T3054

Cyclodextrin-Based Orally Fast Dissolving Drug Delivery System of Aripiprazole and Its In Vitro Dissolution-Permeation Testing Using µFlux™

Konstantin Tsinman[1], Eniko Borbas[2], Zsombor Nagy[2], Balint Sinko[1], Gyorgy Marosi[2]

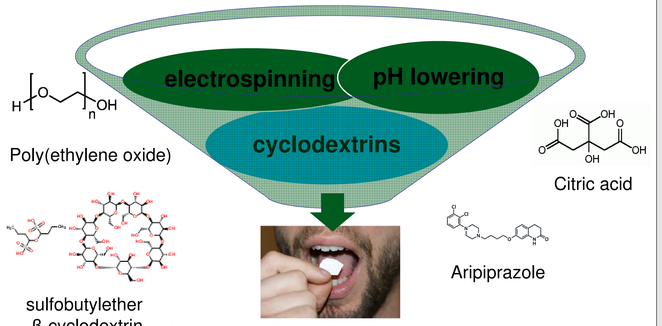
[1]Pion Inc., 10 Cook Street, Billerica, MA 01821, [2] Budapest University of Technology and Economics, 3 Muegyetem rakpart, Budapest, 1111, Hungary

PURPOSE

Since it is a well-established fact that among the newly discovered active pharmaceutical ingredients (APIs) the number of poorly water soluble candidates is continually increasing [1], dissolution and solubility enhancement of poorly water soluble drugs has become one of the central challenges of pharmaceutical studies. So far the preclinical studies have been mainly focused on formulation methods to enhance the dissolution of APIs, in many cases disregarding the fact that the formulation matrix not only affects the dissolution but also has an effect on the transport through biological membranes, changing permeation of the drug molecules [2,3]. This effect is clearly shown by a case study of meloxicam formulations with different polymer and cyclodextrin additives.
The formulation development for a poorly water soluble antipsychotic drug aripiprazole is presented using µFlux™ apparatus, a technique, which, besides measuring dissolution follows the flux at the same time enabling to achieve better in vitro-in vivo correlation.

METHODS

Combining formulation techniques in order to prepare an orally fast-dissolving drug delivery system



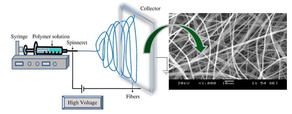


Figure 1. Electrospinning apparatus

The µFLUX™ device is an add-on option to the µDISS Profiler™ instrument (Pion Inc.) consisting of three pairs of temperature controlled side-by-side permeability chambers mounted on top of the stirring platform.
Each pair (Figure 2) consists of a donor and an receiver compartment separated by a filter-supported GIT-optimized artificial membrane (Double-Sink™ PAMPA 2). The donor compartment is filled with 20 mL of the media of interest. For this study the receiver compartment contained Acceptor Sink Buffer at pH 7.4 (ASB-7.4, Pion Inc). The integrated fiber-optic UV probes were positioned in the donor and receiver compartments allowing real time concentration monitoring in all chambers. Membrane area was 1.54 cm².

The polymer, the ARP, the cyclodextrin and the citric acid of calculated amounts were added into 10 mL solvent (ethanol and water 1:1) and stirred by a magnetic stirrer at 600 rpm until the dissolution completed. The electrical potential applied on the spinneret electrode was 40 kV . A grounded aluminum plate covered with aluminum foil was used as collector (50 cm from the spinneret). Polymer solutions were dosed with 2 mL/h at room temperature (25˚ C) by a SEP-10S Plus type syringe pump .

