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Microscale oral delivery devices incorporating nanoparticles

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“Macrodelivery devices incorporating nanoparticles will go a long way at increasing the efficiency of oral nanoparticle delivery, making the ‘gene-pill’ a reality”

Many promising new drug candidates ensuing from genomic and proteomic revolutions can now target diseases at the molecular level. However, many of these therapeutic entities, often peptide and nucleic acid in nature, require an effective intracellular delivery system to exert their effect. Nanoparticle-mediated delivery represents a logical solution. If such drug-loaded nanoparticles can be effectively administered orally to reach their intended intracellular targets, the appeal of this future generation of peptide- and DNA-based therapeutics would be even more widespread.

Bioavailability of oral drugs remains low due to the harsh gastrointestinal (GI) tract environment; the bioavailability of nanoparticles delivered orally can be expected to be even lower due to higher transport resistance through the gut epithelium. Many material- and device-based strategies have been proposed to achieve effective oral drug delivery. Environmentally responsive materials are commonly used to achieve some level of spatial and temporal control over drug release in the GI tract. These materials can still be applied in nanoparticle-loaded macrodelivery devices[1]. They include mucoadhesive polymers such as carbopol to delay intestinal clearance; pH-responsive, fast-melting polymers, such as Eudragit, to release the payload in the intestine; enzyme-responsive polymers such as guar gum to be degraded by colonic enzymes secreted by gut flora; and pressure-sensitive polymers, such as PEG-ethylcellulose, to burst the capsule in the colon when subjected to increased peristaltic pressure. These materials are frequently incorporated into a device to improve oral delivery.

Innovation in microscale delivery device

In an intestinal patch, a drug/carbopol mixture is sandwiched between an insoluble backing layer of ethylcellulose and a pH-sensitive enteric layer of Eudragit, and cut into 1 mm size patches with a heat sealing punch [2]. An alternative design is to embed human serum albumin microparticles in a carbopol/pectin thin film and subsequently overlaid with an insoluble ethylcellulose film [3].

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A more sophisticated design is to exploit the pH sensitivity of certain biomaterials [4]. Using soft lithography, a drug/carbopol thin film is overlaid on a pH-sensitive hydrogel bilayer made of swellable poly(methacrylic acid) (PMAA) and less swellable poly(hydroxyethyl methacrylate) (PHEMA). This microstructure is further embedded, using microimprinting techniques, in a cross-shaped millimeter size structure. Owing to different swelling rates, the PMAA/PHEMA bilayer bends, inducing all four protruding arms of the cross-shaped structure to fold inwards, thereby penetrating into the intestinal mucus. In this way, mucoadhesion is achieved by physical docking into the mucus layer (Figure 1).

A similar gripping device has been developed by Randhawa *et al.* using photolithography and plasma-etching techniques [5]. A flat, micron-scale star-shaped metal/polymer composite is chemically triggered by acid to cause the protruding arms to fold inwards, initiating a gripping action. Subsequently, the folded microcage can be opened in the presence of peroxide. As materials used to synthesize the microcage can be modified to accommodate GI-compatible chemical triggers, this ‘pick-and-place’ device-is potentially applicable for oral delivery of nanoparticles. The metallic microcage may also, in principle, be magnetically accumulated at desired GI sites and held in place for as long as required.

Innovation in particle synthesis

Significant advances have been made in particle fabrication technology to achieve a better control of size and shape [1]. Examples include rapid expansion of supercritical fluids [6], hydrodynamic focusing [7], microdroplet generation [8] and nanoimprinting [9]. In rapid expansion of supercritical fluids, a polymer dissolved in a supercritical fluid is nucleated via rapid expansion through a nozzle. It should be possible to encapsulate drugs into the particles in this process. In hydrodynamic focusing, streams of polycations and polyanions converge from microfluidic channels to form coacervated nanoparticles at the interface. A variation of the microfluidic approach is to synthesize the drug-loaded nanoparticles in microdroplets generated by emulsion in the channels. In top-down imprint lithographic methods, the drug/polymer fluid mixture fills up a ‘non-stick’ mold template and is subsequently photochemically cured. The lithography approach affords the best control in size and shape since they are precisely determined by the template.

