUCTION

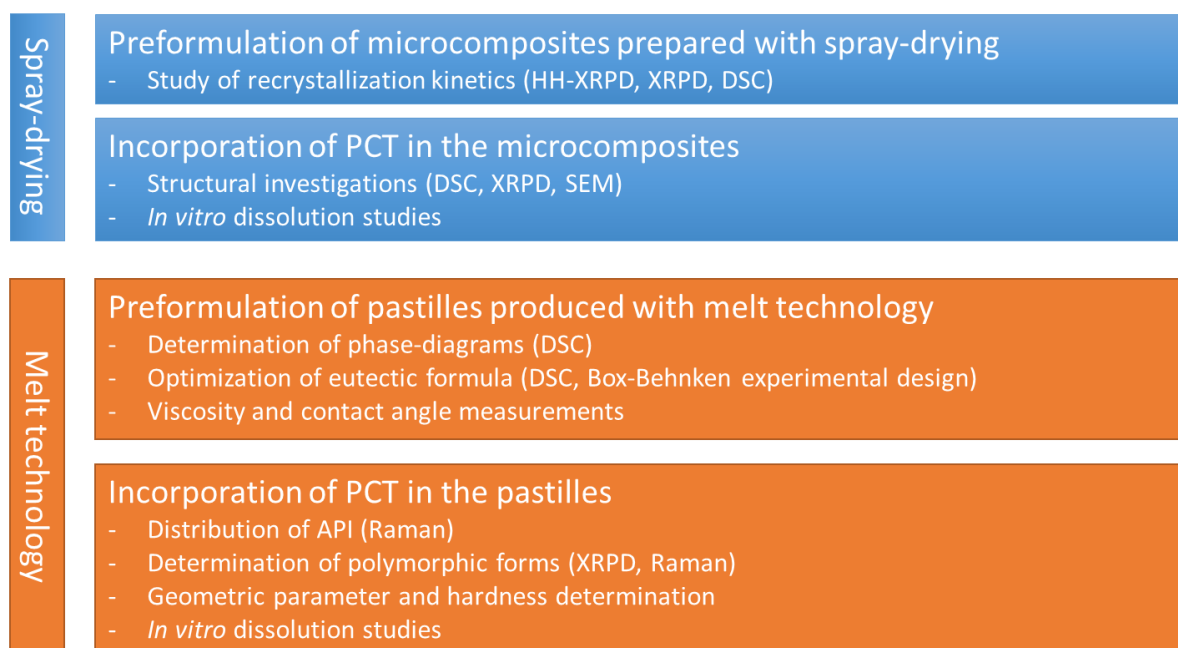
Nowadays pharmaceutical industry uses many technological operations and the number of excipients applied during production is growing. The diversity of the operation parameters can influence the quality of the product. With the innovation of production protocols, raw materials or waste elimination could be utilized efficiently, the use of toxic and/or hazardous reagents and solvents can be avoided in the manufacture and application of products. Through the minimization of the number of applied excipients, pharmaceuticals would be more “natural”. It is an important aspect for patients to reduce the contamination with different chemicals, thereby to decrease the incidence of allergy.

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving pharmaceutical development, manufacturing and quality assurance through innovation in product and process development, analysis and control (<http://www.fda.gov>). Novel trends like nanotechnology or biotechnology are in the spotlight of innovation, but the conventionally used technological processes as spray-drying or melt technology can have new approaches, which result in innovative products. These technologies can be applied in an organic solvent free manner, which adapts well to the increasing effort in the industry to introduce “green” pharmaceutical practice. Through the optimization of operation parameters, energy, production time and costs can be saved. With the reduction of e.g. temperature, the active pharmaceutical ingredient (API) can be protected from decomposition, moreover, the intermediates (microcomposites) or product (pastille) can be produced in one single operation step. In the preformulation a drug delivery system (DDS) can be developed using a factorial design, taking special requests (e.g. paediatric preparations) into account.

In paediatrics, low amounts of APIs are incorporated in DDSs, so the formulation of DDSs plays a key role in the production process. Children are special patients, their compliance can be increased by choosing a liked administration route (e.g. per os) instead of injections or suppositories. It is known that “value added” preparations are especially important in paediatric therapy, which belongs to the category of “unmet medical need”. So with the application of conventional technologies as spray-drying (Thi et al., *Int. J. Pharm.* 2012, Aguiar et al., *J. Pharm. Pharmacol.* 2016, Kaushik et al., *J. Chem. Pharm. Res.* 2015) or melt technology (Phaemachud et al., *Res. J. Pharm. Biol. Chem. Sci.* 2010) there is an opportunity to develop innovative paediatric preparations (e.g. dose sipping form and lozenge).

## 2. AIMS

The aim of our research work was to apply conventional technologies such as spray-drying and melt technologies with new approaches to research and develop innovative paracetamol (PCT) containing solid DDSs for paediatric administration. The spray-drying process was applied to prepare microcomposites for dose sipping form and the melt process was suitable to formulate pastilles with “*in situ* coating” technology as lozenge. For both technologies our research work consisted of two parts (i) development of a DDS in preformulation and (ii) incorporation of API in the DDS as carrier system. The technologies and investigations are presented in Figure 1.



**Fig. 1:** Applied technologies and investigations in the research work

The main aspects of the research work are the following:

- I. to survey the literature background of the preparation of innovative forms used in paediatric therapy with conventional methods, spray-drying and melt technology,
- II. to use these technologies innovatively, as organic solvent free methods, for producing dosage forms which do not contain any colouring agents or preservatives,
- III. to investigate the excipients used in preformulation studies of carrier systems with different screening methods,
- IV. to incorporate a low amount of PCT as model drug in the carriers, thereby designing a composition in paediatric therapy,
- V. to suggest a formulation for industrial utilization.

### 3. MATERIALS AND METHODS

#### 3.1. Materials

PCT as model drug was chosen for our experimental work; it was obtained from Sanofi Aventis (Frankfurt am Main, Germany) and D-(+)-trehalose dihydrate (TRE dihydrate) from Karl Roth GmbH+Co. KG. (Karlsruhe, Germany). This was regarded as 100% crystalline material. Anhydrous D-(+)-trehalose ( $\beta$ -form) was produced by dehydration of TRE dihydrate at 85 °C during 4 h under vacuum (Nagase et al., *Carbohydr. Res.* 2002) and checked within 24 h both with differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRPD). D-Xylitol (XYL),  $\beta$ -D-mannitol (MAN), polyethylene glycol 2000 (PEG 2000) and polyethylene glycol 6000 (PEG 6000) were purchased from Sigma-Aldrich Chemie GmbH (Mannheim, Germany) and D-Sorbitol from Molar Chemicals Ltd. (Halásztelek, Hungary).

