

Special Section on Drug Delivery Technologies—Minireview

Oral Drug Delivery Technologies—A Decade of Developments

G. Kaur, M. Arora, and M.N.V. Ravi Kumar

Department of Pharmaceutical Sciences, College of Pharmacy, Texas A&M University, College Station, Texas

Received December 14, 2018; accepted April 17, 2019

ABSTRACT

Advanced drug delivery technologies, in general, enable drug reformulation and administration routes, together contributing to life-cycle management and allowing the innovator to maintain the product monopoly. Over the years, there has been a steady shift from mere life-cycle management to drug repurposing—applying delivery technologies to tackle solubility and permeability issues in early stages or safety and efficacy issues in the late stages of drug discovery processes. While the drug and the disease in question primarily drive the choice of route of

administration, the oral route, for its compliance and safety attributes, is the most preferred route, particularly when it comes to chronic conditions, including pain, which is not considered a disease but a symptom of a primary cause. Therefore, the attempt of this review is to take a stock of the advances in oral delivery technologies that are applicable for injectable to oral transformation, improve risk-benefit profiles of existing orals, and apply them in the early discovery program to minimize the drug attrition rates.

Introduction

Biomedical research has advanced our understanding of diseases—their causes and remedies. Specifically, the remedies that include approaches to prevent, manage, or treat a particular disease using a drug (e.g., chemical and biologic molecules) or a drug-like (e.g., supplements) compound. The pace at which new diseases, newer pathways of already known diseases, and increasing understanding of the drug-resistant mechanisms are being uncovered is accelerating. This pace is not met by the discovery of new and effective medicines (Silber, 2010). To meet this gap, increasing attention is paid toward drug repositioning, where an existing drug discovered for a specific target is repurposed for other targets (Huang et al., 2018; Pushpakom et al., 2018). The primary advantage of drug repurposing is that scientists already understand the pharmacology and safety profiles that can greatly reduce the risk of attrition in drug development in clinical phases. The drug repurposing aided by artificial intelligence, systems pharmacology, and other computational approaches validate the drug targets (Bai, 2016; Scannell and Bosley, 2016; Peska et al., 2017; Cha et al., 2018). The effective delivery strategies would improve risk-benefit profiles and switch routes of administration (Cipolla and Gonda, 2012; Paulmurugan et al., 2016). Each mode of delivery such as oral, nasal, injection, sublingual, rectal, vaginal, ocular, optic, or nasal

has its respective advantages and disadvantages (Mignani et al., 2013). Nevertheless, oral drug delivery (pills, powders, suspensions, and solutions) is the singular, superior method of administration due to its convenience and safety compared with other methods (Mignani et al., 2013). Enterocytes, goblet cells, and Peyer's patches with M cells make the intestinal epithelium an optimal platform for drug absorption. Especially regarding diseases that require frequent administration for a long duration, patient comfort proves oral drug delivery's eminence. The advantages of oral drug administration over other methods include ease of use, being painless, lower cost of care, lesser patient supervision, and higher patient compliance.

However, the oral route of drug administration has some disadvantages when it comes to the drug molecules exhibiting low solubility, lesser permeability, and degradation rates. Moreover, the uptake of certain biomolecules/drugs in oral route is largely affected by physiologic barriers such as pH change in gastrointestinal tract (GIT): acidic pH in the stomach followed by basic pH in the intestine and enzymatic degradation (Knipe et al., 2015). Almost 60% of drugs degrade in the harsh gastric environments of the stomach. Many have theorized making salts out of the drugs, thereby increasing its solubility and bioavailability (Serajuddin, 2007; Elder et al., 2013). Unfortunately, in practice, pairing the parent drug with an appropriate counter ion, for sufficient ionic interaction, has proven difficult. Only under ideal thermodynamic conditions will the salt drug precipitate. Furthermore, counter ions increase the weight of the drug

This work was supported by National Institutes of Health National Eye Institute [Grant No. R01EY028169 to M.N.V.R.K.].
<https://doi.org/10.1124/jpet.118.255828>.

