UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI SCIENZE DEL FARMACO

Time-Based Approaches to Oral Colon Delivery of Drugs

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Oral Delivery

Time-Controlled Release

Release of drugs after a lag phase of programmable duration

- **Chronotherapy**
  Chronic pathologies with typical night or early-morning peaks (ischemic heart disease, bronchial asthma, rheumatoid arthritis).

- **Multiple daily administration**
  When prolonged release is not viable, because of pharmacokinetic or pharmacodynamic constraints.

- **Antibiotic therapy**
  Alternative strategy in antibiotic therapy, to limit development of resistant bacterial strains.

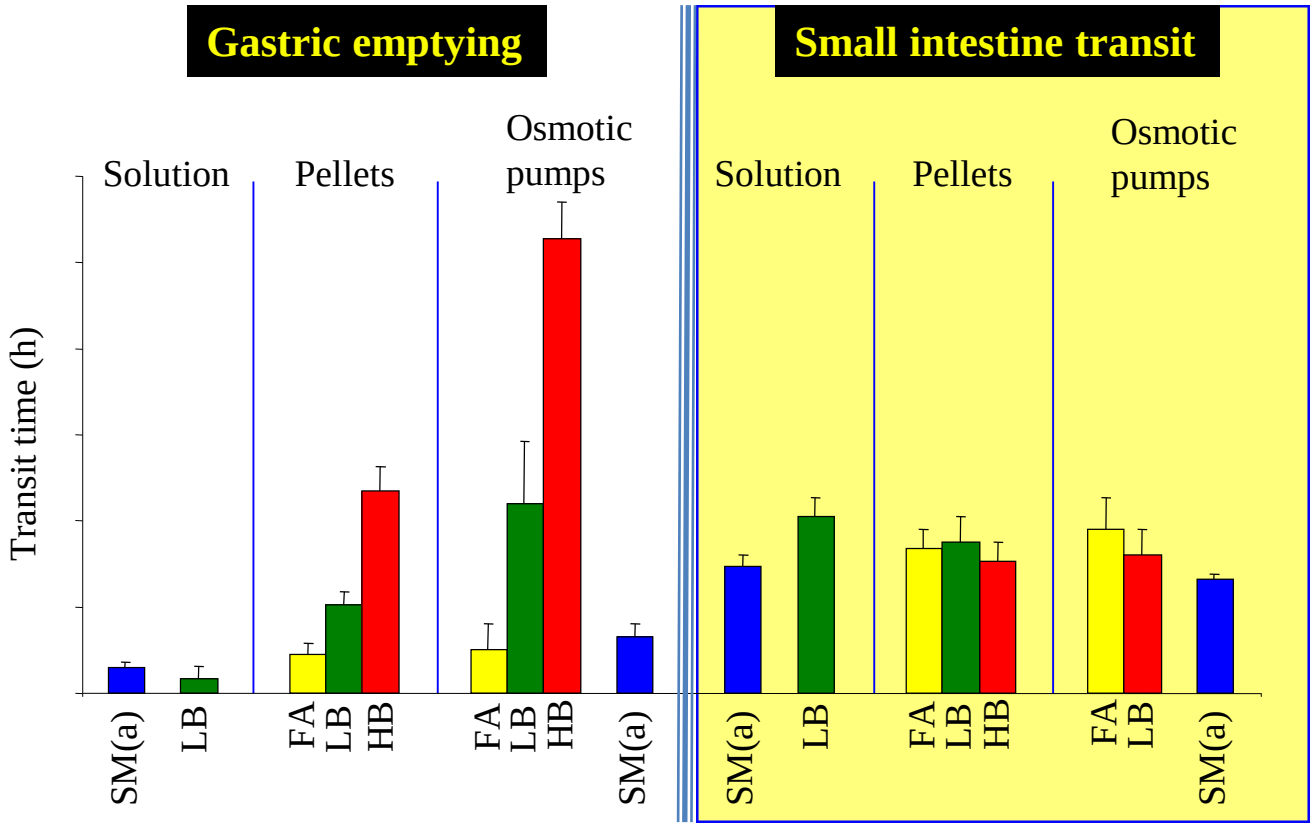
Oral Delivery

Time-Controlled Release

Release of drugs after a lag phase of programmable duration

- **Avoidance of drug interactions in the GI tract**
  In polytherapy, thus enhancing patient convenience and compliance.

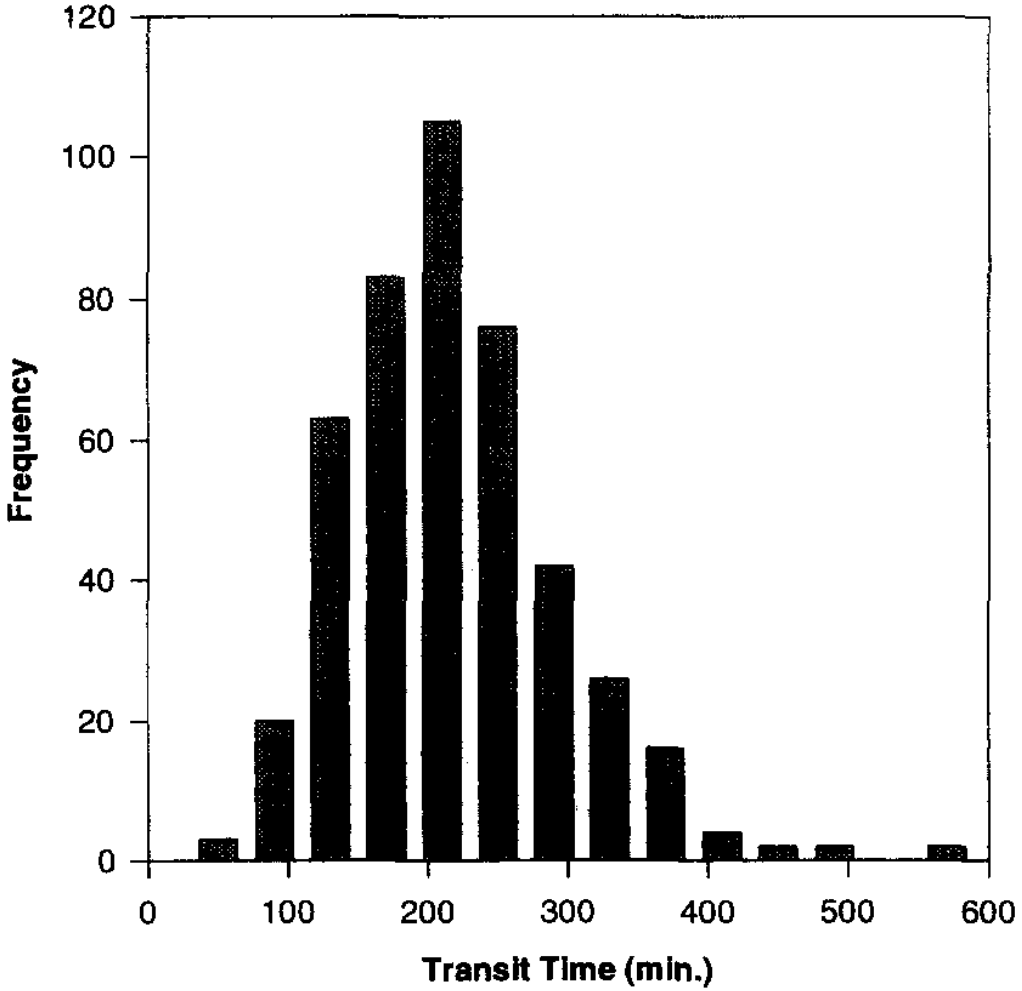
- **Colon delivery**
  Inflammatory Bowel Disease, irritable bowel syndrome, dysbiosis, peptide delivery.



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

Gastric and small intestinal transit time distribution based on the frequency in number (over 150 subjects).

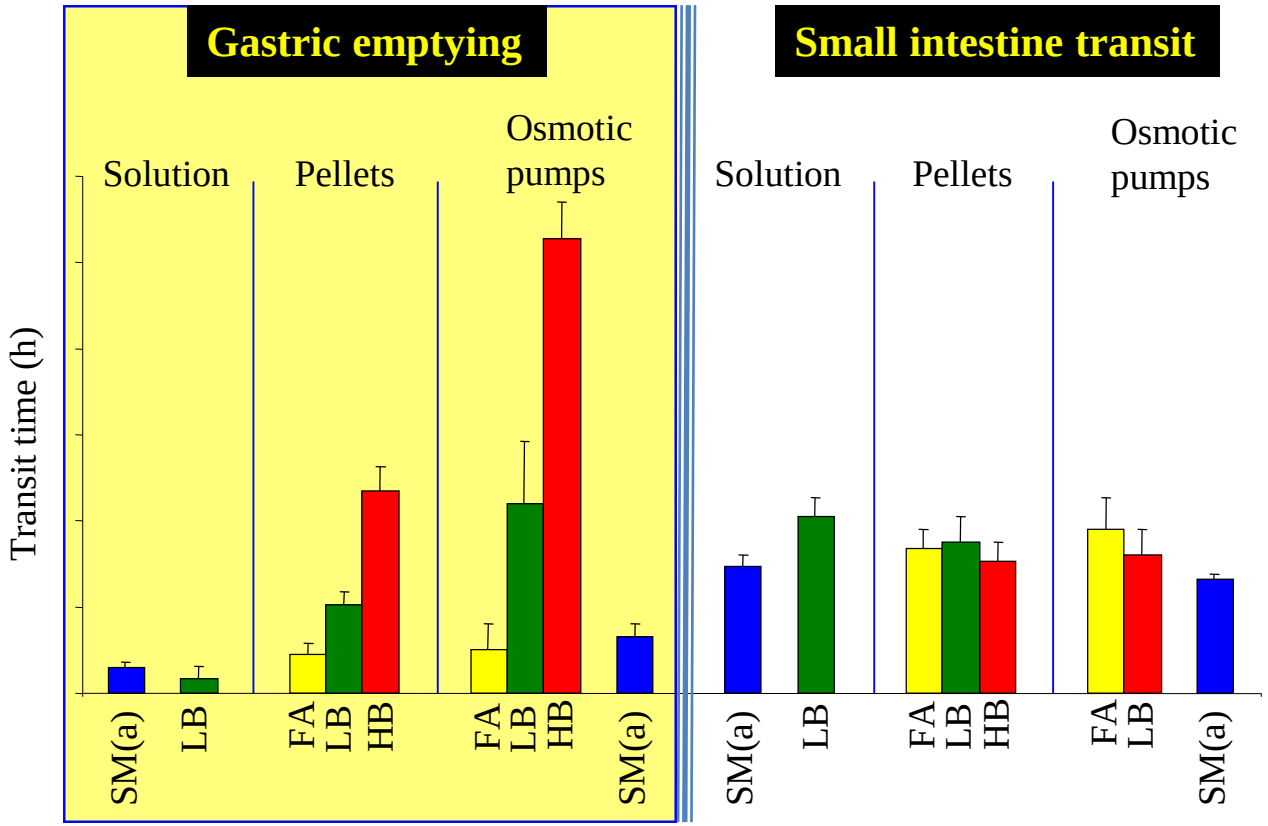
S.S. Davis et al., J. Control. Release 2, 27 (1985)



Mean = 199 min
SD = 78 min
95% CI = 7 min

Small intestinal transit time distribution based on the frequency in number (400 subjects).

L.X. Yu et al., Int. J. Pharm. 140, 111 (1996)



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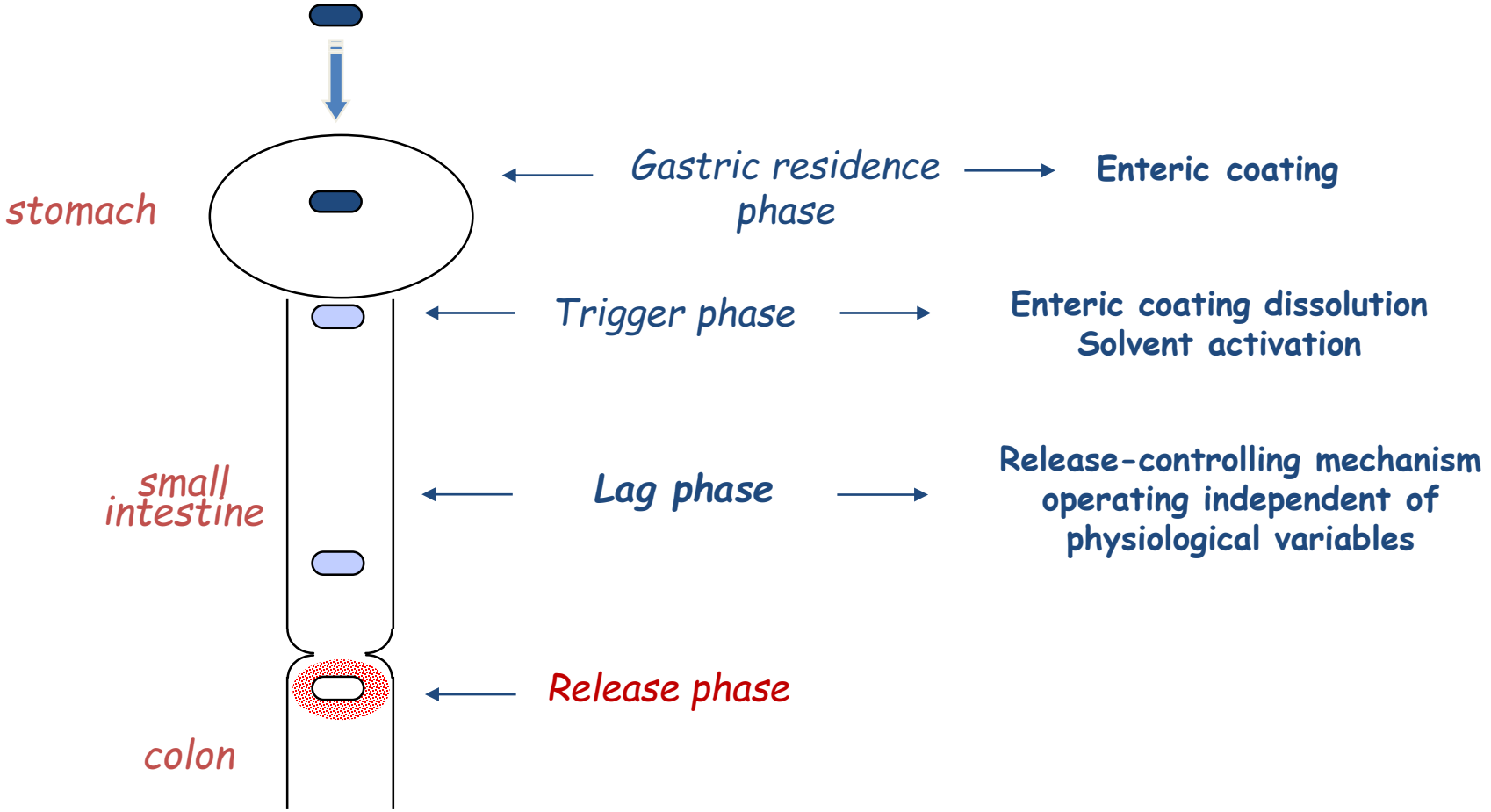
S.S. Davis et al., J. Control. Release 2, 27 (1985)

