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OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

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FORMULATION OF ANTIPSYCHOTIC DRUGS AND THEIR *IN VITRO* ANALITICAL TESTS

Enikő Borbás

Superviser: Dr. Zsombor Kristóf Nagy

Dr. György Marosi

Budapest University of Technology and Economics

Pion

STUCTURE OF THE PRESENTATION

- I. Case study : formulation development of a poorly watersoluble antipsychotic drug, Aripiprazole

- II. Importance of in vitro analitical tests in formulation development:Formulation screening with different analitical test

- III. Solubility-permeability interplay and effect of commonly used solubility enhancers on membrane permeability

Formulation of poorly watersoluble antipsychotic drugs

- 80% of the newly discovered active pharmaceutical ingredients (API) are poorly watersoluble



Are they really taking it?

Formulation of drugs







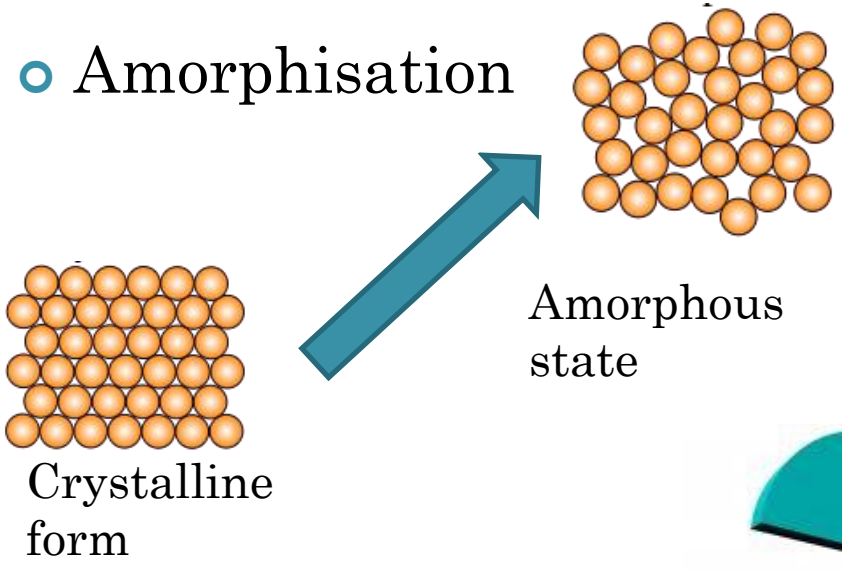
Is there a painless solution for the patient?

Formulation strategies

- Noyes-Whitney equation:

$$\frac{dC}{dt} = \frac{D \times A \times (Cs - Ct)}{h \times V}$$

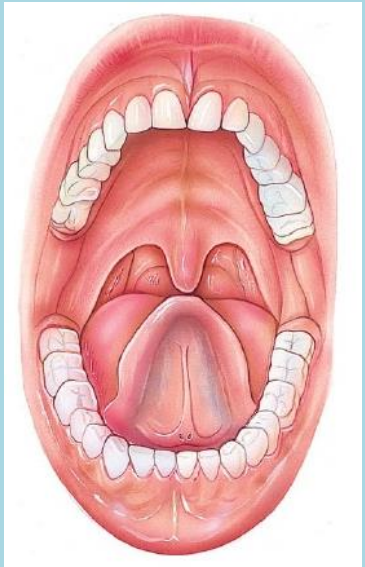
- Amorphisation



- Watersoluble polyme matrix



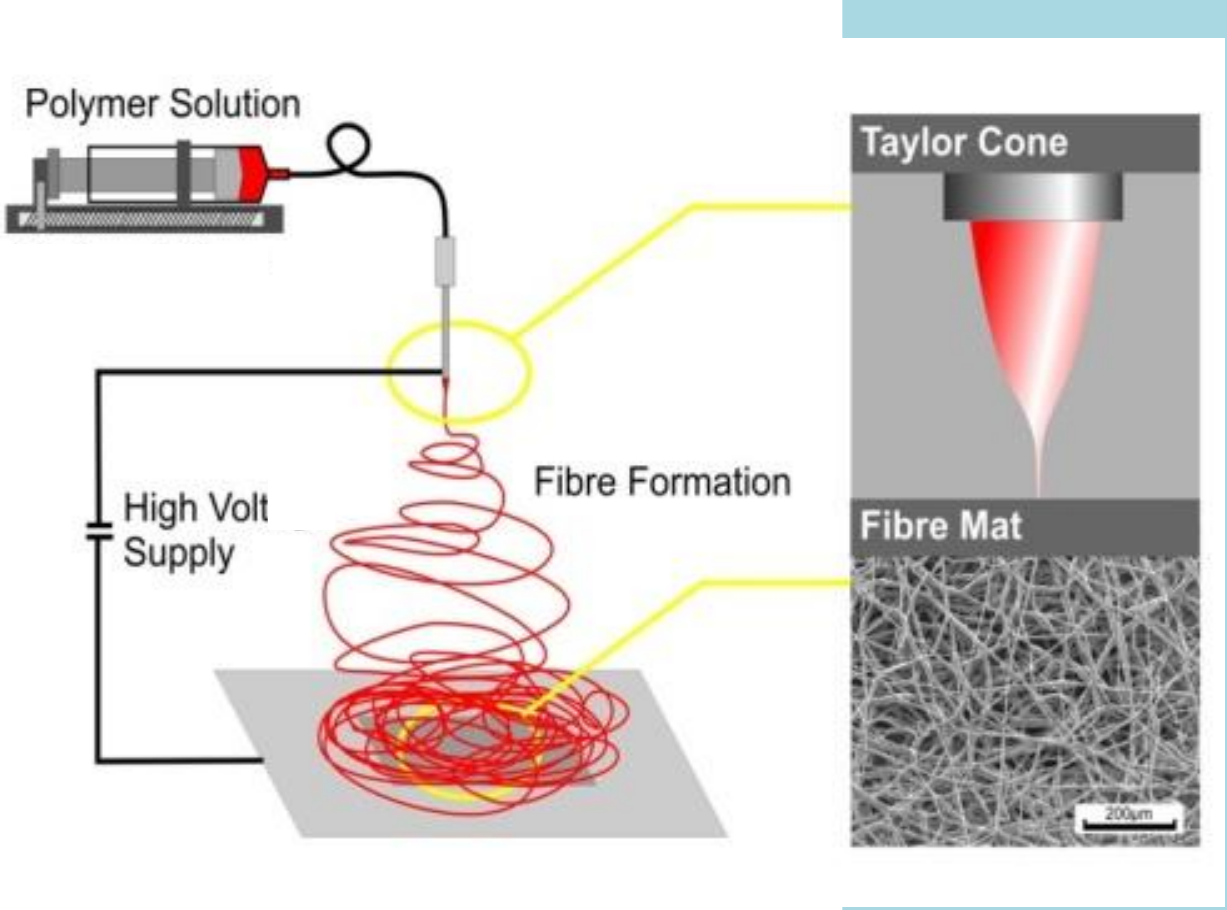
Orally fast dissolving drug delivery system



- Fast effect
- Escaping the first pass metabolism
- Less harmful for the liver
- Smaller doses

Enhanced bioavailability!!

PRODUCTION OF ORALLY FAST DISSOLVING DRUG DELIVERY SYSTEM BY ELECTROSPINNING



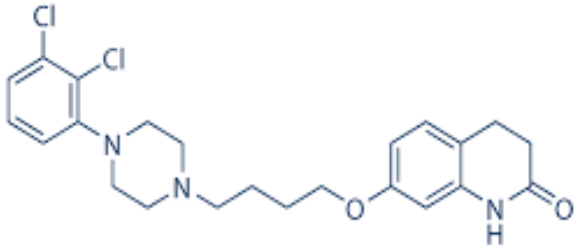


Solution for the technological and therapeutical challenges!