ABBREVIATIONS: 3D, three-dimensional; GA, gambogic acid; GIT, gastrointestinal tract; MAA, methacrylic acid; NVP, *N*-vinyl pyrrolidone; PTH, parathyroid hormone; TfR, transferrin receptors.

but are therapeutically inactive, thus obligating increased and frequent dosage, which has unavoidable side effects on the body. Moreover, these counter ions increase the hygroscopic nature of the drug by forming hydrates, and in consequence, reduce the drug's shelf life. Some counter ions also exhibit a corrosive nature, like hydrochlorides, and hence reduce the solubility of the drug in the stomach as explained by the counter ion effect (Makary, 2014). These issues motivated researchers to attempt innovative forms of conventional carriers like capsules, tablets, microcapsules, or non-conventional approaches such as intestinal patches and nanoparticles. The successes with non-conventional delivery systems corroborate our belief that oral delivery deserves more attention for its possible advantages.

The recent developments in the area of oral controlled release delivery systems such as dome tablets, dual drug tablets, intestinal patches, polymer nanosystems, or bioinspired delivery systems such as exosomes, have revolutionized the field. This review is an attempt to summarize the oral drug delivery techniques available and under development, with current status for use and future prospects.

Tablets

Oral tablets are the most common, convenient, and easy method for drug administration. Tablets are conventionally made by compressing drug powder with appropriate excipients that result in rapid release of the drug in the body when taken. The drawback of conventional tablets is that rapid drug release makes it difficult to maintain multi-component drug release. Many controlled drug release-based technologies such as matrix tablets, multilayer tablets, Dome-matrix based tablets, core-in-cup devices, three-dimensional (3D) tablets, etc., have been developed or are under development (Moodley et al., 2012; Preis, 2015; Hong et al., 2016) to deal with the drawbacks faced in conventional tablets.

Matrix-tablets have been developed to tackle the controlled drug delivery issues faced in conventional tablets (Fig. 1) (Nokhodchi et al., 2012; Zimmer et al., 2014; Guarascio and Slain, 2015). The advantages of matrix tablets include less frequent dosing, cost effectiveness, side-effect reduction from dose dumping, etc. Matrix-based systems are divided into three types: 1) osmotic pump systems; 2) reservoir matrix systems; and 3) monolith matrix systems.

The osmotic pressure plays an important role in osmotic pump systems in which a semipermeable membrane with an orifice controls the drug release. In the case of reservoir matrix systems, a membrane controls the diffusion of the drug from the system, whereas, in monolith matrix systems, the drug has been dispersed or encapsulated in a hydrophobic or hydrophilic system, which controls the drug release.

Multilayered tablets, including bilayered, triple layered, and quadruple layered, etc., can be designed to release multiple drugs at different rates and are superior to conventional tablets. In general, the multilayered tablets consist of a drug core that is surrounded by a hydrophobic or hydrophilic polymer layer that controls the drug release in the GIT. Many multilayered tablets have been developed, such as Geomatrix multilayer tablet technology, Smatrix technology, Sodas multilayer tablet technology, VersaTab bilayered tablet technology, Geolock technology, Procise technology, Chronotropic, CODES, etc. (Table 1) (Moodley et al., 2012; Choonara et al., 2014).

The dome matrix-based drug-releasing devices consist of a dome-shaped swellable matrix module with a convex front and concave base as shown in Fig. 2. These tablets have two configurations: 1) void configuration and 2) piled configuration. The drug release patterns in case of dome-matrix tablets are controlled by the configuration of modules (Hascicek et al., 2011). A higher drug release rate has been observed for the convex front in comparison with the concave base. The dome-matrix tablets showed a higher initial drug release rate compared with conventional tablets. Prolonged delivery of norfloxacin as dome-matrix tablet techniques has also been established in the past (Oliveira et al., 2011), but due to the complexity of these module systems, these tablets are not as popular as other controlled release systems yet. To the best of our knowledge, this technology is still at exploratory level. However, such technologies will have significant impact in treating acute/chronic diseases involving multiple progression pathways, where multiple drugs are needed to block the disease progress.

