Impact studies of biopolymers on solubility of poorly water soluble drugs: a case study of tebipenem pivoxil.

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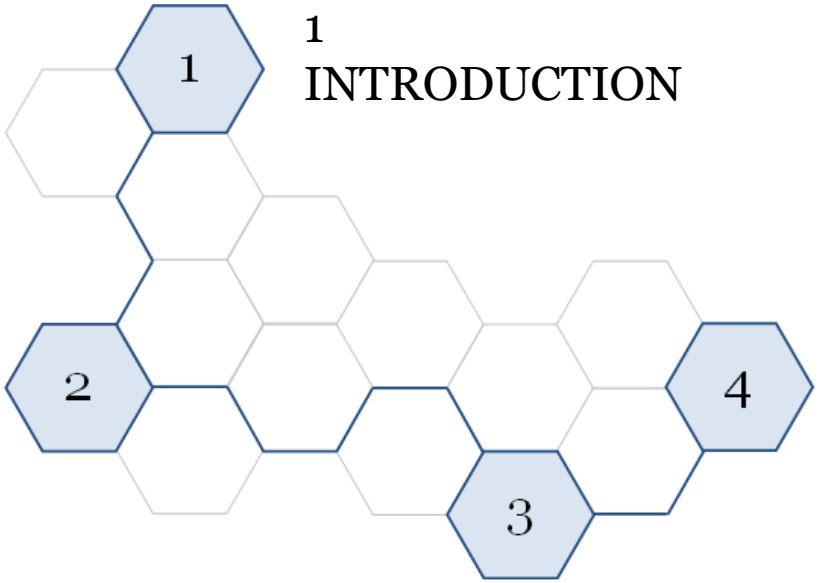
Outline