Time-Controlled Colon Delivery Systems



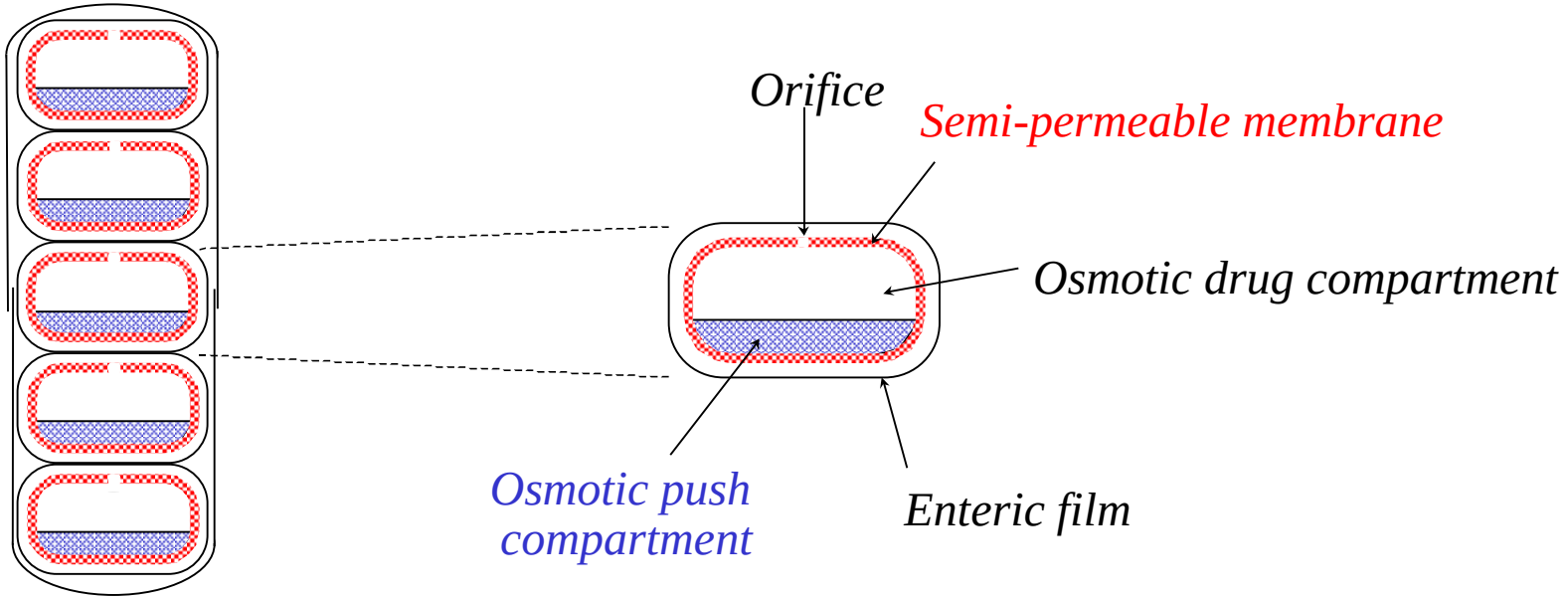
Time-Controlled Colon Delivery Systems

- Osmotic pumps
- Capsular devices with release-controlling plugs
- Reservoir devices with release-controlling coatings

Time-Controlled Colon Delivery Systems

- **Osmotic pumps**
- Capsular devices with release-controlling plugs
- Reservoir devices with release-controlling coatings

Oros-CT®

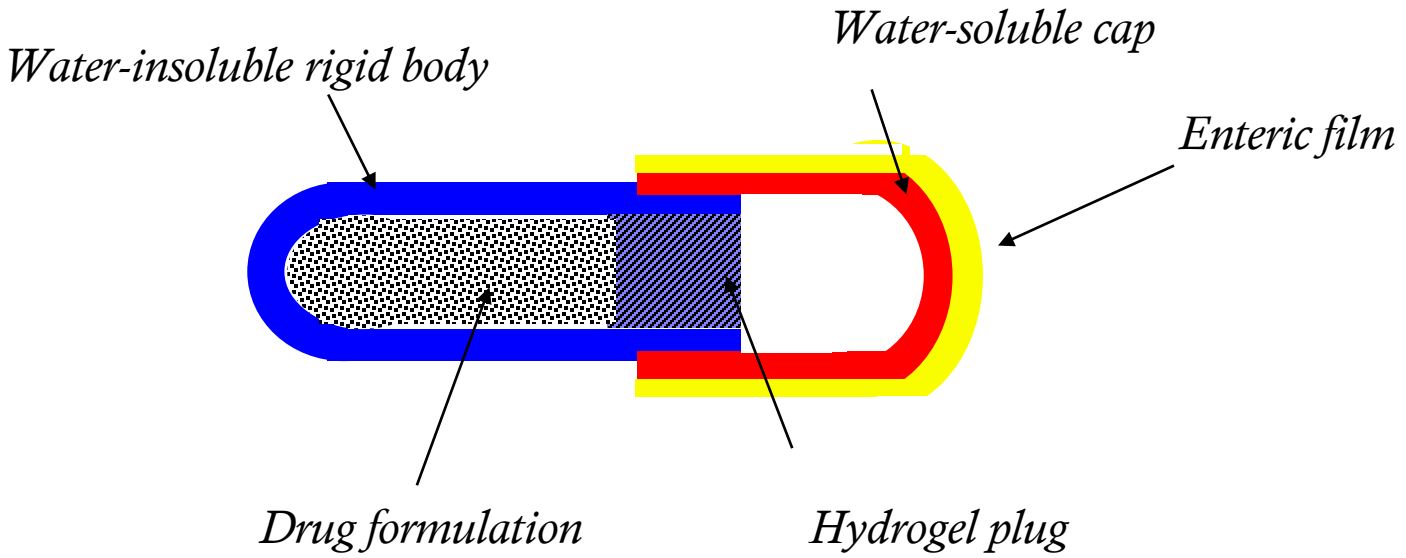


F. Theeuwes et al., US Patent 4,904,474 (1990)

Time-Controlled Colon Delivery Systems

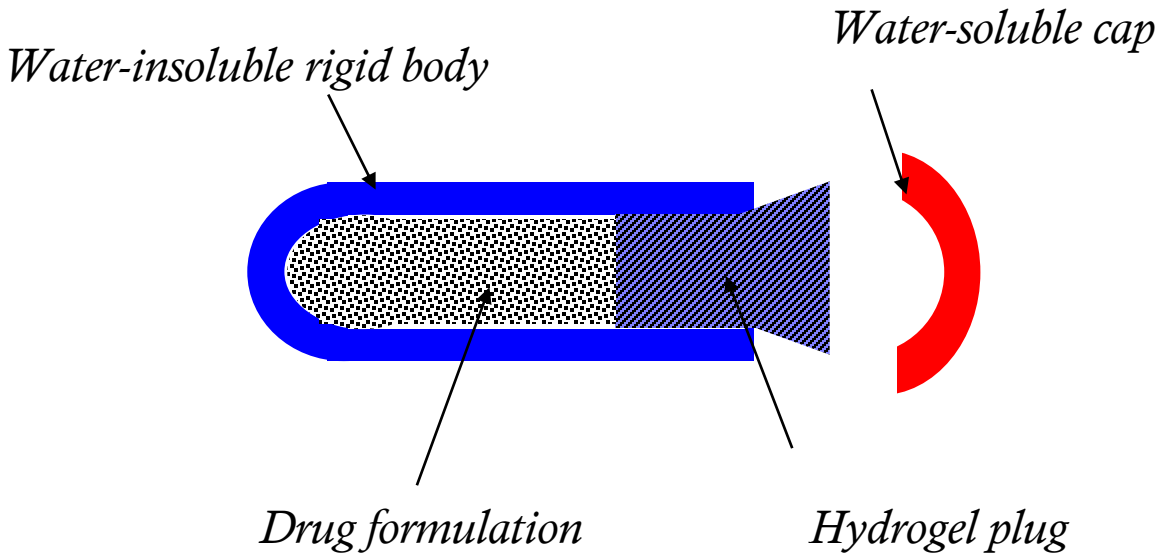
- Osmotic pumps
- **Capsular devices with release-controlling plugs**
- Reservoir devices with release-controlling coatings

Pulsincap™



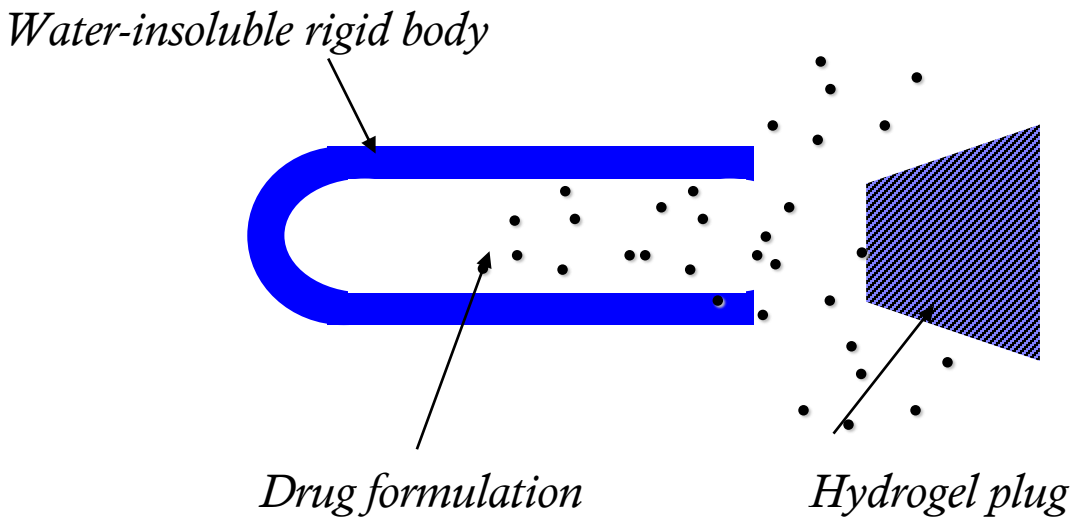
M.E. McNeil et al., WO 90/09168 (1990)

Pulsincap™



M.E. McNeil et al., WO 90/09168 (1990)

Pulsincap™



M.E. McNeil et al., WO 90/09168 (1990)

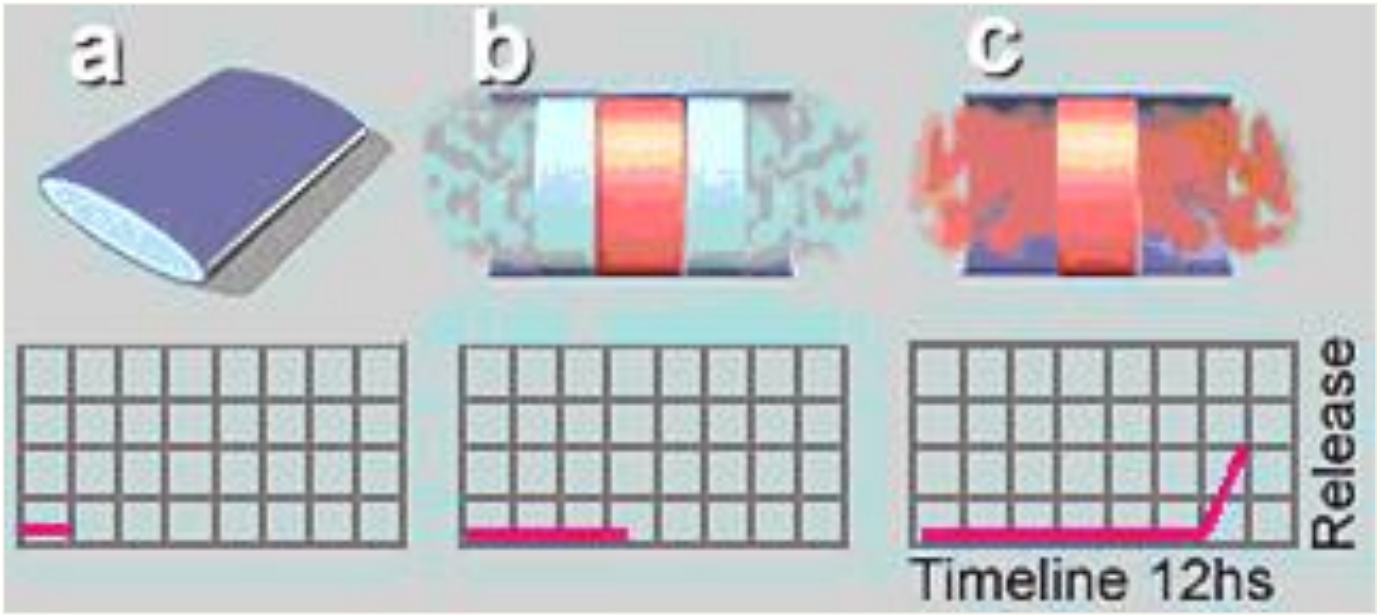
Pulsincap™

Transit and plug separation times (h) of *placebo* units in 6 fasted volunteers

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

C.G.Wilson et al., Drug Deliv. 4, 201 (1997)

Egalet®



W.W. Lee et al., Proceed. Int'l Symp. Control. Rel. Bioact. Mat., 27 (2000)

Egalet®

Transit times (h) and site of release of labeled units in 6 fasted volunteers

Subject	*Gastric emptying*	*Release time*	*Release site*
1	1.00	5.67	**Ascending colon**
2	0.67	6.33	**Ascending colon**
3	0.33	7.00	**Transverse colon**
4	1.67	8.00	**Transverse colon**
5	0.67	5.67	**Ascending colon**
6	0.67	8.00	**Ascending colon**
Mean	0.835	6.78	
SD	0.46	1.07	

W.W. Lee et al., Proceed. Int'l Symp. Control. Rel. Bioact. Mat., 27 (2000)

Time-Controlled Colon Delivery Systems

- Osmotic pumps
- Capsular devices with release-controlling plugs
- **Reservoir devices with release-controlling coatings**

Time-Controlled Colon Delivery Systems

- Osmotic pumps
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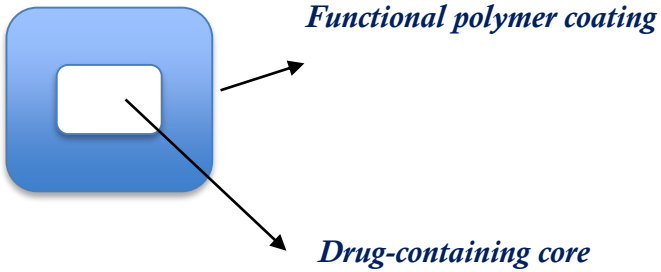
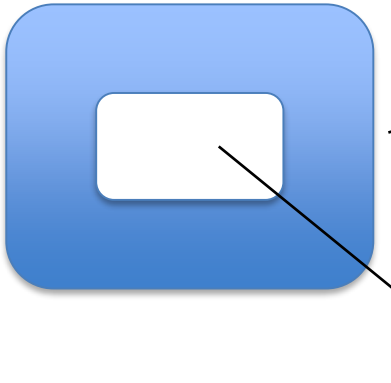


- *Rupturable coatings*
- *Permeable coatings*
- ***Erodible coatings***

Time-Clock®



Erodible coating based on natural waxes (carnauba wax, white beeswax)

