

# Aplicações do Aparato IV de Dissolução no Desenvolvimento de Medicamentos Genéricos

*Seminário de Dissolução USP 4 - 2012*

*Fábio Pinheiro de Souza*

*Departamento de P&D*

# Desenvolvimento de Medicamentos Genéricos



Medicamento Referência

Lei n. 9.787 de 10/2/1999



Intercambialidade



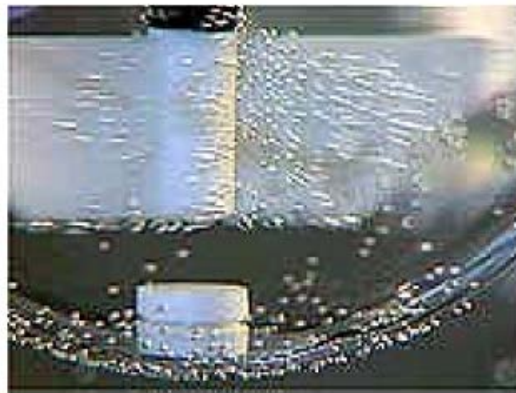
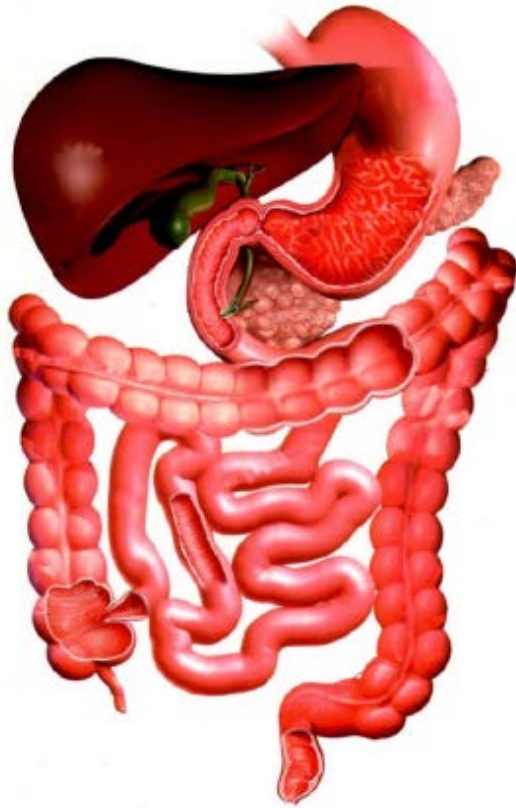
# Qual é o grande desafio?





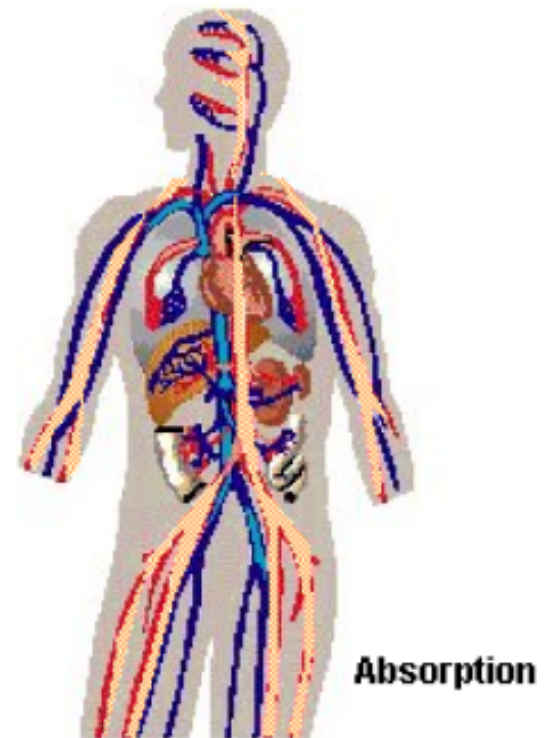
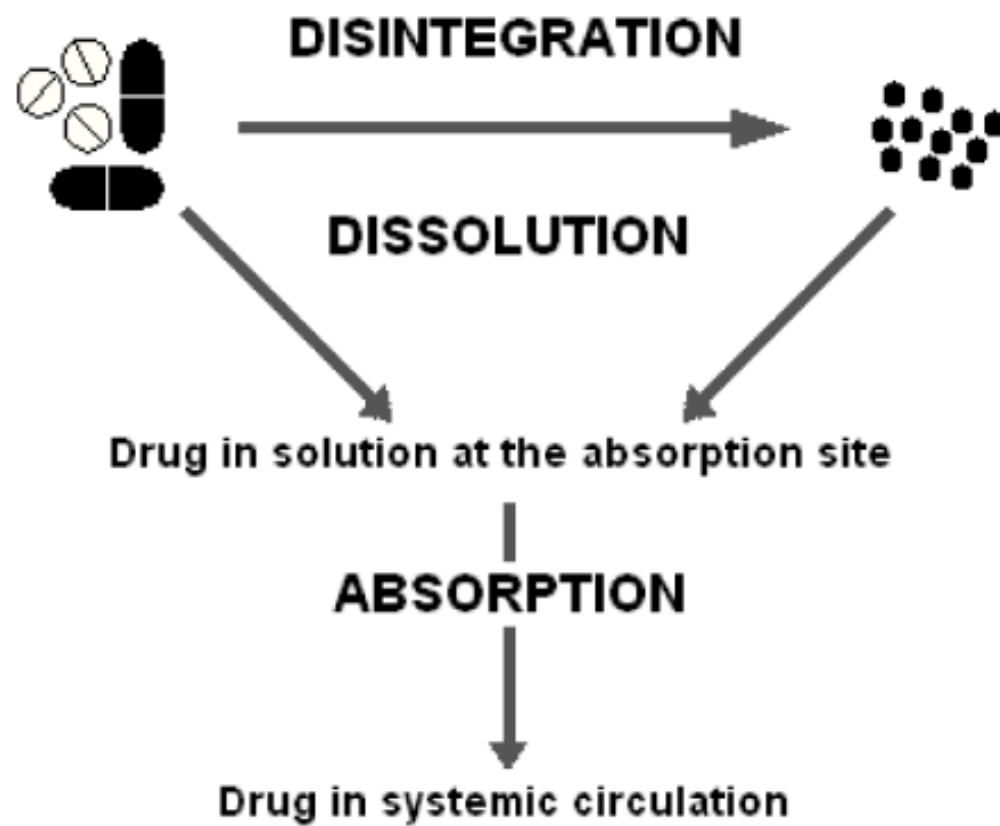
## Prever o comportamento in vivo ...