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INTRODUCTION

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EXPERIMENTAL

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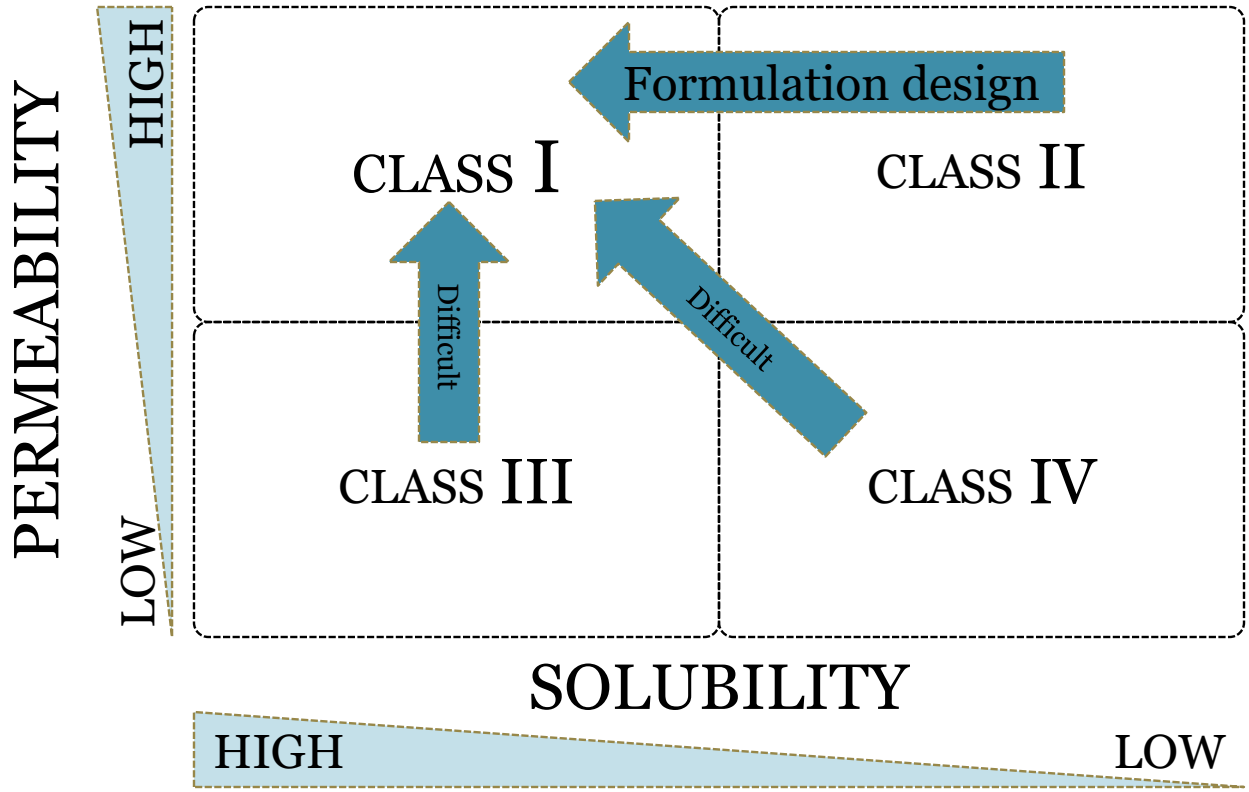
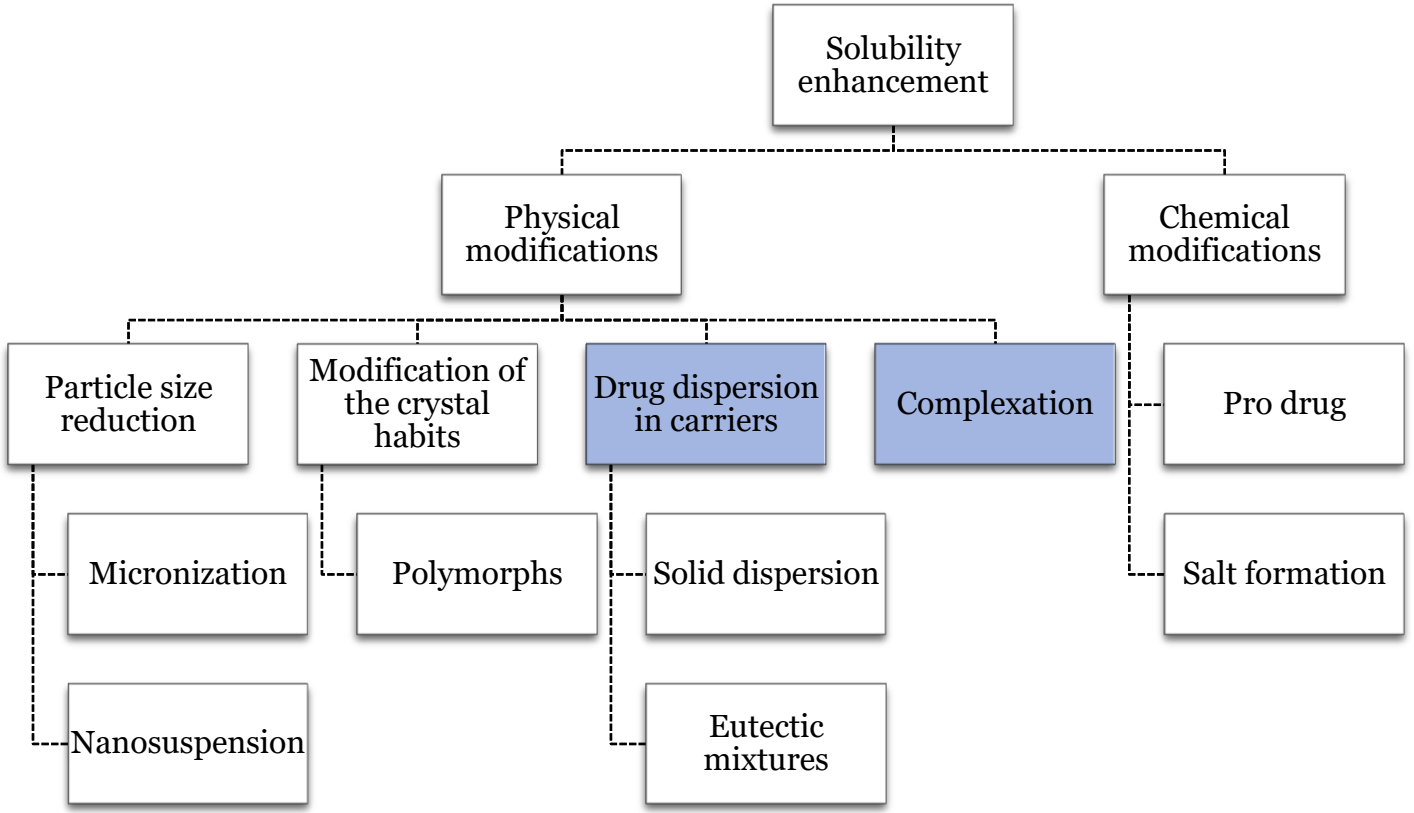
CONCLUSIONS