The ability to control particle size and shape has profound implications on intracellular delivery. Studying particles fabricated by imprint lithography, Gratton *et al.* have demonstrated that certain shapes, especially rod-like geometries, exhibit higher rates of cellular internalization [8]. They also show that non-spherical particles with sizes up to 3 μm can be internalized by HeLa cells. If enterocytes show similar endocytic response, one can begin to explore the possibility of encapsulating nanoparticles in a uniquely shaped micron-size macrodelivery device. The entire device-may be endocytosed, allowing nanoparticle to be released inside the cells or even transcytosed into the systemic circulation.

Current status of macrodelivery devices incorporating nanoparticles

Nanoparticle delivery via a macrodelivery devices attractive as it would decouple the mucoadhesive and GI tract protection requirements and allow polymer property design to be focused more towards overcoming intracellular barriers, such as endosomal escape and payload release. This idea was recently illustrated by Bhavsar *et al.* using a double emulsion technique [10]. Lyophilized hydrophilic gelatin-DNA nanoparticles are encapsulated in polycaprolactone microspheres via solvent evaporation of a water-oil-water emulsion. The microparticle formation is controlled by adjusting the concentration of PCL during the initial dispersion as well as the rate of stirring during the final homogenization process. The optimized ‘nanoparticle-in-microsphere-oral delivery-system’ (NiMOS) shows a mean particle size of 5 μm and reasonably uniform distribution of gelatin nanoparticles inside the spherical PCL

microspheres. *In vivo* biodistribution studies show a higher concentration of NiMOS in the small intestines than gelatin-DNA nanoparticles alone up to 6 h postadministration. As only 5% of gelatin-DNA particles are found in the stomach 1 h postadministration, compared with 70% for NiMOS, the observed unproved biodistribution could be attributed to the ability of NiMOS to prolong GI retention. Despite longer GI retention, the DNA encapsulated in the NiMOS is still bioactive and able to transfect the enterocytes *in vivo*.

Challenges ahead

No other successful *in vivo* delivery devices incorporating nanoparticles have been reported, suggesting that many challenges remain unresolved. A notable example is matrix–nanoparticle interactions (Figure 1). Electrostatic interactions between the continuous phase (matrix molecules) and the discrete phase (nanoparticles) might lead to aggregation. This might lead to restricted release from the microscale device. In addition, if the matrix molecules have a higher affinity towards either the carrier (e.g., cationic lipids/polymers used to encapsulate the drug) or the drug (peptide, DNA, RNA), integrity of the nanoparticles may be compromised. This issue is avoided in NiMOS through the use of immiscible fluids, thus the matrix and the nanoparticles are ‘non-stick’. It remains to be seen whether this non-stick concept will hold up for nanoparticle macroformulation in imprint lithography. Uniform introduction of a nanoparticle dispersion into the mold may pose a challenge, compounded by settling of the nanoparticles during the curing phase.

While nanoparticles may form a stable colloid in water, they may not disperse so favorably in a monomer or polymer solution, which has very different fluid properties. First, the nanoparticles may aggregate or disassemble due to disparate particle–particle and particle–matrix interactions. Second, the interactions may restrict nanoparticle release. Third, the polymer matrix may contaminate the nanoparticles, leading to two possible undesirable consequences: an increase in particle size or shift of ζ potential to interfere with cellular uptake; and attachment of matrix material on the surface of nanoparticles, which may also increase opsonization and hasten clearance by the reticuloendothelial system if they ever reach the systemic circulation.

Nevertheless, there are obvious advantages when nanoparticles are encapsulated in a macrodelivery device for oral delivery. By sequestering the nanoparticles from the external environment, a greater portion of intact nanoparticles might reach the desired GI tract segments. Cellular targeting of the nanoparticles may also have a higher probability of success because the surface-conjugated ligand would not be destroyed in transit to the target tissue.

Concluding remarks

Oral delivery of drug remains the most attractive mode of drug administration. However, unlike drug molecules, nanoparticles face additional delivery barriers even after systemic-absorption, for instance in avoiding clearance by RES and overcoming intracellular barriers. Unsurprisingly, the expected overall efficiency would be low. Nevertheless, these limitations can be mitigated by the large absorption area in the GI tract, ease of administration and application of innovative macrodelivery devices. As such, oral delivery of nanoparticles remains a fertile direction of research, especially in genetic immunization, where target cells residing in the Peyer’s patch would obviate the need for systemic absorption. Macrodelivery devices incorporating nanoparticles will go a long way at increasing the efficiency of oral nanoparticle delivery, making the ‘gene-pill’ a reality.

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Figure 1. Schematic of opportunities and challenges to achieve oral delivery of nanoparticles by microscale devices.