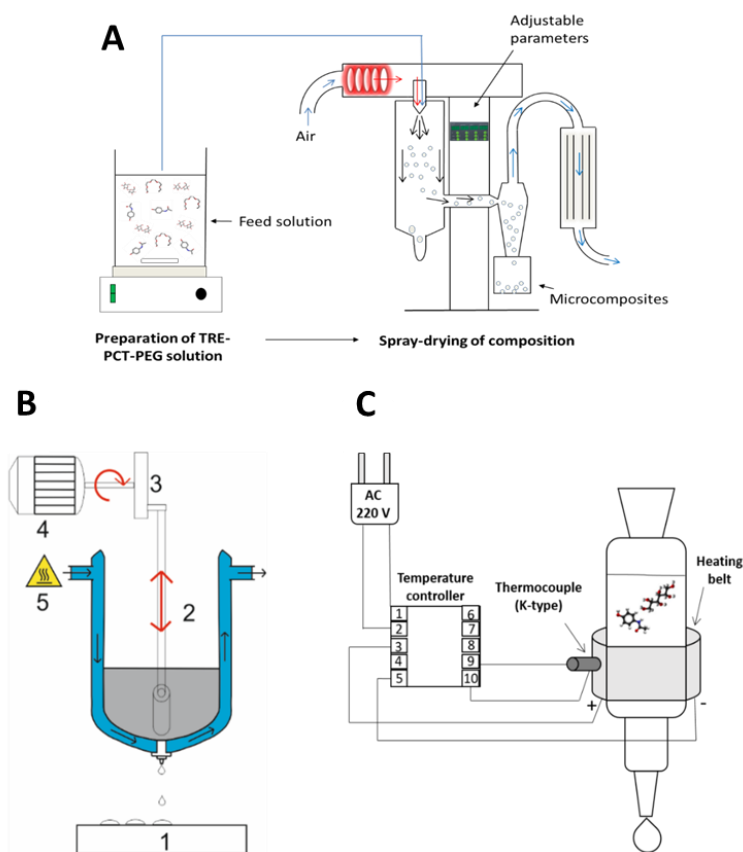
#### 3.2. Methods

##### 3.2.1. Preparation of PCT containing microcomposites and pastilles

For the investigation of recrystallization kinetic TRE dihydrate was spray-dried from 10% solutions in water using a Büchi 191 Mini Spray Dryer (Büchi, Switzerland) (Fig. 2A). The aqueous solutions used for the preparation of microcomposites contained 7.5% TRE, 1.5% PCT and 1.5% PEGs. The spray-dried products were stored in a desiccator over cobalt (II) chloride contaminated silicon-dioxide (25 $\pm$ 2 °C, 32 $\pm$ 5% RH) until use.

For pastillation, the one-drop pastillation device developed by Kaiser Steel Belt Systems GmbH (Krefeld, Germany) was used (Fig. 2B). Physical mixtures of XYL-MAN with PEG as carrier additive were prepared and melted in a temperature-controlled double-walled vessel at 110 °C. A crank shaft moved at constant rate by an engine pressed the mixture in drop form through a valve at the bottom of the vessel onto a 25 °C thermostated cooling plate, where it solidified into a flat-bottomed pastille (Wendt et al., *Chem. Eng. Technol.* 2014).

Eutectic mixtures of XYL-SORB with PEGs as carrier additives were prepared and melted in a heated pipette at 110°C. PCT was dispersed in the melted carrier. The melted solid dispersion was dropped onto a 25°C thermostated cooling plate, where it solidified to form flat-bottomed pastilles (Fig. 2C) (Bülau et al., *Shaker Verlag* 1997).



**Fig. 2:** Preparation of microcomposites with BÜCHI B-191 spray-dryer (A), one-drop pastillation device (1 - temperature controlled plate, 2 - double walled vessel, 3 - crank shaft, 4 - engine, 5 - thermostat) (B), heated pipette (C).

### 3.2.2. X-ray powder diffraction (XRPD)

XRPD analysis was performed with a Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) with Cu K  $\lambda$ I radiation ( $\lambda = 1.5406 \text{ \AA}$ ) and a VÅNTEC-1 detector. The samples were scanned at 40 kV and 40 mA. The angular range was  $3^\circ$  to  $40^\circ$   $2\theta$ , at a step time of 0.1 s and a step size of  $0.007^\circ$  in a quartz holder, at ambient temperature and RH. The determination of the polymorph forms was based on the Cambridge Crystallographic Data Centre (CCDC ID: AI631510) X-ray powder diffractograms.

### 3.2.3. Differential scanning calorimetry (DSC)

DSC measurements were carried out with a Mettler-Toledo 821<sup>e</sup> DSC instrument (Mettler-Toledo GmbH, Switzerland). Samples were crimped in aluminium pans and were examined at different temperature intervals and heating rates under a constant argon flow of 150 mL/min.

### 3.2.4. Determination of flowability parameters

The parameters of flowability were determined with software-controlled PharmaTest PTG-1 powder testing equipment (PharmaTest, Hainburg, Germany).

### 3.2.5. Particle size distribution (PSD)

PSD of the spray-dried powders were determined by laser diffraction using Malvern (Malvern Mastersizer Scirocco 2000; Malvern Instruments Ltd., Worcestershire, UK). The PSD was characterized by the  $d(0.5)$ ,  $D[3,2]$  and  $D[4,3]$  value.

### 3.2.6. Scanning electron microscopy (SEM)

The morphology of the particles was examined by SEM (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan). A sputter coating apparatus (Bio-Rad SC 502, VG Microtech, Uckfield, UK) was applied to induce electric conductivity on the surface of the samples.

### 3.2.7. Raman spectroscopy (Raman)

The uniformity of PCT content in the pastilles was investigated with Cobalt TRS 100 instrument (Cobalt Light Systems Ltd., Abingdon, UK) over the wavenumber range 1700-200  $1/\text{cm}$ . For the determination of different PCT polymorphs, a Thermo Fisher DXR Dispersive Raman instrument (Thermo Fisher Scientific. Inc., Waltham, MA, USA) equipped with a CCD camera and a diode laser operating at a wavelength of 780 nm was used.