Polymer-based 3D printed tablets have been fabricated to maintain controlled drug release over a particular time period to retain the therapeutic level of the drug intake. The 3D printed tablets can be produced by various methods such as 3D inkjet printing (Kyobula et al., 2017), an extrusion-based (Khaled et al., 2018), or a fused deposition modeling (Sadia et al., 2018). These tablets demonstrate high drug

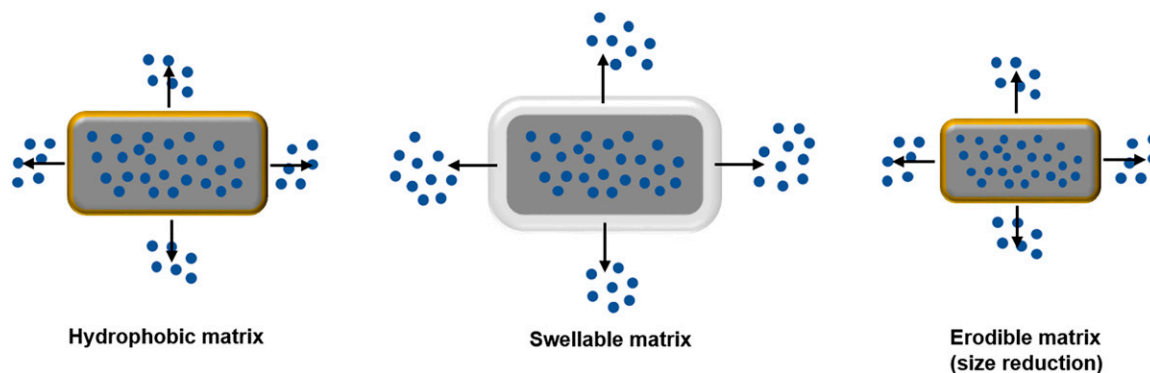


Fig. 1. Image showing drug release from the matrix tablets. Adapted and modified from Nokhodchi et al. (2012).

TABLE 1

Summary of various advanced tablet technologies

Adapted and Modified from Moodley et al. (2012), Choonara et al. (2014).

Drug	Technology	Design	Factors Affecting Drug Release	Advantages	Reference
Venlafaxine hydrochloride	Procise	Drug core with a hole	Core geometry	Zero-order kinetics or drug release according to core geometry	Malewar et al. (2015)
Diltiazem	Geomatrix	Multilayer tablet	Polymer type, thickness of layer	Zero-order kinetics and controlled drug release	Wilding et al. (1995)
Indomethacin	Smaratrix	Multilayer tablet with specific shape of core layer	Polymer type, shape of core layer	Zero-order kinetics or drug release according to shape of core layer	Omer et al. (2017)
Methylphenidate	Sodas (spheroidal oral drug absorption system)	Multilayer tablet	Layer thickness, shape of core layer	Pulsatile drug release	Biederman et al. (2003)
Norfloracin	Dome matrix	Dome-shaped swellable matrix module	Polymer used, module arrangement	Drug release based on module arrangement	Oliveira et al. (2011)
Fenofibrate, captopril, glipizide, and nifedipine	3D printed tablets	Fabrication through 3D inkjet printing or an extrusion-based or fused deposition modelling	Polymer used, drug used	Immediate or controlled release	Khaled et al. (2015); Kyobula et al. (2017)
Insulin, camostat mesilate	Chronotropic	Multilayer tablet	Polymer layers	“Two pulse” release and controlled release	Del Curto et al. (2011)
Heparin	GIPET	Permeation enhancement technology	Polymer layer, medium fatty acid chains	Immediate or modified release	Leonard et al. (2006)
Calcitonin	Peptelligence	Permeation enhancement technology	Polymer layers, a permeation enhancer and the main excipient citric acid	Immediate or modified release	Binkley et al. (2012)
Insulin, lactulose	CODES	Multilayer tablet	Polymer layers, pH-based release	Immediate or controlled release	Katsuma et al. (2004)

