THE CHRONOTOPIC™ TECHNOLOGY PLATFORM

ChronoCap™: a Novel Pulsatile Delivery System

A novel capsular device intended for oral pulsatile (time-controlled) release of differing drug formulations is proposed. The units are prepared by INJECTION MOLDING or 3D PRINTING

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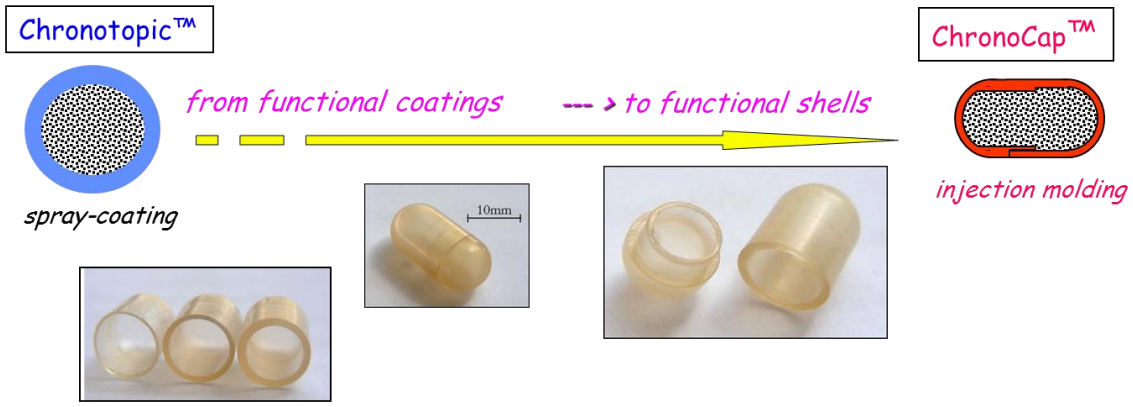
- Injection-molding of powder blends based on swellable/erodible hydrophilic polymers (GRAS materials).



thickness µm	*capacity mL*
300	0.64
600	0.51
900	0.45

Thermoplastic hydrophilic swellable polymer: HPC (hydroxypropylcellulose) T_g 160-190°C

Mold and lab-scale IM press BabyPlast 6/10P, Cronoplast, Spain)

The resulting capsule shells are capable of delaying the liberation of the conveyed drug for a programmed time period through their slow interaction with the gastrointestinal fluids.

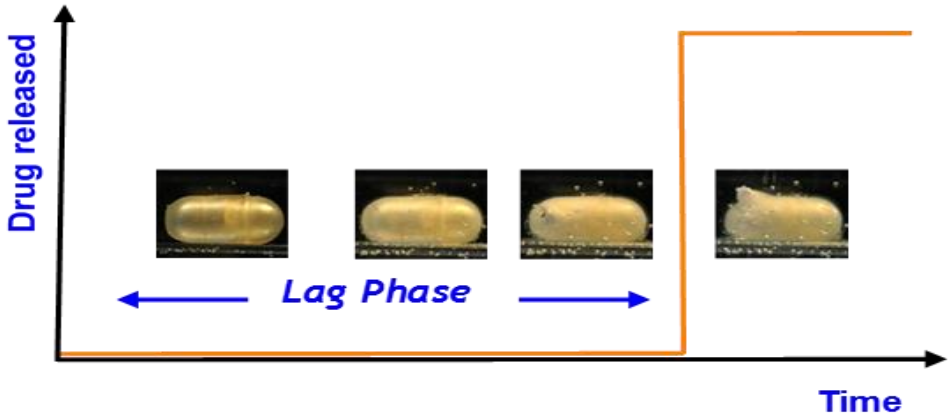
Perfectly matching bodies and caps with varying thickness can be obtained, thus ideally providing a "library" of devices able to elicit diverse *in vivo* performances.

Moreover, they can be filled with solid or liquid preparations (e.g. powders, tablets, pellets, solutions, dispersions).