Mas como??



Flow through cell





# Criteria for dissolution test design

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## Media to simulate gastrointestinal passage

- pH-value / pH profiles
- volume
- composition

## Dissolution equipment

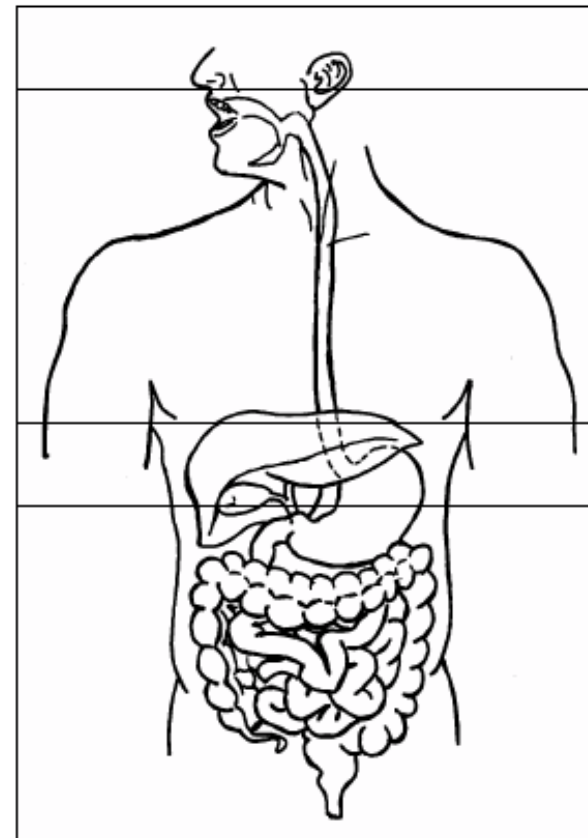
- apparatus
- hydrodynamic conditions

## Passage times

- multiple units ↔ single unit dosage form

## Food effects

- fasted ↔ fed state conditions





## Utilização do Aparato USP 4 na previsão com comportamento *in vivo*



# Vantagens e Desvantagens

**Table I: Advantages and disadvantages of the flow-through dissolution apparatus**

## **Advantages:**

- Laminar flow characteristics over a wide range of solvent flow rates
- Infinite sink ideal for low solubility drugs
- Differential rather than cumulative time profile of dissolved drug concentration
- Dwell time of dosage form in medium is minimal, reducing risk of drug degradation
- pH modification of dissolution medium is easy
- Samples for analysis easily obtained without altering dissolved drug concentration

## **Disadvantages:**

- Large volumes of media required to maintain flow rate
- Risk of clogging of filters
- Validation of flow rate during testing is difficult



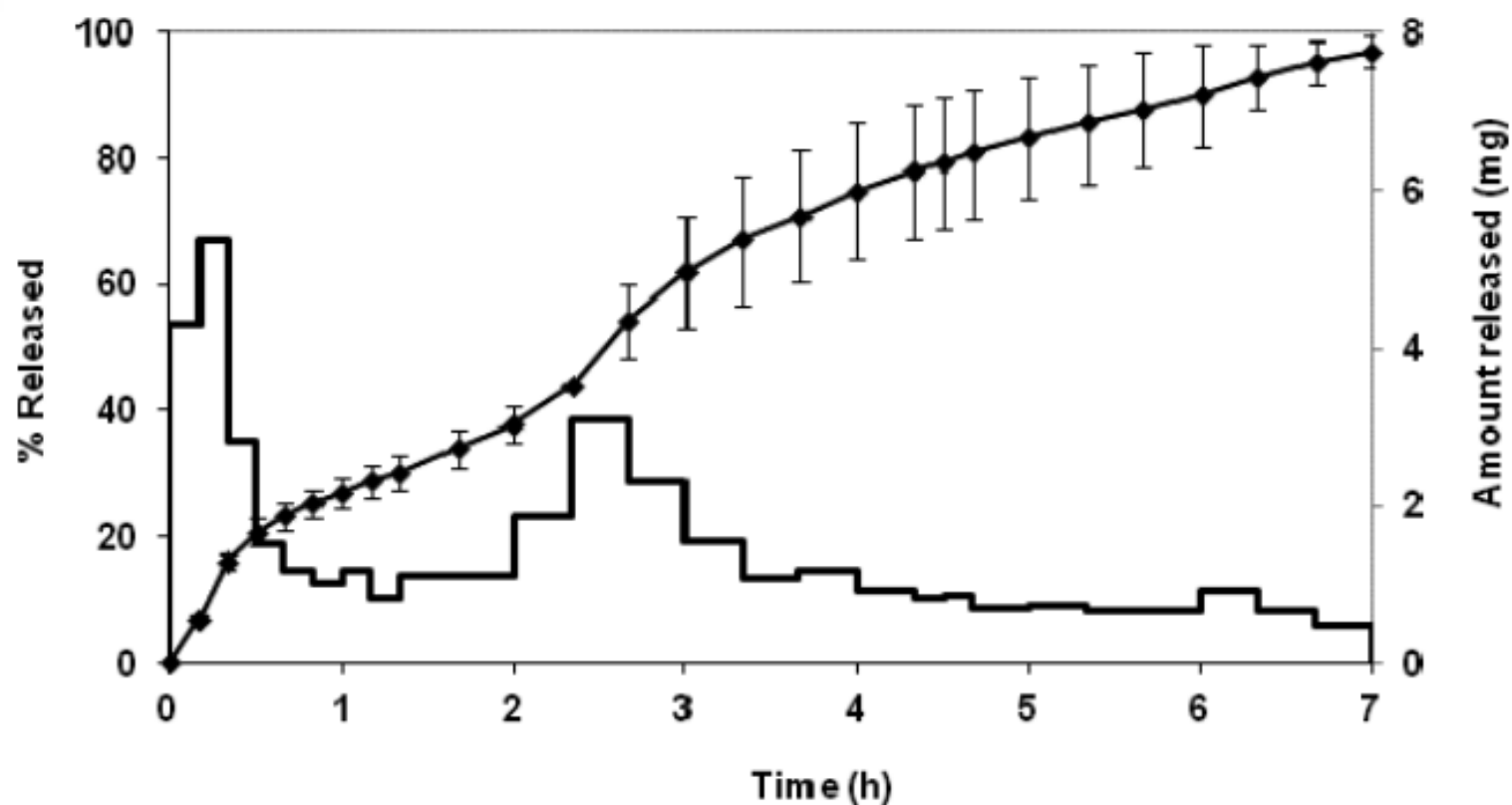


Figure 4. Dissolution/release data collected using the flow-through cell apparatus in noncumulative form and transformed to cumulative form.

