BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
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GEORGE A. OLAH DOCTORAL SCHOOL

The role of formulation additives in the bioavailability of active pharmaceutical ingredients

Summary of Ph.D. dissertation

Author: Enikő Jaksáné Borbás
Supervisor: Dr. Zsombor Kristóf Nagy
Co-supervisor: Dr. Bálint Sinkó

Technology of Pharmaceutical, Environmental and Safety Materials Research Group
Department of Organic Chemistry and Technology
Budapest, Hungary
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ITRODUCTION

Traditional dissolution tests have been used in the pharmaceutical industry to perform quality control of manufacturing process for drug products, and to compare performance of different drug product formulations during their development process. Although dissolution tests are well suited for quality control purposes providing a simple, reproducible and cost-effective way of analyzing final dosage forms, the results of these tests are often not *in vivo* predictive.[1]

From the research and development point of view however the industry seeks new tools for improving the biorelevance and the *in vivo* predictability of the *in vitro* tests. Underneath the urge to minimalize clinical trials by using *in vitro* and *in silico* tools lay many ethical and economic reasons. Since it is common cause, multiple research co-operations were founded worldwide to better understand *in vivo* processes of the gastrointestinal tract (UNGAP project in the European Union) and to develop new tools that might be able to predict the drug performance in patients (ORBITO project in the European Union and formulation predictive dissolution (fPD) project in the United States of America). Although it cannot be compared to the abovementioned research co-operations in size and budget, a research partnership has also been made by Pion Inc., Semmelweis University (SE) and Budapest University of Technology and Economics (BME). Pion Inc. builds new *in vitro* apparatuses that enable the use of simultaneous dissolution-permeation tests with artificial membranes, while the two Universities provide theoretical background in pharmaceutical chemistry and formulation development in order to understand how *in vitro* dissolution and permeation processes work in the presence of formulation additives and also to establish *in vitro- in vivo* correlation (IVIVC).

This PhD thesis was prepared in the framework of the Pion-SE-BME research partnership. Therefore the aim of this thesis work was to understand how simultaneous dissolution-permeation assays work on a molecular level in presence of formulation additives and to use that knowledge for formulation development and establishing IVIVC.

1. LITERATURE REVIEW

Although a simple dissolution test can be used in biowaiver studies to prove the bioequivalence of a drug product containing active pharmaceutical ingredients (APIs) from Biopharmaceutical Classification System (BCS) I class, with the increasing number of poorly water soluble drugs on the market, the need for more biorelevant and therefore more *in vivo* predictive *in vitro* tool for BCS II and BCS IV class APIs is increasing from both industrial and regulatory sides. In recent years many new *in vitro* tools have been developed to improve the IVIVC by the simultaneous testing of dissolution and permeation.[1] Parallel Artificial Membrane Permeability Assay (PAMPA) has been shown to be predictive of passive transcellular permeability[2], while having the advantage of being a reproducible and cost-effective way of testing formulations compared to cell-based assays or animal tests. Therefore, it was proposed that a scaled-up version of a PAMPA-like setup could become a way of combining dissolution and permeation testing. Although by enabling simultaneous measurement of dissolution and permeation, it has the potential to improve IVIVC.[3]

In case of a development of a new *in vitro* apparatus the understanding of its working mechanism in a molecular level can be crucial. It was shown by many publications, that the driving force of membrane transport through *in vivo* and *in vitro* lipophilic barriers cannot be simplified to the concentration gradient, especially in cases, where solubility of the API is altered, namely by increasing the solubility, the permeability decreases.[4] Surprisingly, in the case of studying flux across regenerated cellulose-based size-exclusion membranes, the interplay between solubility and permeability was also observed when using solubilizing agents on the donor side.[5] This is an interesting phenomenon because the transport of pure API is mechanistically different through lipophilic and size-exclusion membranes.

For that reason the aim of the first part of the thesis work was to investigate the universal driving force of membrane transport through lipophilic and size-exclusion membranes and provide a mathematical description of it, which is independent from the type of formulation.

