

## Particulate Carriers for Local Colon Drug Delivery

Marija Glavas-Dodov\*

Center of Pharmaceutical Nanotechnology, Department of Pharmaceutical Technology, Faculty of Pharmacy, Ss. Cyril and Methodius University, Skopje, Macedonia

### Editorial

Targeted drug delivery into the colon is highly desirable for efficient treatment of a variety of bowel diseases such as inflammatory bowel diseases, amoebiasis and helminthiasis, colonic cancer, as well as systemic delivery of protein and peptide drugs. The concept of colon specific delivery *via* per oral route is to achieve improved localization and controlled release of the drug substance at the site of action, thus minimizing the premature release and subsequent absorption in the blood circulation. In addition, minimizing the intestinal absorption using different formulation design approaches could improve the safety and reduce the adverse effects of the treatments. However, the main disadvantage of today's therapy and designed drug delivery systems is the inability to target the drug directly to the affected tissue and/or to maintain high local concentration. The colon is having high water absorption capacity, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. In addition to poor localization, extensive metabolism at the level of the epithelial cells of the intestinal wall might further impair local concentration required for improved drug efficacy.

With the arrival of newer innovations, a large number of breakthrough technologies have emerged for targeting drug molecules to the colon. Knowledge and experience from micro- and nanotechnology and advanced polymer chemistry, combined with the understanding of cellular and molecular pathogenesis of the specific colon disease could overcome limited performance of conventional therapy and could enable safe and efficacious delivery of newly developed therapeutic agents.

This editorial article is not intended to offer a comprehensive review on drug delivery systems, but shall familiarize the readers with the novel formulation technologies (particulate carrier systems) that have been developed for attaining colon-specific drug delivery.

The selection of carrier for particular drug substance depends on the physico-chemical nature of the drug as well as the disease for which the system is to be used. Polymer-based carriers (used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the designed systems. Among the most recent systems developed for colon-specific delivery, particulate carriers such as micro- and nano-particles (MP and NP) are unique in terms of increasing drug stability *via* encapsulation, achieving *in vivo* site specificity (passive targeting to colon mucosa or active targeting with site-specific ligands), controlled drug release, design rationale and feasibility of the manufacturing process. Very well-known fact is that the optimal particle size of the carrier for localization and prolonged residence time in the colon region is between 4 and 15  $\mu\text{m}$ , in order to achieve a relatively large surface area and excessive adhesion at the site of action. Carrier systems in that size range are able to attach more efficiently to the mucus layer and accumulate in the targeted region. In animal studies, luminal uptake into inflamed mucosal areas has been shown to be size dependent. When particles of different sizes are compared one simple conclusion can be drawn; that increased retention of particles of all sizes below 10  $\mu\text{m}$  is noticed in inflamed

tissue and with further size reduction the retention effect is maximized and the clearance minimized at the size of approximately 100 nm [1].

Therefore, MP prepared from natural biodegradable polysaccharides (e.g., pectin, guar gum, inulin, chitosan, chondroitin sulfate, alginates and dextran) and their combinations were extensively studied in the past years for treatment of colon specific diseases. Polysaccharides based particles are assumed to remain intact in the physiological environment of stomach and small intestine, but once they reach in the colon, they are acted upon by the bacterial polysaccharidases and result in the degradation of the carriers. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature, and swell under exposure to upper GI conditions, which leads to premature drug release. To overcome this problem, the natural polysaccharides were chemically modified and mixed with hydrophobic water insoluble polymers, whereas in the case of MP formulations they are usually coated with pH sensitive (enteric coating) polymers. Implementing above stated targeting principles (particle size, polymer properties, surface charge, pH dependent solubility and/or swelling) considerable amount of research works has been carried out using MP for local colon delivery of metronidazole, budesonide, prednisolone, 5-fluorouracil, ondansetron, 5-aminosalicylic acid, etc. [2,3].

NP composed of natural or synthetic polymers have also been investigated as carriers for targeted administration to specific organ or cells or controlled drug delivery. Orally administered NP serve as carriers for different types of drugs and have been shown to enhance their solubility, permeability and bioavailability. For colonic pathologies, it was shown that NP tends to accumulate at the site of inflammation in inflammatory bowel diseases and colonic cancer. However, an important area of concern is to prevent loss of NP in the early transit through GI tract in order to optimize therapeutic efficacy. Moreover, particle uptake by Payer's patches and/or enzymatic degradation may cause the release of entrapped drug leading to systemic drug absorption and side effects. In order to overcome this problem, drug loaded NP could be encapsulated into pH sensitive microspheres, which serve to deliver the incorporated NP to their site of action, thereby preventing an early drug leakage. The use of bioadhesive NP has also been investigated for successful active targeting in colon-specific diseases. NP has a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of nonspecific nature, bioadhesion

\*Corresponding author: Marija Glavas-Dodov, Center of Pharmaceutical Nanotechnology, Department of Pharmaceutical Technology, Faculty of Pharmacy, Ss. Cyril and Methodius University, Vodnjanska 17, Skopje, Macedonia, E-mail: [magl@ff.ukim.edu.mk](mailto:magl@ff.ukim.edu.mk)

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can be achieved by chemical alteration of nanosized drug carriers with targeting components that precisely recognize and specifically interact with cell surface carbohydrates, receptors or antigens, thus provoking cytoadhesion, cellular internalization and drug release at the desired target site [1,4]. Therefore, advents in nanotechnology have opened new avenues to transform the Paul Ehrlich's concept of "magic bullet" into clinical reality.

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