Drug-containing tablet

F. Pozzi et al., J. Control. Release 31, 99 (1994)

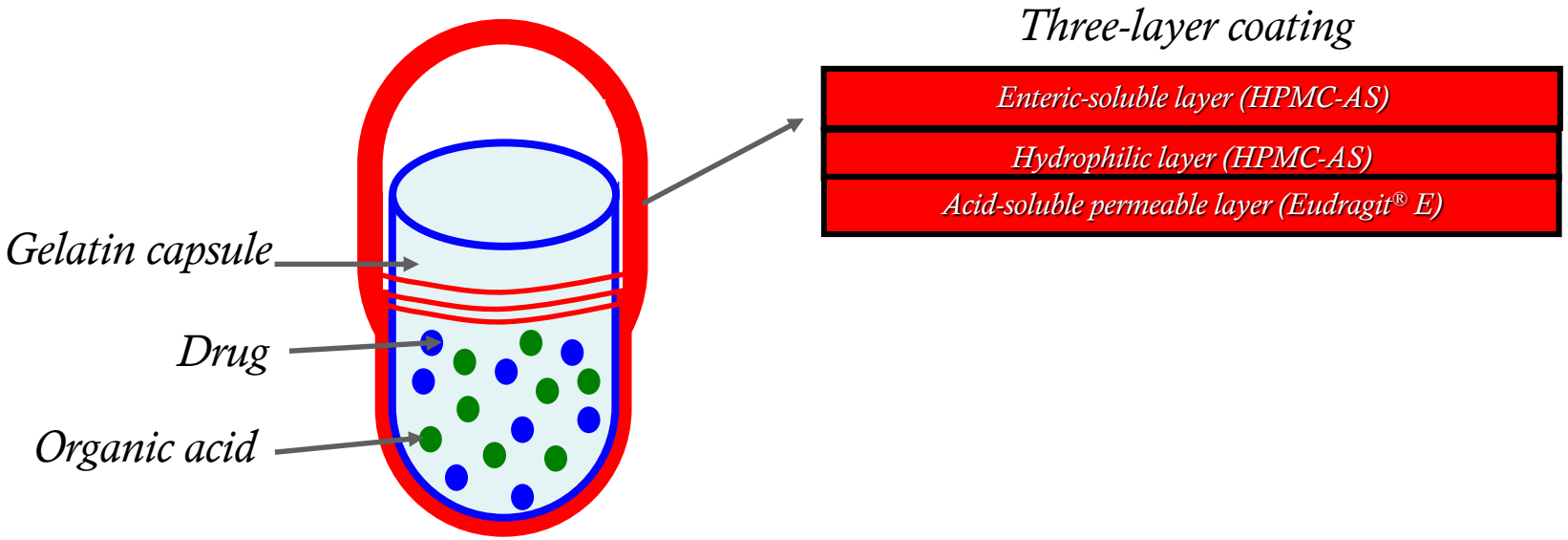
Time-Clock®

Transit and disintegration times (min) of labeled *placebo* units in 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	

I.R. Wilding et al., Int. J. Pharm. 111, 992 (1994)
K.P. Steed et al., J. Control Release 49, 115 (1997)

Colon-Targeted Delivery Capsule (CTDC)



T. Ishibashi et al., Int. J. Pharm. 168, 31 (1998)
T. Ishibashi et a.l, J. Pharm. Sci. 87, 531 (1998)

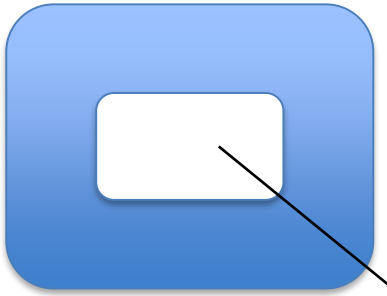
Colon-Targeted Delivery Capsule (CTDC)

Time and site of disintegration of *placebo* CTDC in 8 fasting volunteers

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*	

T. Ishibashi et a.l, J. Pharm. Sci. 87, 531 (1998)

Chronotopic™

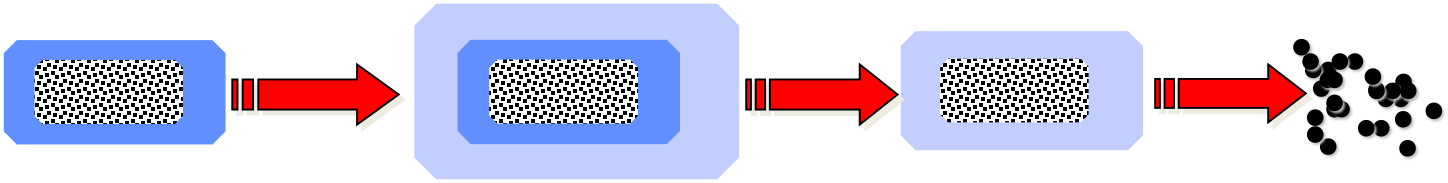


Swellable / erodible hydrophilic coating (low-viscosity HPMC)

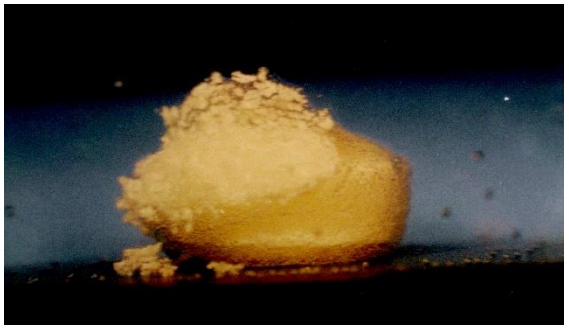
Drug-containing core (tablets, capsules, minitablets)

A. Gazzaniga et al., Boll Chim. Farm. 132, 78 (1993)

Chronotopic™

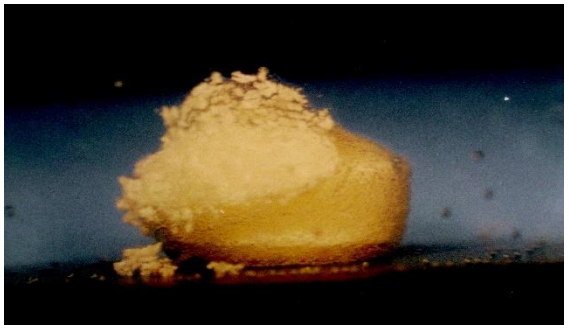


glassy rubbery
drug particles



Chronotopic™

- Physico-chemical properties of the polymer
- Coating level
- Manufacturing technique



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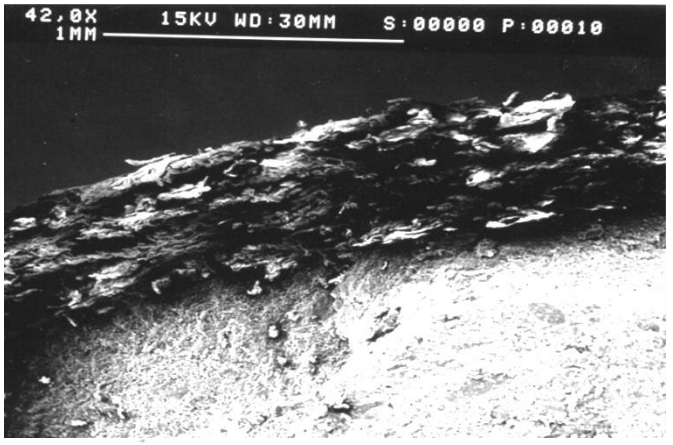
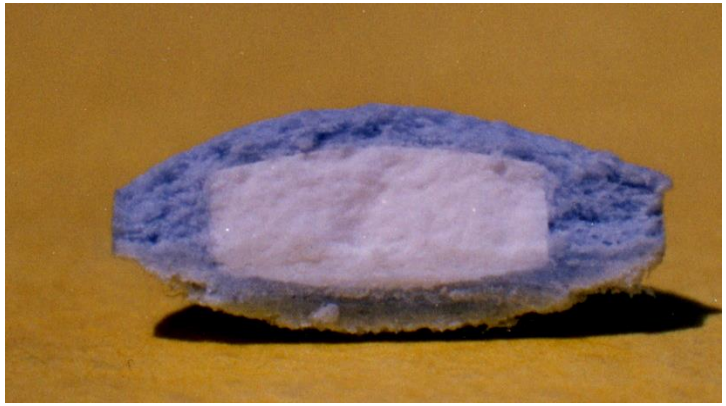
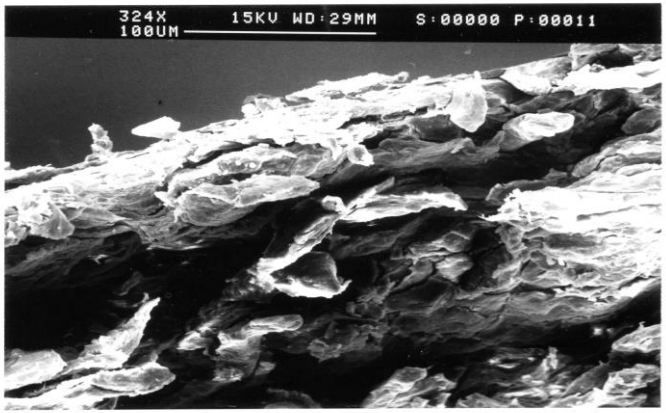
Double-compression







A. Gazzaniga et al., Eur. J. Pharm. Biopharm. 40, 246 (1994)

Chronotopic™

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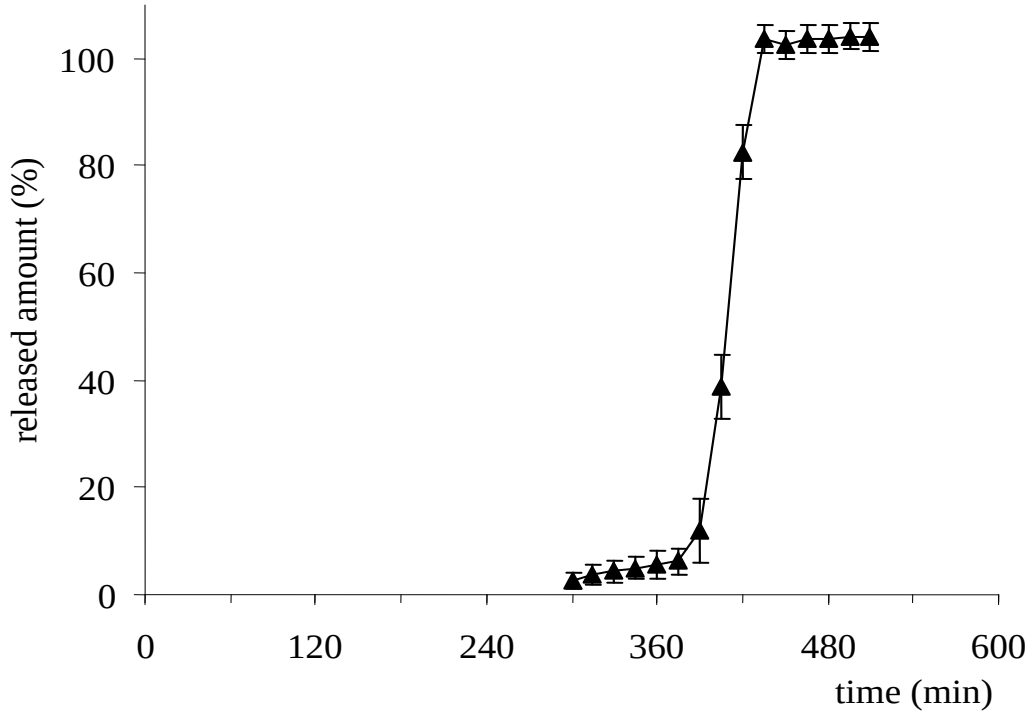


Mean verapamil HCl release profiles from Methocel® K100 LV-coated systems with 150% weight gain (paddle apparatus, 900 ml distilled water, 37±0.5°C, 50 rpm, 278 nm UV detection, n=6).

A. Gazzaniga et al., Eur. J. Pharm. Biopharm. 40, 246 (1994)

Chronotopic™

Film-coating *(hydro-organic)*

- Scalability
- Broad range of viable core formulations (large tablets, gelatin capsules, multiple units)

- Limited technical background available
- Low-viscosity polymer grades applied as thin protective, taste-masking or cosmetic films
  (5 mPa.s of 2% w/V solutions at 20 °C)

Methocel® K4M, Methocel® K15M

Viscosity of 4000 mPa·s and 15000 mPa·s, respectively, of 2% w/V solutions at 20 °C

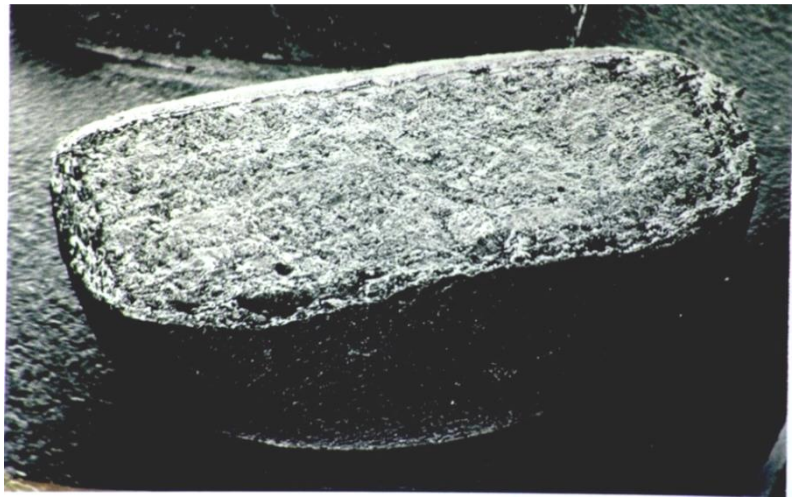
Suitable for delays in the order of hours without involving excessive coat thickness

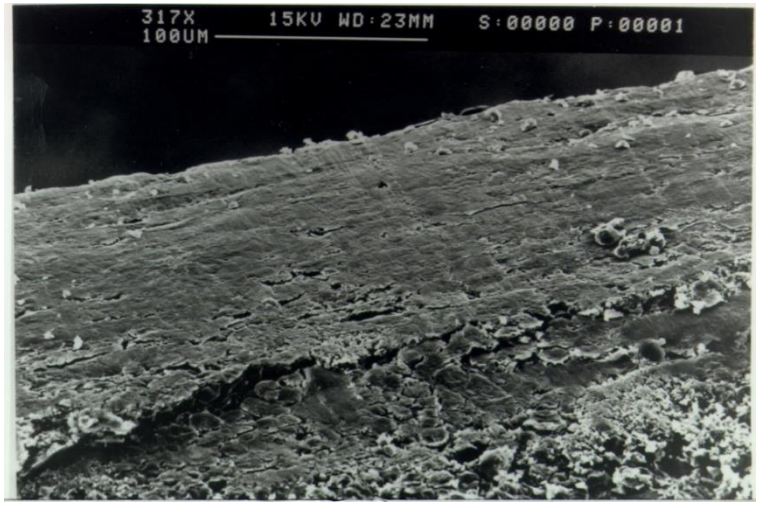
Ethanol/Water ~ 92:8, polymer concentration ~ 5 %

To counteract the thickening effect of the polymers upon hydration expected to hinder nebulization