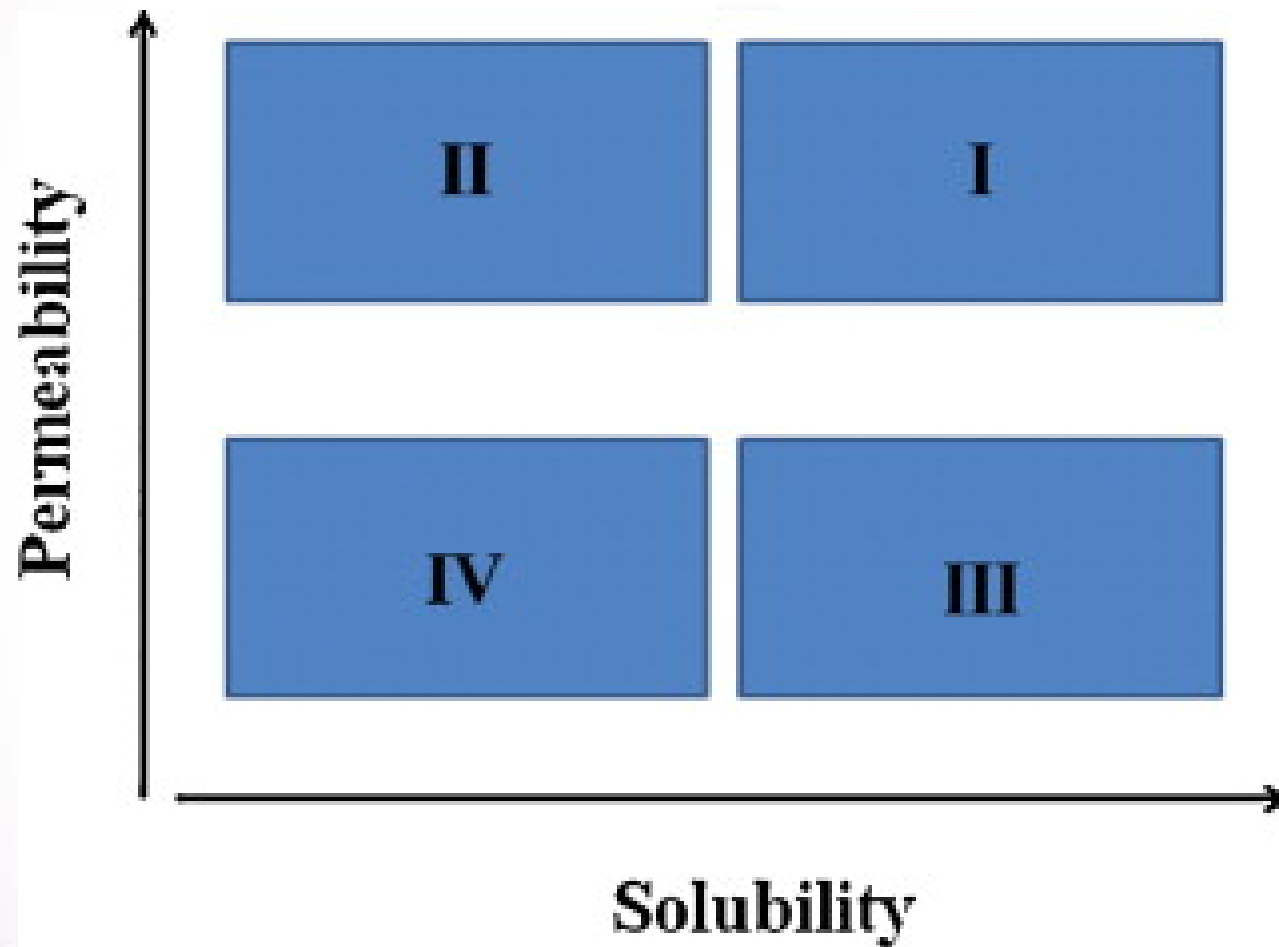
# Princípios do desenvolvimento de metodologias de dissolução utilizando *Flow Through Cell Method*



