Universita' degli Studi di Milano

Corso di Laurea Magistrale in Chimica e Tecnologia Farmaceutiche

Chimica Farmaceutica Applicata - 8 CFU

Prof. Andrea Gazzaniga

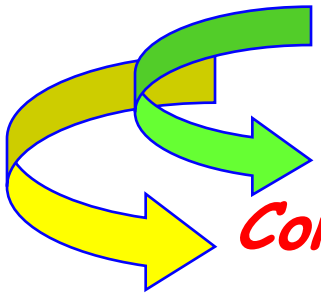
Rilascio Modificato via Orale – Sito-Specifico (Colon)

Sistemi per il rilascio modificato per via orale

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

gazza

Sistemi a Rilascio Modificato per via Orale



Controllo spaziale del rilascio

Controllo del rilascio

sito — *diminuzione della velocità di transito G.I.*

(es. sistemi bioadesivi)

rilascio in specifiche regioni del tratto G.I.

(es. sistemi per il rilascio al colon e sistemi gastroretentivi)

gazza

Colonic Drug Delivery

Traditionally → interest tied up to local treatment of large bowel diseases

→ colon generally seen as a region with very poor absorption properties

Nowadays → local or systemic therapies

gazza

When and why the colon has been reconsidered as a possible site of absorption ?

Small intestine: known as a good site of absorption

Colon: known as unsuitable for absorption

- reduced surface area
- wider lumen
- low volume of dissolution fluids
- poor permeability of the mucosa
- higher viscosity of the content

With the development of:

- once and twice-a-day oral prolonged-release systems.

- pharmacoscintigraphy enabling a correlation between the G.I. location of the dosage form and the plasma levels of the drug.

It has definitively been proved that a significant absorption can occur along the whole colon.

gazza

…furthermore…

…since peptidases are generally believed to be less concentrated in the large bowel, the colon has also been suggested as a site for selective delivery of drugs having peptidic structure.

gazza

Colon Targeting

Local goals

(IBD) Inflammatory Bowel Disease – ulcerative colitis, Crohn's Disease
Adenocarcinoma
Irritable Bowel Syndrome
. . . . .

Systemic goals

Improvement in the oral bioavailability of peptides and proteins (less hostile environment in the colon - more than 50 different types of peptidases in the small intestine)

gazza

The Digestive System

… Colon….

… begins from the ileo-caecal valve and the caecum and ends with the rectum

… approx.

1.2 meter long
6-7 cm wide

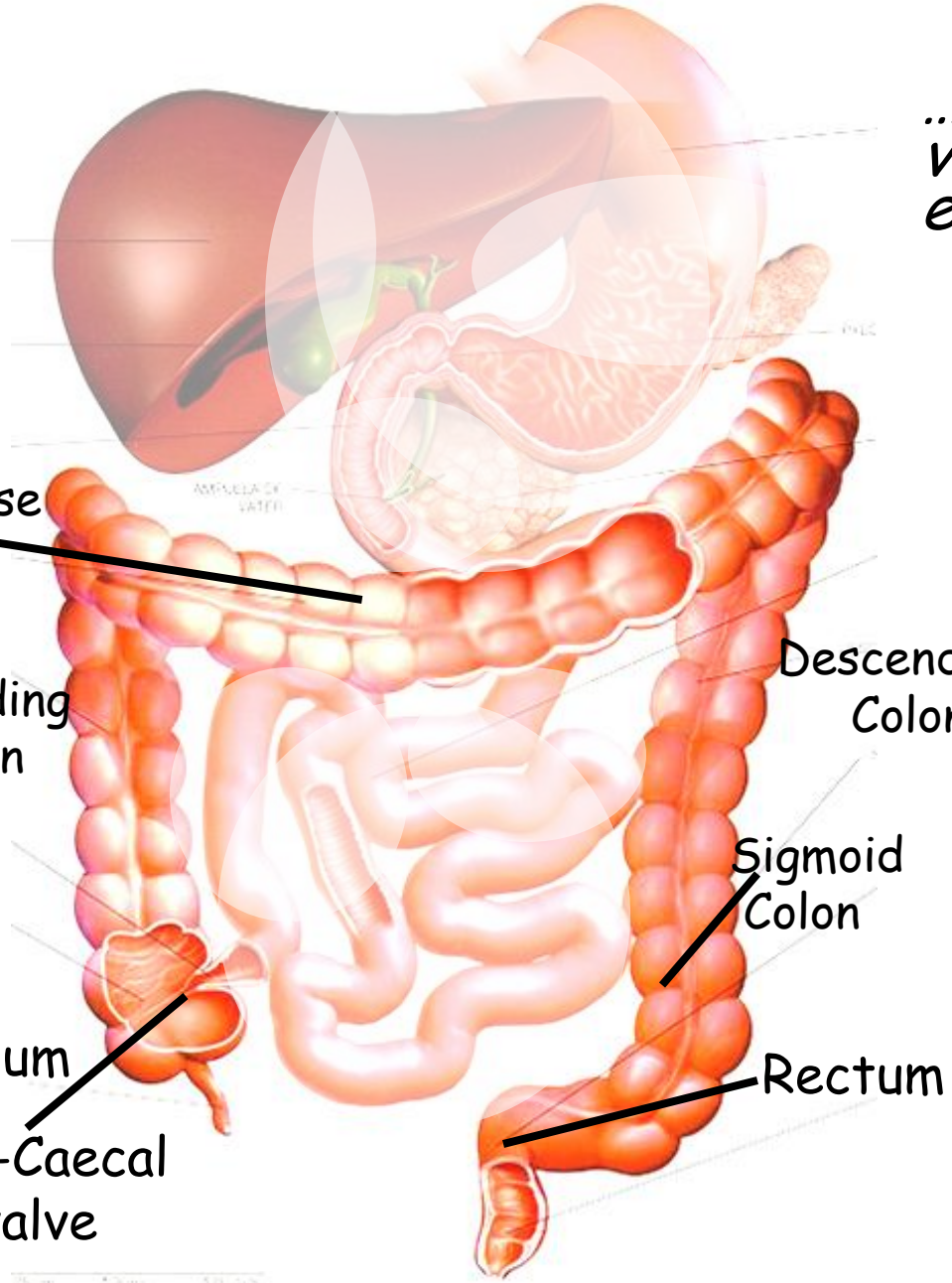
… divided in .. **A, T, D, S Colon**

..the wall consists of 4 layers

mucosa
submucosa
muscularis
serosa

..the fibers of the muscularis externa are collected into 3 longitudinal bands

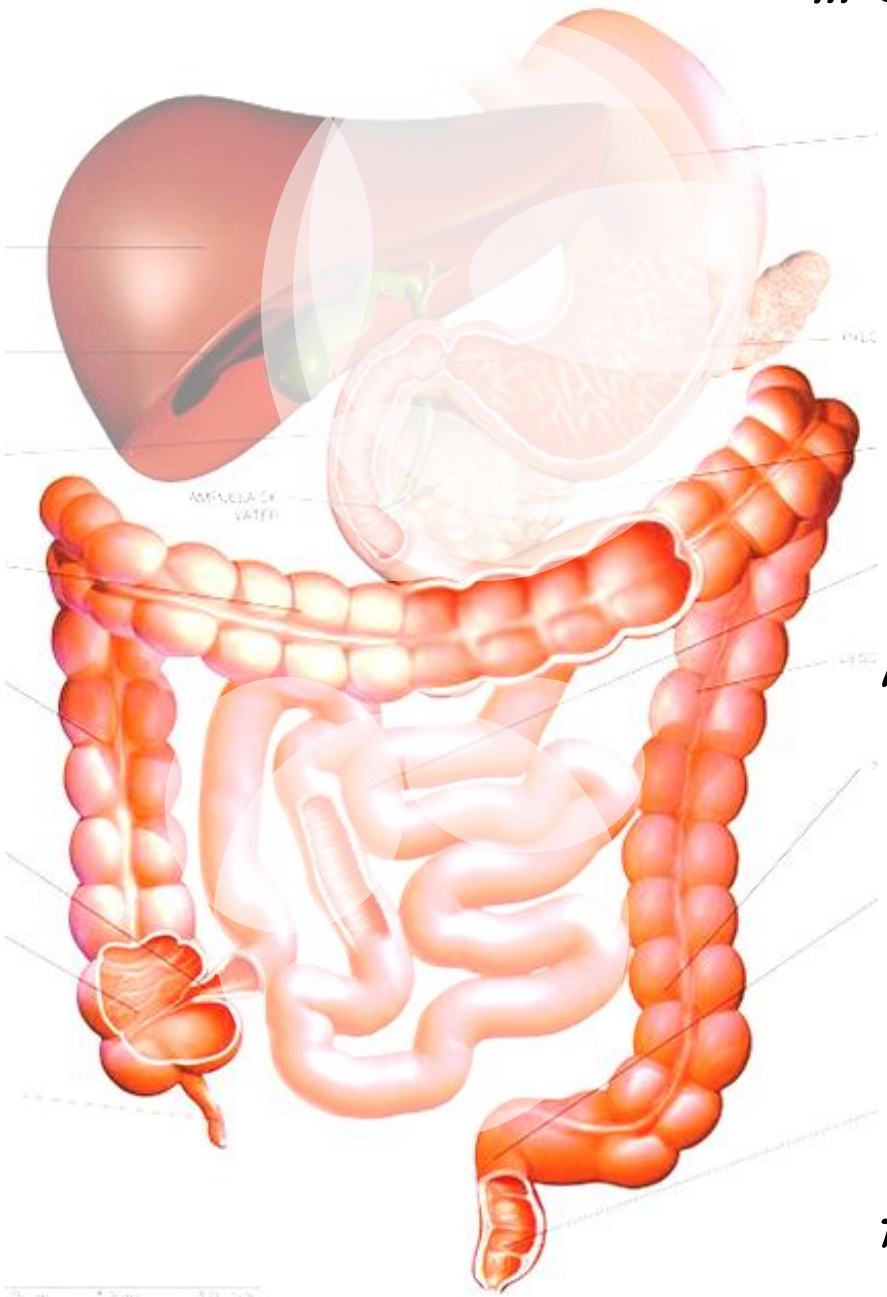
teniae coli



gazza

The Digestive System

… Colon….



Movements:
segmentation contractions
peristaltic/antiperistaltic waves.

Transit:
the first part of the meal reaches the caecum in about 4 h
As much as 25 % of the residue of test meal may still be in the rectum after 72 h

Absorption:
..drained by mesenteric veins and lymphatic wessels
… enterocytes with brush border and tight junctions
the barrier can be crossed via transcellular or paracellular pathway.

gazza

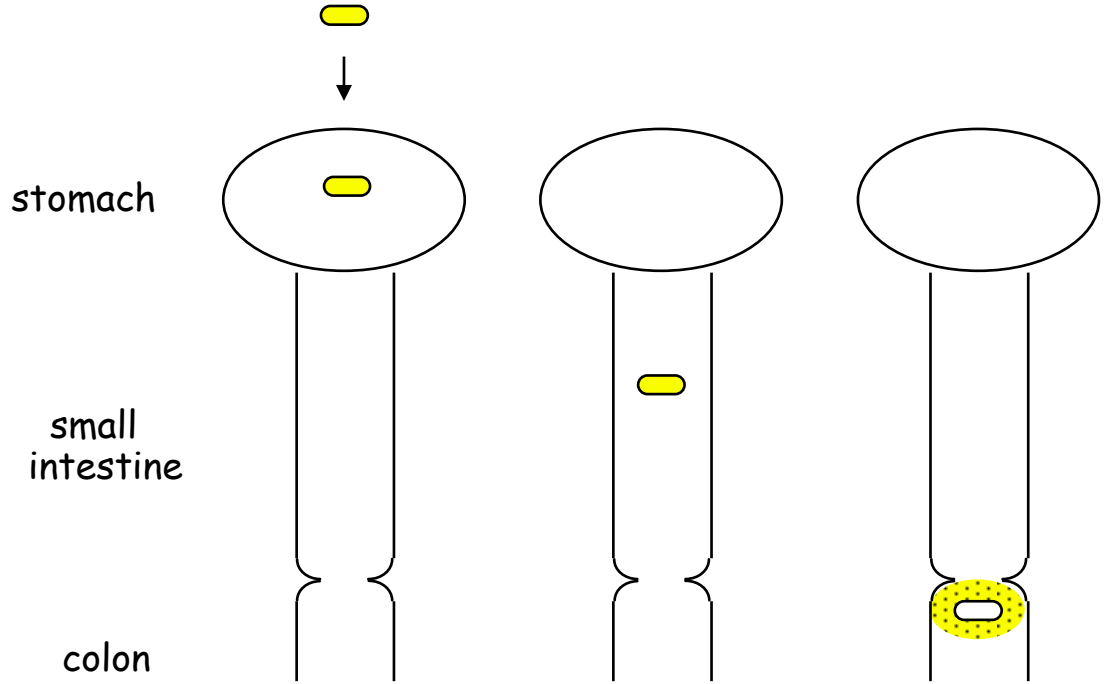
Oral Colon Targeting

Proximal colon achievable only by oral route.

Distal colon achievable in some cases also by rectal route.

gazza

Oral Colon Targeting

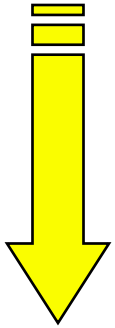


system able to move intact through the stomach and the small bowel ⇒ *a suitable mechanism that triggers release when the colon is reached*

gazza

Oral Colon Targeting

… any possible formulation strategies require a sophisticated approach based on the anatomical and physiological features of the region.



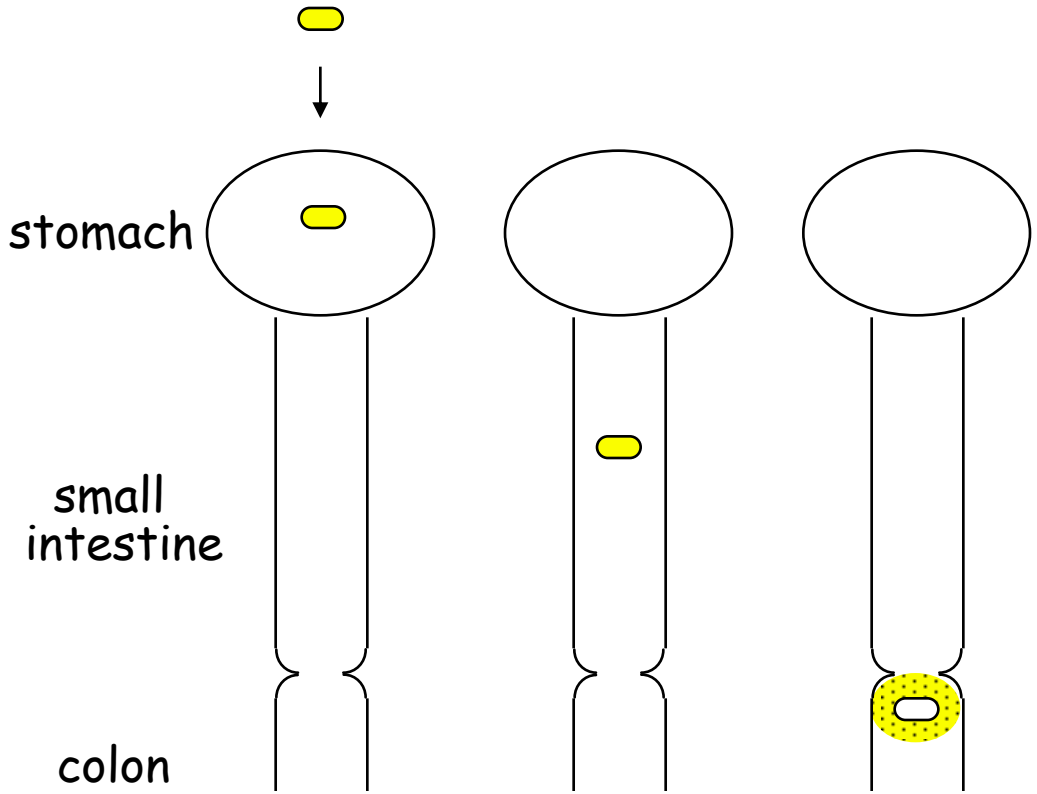
spatial and/or temporal parameters

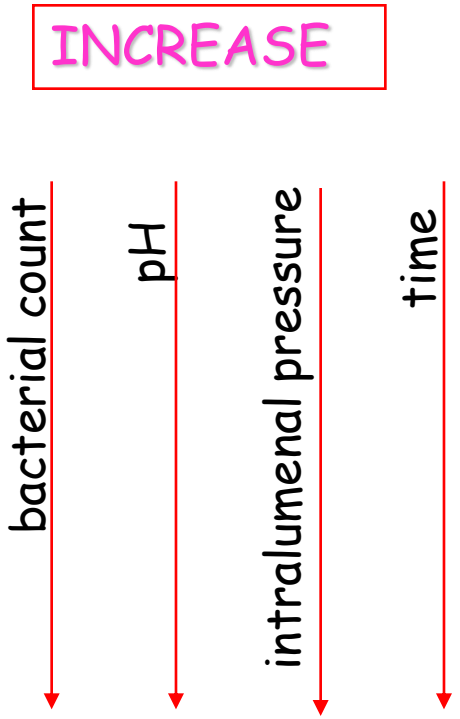
(i.e. bacterial count, pH, intralumenal pressure and time taken by the unit to transit the digestive tract)

possibility of exploiting their increase along the G.I. tract

gazza

Oral Colon Targeting





possibility of exploiting their increase along the G.I. tract

gazza

Oral Colon Targeting

Variety of mixed strategies including the use of:

