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Multiparticulate Carriers for Controlled Oral Drug Delivery

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Oral delivery is the most common route of drug administration for systemic use; it has many advantages including ease of administration, dosing and dosage form flexibility, together with advantages related to the cost and simplicity of manufacturing process compared to other routes of systemic drug delivery [1].

Oral route avoids many parenteral-related problems due to non-invasiveness, lower risk of complications and drug intoxication during and after drug administration in addition of being cost-effective and easier to manufacture and scale-up[2].

From the anatomical point of view, the gastrointestinal tract (GIT) can be divided into a lower and upper part. The upper GIT consists of the mouth, oesophagus and stomach. The lower GIT is divided into the small intestine (duodenum, jejunum and ileum) and large intestine (caecum, colon and rectum). Tight junction epithelial cells that are covered by a protective surface coating of mucus are lining the GIT. Numerous bacteria colonize the intestinal mucosa and provide a barrier against environmental threats and pathogens[3].

The protective mucoid lining is a negatively charged matrix that varies in thickness and mucoadhesion capability along the GIT, this structure provides surface adherence and drug retention enhancing drug absorption to the systemic circulation[4].

Beside the numerous advantages listed above for oral delivery, there are many obstacles and problems facing this route of administration. These comprise drug-drug as well as food-drug interaction, varying rates of gastric emptying and intestinal transit, inactivation of some drugs by the liver following their absorption from the gut (first-pass metabolism), being unsuitable in some cases like in elderly, neonates, comatosed and sedated patients, as well as in cases suffering from vomiting and diarrhea. In addition to problems related to absorption of some drugs due to their instability in the gastric environment as well as low solubility and/or bioavailability[5].

Traditional delivery systems are characterized by immediate and uncontrolled drug release kinetics and drug absorption is essentially controlled by the body's ability to assimilate the therapeutic molecule and thus, plasma drug concentration suffers from fluctuations which cannot be prevented by repeated drug administration [6].The development of the concept of controlling drug delivery is aiming to maintain drug concentration in the blood or in target tissues at a desired level for the desired period of time[6]. The most desirable release profile would show a constant release rate with time; however, the process of drug release *in-vivo* is more complicated and is affected by different factors[7].

Aiming to overcome problems related to variability of bioavailability due to differences in physiology and preferential site of drug absorption, many attempts have been devoted to design dosage forms to target a specific organ or a part of an organ. Various types of controlled oral delivery systems have been extensively investigated; these comprise: time-controlled and site-specific delivery systems[8].

Site-specific delivery is based on the concept of controlling drug release by environmental factors like the pH or enzymes present in the gastrointestinal lumen, however, drug release from time-controlled systems is mainly dependant on the delivery device itself and not by the environment [8].

A great diversity of controlled delivery systems have been developed, among them, multiparticulate systems seem to have great benefits when compared to monolithic ones. These benefits are: the reduction of the inter- and intra-subject variability indrug absorption, avoiding all-or-nothing emptying from the GIT, more predictable drug release kinetics and less chance of localized mucosal damage [9].

Many polymers can be used to prepare these multiple-units dosage forms. These polymers can be classified according to

their source into natural polymers (chitosan, Na alginate, pectin, guar and carrageenan), semi-synthetic polymers (celluloses) and synthetic polymers (different types of Eudragits®, Polyvinyl pyrolidone, Polyvinyl alcohol and Poloxamer® 407) and according to their chemical nature into nonionic polymers (Eudragit® NE 30D, guar, hydroxyethyl cellulose and Poloxamer® 407), anionic polymers (Na alginate, pectin, carrageenan and Na carboxymethyl cellulose) and cationic polymers (chitosan, Eudragit® RL PO and Eudragit®RS PO).

A major request during the choice of suitable polymers to be used as drug carriers is their safety and biocompatibility. Recent trends in drug delivery technology have been toward biodegradable polymer excipients. The most widely investigated and advanced polymers in regard to available toxicological and clinical data are the aliphatic polyesters based on lactic and glycolic acids. The family of homo- and copolymers derived from these monomers has received considerable attention. Features such as biocompatibility, predictability of biodegradation kinetics and ease of fabrication have attracted investigators to lactic and glycolic polymers[10].

The use of many, single or mixed, polymers can allow the development of mucoadhesive delivery systems by simple preparation procedure [11, 12]. Oral mucoadhesive systems provide a great importance due to capability of these drug carriers of adhering to certain gastrointestinal segments which can offer various advantages due to prolonged gastric or small intestinal residence time, and the intimate contact of the delivery system with the absorption membrane which can increase drug absorption and bioavailability. The use of multifunctional polymers, able to interact with the GIT mucosa or able to act as permeation enhancer or enzyme inhibitor, has been of great interest [4].

The process of mucoadhesion is attained mainly by the formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus layer and the polymers. This process can be enhanced by the use of drug carriers of small sizes which can guarantee a greater contact surface with the mucous membrane. The different theories explaining the mechanisms of bioadhesion have been widely discussed before [13].

Drug release from these polymeric multiparticulate dosage forms is influenced by several factors including the chemical properties of both the polymerand the drug, distribution of drug distribution within the polymer matrix, rate of polymer degradation, porosity and size of the particles [7]. The controlled release of medications from these systems can be achieved by manipulating the physical and chemical properties of the polymers as well as those of the formulated particles. In other words, we can say that the formulated delivery systems can be tailored to fit a certain desired release.

Therefore, multiparticulate delivery systems allow obtaining controlled drug release in localized areas and can be employed to reduce medication doses and its frequency of administration.

Broad scope application of multiparticulate delivery systems requires testing on case-by-case studies as it is not always clear how these systems will perform during *in-vivo* studies due to inter- and intra- subject variations. This large variability is due to differences of degradation and absorption environments in biological systems. *In-vitro/in-vivo* correlation is necessary for the prediction of the performance of these systems after oral administration.

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