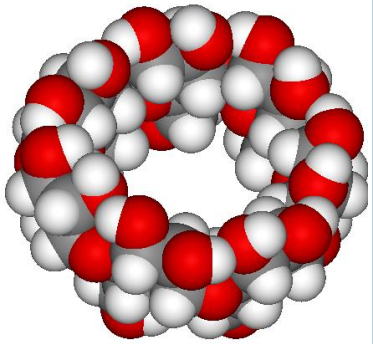
AIM OF THIS STUDY

- Aripiprazole containing orally fast dissolving and absorbing drug delivery system



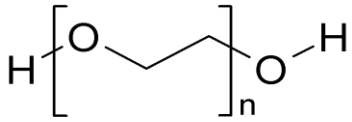
Plans for the formulation:

- Cyclodextrin-based formulation



- Minimization of the fiber forming polymer contant: poly(ethylene-oxide)

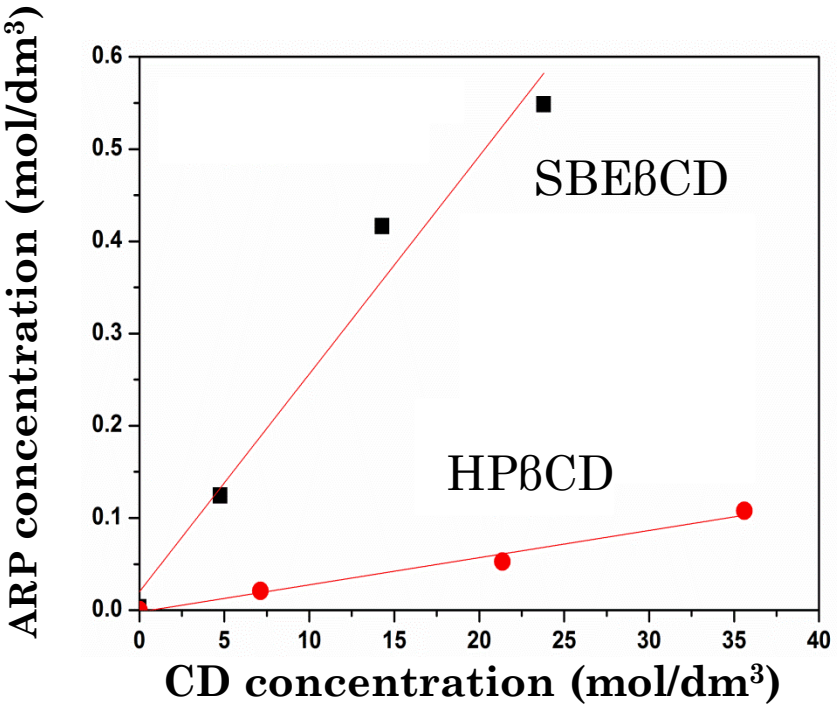
Retard effect of the polymer

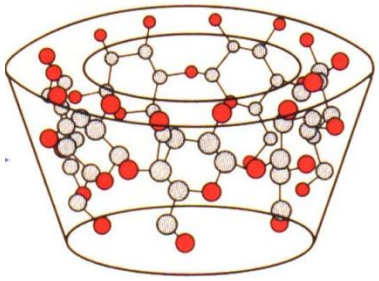


CYCLOLAB

OPTIMIZATION OF THE FORMULATION MATRIX

- Sulfobutylether-ß-cyclodextrin

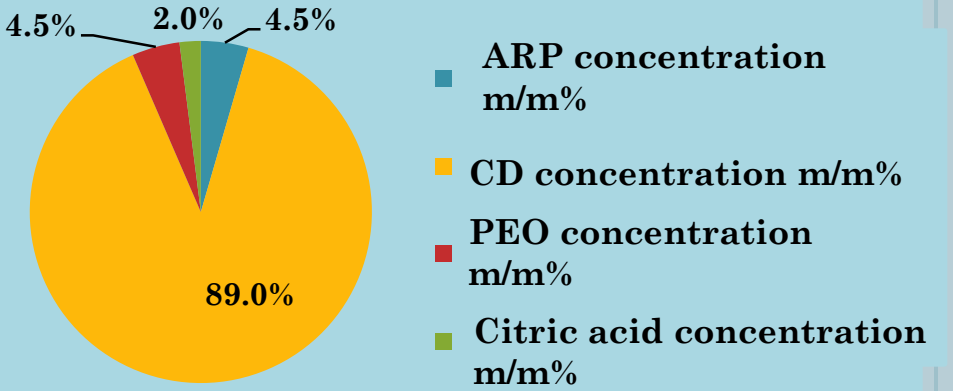




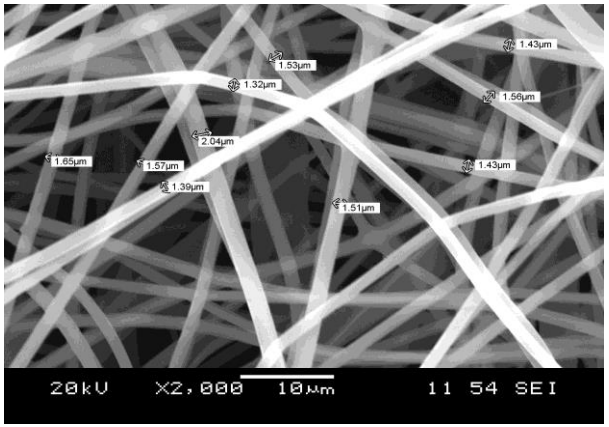
- Optimization of the fiber former polymer concentration in the polymer solution:

Molecular weight (g/mol)	Concentration w/V %
7 million	0,5%
4 million	
2 million	0,75%

Content of the formulation matrix

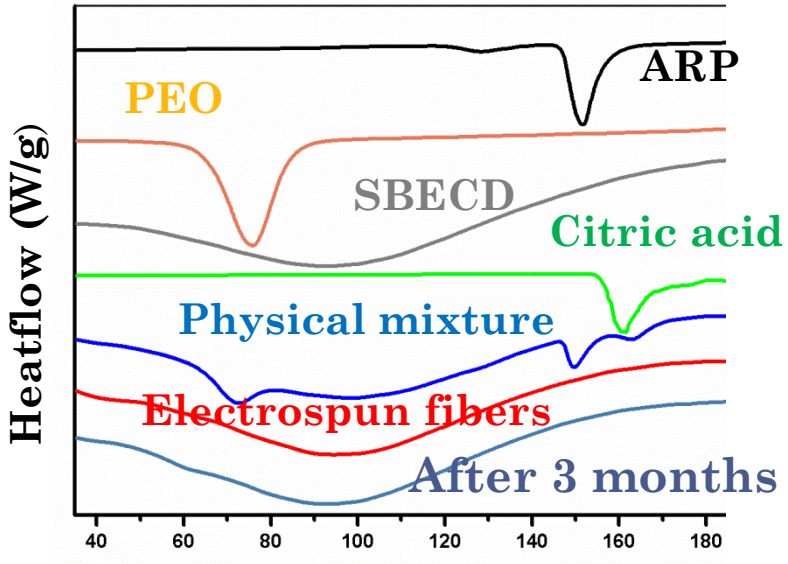


ANALITCAL TESTS OF THE ELECTROSPUN CYCLODEXTRIN-BASED FORMULATION OF ARIPIPRAZOLE



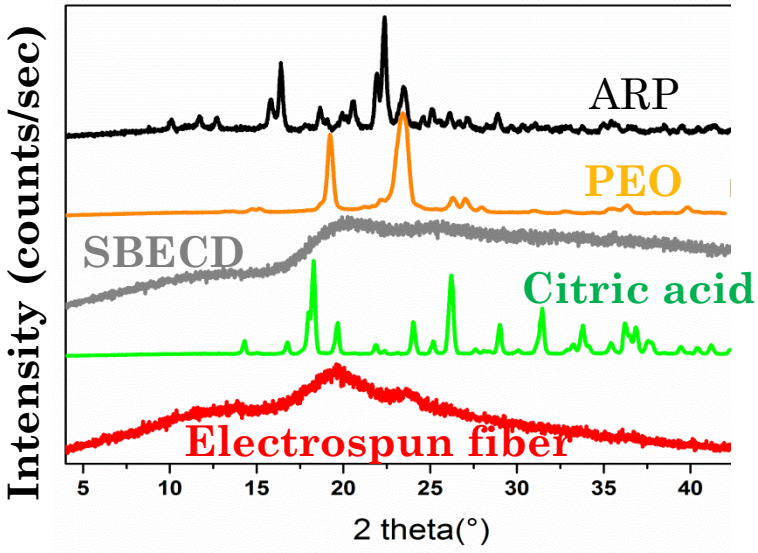
Scanning electronmicroscopic image (800nm-2000nm)