- prodrugs and polymeric matrices/coatings degraded by enzymatic activity of colonic bacteria

- Chemical / microbiological approach

- polymeric coating which dissolves at specific pH
- devices capable of exploiting the relatively constant SITT

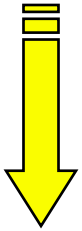
- Technological / physiological approach

gazza

Chemical / Microbiological Approach

Microbially-Controlled Drug Delivery Systems

Exploitation of the selective presence in the colon of bacterial species capable of catalyzing enzymatic reactions on substances which have not been degraded in the upper G.I. tract



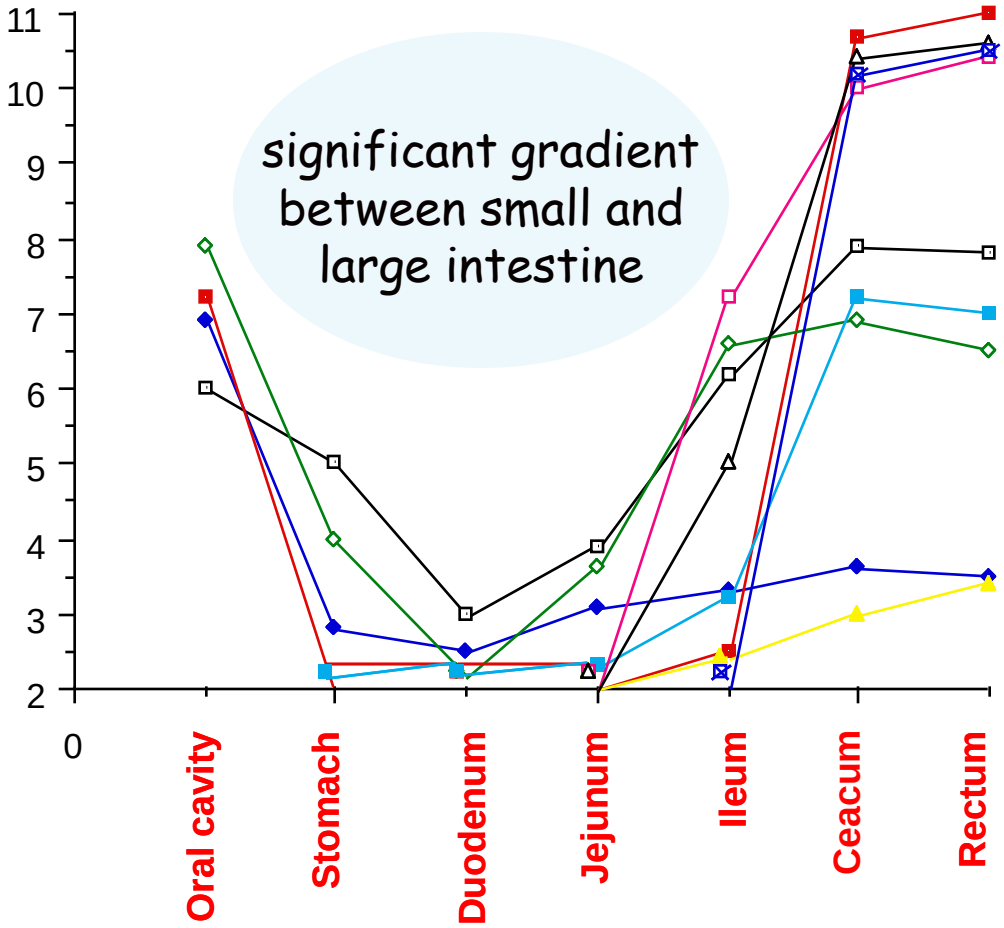
Use of either natural or synthetic compounds selectively degraded in the colon

gazza

Quali-Quantitative Microflora Composition along the Human G.I. Tract

Adapted from Mitsuoka T., Intestinal Bacteria and Health, Harcourt Brace Jovanovich, Tokjo, 1978

Log number of selected bacterial species per g content of alimentary tract



- Enterococci
- Veillonellae
- Bacteroides
- Lactobacilli
- Coliform bacteria
- Bifidobacteria
- Clostridium perfrigens
- Eubacteria
- Anaerobic streptococci

Microflora population INCREASES PROCEEDING DOWNWARDS IN THE G.I.TRACT - q.q. abundance in the colon

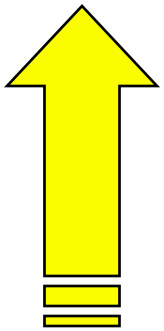
> 400 bacterial species identified in the colon

gazza

Enzymatic Reactions Catalyzed by Colonic Microflora

- hydrolysis of glycosides
- hydrolysis of -CO-NH c.
- hydrolysis of esters
- dehydroxylation
- C- dehydroxylation
- N- dehydroxylation
- decarboxylation
- dealkylation
- O-demethylation
- N- demethylation

- dehalogenation
- reduction of double bonds
- reduction of nitro-groups
- reduction of azo-groups
- reduction of aldehydes
- reduction of ketones
- reduction of alcohols
- deamination
- nitrosamine formation
- acetylation
- esterification



> 400 bacterial species identified in the colon

gazza

Chemical / Microbiological Approach

Prodrugs

Undegradable and negligibly absorbed as such in the upper G.I. tract

selectively activated *in the colonic microbial environment*

Polymeric excipients for colonic delivery systems

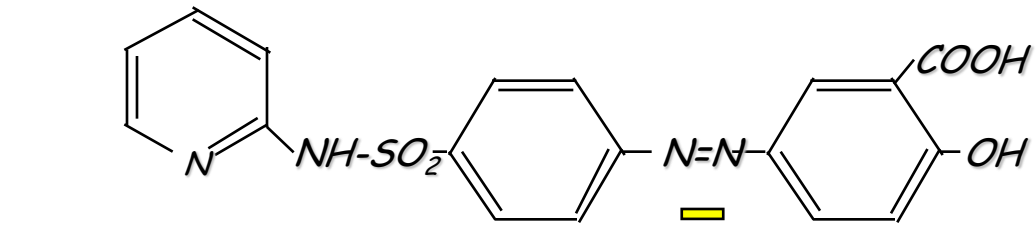
Undegradable and insoluble in the upper G.I. tract

selectively degraded *in the colonic microbial environment*

gazza

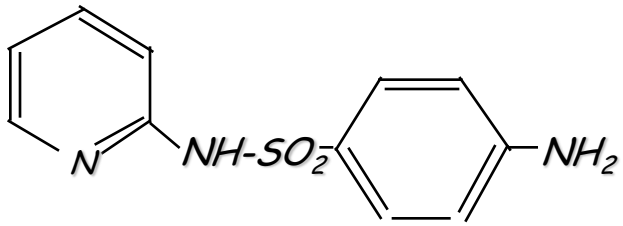
Reduction of Azo-Groups

catalyzed by bacterial azoreductases

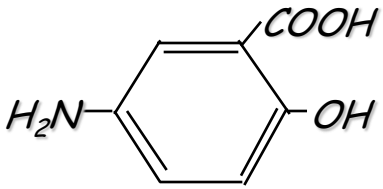


Sulphasalazine

Bacterial azoreductases



+

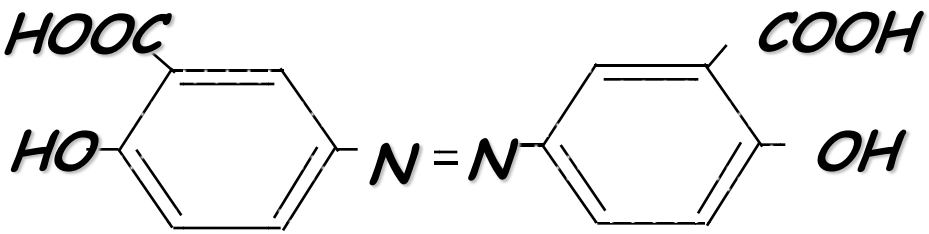


Sulphapyridine

5-aminosalicylic acid (5-ASA)

Sulphasalizine is a prodrug which prevents 5-ASA from being absorbed in the upper G.i>. tract

gazza



Olsalazine

Dipentum®

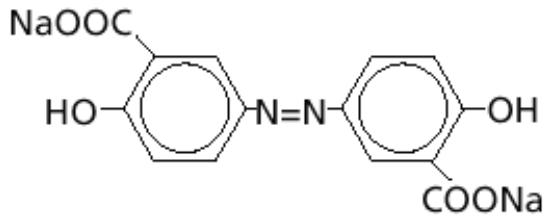
olsalazine sodium capsules

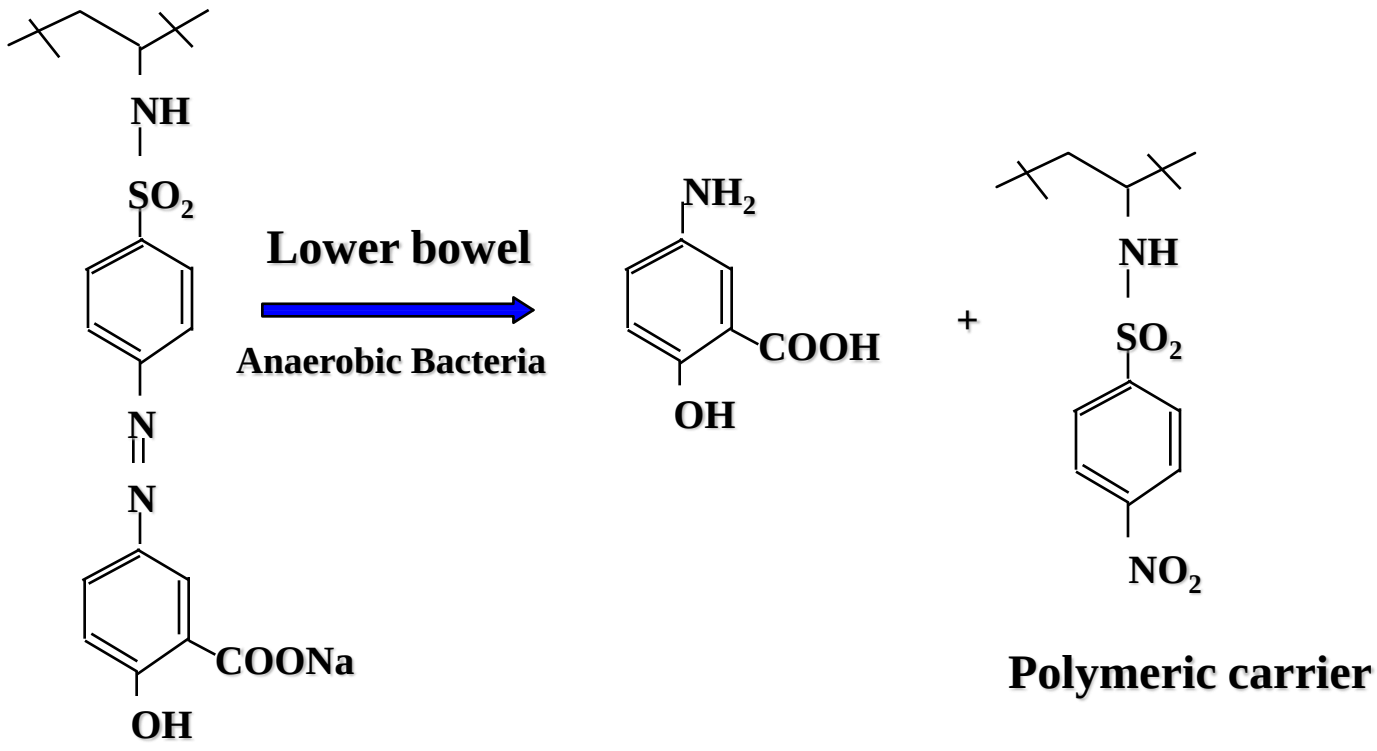
PHARMACIA

DESCRIPTION

The active ingredient in DIPENTUM Capsules (olsalazine sodium) is the sodium salt of a salicylate, disodium 3,3'-azobis (6-hydroxybenzoate) a compound that is effectively bioconverted to 5-aminosalicylic acid (5- ASA), which has anti-inflammatory activity in ulcerative colitis. Its empirical formula is $C_{14}H_8N_2Na_2O_6$ with a molecular weight of 346.21.

The structural formula is:





Brown J.P. et al., J. Med. Chem. 23, 1300 (1983)

gazza

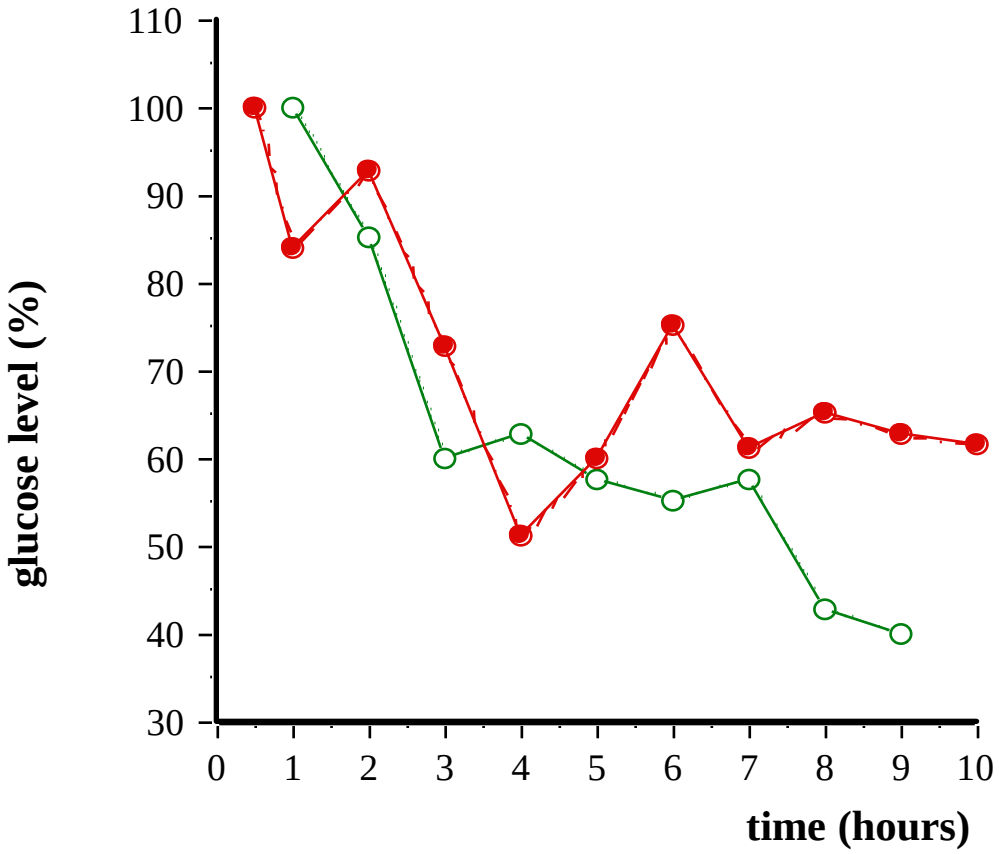
Azopolymers for Colon Delivery Systems

A New Approach to the Oral Administration of Insulin and Other Peptide Drugs

Saffran M. et al., Science, 233, 1081-1084 (1986)

Insulin-containing pellets coated by azoaromatic polymer (styrene and hydroxyethyl methacrylate copolymer cross-linked by divinyl azobenzene) administered to rats made diabetic with streptozocin

gazza



Effect on the blood glucose levels of the oral administration of an azoaromatic polymer-coated pellet containing 1 IU (about 28 nmol/Kg body weight) of insulin to two rats made diabetic with streptozocin. Initial blood glucose levels were 400 and 290 mg/100 ml, respectively.

The fall in blood glucose became significant 3 hrs post-dose.

