



*Universita' degli Studi di Milano*

## *Corso di Laurea Magistrale in Farmacia*



*Tecnologia e Legislazione Farmaceutiche I*  
*9 CFU*

*Prof. Andrea Gazzaniga*

**Rilascio Modificato via Orale - Sito-Specifico (Stomaco)**

# *Sistemi per il rilascio modificato per via orale*

- Introduzione generale*
- Teoria Trasporto di Massa*
- Rilascio Prolungato*
- Fast (?) release*
- Rilascio Ritardato*
- Rilascio Sito-Specifico*

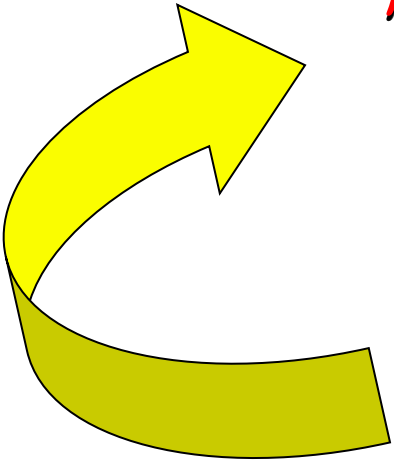
# Oral Drug Delivery

Release control in terms of:

**site** - release in specific regions of G.I. tract

**rate** - accelerated/fast or prolonged release

**time** - delayed/pulsatile release



**Temporal and/or  
Spatial Control of Release**

# Oral Drug Delivery

Release control in terms of:

*site*

**gastroretentive DDS**

*release into the stomach*

*-Local action - (anti-infective agents / helicobacter pylori)*

*-Systemic action - exploitation of absorption windows*

*polar drugs and those that rely on some form of facilitated transport generally display good absorption from proximal small intestine*

*-acyclovir, ciprofloxacin, levodopa, gabapentin, furosemide, riboflavine, metformin) --> **improvement in BA***

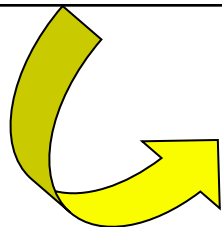
# Oral Drug Delivery

Release control in terms of:

*site*

**gastroretentive DDS**

release into the stomach



*target release profile* the target release kinetics (shape of release curve) is the zero-order, at appropriate rate for optimal exploitation of the absorption window

---> concept advanced many years ago

... extensive research, publications and patents filings

... some good results but many failures

---> the "real" goal remains the retention of the delivery system in the **fasting** human stomach

... a single- or multiple-unit system can empty rapidly from the fasted stomach.

# Oral Drug Delivery

Release control in terms of:

*site*

**gastroretentive DDS**

*release into the stomach*

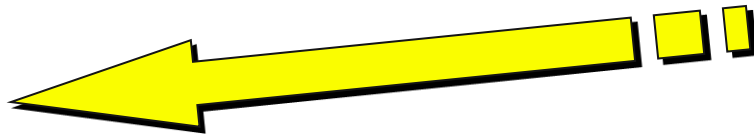
-----> some debate in the past concerning the cut-off size of retention - the open pylorus: 15 mm in diameter

.... only a system that displays adhesion to the stomach wall **or** is greater than 15 mm will possibly be retained in the stomach both in fasted or fed state

*most data from dogs or pigs, scarcely reliable, generally extrapolated to humans without any attempt at scaling ...the best model for human is human*

**-Different strategies**

*bioadhesive, floating and size-increasing systems)*



# Oral Drug Delivery

Release control in terms of:

*site*

**gastroretentive DDS**

*release into the stomach*

**Size-increasing/swelling expanding systems --- > most promising approach**

**Floating systems need fluids (... can work in fed state only)**

**Bioadhesive systems : uncertainty conflicting results**

**-Different strategies**

***bioadhesive, floating and size-increasing systems***

# Oral Drug Delivery

Release control in terms of:

*site*

**gastroretentive DDS**

*release into the stomach*

**Size-increasing/swelling expanding systems --- > most promising approach**

*... should*

- i) expand in situ to a size large enough to be retained in the fasted stomach*
- ii) have sufficient rigidity to withstand mechanical forces*
- iii) decrease in size (degradation) after their performance*

*... the increase in size is usually achieved through a process of swelling or unfolding (novel geometries)*



# Oral Drug Delivery

Release control in terms of:

*site*

**gastroretentive DDS**

*release into the stomach*

**Size-increasing/swelling expanding systems --- > most promising approach**

*Swelling*



**AcuForm™** Drug Delivery Technology

polyethylene oxide (PEO) and hydroxypropyl methylcellulose swellable matrix

*Unfolding*



**Accordion Pill™**,

Polymeric composite degradable matrix folded in an accordion-like shape into a capsule.