Enhancement of surface area



DSC thermogram

Amorphisation

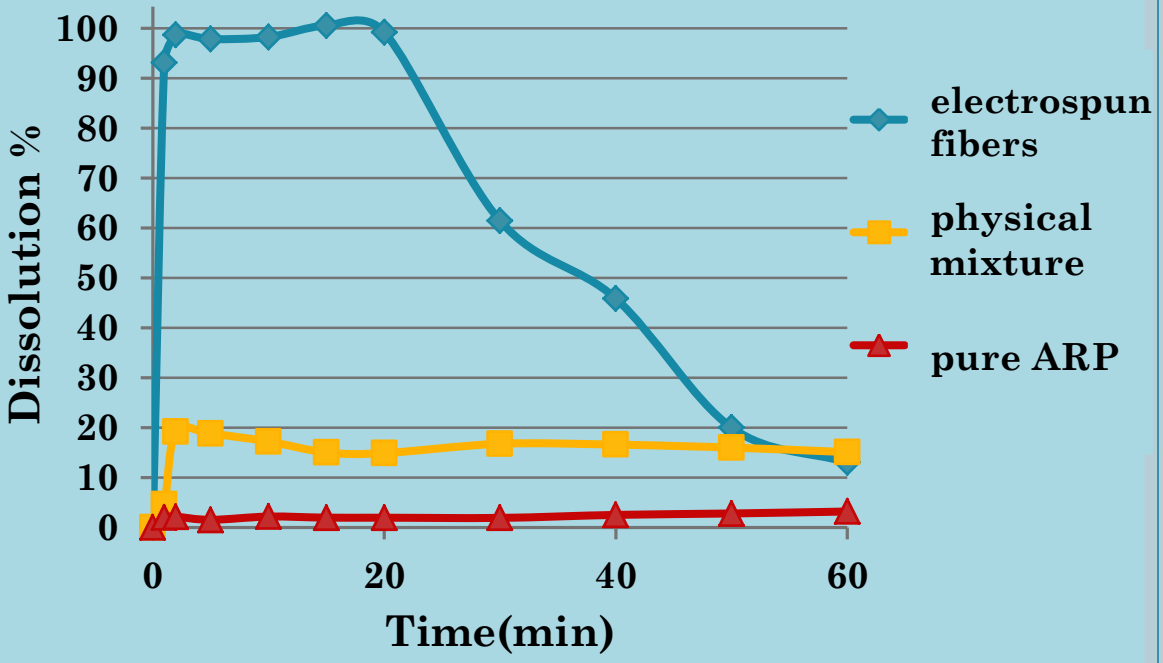


X-ray diffractogram

„IN SYRINGE" DISSOLUTION TESTING



5ml pH 6,8
phosphate buffer



Novel method for testing orally dissolving drug delivery systems!

Dissolution is fast and efficient!

Escaping the retard effect of the polymer!

Watersoluble polymer matrix

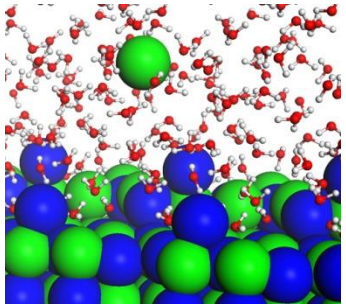


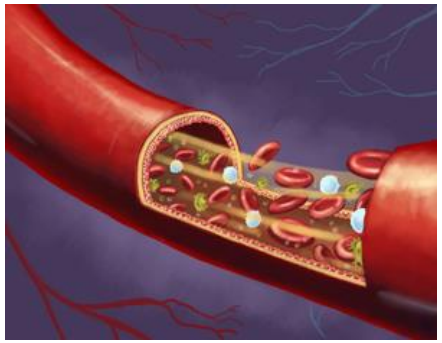
THE ROUTE OF THE API IN THE HUMAN BODY

Dissolution **Absorption**

Formulation → Dissolved API → API in the blood circuit





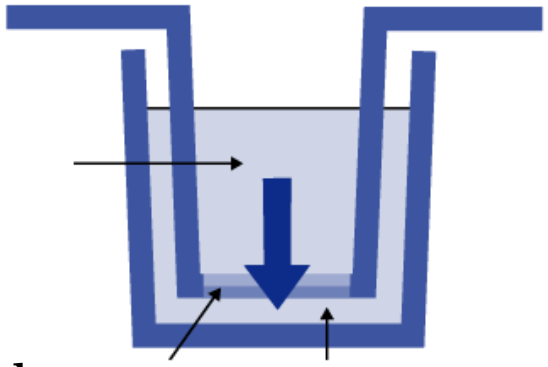


Cyclodextrin content

Precipitation of the API

Is it going to absorb?

PERMEABILITY TESTS:IT DISSOLVES, BUT IS IT GOING TO ABSORB?

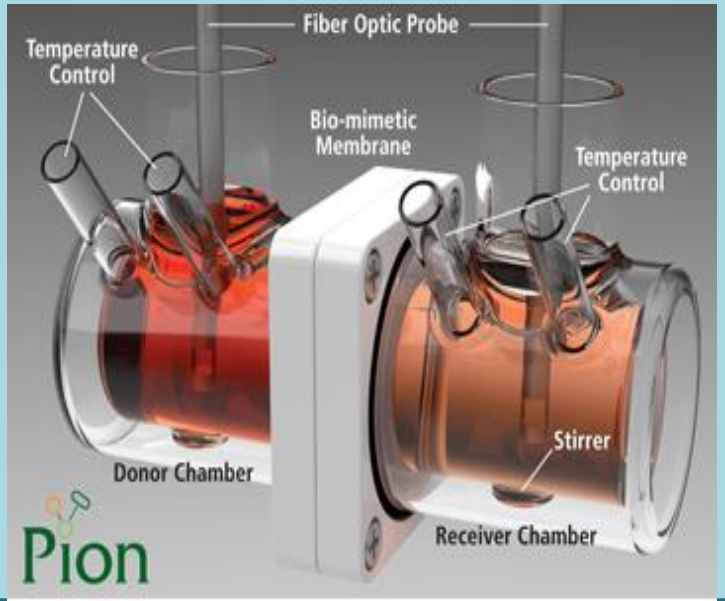




Used in drug development

150-300µl

PAMPA (Parallel Artificial Membrane Permeability Assay)



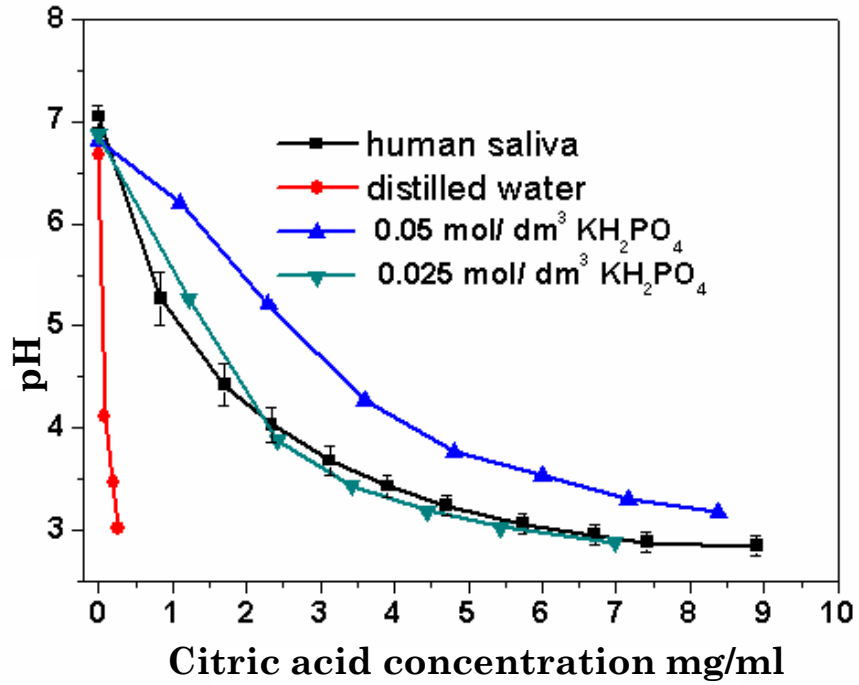
Microflux

Novel method in the formulation development!

10-20ml

PAMPA and Microflux optimization to modell buccal absorption

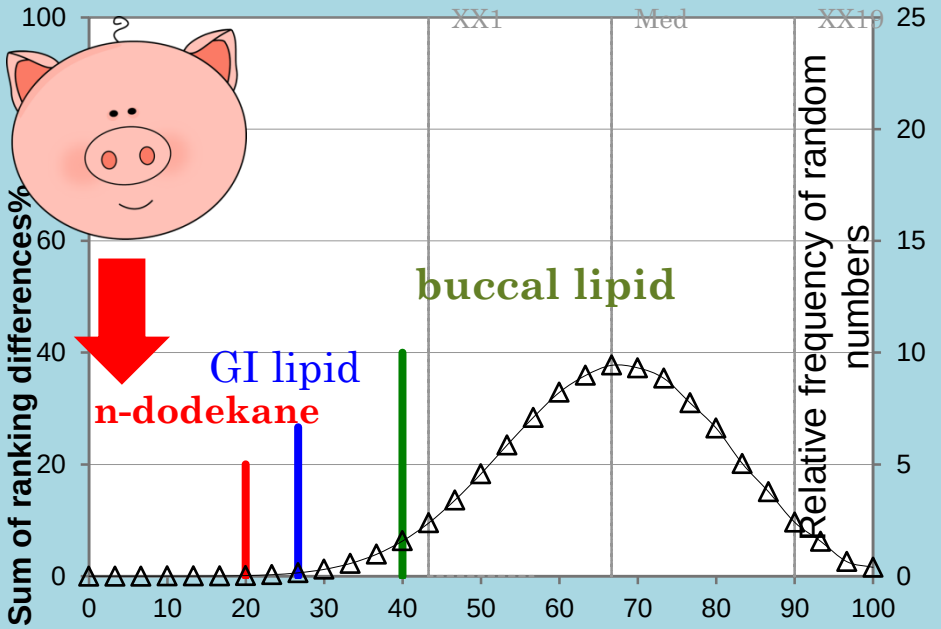
- Optimization of donor buffer pH, and buffercapacity



pH and buffercapacity of the buffer and human saliva is the same!