Adapted from Saffran M. et al., Science, 233, 1081 (1986)

gazza

Hydrolysis of Glycosidic Bonds

catalyzed by bacterial β-glycosidases

Historical background

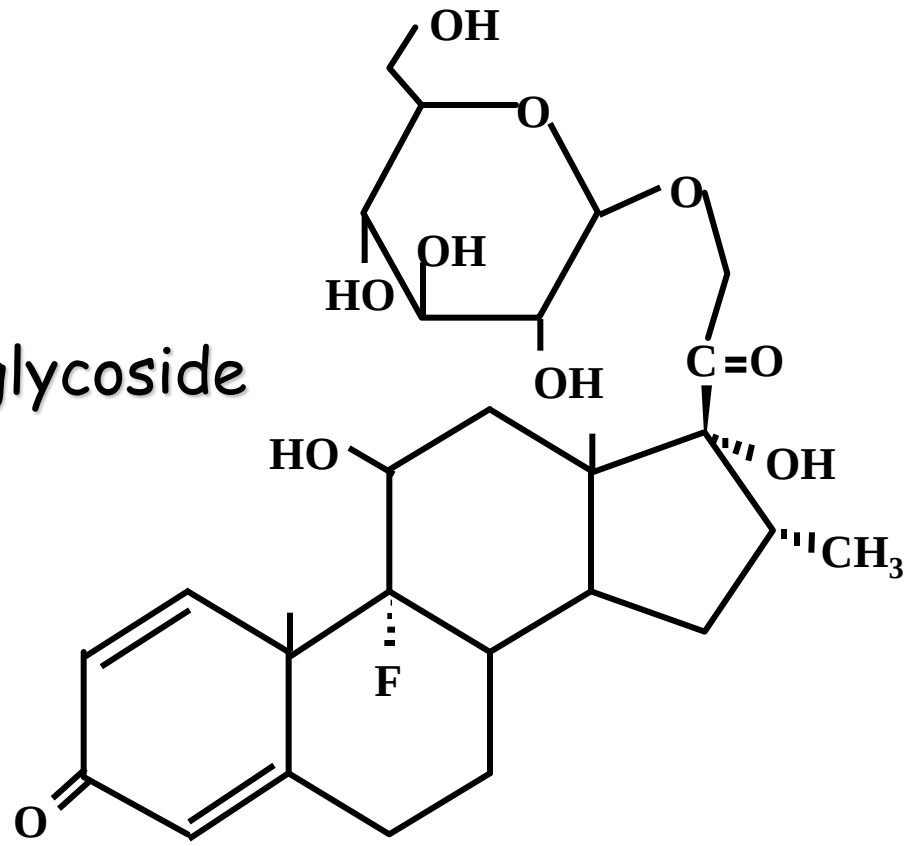
Cathartic action of glycosidic derivatives contained in senna and cascara sagrada

The aglycone is responsible for the therapeutic effect after enzyme-dependent cleavage of the glycosidic bond in the colon

The saccharidic moiety, due to its hydrophilicity prevents the molecule (glycosidic compound) from absorption in the upper G.I.

gazza

dexamethasone-21β,D-glycoside



Friend D.R. et al., J. Pharm. Pharmacol. 43(5), 353 (1991)

gazza

Natural Polysaccharides for Colon Delivery Systems

Pectin *D-galacturonic acid and methyl ester polysaccharide, cell wall constituent.* Used as a compression coat as well as a matrix forming agent in the form of calcium salt or methoxylated derivative, or else blended with ethylcellulose, Eudragit®RS, chitosan

Ashford M., Fell J.T. et al., J. Control. Rel. 26(3), 213 (1991)

Chondroitin sulphate

Mucopolysaccharide contained in the dietary meat. Used as a matrix forming agent after cross-linking.

Rubinstein A. et al., Pharm. Res. 9(2), 276 (1992)

Guar gum

Galactomannan. Used as a matrix forming agent in blends with acrylic resins (Eudragit®RS, RL, NE).

Lehmann K.O.R. and Dreher K.D., Proceed. Int.'l Symp. Control. Rel. Bioact. Mater. 18, 331 (1993)

Amylose

D-glucose polymer constituent of starch with amylopectin. Used in the glassy form, which is pancreatic amylase resistant, blended with ethylcellulose (1:4) for aqueous film-coating. Tested in vivo by pharmacoscintigraphy, the coating mixture applied on 5-ASA containing pellets was demonstrated suitable for colon delivery

Milojevic S., Newton J.M. et al., STP Pharma Sci. 5, 47 (1995)

Chitosan

High molecular cationic polysaccharide obtained by chitin (shellfish exoskeleton constituent) N-deacetylation. Used as a coating agent or capsule forming material. Acid-soluble, requires gastric resistant coating. Absorption enhancer

Rubinstein A. et al., Pharm. Res. 9(2), 276 (1992)

gazza

Natural Polysaccharides for Colon Delivery Systems

Pectin
Chondroitin sulphate
Guar gum
Amylose
Chitosan

.. although these materials have demonstrated to undergo selective enzyme degradation in the colon, their overall important limitation is the solubility in the aqueous fluids.

..... when used as such or in physical mixtures within the formulation, they would likely fail to prevent drug release prior to colon arrival of the dosage form.

..... the suitability as coating or matrix-forming agents for colon delivery is therefore rather uncertain

... whereas the use of derivatives (salts, cross-linked compounds) or coating formulations consisting of blend with film forming insoluble polymers , such as EC or Acrylic resins, may be useful

gazza

Oral Colon Targeting

Limits to the Chemical / Microbiological Approach

- Great efforts *[time and costs]* required for development and approval of new chemical entities (NCE) *[both new prodrugs and polymers]*
- Limited reproducibility in enzymatic activity

gazza

Oral Colon Targeting

Variety of mixed strategies including the use of:

- prodrugs and polymeric matrices/coatings degraded by enzymatic activity of colonic bacteria

- Chemical / microbiological approach

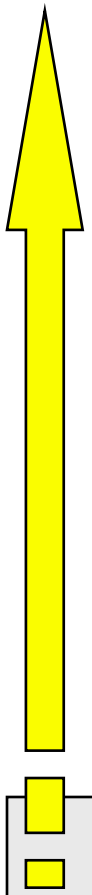
- polymeric coating which dissolves at specific pH
- devices capable of exploiting the relatively constant SITT

- Technological / physiological approach

gazza

Oral Colon Targeting

Exploitation of:



pH variation along the G.I. tract

classical

relatively constant small intestine transit time (SITT)

innovative

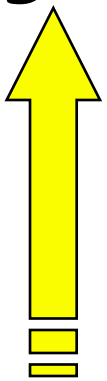
- Technological / physiological approach

Systems devised as drug reservoirs coated by polymers or polymeric blends soluble at pH>6-7

Several examples

conflicting results

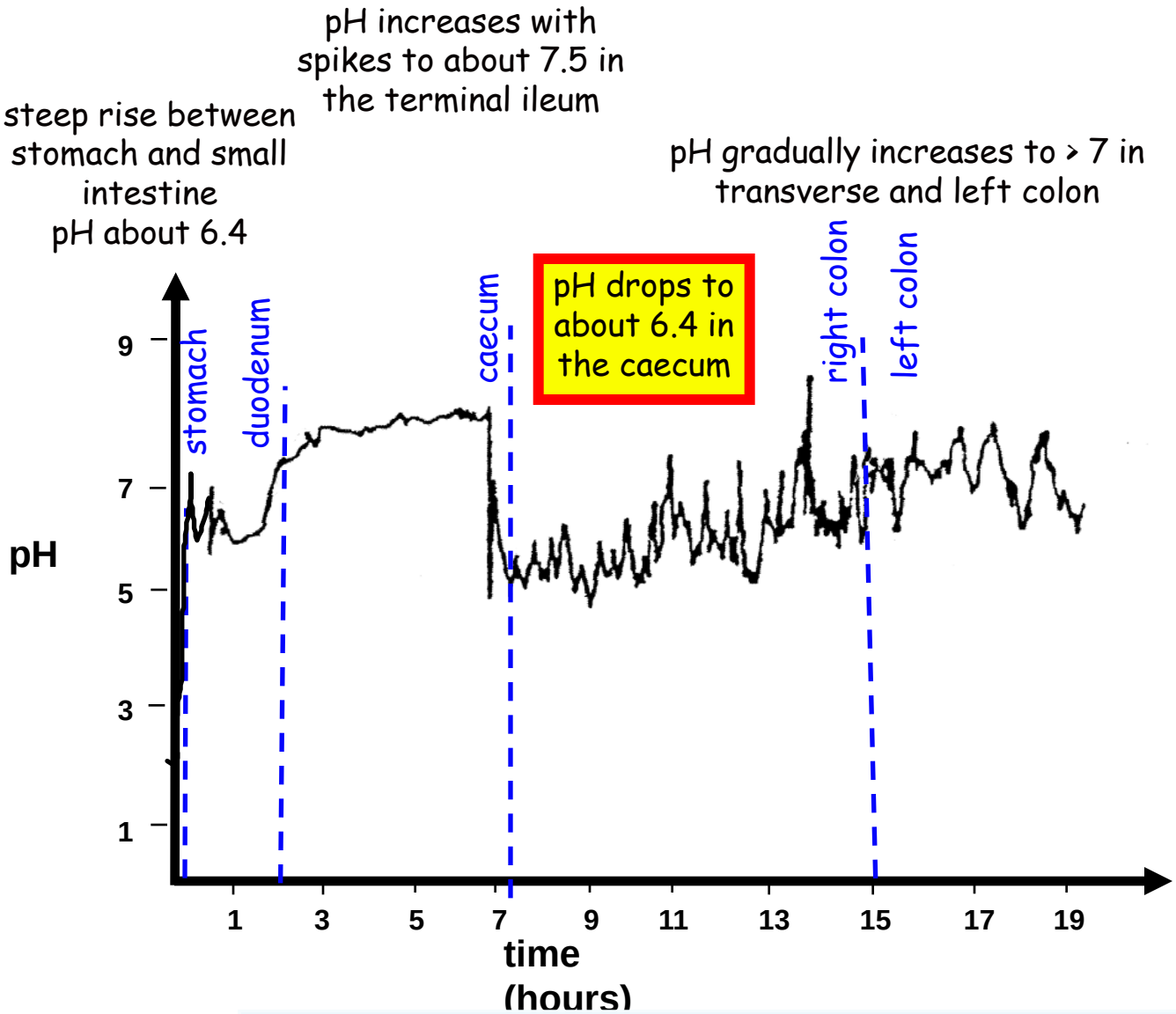
Initial hypothesis: *progressive pH increase from the stomach to the distal colon*



pH-Controlled Colon Delivery Systems

gazza

Technological / physiological approach



pH profile in the G.I. tract assessed using a radio telemetric device

Adapted from Evans D.F., Gut 29, 1035 (1988)

pH-Controlled Colon Delivery Systems

gazza

..Nevertheless..

products on the market

- Asacol® Eudragit®S (soluble pH ≥ 7.0)
- Salofalk®, Claversal® Eudragit®L (soluble pH ≥ 5.5)

Uncertainty

location

in which the pH-dependent formulations can start the release

pH-Controlled Colon Delivery Systems

gazza

pH-Controlled Colon Delivery Systems

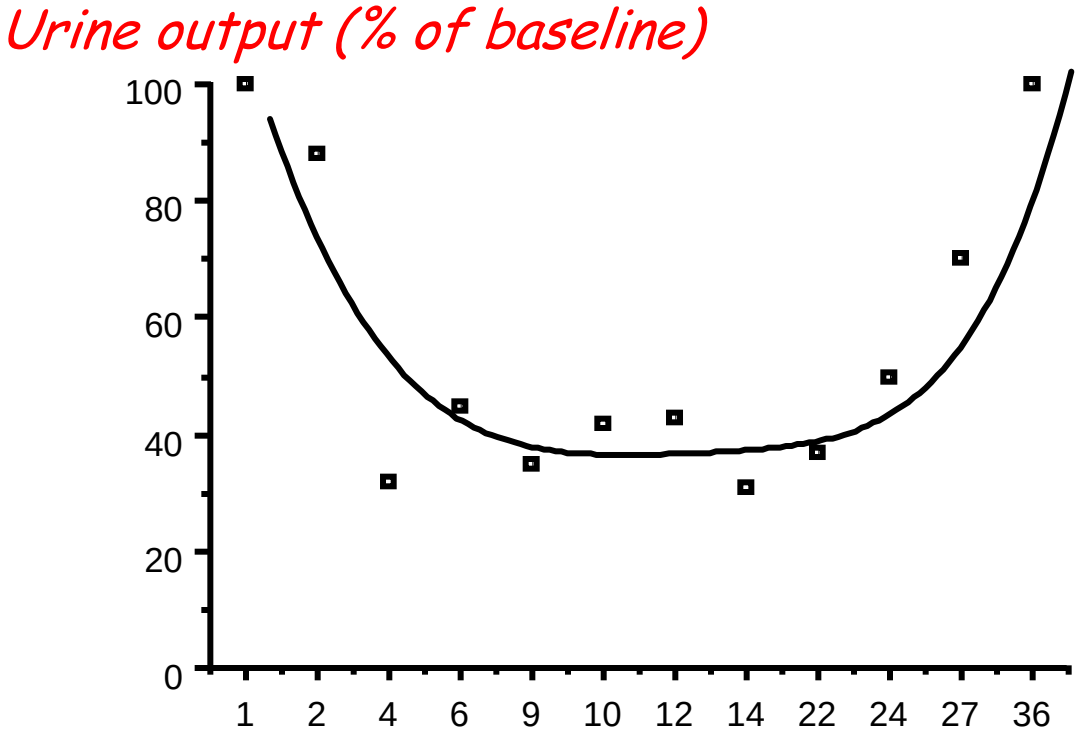
Development and In Vitro / In Vivo Evaluation of a Colonic Release Capsule of Vasopressin

Rao S.S. and Ritschel W.A., Int. J. Pharm. 86, 35 (1992)

Vasopressin-containing hard gelatin minicapsules coated with a mixture of Eudragit® S100 and Eudragit® NE 30 D (3:7) and by an external cellulose acetate phthalate film.

gazza

Significant and long lasting decrease in the urine output following administration to rats with diabetes insipidus.

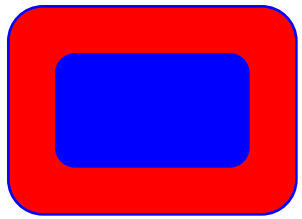


Adapted from Rao S.S. and Ritschel W.A., Int. J. Pharm. 86, 35 (1992)

gazza

Colonic Targeting of the Polypeptide Drug Nisin

Habib W.A. and Sakr A., Proceed. Int.'l Symp. Control. Rel. Bioact. Mater. 25, 166 (1998)



Core: nisin tablet

Coat: Eudragit®L30 D-55 soluble pH≥ 5.5

thickness ~ 400μ

gazza

Colonic drug delivery via the use of pH-dependent polymers, an in vitro investigation.

M. Ashford et al., Proceed. 6th Intern. Confer. on Pharmaceutical Technology, II, 59-65 (1992)

The effect of a model, pH dependent polymer coating, EUDRAGIT S, on the release of drug from standard, rapidly disintegrating tablets under conditions likely to be incurred in vivo during mouth to colonic transit has been investigated systematically.

Dissolution is affected by pH, buffer system and strength of the dissolution medium. pH profiles constructed to mimic extremes of conditions in vivo indicate that tablet disintegration may commence in the duodenum or not occur at all.

Therefore, due to variability in the gastrointestinal tract conditions, pH dependent polymers may not provide the best method of targeting to the colon.

gazza

pH variation along the G.I. tract

classical

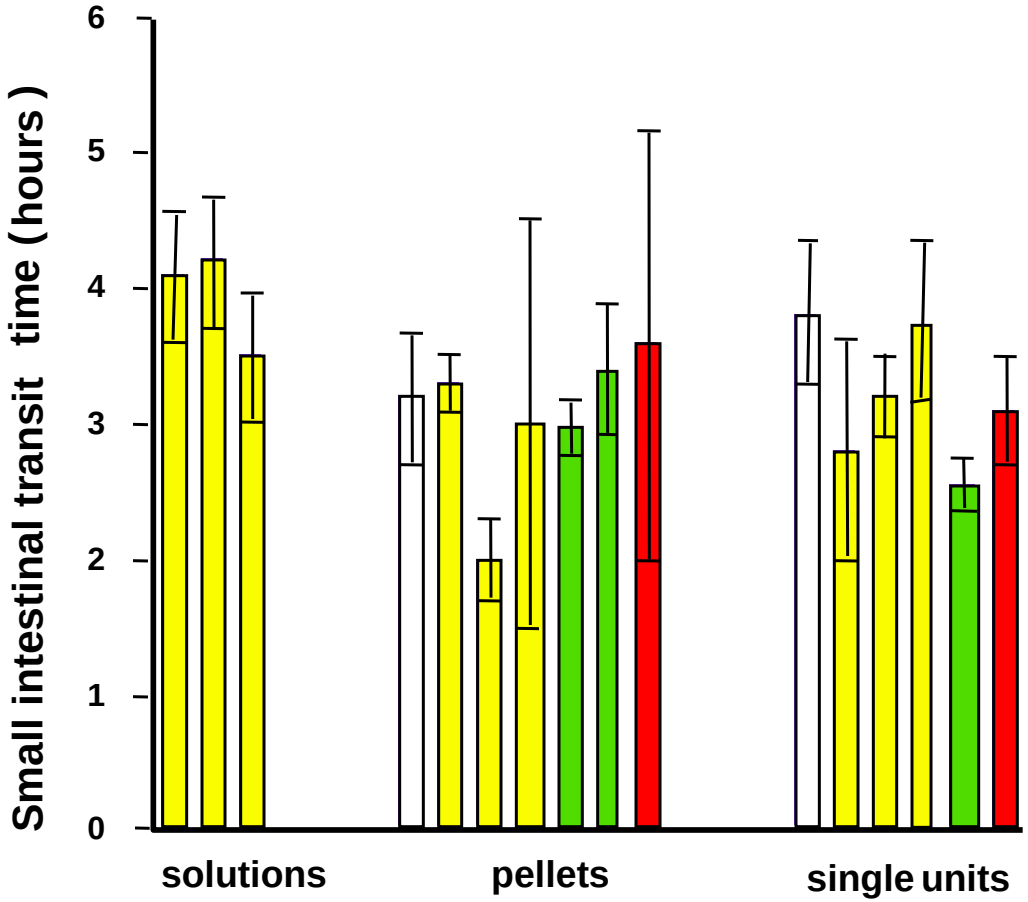
relatively constant small intestine transit time (SITT)

innovative

gazza

Small Intestine Transit

Adapted from Davis S.S et al., Gut 27, 886 (1986)



