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FDA Workshop on „Current State and Future Perspectives of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls“
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Value of Biorelevant Media for Measuring Solubility and Developing Biopredictive Dissolution Methods

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Agenda

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What are Biorelevant Media?

- Typical compositions of Biorelevant Media
- Comparison of solubility in biorelevant media and human intestinal fluid (HIF)
- Comparison of solubility in quality control media and HIF
- Myths around Biorelevant Media (ease of preparation and reproducibility)
- The Future: addressing intersubject variability in drug solubility *in vivo*

What are Biopredictive Media?

- Biorelevant Media in the broader context – the Levels Paper
- Application of the Levels paper to pharmaceutical products – case examples

Biorelevant media in dissolution testing

- The OrBiTo Dissolution Decision Tree

What are Biorelevant Media?

Biorelevant media – the original approach

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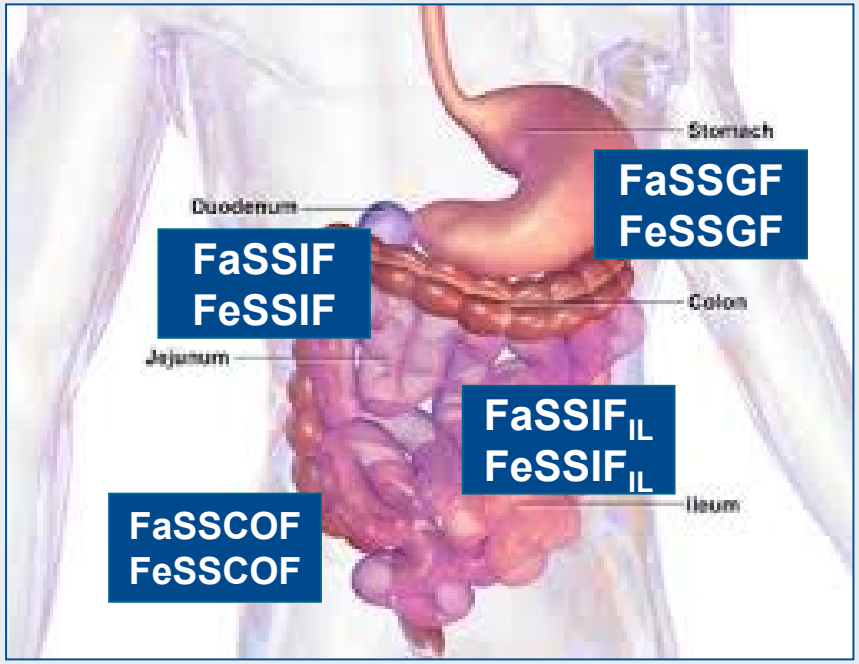
Biorelevant media were first proposed in 1998 to address the need to understand how well poorly soluble drugs would dissolve in the GI tract.

Since then, media have been developed to represent different parts of the GI tract in the fasted and fed states



Key references:

Pharm. Res. 15: 11-22 (1998)

Dissolution Technologies 21:6-10 (2014)

EJPB 93: 173-182 (2015)

Biorelevant media representing the fasted state

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Stomach:

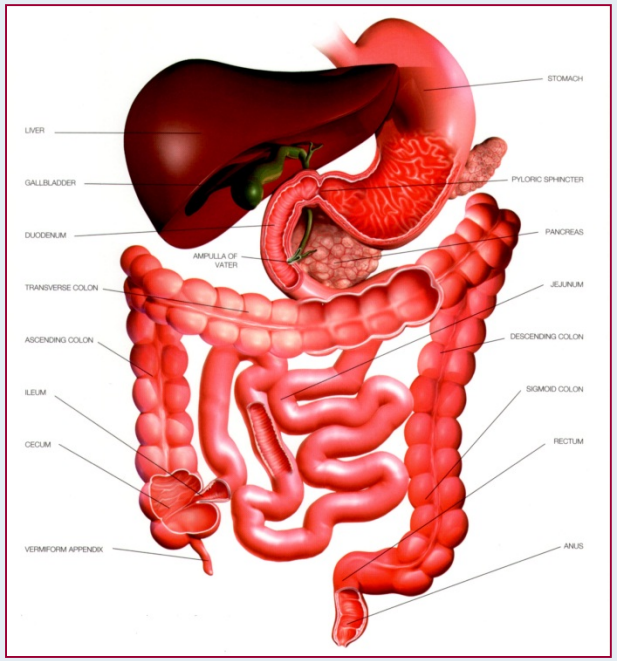
- **FaSSGF: simulates reduced surface tension in the stomach**

Small intestine:

- **FaSSIF-V1 simulates basal bile secretion in upper SI. There are two additional versions (V2 & V3)**

Colon:

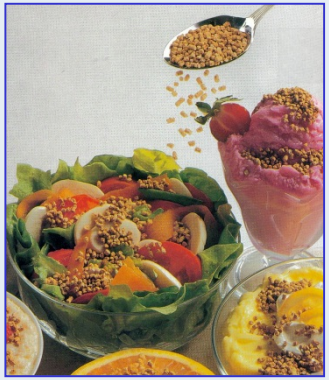
- **FaSSCOF simulates conditions in a fasted state PK study**

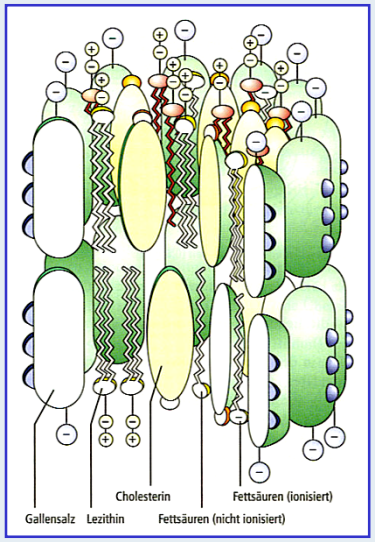


Vertzoni et al. EJPB 2005, Dressman et al. Pharm. Res. 1998
Vertzoni et al. Pharm. Res. 2010, Fuchs et al. 2014

Biorelevant media representing the fed state

- **Stomach:**
  - **FeSSGF: Originally a milk/buffer pH 5 combination to simulate gastric conditions after a standard breakfast.**
  - **FeSSGEm is similar, but uses Lipofundin instead of milk to reduce analytical issues (*note: in recent papers, this composition is referred to as FeSSGF*)**
- **Small intestine:**
  - **FeSSIF-V2 simulates postprandial bile secretion, lipolysis products, increased buffer capacity and osmolality in upper SI after food intake**
- **Colon:**
  - **FeSSCOF simulates the ascending colon in the fed state**