**Levantamento Bibliográfico**



## Fatores relacionados ao fármaco



**SCB**





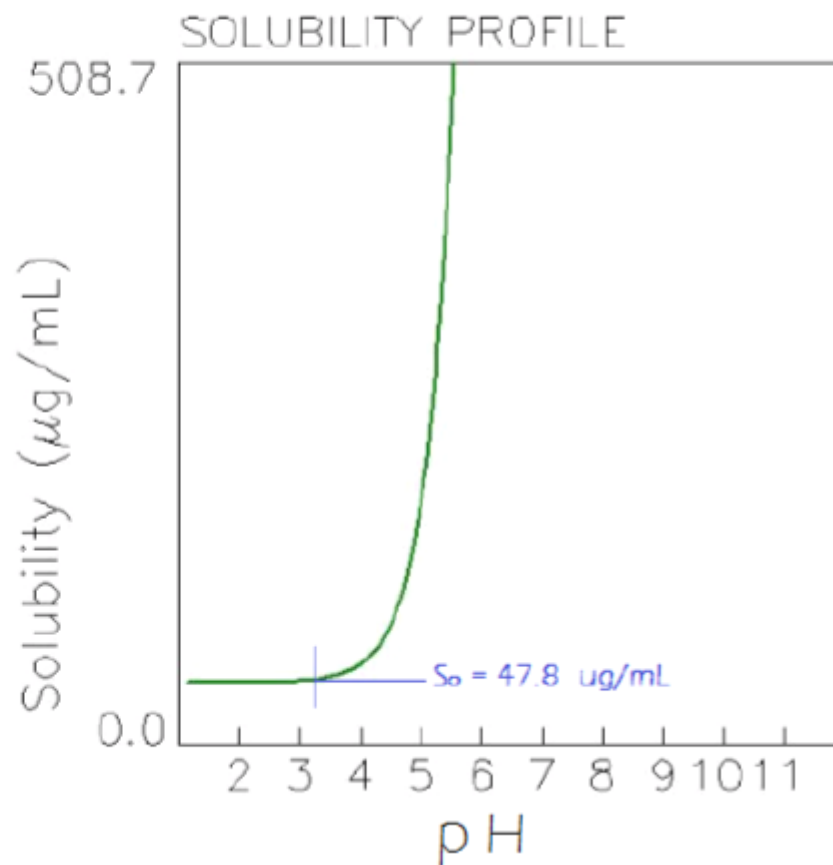
## Fatores relacionados ao fármaco

**ANALITO: IBUPROFENO (ACIDO DEBIL)**

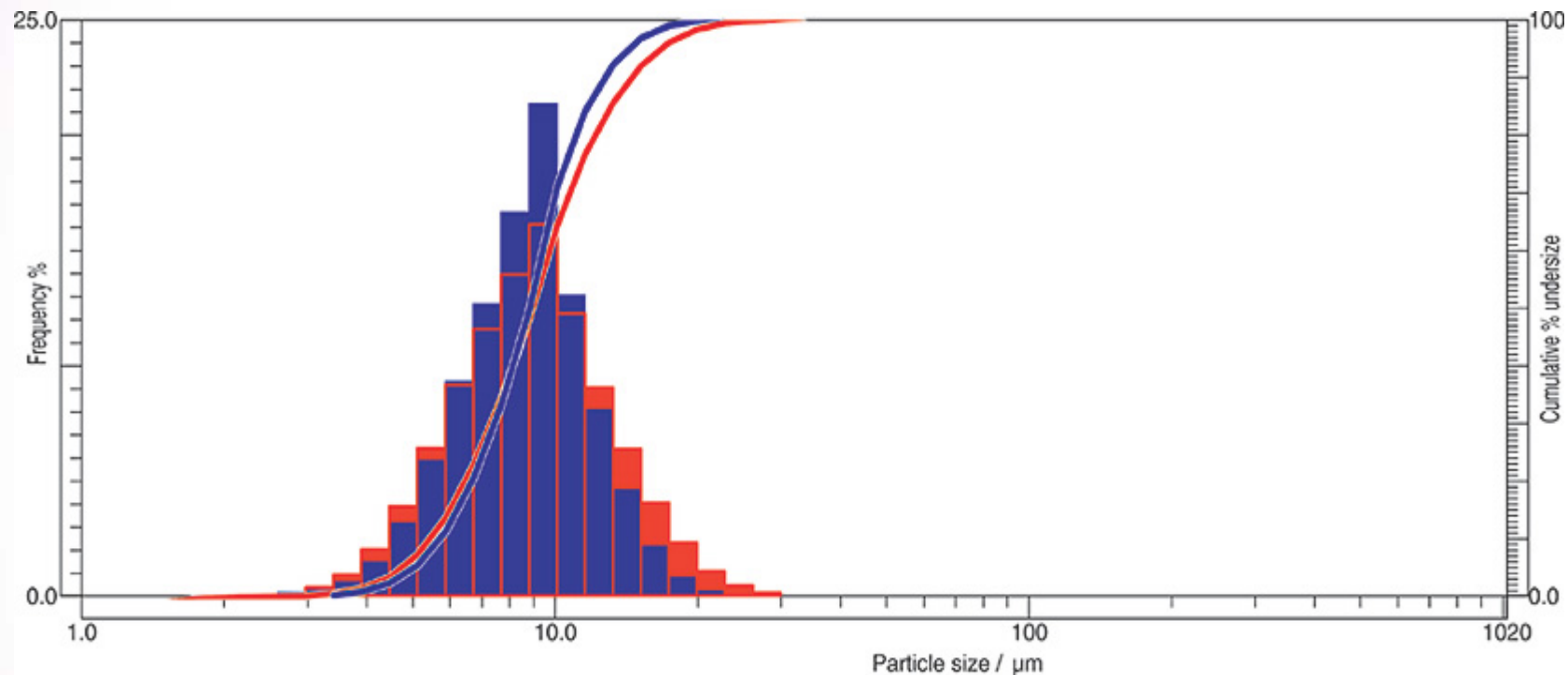
**ESTABILIDADE  
EM SOLUÇÃO**



PH	S (µg/ml)
3.404	51.22
3.803	56.36
4.186	68.47
4.534	93.87
4.915	158.57
5.007	184.71
5.181	252.18
5.257	291.26
5.329	335.16
5.448	425.74
5.534	508.51
5.6	584.12
5.847	994.97
5.938	1215.76
6.152	1959.54
6.281	2620.73
6.431	3682.16
6.614	5586.76
6.984	13032.38



## Fatores relacionados ao fármaco



**Avaliação de Filtros**

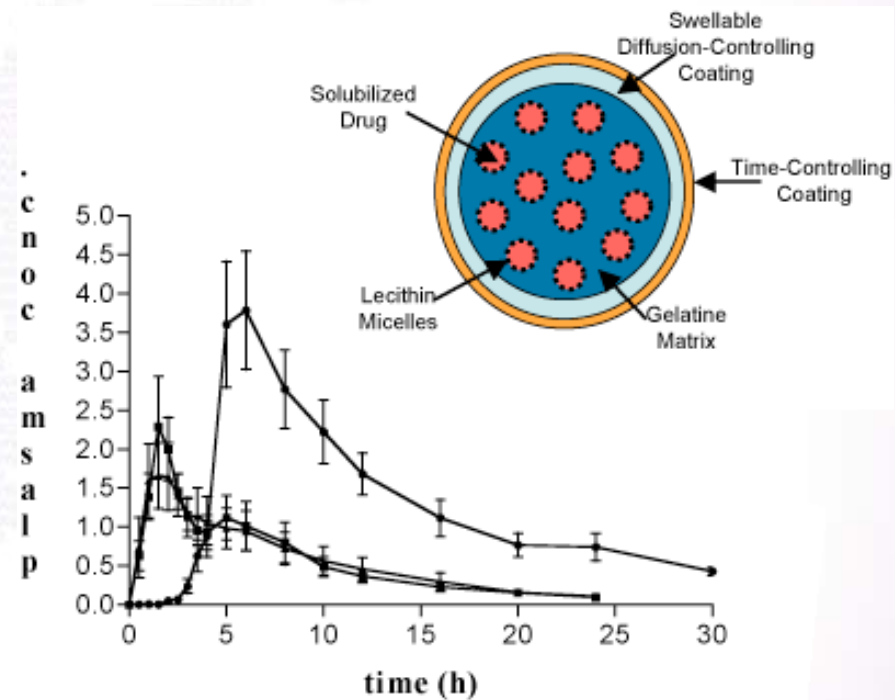
## Fatores relacionados à Forma Farmacêutica

