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Review

Coated pellets for oral colon delivery

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ABSTRACT

Because of their spherical or pseudo-spherical shape, uniform size and smooth surface, pellets are of particular interest for use as cores in the manufacturing of coated oral delivery systems. When intended for colon delivery, pellet formulations may be provided with enzymatically-degradable, pH-sensitive or time-controlled polymer coatings. While layers that are liable to microbial breakdown or pH-dependent dissolution would enable targeted release as triggered by physiological characteristics of the environment where the drug is intended to be delivered, time-based coats possess an intrinsic ability to defer its release throughout the small intestinal transit of the dosage form irrespective of regional differences in terms of pH, microbial population and other variables. Rupturable, erodible and permeable coats have been described for time-based colonic release. According to their formulation strategies, coated pellets that have been proposed for colon delivery are reviewed and discussed in the present article.

1. Introduction

Pellets are multiple-unit pharmaceutical dosage forms, characterized by spherical or pseudo-spherical shape, smooth surface, dimensions generally comprised between 500 and 1500 μm, relatively high density and excellent flowability [1–3]. They are generally administered orally in hard-gelatin capsules or tablets, able to release, after intake, a large number of subunits, each containing a fraction of the total dose [4].

The production techniques for obtaining pellets are usually described as size-enlargement processes. These include direct pelletization (by high-shear mixer or fluidized bed), hot melt extrusion (HME) or wet extrusion (extrusion/spheronization), layering of drug powders, suspensions or solutions onto inert cores (powder-, suspension- and solution-layering) and also the compaction of powders to small tablets, 1.5–2.5 mm in diameter, known as minitablets [1–3].

Pellets find specific application in the preparation of modified-release oral dosage forms when formulated as either matrix systems or coated reservoirs. Matrix systems are composed of an active ingredient closely dispersed within inert or swellable excipients able to control the drug release behaviour [5–7]. On the other hand, reservoir systems are designed as drug-containing cores, coated with one or more layers capable of defining the release kinetics. The release profiles are therefore determined by the thickness and the formulation characteristics of the coatings applied. The various techniques described in the literature for the application of coatings to pellets involve the formation of membranes produced by film-forming agents (mainly polymeric materials) delivered onto the surface of the cores as liquids or solids [8,9]. When the coating systems are delivered as liquids, the film-forming agents are typically nebulized onto the surface of the cores as a solution or suspension in organic solvents or water. Since the cores are simultaneously heated by a flux of hot air, the liquid vehicle evaporates leaving a dry and solid film on their surface. In order to avoid or limit the use of solvents during the coating process, the film may be applied by spraying molten materials, which cool when in contact with the cores, or powders. Dry powder coating uses solid materials only, thus completely avoiding the need for liquids of any kind, while liquid-assisted powder coating requires liquid aids for promoting the adhesion of the powders onto the surface (liquid binder) or enabling the film formation process (liquid plasticizer) [10]. In this way, solid particles can eventually coalesce to form a continuous film. Coating processes for pellets can industrially be performed by fluid bed equipment (top, bottom or tangential spray) or coating pan. As regards fluid bed, the bottom-spray mode, which was purposely devised for the coating of small-unit substrates, is generally preferred, although tangential spray is also used at present [11]. In case the coating of pellets is performed by pan, non-perforated drums are employed with few

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modifications, such as the air flow pattern, with respect to when single-unit dosage forms are processed. However, examples of perforated pans suited for pellet coating are also available.

The use of pellets as cores offers many advantages in terms of technological characteristics and biopharmaceutical properties. From a technological point of view, it is possible to count on their regular shape, surface smoothness and adequate mechanical resistance that overall promote the application of coatings, and the fact that pellet cores can be loaded with high drug doses [12–14]. On the other hand, the biopharmaceutical advantages are mainly related to the lower variability of the drug absorption profile that is expected when modified-release dosage forms are formulated as multiple units rather than as single units [15,16]. As a matter of fact, for single-unit systems the gastric emptying time is strongly influenced by the inter-digestive or digestive phase in which administration takes place. In contrast, multiple-unit dosage forms consisting of numerous small subunits may be able, depending on their size and density, to pass the stomach when the pylorus is contracted and spread along the gut, thus possibly reducing the gastrontestinal transit variability and, particularly when the drug absorption rate is affected by the release site, the inter- and intra-subject differences in the absorption profiles. Another advantageous aspect of pellets is related to the subdivision of the dose in several subunits, which allows a distribution of the delivered dose on an extended surface area thus lowering the potential risk of mucosal injury caused by high local drug concentrations. Moreover, the subdivision of the dose reduces the possibility of dose-dumping.

