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Modified-Release Drug Delivery Technology

Second Edition

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Pulsincap™ and Hydrophilic Sandwich Capsules: Innovative Time-Delayed Oral Drug Delivery Technologies

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INTRODUCTION

Chronopharmaceutical drug delivery (1) discussed the delivery of drugs in accordance with the circadian rhythms of the disease. The identification of a specific time-dependent "trigger" capable of provoking drug release from an oral formulation after a pre-determined time interval represents a significant challenge to the pharmaceutical formulator.

PULSINCAP™ TECHNOLOGIES

Three variants on a capsule theme have been developed that trace their origins back to PolySystems Ltd, a small Scottish company in the late 1980s. The first concept consisted of a device based on the separation of a plug from an insoluble capsule body which was first described by Rashid (2). This formulation, which was described in the patent literature, comprised a water permeable body (Fig. 1) prepared from a water swellable hydrogel cross-linked polyethylene glycol (PEG) polymer. Depending on their composition, such polymers have the capacity to swell significantly, but in a controlled manner, in aqueous media. A swelling agent (powdered high-swelling polymer) mixed with drug, was filled into the internal cavity of Rashid's molded capsule body and a plug (also of high-swelling polymer) was used to seal the contents into the internal cavity. The rate at which water diffused

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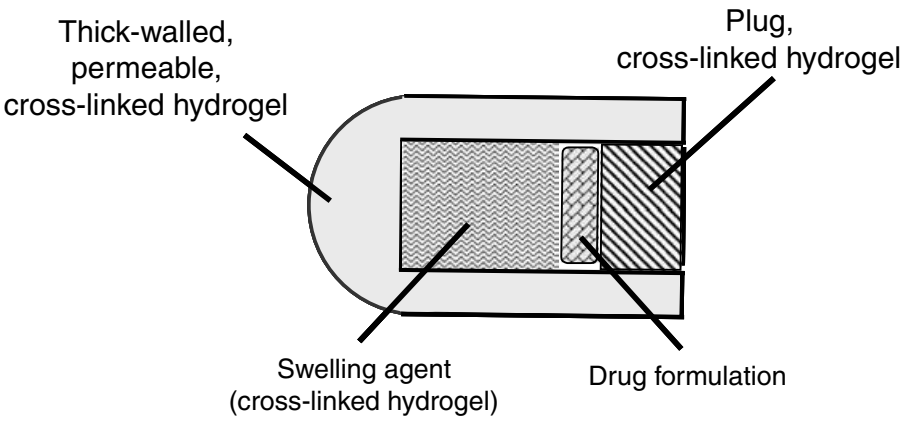

Figure 1 Pulsatile hydrogel capsule. *Source*: From Ref. 2.

into the core was controlled by the hydrogel composition and wall thickness of the capsule. The delay period prior to drug release was defined by the time taken for fluid to diffuse through the wall. When fluid came into contact with the capsule contents, the high-swelling polymer absorbed water rapidly, swelled and caused internal pressure to be generated inside the capsule. This pressure caused the plug to be expelled from the neck of the capsule and drug to be released in a pulsatile manner. Optimization of the construction of the components and the chemistry of the hydrogel polymers enabled time-delays to be controlled reproducibly.

A manually prepared prototype formulation with a 5-hour lag time was the subject of a pharmacokinetic study in man designed to release captopril in the colon of the fasted volunteers. Scintigraphic observations confirmed that drug was released from the capsule at the target site, however, pharmacokinetic analysis confirmed that minimal absorption had taken place from the colon (3).

Molding the thermosetting hydrogel polymers required for the capsule body was a very complex process that did not lend itself to industrial scale-up. Further developments of this technology, now more widely referred to as Pulsincap™, were undertaken and improved devices were described in the patent literature (4). Polysystems was acquired by RP Scherer Corporation in 1990 and the Pulsincap technology was then developed by Scherer DDS Ltd. This second generation Pulsincap device was less complex than Rashid's earlier capsule and the hydrogel body of the earlier formulation was now replaced by a gelatin capsule, film-coated with ethyl cellulose to render it impermeable (Fig. 2). The link to hydrogel polymer chemistry was retained and a molded hydrogel plug was used to seal the drug contents into the capsule body. In the presence of fluid, the plug swelled at a controlled rate that was independent of the nature or pH of the medium (5).