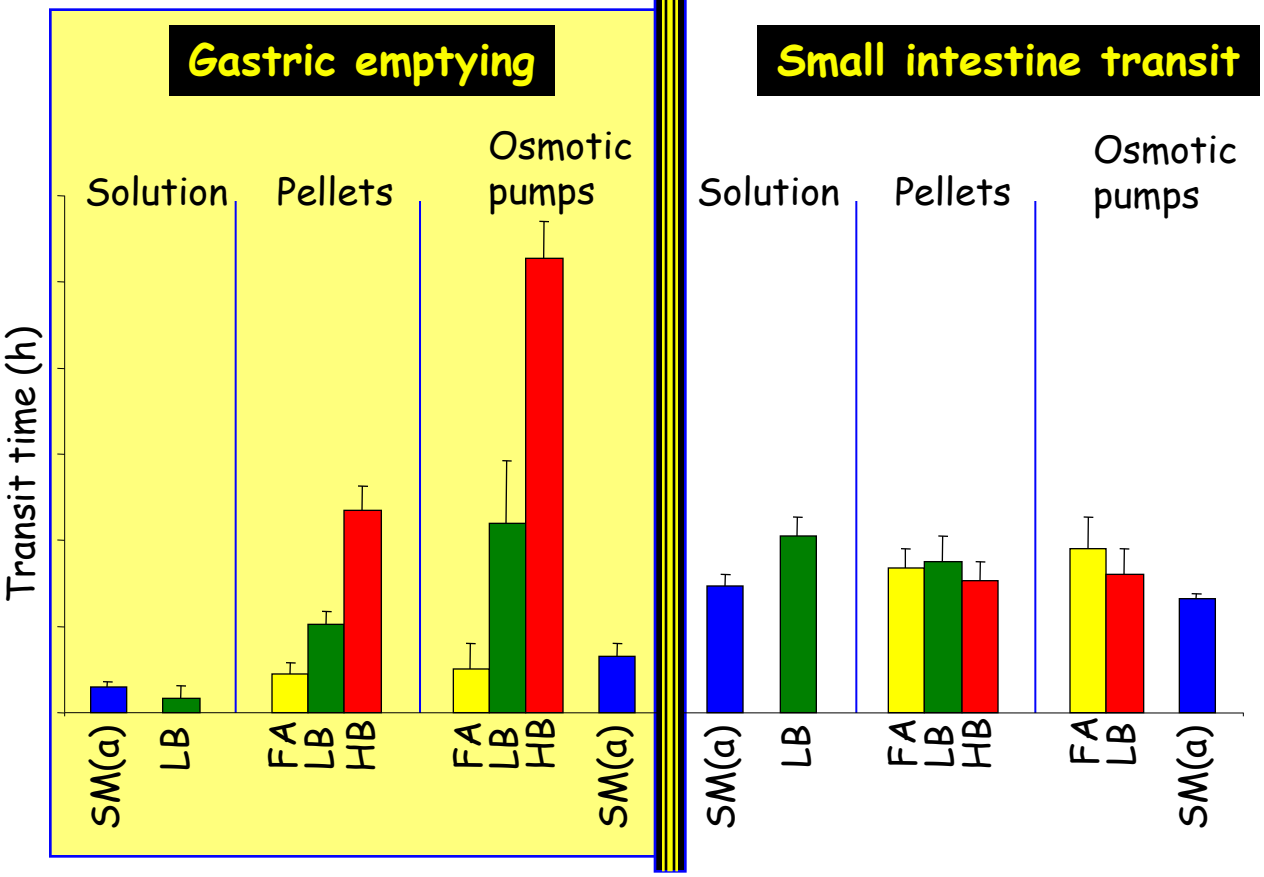
practically independent [3h±1 s.d.] of dosage form characteristics and fed/fasted condition

- *Fasted*
- *Light breakfast*
- *Heavy breakfast*
- *Varied breakfast*

relatively constant small intestine transit time (SITT) of dosage forms

gazza

Time-Controlled Colon Delivery Systems



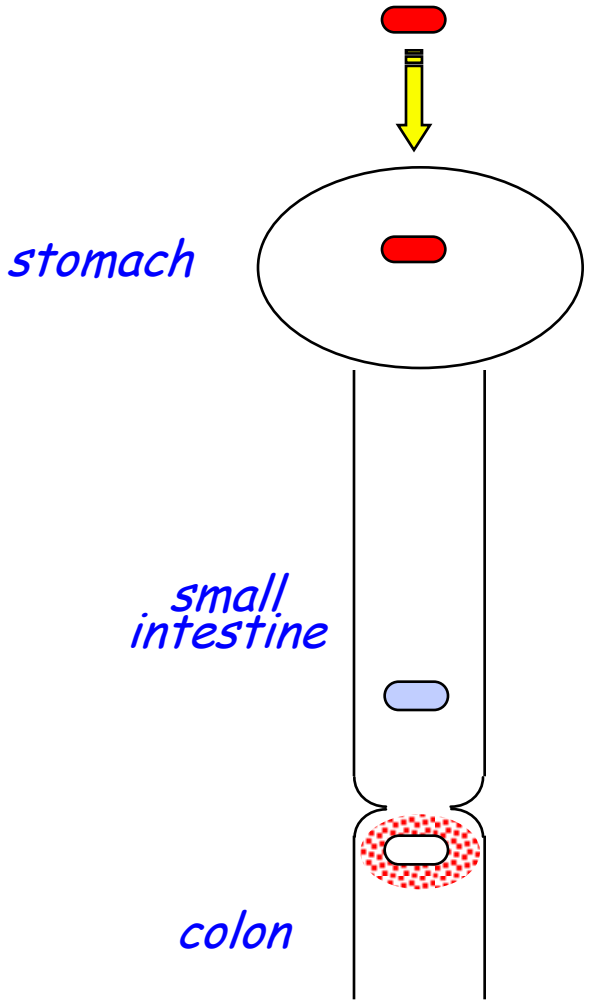
Redrawn from S.S. Davis, J. Control. Release, 2 (1985) 27-38.

LB: light breakfast
HB: heavy breakfast
FA: fasted
SM: standard meal

high variability in gastric emptying

need to zero its influence

Time-Controlled Colon Delivery Systems



The unit, following oral administration

*1] is expected to **remain intact** in the stomach*

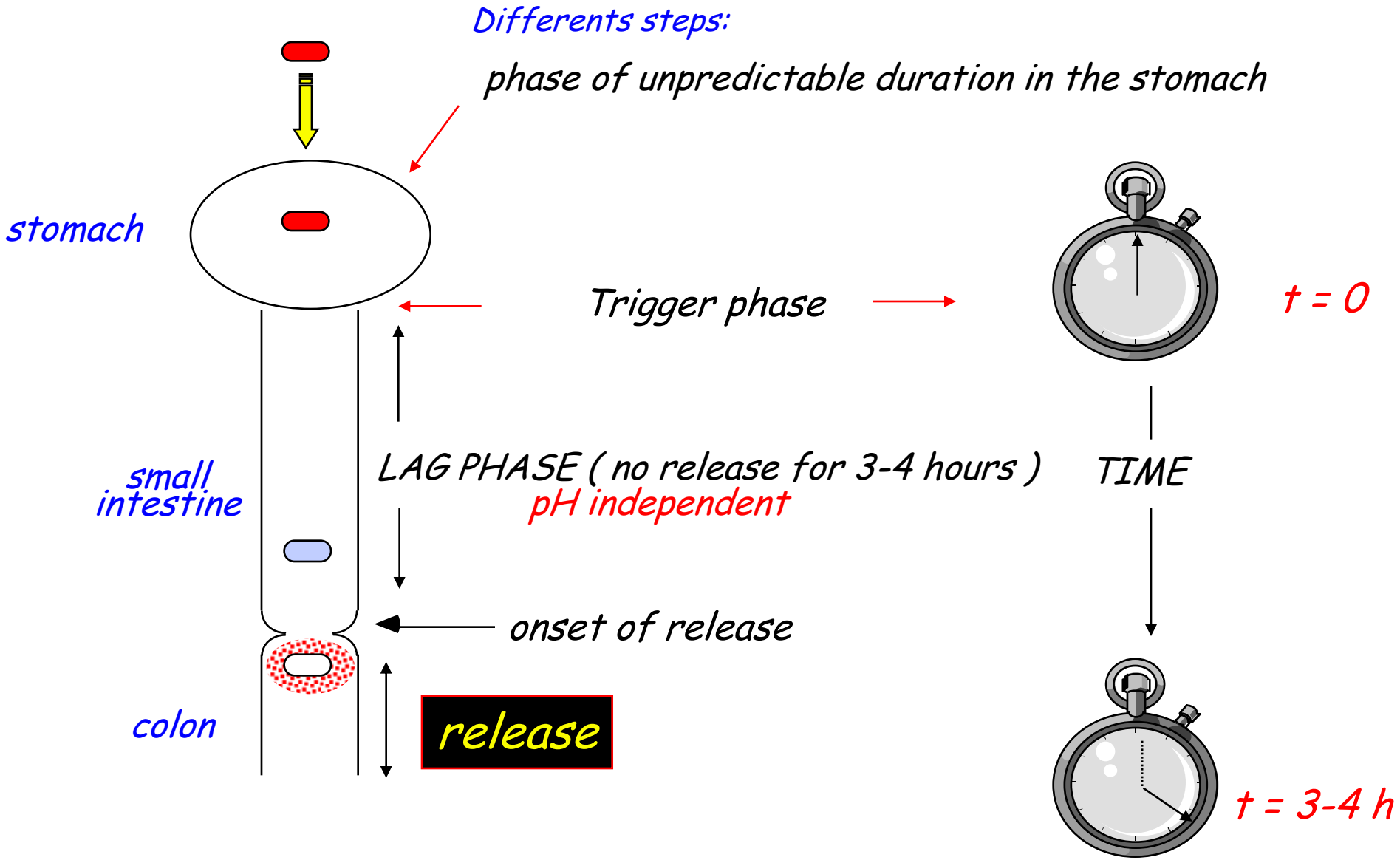
*2] **should "know"** that it **has left** the stomach entering the small intestine (**triggering phase**)*

*3] the **delay phase** (during which no release occurs) **can start**, lasting a period of **3-4 hours** (time required to reach the colon).*

4] release of the active

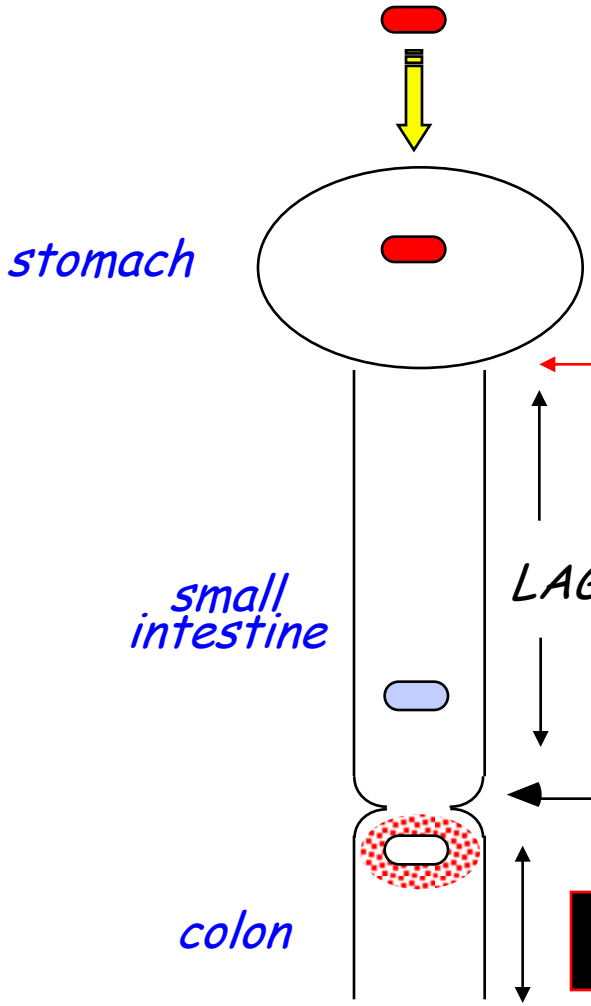
gazza

Time-Controlled Colon Delivery Systems



gazza

Time-Controlled Colon Delivery Systems



Trigger phase → relies on pH gradient between stomach and intestine environments

LAG PHASE → retarding mechanism based on solvent activation [dissolution, erosion, dispersion] of differing polymeric or non polymeric elements

onset of release

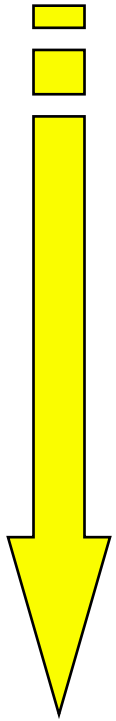
release → release behaviour according to the design and features of the core unit

gazza

Time-Controlled Colon Delivery Systems

Trigger phase

Lag phase



…in principle, all systems able to provide a lag phase prior to release, i.e. delayed/pulsatile delivery devices, are potentially suitable for **Time-Controlled Colon Delivery**

gazza

Time-Controlled Colon Delivery Systems

- *Osmotic pumps*

  Oros-CT®

- *Capsular devices with release-controlling plugs*

  Pulsincap®

  PORT™ (Programmable Oral Release Technologies) system

- *Reservoir systems with release-controlling coatings*

  TES (time-Controlled Explosion System)

  Time-Clock® system

  CTDC (Colon-Targeted Delivery Capsule)

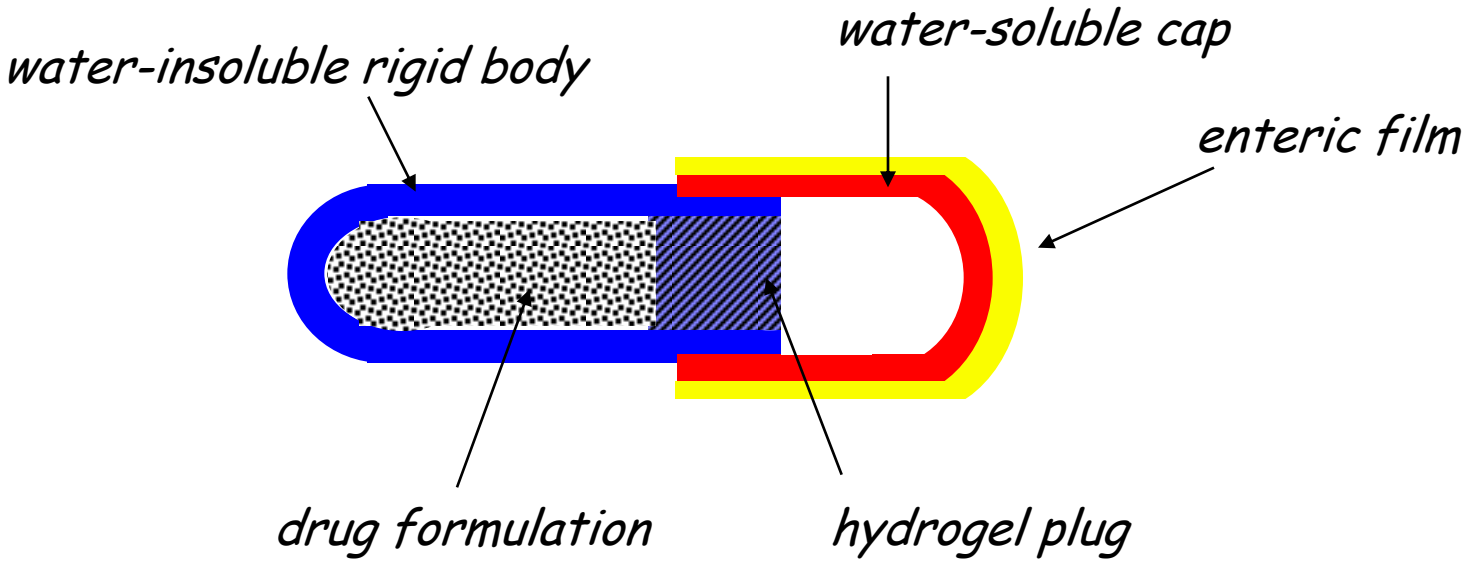
  EDP (Enteric Coated Timed-Release Press-Coated Tablets)

