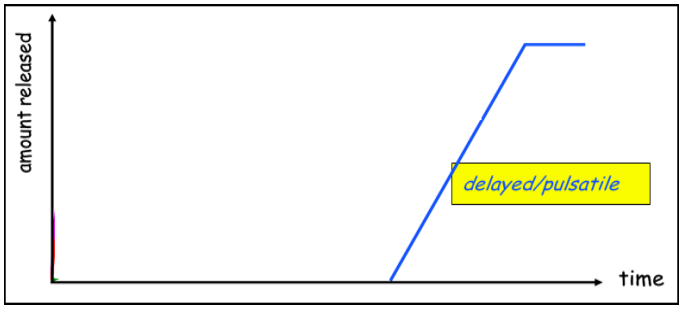
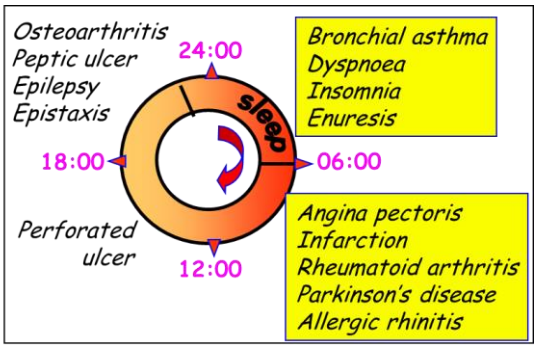
THE CHRONOTOPIC™ TECHNOLOGY

The Chronotopic™ technology relates to an oral delivery system designed for time-based pulsatile release, which is generally referred to as the liberation of drugs after a predetermined lag phase starting at the time of administration



In contrast to triggered pulsatile delivery, in which release is initiated by external chemical, thermal, electrical, magnetic, ultrasonic or enzymatic stimuli, in the case of time-based devices only inherent mechanisms are exploited to control the onset of release, irrespective of environment variables such as pH, ionic strength and temperature].

The primary rationale behind time-based oral pulsatile delivery is to enable the chronotherapy of pathologies with symptoms mainly recurring in the night or on awakening, such as ischemic heart disease, bronchial asthma and rheumatoid arthritis .



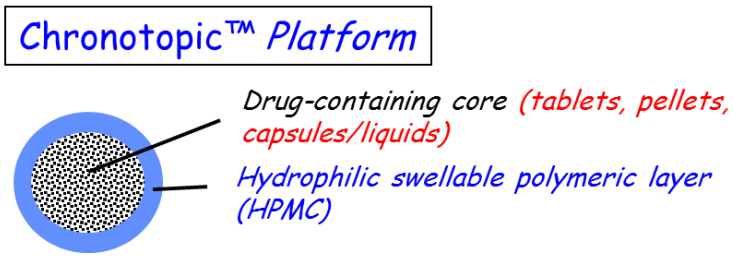
In fact, provided that release is programmed to take place at that particular time, higher drug levels after evening dosing could be achieved when they are especially required.

This would expectably improve both the efficacy and tolerability of the pharmacological treatment, without entailing any concomitant impairment of patient compliance .

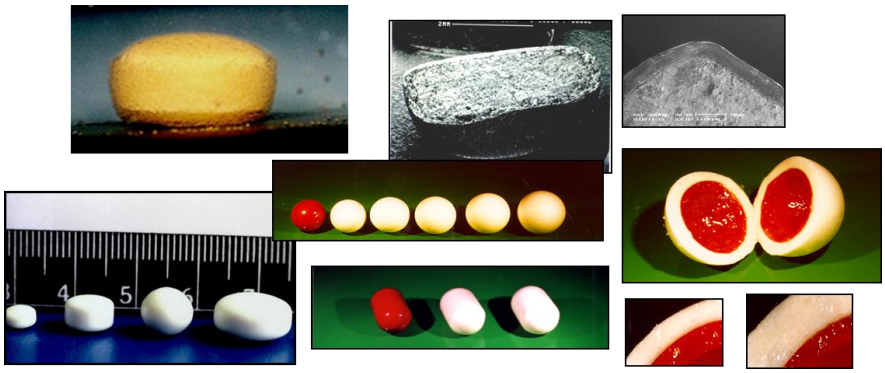
As a further application, colon delivery, which is regarded as potentially beneficial to the treatment of inflammatory bowel disease (IBD) and the enhancement of oral peptide bioavailability, is pursued relying on the time-dependent approach.