### Sistema de Liberação do Fármaco

Liberação Imediata

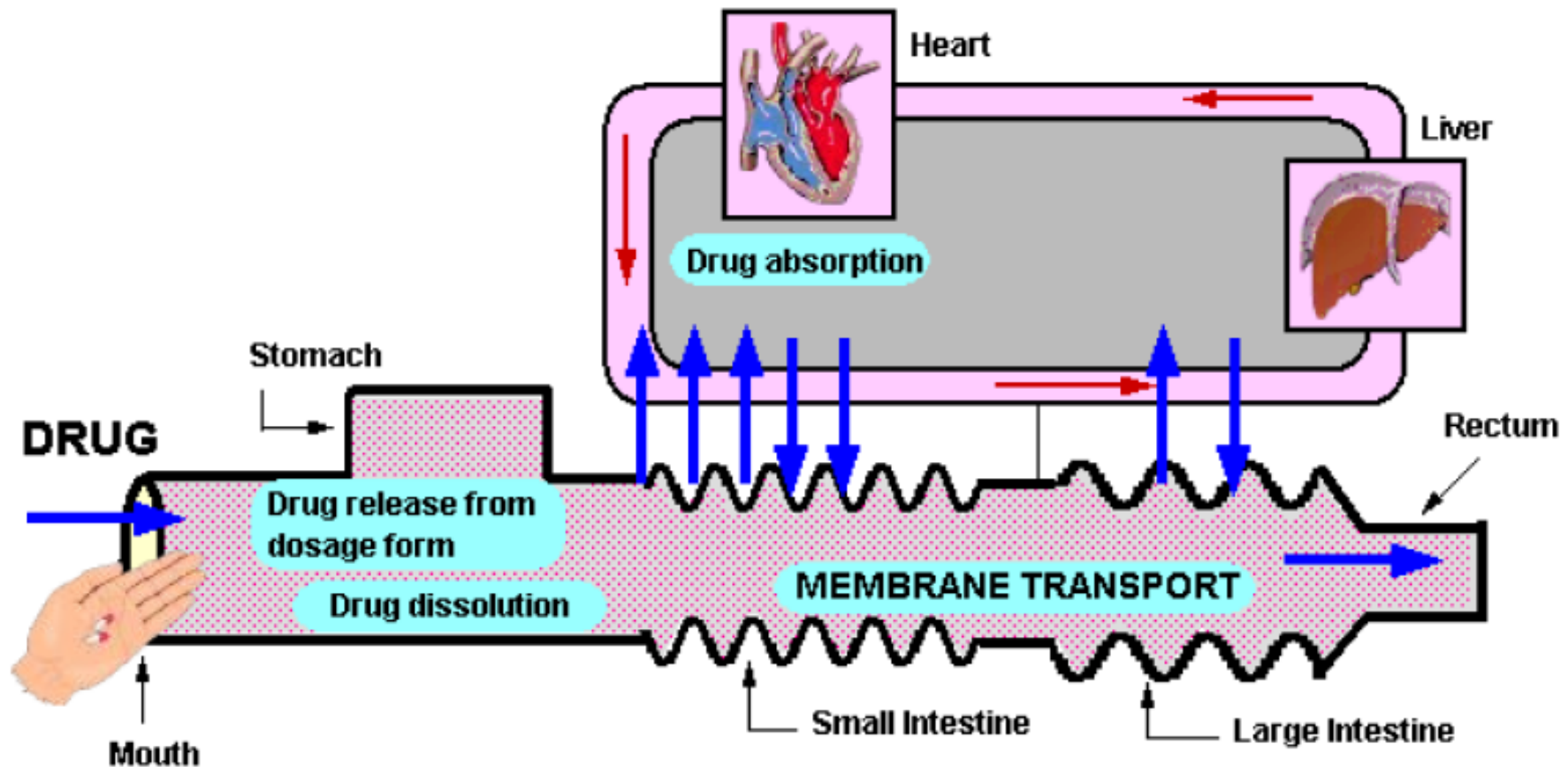
Liberação Retardada

Liberação Prolongada





# Movimento do fármaco através do TGI



# Transit Rule of '3'

**Modern Biopharmaceutics V6**

MB Modules | Calculation Tools | Capsule Library | Quiz | Glossary | Index | Print Screen | EXIT

*Module: Oral Delivery Systems*

## Small Intestinal Transit Time

Transit time in the small intestine has been measured using the  $\gamma$ -scintigraphy technique. The time it takes to transit from pylorus to the ileal cecal region of the intestine is remarkably constant (about 3 - 4 hours) in both fasted and fed states. The transit time is also remarkably independent of dosage form type. We use 3 hours as the mean transit time in estimating absorption.

A useful approximate rule for gastrointestinal transit times is "The Rule of '3'".

- Gastric Emptying = 0.3 hr (fasted)
- Gastric Emptying = 3 cal/min (fed)
- Intestinal Transit = 3 hr
- Total Gastrointestinal Transit = 30 hr

Dosage Form	Transit Time (hr)
Solution	~3
Pellets	~3
Single Unit	~3

MB

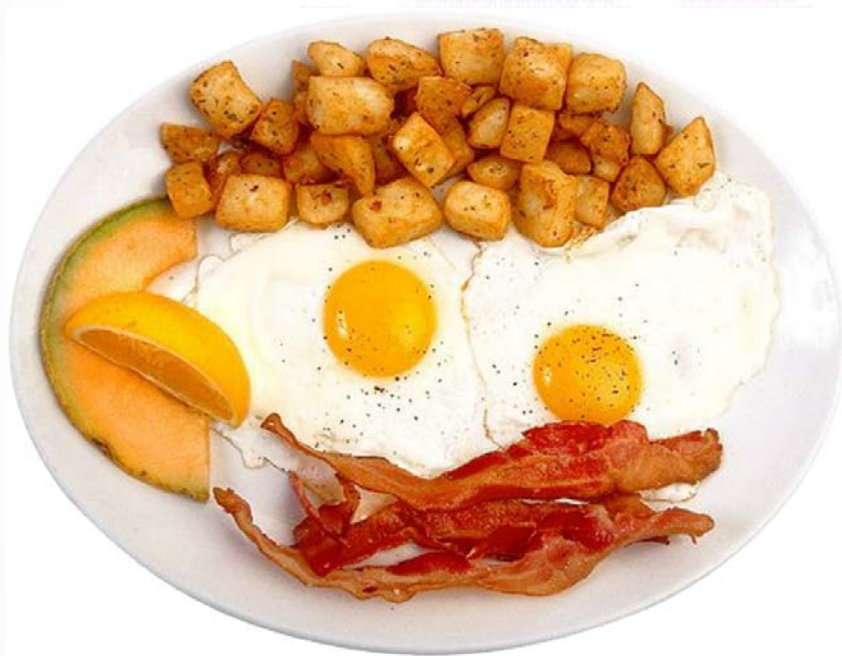
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**Navigation Menu:**