Membrane composition:

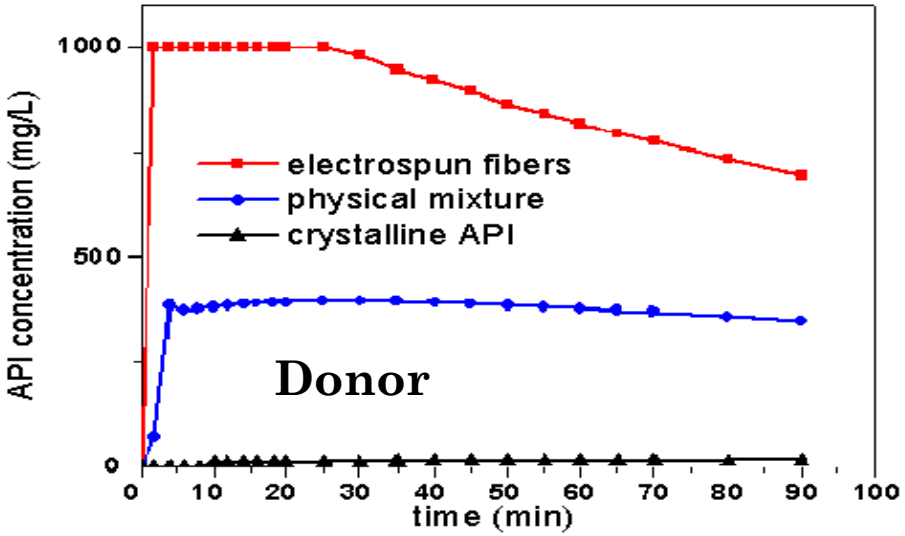
Reference: permeation through porcine buccal mucosa *(ex vivo)*

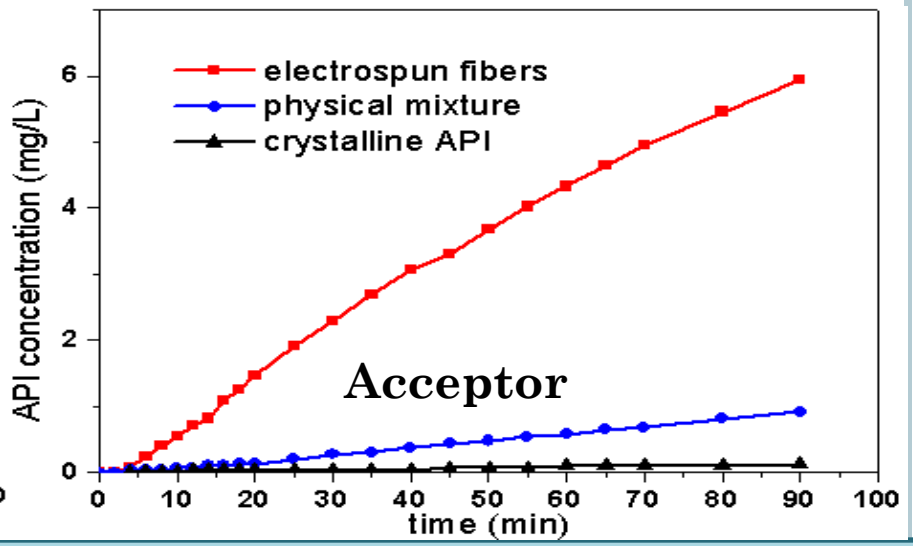


rank= difference from the reference ranking

*Kokate, Amit, et al. "In silico prediction of drug permeability across buccal mucosa." *Pharmaceutical research* 26.5 (2009)

DISSOLUTION-ABSORPTION TEST OF THE ARIPIRAZOLE CONTAINING ELECTROSPUN FIBERS



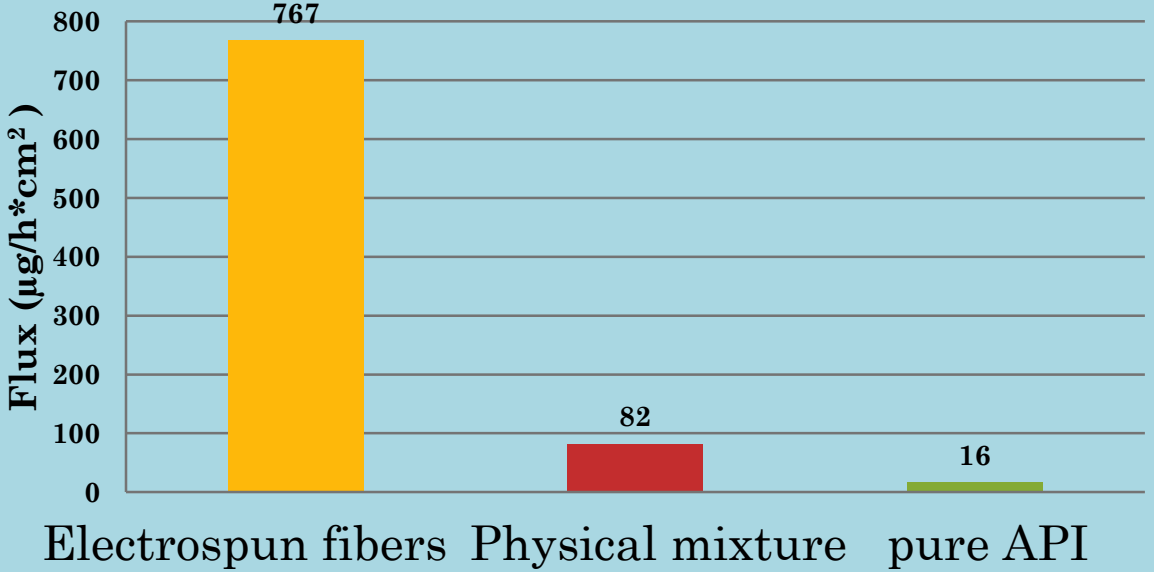


Flux

$$J(t) = \frac{dm}{A \cdot dt}$$

m= weight(µg), t=time(h),
A=membrane surface (cm^2)

Membrane surface=8,55cm^2



SUMMERY OF THE CASE STUDY

Technological results

- Aripirazole containing cyclodextrin based formulation
- Modelling the oral cavitiy in dissolution-absortion testing
- Biorelevant analitical testing
- Less animal tests are needed

Therapeutical results

- Ensuring the treatment of psychiatric patients
- Fast effect
- Painless treatment



II. Importance of in vitro analitical tests in formulation development: Formulation screening using conventional and novel analitical tests