Markopoulos, Andreas et al. EJPB 2015

Composition of biorelevant media: a case example

As an example of the composition of biorelevant media, the composition of FeSSIF-V2, which represents the fed state in the upper small intestine, is shown below:

Component	Concentration (mM)
Sodium Taurocholate	10
Lecithin	2
Glycerylmonooleate	5
Sodium Oleate	0.8
Maleic acid	71.9
NaOH	102.4
NaCl	125.5

Parameter	Value
Osmolality	390 mOsm/kg
Buffer Capacity	25 mmol/L/pH unit
pH	5.8

Comparison of solubility in biorelevant media and HIF for poorly soluble drugs

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In most cases the solubility in biorelevant media is similar to HIF for poorly soluble drugs (as indicated in green)

Drug / Medium	felodipine	nifedipine	carbamazepine	ciclosporine	danazol	Indinavir	ibuprofen	dipyridamole	ketoconazole
HIF	14 µg/mL	10-45 µg/mL	170-336 µg/mL	3.5-13 µg/mL	2-13 µg/mL	51 µg/mL	1.99 mg/mL	20-29 µg/mL	29-336 µg/mL
FaSSIF-V1	**46.4**	**24.2**	**298**	**31.9**	**10.1**	**28.7**	**1.98**	**29.9**	**21.7**
FaSSIF-V2	**12.8**	**15.5**	**295**	**12.9**	**2**	**29.6**	**1.92**	**16.3**	**15.3**
FaSSIF-V3	**11.6**	**16.2**	**312**	**12.5**	**3**	**26.1**	**1.44**	**27.3**	**19.1**

Data from Fuchs et al. EJPB 90:229-240 (2015) und Klumpp et al. Dissolution Technologies (in press, 2019)

Comparison of solubility in quality control media and HIF for poorly soluble drugs

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Drug / Medium	felodipine	nifedipine	carbamazepin	ciclosporine	danazol	fenofibrate	glibenclamide	dipyridamole	ketoconazole
buffer	1.1 µg/mL	11.8 µg/mL	245 µg/mL	4.2 µg/mL	0.3 µg/mL	0.3 µg/mL	2.7 µg/mL	5.1 µg/mL	8.3 µg/mL
HIF	14	10-45	170-336	3.5-13	2-13	12-19	9-15	20-29	29-336
Buffer + 0.5% SLS	606	162	1388	2488	209	154	36.7	831	1787

Green – values which agree with solubility in HIF,

Red – values which are well outside the range in HIF

⇒ **For poorly soluble drugs, biorelevant media clearly show an advantage over quality control media (buffers or buffers with SLS added) in predicting solubility in HIF**

Data from Fuchs et al. EJPB 90:229-240 (2015)

Myths around Biorelevant Media (ease of preparation and reproducibility)

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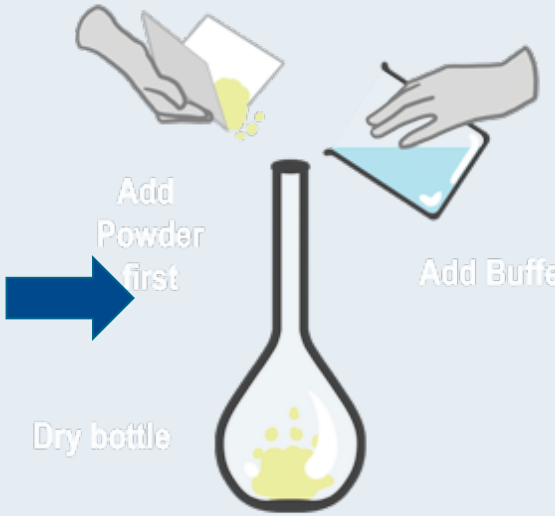
Back then…… in 1998 we were preparing the media manually

Now…… the instant powders are available from Biorelevant.com



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Myths around Biorelevant Media (ease of preparation and reproducibility)

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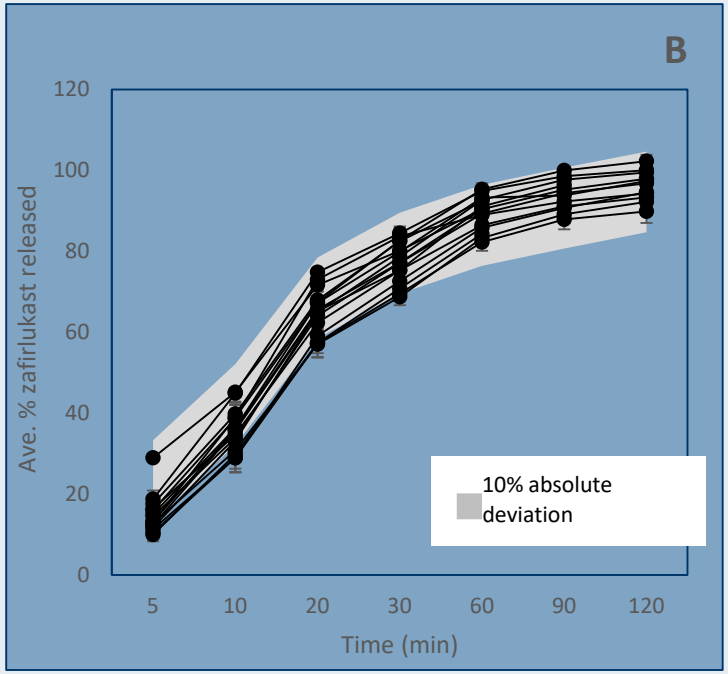
An OrBiTo study addressed reproducibility of results with biorelevant media in studies involving seventeen different academic and industrial dissolution labs.

Results for Zafirlukast (Accolate 20mg tablets) in FaSSIF (n=15 labs participated in this arm of the study) all fell within a 10% absolute deviation from the mean profile indicating excellent reproducibility



Mann et al. (2017) Validation of dissolution testing with biorelevant media: An OrBiTo Study. Mol. Pharm. 14: 4192-4201

