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Progress in novel formulation nanotechnologies can come up with solutions that can overcome the challenges in oral drug delivery.

Is nanotechnology a boon for oral drug delivery?

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The oral route for drug delivery is regarded as the optimal route for achieving therapeutic benefits owing to increased patient compliance. Despite phenomenal advances in injectable, transdermal, nasal and other routes of administration, the reality is that oral drug delivery remains well ahead of the pack as the preferred delivery route. Nanocarriers can overcome the major challenges associated with this route of administration: mainly poor solubility, stability and biocompatibility of drugs. This review focuses on the potential of various polymeric drug delivery systems in oral administration, their pharmacokinetics, *in vitro* and *in vivo* models, toxicity and regulatory aspects.

Introduction

Oral delivery is the most convenient and extensively used route of drug administration. Because oral dosage provides the benefit of effortless administration, most drugs are designed for oral ingestion [1]. The choice of route is driven by patient acceptability, properties of the drug, access to a disease location and effectiveness in dealing with the specific disease. It is by far the most dominant and convenient administration route with good patient compliance, especially in the opinions of patients themselves. Despite these benefits, there are also disadvantages associated with oral administration usually related to immediate release of the drug causing toxicity in practice, low aqueous solubility and low penetration across intestinal membranes [2]. Nevertheless, current knowledge on mechanism of drug absorption, gastrointestinal (GI) transit, microenvironment of GI tract and stability within the GI tract is still incomplete and challengeable [3]. Oral administration is also beset by constraints such as chemical degradation, gastric emptying and intestinal motility. Although convenient from a patient perspective, there has been demand for more-patient-compliant dosage forms.

The GI tract forms barriers to severe physiological factors (e.g. varied enzymatic activities, difference in pH, and specific transport mechanisms), which restrict intestinal drug absorption. Moreover, oral bioavailability of drugs is strongly influenced by solubility and permeability. Drugs are divided into four categories based on their solubility and permeability according to the Biopharmaceutic Classification System [4]. A drug that is administered orally must survive in the

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GLOSSARY

Controlled release Includes any drug delivery system from which the drug is delivered at a predetermined rate over a prolonged period of time.
Dendrimer Dendrimers are highly branched symmetrical macromolecules of nanosized dimensions, have well-defined molecular mass and geometry consisting of a central core, repeating units and terminal functional groups.
Micelles Micelles are nanoscopic aggregates of colloidal dimensions (i.e. association of colloids) formed reversibly from amphiphile molecules. They have the ability to solubilize hydrophobic drugs and bring about site-specific delivery by passive and active targeting.
Microsphere Solid spherical particles in the micron range, used as matrix dosage forms.
Nanoparticles Nanoparticles are subnanosized colloidal structures composed of synthetic or semi-synthetic polymers.
Nanotechnology The design, characterization, production and application of structures where particles in the size range 0.1–100 nm play a significant part in drug delivery.
Polymer A chemical compound, typically formed by connecting monomer units together, that consists of repeating structures, often arranged in a chain.
Recptor A molecule or polymeric structure in or on a cell that specifically recognizes and binds a compound acting as a molecular messenger (neurotransmitter, peptide, folic acid, hormone, among others).
Sustained release Includes the drug delivery systems that achieve and ensure slow release of drugs over an extended or prolonged period of time or at a constant release (zero order) rate to attain and maintain therapeutically effective levels of drug in the circulation. Here the absorption rate is equal to the elimination rate over an extended period of time.
Targeted drug delivery Nanomaterials uniquely capable of localizing delivery of therapeutics and diagnostics to diseased tissues. The targeted drug delivery system has the ability to achieve high local concentration of drugs at a target site.
Toxicity The ability of the substance to induce harmful effects.

harsh environment of the GI tract and should be absorbed. The bioavailability of drugs where dissolution is rate limiting becomes a challenge for effective delivery via the oral route. Hence, protective measures are required to avoid drug destruction on one hand and potentiation of absorption on the other hand in the GI tract. This objective can be accomplished by incorporating the drug into various novel drug delivery systems. A significant number of polymeric nanocarrier systems have emerged, encompassing diverse routes of drug administration, to achieve controlled and targeted drug delivery [5].

Challenges to oral delivery

More than 60% of conventional small molecule drug products available on the market are administered via the oral route. The physiological and anatomical barriers to bioactive absorption via the GI tract are primarily chemical, enzymatic and permeability related (e.g. mucus layer, intestinal epithelium). Poor hydrophilicity and intrinsic dissolution rate are the major factors that affect oral delivery of many existing drugs. Figure 1 compiles all the essential challenging parameters for oral bioactive delivery. Numerous drug discovery approaches such as (i) chemical entity modification, (ii) use of permeation enhancers, (iii) use of enzyme inhibitors to lower the activity of proteolytic enzymes, (iv) modulation of GI transit time, (v) minimization of hepatic first pass elimination and (vi) design of novel drug delivery systems have been screened to overcome barriers and to enhance the bioavailability of drugs. Targeted systems are expected to release drugs at the specific site of the gut, where proteolytic activity is relatively low, so that the drugs can be protected from luminal proteolytic degradation for absorption with improved bioavailability [6].

Nanotechnology presents some promotional benefits to the drug delivery field in general and oral drug delivery in particular. It permits (i) delivery of poorly water-soluble drugs, (ii) targeting of drugs to precise parts of the GI tract, (iii) transcytosis of drugs across the GI tract barrier and (iv) intracellular and transcellular delivery of large macromolecules [7]. Nanoconstruct-based oral delivery can improve efficacy, specificity, tolerability and therapeutic index of corresponding drugs. Figure 2 gives the schematic representation of various drug uptake mechanisms in the intestine.

Polymer-based drug delivery systems addressing the challenges of oral drug delivery

A large number of polymers are available to form various nanocarrier systems and can be categorized into either natural or synthetic polymers. Natural materials used for the nanoparticle formulation include chitosan, dextran, gelatin, alginate and agar (Fig. 3). Poly(lactide) (PLA), poly(glycolide) (PGA), poly(lactide-co-glycolide) (PLGA), poly(cyanoacrylate) (PCA), polyethylenimine (PEI) and polycaprolactone (PCL) are the synthetic polymers that are used in the design of nanocarriers [8]. Various biodegradable polymers used for oral drug delivery are shown in Fig. 4. Robust structural characteristics impart stability and a high degree of controlled release of drug molecules in the GI tract. A diverse range of pharmacophores including small molecules such as estradiol, anticancer drugs, antigens, peptide and nonpeptidic drugs such as insulin have been successfully delivered by polymeric nanoparticles [9].

The surface of the nanocarriers can be modified by adsorption or grafting of hydrophilic molecules [e.g. polyethylene glycol (PEG)], ligands (such as antibodies) and glycoproteins or peptides to increase interactions with the intestinal mucosa and to deliver medicines to target specific cells, diseases or areas of the intestine. The surface ligands that are used for the oral delivery of bioactives include: bioadhesins, mainly lectins [10]; folic acid [11]; peptidic ligands such as RGD [12]; and bile acids [13]. Prolongation of the residence time in the gut by mucoadhesion, endocytosis of the particles and/or permeabilizing effect of the polymer are the factors that govern increased uptake of the polymeric nanocarriers. Several physicochemical parameters including hydrophobicity, polymer nature and particle size influence translocation of particles across the epithelium. Table 1 shows the various nanocarriers employed for oral drug administration.

Polymeric nanoparticles

Nanoparticles are novel carriers that are collectively known as the colloidal drug delivery system. *In vitro* cytotoxicity of the

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