The Biopharmaceutics Classification System



Solubility enhancement

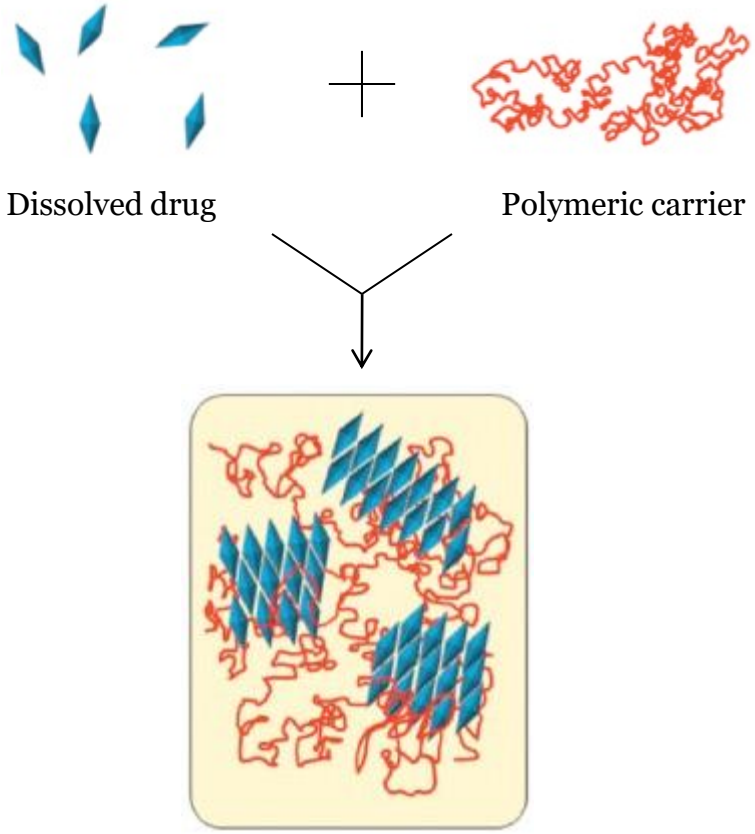
1



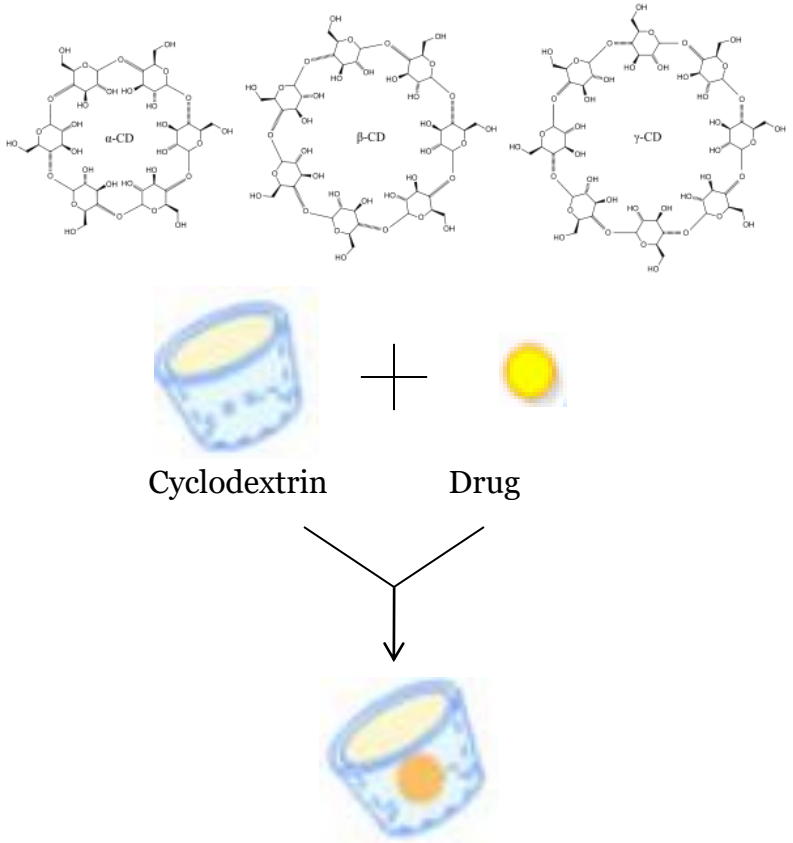
Solubility enhancement

1

Drug dispersion in carriers



Complexation with cyclodextrins



Aim

1

influence of polymers

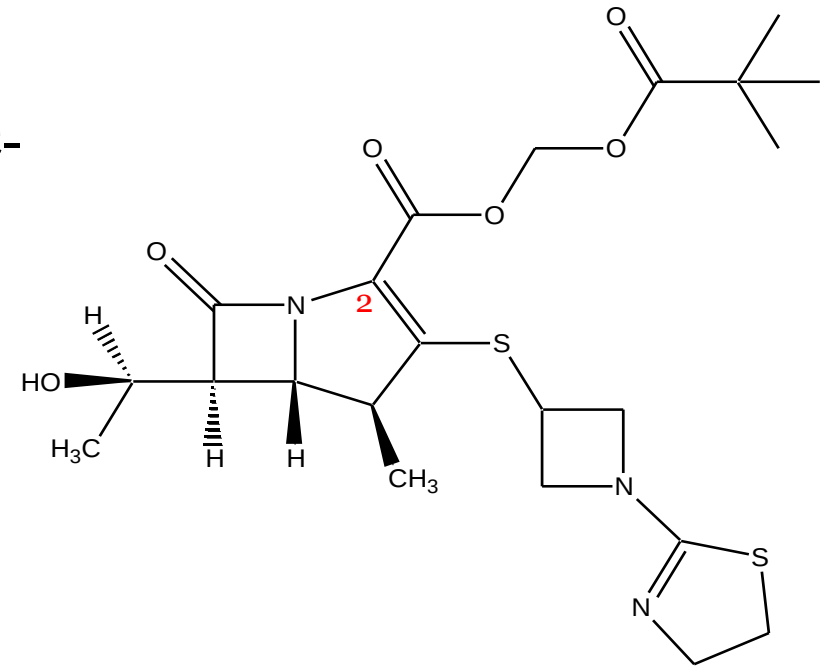
- hydroxypropylmethylcellulose
- cyclodextrin (β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and metyl-β-cyclodextrin)

on tebipenem pivoxil solubility

Tebipenem pivoxil

- first oral carbapenem antibiotic
- esterification of carboxylic group at C-2 increased chemical stability permitting oral administration
- prodrug

Tebipenem pivoxil —carboxyesterase→ Tebipenem