  Chronotopic™ system

gazza

Capsular device with release-controlling plugs

Pulsincap™

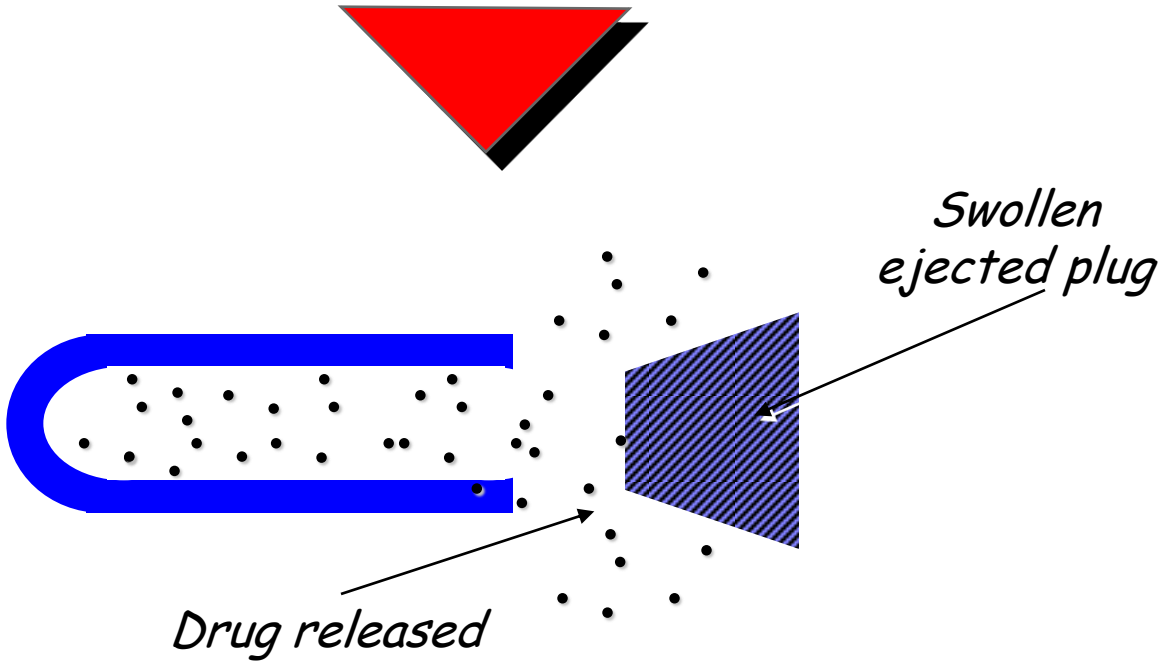


McNeil M.E. et al., Intern. Patent WO 90/09168 (1990)
Wilding I.R. et al., Pharm. Res. 9(5), 654-657 (1992)
Binns J.S. et al., Proceed. Int'l. Symp. Control. Rel. Bioact. Mater. 20, 226 (1993)
Wilson C.G. et al., Drug Delivery 4, 201-206 (1997)

gazza

Capsular device with release-controlling plugs

Pulsincap™



Stage 0 - Dissolution of enteric film
Stage 1 - Dissolution of the cap
Stage 2 - Swelling of the plug *[plug removal, and then lag phase, depends on its size and position within the capsule body]*
Stage 3 - Rapid release of the active

gazza

Capsular device with release-controlling plugs

Pulsincap™

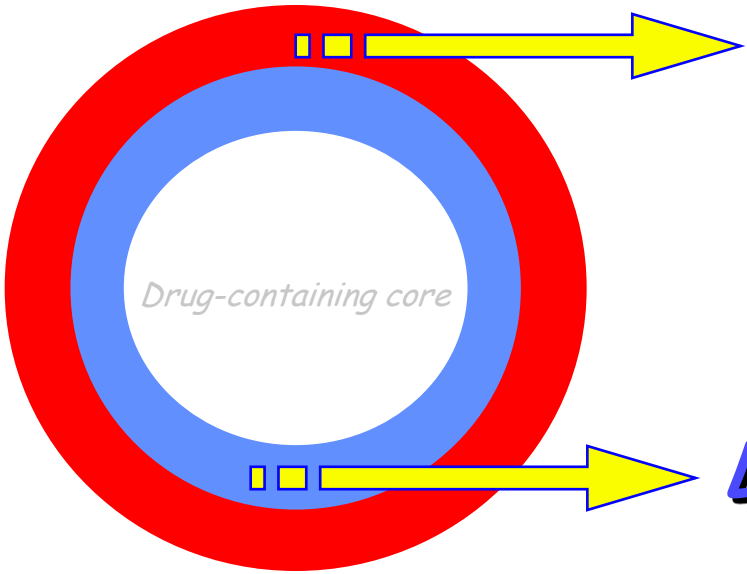
Gastrointestinal transit and plug separation times (h)

Subject	Gastric residence	Small intestine transit	Colon arrival	Plug separation post-dose	Plug separation post-gastric emptying	Ascending colon residence
1	0.19	3.31	3.50	3.68	3.49	6.33
2	0.56	3.38	3.94	4.52	3.96	5.14
3	0.86	2.77	3.63	5.07	4.21	7.73
4	0.27	3.33	3.60	4.13	3.86	2.63
5	0.81	3.07	3.88	4.50	3.69	6.03
6	0.26	3.32	3.58	(10.48)	(10.22)	8.20
Mean	0.49	3.20	3.69	5.40	4.91	6.01
SD	0.30	0.24	0.18	2.53	2.62	2.00

Adapted from C.G. Wilson et al., Drug Delivery 4, 201-206 (1997)

Reservoir systems with release-controlling coatings

General scheme → at least two-layer coatings



Trigger layer

Lag phase layer [retarding layer]

gazza

Reservoir systems with release-controlling coatings

General scheme ⇒ at least two-layer coatings

Lag phase layer

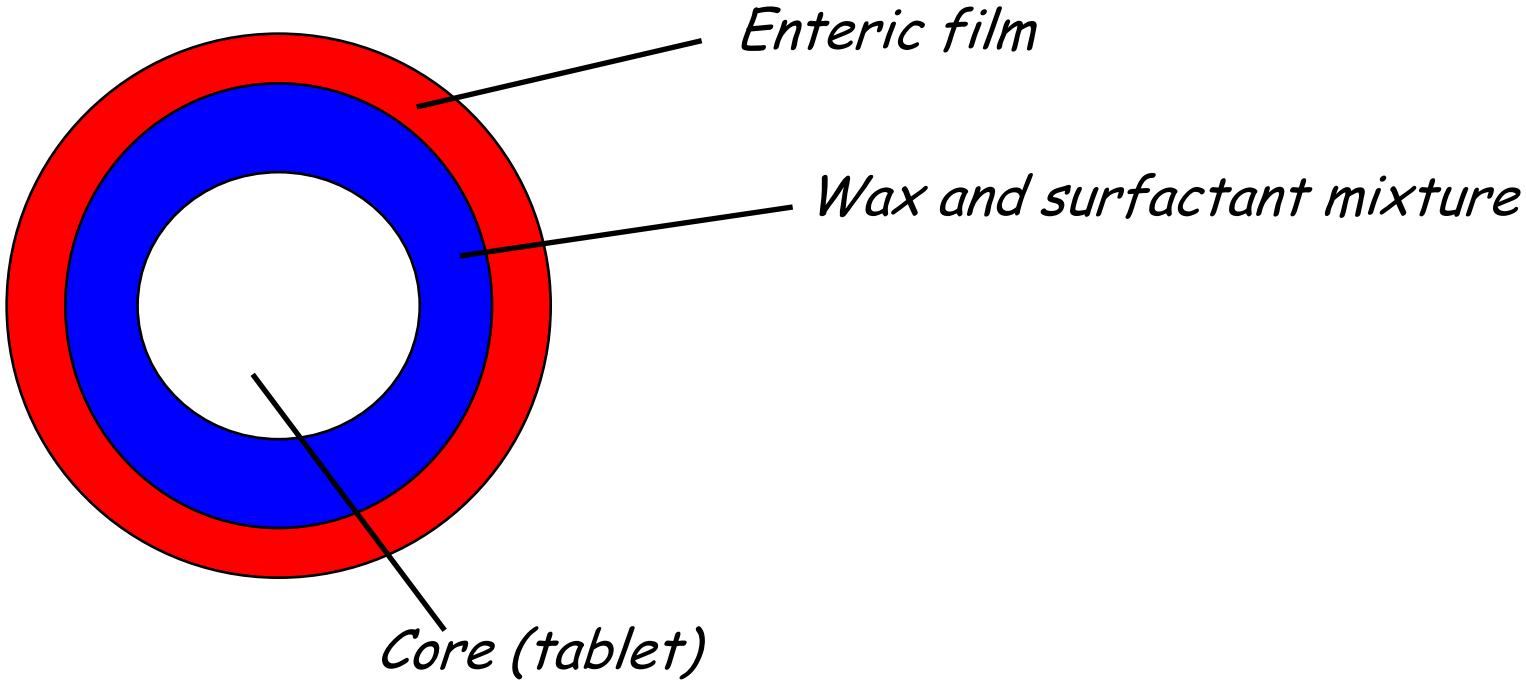
- Dispersible hydrophobic polymeric coatings
- Internal pH-mediated soluble polymeric coatings
- Erodible/dissolving hydrophilic swellable polymeric coatings

gazza

Time-Clock® System

Pozzi F. et al., J. Control. Release 31(1), 99 (1994)
Wilding I.R.. et al., Int. J. Pharm. 111, 99-102 (1994)
Steed K.P. et al., J. Control. Release 49, 115 (1997)

following administration



Stage 0 - Dissolution of enteric film
Stage 1 – Erosion/dispersion of the wax layer
Stage 2 - Rapid release of the active

gazza

Time-Clock® System

Adapted from Wilding I.R. et al., Int. J. Pharm. 111, 99-102 (1994)

Transit and disintegration times (min) of placebo units

6 fed (light breakfast) volunteers

Subject	Gastric emptying	Small intestinal transit	Colon arrival	Tablet dispersion	Position of dispersion
1	103	248	351	655	caecum
2	251	168	419	656	proximal colon
3	154	267	421	655	caecum
4	123	186	319	593	proximal colon
5	87	163	250	523	descending colon
6	201	251	452	575	proximal colon
Mean	153	261	369	610	
SE	27	19	31	23	

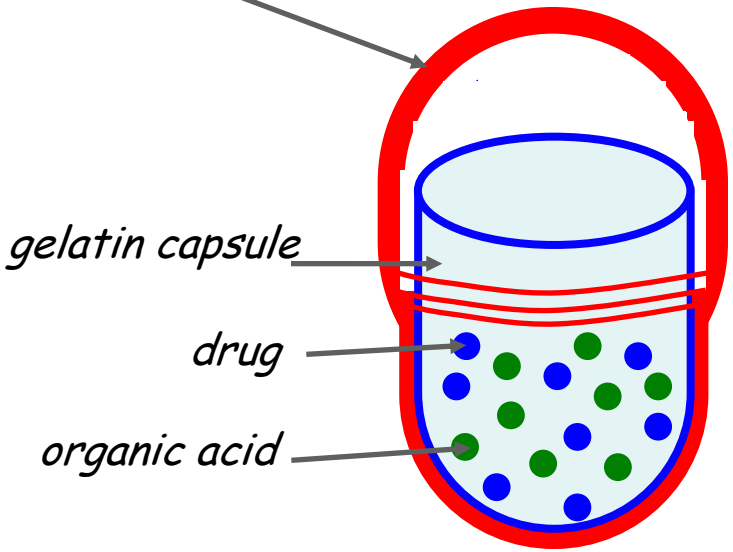
gazza

Colon-Targeted Delivery Capsule (CTDC)

following administration

three-layered coating

enteric layer	HPMC-AS
intermediate hydrophilic layer	HPMC Low Viscosity Grade
acid soluble permeable layer	Eudragit® E 100



Stage 0 - Dissolution of outer enteric and intermediate hydrophilic films
Stage 1 - External fluids diffuse into the capsule trough the permeable Eudragit® E layer
Stage 2 - Ionization of organic acid and subsequent dissolution of the Eudragit® E layer
Stage 3 - The capsule content is fully exposed to the external fluids

gazza

Colon-Targeted Delivery Capsule (CTDC)

CTDC Disintegration Profile after an Overnight Fast

subject	Initial disintegration			Complete disintegration	
	min post-dose	min post-GE	Anatomical position	min post-dose	Anatomical position
1	371	324	ICJ	422	AC
2	310	282	AC	421	AC
3	304	241	ICJ	514	AC
4	298	272	DC	469	DC
5	385	349	AC	495	AC
6	663	590	AC	685	AC
7	240	201	AC	301	AC
8	283	270	AC	502	TC
mean	357	316		476	
SD	132	120		109	

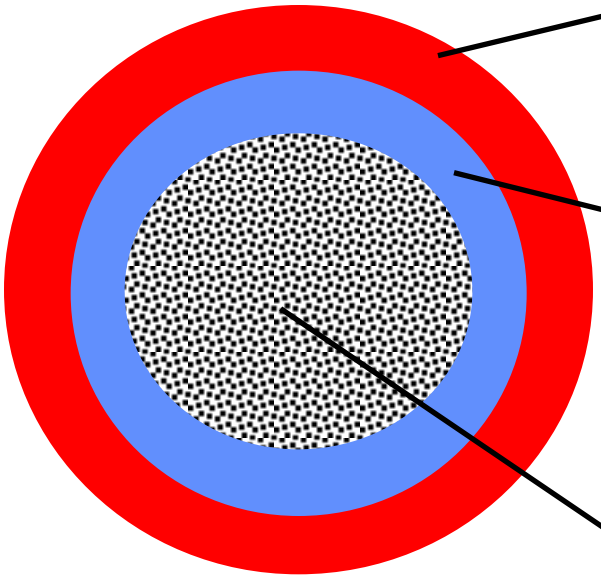
Redrawn from T. Ishibashi et al., J. Pharm. Sci. 87(5), 531-535 (1998)

Chronotopic™ System

Gazzaniga A. et al., Boll. Chim. Farm. 132(2), 66 (1993)
Sangalli M.E. et al., J. Control. Release 73(1), 103 (2001)
Sangalli M.E. et al., Eur. J. Pharm. Sci. 22(5), 469 (2004)

Gazzaniga A. et al., Eur. J. Pharm. Biopharm. 40(4), 246 (1994)
Gazzaniga A. et al., Int. J. Pharm. 108(1), 77 (1994)
Gazzaniga A. et al., S.T.P. Pharma Sci. 5(1), 83 (1995)

following administration



Enteric film

Hydrophilic swellable polymeric layer
(HPMC, different viscosity grades)

Drug-containing core [single/multiple unit]

Stage 0 - Dissolution of enteric film
Stage 1 – Swelling/Dissolution/Erosion of the polymeric layer
Stage 2 – Rapid/Slow release of the active

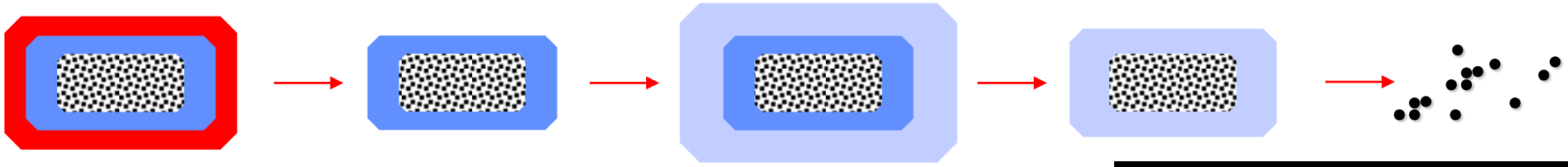
gazza

Chronotopic™ System

Adapted from Gazzaniga A. et al.- Eur.J. Pharm. Biopharm. 40(4), 246 (1994)

Lag phase

physical-chemical characteristics and coating level of the retarding layer

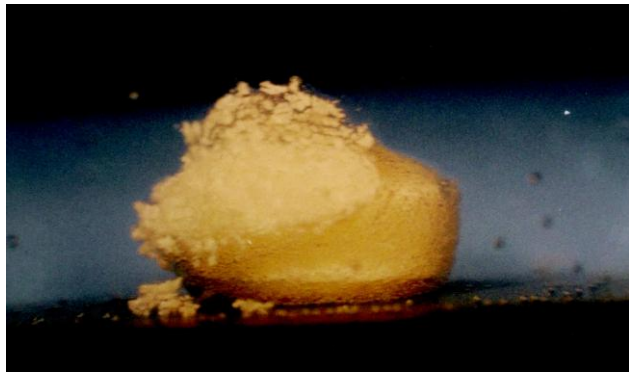


gastroresistant layer

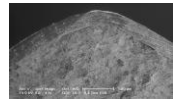
glassy

rubbery

drug particles



gazza



Chronotopic™ System

in vivo study on Antipyrine-containing units

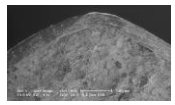
Model drug:	Antipyrine (50 mg)
Disintegrating core:	∅ 6 mm, 158 mg
Retarding layer:	Methocel®E50 (thickness 325, 575 and 1020 μm)
Spraying equipment:	Fluid bed (Uniglatt, Glatt GmbH)
Volunteers:	4 healthy male (age 36-45, weight 70-80Kg)
Sampling	Antipyrine was quantified in saliva by HPLC