The Future: addressing intersubject variability of drug solubility *in vivo*

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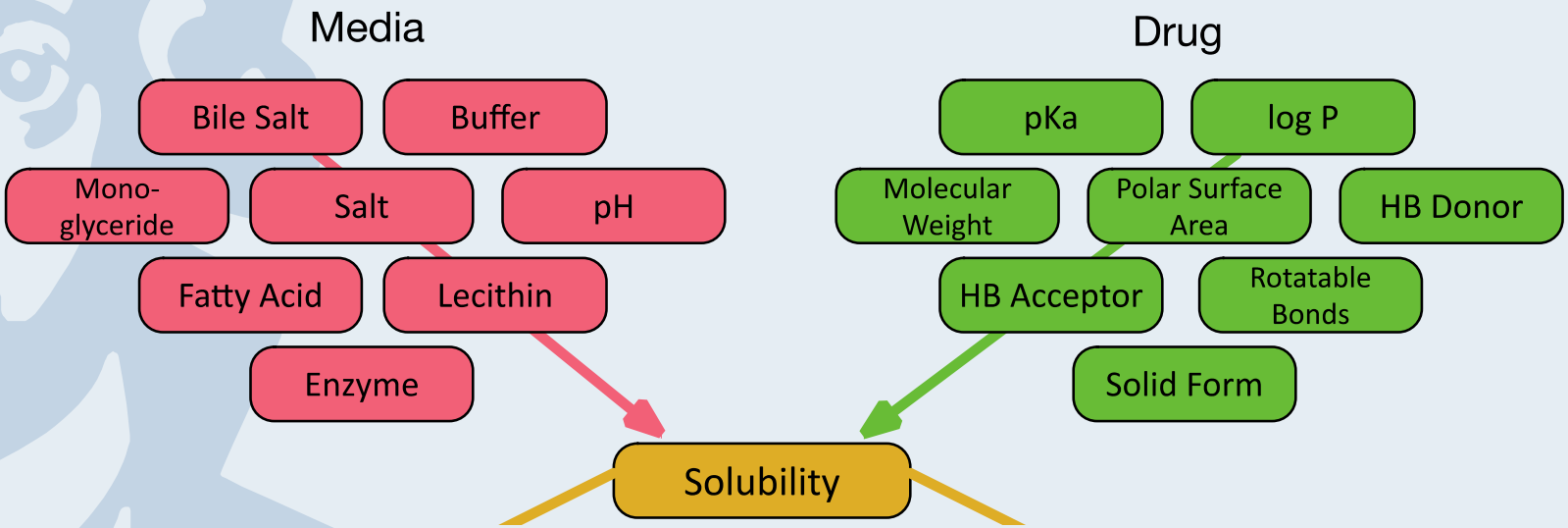
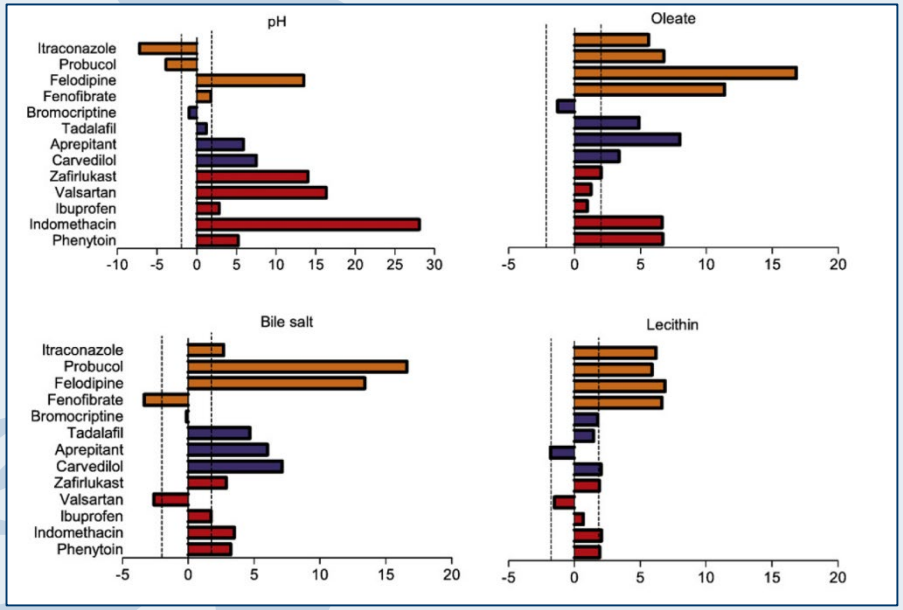
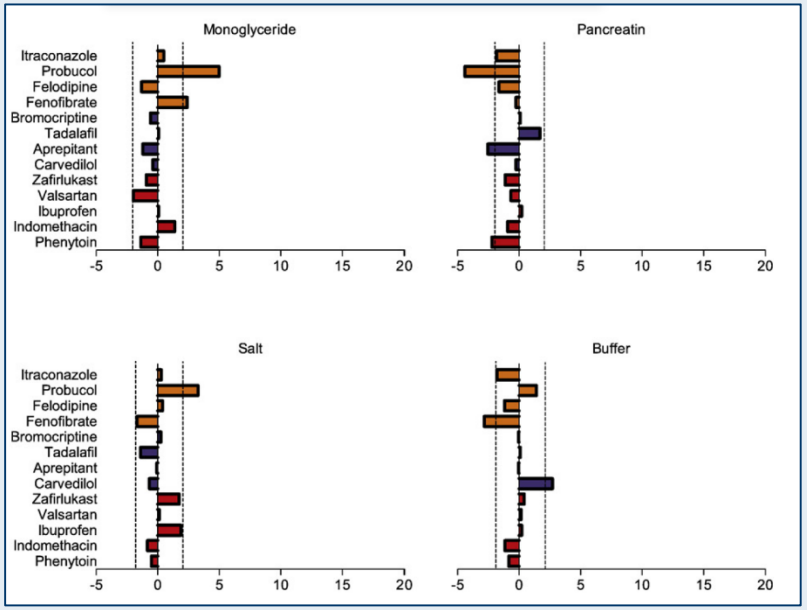
Scientists at Strathclyde University are exploring a DOE approach to make it possible to estimate not only the average *in vivo* drug solubility but also the intersubject variability in solubility. Factors that are taken into account are shown on this diagram (courtesy of Prof. Gavin Halbert and Dr. Ibrahim Khadra).



The Future: addressing intersubject variability in drug solubility *in vivo*

Some factors have more influence on solubility than others: the „heavy hitters“ appear to be pH, bile components and fatty acids. Covariate effects were also explored in that study.





Data from Zhou et al. (2017) EJPS 99: 95-104

What are Biopredictive media?

Biorelevant media – the updated approach

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While the biorelevant media were originally developed to better predict the solubility and dissolution of poorly soluble drugs *in vivo*, there are also many occasions where less complex media can be appropriate and some cases where additional factors need to be taken into consideration.