- broad antibacterial activity
- bioavailability 34-79% [1]

[1] Kijima K, Morita J, Suzuki K, Aoki M, Kato K, Hayashi H, Shibasaki S, Kurosawa T. Pharmacokinetics of tebipenem pivoxil, a novel oral carbapenem antibiotic, in experimental animals. Jpn J Antibiot 2009, 62(3):214-40.

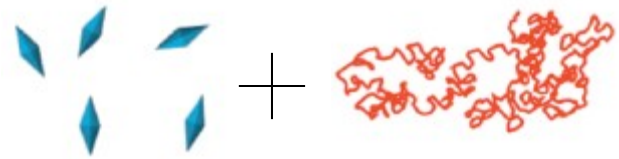
Preparation

2

Drug dispersion in carriers

Complexation with cyclodextrins

PREPARATION of TP-polymer systems



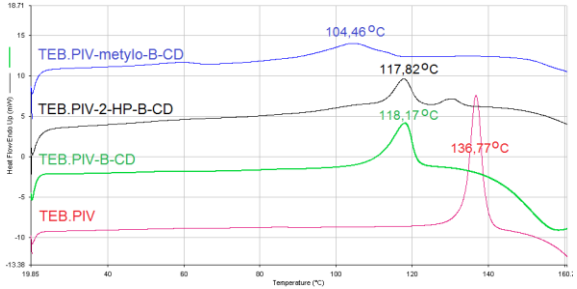
1:1

stirring
for 30 min

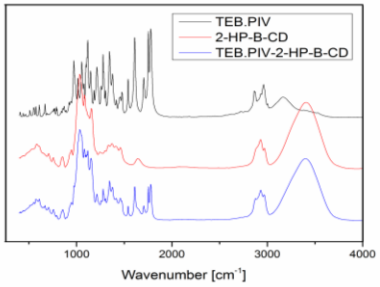
308 K
at an ambient
relative air humidity

IDENTIFICATION of TP-polymer systems

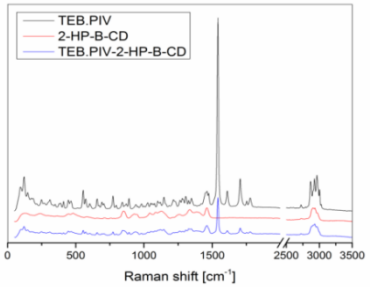
Differential Scanning Calorimetry (DSC)