loading and immediate drug release while maintaining the active physical form of the drug. The size, as well as the shape of the contrived tablets can be modified according to the personalized use. These tablets can also be fabricated with a large number of shorter perforated channels with particular width and length to control the drug release as the show in Fig. 3.

Roberts and coworkers (Khaled et al., 2015) fabricated a 3D polypill with multiple active drug molecules confined in well-defined separated compartments for controlled drug release for the treatment of hypertension in type I diabetic patients. Captopril, glipizide, and nifedipine were used to make a 3D polypill (Fig. 4). The captopril drug release was maintained through an osmotic pump-based mechanism, whereas glipizide and nifedipine showed the Korsmeyer-Peppas release kinetics. The study showed that a 3D polypill was able to deliver all three drugs without any detectable interaction between them.

The aim of these technologies is to enhance the bioavailability of drug molecules. Many of the above mentioned technologies are under clinical trials, but there are still numerous challenges that need to be tackled to use these

technologies in real time. A summary of various controlled release tablet technologies has been done below (Table 1).

Capsules

Capsules are the safest and most acceptable form of oral administration to patients, especially if the drug has a bad taste, odor, or is photosensitive. There are two types of capsules: 1) hard gelatin capsules with solid-fill formulations and 2) soft gelatin capsules with liquid-fill or semisolid-fill formulations, such as vitamin E, cough preparations, etc., with suitable excipients that aid the dosage form. The shape of a capsule makes it easy to swallow, and the lubricant coating is soothing and moisturizing. Like tablets, capsules can also facilitate sustained release with target specificity across the GIT. In this section of the review, we focused on 1) the innovation of the materials used to make capsules and 2) the fillings of drug complex/drug/drug conjugate/micro- or nano-formulation used for better bioavailability of the drug in the body. Scientists have scrutinized the literature for various aspects of capsule formation, such as the use of polymers (Ma, 2014; Lamb et al., 2016), and for the target delivery of drugs and for surgical treatments, such as medical robot capsules

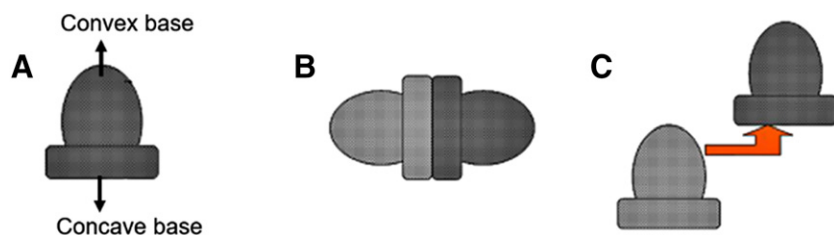


Fig. 2. (A) Dome matrix tablet module with void configuration (B) and piled configuration (C). Adapted and modified from Moodley et al. (2012).