Peculiar advantages are the chance of undergoing an independent pharmaceutical development regardless of filling (drug formulation), the scalability of the manufacturing process and a remarkable versatility.

Description of the product

The ChronoCap technology relates to an oral capsular device intended for pulsatile (time-controlled) release of drugs. Such capsules are prepared from hydrophilic polymeric materials that undergo a glassy-rubbery transition when exposed to aqueous fluids, thereby delaying the release of the contents for a programmable period of time following administration.



The lag time that precedes the onset of release can be modulated as a function of the thickness and composition of the capsule shell. ChronoCap devices can be filled just like hard gelatin capsules and may convey solid (powders, capsules, tablets, granulates, pellets, micro- or nano - particles), semi-solid or liquid drug formulations.

The ChronoCap can optionally be coated with gastric-resistant polymers thus being adapted to a time-dependent colon delivery system.

Colonic release is of high interest not only for the therapy and prevention of pathologies that affect the large intestine (ulcerative colitis, Crohn's disease, colorectal adenocarcinoma, microflora disorders), but also for pharmacological treatments that require a systemic absorption of the drug.

Innovative aspects of the product

The ChronoCap can be manufactured in different types and sizes of bodies and caps with varying thickness and composition, which ideally provides a "library" of devices able to elicit a range of *in vivo* performances.

Moreover, the ChronoCap can be filled with solid as well as liquid preparations (e.g. powders, tablets, pellets, solutions, dispersions). Due to its nature of "functional container", the product could undergo an independent pharmaceutical development regardless of the filling.

Main advantages

The ChronoCap provides a tool for the delivery of drugs to be used for therapies in which a lag phase is desired after administration.

In particular, this technology is exploitable in those cases in which disease symptoms are predominantly experienced during the night or early morning hours. Examples of such pathologies are bronchial asthma, with more frequent dyspneic attacks during the night hours, sleep disorders such as early morning awakening, rheumatoid arthritis and cardiovascular disease with prevailing incidence in the early morning.

ChronoCap devices would in these instances allow the release and absorption of the active ingredient to be aligned with the appearance of the symptoms, thus enhancing the efficacy and safety of the therapy.

The ChronoCap delivery technology is reasonably expected to meet general feasibility and scale-up criteria and to involve a relatively limited regulatory burden.

References

A Novel Injection-Molded Capsular Device for Oral Pulsatile Delivery Based on Swellable/Erodible Polymers - A. Gazzaniga, M. Cerea, A. Cozzi, A. Foppoli, A. Maroni, L. Zema
AAPS PharmSciTech, **12**, 295 (2011)

Injection Molding and its application to drug delivery - L. Zema, G. Loreti, A. Melocchi, A. Maroni, A. Gazzaniga
J. Control. Release **159**, 324 (2012)

Gastroresistant capsular device prepared by injection molding - L. Zema, G. Loreti, A. Melocchi, A. Maroni, L. Palugan, A. Gazzaniga
Int. J. Pharmaceut. **440**, 264 (2013)

Enteric-coating of pulsatile-release HPC capsules prepared by injection molding - E. Macchi, L. Zema, A. Maroni, A. Gazzaniga, L.A. Felton
European Journal of Pharmaceutical Sciences, **70**, 1 (2015)