Infrared spectroscopy (FT-IR)



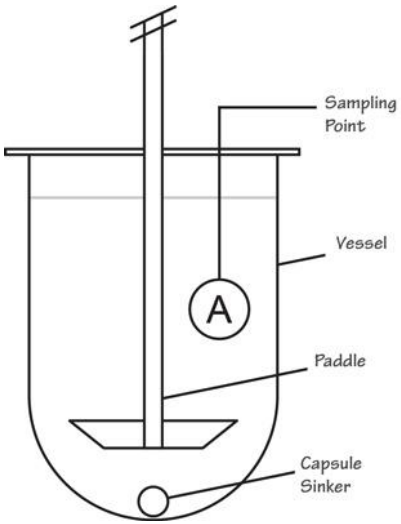
Raman spectroscopy



In vitro dissolution studies

- European Pharmacopoeia 6.0
  - Apparatus 2 (Paddle apparatus)
  - 'sink conditions'
  - 37 ± 0.5 °C
  - Dissolution medium 500 mL
  - pH 1.2 – 7.4
  - Number tested: 6

- Drug concentrations: HPLC-DAD method

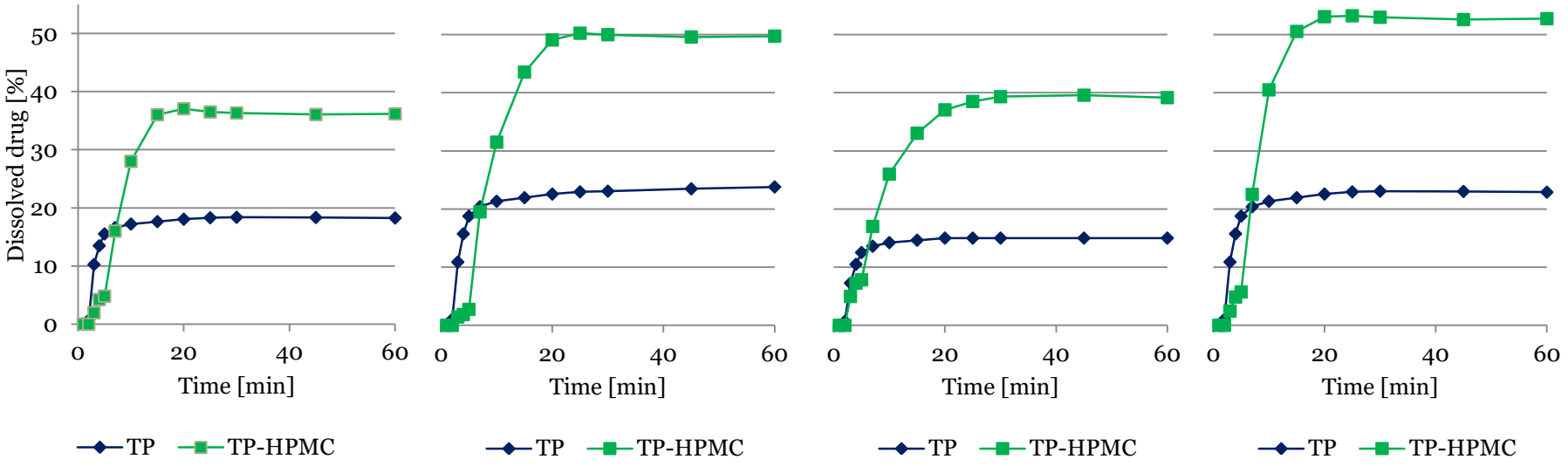


In vitro dissolution studies - results

3

TP – HPMC

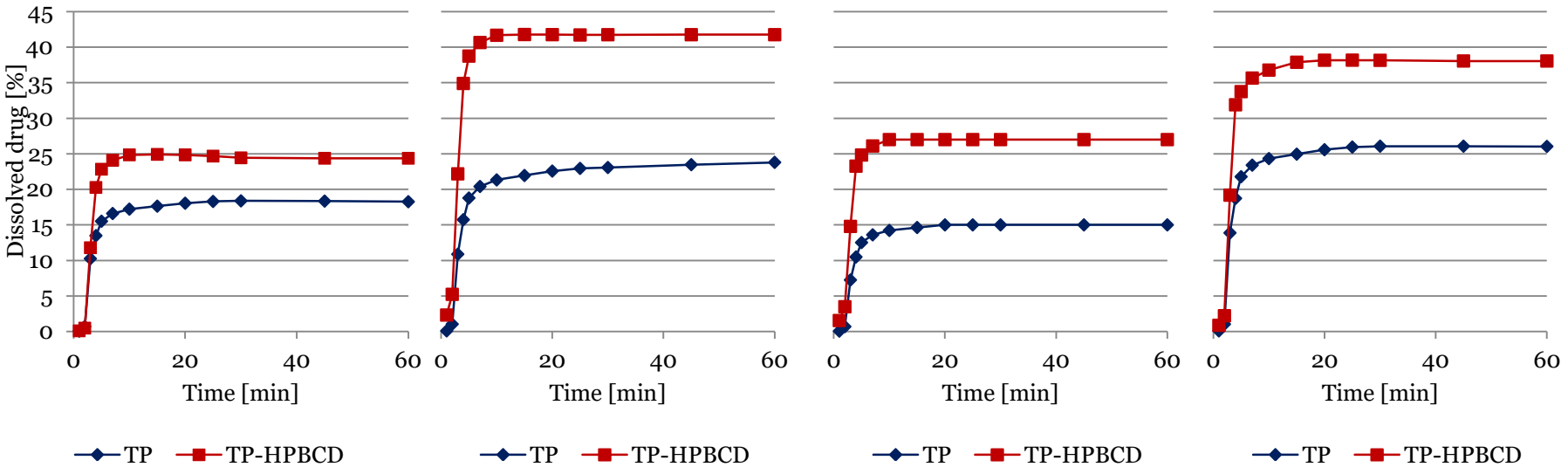
STOMACH		INTESTINE	
Fasted state (pH 2)	Fed state (pH 4-6)	Fasted state (pH 7)	Fed state (pH 5-6)



In vitro dissolution studies - results