The PCT-containing pastilles were investigated by Raman chemical mapping to localize the different forms of PCT in the composition. The chemometric processing of vibrational chemical images was studied by multivariate curve resolution alternating least squares (MCR-ALS) chemometric method.

### 3.2.8. In vitro dissolution studies

The dissolution profile of PCT from microcomposites and pastilles of different compositions was determined according to the USP-2 paddle method (Pharmatest, Hainburg, Germany). The rotating velocity of the paddle within the dissolution vessel was 75 rpm. The dissolution studies were carried out in 100.0 mL of phosphate buffer solution at  $\text{pH } 6.8 \pm 0.1$  characteristic of the oral cavity and at normal body temperature of  $37 \pm 0.5^\circ\text{C}$ , as well as in 900.0 mL of 0.1 N HCl at a gastric pH of  $1.2 \pm 0.1$  at  $37 \pm 0.5^\circ\text{C}$  (Mashru et al., *Drug. Deliv. Ind. Pharm.* 2005, Gahel et al., *Curr. Drug. Deliv.* 2009) determined spectrophotometrically at 244 nm.

## 4. RESULTS AND DISCUSSION

### 4.1. *Preformulation studies of TRE based microcomposites*

In the preformulation we investigated and quantified the physical changes of the spray-dried amorphous TRE through the use of various analytical techniques. The recrystallization kinetics can be followed, which is important because of the appearance of polymorphic forms.

#### 4.1.1. *Hot-humidity stage XRPD analysis (HH-XRPD)*

For the development and qualification of solid compositions, it is important to investigate and determine changes of the crystalline phases or the effect of crystallization inhibitor when materials are exposed to changing humidity and temperature. By increasing the RH in small intervals (10%) at the exact temperature, good estimation could be gained in a few hours at the exact temperature about the behaviour of the samples, which could be reflected in the results of the conventional stability test. There is no need for additional hygrometers and extra samples, the measurement takes place directly in the chamber connected to the instrument. The RH was set at 10, 20, 30, 40, 45, 50, 60 and 70% at 40 °C, 60 °C and 70 °C controlled temperatures, and the samples were kept in each condition for 1 h before measurement. These investigations are not only important to establish procedures for storage, production and shipment, but also emulate the digestion of the respective drug and its first interactions with the patient. In this context HH-XRPD was used to predict the tendency to recrystallization. The samples measured at 40 and 60 °C were amorphous up to 45% RH, when recrystallization began in the TRE dihydrate polymorph. The samples measured at 70 °C were amorphous up to 30% RH, then they recrystallized to dihydrate form and up to 60% RH the anhydrous form appeared, too. The diffractograms measured at 40, 60 and 70 °C showed an increasing tendency to recrystallization. The relative intensities and integrals of the peaks increased with the temperature, therefore the temperature influences the tendency of TRE to recrystallize.

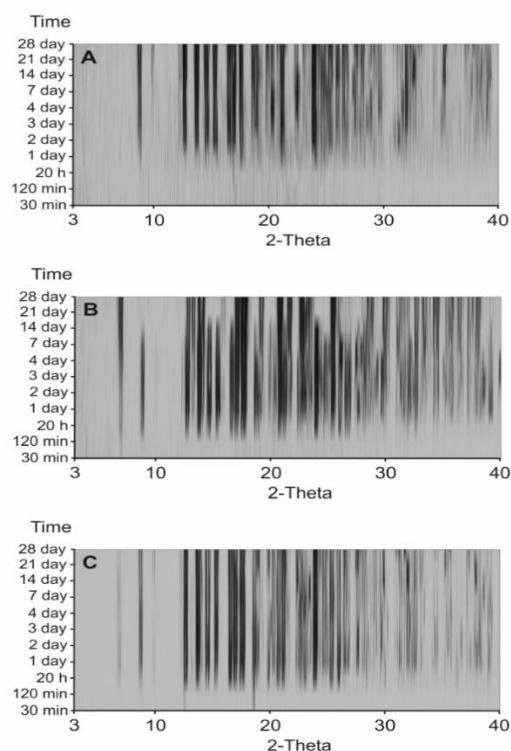
#### 4.1.2. *Analysis of samples stored in hygrometers (XRPD)*

Spray-dried products were stored for 28 days at 40 °C and 60 °C, in 3-3 hygrometers, where the RH was set to 30%, 40% and 50% RH. With this investigation we can get information about suitable storage conditions of spray-dried products.

The fractions of recrystallized TRE were measured at different times during the 28 days of storage. The conventional XRPD analysis showed that the samples stored at 40 °C, 30% and 40% RH, and at 60 °C, 30% RH remained amorphous. The samples stored at 40 °C, 50% RH recrystallized in the dihydrate form. The storage conditions at 60 °C, 40% RH resulted in the



recrystallization of the anhydrous form, and in the sample stored at 60 °C, 50% RH, both polymorphs appeared, the h-form (dihydrate) and the  $\beta$ -form (anhydrous) (Fig. 3).



**Fig. 3:** Top-view pictures of XRPD investigations of samples stored for 28 days at 40 °C, 50% RH (A), 60 °C, 40% RH (B) and 60 °C, 50% RH (C)

Figure 3B shows that the stripe at  $8.531^\circ 2\theta$  disappears after storage for 14 days, and there is a polymorph conversion of TRE dihydrate into the anhydrous form, confirmed by the characteristic thick stripe at  $6.572^\circ 2\theta$ . Figures 3A and C do not indicate any polymorph conversion.

By means of the 28-day stability tests, the different recrystallized polymorph forms can be detected and quantified. The results showed that at 40 °C and 50% RH the dihydrate was detected, but the bulk of the investigated sample remained amorphous. Storage at 60 °C and 40% RH resulted in the appearance of the anhydrous form and only a minor proportion of the sample remained amorphous. At 60 °C and 50% RH, both polymorphic forms were detected and almost the whole sample recrystallized. This conventional method is often used as a long-term stability test in the development of a drug delivery system.