- Aims, Objectives and Prerequisites
- Oral Delivery Forms
- Dissolution
- Controlled Release
- CR Types
- GI Transit**
- FDA Guidance
- Gastric Emptying
- Small Intestine Transit**
- Transit Movie
- MVC
- BABE Regulation
- References

Gordon Amidon

## Fatores relacionados à condução do estudo de bioequivalência



*Estado Alimentado*



*Estado de Jejum*



## Biorelevant pH-gradient methods

GI-section	Media and pH-values preprandial pH-Gradient				Passage time [min]	
	Compendial media	pH	Biorelevant media	pH	Tablets	Pellets
Stomach	SGFsp*	1.8	FaSSGF	1.8	60	30
Proximal Jejunum	Blank FaSSIF	6.5	FaSSIF	6.5	15	45
Distal Jejunum	Blank FaSSIF	6.8	FaSSIF*	6.5	15	45
Proximal Ileum	Blank FaSSIF	7.2	FaSSIF*/**	7.2	30	45
Distal Ileum	Blank FaSSIF*	7.5	Blank FaSSIF*	7.5	120	45
Proximal Colon	SCoF	5.8	SCoF	5.8	240	240
* pH modified, ** Concentration of bile components modified						
GI-section	Media and pH-values postprandial pH-Gradient				Passage time [min]	
	Compendial media	pH	Biorelevant media	pH	Tablets	Pellets
Stomach	Acetate buffer / SGFsp*5.0 / 2.0		Ensure Plus (Milk)	6.5	(120/120) 240	120
Proximal Jejunum	Blank FeSSIF	5.0	FeSSIF	5.0	45	45
Distal Jejunum	Blank FaSSIF	6.5	FeSSIF*	6.5	45	45
Proximal Ileum	Blank FaSSIF	6.5	FeSSIF*/**	6.5	45	45
Distal Ileum	Blank FaSSIF*	7.5	Blank FaSSIF*	7.5	45	45
Proximal Colon	SCoF	5.8	SCoF	5.8	---	240
* pH modified, ** Concentration of bile components modified						

GI-segment	pH	Media	Passage time	
			single unit dosage forms	multiple unit dosage forms
Stomach	1.8	Simulated Gastric Fluid (SGFsp)*	60 min	30 min
Proximal Jejunum	6.5	Phosphatpuffer pH 6.5	15 min	45 min
Distal Jejunum	6.8	Simulated intestinal fluid pH 6.8 (SIFsp) USP 24	15 min	45 min
Proximal Ileum	7.2	Phosphatpuffer pH 7.2 <i>R</i> (Ph. Eur 1997)	30 min	45 min
Distal Ileum	7.5	Simulated intestinal fluid pH 6.8 (SIFsp) USP 23	120 min	45 min
Proximal Colon	6.5	Phosphatpuffer pH 6.5	360 min	360 min
Proximal Colon	6.5	Phosphatpuffer pH 6.5	240 min	240 min
Distal Colon	6.8	Simulated intestinal fluid pH 6.8 (SIFsp) USP 24	360 min	360 min
Distal Colon	6.8	Simulated intestinal fluid pH 6.8 (SIFsp) USP 24	240 min	270 min
* pH modified				

## Hidrodinâmica – Avaliação de Fluxo



# Hidrodinâmica – Avaliação de Fluxo

Linear Flow Rate vs Volumetric Flow Rate

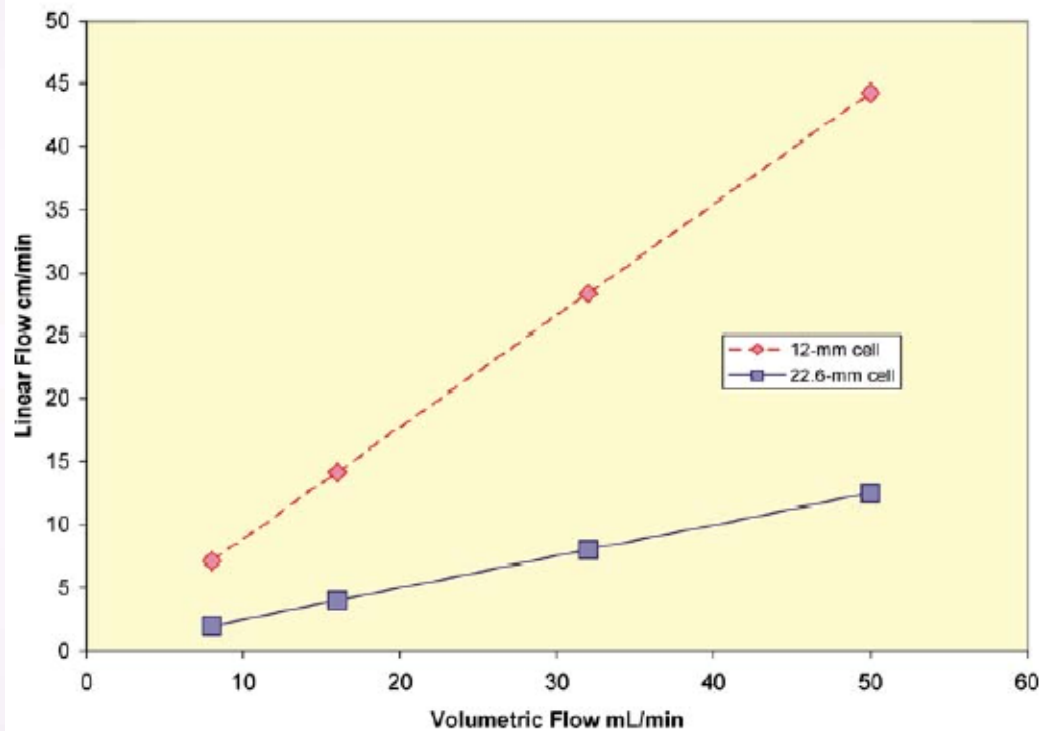


Figure 1. Comparison of linear flow rates for the 22.6- and 12-mm flow-through cells at identical volumetric flow rates.