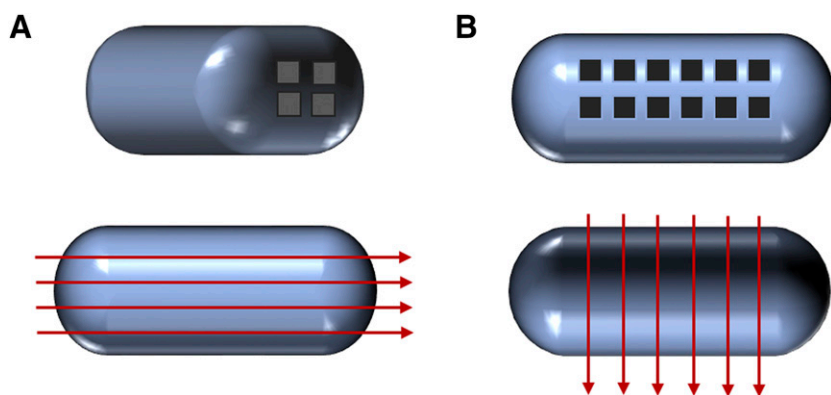


Fig. 3. Image showing perforated channels in 3D channeled tablet: (A) parallel and (B) at right angle to long axis. Adapted and modified from Sadia et al. (2018).

(Mapara and Patravale, 2017). A summary of recent developments in capsule technologies is presented in Table 2.

Intestinal Patches

Intestinal patches are millimeter in size, two- to four-layered oral drug delivery devices inspired by transdermal patches. They were invented to enhance bioavailability, decrease, the GIT degradation of drugs, and avoid the painful injection of drugs, such as insulin for diabetes and anticancer drugs for cancer chemotherapy (Tao and Desai, 2005; Wong, 2010; Teutonico and Ponchel, 2011; Banerjee and Mitragotri, 2017; Kirsch et al., 2017) (Fig. 5).

The intestinal patches are divided into three kinds, depending upon the number of layers used in the design of a patch: 1) two-layered patch, 2) three-layered patch, and 3) four-layered patch (Fig. 5). The two-layered intestinal patches are composed of a backing layer and a drug-loaded mucoadhesive layer. The backing layer generally consists of hydrophobic polymers such as cellulose acetate and its derivatives (Eiamtrakarn et al., 2002). The backing layer supports the unidirectional release of drug toward the intestinal mucosal side. The mucoadhesive layer is generally made up of mucoadhesive polymers, such as chitosan derivatives, alginates, hydroxypropyl cellulose, etc. (Thanou et al., 2001).

The mucoadhesive polymers have been reviewed in detail by other groups (Andrews et al., 2009; Roy et al., 2009). The purpose of a mucoadhesive layer is to ensure the strong attachment toward the intestinal mucosal layer (Banerjee et al., 2016). In three-layered intestinal patches, an additional pH-sensitive layer has been introduced for the protection of

the drug layer against the acidic pH of the stomach, whereas the four-layered intestinal patch consists of two separate layers for drug and mucoadhesive polymers (Fig. 5).

The mucoadhesive intestinal patches are generally prepared by an evaporation-lyophilization method (Fig. 6) (Toorisaka et al., 2012). Generally, the backing layer or drug impermeable layer is prepared with 5% w/w ethyl cellulose in acetone solution. The solution is poured into silicon molds and allowed to evaporate at room temperature. The aqueous mucoadhesive polymer solution is added and lyophilized for 1 day. Furthermore, the suspension containing drug was added into a lyophilized layer.

The functioning of a typical intestinal patch is based on the pH conditions in the GIT (Fig. 7). The intestinal patches, with the backing layer and drug-loaded mucoadhesive layer, can be filled in pH-sensitive capsules to protect them from acidic conditions and enzymatic degradation in the stomach for the enhanced intestinal delivery of the drugs. In the intestine, these patches attach to the mucosal layer of the intestine due to presence of the mucoadhesive polymer layer and secure the unidirectional flow of loaded drug molecules toward the intestinal epithelium for adsorption, resulting in better bioavailability of the drug in body (Gupta et al., 2016). Mitragotri and his coworkers (Gupta et al., 2013) reported that the intestinal patches developed in their laboratory as more efficient in the rat intestine in comparison with the Caco-2 monolayer intestinal cells due to absence of mucosa in cell monolayers.