TP – HP-β-CD

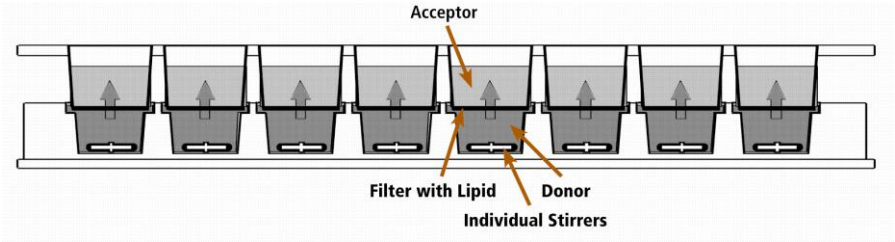
STOMACH		INTESTINE	
Fasted state (pH 2)	Fed state (pH 4-6)	Fasted state (pH 7)	Fed state (pH 5-6)



Solubility of TP was modified.
What next?

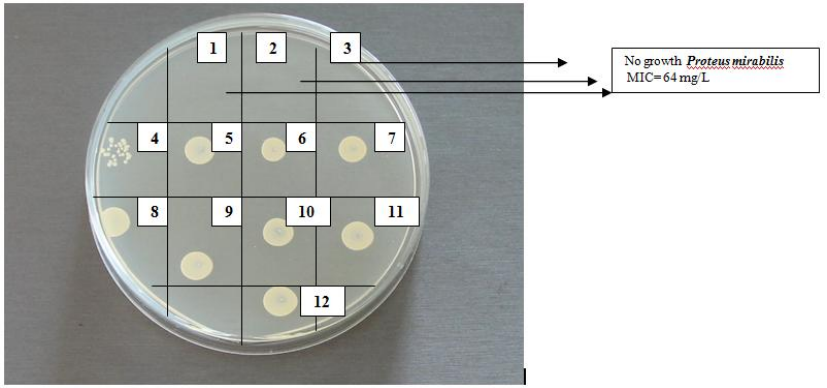
PERMEABILITY STUDIES

- **PAMPA** (**P**arallel **A**rtificial **M**embrane **P**ermeability **A**ssay) Pion®
- Gastro Intestinal Track (GIT) model
- 37 ± 0.5 °C
- pH 1.2 – 7.4
- number tested: 3



MICROBIOLOGICAL ACTIVITY

- **MIC**s analysis
- ATCC reference strains and clinical isolates
- bacteria cultured under aerobic conditions (300 K, 24 h)
- concentrations: 0.02–250 mg/L