In modified-release oral dosage forms, coating layers may be responsible for sustaining drug release, modifying the relevant onset or preventing it from taking place in specific regions of the gastrointestinal tract. In the latter instance, the coatings are required to ensure that the delivery system conveys its drug load to the target site and that the contact between the drug compartment and the biological fluids is hindered until release.

In the case of colon delivery, the release of the active ingredient needs to be prevented during gastric residence as well as throughout small intestinal transit of the dosage form. Release would then occur based on environmental differences between the small and the large intestine, such as those encountered in the quali-quantitative composition of the microbiota and pH of the contents, or on transit times [17,18].

Notably, the microbial population present in the colon is much more abundant than that residing in the small intestine and catalyzes an array of enzymatic reactions, many of which do not take place in the upper intestine [19–21]. Accordingly, various natural or synthetic polymers that are selectively degraded by colonic bacteria have been used for colon targeting either as carriers in prodrugs or as coating or bulking excipients in drug delivery systems. Such polymers generally bear glycoside or azo bonds that are susceptible to cleavage by the resident microbiota.

The pH of the fluids in the caecum and ascending colon is known to be slightly acidic because of bacterial fermentation activities that cause local accumulation of short-chain fatty acids [22,23]. Moving down to the transverse and descending branches of the colon, a neutral to weakly basic environment is re-established due to the progressive absorption of fermentation products. Therefore, polymers with pH-dependent solubility, soluble at pH values above 5 (enteric polymers), have frequently been applied as relatively thick films intended to protect the core formulation during gastric residence and transit through the proximal small bowel. These films dissolve in the distal ileum or colon regions. Alternatively, polymers soluble at pH values below 5 have been proposed as coating agents to match the fall in pH that is commonly observed in the proximal colon [24]. In this case, however, an outer enteric film needs to be added to prevent the dissolution of the targeting layer while the dosage form is positioned in the stomach.

Lastly, unlike transit through the stomach, the mean transit time throughout the small intestine was reported to be fairly consistent (3 ± 1 h) and poorly dependent on the size and density of the dosage forms as well as on the feeding state of the subjects, although significant acceleration was observed upon administration of non-disintegrating single units in a pre-feed state [25–29]. In the colon, solid substrates generally reside for longer periods than in the small bowel because of less frequent propulsive peristaltic waves [30]. Therefore, systems intended to release the active ingredient after a sufficiently extended lag phase to cover residence in the small intestine have been exploited as time-dependent colon delivery platforms [17,18,31,32]. These systems require the application of an external enteric coating in order to circumvent the variability of gastric emptying time.

The colon represents an important release site for locally-acting molecules administered via the oral route. At present, long-term therapy of inflammatory bowel disease (IBD) mainly relies on targeted release of anti-inflammatory drugs [33,34]. Moreover, it has been suggested that local delivery of cycloxigenase-2 inhibitors and anti-cancer drugs would enable more tolerable chemopreventive and chemotherapeutic treatments for colorectal adenocarcinoma, respectively [35–37]. The release of β-lactamases into the large bowel could also provide a means of inactivating antibiotic residues that could harm the health state of the mucosa [38,39]. In addition, the colon has been investigated as an absorption site for biotechnological drugs intended for a systemic action, such as peptides and proteins, that often show poor stability and permeability in the GI tract [40–42]. Because of the limited protease concentration and of a greater susceptibility of the epithelium to permeation enhancement, the colon may indeed represent a more convenient release environment for these molecules.

In the following sections, pellet formulations provided with colon targeting coatings are described according to the inherent design strategies. In Tables 1–3, reviewed pellet-based delivery systems with enzymatically degradable, pH-sensitive and time-controlled coats are listed, respectively, along with details on the relevant processing and composition.

2. Pellets with enzymatically degradable coatings

Naturally-occurring polysaccharides, such as pectin, chitosan, galactomannan and amylose, are generally preferred coating materials because of their safety profiles and administration as food additives.

2.1. Pectin-based coatings

Pectin is a heteropolysaccharide having a high α-D-galacturonic acid content achievable from plant cell walls [43]. It is commercially available in low- and high-methoxylated forms (LM and HM) depending on the amount of etheric residues bestowing different reactivity, viscosity and solubility properties. Pectin has been employed for colon delivery as a matrix-forming or compression-coating agent [44]. In this case, it is generally admixed with insoluble polymers in order to achieve a more effective protection for the drug core.

A pectin/ethylcellulose (EC) mixture was applied to pellets containing either paracetamol or 5-aminosalicylic acid (5-ASA) for the treatment of IBD [45,46]. Different ratios between pectin and EC were used, and theoretical weight gains from 12 to 55% were reached. Enhanced barrier properties of the coating were observed in simulated small intestinal fluid at pH 7.4 when an initial acid phase of the test (30 min or 2 h at pH 1.4) was performed. The