#### 4.1.3. DSC investigation

Samples loaded at different RH (10, 20, 30, 40, 45, 50 and 70%) in the XRPD humidity chamber for 1 h were crimped in aluminium pans and were examined in the temperature interval

25-250 °C at a heating rate of 10 °C/min. The amount of recrystallized TRE dihydrate was calculated from the integral of the endothermic peaks at 108 °C, which is the melting point of TRE dehydrate  $\beta$ -form. The amount of crystalline fractions showed that the recrystallization of the amorphous sample is more significant with increasing RH and at 70% RH total recrystallization of the samples occurred at all 3 temperatures. The comparison of these results showed that DSC and HH-XRPD measurements correlate well. With this method, only the fraction of recrystallized TRE dihydrate can be determined. Since the anhydrous form has high melting point, the dihydrate form is converted into the anhydrous form resulting in false measurement data. However, the method can be used for fast stability testing during the preformulation.

The crystalline fractions calculated from the HH-XRPD and DSC data were plotted against time for each temperature. The sigmoidal curves showed that increased temperature accelerates the recrystallization and reduces the crystallization half-time. To acquire information about the velocity of the process and the dimensions of crystal growth, the Avrami parameters should be determined. The parameters  $K$  and  $n$  were determined by using the linearized Avrami equation. A plot of  $\ln [-\ln (1-\alpha)]$  against  $\ln (t)$  yields a straight line with slope  $n$  and intercept  $\ln K$ . The activation energy was calculated via the logarithmic form of the Arrhenius model (Table 1).

**Table 1** Avrami parameters and activation energy of recrystallization investigated with HH-XRPD and DSC

Method	$t$ (°C)	$n$	$K$	$E_a$ (kJ/mol)
HH-XRPD	40	3.373	5.79E-04	47.215
	60	3.566	1.70E-03	
	70	3.934	2.84E-03	
DSC	40	3.378	1.69E-03	41.645
	60	2.989	5.98E-03	
	70	3.156	6.29E-03	

#### 4.2. Incorporation of PCT in the microcomposites

After the preformulation studies of TRE containing carrier systems PCT was incorporated with the aim to produce microcomposites for preparation of dose sipping form. Because spray-drying results in amorphization in TRE, the dissolution time is fast enough for the liberation of the API to occur in the liquid media during application. By assuring low RH during the preparation and storage, the amorphous form can be preserved. To reduce the adhesion of microparticles due to the electrostatic charge, PEGs were added to the formulation. After spray-drying the PCT-containing microcomposites, dosage form investigations were carried out. First, we studied the

moisture content, flowability of the products, then the structure of microcomposites was checked before and after storage, finally the dissolution extent was measured.

#### 4.2.1. Moisture content determination and flowability study

Analysing the moisture content of microcomposites is important because of the microbiological stability, as TRE is a good soil of microorganisms and to avoid recrystallization. That is why we tried to minimize it in the samples. Moisture content determination was carried out with thermogravimetric analysis (Mettler-Toledo TG/DSC1), another important parameter is flowability because of the filling of microcomposites in the straw (Table 2).

**Table 2** Moisture content and flowability parameters of spray-dried samples

Sample	Flow time (s)	Angle of repose (°)	Volume (mL)	Mass (g/100 mL)	Bulk density (g/mL)	Moisture content (%)
TRE-PCT	16.5	19.6	46.6	16.65	0.167	6.24
TRE-PCT- PEG 2000	12.6	8.8	27.5	14.31	0.143	4.05
TRE-PCT- PEG 6000	9.6	6.3	20.2	12.81	0.128	2.79

It can be concluded that the PEG containing samples have shorter flow time because of the low electrostatic charge. PEG containing samples also have lower moisture content, which can predict a better microbiological stability.

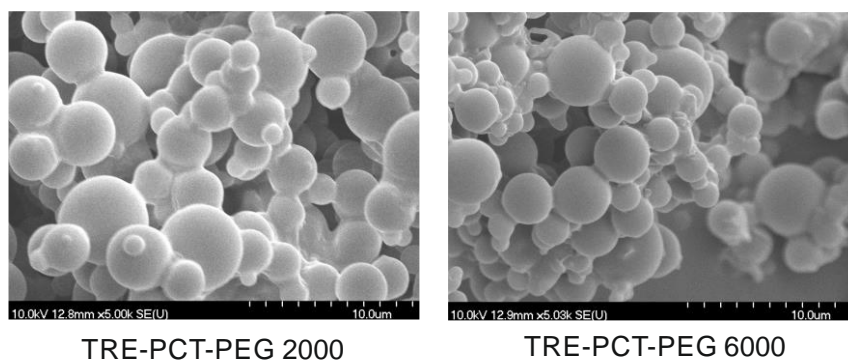
#### 4.2.2. PSD and SEM images

As moisture content determination and flowability studies showed that PEG containing samples have better properties, the further investigations were carried out only with these samples. The particle size and the PSD of spray-dried PEG containing samples were determined with laser diffraction analysis (Table 3).

**Table 3** Influence of different PEGs on PSD of microcomposites

Samples	d(0.5) [ $\mu\text{m}$ ]	D[3,2] [ $\mu\text{m}$ ]	D[4,3] [ $\mu\text{m}$ ]
TRE-PCT-PEG 2000	10.711	8.893	13.685
TRE-PCT-PEG 6000	6.897	5.667	7.938

Laser diffraction analysis shows the average particle size of PEG 6000 containing microcomposites is smaller than that of PEG 2000 containing ones. Spray-drying resulted in monodisperse distribution in both PEG containing compositions. Their morphology was investigated with SEM (Fig. 4).



**Fig. 4:** SEM images of PEG containing samples

The SEM images reveal that in both cases spherical microcomposites were produced, their surface was uniform, no fracturing could be observed on it.

#### 4.2.3. *In vitro* dissolution

In the *in vitro* dissolution studies three parallel measurements were carried out, in which the PCT dissolutions of different PEG containing microcomposites were compared at the oral cavity pH (pH  $6.8\pm 0.1$ ) and in the gastric juice (pH  $1.2\pm 0.1$ ).

In both cases, the PCT was practically fully dissolved from the microcomposites in the medium of the oral cavity (pH  $6.8\pm 0.1$ ) within 2 min. The fast dissolution kinetics can be explained with the high specific surface. In the acidic medium (pH  $1.2\pm 0.1$ ), the PCT also practically fully dissolved from the microcomposites within 2 min. A burst effect can be observed on the curve of the PEG 2000 containing product, which can be explained with the amorphization of the sample.