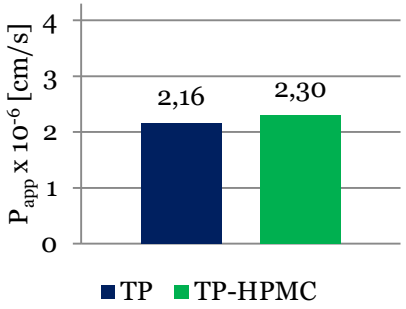
Permeability studies - results

3

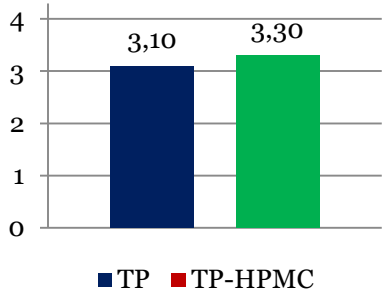
TP – HPMC

STOMACH

Fasted state (pH 2)

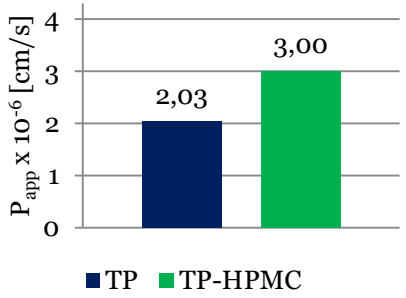


Fed state (pH 4-6)

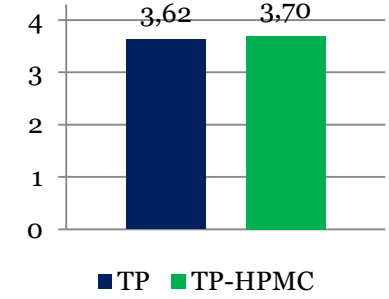


INTESTINE

Fasted state (pH 7)



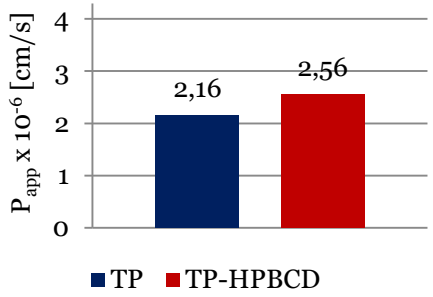
Fed state (pH 5-6)



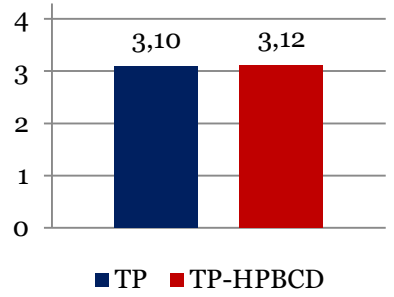
TP – HP-β-CD

STOMACH

Fasted state (pH 2)

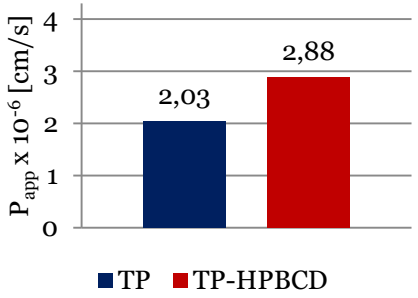


Fed state (pH 4-6)

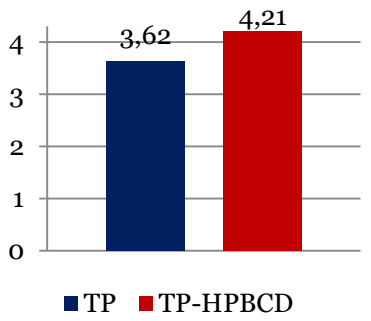


INTESTINE

Fasted state (pH 7)

