Journal of Drug Delivery Science and Technology 32 (2016) 229–235

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Research paper

Erodible drug delivery systems for time-controlled release into the gastrointestinal tract

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ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form
1 October 2015
Accepted 2 October 2015
Available online 8 October 2015

Keywords:
Oral pulsatile release
Oral colon delivery
Coating
Swellable/erodible hydrophilic polymers
Injection-molding
Fused deposition modeling 3D printing

ABSTRACT

In oral delivery, lag phases of programmable duration that precede drug release may be advantageous in a number of instances, e.g. to meet chronotherapeutic needs or pursue colonic delivery. Systems that give rise to characteristic lag phases in their release profiles, i.e. intended for time-controlled release, are generally composed of a drug-containing core and a functional polymeric barrier. According to the nature of the polymer, the latter may delay the onset of drug release by acting as a rupturable, permeable or erodible boundary layer. Erodible systems are mostly based on water swellable polymers, such as hydrophilic cellulose ethers, and the release of the incorporated drug is deferred through the progressive hydration and erosion of the polymeric barrier upon contact with aqueous fluids. The extent of delay depends on the employed polymer, particularly on its viscosity grade, and on the thickness of the layer applied. The manufacturing technique may also have an impact on the performance of such systems. Double-compression and spray-coating have mainly been used, resulting in differing technical issues and release outcomes. In this article, an update on delivery systems based on erodible polymer barriers (coatings, shells) for time-controlled release is presented.

1. Introduction

Oral delivery systems for time-controlled release are able to defer the onset of drug release into the gastrointestinal tract for a programmable lag period independent of pH, ionic strength, enzyme concentration and other physiological parameters. It is by now recognized that a delay prior to release may be advantageous for effective pharmacological treatment of several pathologic conditions [1]. This is typically the case with a variety of high-morbidity rheumatic, cardiovascular and respiratory chronic diseases, which show cyclic patterns in their signs and symptoms [1,2]. When these mainly recur at night or in the early morning hours, bedtime administration of drug products having a proper lag phase in their release profile would help provide pharmacological protection as needed. On the other hand, both untimely awakenings, as an immediate-release dosage form would require, and exposure to unnecessarily sustained therapeutic drug levels, as prolonged-release formulations taken before sleep would entail, could thereby be overcome. As a result, not only the efficacy and safety of a treatment but also the relevant patient compliance may greatly be enhanced through the use of chronopharmaceutical delivery systems.

Besides, a lag phase prior to release allows to target the colonic region with drug molecules intended for either a local action, e.g. to treat Inflammatory Bowel Disease (IBD), or for systemic absorption, especially of biotech molecules that pose stability issues in the proximal gut and may benefit from the aid of enhancers for mucosal permeation [3,4]. When colon delivery is sought, the lag phase is expected to last throughout the entire small intestinal transit (3 h ± 1 SD), which was reported not to be strongly influenced by the characteristics of dosage units and by food intake [5,6]. Moreover, the lag period should be started upon emptying from the stomach rather than on administration, owing to the high variability of gastric residence that cannot reliably be predicted. Hence, in order to attain colonic release based on a time-controlled approach, enteric coating is generally required.

Repeated lag phases, each followed by the release of a drug dose fraction, may be exploited to fulfill multiple daily administration

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http://dx.doi.org/10.1016/j.jddst.2015.10.001
1773-2247/

regimens when prolonged release is not a viable option, e.g. because of pharmacokinetic (strong first-pass effect) or pharmacodynamic (tolerance) constraints. Successive release pulses are also proposed as an alternative strategy in antibiotic therapy, possibly resulting in restrained growth of resistant bacterial strains [7].

Finally, properly modulated lag phases prior to the release of co-administered bioactive compounds may avoid undesired drug–-drug interactions in the gastrointestinal tract and overcome the need for differing dosing schedules, thus improving the overall patient convenience and compliance [8].

Peroral delivery systems for time-controlled release are expected to yield lag phases on the order of few hours, which may be consistent with their mean residence time within the digestive tract. These are often pursued through functional polymeric barriers that enclose an inner drug formulation [9,10]. According to the physico-chemical properties of their polymeric components and type of excipients added (plasticizers, pore formers, bulking agents), such barriers delay the onset of release via differing mechanisms. They may indeed undergo time-programmed disruption, become leaky or be subject to progressive erosion/dissolution. In particular, erodible systems are generally single-unit dosage forms based on a drug containing-core, such as an immediate-release tablet or capsule, and a swellable hydrophilic barrier of adequate thickness and polymer viscosity. Such a barrier may be a coating or, in more recent and innovative instances, a freestanding release-modifying shell ready for filling with any drug formulation.