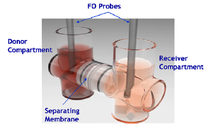
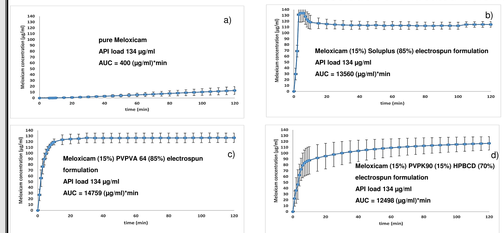


Figure 2. A fragment of the µFLUX apparatus showing a pair of the donor and receiver chambers. FO probes attached to the µDISS Profiler monitor concentrations in the donor (left) and receiver (right) compartments. The chambers can be separated by PAMPA, cell-based (Caco-2 or MDCK), dialysis, or other types of membranes mounted in the Membrane Holder.

RESULTS of meloxicam containing formulations

Effect of different additives (polymers and cyclodextrins) on dissolution and permeation of meloxicam

Dissolution of untreated meloxicam and electrospun formulations



Dissolution of Meloxicam and its formulations were performed in 20 mL of pH 6.8 phosphate buffer using API load 62 µg/ml, 104 µg/ml and 134 µg/ml. Figure 3 shows the results for 134 µg/ml API load (the results for 62 µg/ml, 104 µg/ml API load are not presented here, but the data is consistent with the results of 134 µg/ml API load). From dissolution profiles it is evident that from all formulations the dissolved amount of drug was over 90%, which means a significant improvement compared to the crystalline API, from which less than 10 % of the API load dissolved. Among the three dissolution profiles of electrospun formulations there are only slight differences. From the Soluplus and PVP VA 64 containing formulations the drug dissolves faster than from Hydroxypropyl-ß-cyclodextrin (HPBCD) containing formulation. Comparing the areas under the concentration versus time curves the PVP VA 64 containing formulation seems to be the best choice in case immediate release is desired.
The same formulations and the untreated API was assayed with µFlux (Figure 4.). In case of the untreated meloxicam the concentration in the acceptor chamber was lower than 0,1 µg/ml after 120 minutes. In comparison the electrospun formulations showed linear concentration profile. The donor chamber results show that the PVP VA 64 containing formulation could reach the highest concentration when dissolving, giving consistent result with dissolution tests. However, when considering the acceptor chamber concentration (AUC), then the Soluplus containing formulation seems slightly better than the PVP VA 64 containing one after 120 minutes, and during the total 16 hour long assay this difference only grows, so the final concentration in the acceptor chamber is 3.7 µg/ml in case of PVPVA 64, and 7.0 µg/ml in case of Soluplus formulation.

Figure 3. Examples of dissolution profiles (µg/mL versus minutes) for Untreated Meloxicam (a), Soluplus Formulation (b), PVPVA 64 Formulation (c) and PVPK90/HPBCD Formulation (d). Assays were performed in 20 mL of pH 6.8 phosphate buffer

µFlux results for meloxicam formulations

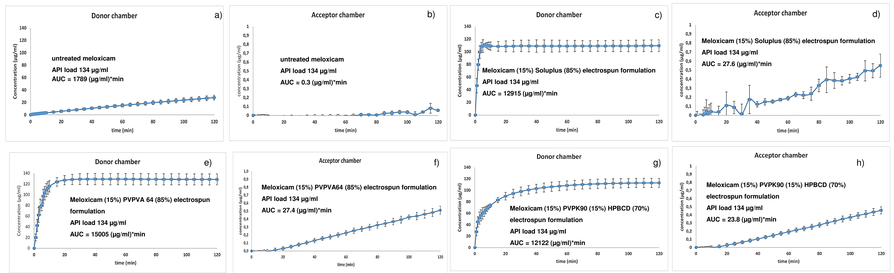


Figure 4. Concentration – time profiles of meloxicam (µg/mL vs. min) in donor compartments a), c), e), g) and acceptor chambers b), d), f), h) in the µFLUX assay. Area under the concentration versus time curves (AUC) are presented in all diagrams. The diagrams show the first 120 min of the 16 hour long assays.