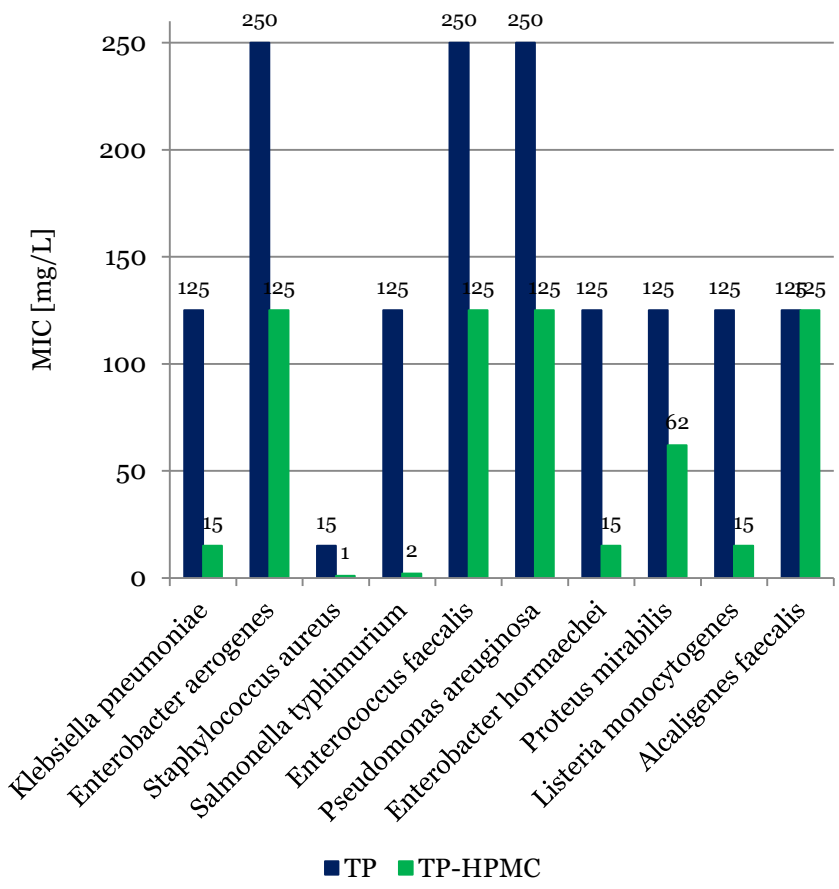


Fed state (pH 5-6)

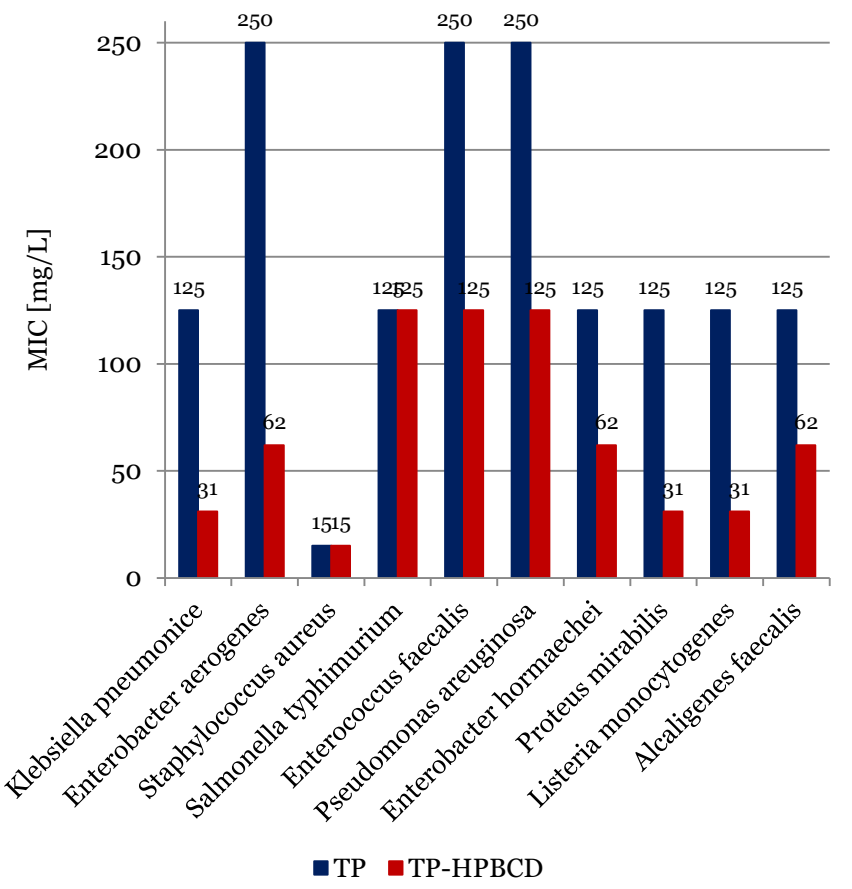


Microbiological activity studies - results

TP – HPMC



TP – HP-β-CD



Conclusion

- HPMC slow down the release profile of TP
- CDs increased apparent solubility in acceptor solutions
- Combination with polymers increased permeation of TP through membrane
- TP-polymer systems showed higher microbiological activity

Acknowledgements

- Judyta Cielecka-Piontek
- Daria Szymanowska-Powalowska
- Wioletta Blaszczak

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'Assessment of the effects of interactions between biopolymers and chemotherapeutics crucial to the treatment of serious bacterial infections'

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