saliva and blood concentrations of Antipyrine are known to be consistent

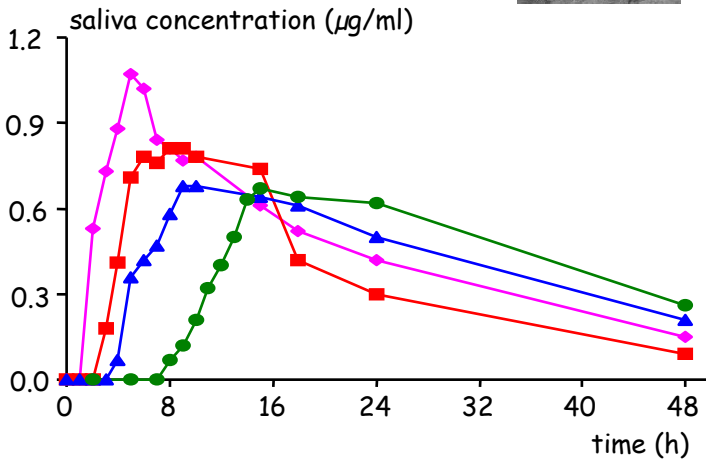
gazza

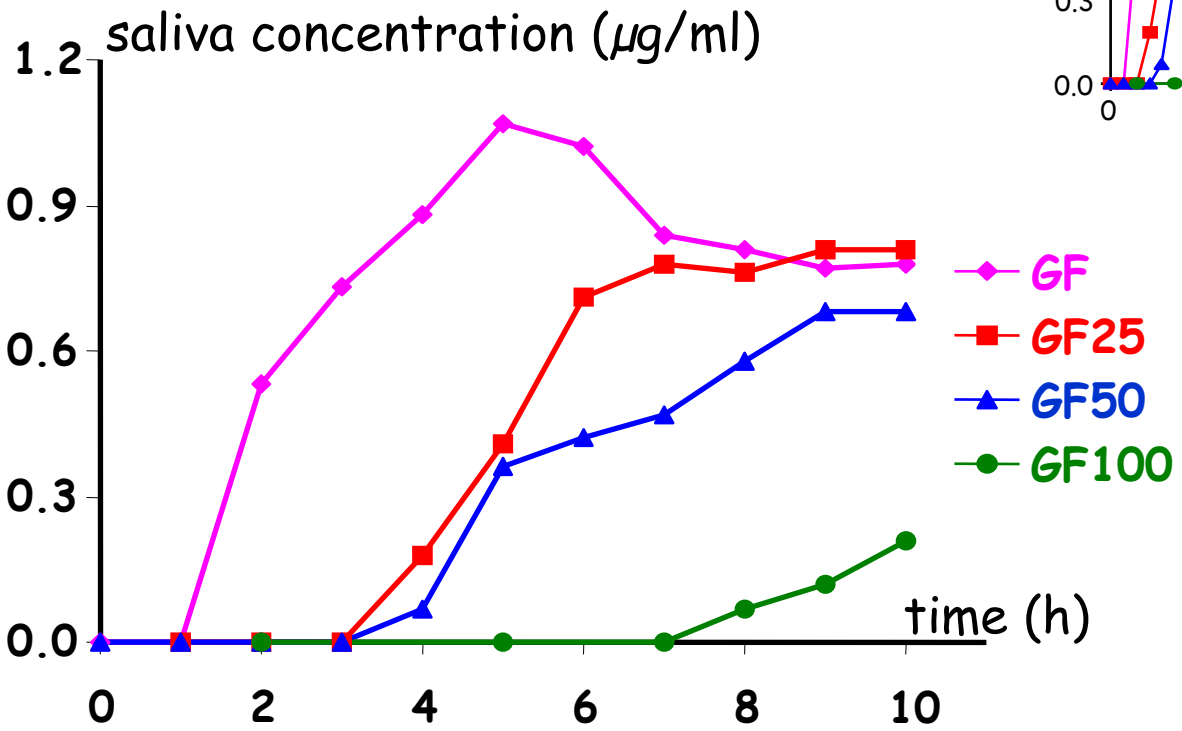
Chronotopic™ System

Adapted from Sangalli M.E. et al., J. Control. Release 73, 103 (2001)



Two-layer units (gastroresistant- Eudragit® L)



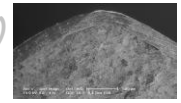


Average Antipyrine saliva levels after oral administration of gastroresistant cores (formulation GF) and finished systems (formulation GF25, GF50 and GF100, HPMC layer thickness 325, 575 and 1020 µm).

gazza

Chronotopic™ System

Adapted from Sangalli M.E. et al., J. Control. Release 73, 103 (2001)



Two-layer units (gastroresistant- Eudragit® L)

PLACEBO units

γ-Scintigraphic Study

Chronotopic® units : Samarium oxide containing core, diameter = 6 mm, weight = 160 mg.

Retarding layer: Methocel® E50 (thickness 1000 µm).

Enteric layer: Eudragit® L,

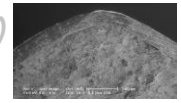
Volunteers: 6 healthy male, aged 30-48 years (70-85Kg)

Images: 30 min intervals

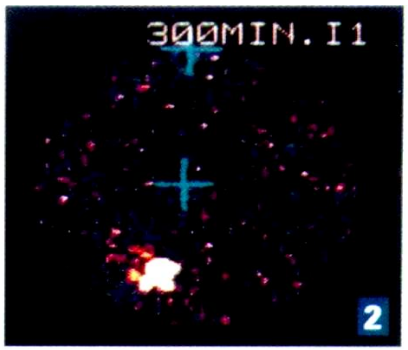
gazza

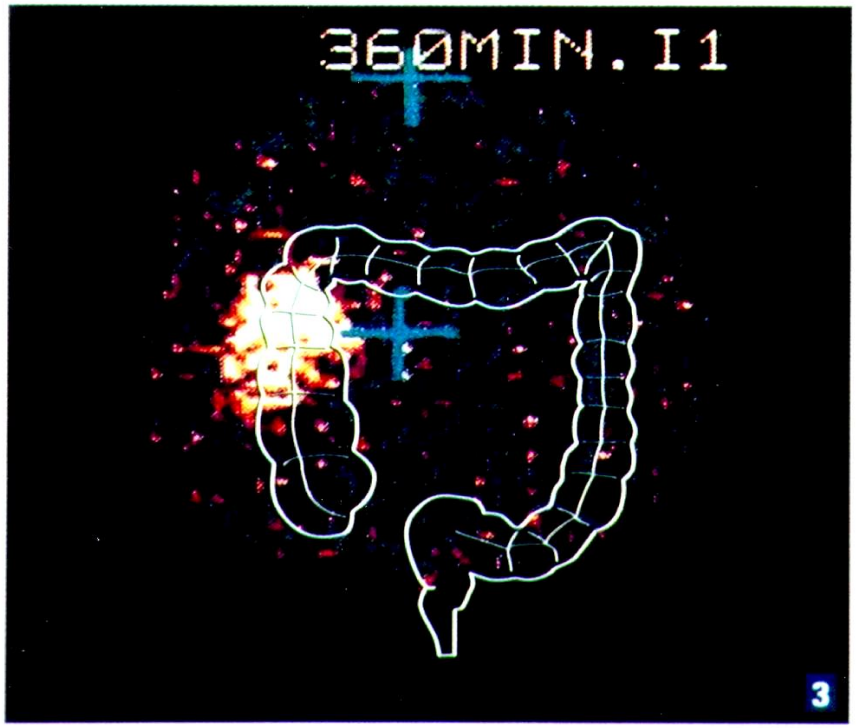
Chronotopic™ System

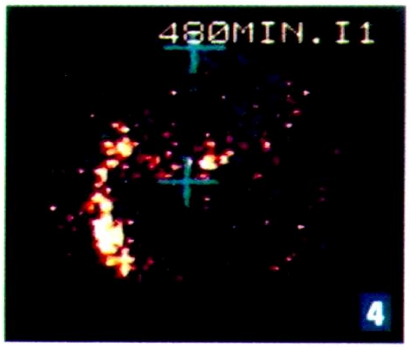
Adapted from Sangalli M.E. et al., J. Control. Release 73, 103 (2001)



Two-layer units (gastroresistant- Eudragit® L)



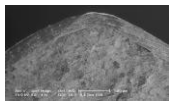




gazza

Chronotopic™ System

Adapted from Sangalli M.E. et al., J. Control. Release 73, 103 (2001)



Two-layer units (gastroresistant- Eudragit® L)

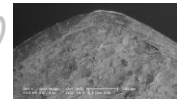
γ-Scintigraphic Data

core: placebo tablet, 6 mm, 160 mg; coating: low-viscosity HPMC (Methocel® E50), coating thickness 1000 μm; 6 healthy volunteers, fasted state

Volunteers	Gastric residence (h)	Small Instestine Transit time (h)	Colon Arrival (h)	Break-up time after gastric emptying (h)	Break-up site
1	1.0	7.0	8.0	7.0	Caecum/Ascending colon
2	2.0	5.0	7.0	6.0	Ascending colon
3	0.5	3.5	4.0	4.5	Caecum/Ascending colon
4	0.5	4.5	5.0	5.5	Ascending colon
5	1.0	4.5	5.5	5.0	Caecum/Ascending colon
6	0.5	5.5	6.0	6.0	Ascending colon
Mean (s.d.)	0.9 (0.5)	5.0 (1.1)	5.5 (1.3)	5.7 (0.8)	

gazza

Adapted from Sangalli M.E. et al., J. Control. Release 73, 103 (2001)

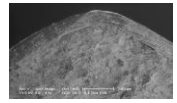


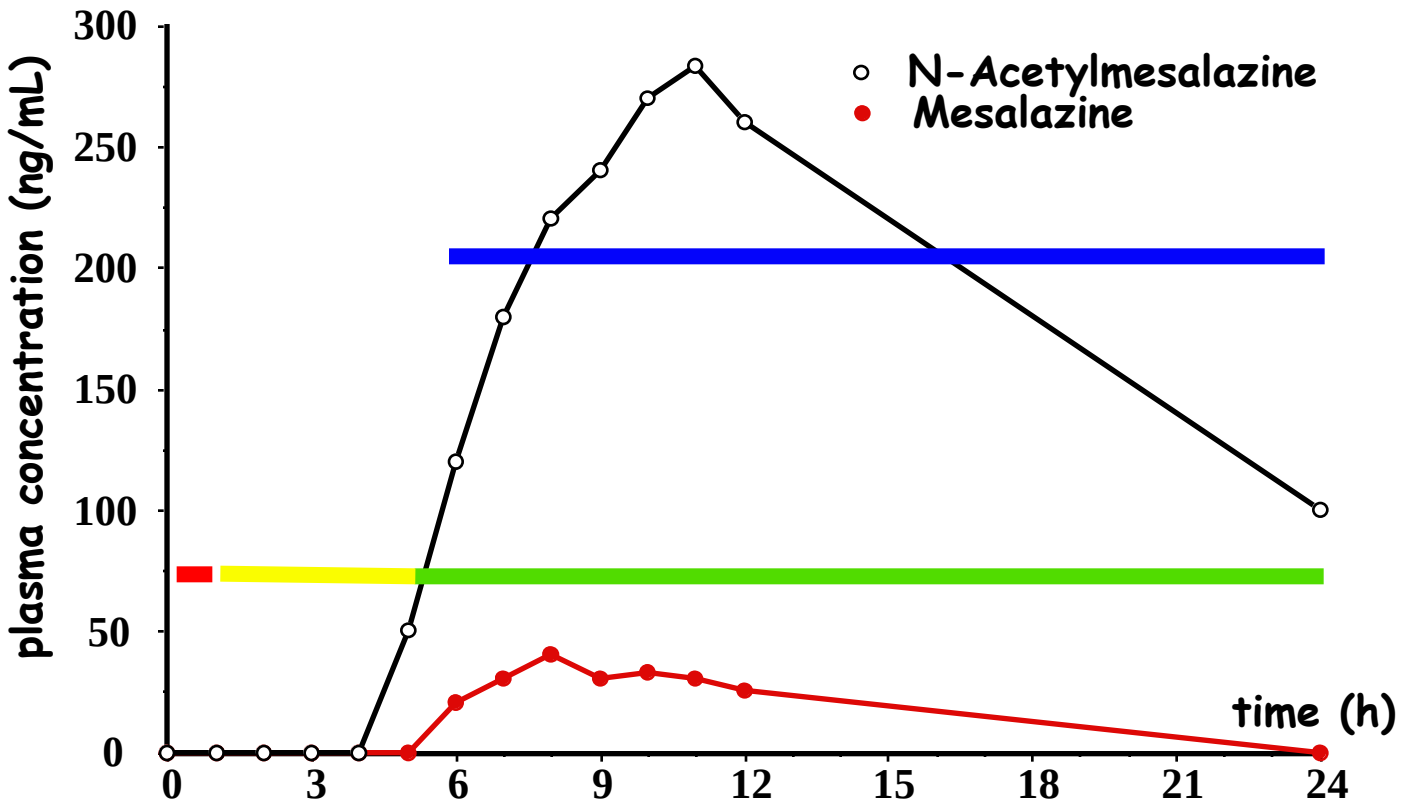
Pharmaco-scintigraphic study on 5-ASA containing Chronotopic™ systems

Model drug:	Mesalazine [5-aminosalicylic acid] (400 mg)
Disintegrating core:	∅ 11 mm, 550 mg
Retarding layer:	Methocel® E50 (weight gain 50%, thickness~1000 μm)
Enteric layer:	Eudragit® L
Spraying equipment:	Fluid bed (Uniglatt, Glatt GmbH)
Volunteers:	6 healthy male (age 29-39)
Images:	1 h intervals in the 0-12 h post-dose period, and then at 24 h.

gazza

fasted state





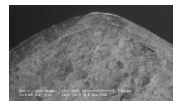
Individual mesalazine and N-acetylmesalazine plasma levels after administration of the Chronotopic® system in the fasted state. Gastric, small intestine, and large bowel residences of the device are indicated as red, yellow, and green lines; disintegration is indicated as the blue line.

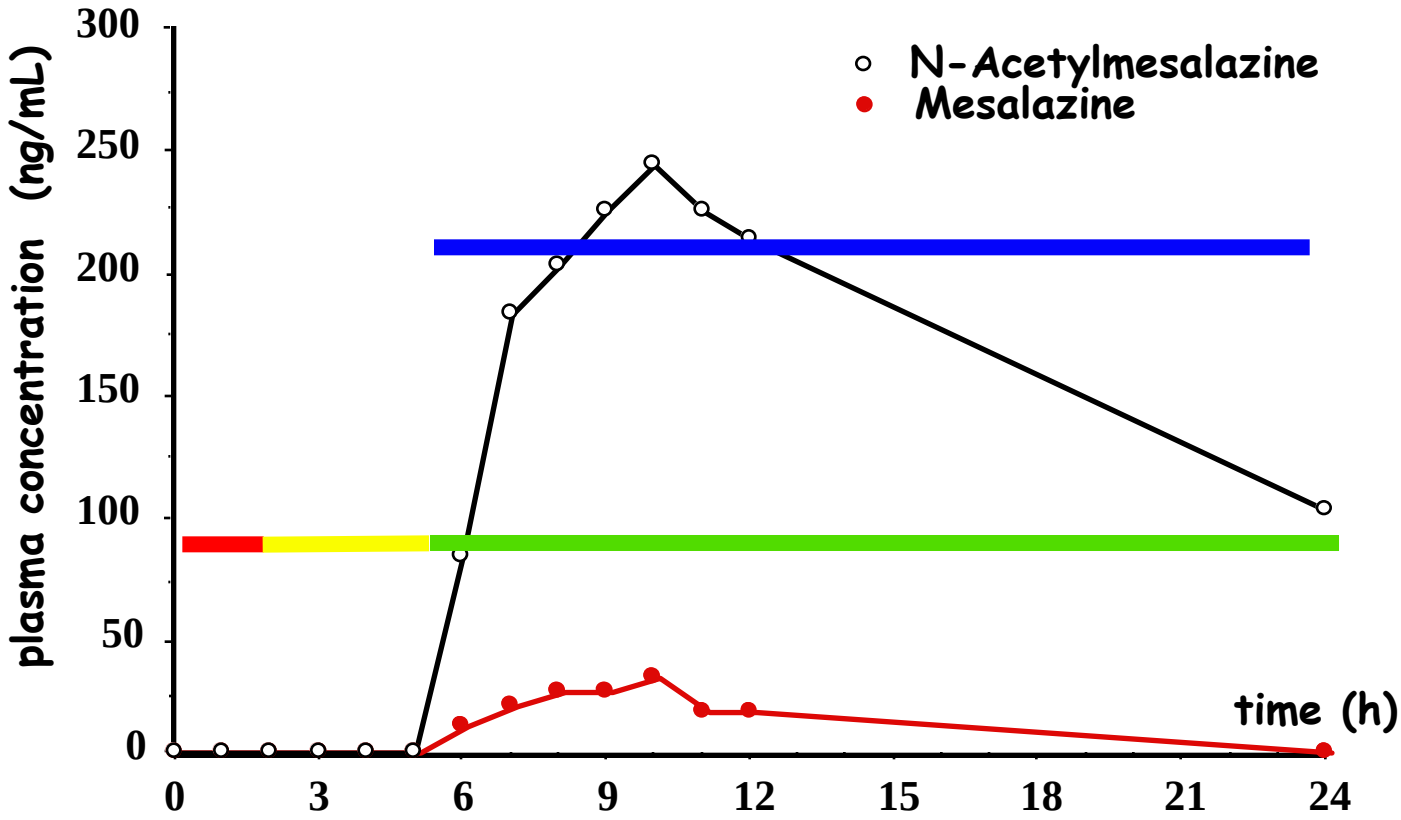
Sangalli M.E. et al., Unpublished Results.

gazza

Chronotopic™ System

fed state





Individual mesalazine and N-acetylmesalazine plasma levels after administration of the Chronotopic® system in the fed state. Gastric, small intestine, and large bowel residences of the device are indicated as red, yellow, and green lines; disintegration is indicated as the blue line.

