



Universita' degli Studi di Milano

*Corso di Laurea Magistrale in Chimica e
Tecnologia Farmaceutiche*



Tecnologia e Legislazione Farmaceutiche II- 9 CFU

Prof. Andrea Gazzaniga

*Rilascio Modificato via Orale - Sito-Specifico (Stomaco)
/Sistemi Gastroretentivi*

Sistemi per il rilascio modificato per via orale

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

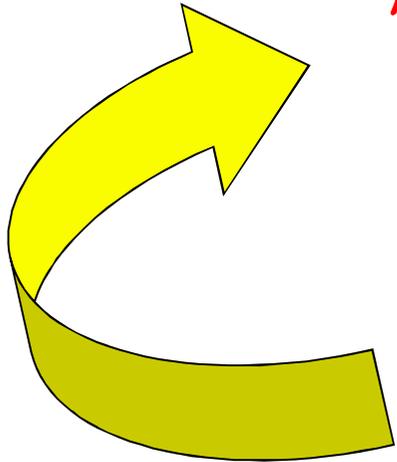
Oral Drug Delivery

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***

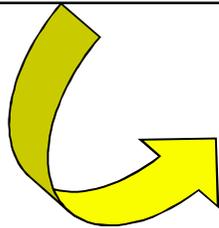
Oral Drug Delivery

Release control in terms of:

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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:

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release into the stomach

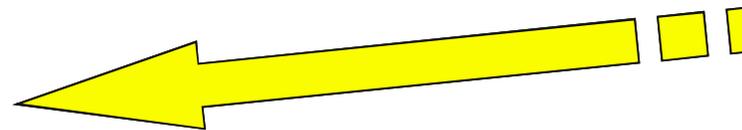
----> some debate in the past concerning the cut-off size of retention - the open pylorus: 15 mm in diameter

... 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)



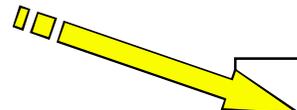
Oral Drug Delivery

Release control in terms of:

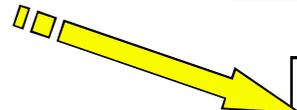
site

gastroretentive DDS

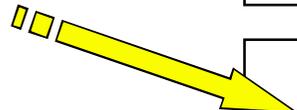
release into the stomach



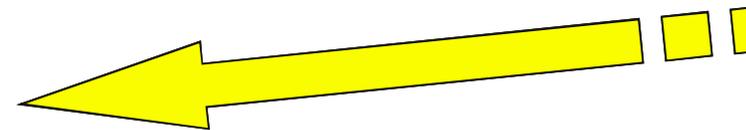
Size-increasing/swelling expanding systems --- > most promising approach



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:

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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

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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



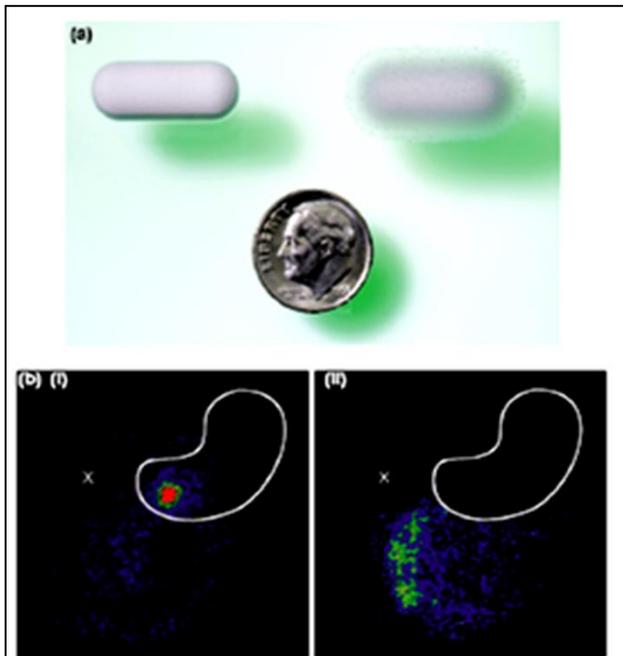
www.depomedinc.com/

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).

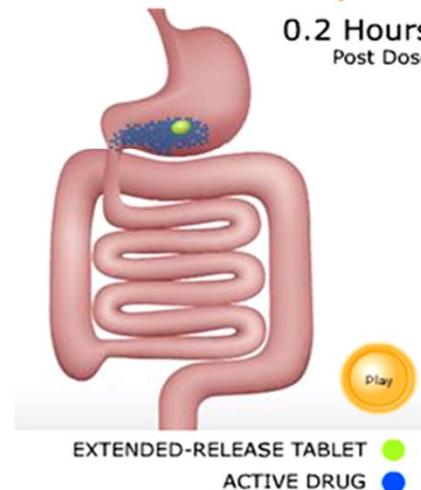
... are presented as having ...

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 period⁵



AcuForm controlled delivery over a 9-hour period⁵



Unfolding

Oral Drug Delivery



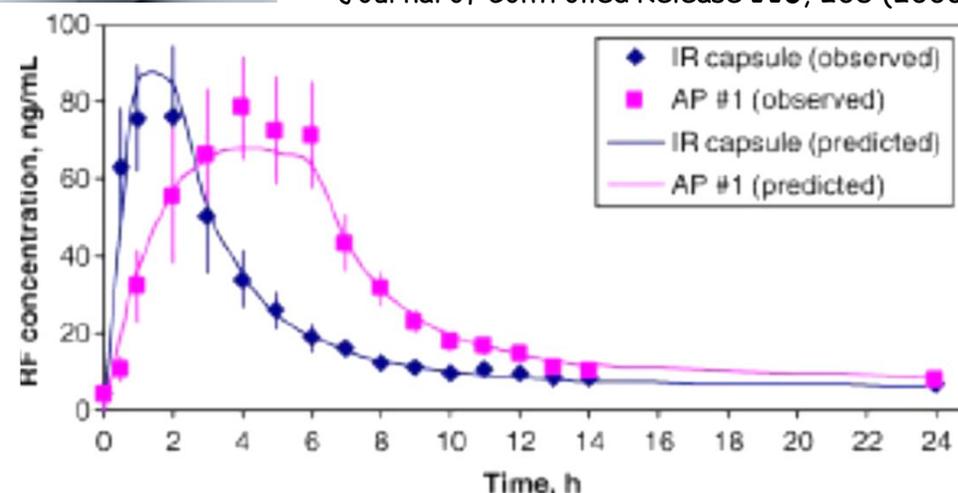
Adapted from Kagan L. et al.
Journal of Controlled Release **113**, 208 (2006)

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.