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[4] Dahan, A. & Miller, J. M. The Solubility–Permeability Interplay and Its Implications in Formulation Design and Development for Poorly Soluble Drugs. *AAPS J.* **14**, 244–251 (2012).

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The second part of the thesis work aims to focus on the applications of the dissolution-permeation assays using lipophilic membranes in formulation development. For that reason the effect of combining formulation techniques came into focus first. While several example in the literature describes the interplay between solubility and permeability in case of the addition of a single formulation additive, in reality in case of BCS II class drugs the combination of different solubility enabling techniques might be necessary to ensure the dissolution of the API. *For that reason further aim of this work was to investigate the in vitro dissolution–permeation properties of a complex formulation matrix using solubilizing additives and amorphous drug as well.*

With all theoretical knowledge in hand it is still a challenge to evaluate the results of a simultaneous dissolution-permeation test and translate it to *in vivo* results. While the comparison of *in vitro* dissolution test results are detailed in regulatory guidelines, in case of flux values new data analyzing methods might be needed to predict bioequivalence and evaluate the effect of formulation additives on permeation. *For that reason it became one of the main focus of this dissertation to compare the in vitro fluxes to in vivo bioequivalence study results of brand and generic formulations and develop a new data analyzing method which could help to identify the effect of excipients on the dissolution and the permeation process separately.*

When studying the *in vivo* predictive power of the dissolution-permeation assays in the literature it was obvious that flux values have yet been sparsely used as an input parameter in a predictive model for the calculation of food effect and bioequivalence from an oral dosage form. Although, it has been suggested that kinetic solubility data may be useful to estimate bioavailability enhancement caused by the amorphisation of the API,[6] this data has only been used sparsely as an input parameter for prediction of fraction of dose absorbed and food effect,[7] and has never been used to estimate the bioequivalence of generic drug products. *Therefore further aim of this thesis work was to predict food effect and bioequivalence for marketed formulations by using the results of state of the art experimental techniques, like kinetic solubility and simultaneous dissolution-permeation measurements, as input parameters for biopharmaceutics modelling and simulations, and then to compare the performance of the different approaches.*

[6] Almeida, L., Reutzel-Edens, S. M., Stephenson, G. A. & Taylor, L. S. Assessment of the Amorphous " Solubility " of a Group of Diverse Drugs Using New Experimental and Theoretical Approaches. *Mol. Pharm.* **12**, 484–495 (2014)

[7] Emami Riedmaier, A. *et al.* Mechanistic Physiologically Based Pharmacokinetic Modeling of the Dissolution and Food Effect of a Biopharmaceutics Classification System IV Compound—The Venetoclax Story. *J. Pharm. Sci.* **107**, 495–502 (2018).

2. METHODS

2.1 Sample preparation

Electrospinning. The small-scale preparation of API containing nanofibers was performed by single needle electrospinning setup consisting of a nozzle with an inner diameter of 0.5 mm, a high voltage direct current supply, and a syringe pump.

2.2 Characterization methods

Equilibrium solubility assay

The crystalline API was added to the media of interest and the resulting mixture was stirred for 6 h followed by 18 h of sedimentation. The concentration of the solution was measured via UV-spectroscopy.

Kinetic solubility assay

The concentrated stock solution of the API was added gradually to the aqueous media of interest until precipitation was observed via UV-spectrophotometer (Pion Rainbow™ Dynamic Dissolution Monitor) detecting the baseline elevation.

Simultaneous dissolution-permeation assays

Small volume dissolution-permeation assays were carried out using μFLUX apparatus (Pion Inc.). It consists of a donor and an acceptor chamber (20 mL volumes) separated by an artificial membrane (polyvinylidenfluoride (PVDF), 0.78 cm^2).