For this reason we introduced the Levels concept in 2015:

C Markopoulos, C Andreas, J Dressman, M Vertzoni, C Reppas

In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: Choosing the appropriate test media

EJPB 93: 173-182 (2015)

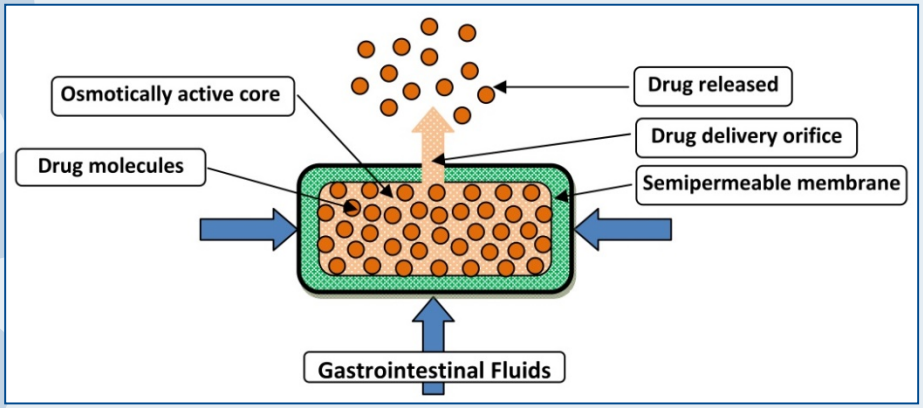
The Levels paper covers the classical "biorelevant media" and puts them in the context of designing *biopredictive* dissolution tests on a more general basis.

Which dissolution test is biopredictive enough?

For some formulations, there is little dependency on GI physiology……..

e.g. Immediate release dosage forms containing highly soluble drugs

e.g. simple osmotic pumps.



For such formulations, media such as water, dilute HCl or phosphate buffer should be sufficient and a simple apparatus (Paddle or Basket) can be used

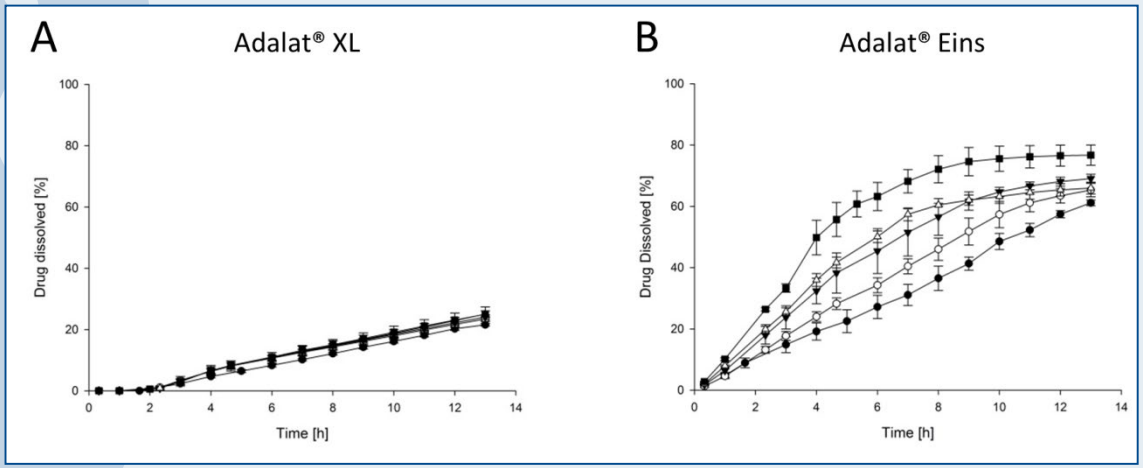
Which dissolution test is biopredictive enough?

.....while for other formulations, release may be highly dependent on GI physiology

e.g. Immediate release dosage forms containing poorly soluble drugs

e.g. enteric coated pellets

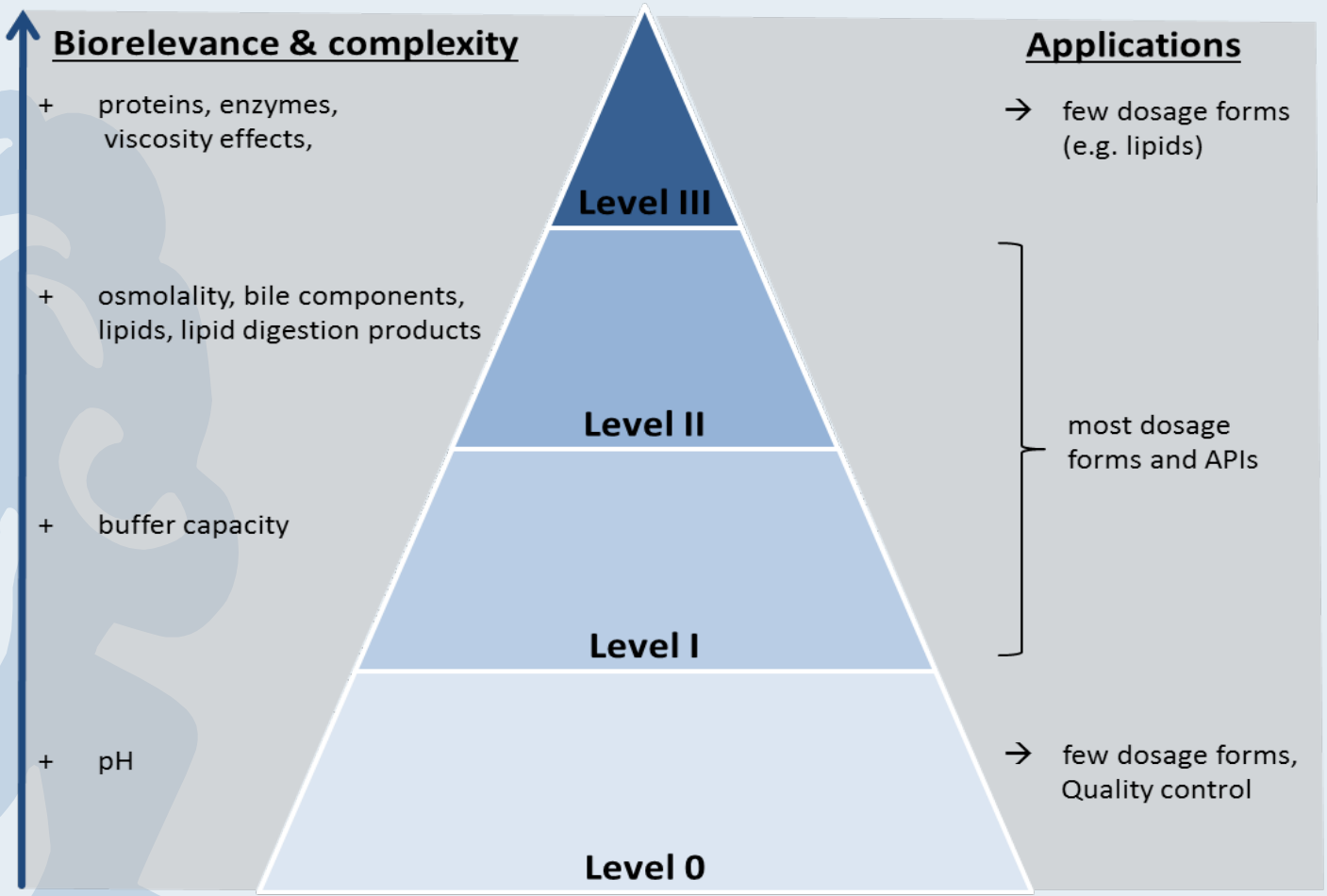
e.g. matrix tablets for modified release