*... the increase in size is usually achieved through a process of swelling or unfolding (novel geometries)*

Swelling

# Oral Drug Delivery



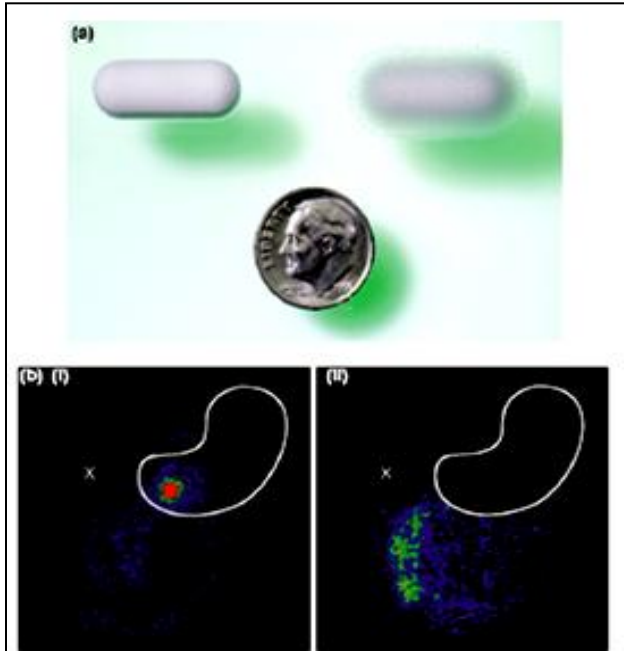
www.depomedinc.com/

AcuForm™ Drug Delivery Technology

polyethylene oxide (PEO) and hydroxypropyl methylcellulose swellable matrix

Louie-Helm, J. Et al.

Proc. Int'l Symp. CRS #118 23 (2003)



S.S.Davis DDT 10 249 (2005)



Proquin® XR (ciprofloxacin hydrochloride) is a once-daily, extended release formulation of ciprofloxacin for the treatment of uncomplicated urinary tract infections (UTIs).

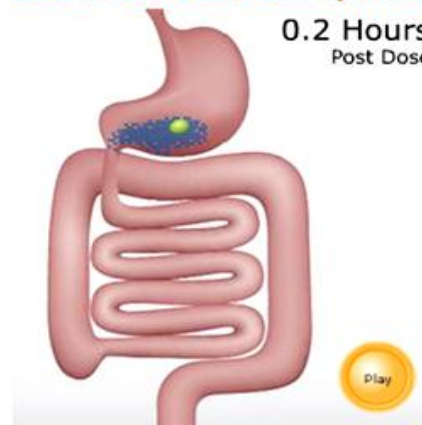
... are presented as having ...

over a nine-hour release period to the upper gastrointestinal (GI) tract where drug is best absorbed



GLUMETZA® (metformin HCl extended release tablets) is a once-daily, extended release formulation of metformin for the treatment of adults with type 2 diabetes.\*

AcuForm controlled delivery over a 9-hour period<sup>5</sup>



EXTENDED-RELEASE TABLET (green dot)  
ACTIVE DRUG (blue dot)

AcuForm controlled delivery over a 9-hour period<sup>5</sup>



EXTENDED-RELEASE TABLET (green dot)  
ACTIVE DRUG (blue dot)

# Oral Drug Delivery



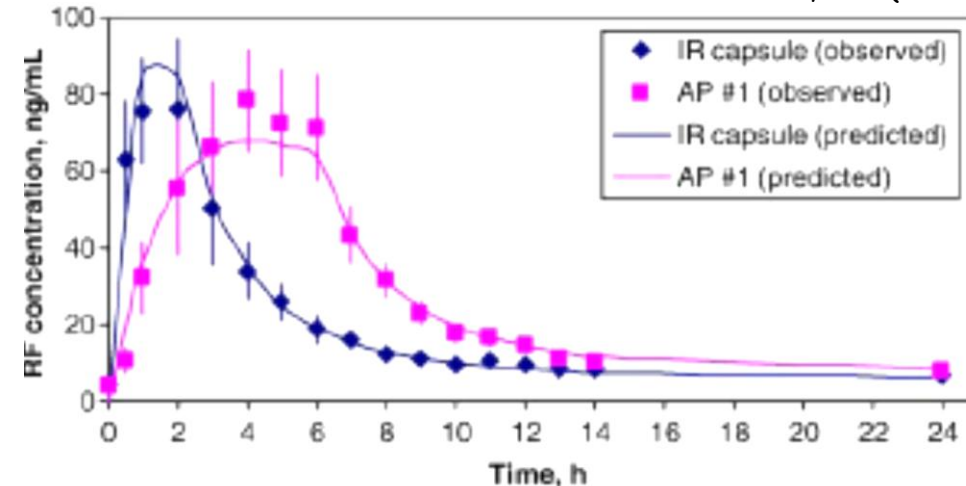
Adapted from Kagan L. et al.  
Journal of Controlled Release **113**, 208 (2006)

## Accordion Pill™

The dosage form is folded in an accordion-like shape into a standard size regular capsule. After the capsule dissolves in the stomach, the accordion unfolds.

The accordion can remain in the stomach more than 12 hours, and may provide immediate and/or sustained release profile.

<http://www.intecpharma.com/>



Plasma concentration vs. time profiles of Riboflavin following administration of AP#1 and control IR capsule to 7 volunteers.