Medium (200-250 mL) and large (850-1062.5 mL) volume assays were carried out using *BioFLUX and MacroFLUX* apparatuses (Pion Inc.) Receiver chamber integrated with filter-supported artificial membrane (hydrophobic PVDF, 3.69 cm^2 /3.80 cm^2), overhead stirrer was inserted in the standard USP II apparatus (Erweka DT 126 Dissolution Tester). The concentration of the API was monitored in real time via UV-probes (Pion Rainbow™ Dynamic Dissolution Monitor) in the donor and accepter chamber.

3. RESULTS

The first part of this work (chapter 3.1 and 3.2) aims to describe and understand the passive membrane transport for complex formulation matrixes in case of lipid and size-exclusion membranes. The second part of the work presents the possible industrial applications of dissolution-permeation tests.

3.1 The real driving force of membrane transport through lipophilic membranes

Meloxicam, a nonsteroidal anti-inflammatory drug, was chosen as a poorly water-soluble model drug and formulated in order to enhance its dissolution using solvent-based electrospinning. Three polyvinylpyrrolidone (PVP) derivatives (K30, K90, and VA 64), Soluplus, and (2-hydroxypropyl)-β-cyclodextrin (HP-β-CD) were used to create five different amorphous solid dispersions of meloxicam.

From dissolution profiles in the donor chambers it was evident that for all formulations the dissolved amount of drug was over 90% for all studied loads meaning a significant improvement in the dissolution rate compared to the crystalline API. Although the dissolution profiles of the formulations were found to be very similar, in case of Soluplus containing formulation the flux was superior, showing that the driving force of membrane transport cannot be simplified to the concentration gradient (**Figure 1.a**). Supersaturation ratio (defined as the ratio of dissolved amount of the drug to its equilibrium solubility in the same media) was found to be the driving force of membrane transport (**Figure 1.b**). It was mathematically derived from Fick's first law, and experimentally proven to be universal on several meloxicam containing ASDs and dimethyl sulfoxide (DMSO) stock solution.

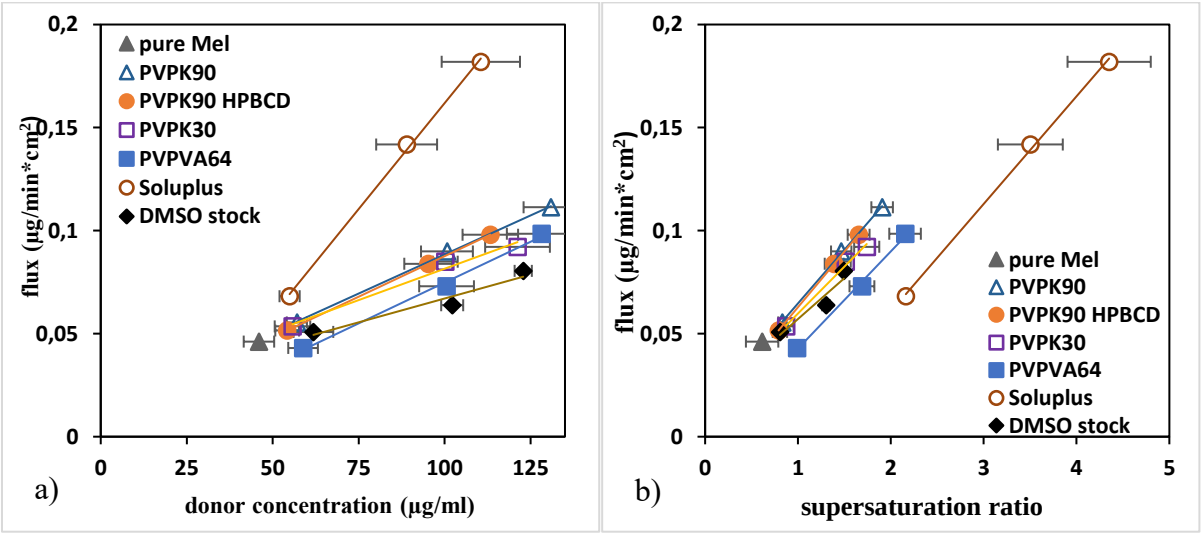

Figure 1.Diffusive flux of pure MEL, MEL containing ASDs and DMSO stock as a function of concentration in the donor chamber (a) and supersaturation ratio (b)