Sangalli M.E. et al., Unpublished Results.

gazza

Chronotopic™ System

… some criticisms are addressed
to time-dependent approach
to colon targeting,
particularly
with respect to
SITT reproducibility

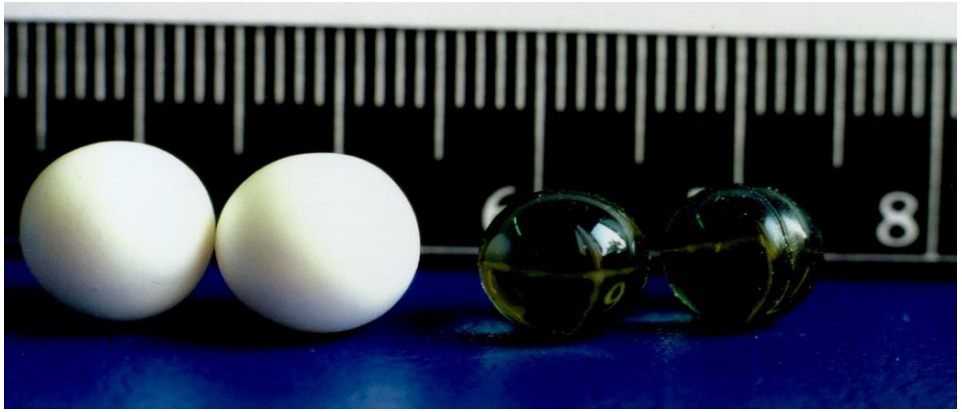
… however, the achievements reported
in literature, in connection with
many different
formulations
and devices,
seem to confirm that, through
time-controlled systems,
colon delivery can be attained.

gazza

Chronotopic™ Technology Platform

Hard and soft gelatin capsules as the core

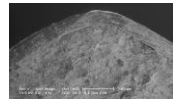
- Line extension
- Possibility of incorporating active principles in liquid or semisolid formulations (suspensions, emulsions, microparticles, microemulsions, pro-liposomes, SMEDDS, SLN …)



important

oral delivery of peptides and proteins

Colon-targeting

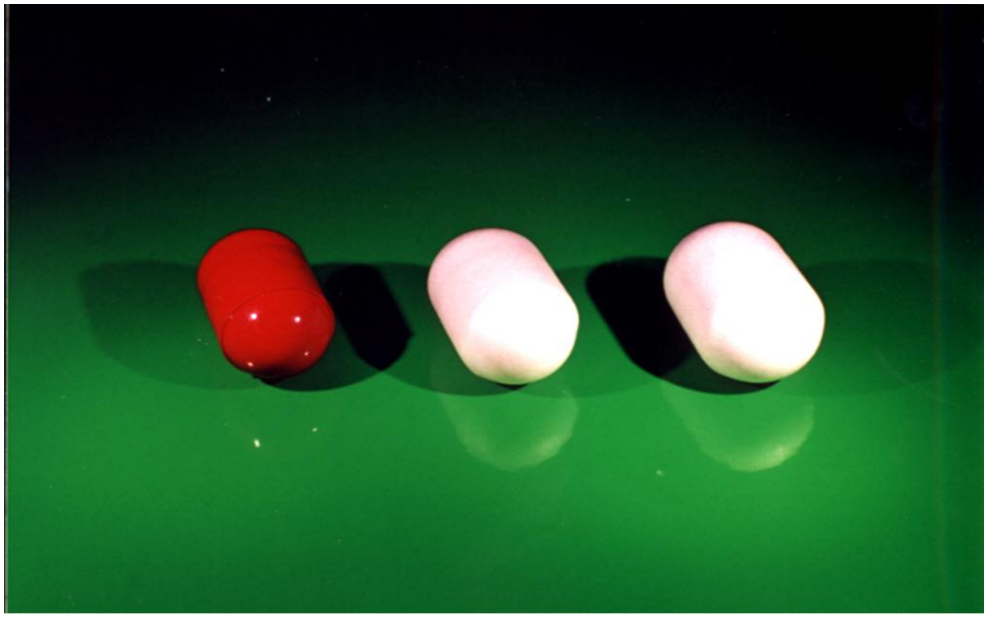


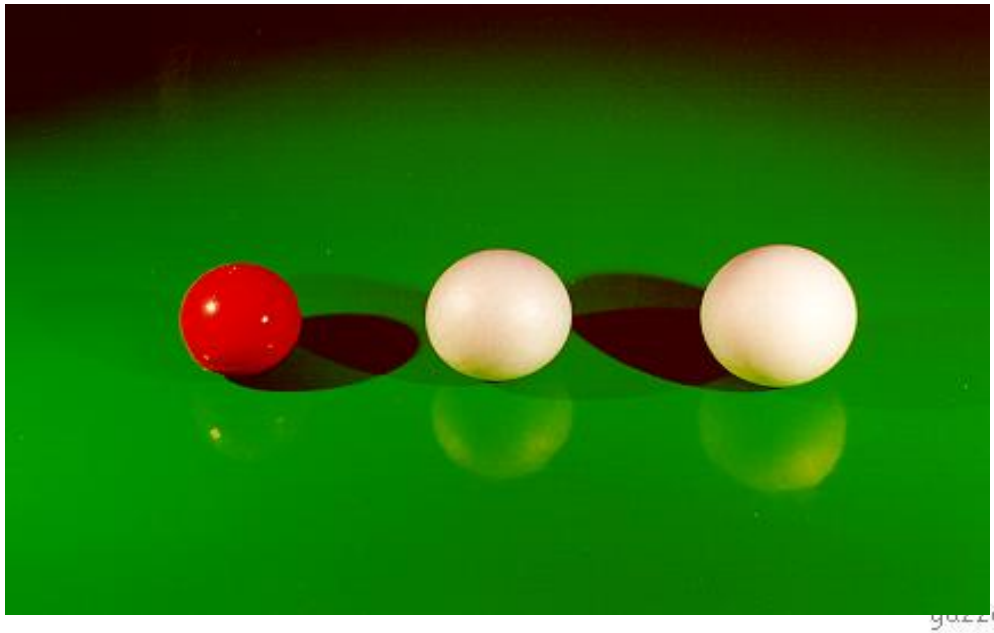
Technological problems of the coating process of gelatine capsules

… TO PREVENT…

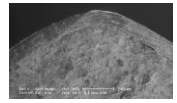
- capsules sticking
  interaction of the gelatin substrate with the aqueous solvent

- volume increase / shrinking of gelatin shells
  operating temperatures



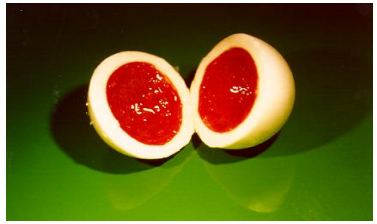


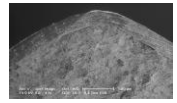
Chronotopic™ Technology Platform



soft gelatin capsules as cores

Chronotopic™ Technology Platform

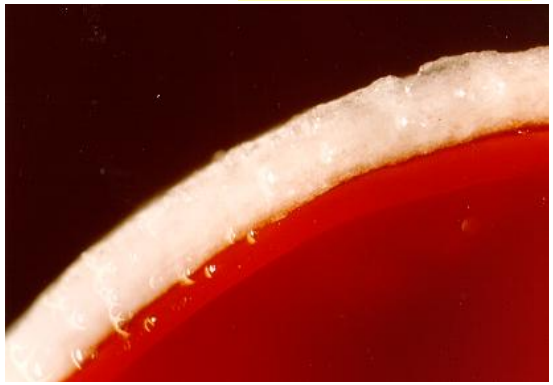




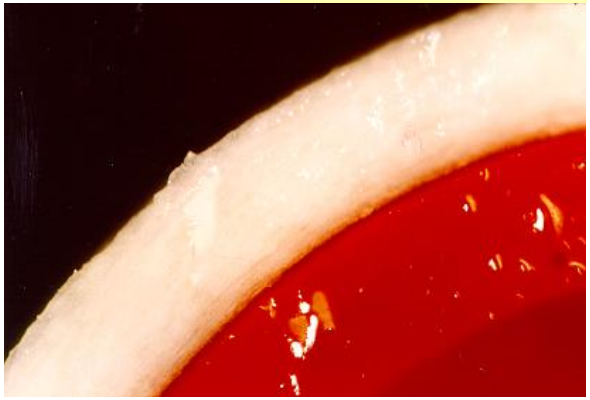
soft gelatin capsules as cores

w.g. 13% - 170 µm

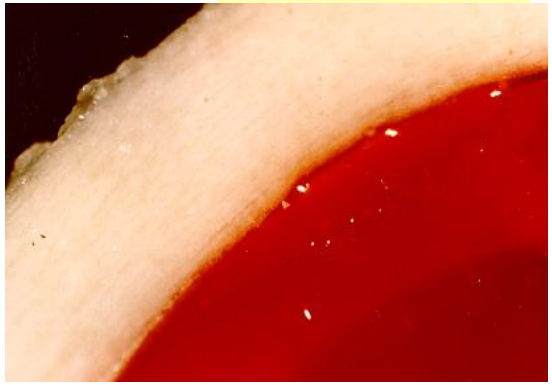
w.g 21% - 315 µm



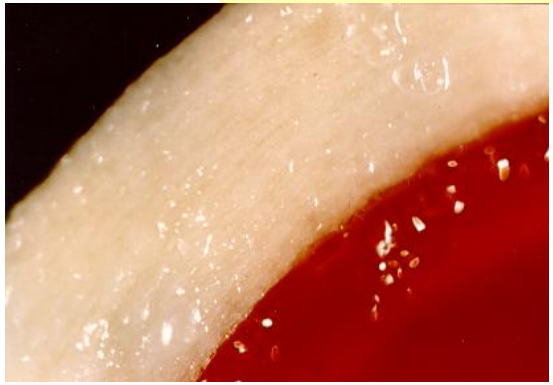
w.g. 51% - 650 µm



w.g. 83% - 950 µm



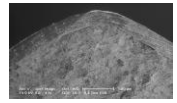
w.g. 103% - 1135 µm



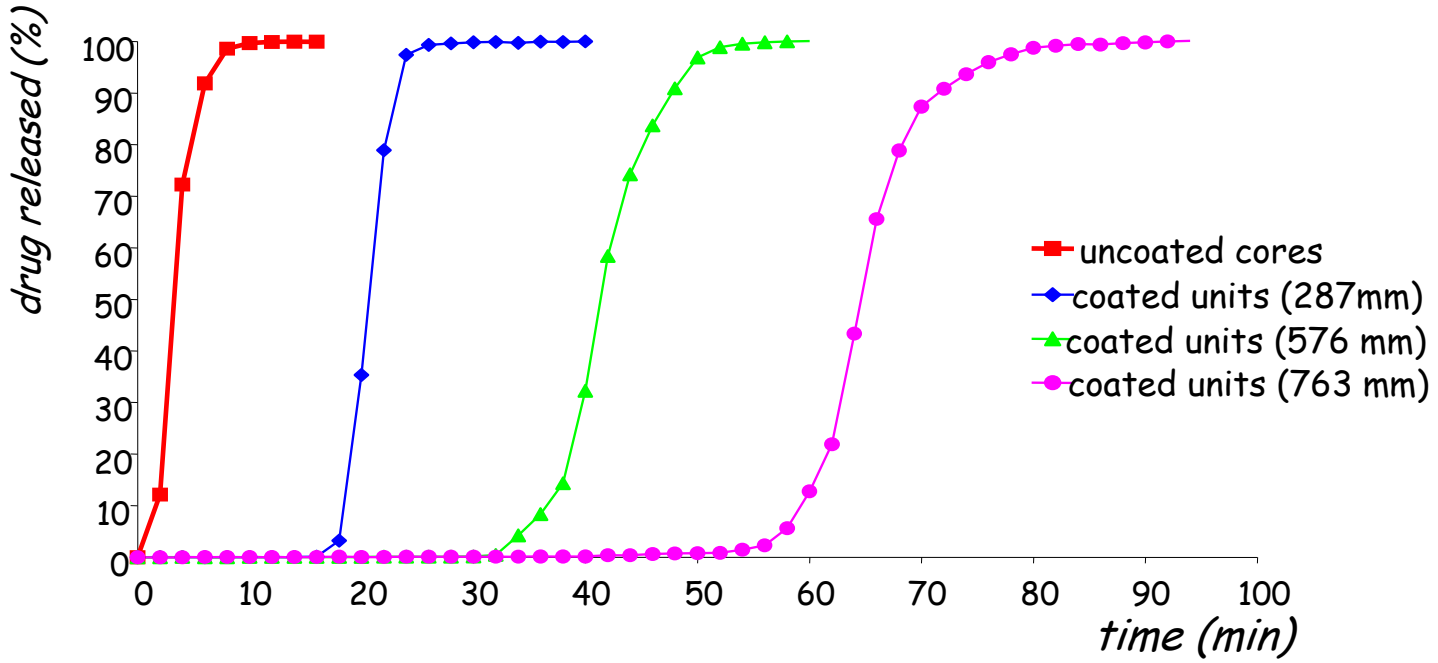
Zema L et al., 4th APGI/APV Meeting, Firenze, 8-11 April 2002

gazza

Chronotopic™ Technology Platform



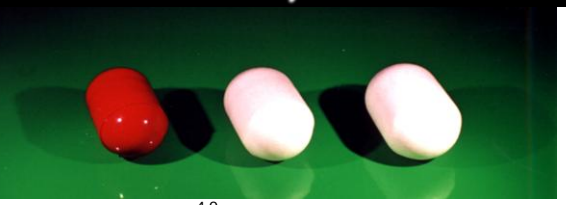
hard gelatin capsules as cores

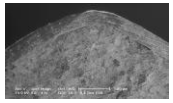


In vitro release profiles of Acetaminophen from uncoated cores and units coated with increasing amounts of Methocel® E50 (CV<15%)

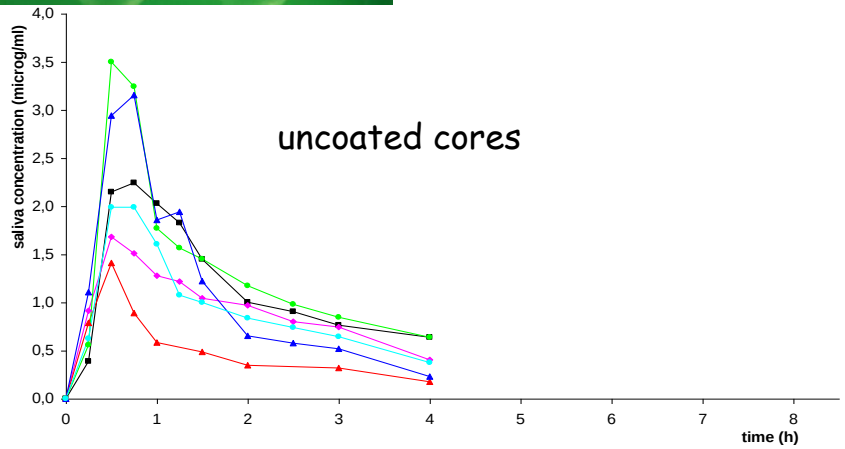
Sangalli M.E. et al., submitted gazza

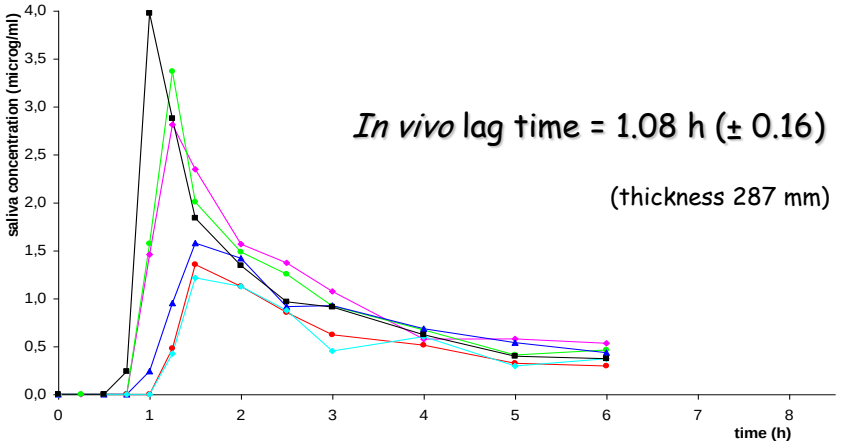
Chronotopic™ Technology Platform

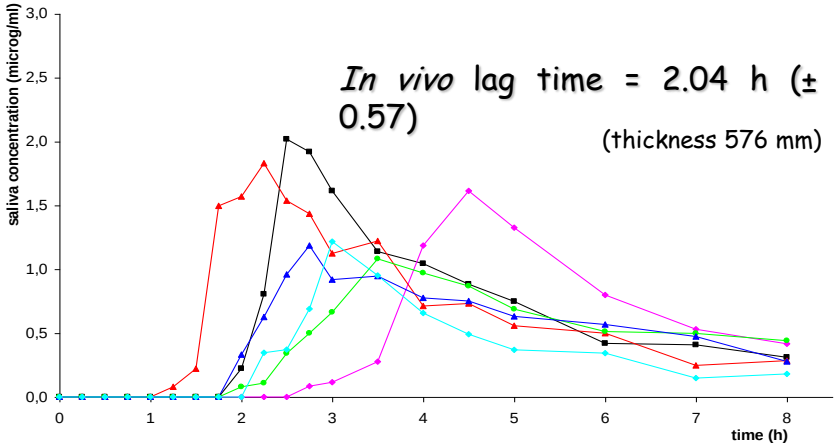


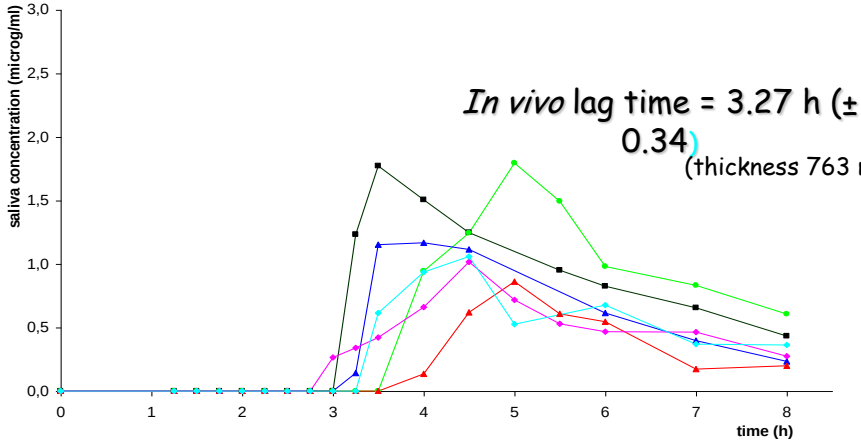


hard gelatin capsules as cores







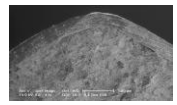


Acetaminophen saliva concentration versus time after oral administration of uncoated cores and units coated with increasing amounts of Methocel® E50 (increasing retarding layer thickness)