In vitro analitical tests
Past -Present –Future in formulation screening

Dissolution testing

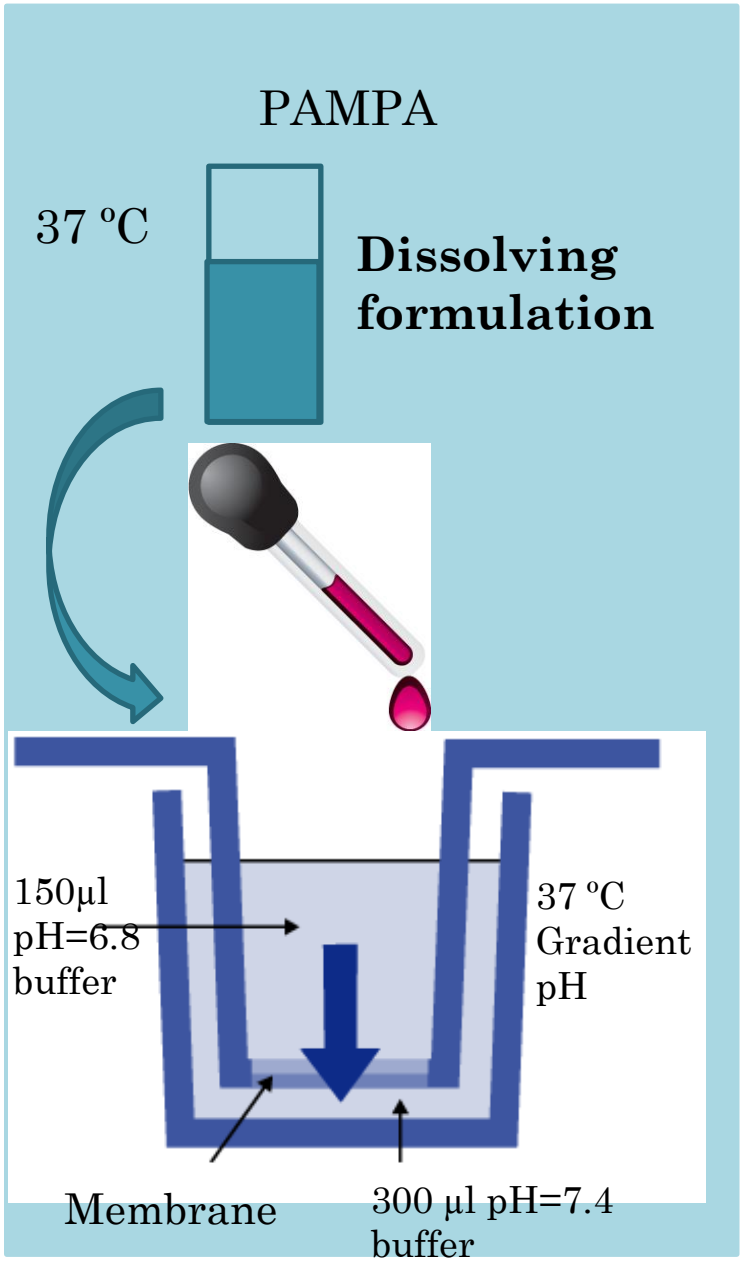


Small volume

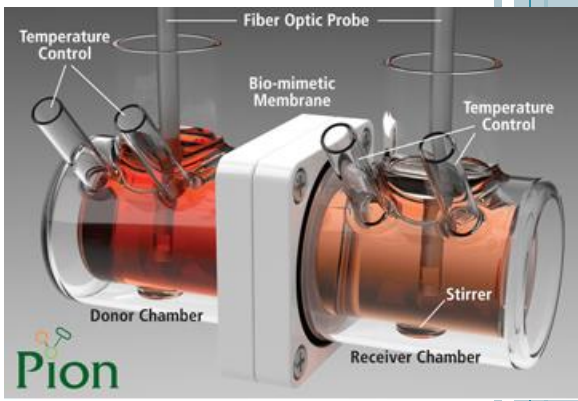


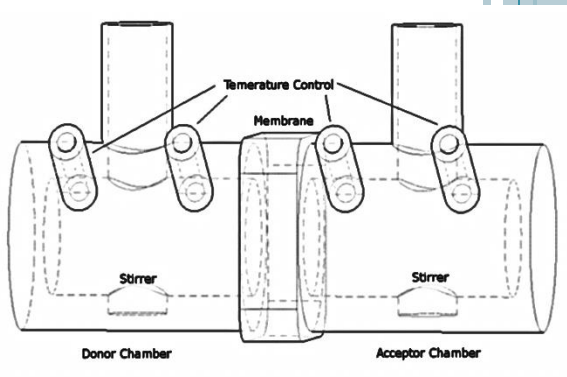
900 ml

PAMPA



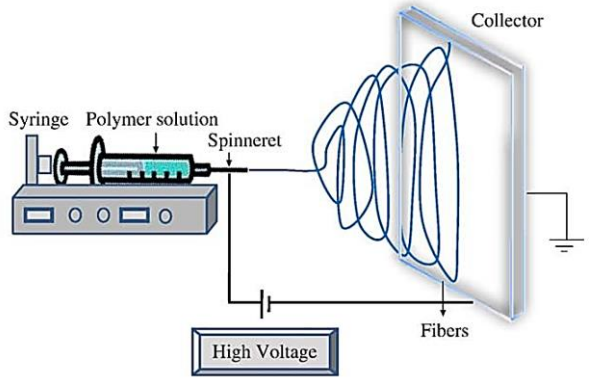
Microflux



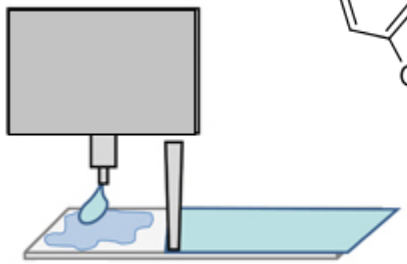


Formulation Screening using dissolution, Pampa and Microflux assays

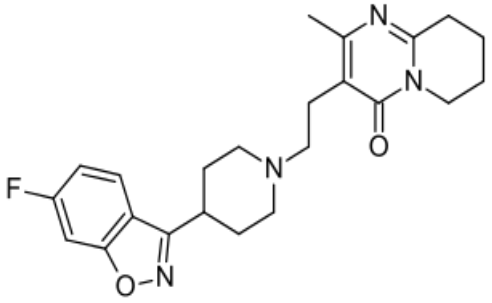
Model compound: Risperidone, poorly watersoluble antipsychotic drug



Electrospinning



Film casting

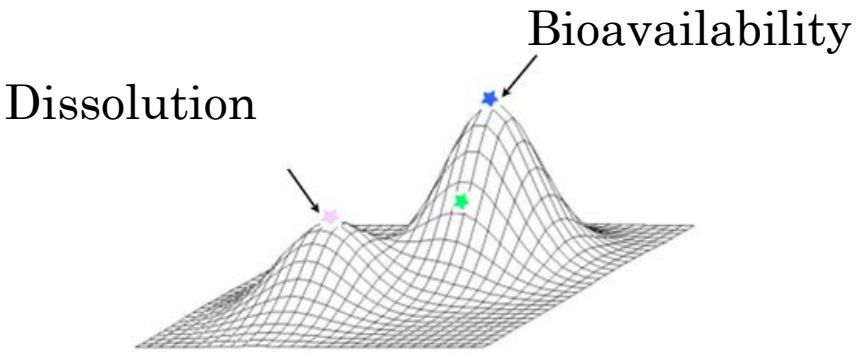


Formulation	API content (w/w%)	polimer content (w/V%)	Cyclodextrin content (w/w %)	Solvent
Casted film: PVP/HPBCD	10	2.5	34	EtOH
Electrospun fiber: PVP/HPBCD	10	2.5	34	EtOH
Electrospun fiber: PVP	10	2.5	0	EtOH

Comparison of Dissolution, PAMPA and Microflux Test Results by Nonparametric Ranking

Formulation	Dissolution	PAMPA	Microflux
Casted Film: PVP/HPBCD	3	1	1
Electrospun fiber: PVP/HPBCD	2	2	2
Electrospun fiber: PVP	1	3	3
Untreated Risperidone	4	4	4

Ranking of the formulations by different analitical test results

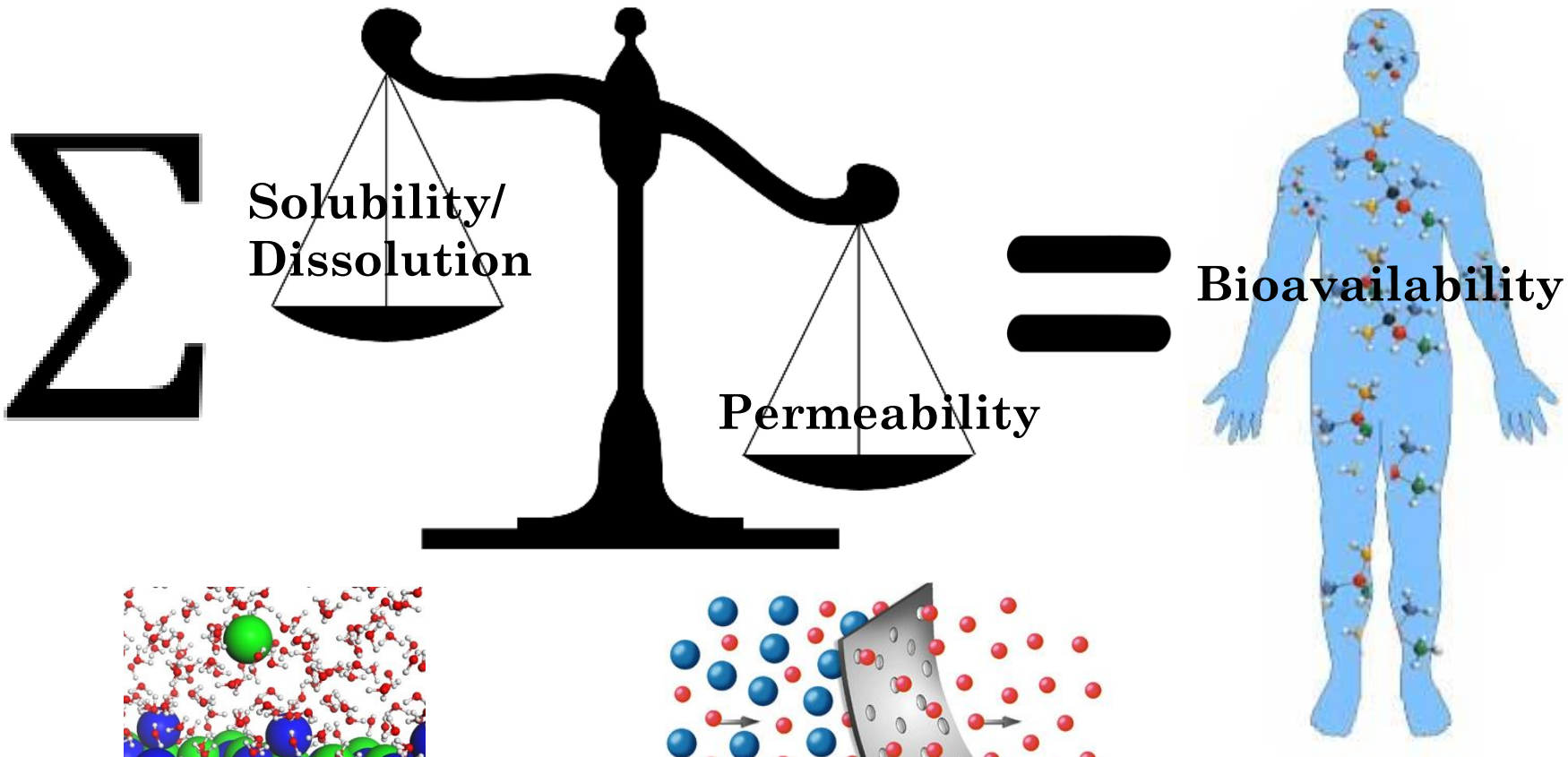


The best formulation from bioavalabitlity point of view cannot be found by only dissolution tests!