Chronotopic™

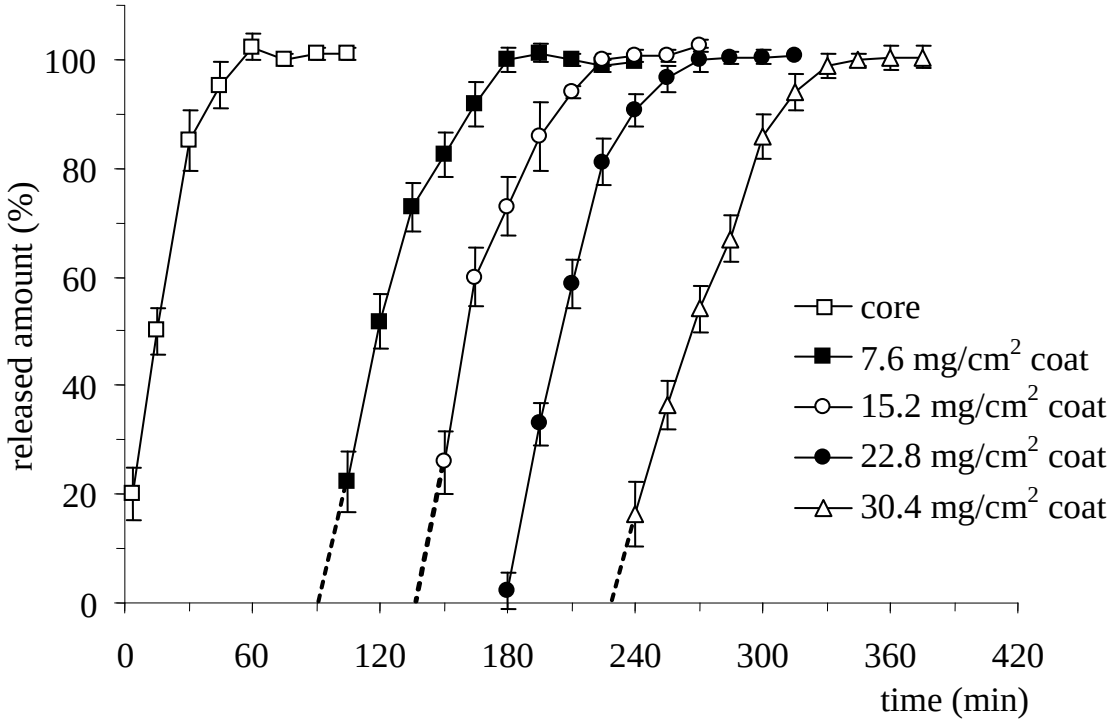
Film-coating *(hydro-organic)*





Chronotopic™

Film-coating *(hydro-organic)*

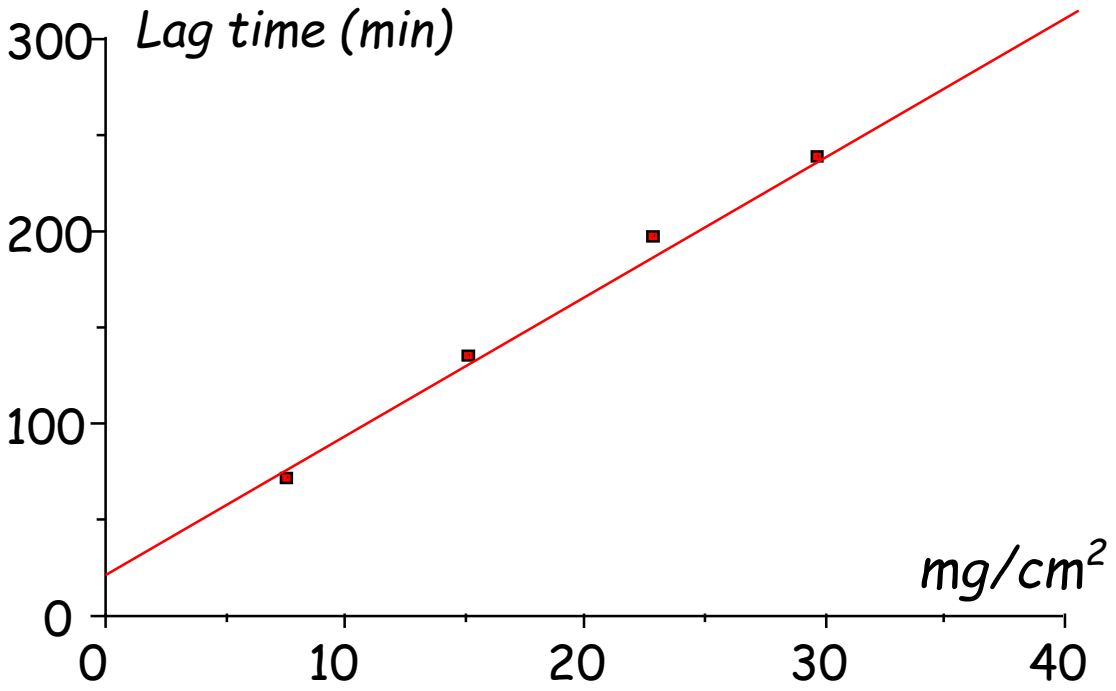


Mean indomethacin release profiles from Methocel® K15M-coated systems with coating levels increasing in the 9-36% weight gain range (paddle apparatus, 900 ml simulated intestinal fluid, 37±0.5°C, 50 rpm, 318 nm UV detection, n=6).

A. Gazzaniga et al., Eur. J. Pharm. Biopharm. 40, 246 (1994)

Chronotopic™

Film-coating *(hydro-organic)*



Relationship between coating level and in vitro lag time from Methocel® K15M-coated systems.

A. Gazzaniga et al., Eur. J. Pharm. Biopharm. 40, 246 (1994)

Chronotopic™

Film-coating *(aqueous)*

Methocel® E5, Methocel® E50, Methocel® K4M

Viscosity of 5 mPa·s, 50 mPa·s, 4000 mPa·s, respectively, of 2% w/V solutions at 20 °C

Coting level

20% weight gain

Polymer concentration in the aqueous coating solutions

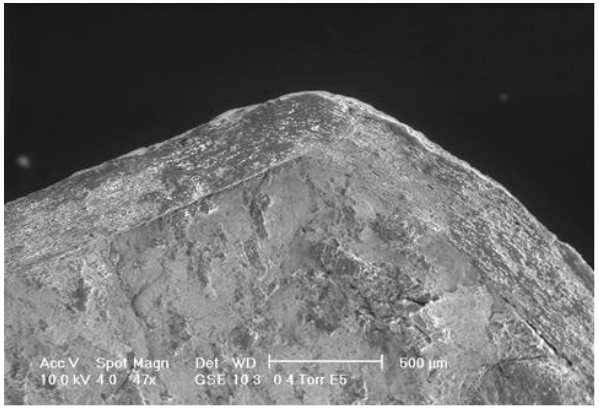
16%, 8%, 2% for Methocel® E5, Methocel® E50, Methocel® K4M, respectively

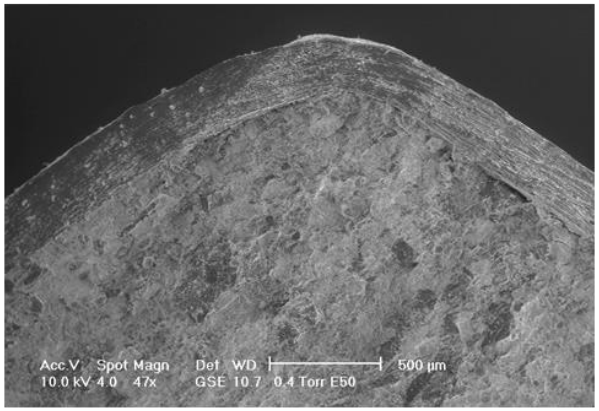
Attentive set-up of process parameters

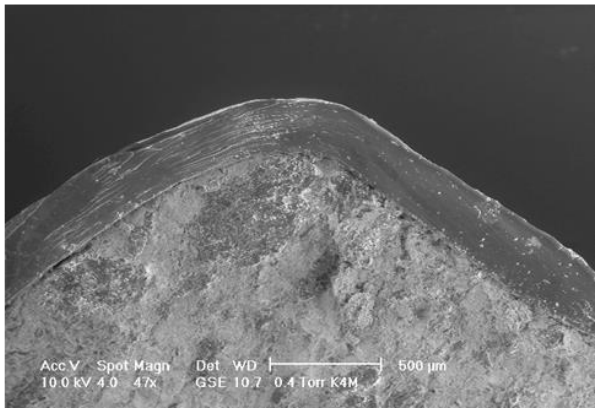
to avoid technical problems (nozzle clogging, powdering, long processing)

Chronotopic™

Film-coating *(aqueous)*



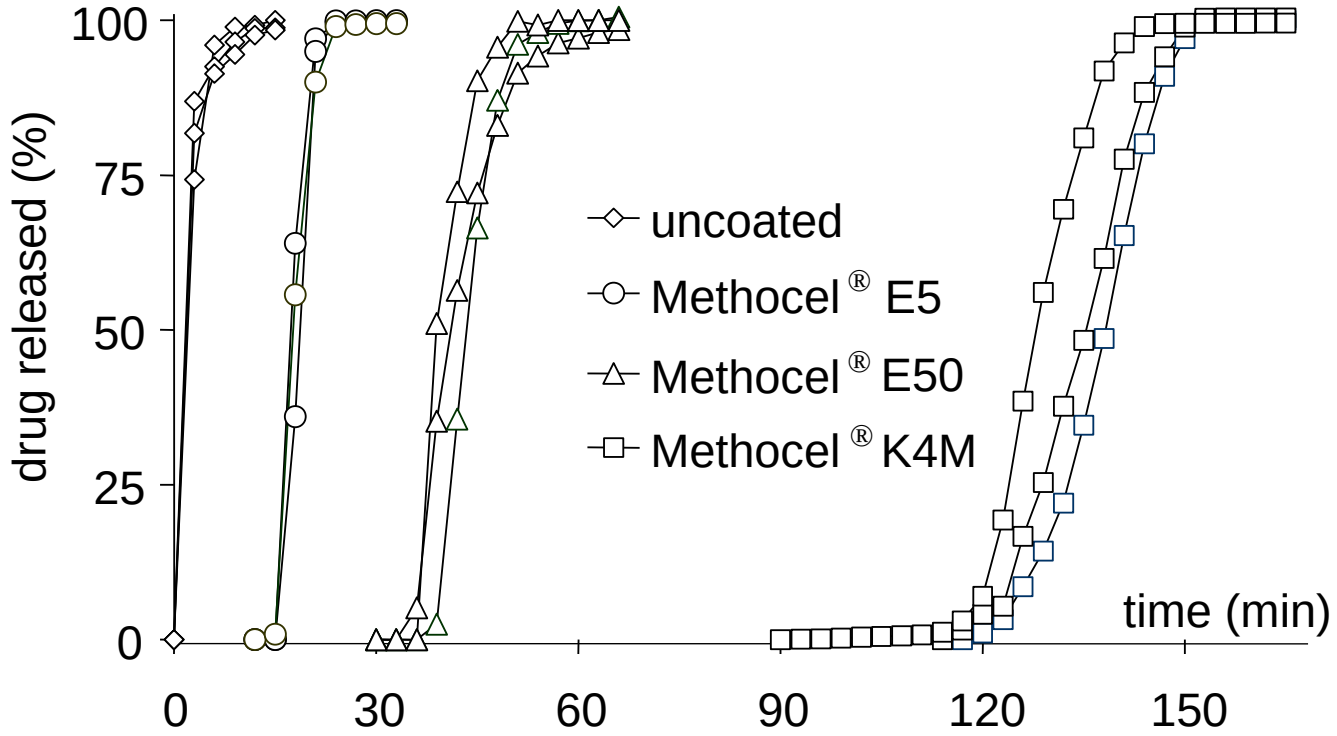




M. E. Sangalli et al., Eur. J. Pharm. Sci. ***22****, 469 (2004)*

Chronotopic™

Film-coating *(aqueous)*

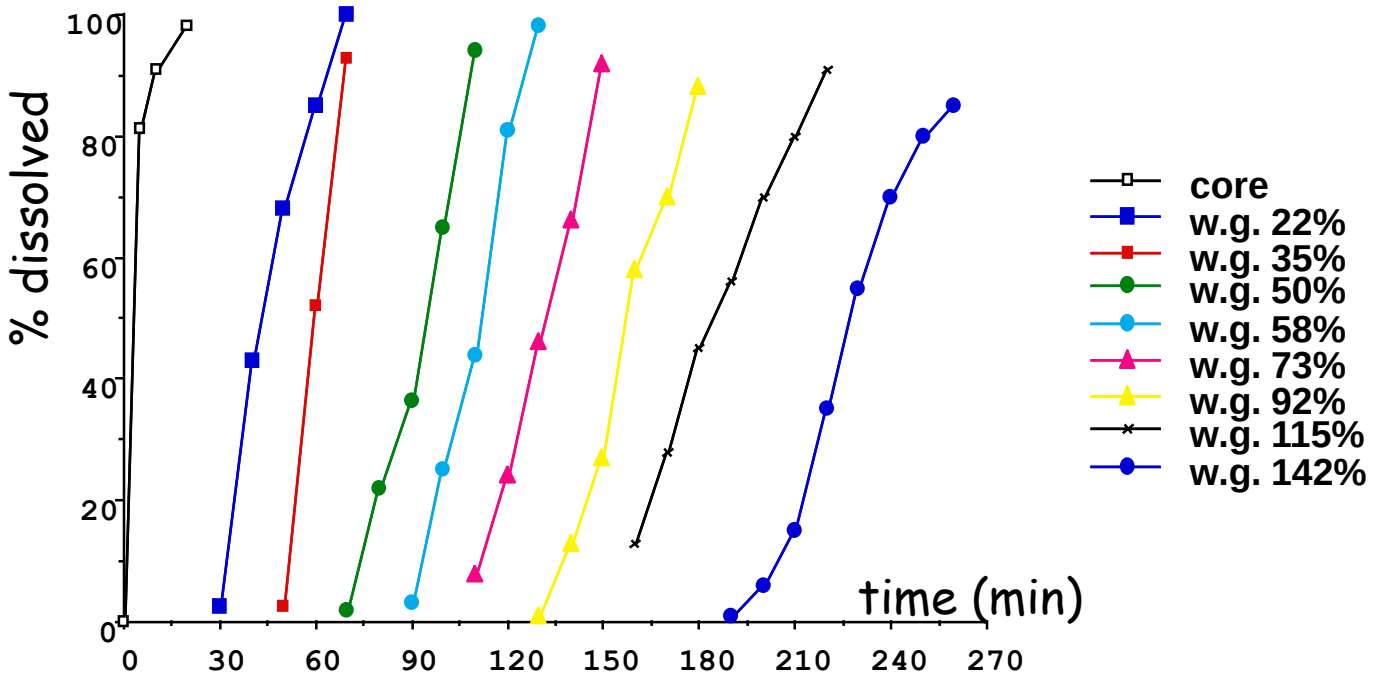


Paracetamol release profiles from systems coated with Methocel® E5, E50 and K4M up to 20% weight gain (modified disintegration apparatus, 900 mL distilled water, 37±0.5°C, 31 cycles/min, 248 nm UV detection).

M. E. Sangalli et al., Eur. J. Pharm. Sci. ***22****, 469 (2004)*

Chronotopic™

Film-coating *(aqueous)*

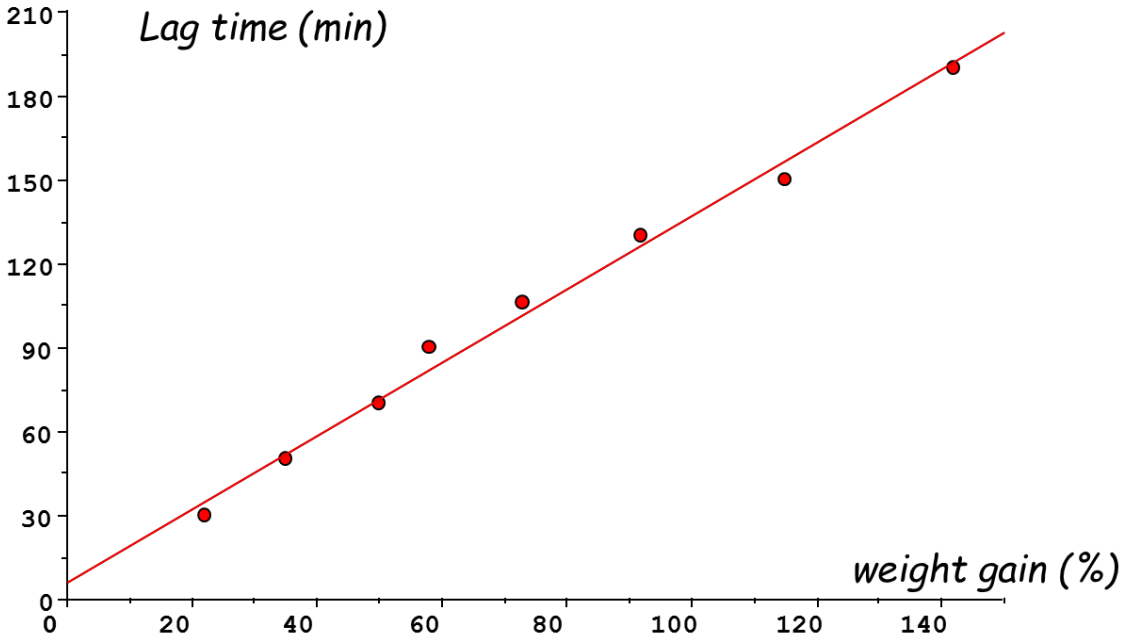


Sodium methyl 4-hydroxybenzoate release profiles from Methocel® E50-coated systems with increasing coating levels (modified disintegration apparatus, 900 mL distilled water, 37±0.5°C, 31 cycles/min, UV detection).