### Summary

In the preformulation study of spray-dried microcomposites, the three analytical methods (HH-XRPD, XRPD, DSC) were compared to investigate the recrystallization of amorphous TRE. In this light, the suitable choice of the storage conditions can protect the amorphous TRE samples from crystallization. In view of these results, TRE is applicable for formulating API containing microcomposites with spray-drying.

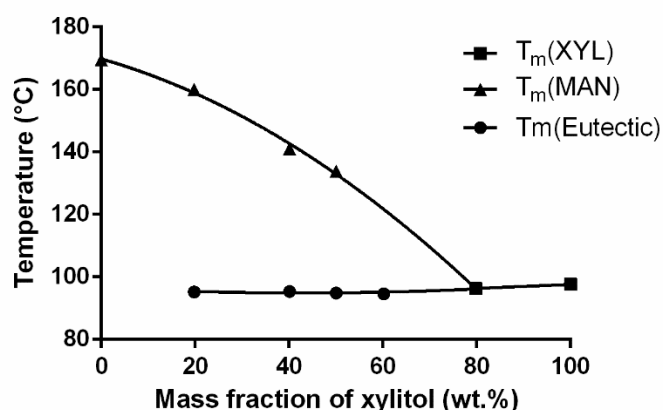
After the incorporation of PCT in microcomposites it was revealed that the use of PEGs in the formulation decreased the electrostatic charge of the particles and produced good flow properties. Dissolution studies showed PCT was fully dissolved in the medium after 2 min. According to these results, the two PEG containing compositions can be utilized for the formulation of dose sipping form and paediatric application.

### 4.3. Preformulation of PCT containing pastilles produced with melt technology

#### 4.3.1. Phase diagrams of sugar alcohols

In the development of a carrier system (DDS) for melt technology, the physico-chemical interactions of the components should be examined in order to determine the optimum composition for pastille-forming method.

Determination of the phase diagram of XYL–MAN and XYL–SORB physical mixtures is necessary to find the eutectic melting temperature and to understand the mechanism of crystallization of the pastille. 100 mg of solid XYL–MAN and XYL–SORB dispersions of different ratios were prepared and the melting temperatures for the phase diagram were collected with DSC. The point of interception of the curves on the binary phase diagrams indicated the eutectic concentration at 90 wt.% XYL–10 wt.% MAN and 50 wt.% XYL–50 wt.% SORB. Because the eutectic mixture of XYL and MAN results in rapid solidification, it is necessary to apply PEG as softener material. The ternary phase diagram of xylitol, mannitol and PEG 6000 was also investigated in certain cases with a constant amount of PEG 6000 (7.81 %) (Fig. 5). It turned out that, in the presence of this quantity of PEG 6000, the eutectic concentration of XYL and MAN was at 80 wt.% XYL and 20 wt.% MAN.



**Fig. 5:** The XYL–MAN phase diagram in the presence of a fixed amount of PEG 6000 (7.81 mg per 100 mg)

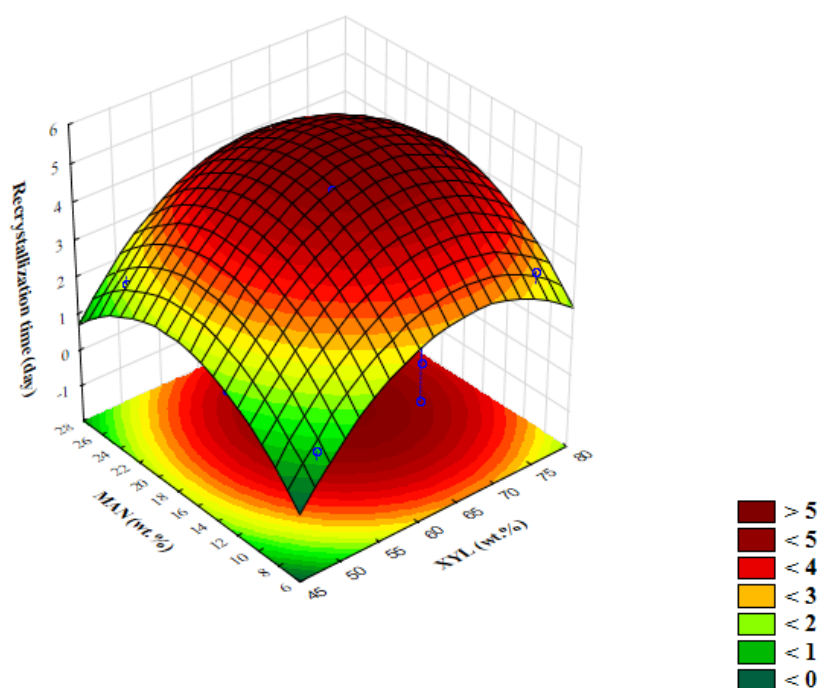
#### 4.3.2. Optimization of eutectic formula

Our target was to develop a pastille containing 40 mg PCT. Since PEG 6000 was found to influence the eutectic concentration of XYL–MAN, a Box-Behnken experimental design was carried out to optimize the formulation as concerns the carrier. Three experimental factors (XYL, MAN and PEG 6000) were varied in the design, at 3 levels in 15 runs so as to construct the surface plot for the optimization process (Table 4) according to the recrystallization time.

**Table 4** Variables and their levels in the Box-Behnken design

Independent variables (factors)	Levels		
	-1	0	1
	<b>Contents of components (wt.%)</b>		
<b>XYL</b>	48.13	61.25	75.94
<b>MAN</b>	6.88	15.31	25.31
<b>PEG 6000</b>	0	7.81	15.63

Recrystallization begins on the shell of the pastille and tends inwards to the core. If this process takes place too quickly, the dissolved melt components with higher melting temperatures (PCT and MAN) recrystallize first and their crystals sink to the bottom of the pastille, resulting in an inhomogeneous distribution. A composition was first sought in which recrystallization was slow enough to preserve the homogeneous distribution of the components. The experimental results showed that each of the three components exerted a significant effect on the recrystallization. At a 95% confidence level, the coefficients differed from zero and the P-values were  $<0.05$ , the time of recrystallization depending significantly on the fractions of the components. The surface plot illustrates the recrystallization times of the different component ratios (Fig. 6).