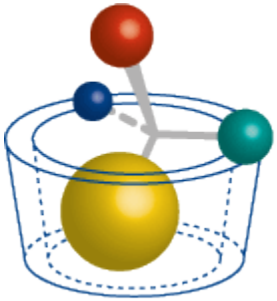
III. Solubility-permeability interplay and effect of commonly used dissolution enhancers on membrane permeability



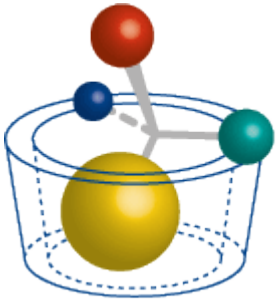
Solubility-Permeability interplay



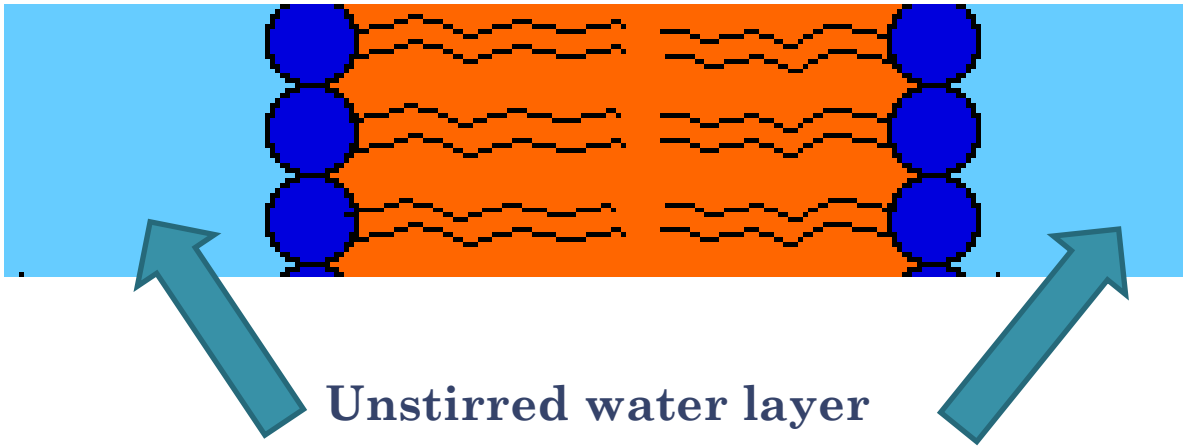
Excepient effect on permeation



Cyclodextrins can form inclusion complexes with cholesterine, affecting membrane integrity!



Phospholipid membrane

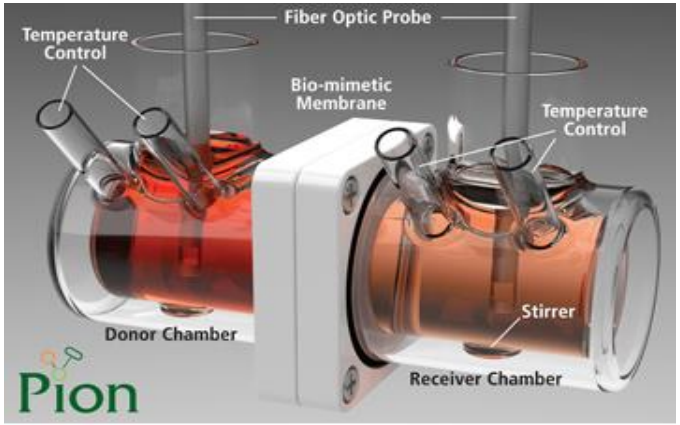


Unstirred water layer

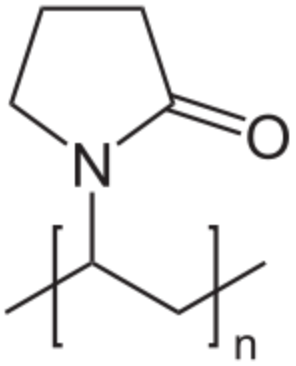
Surfactants can thinner UWL!

Case study: Do polymers Effect membrane permeation?

- Dissolution enhancement of Meloxicam, a poorly water-soluble anti-infammatory model compound
- Formulation screening using several PVP derivatives and Soluplus
- Describing a novel analytical method for testing dissolution and permeation profile of drugs from formulations