A. Gazzaniga et al., STP Pharma Sci 5, 83 (1995)

Chronotopic™

Film-coating *(aqueous)*

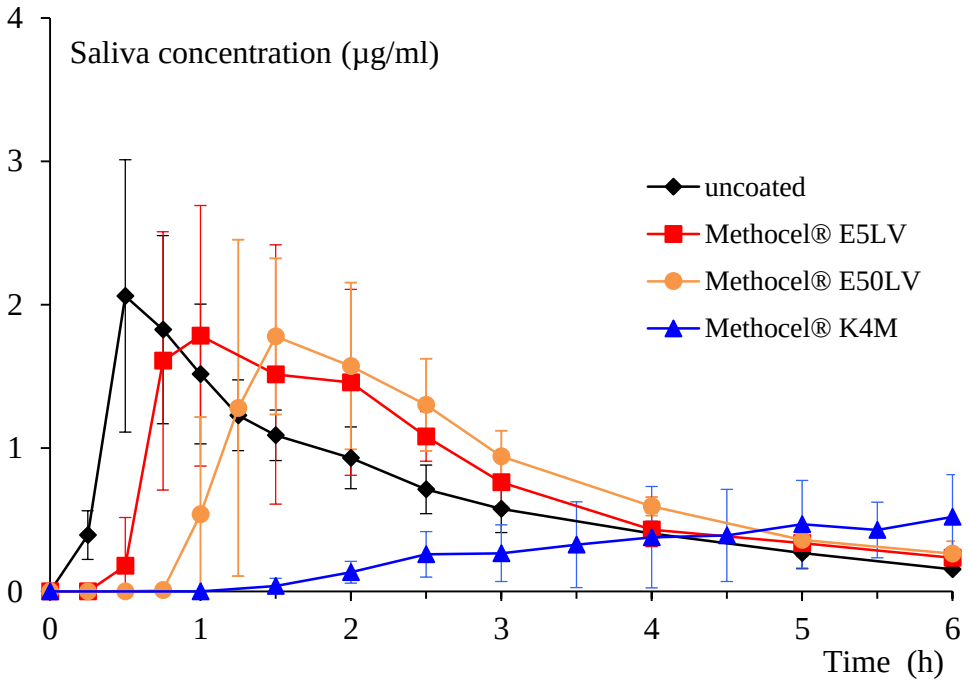


Relationship between coating level and in vitro lag time from Methocel® E50-coated systems.

A. Gazzaniga et al., STP Pharma Sci 5, 83 (1995)

Chronotopic™

Film-coating *(aqueous)*

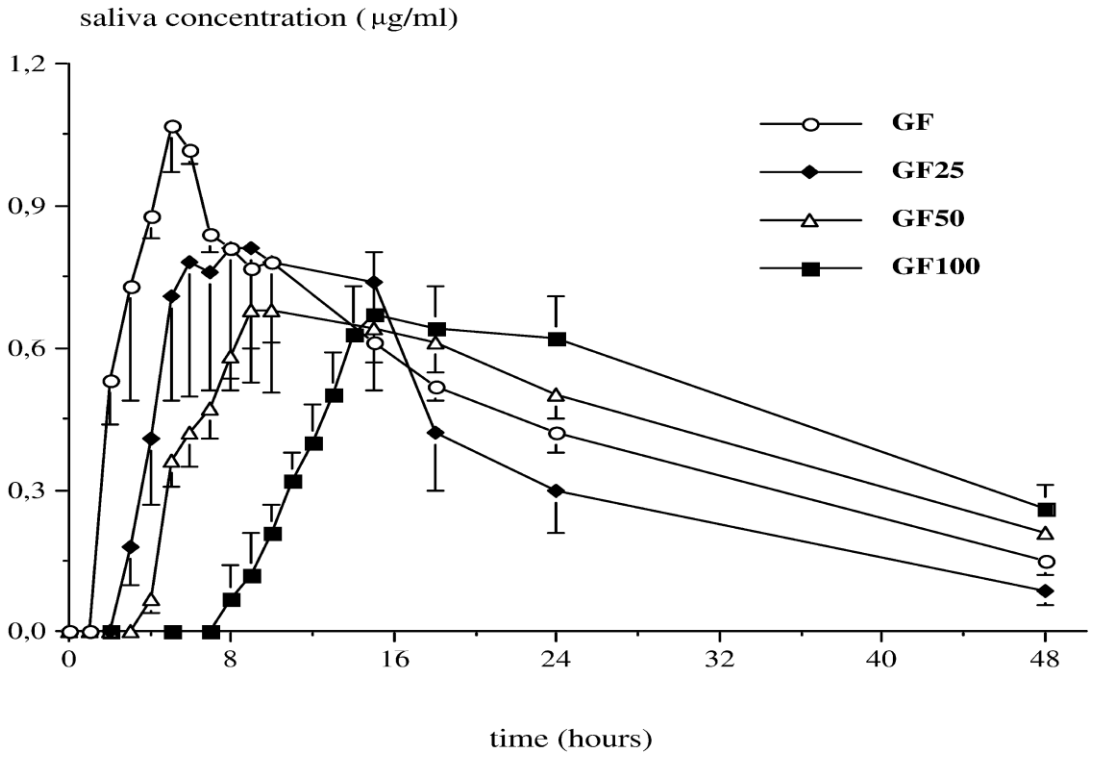


Mean salivary acetaminophen concentration vs. time profiles after intake of uncoated tablets and units coated with Methocel® E5, E50 and K4M up to 20% weight gain (n=6, fasted healthy volunteers).

A. Maroni et al., Proceed. Int'l Symp. Control. Rel. Bioact. Mat., 522 (2002)

Chronotopic™

Film-coating *(aqueous)*

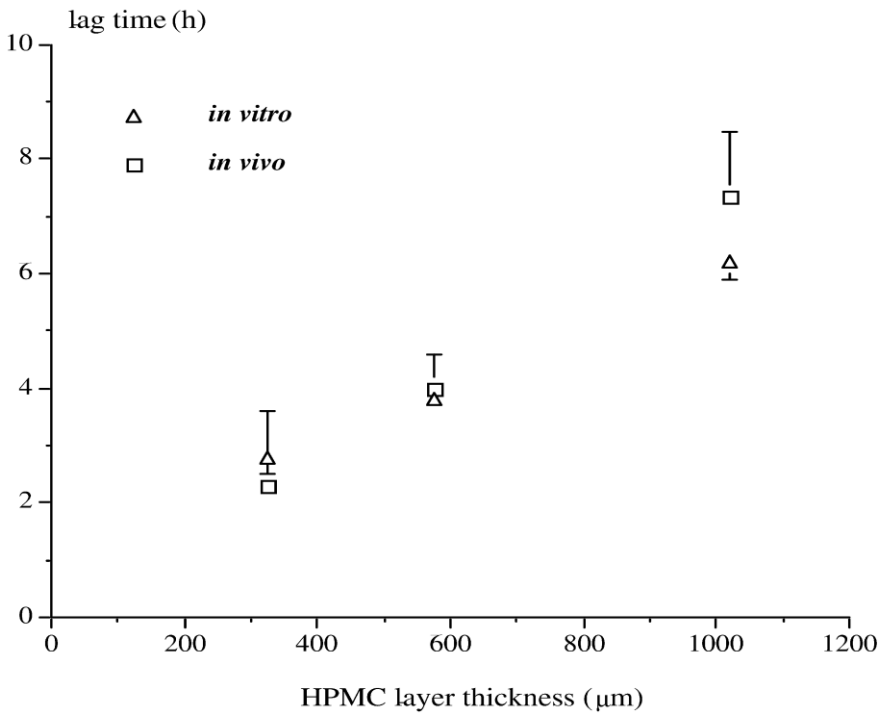


Mean salivary antipyrine concentration vs. time profiles from gastroresistant formulations with increasing Methocel® E50 coating level (n=4, fasted healthy male volunteers).

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

Chronotopic™

Film-coating *(aqueous)*



Relationship between coating thickness and in vitro as well as in vivo lag time in gastroresistant formulations with increasing Methocel® E50 coating level.

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

Chronotopic™

Film-coating *(aqueous)*

Transit times (h) and breakup site of samarium oxide-labeled *placebo* systems (cores 6 mm, 160 mg) coated with Methocel® E50 (100% w.g. ≈ 900 μm thickness) and Eudragit® L in 6 fasted healthy male volunteers.

Subject	*Gastric residence*	*Small Intestine Transit time*	*Colon arrival*	*Breakup time after gastric emptying*	*Breakup 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)**	**5.9 (± 1.3)**	**5.7 (± 0.8)**	

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

Chronotopic™

Film-coating *(aqueous)*

Transit times (h) and disintegration site of samarium oxide-labeled mesalazine-containing systems (cores 11 mm, 550 mg, 400 mg strenght) coated with Methocel® E50 (50% w.g. ≈ 770 µm thickness) and Eudragit® L in 6 healthy male volunteers.

FASTED CONDITION						
Subject	Gastric emptying time GE (h)	Small intestinal transit time SITT (h)	Colon arrival time CA (h)	Time of disintegration t_d (h)	Time of disintegration after gastric emptying $t_{d\text{-}GE}$ (h)	Site of disintegration s_d
1	1.75	3.00	4.75	12.00	10.25	TC
2	0.33	4.50	4.83	4.83	4.50	Caecum
3	0.42	1.50	1.92	11.00	10.58	AC
4	0.42	4.58	5.00	10.00	9.58	AC
5	0.58	4.50	5.08	#	#	TC
6	0.58	1.59	2.17	# (12.55)	# (11.97)	TC
Mean	0.68	3.28	3.96	9.46	8.73	
sd	0.53	1.47	1.49	3.19	2.85	

Fragments from the disintegrated dosage form only observed at 24 h though disintegration most likely occurred in the blind 12-18 h time lapse, as estimated based on a linear relationship between time of disintegration and lag time prior to appearance of N-acetyl 5-ASA in the plasma.

A. Foppoli et al., Int. J. Pharm. 572, 118723 (2019)

Chronotopic™

Film-coating *(aqueous)*

Transit times (h) and disintegration site of samarium oxide-labeled mesalazine-containing systems (cores 11 mm, 550 mg, 400 mg strenght) coated with Methocel® E50 (50% w.g. ≈ 770 µm thickness) and Eudragit® L in 6 healthy male volunteers.

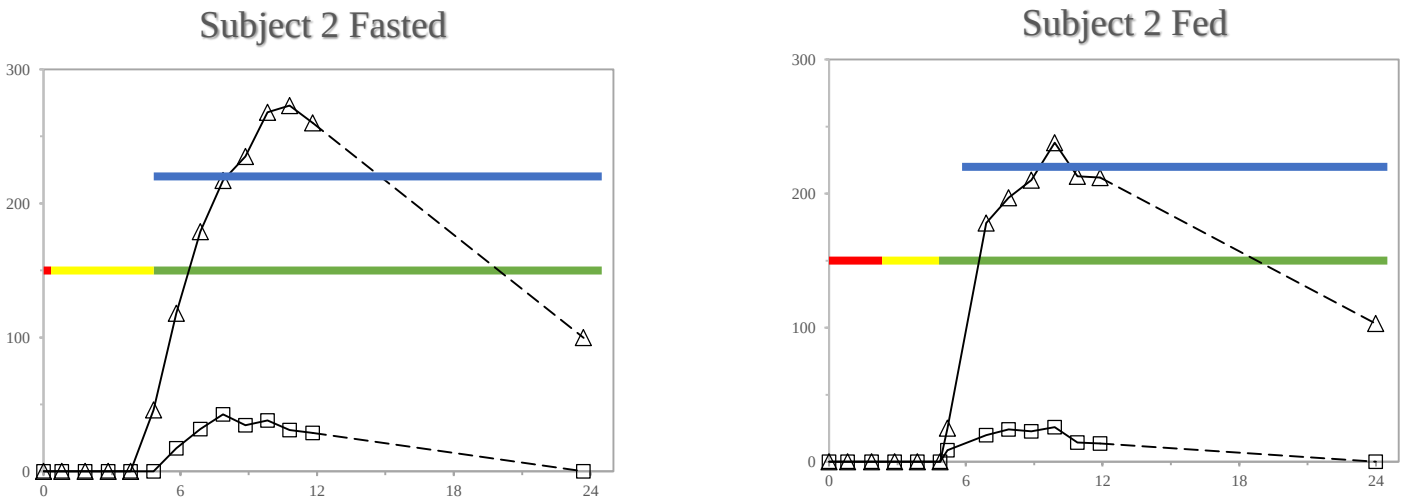
FED CONDITION						
Subject	Gastric emptying time GE (h)	Small intestinal transit time SITT (h)	Colon arrival time CA (h)	Time of disintegration t_d (h)	Time of disintegration after gastric emptying $t_{d\text{-}GE}$ (h)	Site of disintegration s_d
1	1.83	1.92	3.75	-	-	-
2	2.33	2.50	4.83	5.83	3.50	AC
3	1.41	3.51	4.92	8.92	7.51	AC
4	2.50	2.50	5.00	12.00	10.40	AC
5	1.92	3.00	4.92	# (13.87)	# (11.95)	TC
6	0.58	3.59	4.17	10.25	9.67	TC
Mean	1.76	2.84	4.60	9.48	7.77	
sd	0.70	0.65	0.51	2.94	3.10	

Fragments from the disintegrated dosage form only observed at 24 h though disintegration most likely occurred in the blind 12-18 h time lapse, as estimated based on a linear relationship between time of disintegration and lag time prior to appearance of N-acetyl 5-ASA in the plasma.

A. Foppoli et al., Int. J. Pharm. 572, 118723 (2019)

Chronotopic™

Film-coating *(aqueous)*

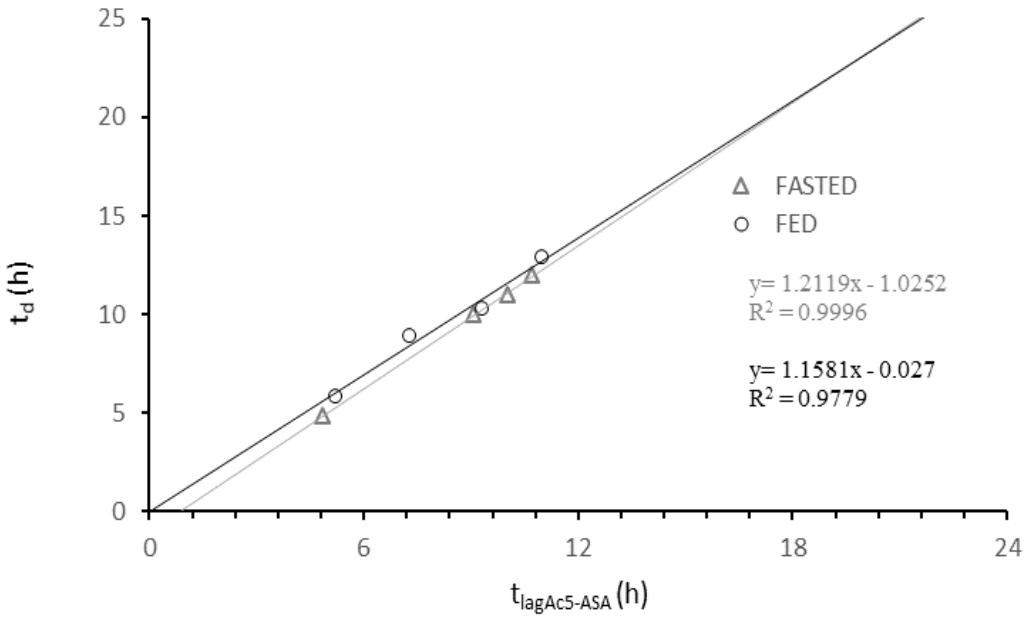


5-ASA (□) and N-acetyl 5-ASA (Δ) plasma concentrations vs time profiles following administration to one volunteer. Red, yellow and green bars (bottom) indicate gastric, small intestinal and colonic residence, respectively; the blue bar (top) indicates disintegration.