osmotic pump **matrix tablet**

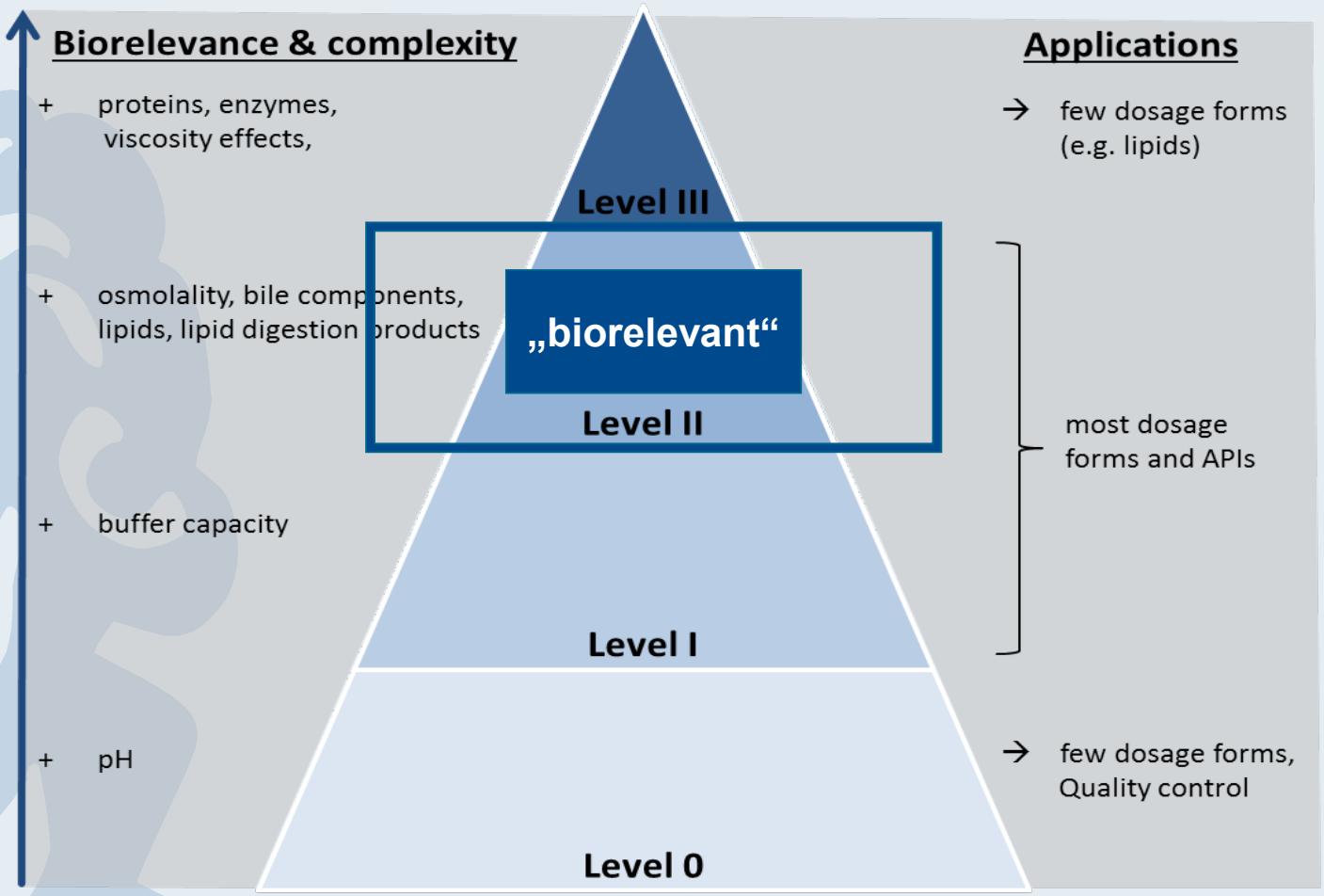
For such formulations, aspects of GI physiology that are key to release should be accounted for, and an apparatus that facilitates media change may be appropriate

The Dissolution Media Pyramid



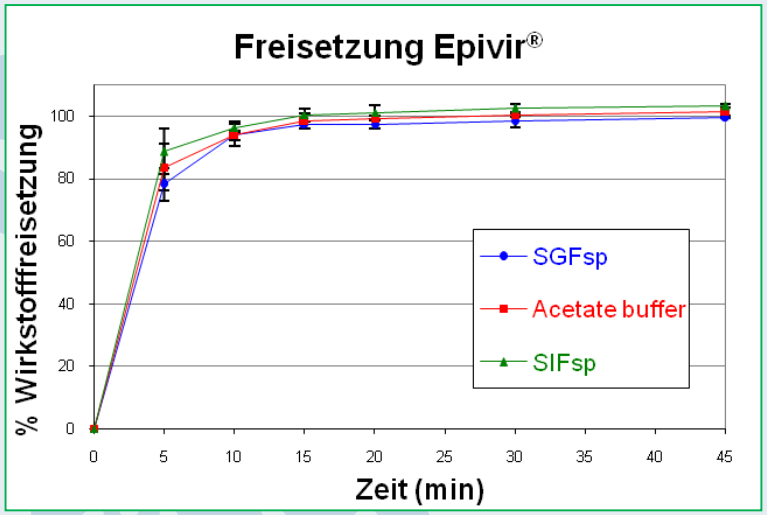
Markopoulos, Andreas et al. Eur. J. Pharm. Biopharm. ***93****: 173-182 (2015)*