Because of the inherent safety and biocompatibility profile as well as of their availability in a range of grades and reasonable costs, hydrophilic cellulose derivatives, namely hydroxypropyl methylcellulose (HPMC) and, less frequently, hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC), are broadly used as the functional polymers in erodible delivery systems [11]. Other polysaccharides, including galactomannans, alginates, xanthan gum, and non-saccharide hydrophilic polymers, such as polyvinyl alcohol (PVA) and polyethylene oxide (PEO), are nonetheless also employed. All of these materials are largely utilized in the food, pharmaceutical, nutraceutical and cosmetic industries mainly as rheology-modifiers, stabilizers, binders and film-coating agents.

Upon water uptake, such polymers typically go through a glassy-rubbery thermodynamic transition that is associated with distension and disentanglement of their macromolecular chains [12–14]. Consequently, the polymer structure may expand, erode due to mechanical attrition and/or dissolve at a rate that chiefly depends on the relevant physico-chemical characteristics and on the ionic strength and temperature of the medium. As the aqueous fluid penetrates into the polymeric layer, a swelling front, i.e. the boundary between the glassy and the rubbery domain, and an erosion front, at the interface between the rubbery polymer and the outer medium, are identified. Depending on the relative movements of the swelling and erosion fronts, which in turn are governed by the hydration, dissolution and viscosity properties of the polymer, a gel layer of varying thickness is formed.

In a few instances, insoluble materials are added to the hydrophilic polymers to modulate the extent of hydration of the barrier, or even used as the main components of mechanically erodible coatings. In the latter case, their erosion in aqueous fluids would need to be promoted by surfactant excipients.

Drug release from hydrophilic erodible systems is in principle deferred until the entire polymeric layer is in the swollen state, i.e. when the swelling front has reached the drug core, possibly followed by extensive dissolution/erosion of the hydrated polymer. The duration of the lag phase is indeed dictated by the physico-chemical properties of the polymer employed, primarily molecular weight and degree of hydrophilicity, and by the thickness of the erodible barrier. The manufacturing technique, which may range from double-compression and spray-coating to hot-processing, can also affect the layer functionality.

In the following sections, oral delivery systems for time-controlled release provided with an erodible polymer barrier are reviewed, and advances in this particular field are illustrated with special emphasis on formulation and performance issues.

2. Erodible systems manufactured by double-compression

The manufacturing of oral delivery systems provided with erodible coatings dates back to the early 90s. Until then, the use of such polymers in the manufacturing of solid dosage forms was tied to tableted hydrophilic matrices for prolonged release. Indeed, double-compression technique, also known as press-coating, was adopted in all initial attempts. The first one concerned a three-layer tablet system that was proposed for two-pulse release of drugs [15,16]. Such a system was composed of two conventional drug (ibuprofen) layers and a high-viscosity HPMC (Methocel® K4M and Methocel® K15M) barrier in between. An impermeable ethyl cellulose (EC) film covered the lateral area and one of the bases of the assembly so that the outer surface of a single drug layer was allowed to interact with solvent upon first contact with the medium. The former dose fraction was thereby released, whereas the latter was released after a lag phase due to the hydration and erosion of the polymer barrier. The delay between the release pulses depended on the viscosity of the polymers employed, and release of the latter dose fraction was slower. This was ascribed to a less efficient activation of the disintegrant incorporated within the inner drug layer that was progressively exposed to the aqueous fluid. The release behavior observed *in vitro* was reflected in two-peak plasma concentration curves in healthy volunteers. However, because of its multiple-layer configuration and the need for a partial coating, the system would involve serious scalability issues. Therefore, a simpler press-coated formulation was designed, wherein the polymer, a low-viscosity HPMC (Methocel® K100 LV), covered the entire surface of the core [17]. The coated system could yield single-pulse release after a lag phase or, administered in combination with an immediate-release tablet, the repeated release performance attained from the previous device. In the double-compression process, positioning of the core tablet in the die represented a critical step. However, by correctly centering it within the polymer powder bed, biconvex tablets with coatings of homogeneous thickness were obtained. As desired, the *in vitro* release was delayed for a reproducible period of time, although leaching of a small percentage of the drug content prior to the quantitative release phase was inferred from the curves. This was ascribed to premature outward diffusion of dissolved drug molecules through the swollen polymer coating.

A low- and a high-viscosity HPMC grade (Methocel® K100 and Methocel® K4M) were used, either alone or mixed with each other, as the coating agents of a delivery system containing ibuprofen, aimed at the chronotherapy of rheumatoid arthritis, or pseudoephedrine hydrochloride, a water-soluble model drug [18–20]. Increasing the coating level or the amount of high- vs low-viscosity polymer resulted in longer lag times and slower *in vitro* release as well as decreased absorption rates in healthy volunteers. Sodium alginate, as compared with HPMC, performed as a less effective barrier-forming polymer. Incorporation of a fraction of the drug dose in the coating layer changed the release behavior, generally yielding biphasic kinetics that depended on the composition of the polymeric coat and its drug load.

High-viscosity HPMC (Methocel® K4M, Methocel® K15M and Methocel® K100M) was employed to prepare a system intended for