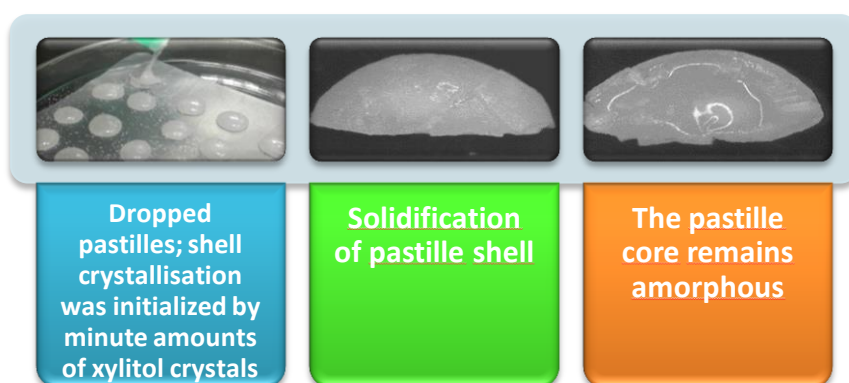
**Fig. 6:** Surface plot illustrating optimization of the XYL–MAN–PEG 6000 containing carrier

The surface plot depicts recrystallization times from 1 to 5 days. The maximum in the plot is observed at 61.25 wt.% XYL, 15.31 wt.% MAN, which corresponds to the eutectic composition. The composition also included 7.81 wt.% PEG 6000, and the PCT content of the pastille was

15.63 wt.%. In case of XYL–SORB pastilles we used 38.28 wt.% XYL, 38.28 wt.% SORB (which corresponds to the eutectic composition), 15.63 wt.% PCT and 7.81 wt.% PEG 2000 / 6000, because PEGs had no significant influence on the eutectic concentration of sugar alcohols.

#### 4.4. Pastillation process with PCT

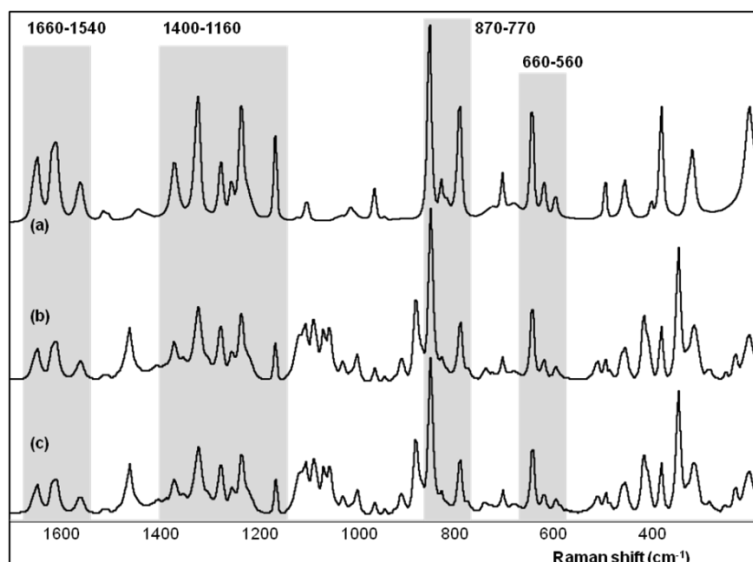
On the basis of the factorial design, for XYL-MAN containing pastilles 61.25 wt.% XYL, 15.31 wt.% MAN, 7.81 wt.% PEG 6000 and 15.63 wt.% PCT (Fig. 6) were used and for XYL-SORB containing pastilles 38.28 wt.% XYL, 38.28 wt.% SORB, 15.63 wt.% PCT and 7.81 wt.% PEG 2000/6000 (Fig. 7). This gave the best pastille shape without visible pores, and a homogeneous shell texture. The PEG content resulted in an appropriate crystallization time and decreased the melting temperature of the mixture through the formation of a solid dispersion (Akiladevi et al., *Int. J. Pharm. Sci.* 2011).



**Fig. 7:** Steps of pastillation process

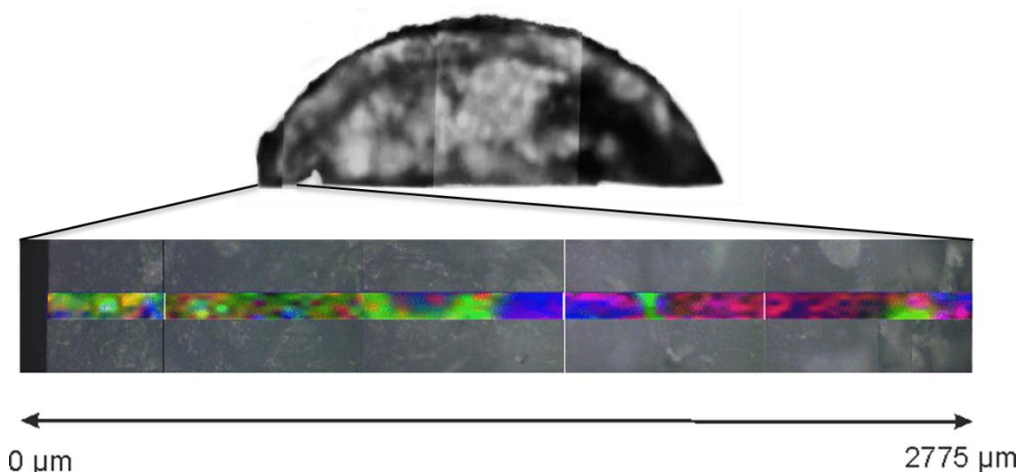
##### 4.4.1. Raman spectroscopy

Because of the slow solidification, the distribution of the PCT in the pastilles was first investigated by TRS. Figure 8 shows the transmission Raman spectra of pure PCT (**a**) and the XYL-MAN-EUT + PCT + PEG 6000 pastille shell (**b**) and core (**c**). The spectra in **b** and **c** are basically identical, the almost negligible differences involving new peaks due to the non-PCT ingredients. The pastille spectra indicated that there was no change in the crystal modification of the material in the sample tray during the measurement, with the main characteristic Raman bands of PCT in the intervals of 1660-1540, 1400-1160, 870-770 and 660-560 1/cm. The identity of spectra **b** and **c** confirmed the uniform distribution of PCT throughout the pastilles.