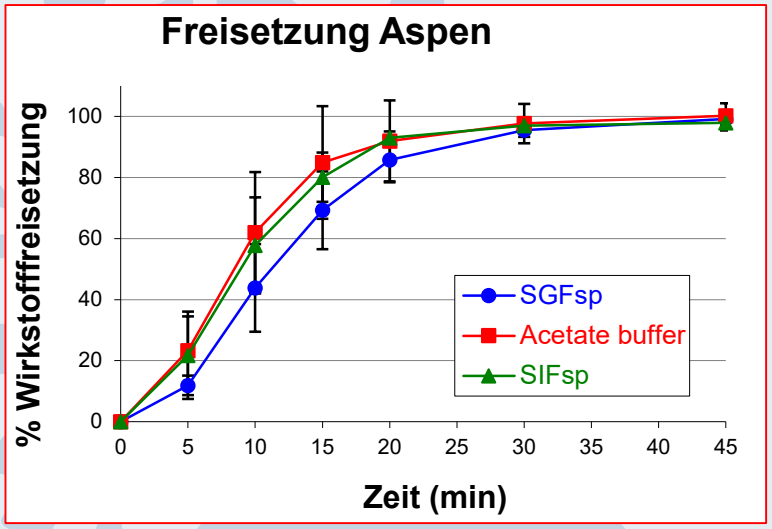
The Dissolution Media Pyramid



Markopoulos, Andreas et al. Eur. J. Pharm. Biopharm. ***93****: 173-182 (2015)*

Examples of the Levels approach to biorelevant / biopredictive media: Level 0





Level 0 media (pH only): e.g. are applied for the BCS-biowaiver approval of immediate release solid dosage forms containing highly soluble drugs (BCS Class I and III). The compendial buffers used have a higher buffer capacity than is observed in the fasted state in the human GI tract, but as the pH values cover the usual pH range in the upper GI tract the media are „fit for purpose“.

In fact, the dissolution testing for BCS-biowaiver is often over-discriminating, as illustrated by the results for a German Lamuvidine generic product (Aspen) that was approved by a PK-based Bioequivalence study.

Examples of the Levels approach to biorelevant / biopredictive media: Level I

Level I media (pH plus buffer capacity):
a good example here is the release from enteric coated products containing drugs which are highly soluble.

In this case, release of the drug is governed by the dissolution of the coating polymer. As a poorly soluble polymer that ionizes, both the pH AND the buffer capacity will affect the rate of polymer dissolution and therefore the onset of drug release

Data from
Ozturk et al. Pharm Res (1988) 5: 550-565

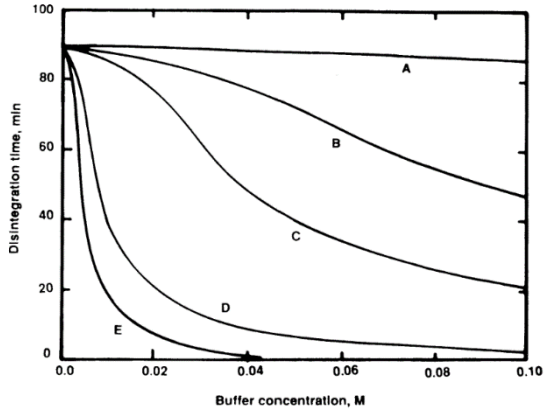


Fig. 9. Model predictions for the effect of buffer concentration (pK_b = 7.1) on disintegration time for aspirin tablets coated with a polymer of pK_p = 4.5. (A) pH_b = 5; (B) pH_b = 5.5; (C) pH_b = 6; (D) pH_b = 6.5; (E) pH_b = 7.

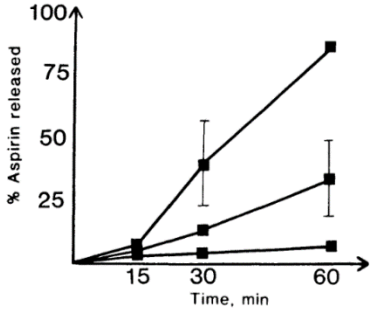


Fig. 10. Percentage aspirin released from PVAP-coated tablets as a function of time at a stirring rate of 100 rpm in 0.025 *M* (lower curve), 0.05 *M* (middle curve), and 0.10 *M* (upper curve) phosphate buffer at pH 6.8.

Examples of the Levels approach to biorelevant / biopredictive media: Level II

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Level II (pH plus buffer capacity plus physiological solubilizing factors):

Level II media are usually the appropriate choice whenever a poorly soluble drug with logP > 2 is under consideration

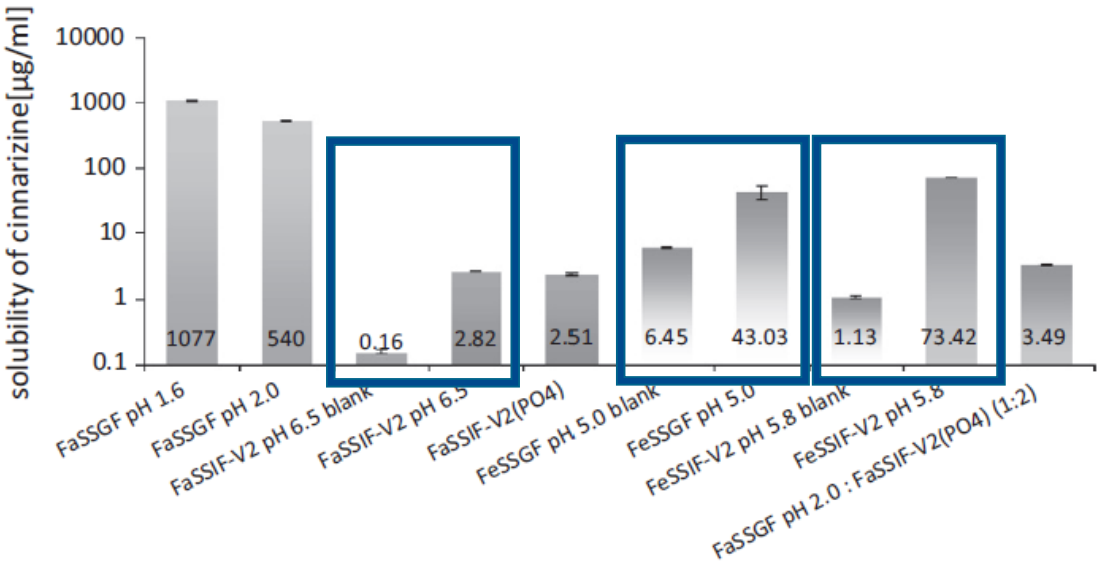
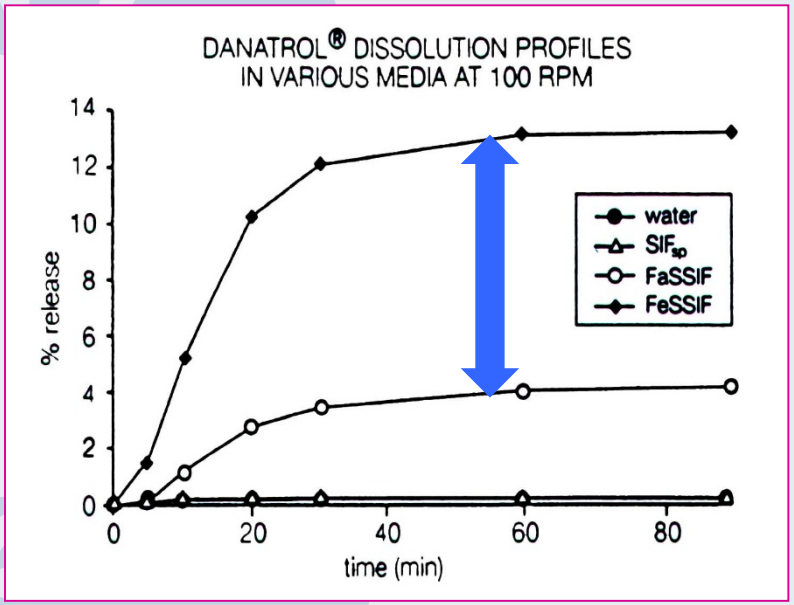
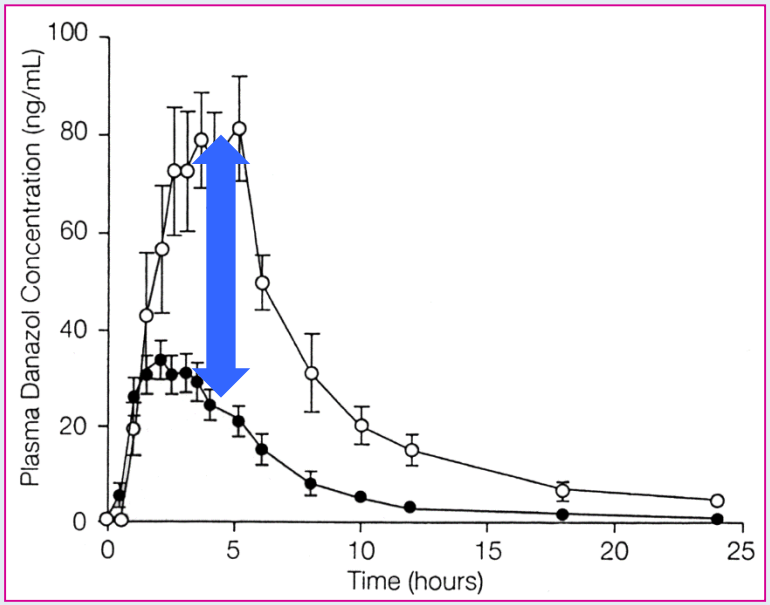