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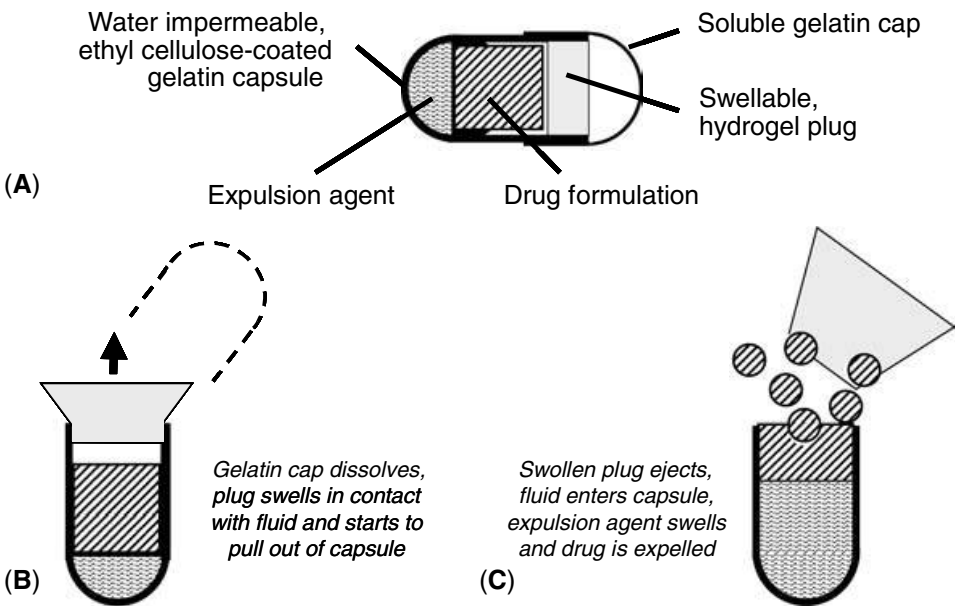

Figure 2 Pulsincap™ delivery system. *Source*: From Ref. 4.

As it swelled, the plug developed a frustro-conical shape and slowly pulled itself out of the capsule. The length of the plug and its insertion distance into the capsule controlled the pulse time reliably.

This second generation Pulsincap formulation has been studied in numerous human volunteer studies (e.g., (6,7)) and was well tolerated in man (8). In order to effect complete drug release from the capsule following plug ejection, an active expulsion system was employed to rapidly and completely expel the contents from the capsule, as demonstrated with delivery of salbutamol to human volunteers, where the expulsion system low-substituted hydroxypropylcellulose (LH-21®, Shin-Etsu) was employed (9,10).

Due to the fact that the mechanism of action was controlled by the plug sliding out of the capsule, a significant factor for the correct operation of Pulsincap was the tightness of fit of the hydrogel plug in the capsule. If the fit of the plug was too slack it ejected prematurely, whereas when it fitted too tightly, drug was released erratically (11). In order to respect the very tight dimensional specifications demanded for predictable operation, each plug was subjected to three-dimensional measurement using laser gauges. As a result of the cost implication of this requirement, the delivery system was never adopted for large scale human healthcare applications. However, a low volume diagnostic test kit based on Pulsincap releasing nutrient components into a microbial test medium after a 6-hour lag time, was commercialized in 1997 (SprintSalmonella™, Oxoid Ltd, Basingstoke, UK).

More recent studies have been undertaken on a further simplified adaptation of the technology. Now working at Strathclyde University Stevens et al. (12) and Ross et al. (13) eliminated reliance on hydrogel

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