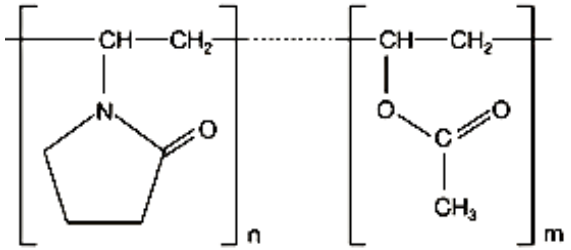


Polyvinilpirrolidone dervatives and Soluplus



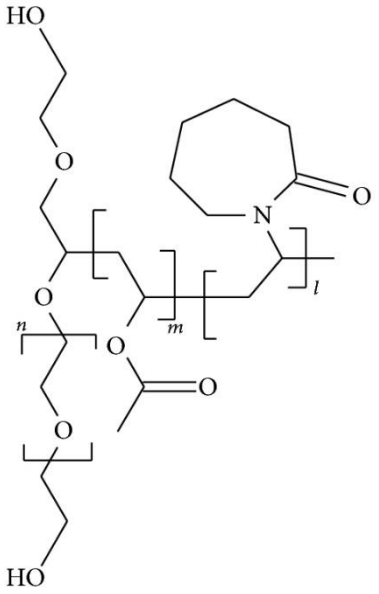
PVP K30
PVP K90

K value refers to instrinsic viscosity and molar mass



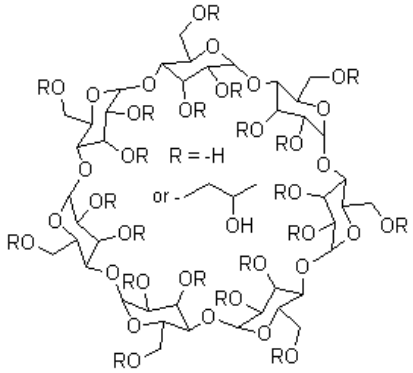
PVP VA 64

Vinylpyrrolidone-vinyl acetate copolymer



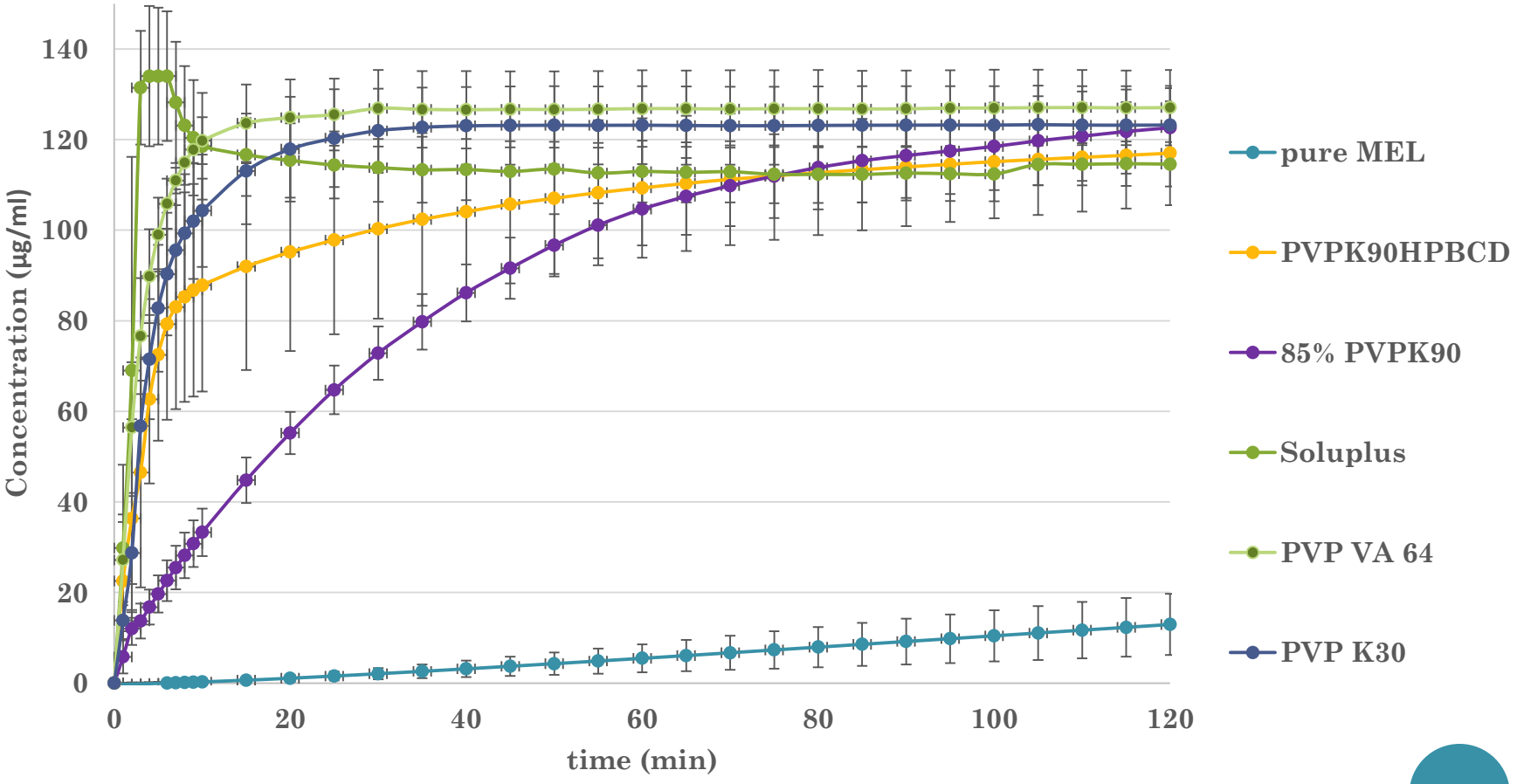
Soluplus

polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer

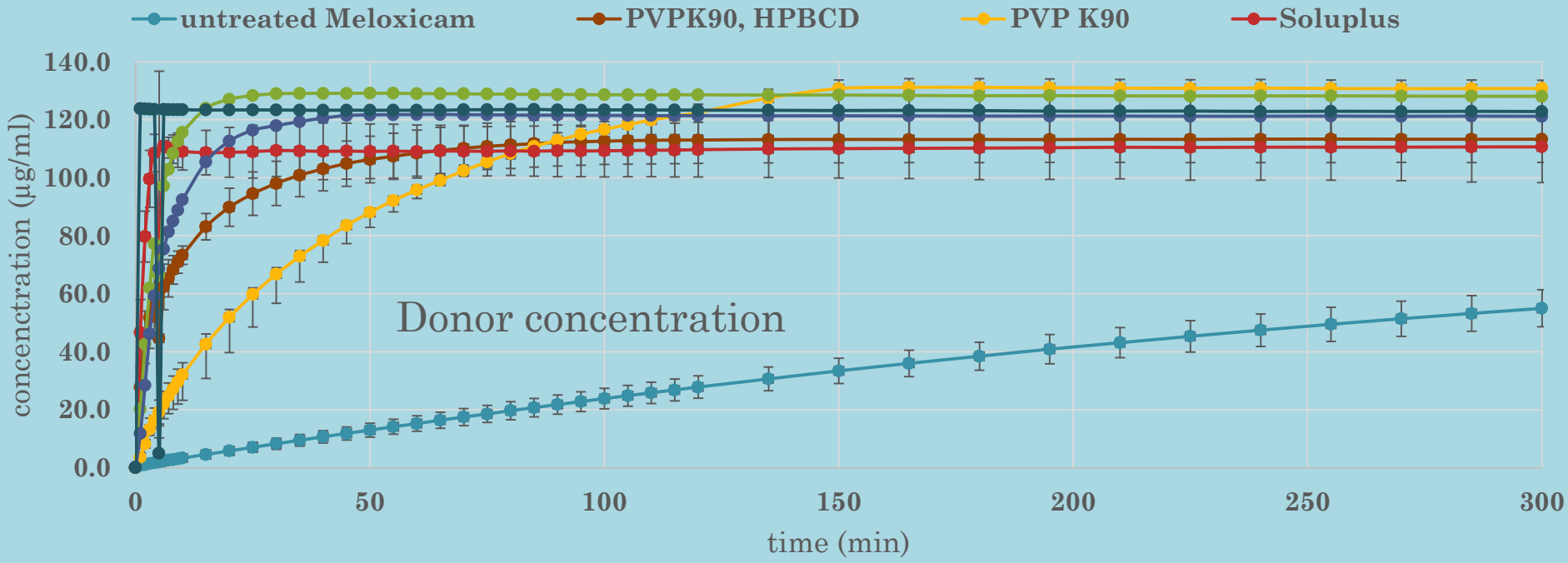


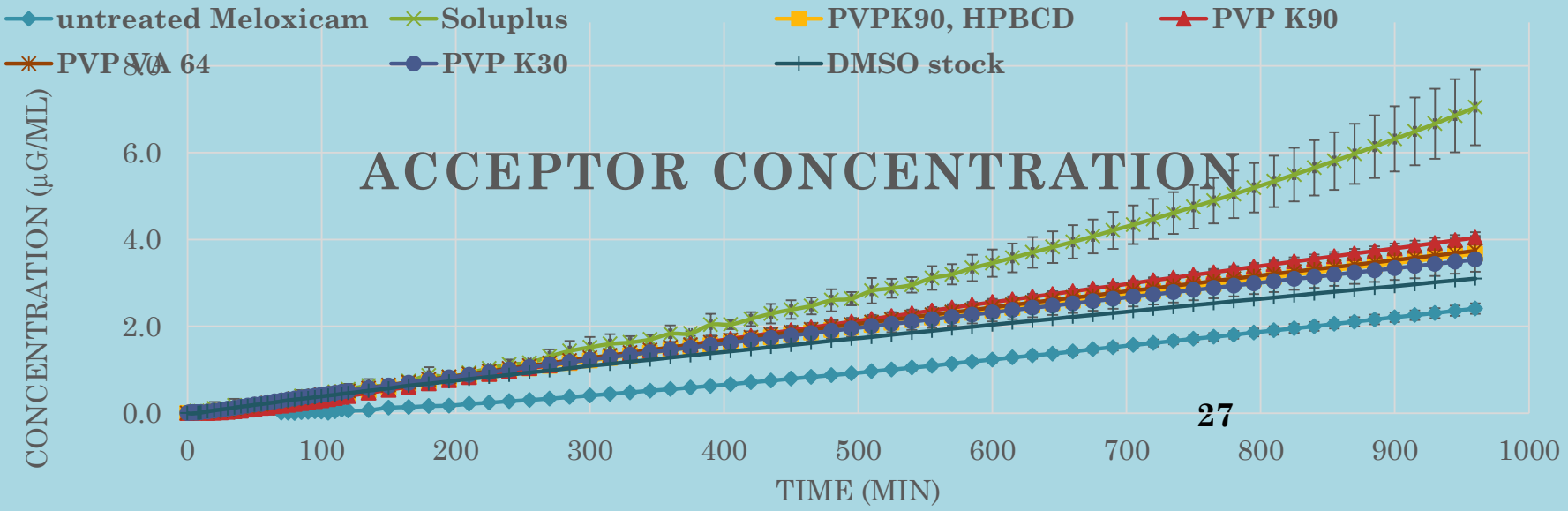
HPBCD
Hydroxypropyl-beta-cyclodextrin

Dissolution test results

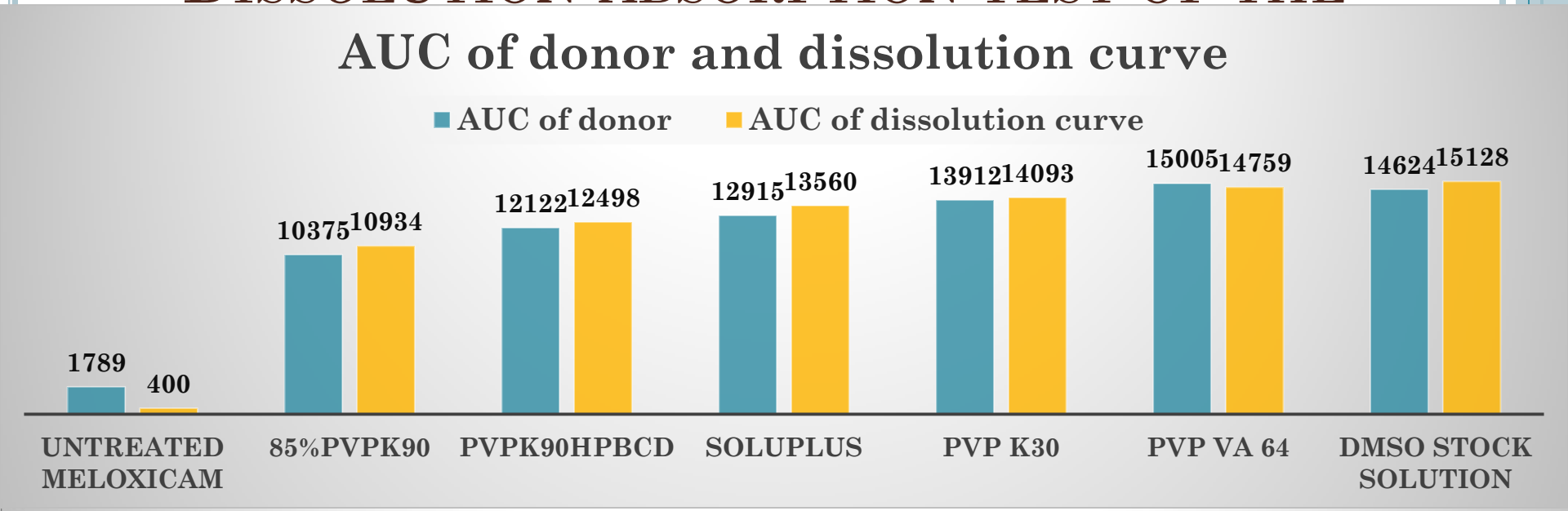


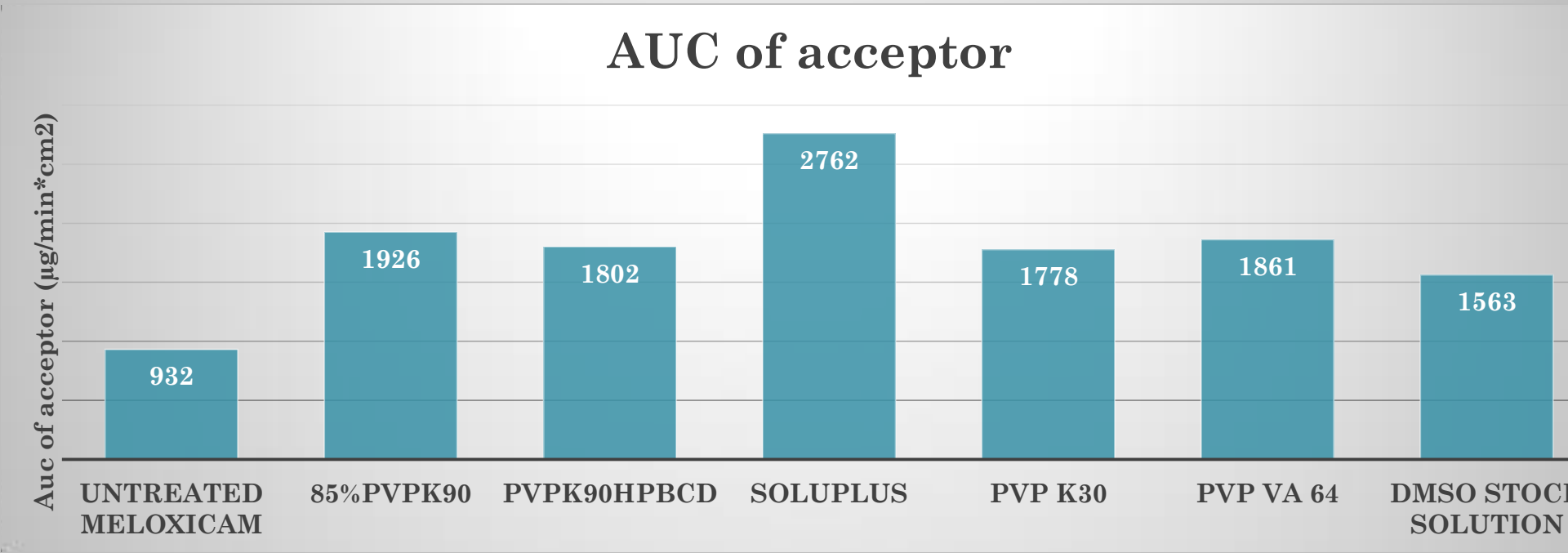
MICROFLUX TEST RESULTS