Fig. 4. Solubility of cinnarizine in biorelevant media (logarithmic scaling). Solubility values in µg/ml along with the standard errors are shown on the bar for each medium.

Examples of the Levels approach to biorelevant / biopredictive media: Level II

Dissolution results in Level II media can be used to predict food effects for poorly soluble drugs e.g. Danazol





The increase in dissolution between FaSSIF and FeSSIF was mirrored in the plasma profiles (Cmax and AUC) in the fasted and fed states.

Data from Galia et al. Pharm. Res. 15: 698 (1999) and Charman et al. J Clin Pharmacol. 33:1207 (1993)

Examples of the Levels approach to biorelevant / biopredictive media: Level III

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Level III media (special purpose): at this level, media are adjusted to answer specific questions or to address special formulations. Examples include the addition of enzymes to the media for gelatin capsules that may show crosslinking, or when release from lipid-based dosage forms is to be measured.

The graphs shown link the *in vitro* performance of four lipid based formulations with their PK in beagle dogs.

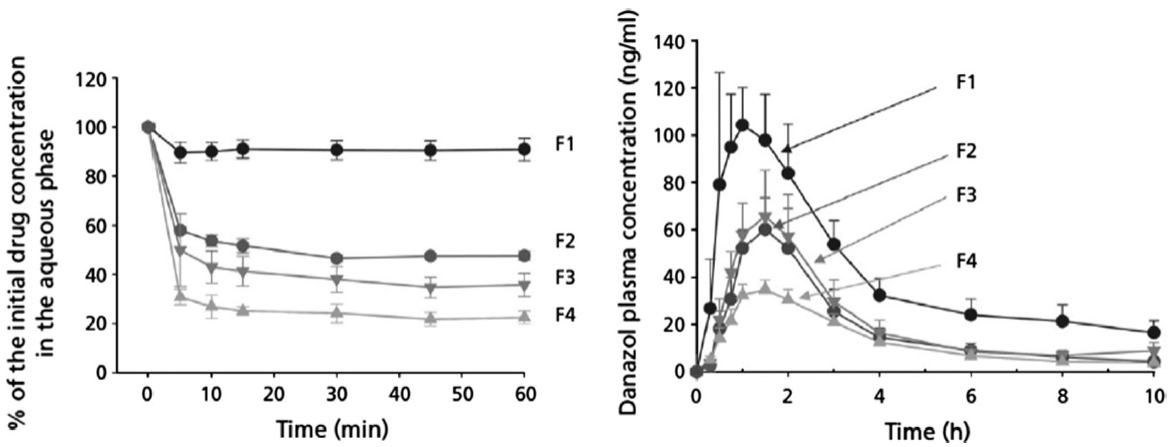


Fig. 6. The results of four lipid formulations of danazol composed with various ratios of lipid (50:50 soybean oil and maisine 35-1), Cremophor EL® and ethanol using the Level III biorelevant media in a simplified *in-vitro* lipolysis model and their corresponding plasma profiles in beagle dogs. The graphs were extracted from Kilic et al. [42].