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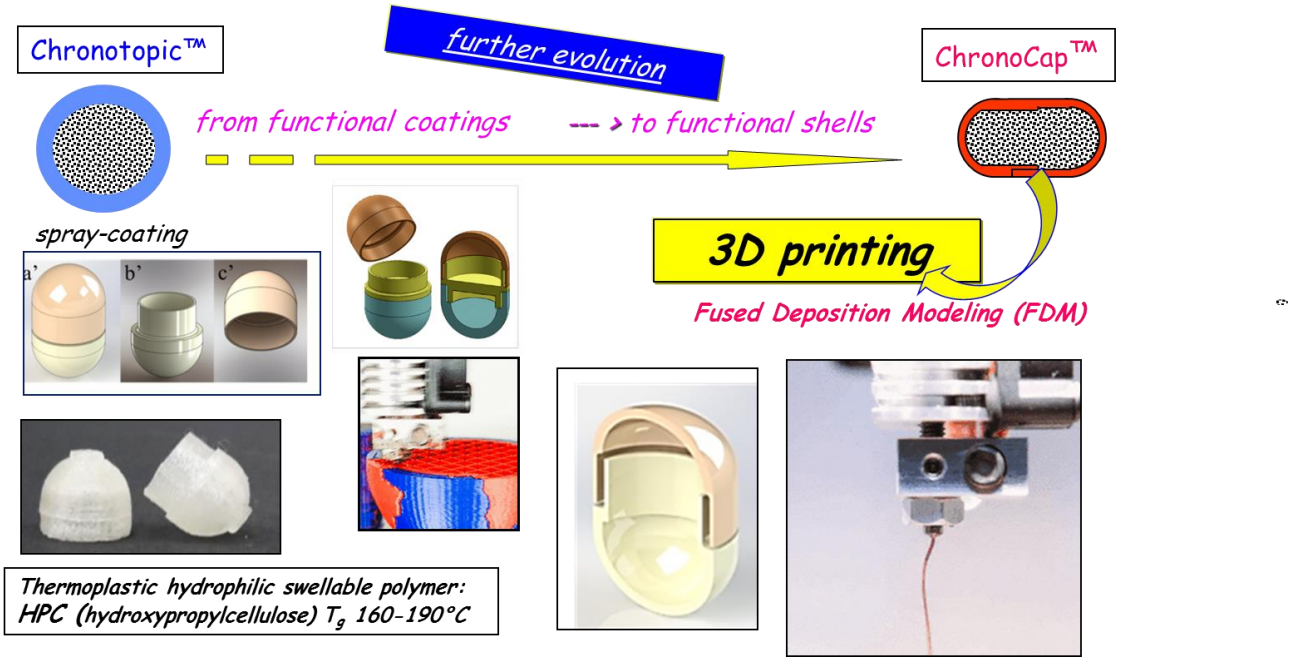
- 3D Printing (Fused Deposition Modeling FDM) of filaments based on swellable/erodible hydrophilic polymers (GRAS materials) was proposed as further evolution of the ***CHRONOTOPIC™ TECHNOLOGY***

Recently, the interest in the 3D printing of drug products has rapidly grown in the prospect of fulfilling upcoming needs of personalized medicine.

Moreover, because of the great flexibility 3D printing can grant, the manufacturing of very small batches might be viable, thus enabling the extemporaneous preparation of customized galenical formulations (e.g. hospital pharmacy).

The feasibility of 3D printing in the manufacturing of HPC-based swellable/erodible capsular devices for oral pulsatile release was first assessed. Fused deposition modeling (FDM) was the selected 3D printing technique.



It involves the use of thermoplastic materials supplied in the form of filaments that are extruded through a tip under defined pressure conditions and progressively layered in a melted/softened state to build up the final product.

The 3D printing process by FDM does not require the use of solvents and, therefore, may be easier, faster and more cost-effective (especially the post-process) with respect to powder solidification processes commonly employed. However, it shows comparable versatility in terms of

design (shape, dimension, presence of cavities, layers, coatings or any type of details), composition and, consequently, release performance achievable.

By using a standard MakerBot Replicator 2 3D printer and the PLA filament supplied, the possibility of printing hollow structures with minimum post-process steps was initially demonstrated. In addition, through the progressive definition of CAD files and modification of the hardware and software of the printer, bodies and caps were obtained, which were assembled to give tight devices analogous to 600 µm Chronocap™ shells.