3.2 The real driving force of membrane transport through size-exclusion membranes

Carvedilol (CAR) an anti-hypertensive drug was chosen as a poorly water-soluble model drug. It was processed to create an amorphous solid dispersion by using solvent-based electrospinning and PVPVA64 or Soluplus® as polymer additives. The load-dependent effect of the polymers

was studied by equilibrium solubility assays and simultaneous dissolution-permeation experiments using regenerated cellulose membrane. While polymer additives generally do not act as solubilizing agents, Soluplus and PVP VA64 were found to increase the equilibrium solubility of poorly water-soluble Carvedilol. Although Soluplus was found to be almost twice as powerful as PVP VA64 in solubilizing CAR, the amount of drug permeated through the size-exclusion membrane was found to be significantly smaller in the case of Soluplus-containing formulations **(Figure 2.a**).

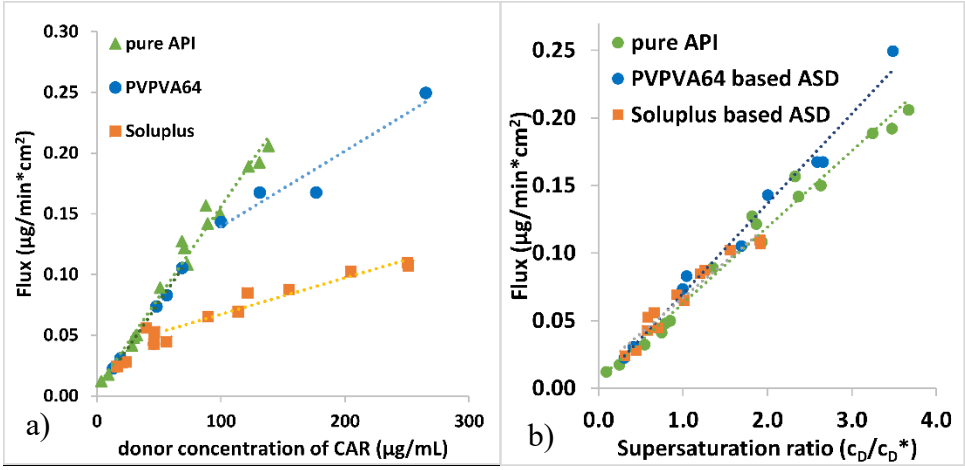

Figure 2. Flux of pure CAR and CAR containing ASDs at 25 °C as a function of concentration in the donor chamber (a) and supersaturation ratio (b)

Supersaturation ratio was found to be the driving force of the transport through a regenerated cellulose membrane as a result of concentration-based mathematical description derived from Fick's first law (**Figure 2.b**).

3.3 Combination of formulation techniques to enhance flux for buccal drug delivery

Various formulation strategies were combined to create amorphous solid dispersions using solvent-based electrospinning, sulfobutylether-β-cyclodextrin (SBEβCD) as solubilizing agent and citric acid as microenviromental pH modifying agent to enhance the dissolution and the flux of a poorly soluble antipsychotic drug, aripiprazole (ARP).

A saliva-modeling dissolution media was developed with pH and buffer capacity optimized for human oral cavity. The results of simultaneous dissolution-permeation test for the electrospun formulation showed that not only dissolution but also flux through artificial membrane could be significantly enhanced via amorphisation of the API (**Figure 3**).