Such strategy envisages the exploitation of the relative reproducibility in small intestinal transit time (SITT), that has been shown to last 3-5 hours, practically independent of characteristics of the dosage forms as well as fasting or fed state of the subjects.

The Chronotopic™ system is basically composed of a drug-containing core provided with an outer release-controlling layer generally obtained by spray-coating.



Both single and multiple-unit dosage forms have been employed as the inner drug formulation, such as tablets and capsules or minitablets and pellets, respectively.

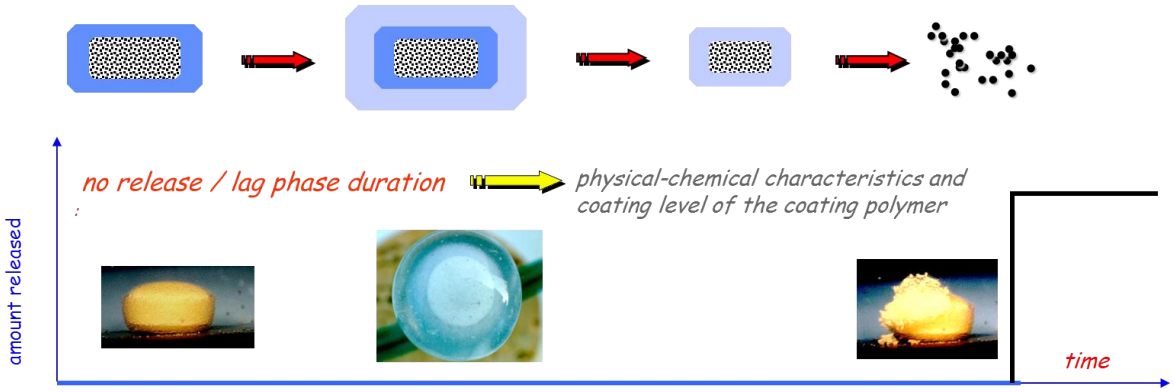


Cores either meant for an immediate or a prolonged liberation of the active principle have been proposed. However, the main focus has so far been on the

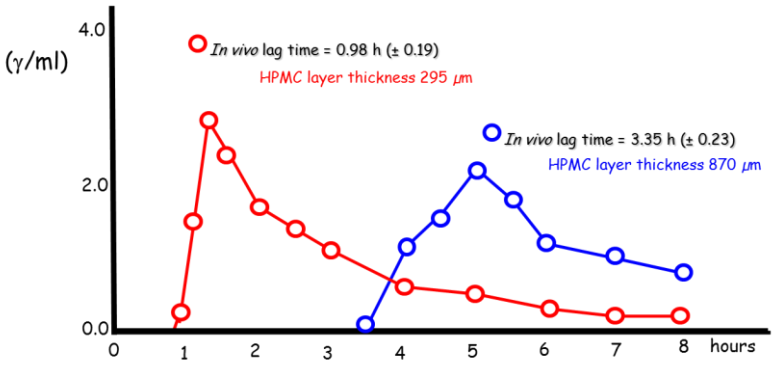
accomplishment of a rapid and transient delayed release, which is generally considered as the most challenging and even appealing pulsatile delivery mode.

The outer barrier has been obtained through the application of swellable hydrophilic polymers of different viscosity grade, typically hydroxypropyl methylcellulose (HPMC), by exploiting a variety of methods.

When exposed to the aqueous fluids, these polymers undergo a glassy-rubbery transition. In the hydrated state, they are subject to permeability increase, dissolution and/or mechanical erosion phenomena, which contribute to delay the delivery of drugs from the core (Figures 2,3).



The system has been shown to afford the pursued pulsatile release behavior *in vitro* as well as *in vivo*, with programmable lag phases followed by drug release according to the core characteristics.

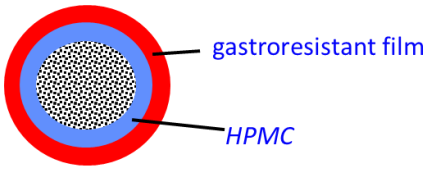


Acetaminophen saliva concentration vs time after oral administration (dose 50 mg) of tablets coated with increasing amounts of Methocel® E50 to six healthy volunteers

In principle, it has turned out possible to finely modulate lag time relying on different coating materials and coating thickness values. Moreover, depending on such variables, diverse mechanisms have been hypothesized and, in some instances, demonstrated to be involved in the control of release [26,27].