HPC filaments suitable for feeding the FDM 3D printing equipment were successfully manufactured by HME, with the aid of purposely-designed tools, such as an appropriate extrusion die and the pulling/calibrating device.
Capsular devices were fabricated starting from a neat HPC filament. Their physico-technological characteristics, morphological changes following interaction with water and release performance turned out comparable with those of analogous molded systems with the same composition, thereby pointing out the real-time prototyping ability of FDM with respect to the Chronocap™ technology.

Data concerning the preparation of ChronoCap™ by FDM were presented at the Annual Workshop of the CRS Italy Chapter "Nanomedicine: pharmacokinetic challenges, targeting and clinical outcomes", Florence, November 6-8, 2014. EXTENDED ABSTRACT and the relevant POSTER communication are available at this link and this link, respectively.

References

3D-printing: application potential for the manufacturing of drug delivery systems in the form of capsular devices - A. Melocchi, F. Parietti, G. Loreti, A. Maroni, L. Zema, A. Gazzaniga
Proceedings of Annual Workshop of the CRS Italy Chapter "Nanomedicine: pharmacokinetic challenges, targeting and clinical outcomes", Florence, 6th November (2014) ---- > Extended Abstract, Poster

3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs - A. Melocchi, F. Parietti, G. Loreti, A. Maroni, A. Gazzaniga, L. Zema
Journal of Drug Science and Technology, **30**,360 (2015)

Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling - A. Melocchi, F. Parietti, A. Maroni, A. Foppoli, A. Gazzaniga, L. Zema
International Journal of Pharmaceutics, **509**, 255 (2016)

3D printed multi-compartment capsular devices for two-pulse oral drug delivery- A. Maroni, A. Melocchi, F. Parietti A. Foppoli, L. Zema, A. Gazzaniga
Journal of Controlled Release - **268**, 10 (2017)

Three-Dimensional Printing of Medicinal Products and the Challenge of Personalized Therapy - L. Zema, A. Melocchi, A. Maroni, A. Gazzaniga
Journal of Pharmaceutical Sciences, **106**, 1697 (2017)

Industrial Development of a 3D-Printed Nutraceutical Delivery Platform in the Form of a Multicompartment HPC Capsule - A. Melocchi, F. Parietti, S. Maccagnan, M.A. Ortenzi, S. Antenucci, F. Briatico-Vangosa, A. Maroni, A. Gazzaniga, L. Zema
AAPS PharmSciTech, **19**, 3343 (2018)

Expandable drug delivery system for gastric retention based on shape memory polymers: development via 4D printing and extrusion – A. Melocchi, M. Uboldi, N. Inverardi, F. Briatico-Vangosa, F. Baldi, S. Pandini, G. Scalet, F. Auricchio, M. Cerea, A. Foppoli, A. Maroni, L. Zema, A. Gazzaniga
International Journal of Pharmaceutics, **571**, 118700 (2019)

Retentive device for intravesical drug delivery based on water-induced shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility – A. Melocchi, N. Inverardi, M. Uboldi, F. Baldi, A. Maroni, S. Pandini, F. Briatico-Vangosa, L. Zema, A. Gazzaniga
International Journal of Pharmaceutics, **559**, 299 (2019)

Lego-inspired capsular devices for the development of personalized dietary supplements: proof of concept with multimodal release of caffeine - A. Melocchi, M. Uboldi, F. Parietti, M. Cerea, A. Foppoli, L. Palugan, A. Gazzaniga, A. Maroni, L. Zema
Journal of Pharmaceutical Sciences, doi: 10.1016/j.xphs.2020.02.013, (2020)

3D printing by fused deposition modeling of single- and multi-compartment hollow systems for oral delivery - A review – A. Melocchi, M. Uboldi, A. Maroni, A. Foppoli, L. Palugan, L. Zema, A. Gazzaniga
International Journal of Pharmaceutics, **579**, 119155 (2020)

Retentive drug delivery systems based on shape memory materials - A Maroni, A Melocchi, L Zema, A Foppoli, A Gazzaniga
Journal of Applied Polymer Science, 48798 (2020)