**Fig. 8:** Transmission Raman spectra of the starting PCT **(a)**, the shell of XYL-MAN-EUT + PCT + PEG 6000 pastille **(b)** and the core of the PCT containing pastille **(c)**

Figure 9 shows the distribution map of different forms of PCT and XYL in one pastille at 10\* magnification. The resolution of the chemical map and therefore the identification of the ingredients present can be produced using multivariate curve resolution – alternating least squares (MCR-ALS) chemometric method. The purpose of the analysis was to investigate the distribution of the PCT and xylitol in the pastille. According to the chemical mapping, in fact, PCT can be found in well-defined packages inside the pastilles, properly to the stratification of the pastille inner structure. The higher XYL (marked in green colour) concentration of the pastille’s outer shell was also confirmed by Raman mapping.

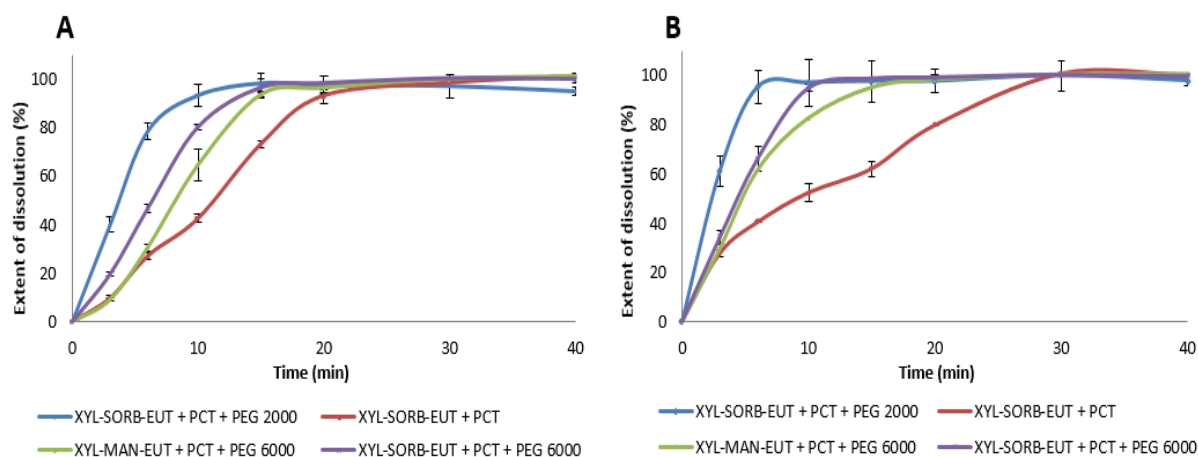


**Fig. 9:** Raman distribution map of two PCT polymorphs (monoclinic PCT-blue, orthorhombic PCT-red) and xylitol (green) in one whole pastille (at 10\* magnification).



#### 4.4.2. *In vitro* dissolution studies

*In vitro* dissolution studies of PCT containing pastilles after the total recrystallization (5 days) were carried out. In three parallel measurements, the PCT dissolutions of the pastilles produced from different compositions were compared at the oral cavity pH (pH 6.8±0.1) and in the gastric juice (pH 1.2±0.1) (Fig 10A and B).



**Fig. 10:** Dissolution extents of drop-melted pastilles at the oral cavity pH (pH 6.8±0.1) and in the gastric juice (pH 1.2±0.1) (average value±SD, n=3).

In all cases, the PCT was practically fully dissolved from the pastilles in the medium of the oral cavity (pH 6.8±0.1) within 20 min. In the acidic medium (pH 1.2±0.1) the PCT also practically fully dissolved within 20 min in the case of the PEG-containing pastilles. The pastille without PEG dissolved only after 30 min. The differences in the extents of dissolution can be explained by the different surface free energies of the pastilles. The lower surface free energy of the (PEG)-containing pastilles resulted in higher polarity and faster dissolution than in the case of the pastille without PEG. When the pastille is swallowed, the liberation of PCT also occurs, but 5 min longer is required than in the mouth. It could be concluded that, by using PEGs, the wettability and therefore the dissolution time of the pastilles were improved, which justified this dosage form.

#### Summary

This part of experimental work discusses the application of developed carrier system and the melt technology to have a PCT containing pastille as new lozenge dosage form for children therapy. The eutectic composition of XYL-MAN and XYL-SORB was first determined by constructing the binary phase diagram from the DSC data. As a component of the carrier, PEG as a softener agent did not inhibit the recrystallization of the components, solidification occurred in the pastilles and the shell especially consisted of XYL. The Raman measurement showed the homogenous distribution of components in the pastille.

## 5. CONCLUSIONS

The aim of our research work was to apply conventional technologies such as spray-drying and melt technologies with new approaches to research and develop innovative PCT containing solid DDSs for paediatric administration. The spray-drying process was applied to prepare microcomposites for dose sipping form and the melt process was suitable to formulate pastilles with “*in situ* coating” technology as lozenge.

I. First we surveyed the literature background of innovative forms used in paediatric therapy with conventional technologies, spray-drying and melt technology. In this part of work, the possibilities of innovation, the viewpoints of development of paediatrics, preparation methods and two innovative dosage forms were surveyed. Examples related to spray-drying and melt technology were collected. Finally, the pros and cons of the dose sipping form and lozenges were collected as “value added” preparations for “unmet medical need”.

II. In the experimental part, two conventional technologies were applied to formulate different innovative DDSs in an organic solvent free manner for oral administration. One of the formulations was microcomposites produced with spray-drying, which can be applied as a dose sipping form. The other drug delivery systems were lozenges formulated with *in situ* coating technology. These formulations did not contain any colouring agents or preservatives.

III. The spray-dried TRE carrier was investigated with different screening methods. The investigation of spray-dried TRE suggested a method which is sensitive and rapid to predict the recrystallization process in the preformulation study. In this light, the suitable choice of the storage conditions can protect the amorphous TRE samples from crystallization. It could be concluded that HH-XRPD is faster than other conventional techniques and a good prediction for the recrystallization of amorphous compounds during preformulation, moreover, the physical changes could be studied on one sample. In view of these results, TRE was applicable for formulating API containing microcomposites with spray-drying.

Melt technology was the development of such crystalline drug carrier/basis for pastilles which consists of two-two well-recrystallized sugar alcohols and PEG as poor crystallization inhibitor. This carrier system is suitable for use in melt technology to formulate pastilles containing recrystallized PCT.