When proper modifications have been introduced into the system design, the Chronotopic™ technology has shown to yield oral time-dependent colon delivery, too [18,28].

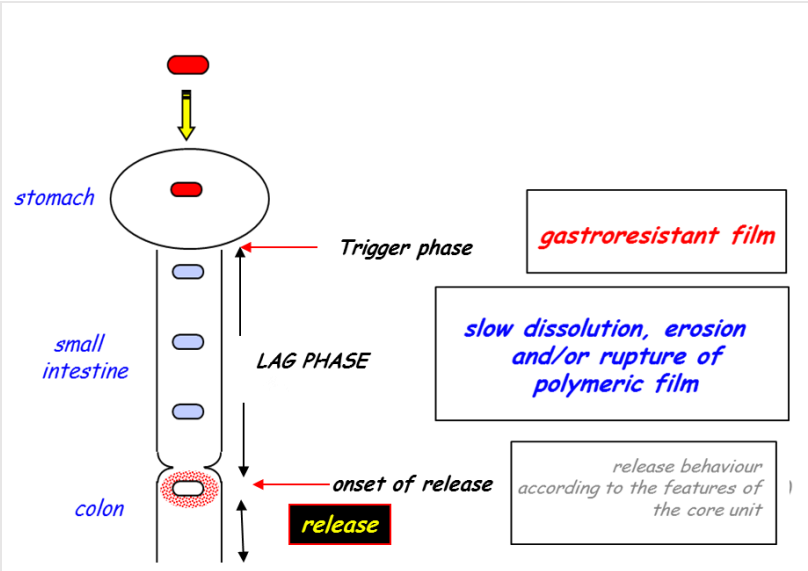
In particular, the application of an outer enteric film has easily allowed the highly variable and unpredictable gastric emptying time to be overcome.



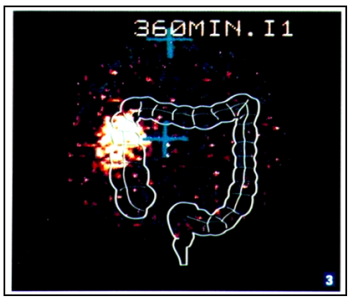
As a result, it has been possible to exploit the relative consistent SITT by purposely selecting the physical-chemical characteristics and amount of the hydrophilic polymer to be employed as the release-delaying agent. Accordingly, the system in its two-layer configuration is expected to keep intact as long as it is located in the stomach.

After gastric emptying, the pH-induced dissolution of the enteric coating enables the interaction of the underlying swellable polymer with the aqueous intestinal fluid,

This works as a triggering signal for the lag phase, which is programmed to protect the core for a period roughly corresponding to the average SITT.



Hence, at the end of the delay time the device is assumed to be positioned in the colon, where drug delivery may take place.



in all cases disintegration of the units in the proximal colon

Transit and disintegration times (h) of placebo units
6 fasted volunteers - γ-Scintigraphic Study

Volunteers	Gastric residence	Small Instestine Transit	Colon Arrival	Break-up time after gastric emptying	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)	5.9 (1.3)	5.7 (0.8)	

The oral pulsatile delivery system is the mainstay of the Chronotopic™ technology.

Basically, the underlying working mechanism relies on a hydrophilic swellable polymeric coating, which delays drug release from an inner core for a programmable time period.

Hence, through the use of conventional pharmaceutical equipment and standard materials, a versatile delivery platform has been obtained, suited for delivering drugs with different physical-chemical properties as well as pharmacological indications. In particular, on account of its special ability to yield lag phases on the order of a few hours, the system could prove a useful means of accomplishing the chronotherapy of illness states with mainly night or early-morning symptoms, such as ischemic heart disease, bronchial asthma and rheumatoid arthritis.

Although the possible chronopharmaceutical application embodies the primary rationale behind the Chronotopic™ technology, it is noteworthy that the attainable delay times are also consistent with those involved by the time-dependent formulation approach to colon delivery, which is being extensively investigated for the local treatment of large bowel pathologies and a potential bioavailability enhancement for orally administered peptide drugs. As regards both pulsatile and colon delivery modes, proof-of-concept has been achieved through preliminary studies on humans.

The inherent advantages of the Chronotopic™ technology can be summarized in the relative simplicity of design, working principle and manufacturing, general availability of the equipment and materials to be employed, versatility in terms of starting core formulations as well as drugs to be delivered and, finally, remarkable flexibility in the modulation of delay.

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