Shen and Mitragotri (2002) introduced the microsphere patches containing three layers: a backing layer, a drug-loaded microsphere layer, and a mucoadhesive

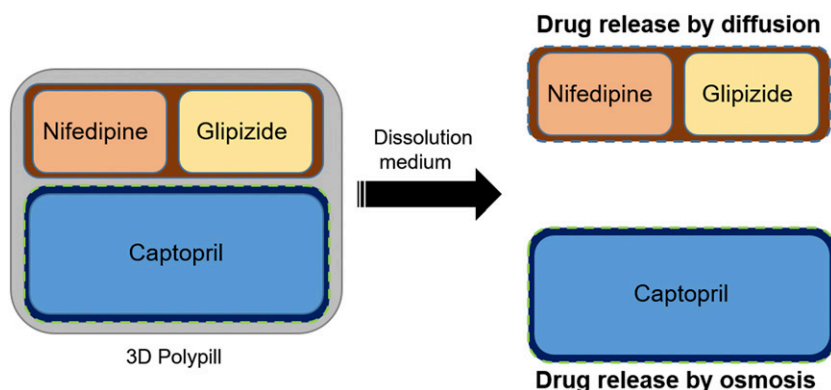


Fig. 4. Image showing 3D polypill containing three drugs, namely, captopril, nifedipine, and glipizide. Adapted and modified from Khaled et al. (2015).

TABLE 2
Summary of advanced capsule technologies

Drug	Capsule	Purpose	Advantage	Reference
Ga-citrate Tributyrin	Gelatin capsules Whey protein and γ -cyclodextrin	To study the gastrointestinal transit time To study in vitro release of butyric acid for the treatment of intestinal disorder	Extended release Controlled release	Wagner et al. (2017) Donovan et al. (2017)
Sulforhodamine 101 (fluorescent probe as model drug)	Rhamnogalacturonan-I	For the treatment of colonic cancer and better protection of the drug throughout the GIT	Controlled release	Svagan et al. (2016)
Ivermectin	PCL elastomers	For extended release of anti-malaria drugs	Controlled and extended release	Bellinger et al. (2016)
Veledimex	Gelatin capsules	To regulate gene expression and studying the drug pharmacokinetics	Controlled release	Mulugeta et al. (2018)
Paracetamol	Sporopollenin exine capsules (SEC) with carboxymethyl cellulose and epichlorohydrin coating	To enhance bioavailability of paracetamol	Extended release	Alshehri et al. (2016)
Curcumin	Mesoporous silica microcapsules using <i>N</i> - hexadecyl palmitate (NHP) in Tween 40	To improve the stability and gastro- resistant delivery intestinal absorption of curcumin	Controlled release	Kim et al. (2016)
Probucol	Chenodeoxycholic acid (CDCA) microcapsules	To improve permeation properties of the drug	Targeted oral delivery	Mooranian et al. (2015)
Gliclazide	CDCA and sodium alginate	To enhance delivery of Gliclazide with CDCA in lower intestine with prolong release	Targeted oral delivery	Mathavan et al. (2016)
Fluorescent particles Sodium salt of Furosemide	Particle-in-particle Microwells of poly-L-lactic acid with coating of Eudragit	For effective colon cancer treatment To deliver the powdered drug to the target site throughout the GIT	Targeted oral delivery Targeted oral delivery	Ma et al. (2015) Nielsen et al. (2015)
Insulin	Whey protein (WPI), polyglycerol and sodium alginate (SA) or carboxymethylcellulose (CMC) coating	To enhance oral drug delivery	Controlled release	Cardenas-Bailon et al. (2015)
Insulin	(PLGA)-lipid -PEG hybrid nanoparticles filled in gelatin capsules with hydro-proxy- propyl methyl cellulose phthalate polymer coating	To enhance bioavailability and protection against acidic environment	Controlled release	Yu et al. (2015)
Oxycodone	DETERx microsphere capsules	To enhance the bioavailability specially for patients with dysphagia	Controlled and extended release	Fleming et al. (2016)
Budesonide	Eudragit S-100 and L-100 gelatin capsules	To increase the lag time to target colon related diseases	Controlled release	Yehia et al. (2011)
Docetaxel	Surfactant based solid dispersions in gelatin capsule	To attain higher solubility and dissolution	Controlled release	Moes et al. (2011)