IV. After the incorporation of a low amount of PCT in the forms, dosage form investigations were carried out. The investigation of microcomposites showed that the use of PEGs in the formulation decreased the electrostatic charge of the particles and produced good flow properties. Spray-drying resulted in amorphization in the samples (TRE, PCT),  $T_g$  could be determined, PEGs remained semicrystalline in the formulations. After 3 months the samples remain amorphous at ambient temperature and RH. In the pastilles solidification occurred after 5 days

and the shell consisted of mainly XYL. The Raman measurement justified the homogenous distribution of the components in the pastille. The *in vitro* dissolution studies showed in the presence of PEGs the extent of PCT dissolution was higher than from the pure eutectic because of its lower surface free energy and higher polarity.

V. All in all, we can conclude spray-drying and melt technology can be utilized in the industry for producing dosage forms without any organic solvents, colouring agents and preservatives, using natural excipients, which can be well tolerated e.g. in children's therapy.

Practical relevance and new approaches of this research work are the followings:

1. Spray-drying and melt technology as conventional technologies are suitable to formulate different innovative DDSs in an organic solvent free manner, without any colouring- or preservative agents, avoiding lactose and sucrose, meeting the requirements of paediatric therapy.
2. TRE based microcomposites made by spray-drying technology can be successful in development of amorphous DDS.
3. Two sugar alcohols and PEG based DDSs result in new compositions for melt technology (*in situ* coating process).
4. Suggested new formulations may be the PCT containing dose sipping form and pastilles as lozenge, which can be utilized in the industry for paediatric preparations.

## Publications related to the thesis

1. **Katona G.**, Jójátrné Laczkovich O., Szabóné Révész P.: A trehalóz, mint amorfizálódásra hajlamos segédanyag, rekrisztallizációjának vizsgálata, *Acta Pharm. Hung.* (2014), 84, 7-14.
2. **Katona G.**, Sipos P., Frohberg P., Ulrich J., Szabó-Révész P., Jójátr-Laczkovich O.: Study of paracetamol-containing pastilles produced by melt technology, *J. Therm. Anal. Calorim.* (2016), 123, 2549-2559. (IF: 2.042, Citation: 2)
3. Jójátr-Laczkovich O., **Katona G.**, Aigner Z., Szabó-Révész P.: Investigation of recrystallization of amorphous trehalose through hot-humidity stage X-ray powder diffraction, *Eur. J. Pharm. Sci.* (2016), 95, 145-151. (IF: 3.773, Citation: -)
4. **Katona G.**, Szalontai B., Budai-Szűcs M., Csányi E., Szabó-Révész P., Jójátr-Laczkovich O.: Formulation of paracetamol-containing pastilles with in situ coating technology, *Eur. J. Pharm. Sci.* (2016), 95, 54-61. (IF: 3.773, Citation: -)

## Other publications

1. **Katona G.**, Jójátrné Laczkovich O., Szabóné Révész P.: Fagyasztva szárítás az innovatív gyógyszerkészítmények előállításában, *Gyógyszerészet* (2014), 58, 546-553.
2. Bartos Csi., Szabó-Révész P., Bartos Csa, **Katona G.**, Jójátr-Laczkovich O., Ambrus R.: The effect of an optimized wet milling technology on the crystallinity, morphology and dissolution properties of micro- and nanonized meloxicam, *Molecules* (2016), 21, 507. (IF: 2.465, Citation: -)

## Presentations related to the thesis

1. **Katona Gábor**, Jójártné Laczkovich Orsolya, Szabóné Révész Piroska: Porlasztva- és fagyasztva szárított trehalóz visszakristályosodásának vizsgálata. Congressus Pharmaceuticus Hungaricus XV., Budapest, Magyarország, 2014. április 10-12. (poster presentation)
2. Jójártné Laczkovich Orsolya, Mártha Csaba, **Katona Gábor**, Szabóné Révész Piroska: Gyógyszertechnológiai formulálások során alkalmazott cukrok, cukoralkoholok amorfizálódási tulajdonságai. MKE Kristályosítási és Gyógyszerformulálási Szakosztály 7. Kerekasztal Konferenciája, Szeged, Magyarország, 2014. május 16-17. (verbal presentation)
3. Jójártné Laczkovich Orsolya, **Katona Gábor**, Szabóné Révész Piroska: Trehalóz rekrisztallizációs kinetikájának termoanalitikai vizsgálata. Termoanalitikai Szeminárium. Szeged, Magyarország, 2014. november 21. (verbal presentation)
4. Orsolya Jójárt-Laczkovich, **Gábor Katona**, Zoltán Aigner, Piroska Szabó-Révész: Investigation of amorphous trehalose using hot-humidity stage X-ray powder diffraction. 6th BBBB - Conference on Pharmaceutical Sciences: Strategies to Improve the Quality and Performance of Modern Drug Delivery Systems, Helsinki, Finland, 2015. szeptember 10-12. (poster presentation)
5. **Gábor Katona**, Péter Sipos, Patrick Frohberg, Joachim Ulrich, Piroska Szabó-Révész, Orsolya Jójárt-Laczkovich: Formulation of paracetamol-containing pastilles with in situ coating technology. 6th BBBB - Conference on Pharmaceutical Sciences: Strategies to Improve the Quality and Performance of Modern Drug Delivery Systems, Helsinki, Finland, 2015. szeptember 10-12. (oral poster presentation)
6. **Katona Gábor**, Sipos Péter, Frohberg Patrick, Ulrich Joachim, Szabó-Révész Piroska, Jójárt-Laczkovich Orsolya: Paracetamol tartalmú pasztillák előállítása "in situ coating" technológiával. Gyógyszertechnológiai és Ipari Gyógyszerészeti Konferencia 2015. Siófok, Magyarország, 2015. október 15-17. (verbal presentation)
7. Jójártné Laczkovich Orsolya, **Katona Gábor**, Bónis Erzsébet, Szabóné Révész Piroska: Kíméletes technológiák, amelyek alkalmasak fehérje természetű anyagok formulálására. Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium '16, Herceghalom, Magyarország, 2016. szeptember 15-16. (verbal presentation)
8. **Katona Gábor**: Paracetamol tartalmú pasztillák formulálása "in situ coating" technológiával. XII. Clauder Ottó emléktverseny, Budapest, Magyarország, 2016.10.20-21. (verbal presentation)