A. Foppoli et al., Int. J. Pharm. 572, 118723 (2019)

Chronotopic™

Film-coating *(aqueous)*



Relationship between N-acetyl 5-ASA in vivo lag time and time of disintegration.

A. Foppoli et al., Int. J. Pharm. 572, 118723 (2019)

Chronotopic™

Film-coating *(aqueous)*

Methocel® E50

8% w/V

Hard- and soft-gelatin capsules

Heat- and moisture-sensitive

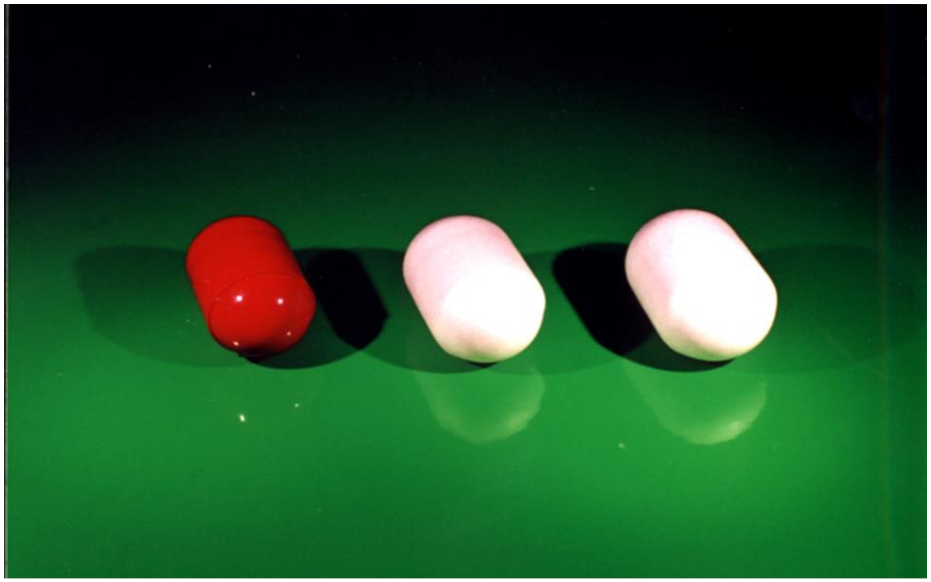
Adjustment of process parameters

to avoid technical problems (sticking, shrinking)

Adequate balance of inlet air temperature and spray rate to promote a rapid solvent evaporation without altering the original capsule volume

Chronotopic™

Film-coating *(aqueous)*

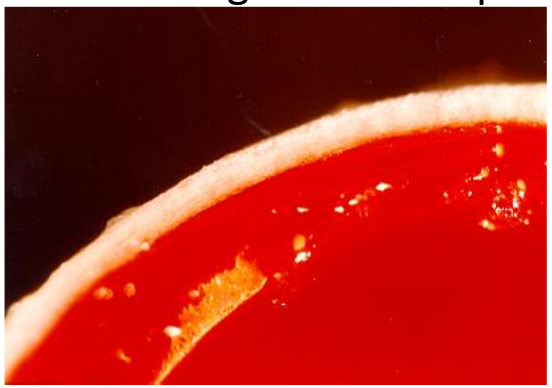


Chronotopic™

Film-coating *(aqueous)*

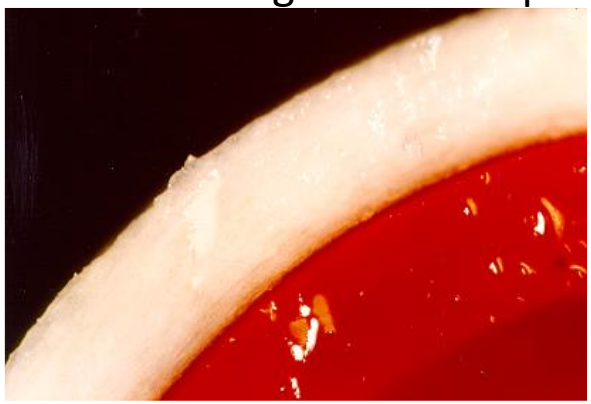
uncoated

w.g. 13% - 170 µm

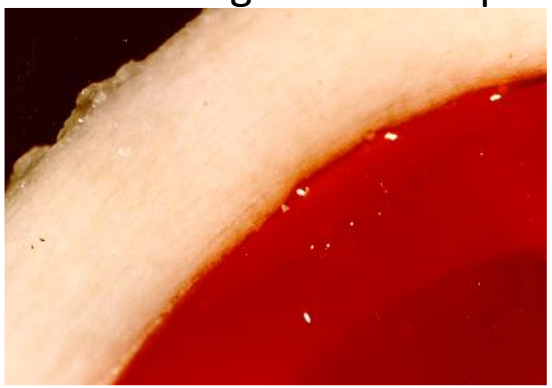


w.g 21% - 315 µm

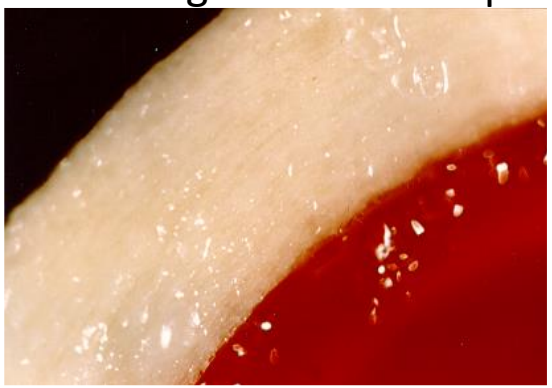
w.g. 51% - 650 µm



w.g. 83% - 950 µm

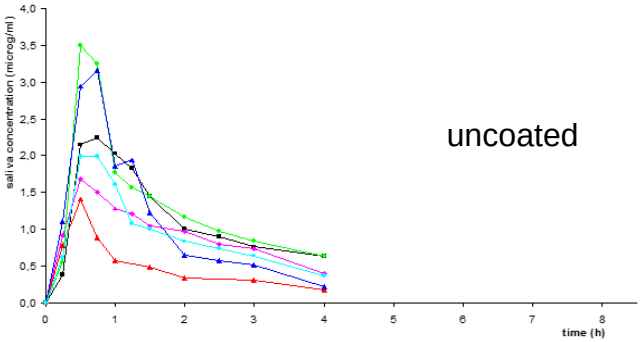


w.g. 103% - 1135 µm

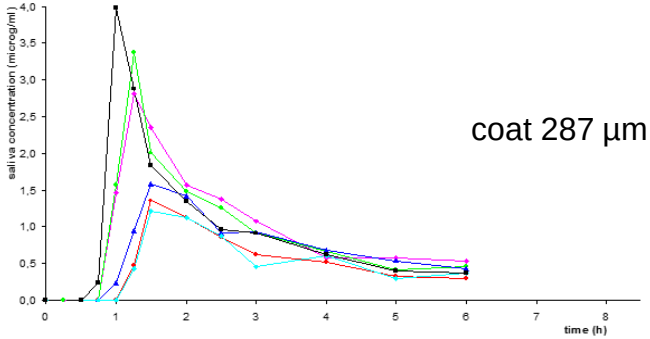


Chronotopic™

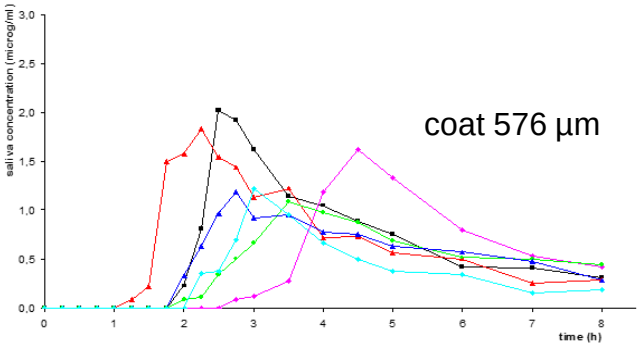
Film-coating *(aqueous)*



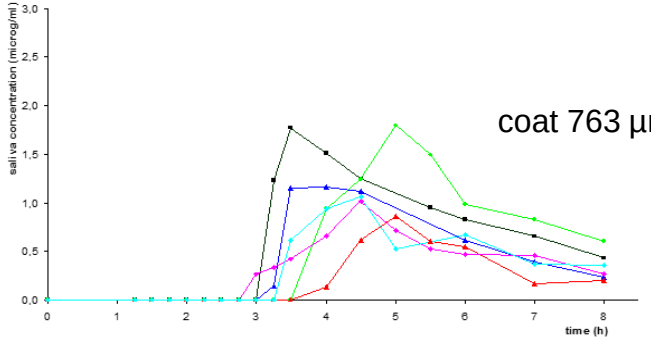
uncoated



coat 287 µm



coat 576 µm



coat 763 µm

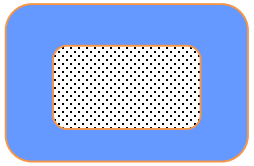
Salivary paracetamol concentration vs. time profiles from uncoated hard-gelatin capsules and Methocel® E50-coated systems with increasing coating levels (n=6, fasted healthy male volunteers).

M.E. Sangalli et al., in B.B.C. Youan (Ed.), Chronopharmaceutics, John Wiley&Sons, Hoboken, US-NJ, 2009, pp. 145-63

Chronotopic™

Film-coating *(aqueous)*

Erodible multiple-unit delivery systems



Relatively high amounts of HPMC needed

Thickness of the coating failing to comply with size requirements of multiple-unit dosage forms

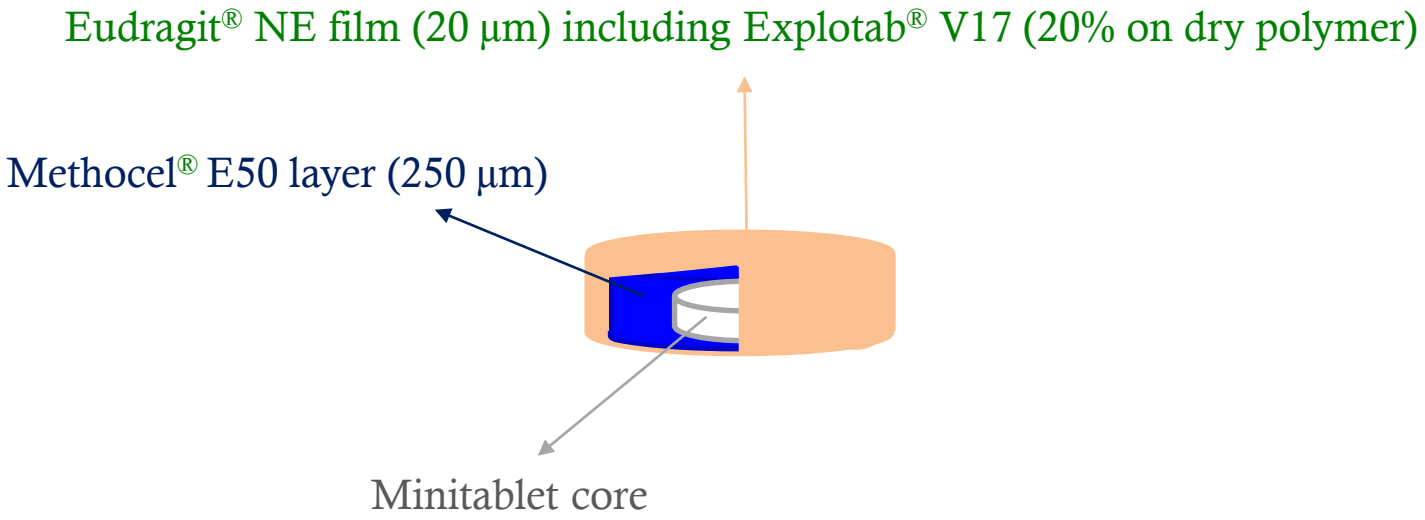
Reduced rate of initial release because of matrix effect of the thick coating

Chronotopic™

Film-coating *(aqueous)*

Erodible multiple-unit delivery systems

Insoluble, flexible, increasingly permeable outer film aimed to slow hydration of the HPMC layer without hindering its swelling



A. Maroni et al., Int. J. Pharm. 440, 256 (2013)

Chronotopic™

Film-coating *(aqueous)*

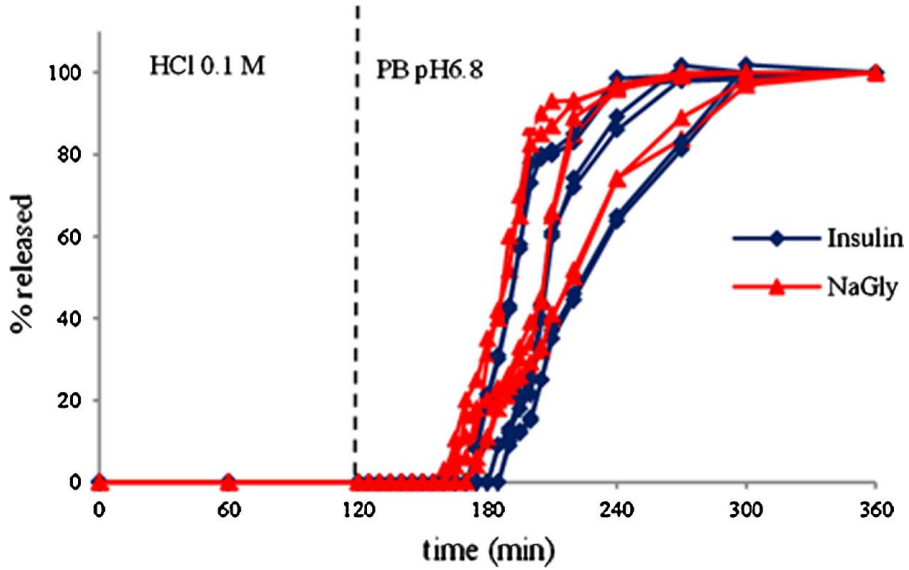
Erodible multiple-unit delivery systems

Insulin delivery system for colonic release

- Minitablets (2.5 mm) containing bovine insulin (0.4 mg) and sodium glycocholate as an absorption enhancer
- Inner Methocel® E50 coating
- Intermediate Eudragit® NE/Explotab® V17 (20% on dry polymer) film
- Outermost HPMC AS enteric-soluble film

Chronotopic™

Film-coating *(aqueous)*

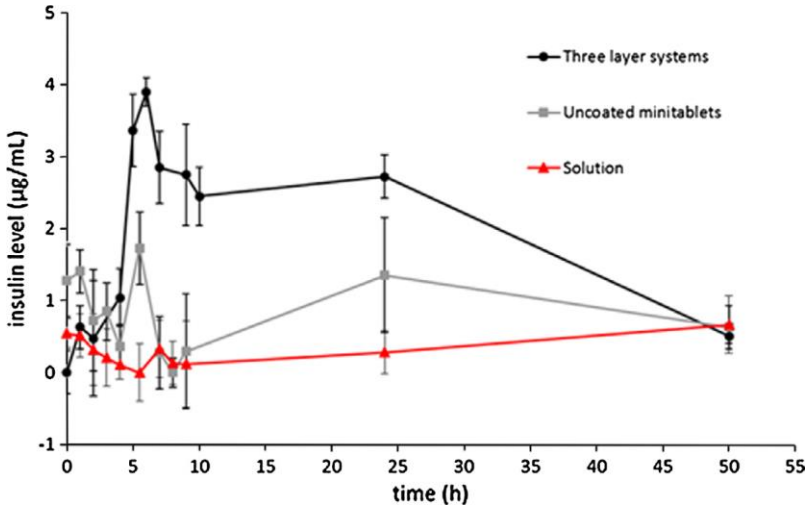


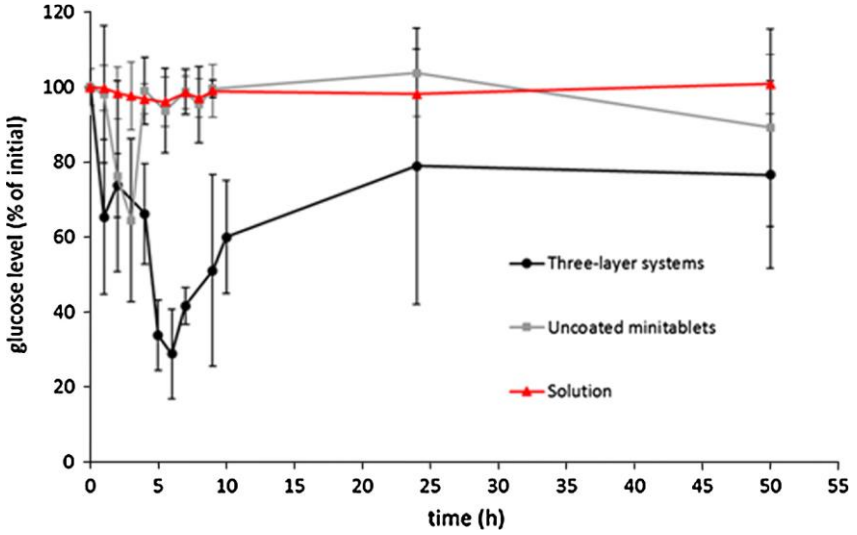
Insulin and sodium glycochlate release profiles from multiple-unit delivery systems with 250 µm Methocel® E50 and 20 µm Eudragit NE – Explotab V17 coatings (modified disintegration apparatus, 900 ml phosphate buffer pH 6.8, 37±0.5°C, 31 cycles/min, RP-HPLC detection).