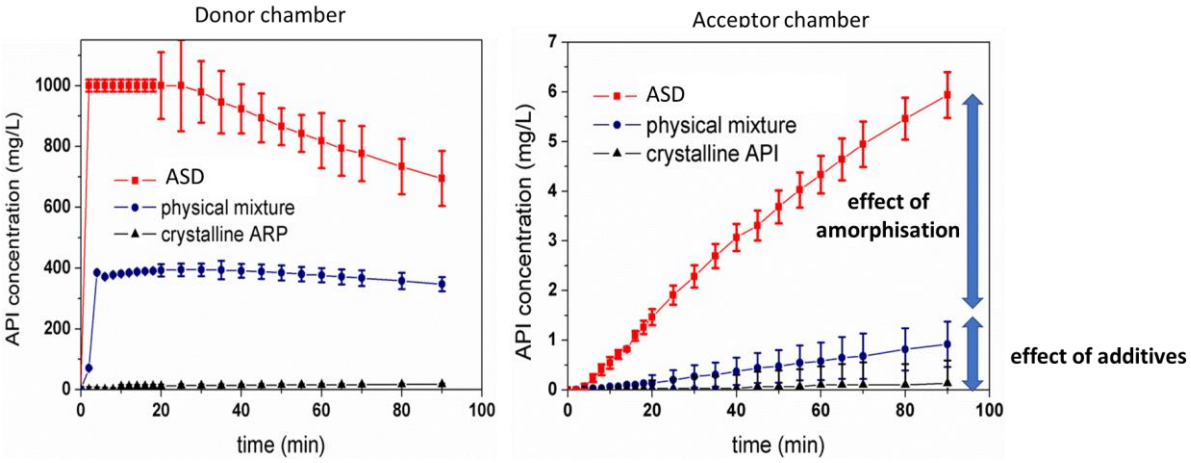

Figure 3. Dissolution-permeation profile of the aripiprazole containing buccal formulation

3.4 Comparison of brand and generic formulation of telmisartan with *in vitro* dissolution-permeation test

In this part of the thesis work brand (Micardis) and four generic formulations of telmisartan (TEL), an antihypertensive drug, were used in *in vitro* simultaneous dissolution-permeation tests investigating the effect of different formulation additives on dissolution and flux through lipophil artificial membrane. The *in vitro* test was found to be sensitive enough to show even small differences between brand and generic formulations caused by the use of different excipients. By only changing the type of filler from sorbitol to mannitol in the formulation, the flux through the membrane was reduced by approximately 10%. Changing the salt forming agent as well resulted in approximately 20% of flux reduction compared to the brand formulation. This significant difference was clearly shown in the published *in vivo* results as well.

In the case of additives delaying the dissolution of the API and impacting the speed of the membrane transport as well, a new graphical data-analyzing method was proposed to evaluate the effect of excipients on only the permeation step. **Figure 4** shows the late flux versus donor concentration in the case of lactose monohydrate containing generic formulation, Tolura and the sorbitol containing brand formulation, Micardis. The data point of the Tolura tablet did not fall on the dotted line, meaning that the extra additive was affecting the permeation compared to the brand product. The addition of lactose monohydrate to the dissolution media of the brand product resulted in a data point also deviated from the dotted line, positioned closely to the data point of Tolura. This way the excipient responsible for the slower membrane transport could be identified.

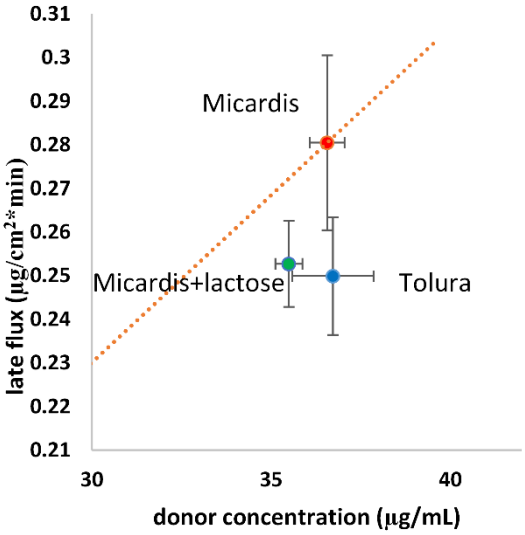

Figure 4. Late flux versus donor concentration diagram for lactose monohydrate containing formulations of telmisartan (dotted line connects the data point of Micardis to the origin)