RESULTS of Aripiprazole containing formulation

Optimization of parameters for biorelevant dissolution and dissolution-permeation tests

Optimization of the donor buffer to model human saliva

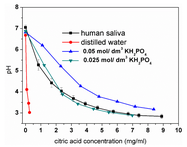


Figure 5. The pH dependency of human saliva and phosphate buffers

For the dissolution tests, the 0.025 mol/dm³ KH_2PO_4 buffer (pH=6.8) was selected (as its buffer capacity was found to be the closest to that of human saliva) in order to be able to study the pH changes that are caused by the citric acid and the API when the formulation dissolves in the biological media.

Optimizing the composition of the artificial membrane to mimic absorption through the oral mucosa using PAMPA

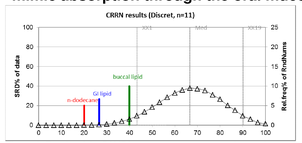


Figure 6. Results of the PAMPA measurements compared to ex vivo permeability results

The SRD value of *n*-dodecane is the lowest from the three model membranes, which means that this membrane gives the closest permeability result to the *ex vivo* porcine permeability reference. Moreover, *n*-dodecane has the advantage that its use is really fast, simple and even cost-effective.

Result of dissolution tests of cyclodextrin-based electrospun formulation of ARP

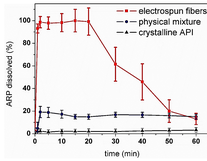


Figure 7 . Comparison of the dissolution rate of electrospun nanofibers, physical mixture and pure API (1000 mg/L max concentration, 0.025 mol/dm³ KH_2PO_4 buffer, 150 rpm, 25 ˚ *C*, *n* = 3)

The dissolution from the nanofibers is rapid; it reaches its maximum (100%) in 3 minutes, while only about 20% dissolution occurs from the physical mixture. The dissolution of the pure API is less than 3% after 60 min. Dissolution of the API from the physical mixture is improved compared to the pure API because of the solubilizing effect of CD and the control of pH, but this dissolution rate still means that only one fifth of the ARP can dissolve in the dissolution media. In contrast, from the amorphous electrospun fibers the total amount of the API was found in solution after only 3 minutes.

How does the observed precipitation of the API influence the drug permeation?

The results of the *in vitro* dissolution-permeability measurement on µFLUX™ platform

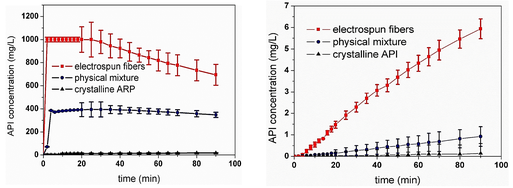


Figure 8. API concentration in the donor compartment and the acceptor compartment (1000 mg/L max concentration, 0.025 mol/dm³ KH_2PO_4 buffer int he donor compartment, *n*-dodecane membrane, sink buffer as acceptor, 150 rpm, 25 ˚ C)

On the acceptor side of the artificial membrane the API concentration was significantly higher in case of electrospun fibers than the physical mixture or the crystalline ARP (Figure 9). This difference between the formulated and non-formulated form could be noticed from their flux as well. The flux during the first 25 minute was found to be 767 µg/h*cm² in case of electrospun sample, while 82 µg/h*cm² for the physical mixture and 16 µg/h*cm² for the crystalline form. This means that approximately 50 times more molecule went through the membrane from the electropun formulation matrix than from the crystalline form.

CONCLUSIONS

In cases, where different formulation techniques are combined dissolution experiments alone cannot correctly predict the in vivo response to formulations due to the peculiar interplay of solubility and permeability and the effect of additiives and pH lowering agents as it was shown in the case study of electrospun meloxicam formulations.

This study shows that µFLUX ™ is useful analitical device for formulation developers in case of complex formulation matrixes.

By optimizing the pH and buffer capacity of donor media and the lipid composition of membrane various biorelevant conditions can be mimicked using µFlux ™ .

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