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).

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**

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Injection Molding and its application to drug delivery - L. Zema, G. Loreti, A. Melocchi, A. Maroni, A. Gazzaniga

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)

- **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.

References


3D printed multi-compartment capsular devices for two-pulse oral drug delivery

Three-Dimensional Printing of Medicinal Products and the Challenge of Personalized Therapy
L. Zema, A. Melocchi, A. Maroni, A. Gazzaniga

Industrial Development of a 3D-Printed Nutraceutical Delivery Platform in the Form of a Multicompartment HPC Capsule
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