**Table 1: Diameters of the cells used for testing orally administered solid products with the flow through apparatus, cross-sectional areas of the cells and linear flow velocities corresponding to specific flow rates (2, 4).**

Diameter (mm)	Area (cm)	Volumetric flow (mL/min)				
		2	4	8	16	32
Linear flow velocity (cm/min)						
11.3	1	2	4	8	16	32
22.6	4	0.5	1	2	4	8

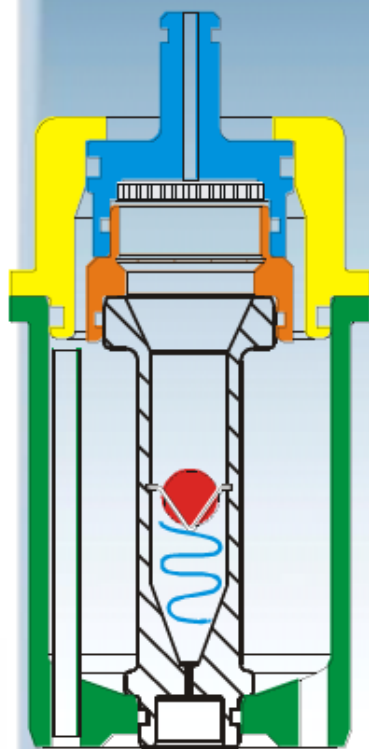


# Hidrodinâmica – Avaliação de Fluxo

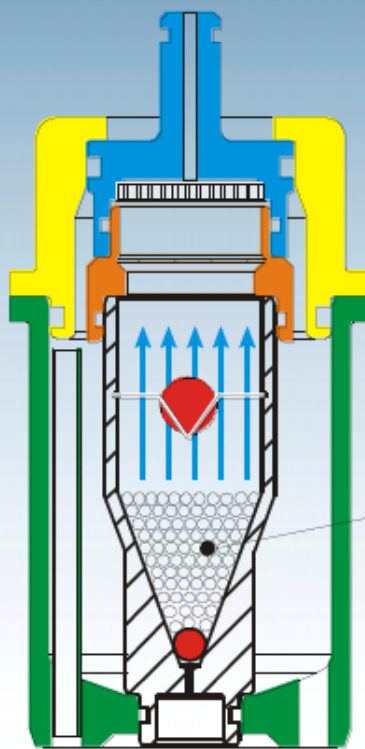


# Hidrodinâmica – Avaliação de Fluxo

## Laminar and turbulent flow



Turbulent



Laminar

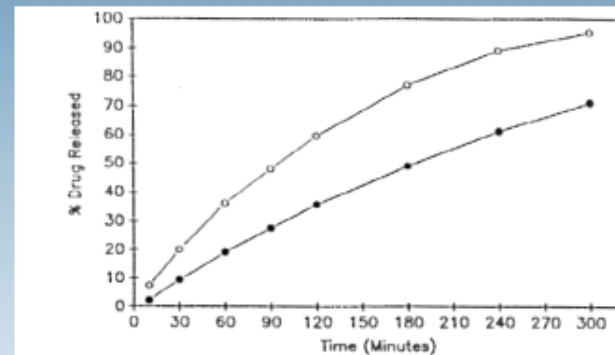


FIGURE 7

Effect of glass beads in the flow-through cell on drug release from erodible tablets at the flow rate of 21.0 mL/min. (○) Without glass beads and (●) with glass beads.

Glass beads

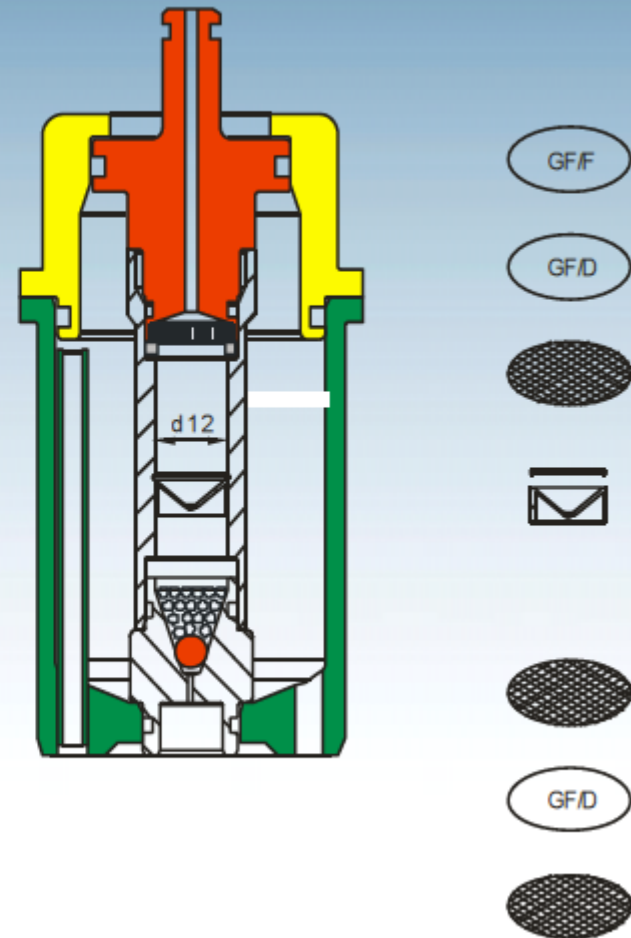
Quando o USP 4 pode ser impactante no desenvolvimento destas formulações?

**SEMPRE !!!!!**



# Dissolução de Fármacos – “Dissolução Aparente”

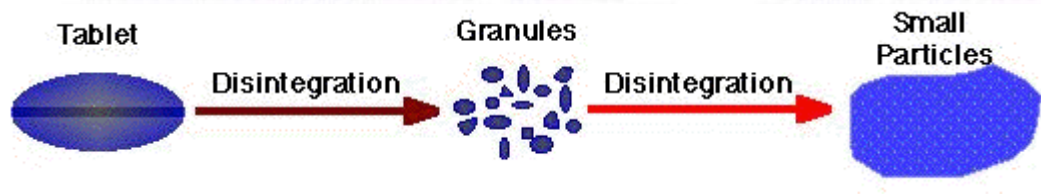
- ▶ Eliminates problems associated with delivering powder to vessel in USP I or II – no floating or sticking to shaft
- ▶ Powder is wet immediately
- ▶ Easy pH change on powders and granules
- ▶ Eliminates build up of heavier granules on bottom of vessel in apparatus USP II
- ▶ An approved alternative to intrinsic dissolution on API's
- ▶ Compare different dissolution rates of the pure substance caused by crystal habit, polymorphism, particle size, etc.