A. Maroni et al., Eur. J. Phrm. Biopharm. 108, 76 (2016)

Chronotopic™

Film-coating *(aqueous)*





Mean insulin and glucose plasma concentration vs. time profiles in fed male Sprague Dawley rats with streptozotocin-induced diabetes mellitus after administration of three-layer systems, immediate-release minitablets or insulin in solution (n=6, glucose and insulin assays by Trinder and ELISA, respectively).

A. Maroni et al., Eur. J. Phrm. Biopharm. 108, 76 (2016)

Chronotopic™

Alternative coating techniques

Need for improved process time and yield as obtained by top-spray film-coating

- Tangential-spray film-coating

  Mainly used for small-sized units

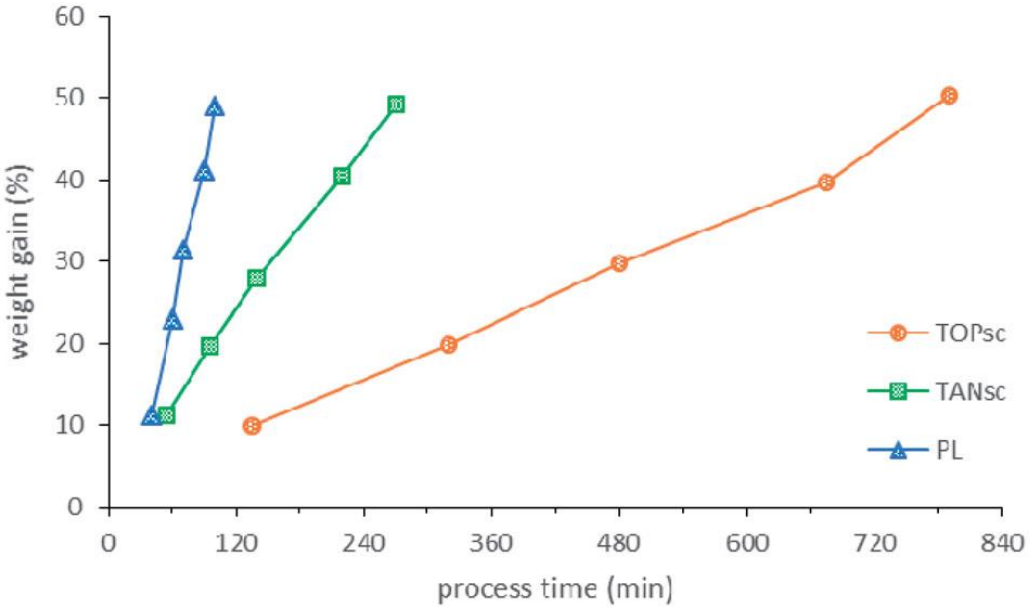
- Powder-layering

  Used for manufacturing of pellets by deposition of powdered active pharmaceutical ingredients onto inert substrate cores

Fluid bed equipment

Chronotopic™

Alternative coating techniques

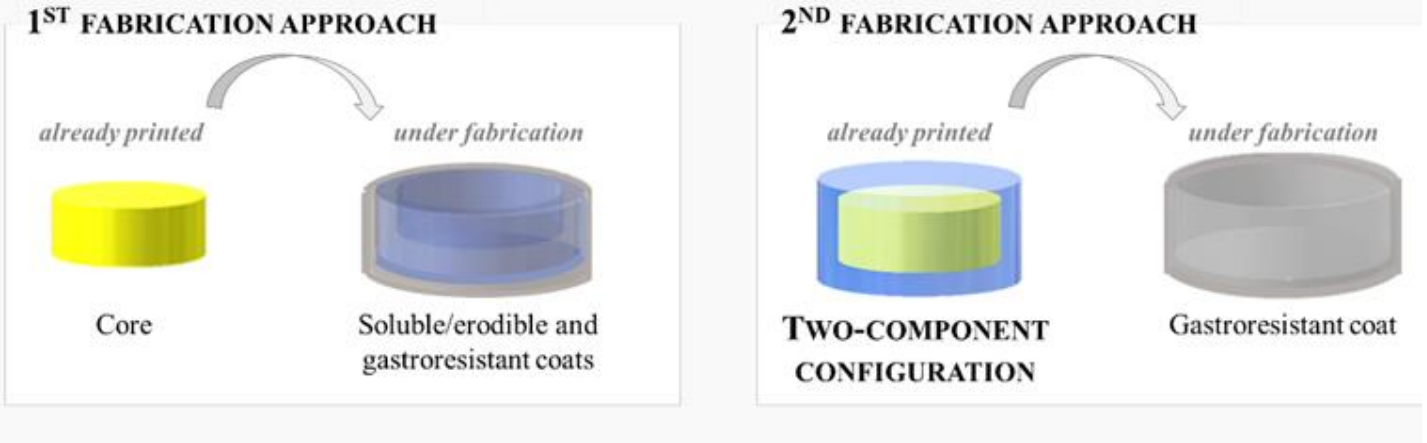


Relationship between weight gain and process time using different techniques: top-spray (TOPsc), tangential-spray (TANsc) and powder-layering (PL).

A. Foppoli et al., Drug Dev. Ind. Pharm. 46, 1230 (2020)

Chronotopic™

Fused Deposition Modeling (FDM)

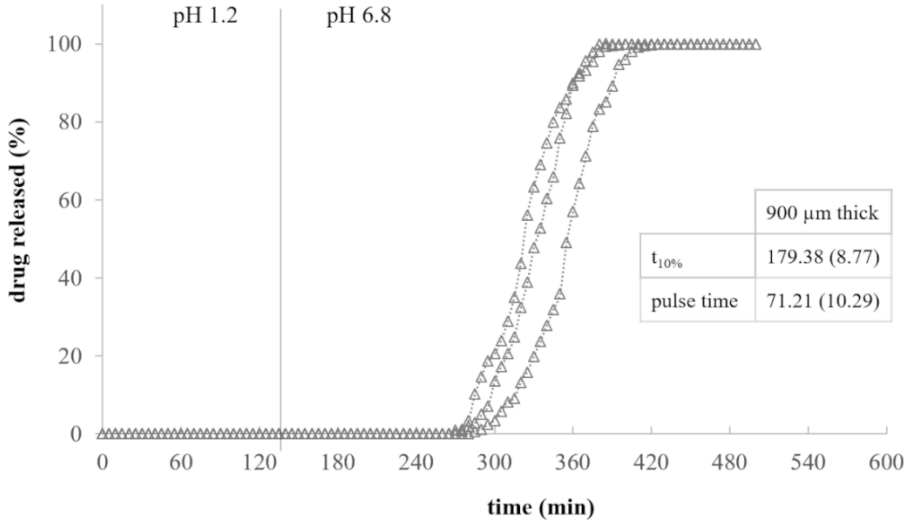


FDM by a Kloner3D 240® Twin (Kloner3D, I) printer equipped with a 0.5 mm nozzle

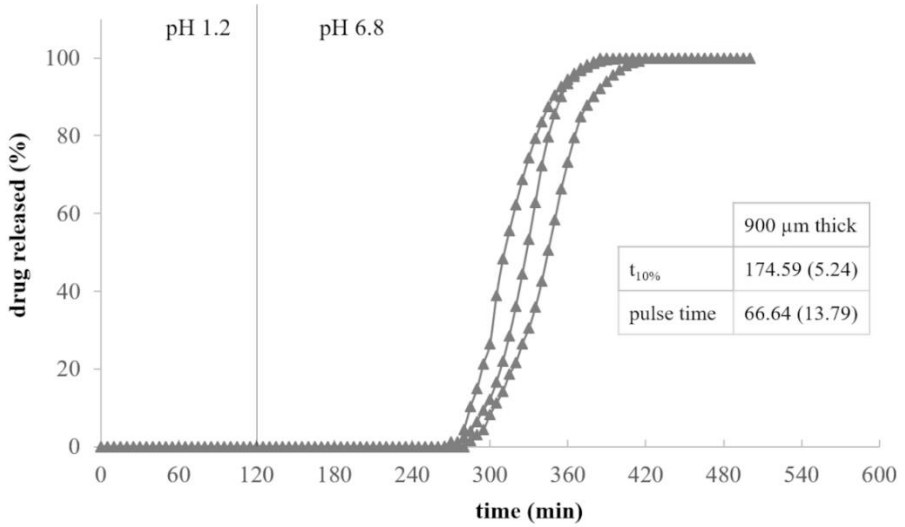
A. Melocchi et al., Pharmaceutics 13, 759 (2021)

Chronotopic™

Fused Deposition Modeling (FDM)



Pre-printed drug core



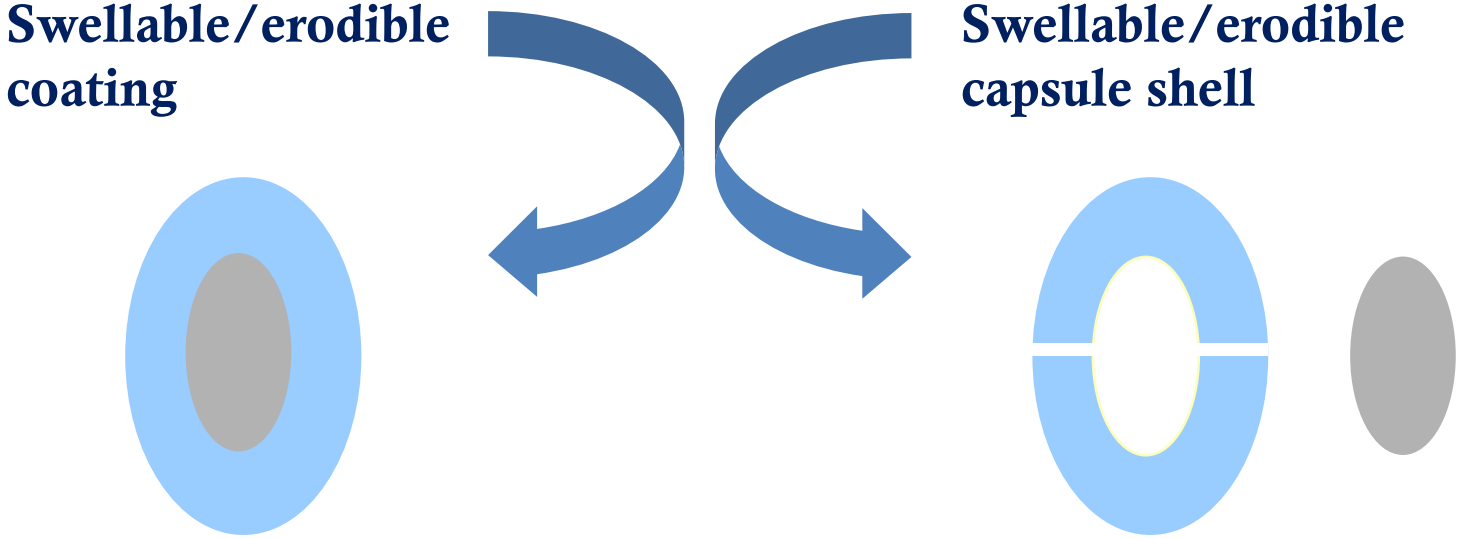
Pre-printed drug core+inner coating

Release profiles from three-part delivery systems fabricated following two different approaches and consisting of:
- core composed of PVA (Gohsenol® EG 03P, Mitsubishi Chemical Holdings), glycerol (15% on polymer), high-amyolse starch (30% on plasticized polymer) and caffeine (10% on plasticized polymer), printed at 50% infill
- 900 µm thick HPC (Klucel™ LF, Ashland)
- 400 µm thick Eudragit® L layer
(modified disintegration apparatus, 800 ml distilled water, 37±0.5°C, 31 cycles/min, UV detection).

A. Melocchi et al., Pharmaceutics 13, 759 (2021)

Chronocap™

Injection-Molding (IM)



Chronocap™

Injection-Molding (IM)

- Capsule shells based on HPC of various viscosity grades

  Klucel™ EF, Klucel™ LF and Klucel™ EF, plasticized with PEG 1500 (10%)

- Injection-molding

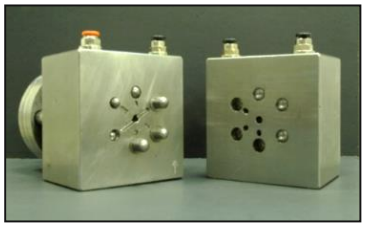
  ✓*enables production of items of any shape by injecting softened/melted thermoplastic/thermoset materials into a closed mold for shaping as desired and ejection after cooling*

  ✓*Derived from the plastics industry*

  ✓*Raises interest in several manufacturing areas though still poorly exploited in the pharmaceutical one*

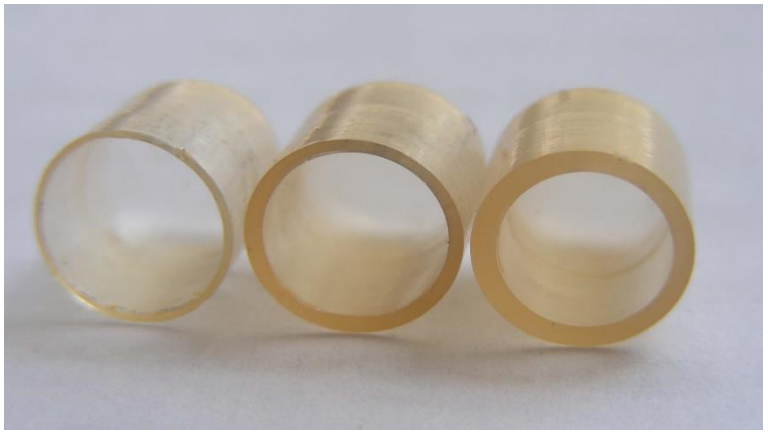
- Bench-top injection-molding press equipped with a special mold supporting interchangeable inserts for cap and body parts of the capsule.