3.5 Prediction of bioequivalence and food effect based on flux and solubility data

Two different approaches have been developed to predict the food effect and the bioequivalence of marketed itraconazole (ITRA) formulations. Kinetic solubility and simultaneous dissolution-permeation tests of three ITRA formulations (Sporanox capsules and solution and SUBA-ITRA capsules) were carried out in simulated fasted and fed states. Fraction of dose absorbed ratios estimating food effect and bioequivalence were calculated based on these results and were compared to the *in vivo* study results published by Medicines Agencies. Both prediction methods were able to determine a slightly negative food effect in the case of the Sporanox solution and also a pronounced positive food effect for the Sporanox capsule. Superior bioavailability was predicted when the Sporanox solution was compared to the Sporanox capsule (in agreement with *in vivo* data).

4. THESIS FINDINGS

1. In case of pharmaceutical formulations containing solubilizing additives it was shown that the driving force of transport through lipophilic membranes cannot be simplified to the concentration gradient when the permeation is membrane limited, instead supersaturation ratio (defined as the ratio of dissolved amount of drug to its equilibrium solubility in the same media) was found to be the real driving force of membrane transport. It was mathematically derived from Fick's first law, and experimentally proven with the help of several meloxicam containing electrospun formulations. [i]

2. The driving force of membrane transport through lipophilic membrane was also studied in the presence of dimethyl sulfoxide as a cosolvent. The solubility of the anionic form of the API was significantly more enhanced than the solubility of the neutral form due to the interaction of the cosolvent and the anionic form. Experimental results showed that only the solubility enhancement of the neutral form caused the driving force of membrane transport to change, the solubility enhancement of the anionic form has no such effect. For that reason the supersaturation ratio of the neutral form was found to be the driving force of membrane transport. [i]

3. In case of pharmaceutical formulations containing solubilizing additives (which are not able to permeate through size-exclusion membrane because of their hydrodynamic size) it was shown that the driving force of transport through regenerated cellulose based size-exclusion membranes cannot be simplified to the concentration gradient, instead supersaturation ratio was found to be the real driving force of membrane transport. It was mathematically derived from Fick's first law, and experimentally proven with the help of several CAR containing electrospun formulations. [ii]

4. For the dissolution enhancement of a poorly water-soluble model drug, ARP a novel cyclodextrin-based electrospun formulation was developed, which was the first SBEβCD-containing electrospun formulation of the API. Even low concentration of polyethylene oxide (PEO) (0.75 w/v%; $M_w = 2*10^6$ g/mol) was enough to create fine, beadless fibers by a solvent-based electrospinning process. The API in the electrospun fibers was found to be in amorphous state and no crystallization was observed even after 3 months. [iii]

5. A saliva-modeling dissolution media was developed with pH and buffer capacity optimized for human oral cavity. The results of small scale dissolution tests of an ARP containing electrospun formulation showed that in such small concentration PEO had no retard effect on dissolution, therefore an orally fast dissolving drug delivery system could be created, which meets the requirements for the therapeutic goal. The results of simultaneous dissolution-permeation test for the electrospun formulation showed that not only dissolution but also flux through artificial membrane could be significantly enhanced compared to the pure API. [iii]

6. Large volume (900 mL) dissolution-permeation apparatus was successfully implemented to compare brand and generic formulations of TEL. The *in vivo* predictability of the method was demonstrated with the good correlation between the *in vitro* flux values and the *in vivo* results of bioequivalence tests. Novel graphical data analyzing method was developed in order to evaluate the effect of formulation additives only on the permeation step, independently from the dissolution step. [iv]

7. Kinetic solubility was used as an input parameter of a predictive model for the first time in order to predict the results of bioequivalence tests. As a model compound ITRA, a poorly water-soluble model drug was used, and its kinetic solubility was determined in biorelevant media containing formulation additives. This data was used as the input parameter of the predictive model for the estimation of fraction of dose absorbed ratios of marketed formulations of ITRA in fasted and fed state as well. [v]