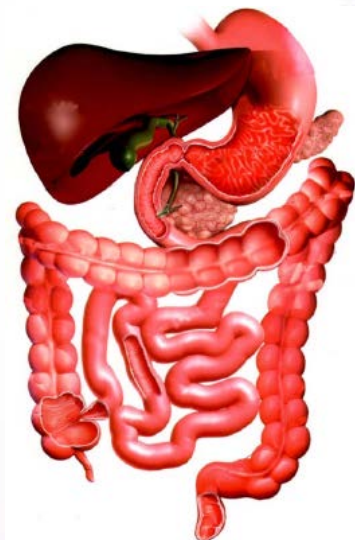
# Formas Farmacêuticas de Liberação Imediata

## Fármacos com Alta Solubilidade

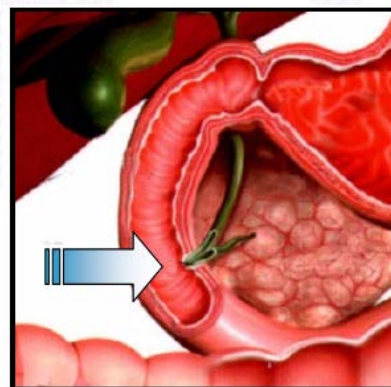


**Hidrodinâmica  
Biorelevante\***

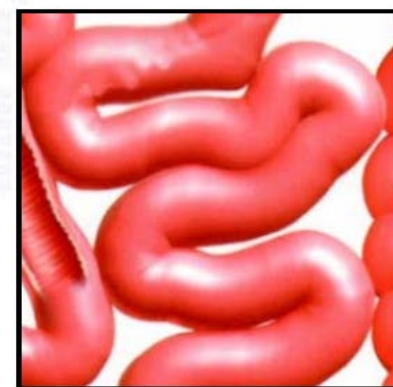
### Desintegração Intraluminal



Stomach



Duodenum

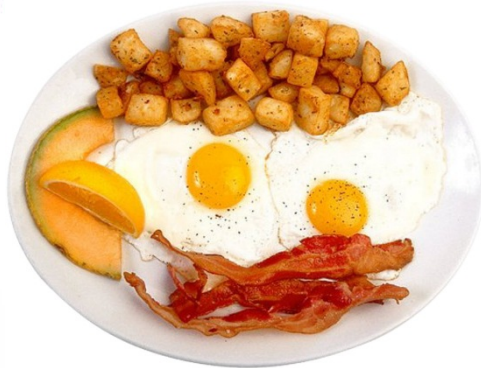
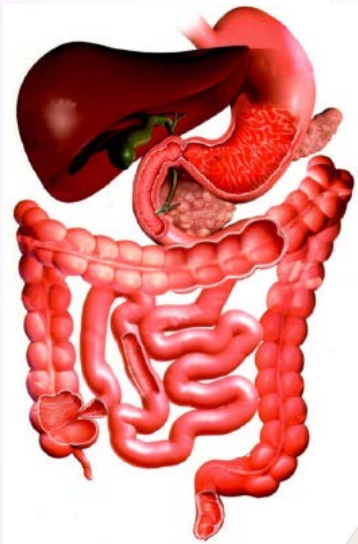


Jejunum

# Formas Farmacêuticas de Liberação Imediata

## Fármacos com Baixa Solubilidade

**SINK  
CONDITIONS**



**Hidrodinâmica  
Biorelevante\***

**Simulação do  
gradiente de pH  
in vivo**

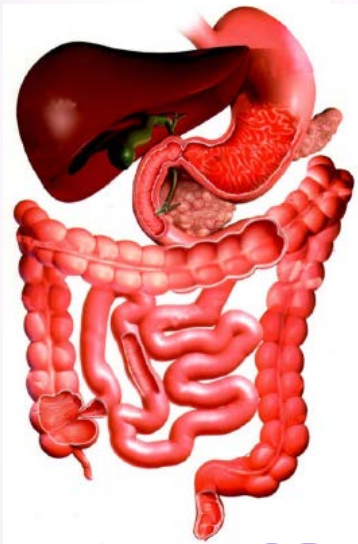
**IVIVC**

*In Vitro – In Vivo Correlation*

**Avaliação da influência do  
tamanho de partículas e  
adjuvantes farmacotécnicos que  
auxiliam a dissolução**

# Formas Farmacêuticas de Liberação Retardada

## Fármacos com Alta Solubilidade



Simulação do gradiente de pH in vivo –  
Avaliação de Lag time  
Troca de pH fácil e sem contato com amostra

Hidrodinâmica  
Biorelevante\*

Hidrodinâmica sensível aos desvios no processo produtivo frequente neste tipo de formulação. Ex: Uniformidade do revestimento

# IVIVC

*In Vitro – In Vivo Correlation*

## Fármacos com Baixa Solubilidade

# SINK

# CONDITIONS



# Formas Farmacêuticas de Liberação Prolongada

## Fármacos com Alta e Baixa Solubilidade

Desenho da formulação caracteriza liberação

Simulação do gradiente de pH in vivo por completo desde a simulação da passagem gástrica até o tempo de liberação colônica

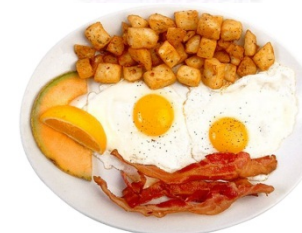
Hidrodinâmica  
Biorelevante\*

Caracteriza tecnologia utilizada no desenvolvimento da formulação

# IVIVC

*In Vitro – In Vivo Correlation*  
NIVEL A – PONTO A PONTO

*Avaliação do efeito da alimentação – ANVISA exige bioequivalência em estado de jejum e alimentado*





## Ou seja ...

- Excelente ferramenta no desenvolvimento de formulações de medicamentos genéricos;
- Aplicável a diversas formas farmacêuticas e diferentes mecanismos de liberação do fármaco;
- Ferramenta importante no desenvolvimento de correlação *in vivo in vitro*.

DÚVIDAS??