  BabyPlast 6/10P; Cronoplast S.L.



Chronocap™

Injection-Molding (IM)

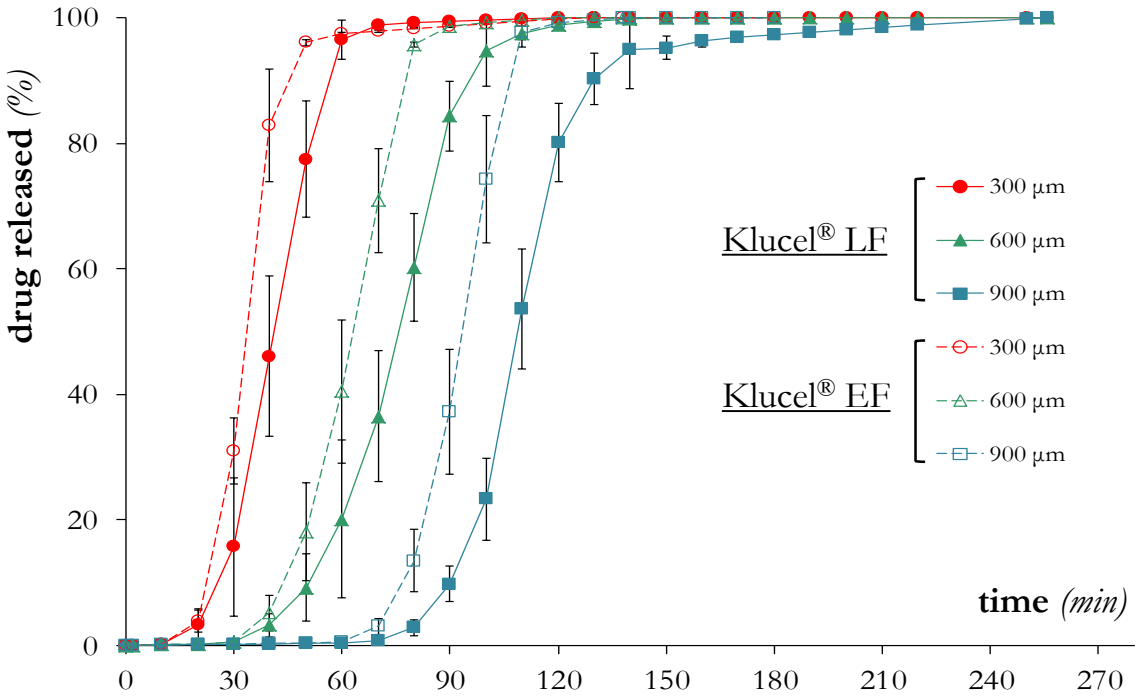


Nominal thickness (μm)	Capacity (ml)
300	0.64
600	0.51
900	0.45

A. Gazzaniga et al., AAPS PharmSciTech. 12, 295, 2011

Chronocap™

Injection-Molding (IM)

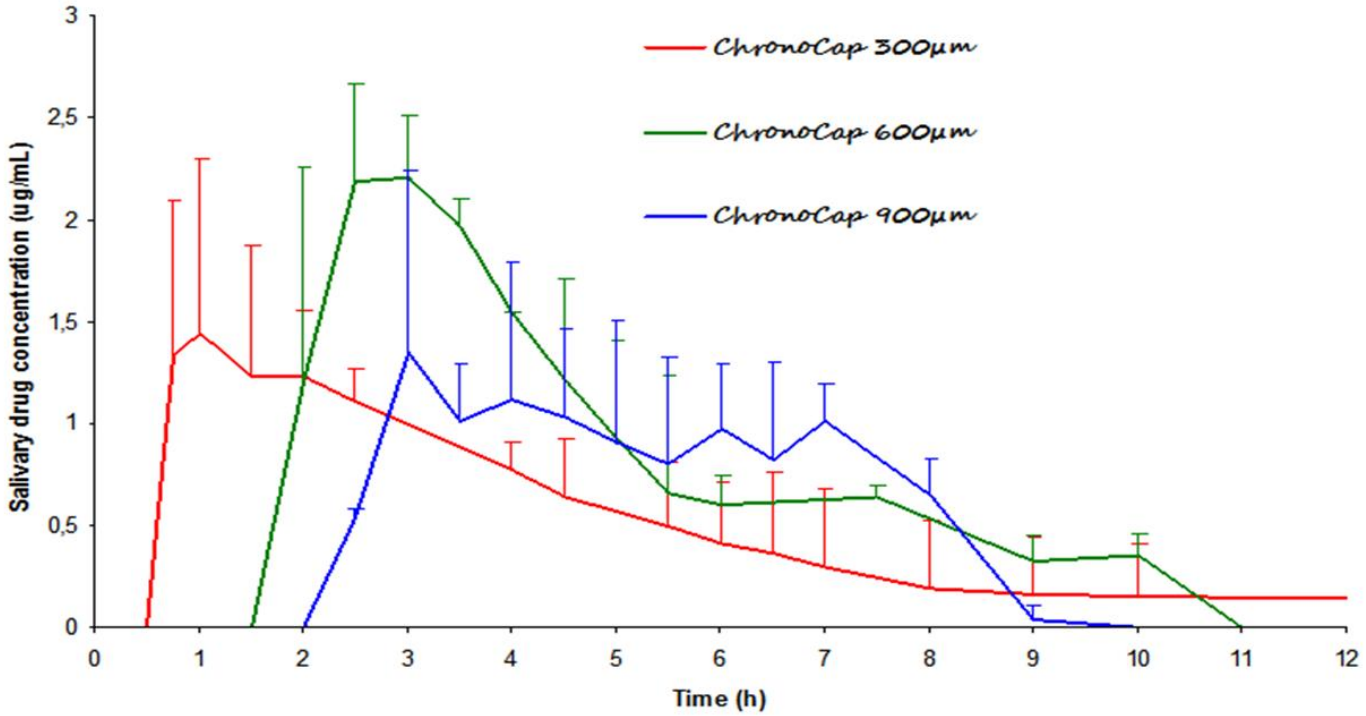


Mean paracetamol release profiles from Klucel® EF or Klucel® LF capsular delivery systems with increasing shell thickness (modified disintegration apparatus, 900 ml distilled water, 37±0.5°C, 31 cycles/min, UV detection).

A. Gazzaniga et al., AAPS PharmSciTech. 12, 295, 2011

Chronocap™

Injection-Molding (IM)

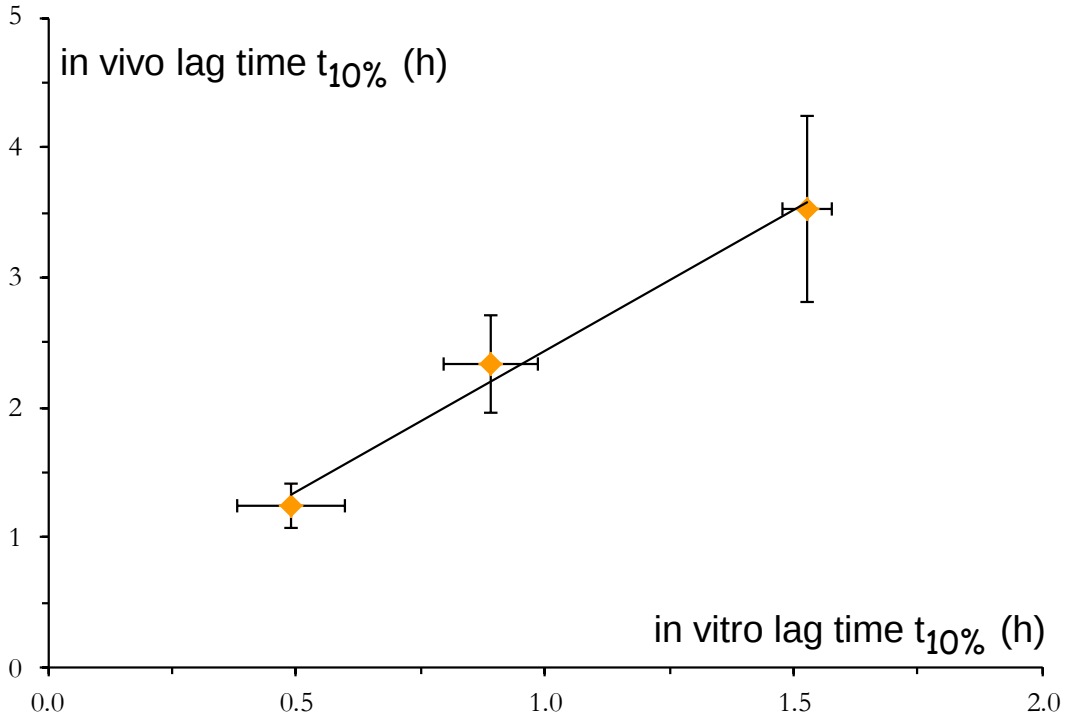


Mean paracetamol saliva levels versus time profiles from Klucel® LF capsular delivery systems with increasing thickness (3 fasted healthy male volunteers).

Unpublished data

Chronocap™

Injection-Molding (IM)



Relationship between in vitro and in vivo lag times, expressed as time to 10% release and time to 10% C_{max}, respectively, from Klucel® LF capsular delivery systems.

Unpublished data

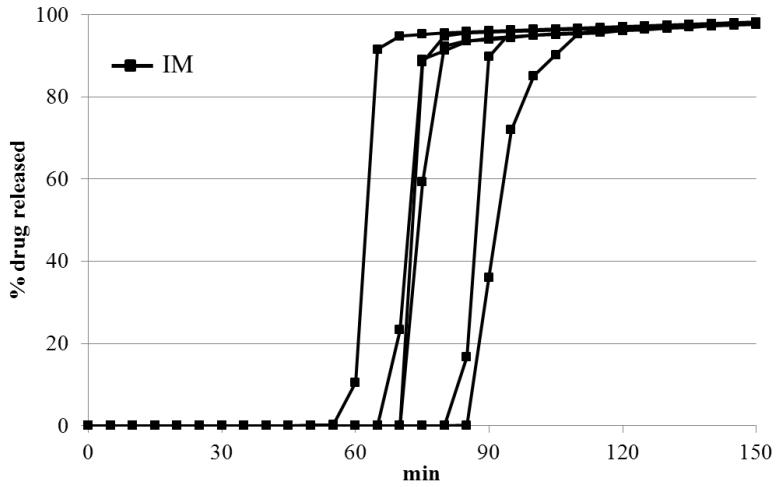
Chronocap™

Fused Deposition Modeling (FDM)

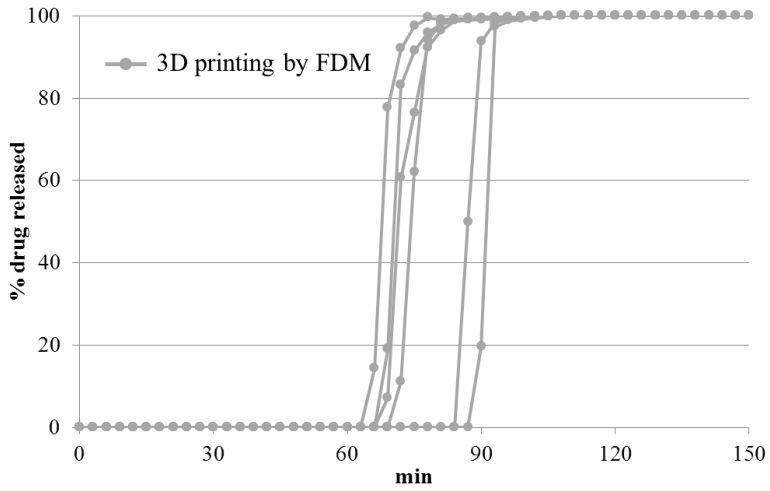
- Capsule shells fabricated from Klucel™ LF plasticized with PEG 1500 (10% on polymer)
- Filaments manufactured in-house by hot-melt extrusiontwin-screw extruder (Haake™ MiniLab II, Thermo Scientific)
- Purposely developed computer-aided design (CAD) files
- Previous study of the possibility of constructing hollow items by FDM
- MakerBot Replicator 2, MakerBot® Industries

Chronocap™

Fused Deposition Modeling (FDM)



Injection-molding



Fused Deposition Modeling

Paracetamol release profiles from Klucel® LF-based capsular delivery systems with 600 µm shell thickness manufactured by injection-molding or fused deposition modelling (modified disintegration apparatus, 800 ml distilled water, 37±0.5° C, 31 cycles/min, UV detection).

A. Melocchi et al., J. Drug Deliv. Sci. Technol. 30, 360 (2015)

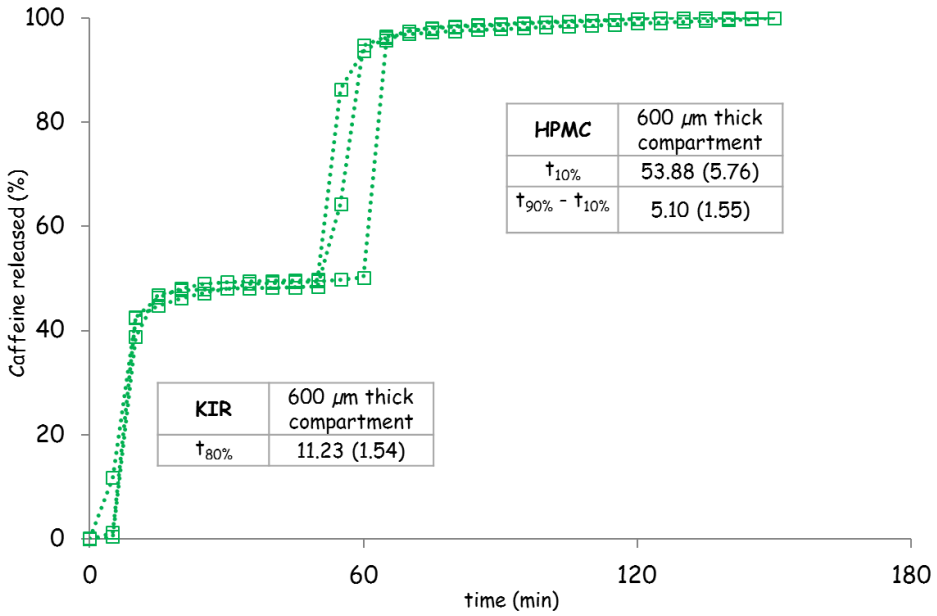
Chronocap™

Fused Deposition Modeling (FDM)

A. Maroni et al., J. Control. Release 268, 10 (2017)

Chronocap™

Fused Deposition Modeling (FDM)



Acetaminophen release profiles from capsular devices including two compartments with 600 μm shell thickness, based on Kollicoat® IR (BASF) and HPMC (Affinisol™ 15cP, Dow), respectively (modified disintegration apparatus, 800 ml distilled water, 37±0.5°C, 31 cycles/min, UV detection).

A. Maroni et al., J. Control. Release 268, 10 (2017)

Conclusions

- Time-controlled colon delivery systems have been presented in the form of osmotic pumps, capsular devices with functional plugs and reservoir formulations with functional coatings.
- Delivery systems provided with HPMC- or HPC-based hydrophilic/swellable functional barriers, in the form of coatings or shells, have successfully been obtained by double-compression, film-coating, injection-molding and fused deposition modeling 3D printing.
- Low-viscosity HPMC (Methocel® E50) and HPC (Klucel® LF) have offered a favorable balance of differing aspects, such as process feasibility, efficiency in delaying drug release, lack of impact on the release rate and modulation of delay time.
- In diabetic rats, multiple-unit insulin delivery systems based on a functional HPMC layer obtained by aqueous film-coating have brought about a clear hypoglycemic response after a lag phase possibly consistent with the small intestinal transit of the animal model.
- Administered to volunteers, delivery systems obtained by aqueous film-coating with HPMC provided with an enteric outer film, have been shown to target the proximal colon.