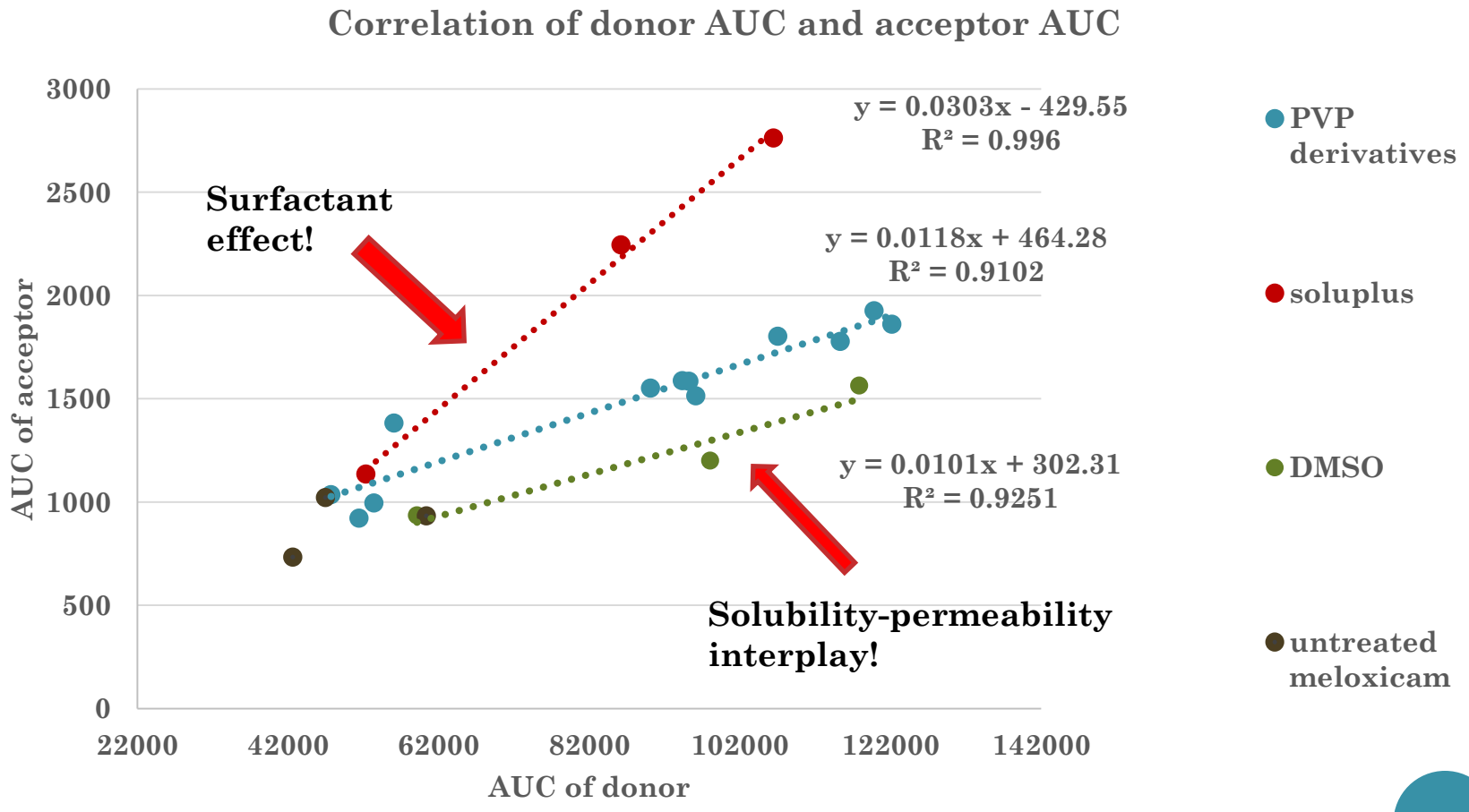


DISSOLUTION-ABSORPTION TEST OF THE





Correlation of donor AUC and acceptor AUC



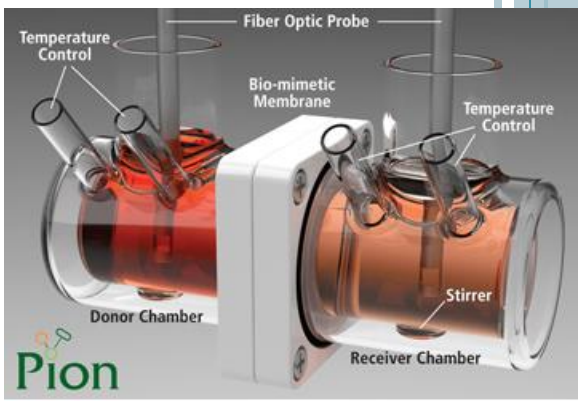
SUMMERY



- I. Case study : formulation development of a poorly watersoluble antipsychotic drug, Aripiprazole
- II. Importance of in vitro analitical tests in formulation development:Formulation screening with different analitical test
- III. Solubility-permeability interplay and effect of commonly used solubility enhancers on membrane permeability







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7th Annual Global Pharma Summit

On

June 20-22, 2016 at New Orleans**, USA**

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