Biorelevant media in Dissolution Testing

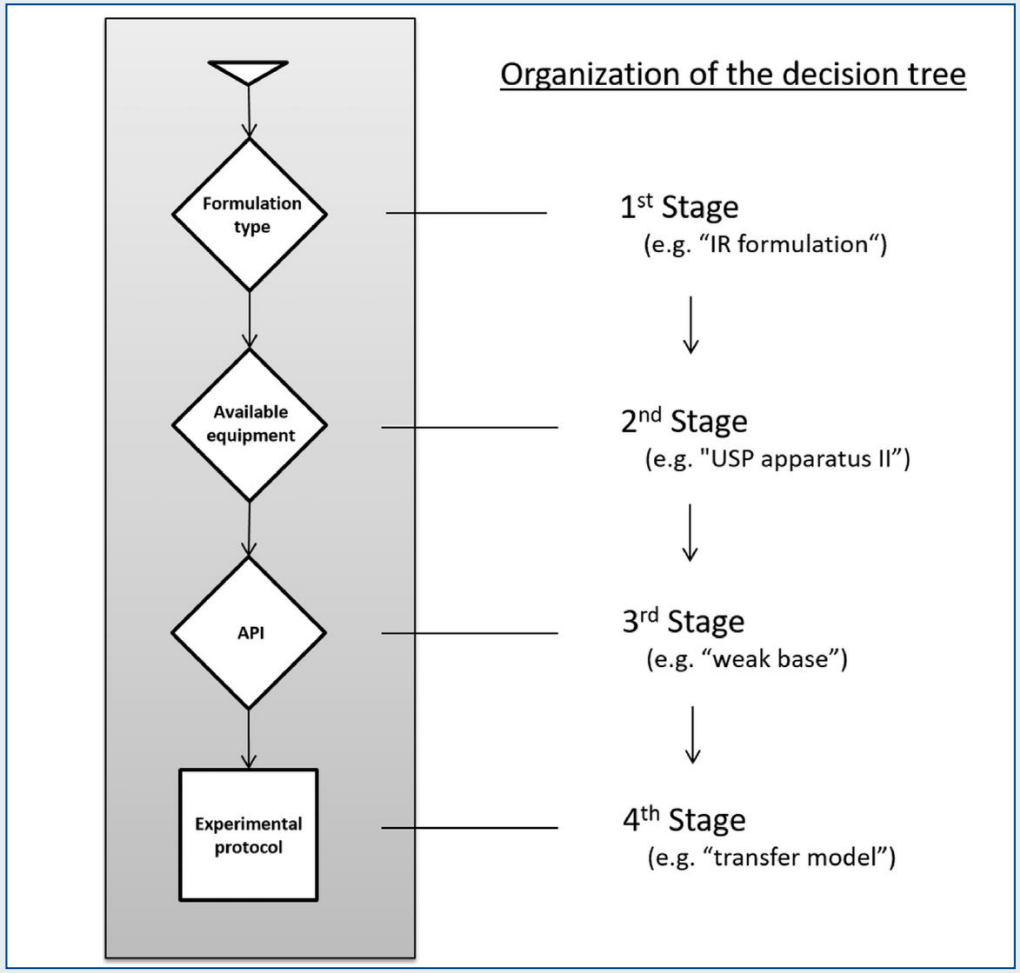
OrBiTo‘s Dissolution Decision Tree

As part of the OrBiTo project, we were asked to summarize the various biopredictive dissolution tests that had been (further) developed into a Decision Tree so that others could have easy access to the results of our five year cooperation.

Andreas, C., Rosenberger J., Butler, P. Augustijns, M. McAllister, Abrahamsson, B., Dressman, J.

An introduction to the OrBiTo decision tree to select the most appropriate in vitro methodology for release testing of oral solid dosage forms during development.

EJPB (2018) 130: 207-213.



OrBiTo‘s Dissolution Decision Tree

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The table shows the variety of the tests, in terms of both dosage form and equipment, that are described in the Decision Tree

Table 2
Overview of dissolution method protocols generated in WP2 of the OrBiTo project according to formulation type.

Immediate release (IR)	Extended release (ER)	Delayed release (DR)
TNO systems [16,17]	TNO systems [16,19]	TNO systems [19]
Artificial stomach duodenum (ASD) model [18]	Dissolution stress test apparatus tester [14,20,21]	Dissolution stress test apparatus [22]
BioGit model [23–25]	USP apparatus II	USP apparatus II
Biorelevant dissolution[a] [7]		
Biphasic dissolution apparatus [26,27]	USP apparatus III[a] [12,13,28]	USP apparatus II (mini paddle) [29,30]
Artificial membrane insert (AMI) system [31]	USP apparatus IV[a] [12,13,28]	USP apparatus III [28]
Transfer model [2,6]		USP apparatus IV [28]
Two stage test[a] [7]		
GastroDuo [32,33]		
USP apparatus II[a]		

[a] Comparative ring studies with at least 6 participating partners were conducted as part of the method validation.

OrBiTo‘s Dissolution Decision Tree: case example

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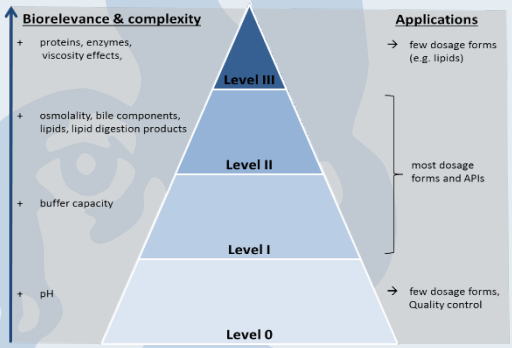
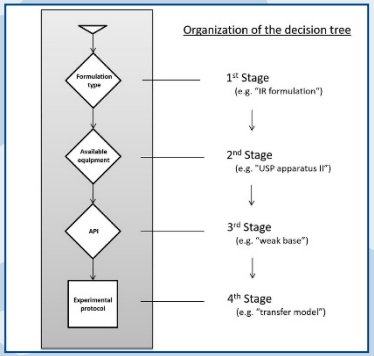
As an example, this table shows a method for biorelevant testing suitable for a monolithic dosage form with extended release, recommended for use during development of the formulation. Both the fasted and fed states are covered, so that potential food effects can be detected early.

GI Region	pH	Medium	Exposure [min]	Total time [min]	Dip rate [dips/min]
			fasted state		
Stomach	1.6	FaSSGF	60	0-60	12
Prox. gut	6.5	FaSSIF-V2	40	60-100	10
Midgut	6.8	$FaSSIF_{midgut}$	80	100-180	10
Dist. ileum	8	SIF_{ileum}-V2	60	180-240	10
Asc. colon	7.8	FaSSCoF	*	> 240	6
			fed state		
Stomach	5	$FeSSGEm_{early}$	20	0-20	12
	3	FeSSGEm	160	20-180	12
	1.6	FaSSGF	60	180-240	12
Prox. gut	6.5	FaSSIF-V2	40	240-280	10
Midgut	6.8	$FaSSIF_{midgut}$	80	280-360	10
Dist. ileum	8	SIF_{ileum}-V2	60	360-420	10
Asc. colon	6.0	FeSSCoF-V2	*	>420	6

* according to the intended duration of release of the dosage form studied.

Main Points of the Presentation





1. **Biorelevant media** are needed to better simulate average *in vivo* solubility and dissolution of poorly soluble drugs. Variations on the media can help anticipate intersubject variability of *in vivo* solubility and dissolution.

2. Biorelevant media form part of a larger approach to establish **biopredictive tests** for various drug / formulation combinations

3. There is a **Decision Tree** available free of charge on the internet to assist the selection of the most appropriate, biopredictive method for a given drug / formulation combination.