8. Flux and kinetic solubility based predictive model could be used in the prediction of the food effect and bioequivalence for ITRA containing marketed formulations. Both prediction methods were highly capable of determining the slightly negative food effect in case of Sporanox solution, and a pronounced positive food effect for the Sporanox capsule. Flux and kinetic solubility based predictive models were compared for the first time in the prediction of bioequivalence test results. While in case of comparing amorphous formulations in biorelevant media the two models showed very similar results, in case of complex media containing bile micelles and cyclodextrins as well, the flux based model gave significantly better *in vivo* prediction than the kinetic solubility based model. [v]

5. APPLICATION OF THE RESULTS

Simultaneous dissolution and permeation experiments are becoming more and more prominent in the formulation development of drug products owing to their obvious advantages compared to simple dissolution tests. The thesis work presented here showed that although the transport through lipophilic and size-exclusion membranes are mechanistically different, in both cases the driving force of membrane transport in presence of additives was found to be the same. This finding may enable the use of size-exclusion membranes as an alternative to lipid membranes (in the case of membrane limited transport) in simultaneous dissolution and permeation experiments for formulation development (in the case that the additive cannot cross the membrane).

The second part of the thesis work showed how bioequivalence and food effect can be predicted based on simultaneous dissolution-permeation test results. These assay protocols and data analysis methods are already being implemented by various pharmaceutical companies (mainly in the USA and in China).

6. PUBLICATIONS

Related scientific articles

i. **Borbás, E**.; Sinkó, B.; Tsinman, O.; Tsinman, K.; Kiserdei, E.; Démuth, B.; Balogh, A.; Bodák, B.; Domokos, A.; Dargó, G. Balogh, G.T.; Nagy, Z.K.; **2016**. Investigation and mathematical description of the real driving force of passive transport of drug molecules from supersaturated solutions. *Molecular Pharmaceutics*, *13*(11), pp.3816-3826. DOI: 10.1021/acs.molpharmaceut.6b00613, IF: 4.440; FI: 30

ii. **Borbás, E.;** Tőzsér, P.; Tsinman, O.; Tsinman, K.; Takacs-Novak, K.; Völgyi, G.; Sinkó, B.; Nagy, Z.K.; **2018**, Effect of formulation additives on drug transport through size-exclusion membranes *Molecular Pharmaceutics 15*(8), pp.3308-3317. DOI: 10.1021/acs.molpharmaceut.8b00343 IF:4.396; FI:2

iii. **Borbás, E**.; Balogh, A.; Bocz, K.; Müller, J.; Kiserdei, É.; Vigh, T.; Sinkó, B.; Marosi, A.; Halász, A.; Dohányos, Z. and Szente, L.; Balogh, G.T.; Nagy, Z.K.; **2015**. *In vitro* dissolution–permeation evaluation of an electrospun cyclodextrin-based formulation of aripiprazole using µFlux™. *International Journal of Pharmaceutics*, *491*(1), pp.180-189. DOI: 10.1016/j.ijpharm.2015.06.019 IF: 3.994; FI:28

iv. **Borbás E**, Nagy, Z.K.; Nagy B, Balogh A, Farkas B, Tsinman O, Tsinman K, Sinkó B, **2018** The effect of formulation additives on *in vitro* dissolution-absorption profile and *in vivo* bioavailability of telmisartan from brand and generic formulations, *European Journal of Pharmaceutical Sciences*; 114, pp. 310-317. DOI: 10.1016/j.ejps.2017.12.029 IF: 3.466; FI:9

v. **Borbás, E**.; Kádár, S.; Tsinman, K.; Tsinman, O.; Csicsák, D.; Takács-Novák, K.; Völgyi, G.; Sinkó, B.; Pataki, H. **2019**. Prediction of Bioequivalence and Food Effect Using Flux-and Solubility-Based Methods. *Molecular Pharmaceutics, 16*(10), pp.4121-4130. DOI: 10.1021/acs.molpharmaceut.9b00406 IF: 4.321

Further related articles:

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vii. Balogh, A.; Farkas, B.; Verreck, G.; Mensch, J.; Borbás, E.; Nagy, B.; Marosi, G. and Nagy, Z.K.; **2016.** AC and DC electrospinning of hydroxypropylmethylcellulose with polyethylene oxides as secondary polymer for improved drug dissolution. *International Journal of Pharmaceutics*, *505*(1), pp.159-166. DOI: 10.1016/j.ijpharm.2016.03.024 IF: 3.649; FI:17

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xii. Ilyés, K.; Kovács, N. K.; Balogh, A.; Borbás, E.; Farkas, B.; Casian, T.; Nagy, Z.K.; **2019**. The applicability of pharmaceutical polymeric blends for the fused deposition modelling (FDM) 3D technique: Material considerations–printability–process modulation, with consecutive effects on *in vitro* release, stability and degradation. *European Journal of Pharmaceutical Sciences*, DOI: 10.1016/j.ijpharm.2019.06.024; if: 3.466; FI:6

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xv. Ilyés, K.; Balogh, A.; Casian, T.; Igricz, T.; Borbás, E.; Démuth, B.; Vass, P.; Menyhárt, L.; Kovács, NK.; Marosi, G. and Tomuță, I.; **2019**. 3D floating tablets: Appropriate 3D design from the perspective of different *in vitro* dissolution testing methodologies. *International Journal of Pharmaceutics, 567,* p.118433. DOI: 10.1016/j.ijpharm.2019.06.024 IF: 4.845; FI:1

xvi. Casian, T.; Borbás, E.; Ilyés, K.; Démuth, B.; Farkas, A.; Rapi, Z.; Bogdan, C.; Iurian, S.; Toma, V.; Știufiuc, R. and Farkas, B.; **2019**. Electrospun amorphous solid dispersions of meloxicam: Influence of polymer type and downstream processing to orodispersible dosage forms. *International Journal of Pharmaceutics, 569,* p.118593. DOI: 10.1016/j.ijpharm.2019.118593 IF: 4.845; FI:5

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Further articles:

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xxi. Casian, T.; Farkas, A.; Ilyés, K.; Démuth, B.; Borbás, E.; Madarász, L.; Rapi, Z.; Farkas, B.; Balogh, A.; Domokos, A. and Marosi, G.; **2019**. Data fusion strategies for performance improvement of a Process Analytical Technology platform consisting of four instruments: An electrospinning case study. *International Journal of Pharmaceutics, 567*, p.118473. DOI: 10.1016/j.ijpharm.2019.118473 IF: 4.845; FI:2

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Selected presentations:

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xxiv. Borbás, E.; Nagy, Z.K..; Marosi, G.; Sinkó, B.; *Formulation of antipsychotic drugs and the development of their in vitro analytical measurements*,12th International Conference "Students for Students", Kolozsvár, 23.04.2015

xxv. Borbás, E.; Sinkó, B.; Nagy, Z.K.; Marosi, G.; *In vitro dissolution-absorption evaluation of electrospun nanofibers using µFlux™*, Global Pharma Summit 2015, Philadelphia, 11.08.2015

xxvi. Borbás, E.; Sinkó, B.; Nagy, Z.K.; Marosi, G.; *Effect of polymer additives on membrane transport of active pharmaceutical ingredients,* International Society of Biomedical Polymers and Polymeric Biomaterials The 3rd Annual Conference & Expo 2016, New Jersey, 12.08.2016

xxvii. Borbás, E.; Sinkó, B.; Csicsák, D.; Völgyi, G.; Takács-Novák, K.; Nagy, Z.K.; *A segédanyagok és az étkezés hatása Itraconazole tartalmú formulációk kioldódás és felszívódás profiljára (In vitro dissolution-permeation study to characterize Itraconazole formulations: The effect of formulation additives, food and dose),* MKE Kristályosítási és Gyógyszerformulálási Szakosztály 12. Kerekasztal Konferenciája (12th Round Table Conference on Crystallization and Formulation of Active Pharmaceutical Ingredients), Balatonszemes, 30.04.2019