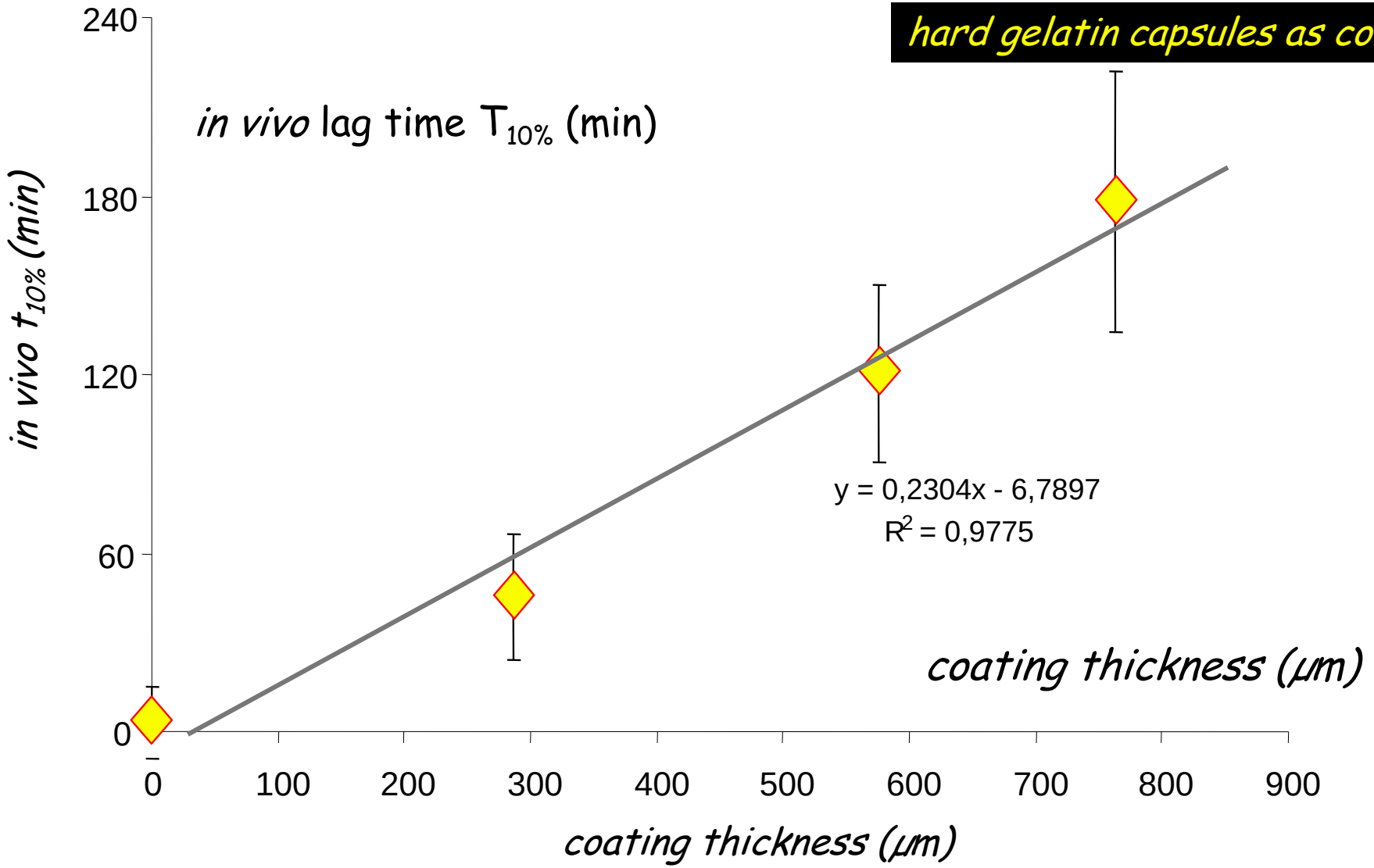
Sangalli M.E. et al., submitted

gazza

Chronotopic™ Technology Platform



hard gelatin capsules as cores

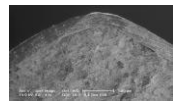


Relationship between in vivo $t_{10\%}$ (time to 10% C_{max}) and coating thickness for hard gelatin capsule-based systems.

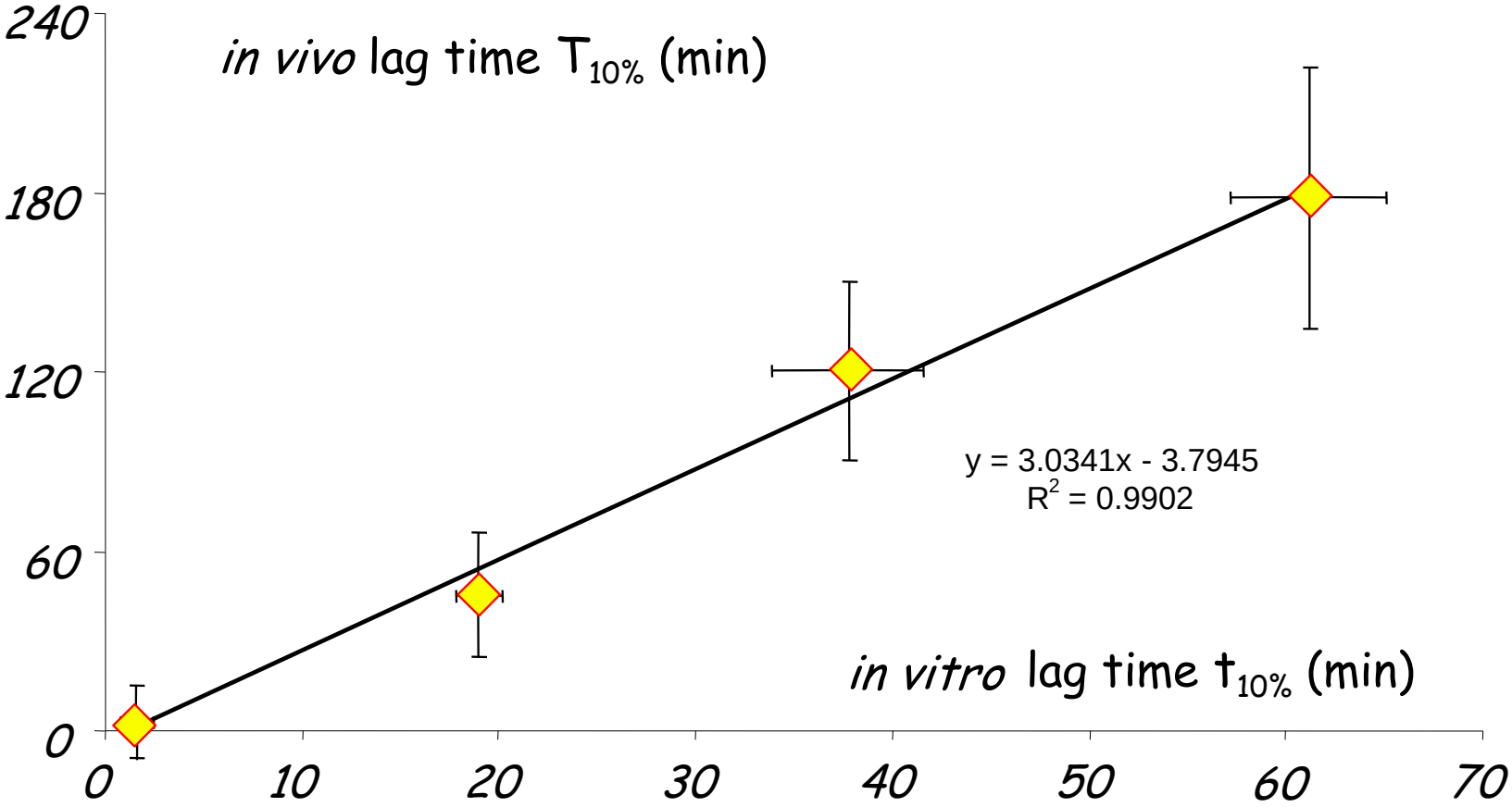
Sangalli M.E. et al., submitted

gazza

Chronotopic™ Technology Platform



hard gelatin capsules as cores

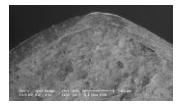


Relationship between in vitro $t_{10\%}$ (time to 10% release of drug labelled content) and in vivo $t_{10\%}$ (time to 10% of C_{max}) for hard gelatin capsule cores and relevant systems with increasing coat thickness. [bars represent s.d.]

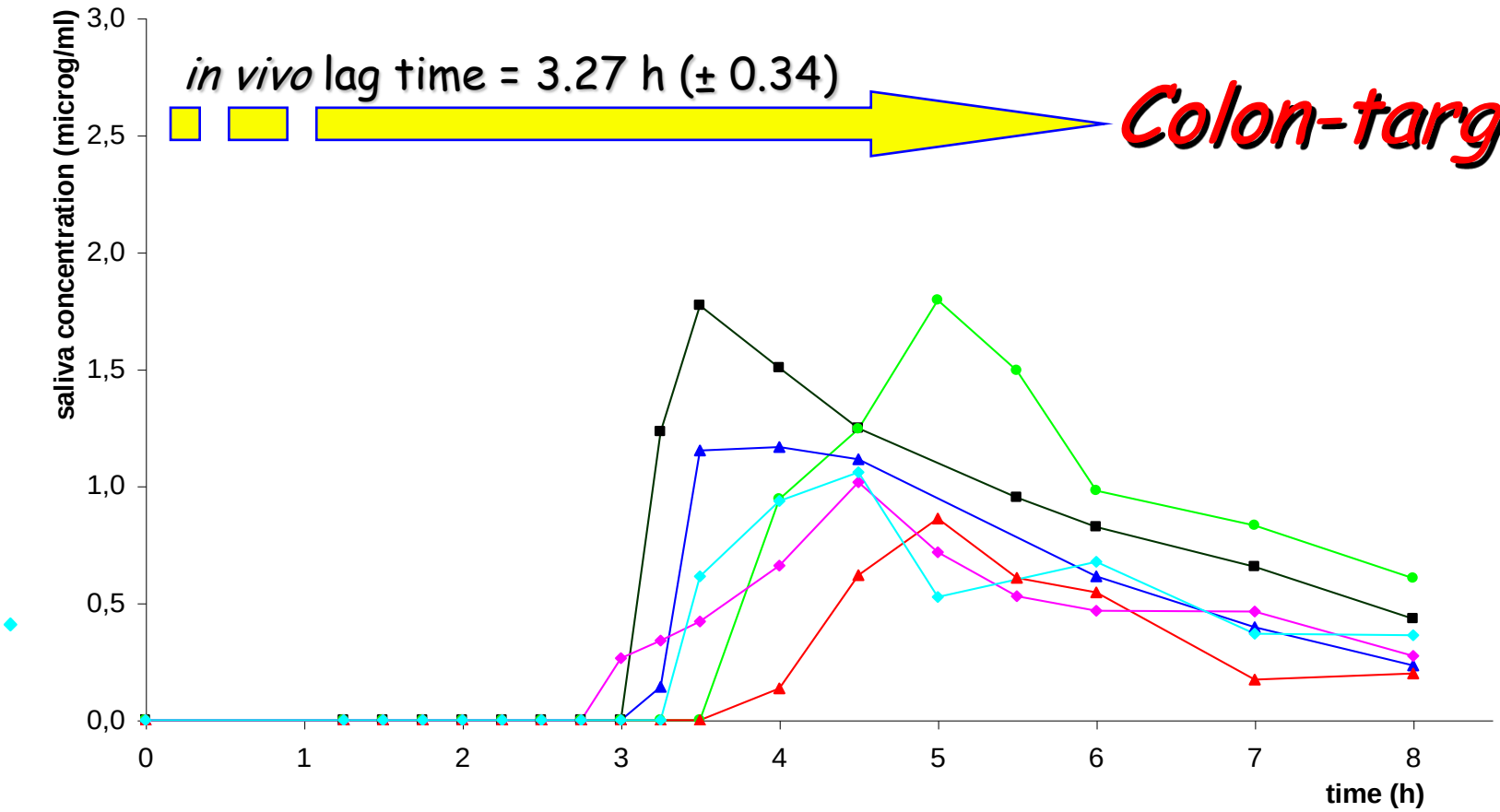
Sangalli M.E. et al., submitted

gazza

Chronotopic™ Technology Platform



hard gelatin capsules as cores



Acetaminophen saliva concentration versus time after oral administration of coated capsules (retarding layer thickness, 763 mm)

Sangalli M.E. et al., submitted

gazza

ChronoCap™

Novel Capsular Pulsatile Device

- *Versatility*
  (ready to use systems with pre-defined performance)

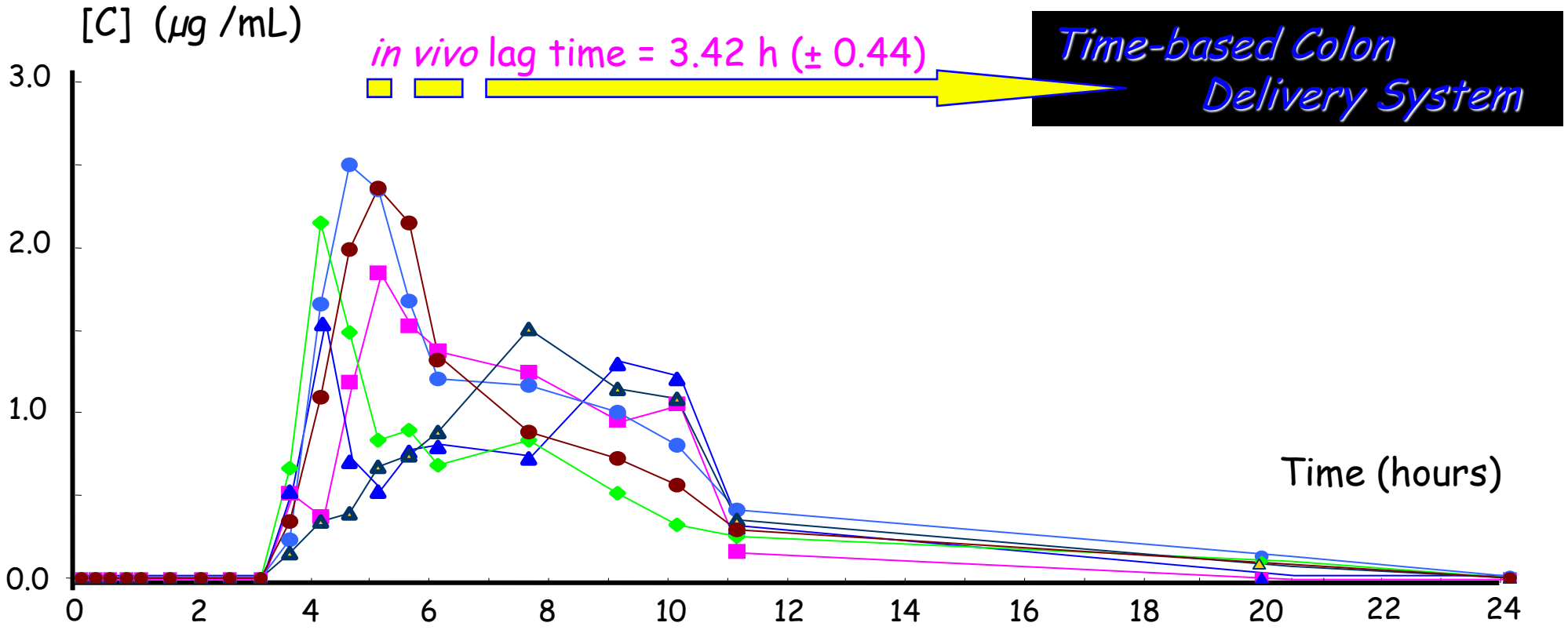
- *Reduced time for pharmaceutical development*
  (limited compatibility and stability study

A Novel Injection-Molded Capsular Device for Oral Pulsatile Delivery Based on Swellable/Erodible Polymers. A. Gazzaniga, et al.- AAPS PharmSciTech 12, 295-303 (2011)

gazza

ChronoCap™

Novel Capsular Pulsatile Device



Acetaminophen saliva concentration versus time after oral administration of ***ChronoCap™*** *units (shell thickness, 1000 µm)*

gazza