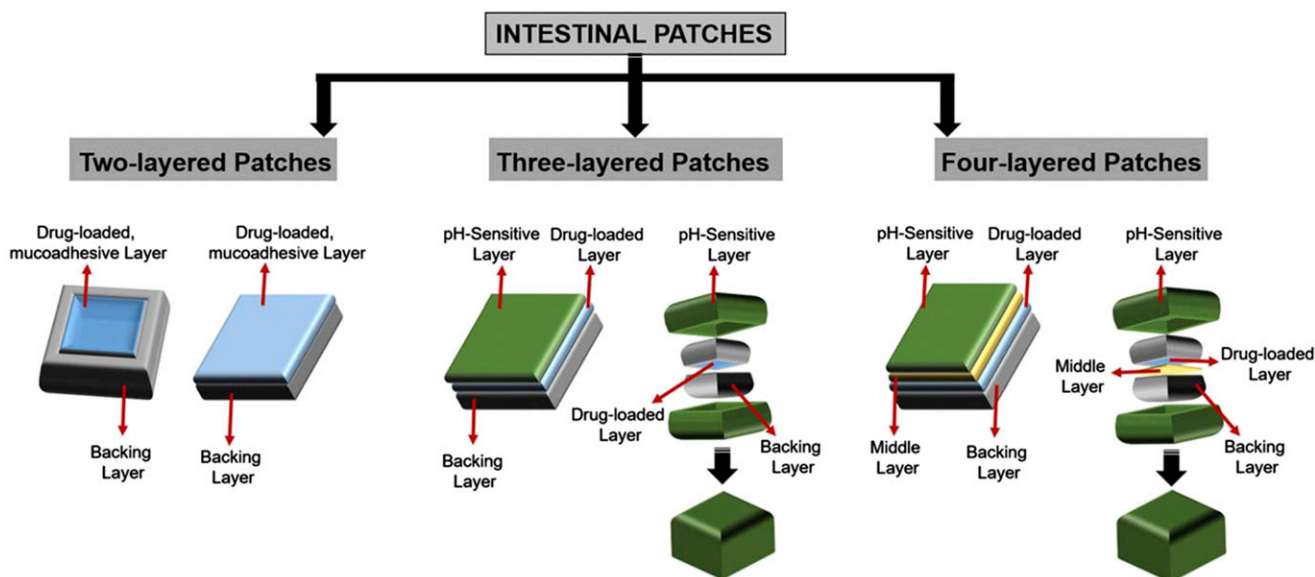


Fig. 5. Types of intestinal patches. Adapted and modified from Banerjee and Mitragotri (2017).

layer (Fig. 8). Sulforhodamine B was used as a model drug to be encapsulated into the bovine serum albumin-based microspheres with a diameter of 10–30 μm . It was observed that 95% of loaded sulforhodamine B was released from the mucoadhesive layer into PBS under in vitro release conditions.

Lee and coworkers (He et al., 2004) introduced pH-sensitive gated hydrogel patches for controlled oral drug delivery. The gated hydrogel patch consisted of two parts: a polymer-based drug reservoir and a pH-sensitive hydrogel gate. The free-radical photo-polymerization reactions were used to prepare

the gated hydrogel patch. At appropriate pH conditions, the hydrogel gate swells up to expose the drug matrix for delivery at appropriate position (Fig. 9).

Bernkop-Schnürch and coworkers (Bernkop-Schnürch, 2005; Hoyer et al., 2009) developed the intestinal patches for oral delivery of insulin. It was observed that the patches were able to release around 75% of loaded insulin in 6 hours. In comparison with subcutaneous insulin injections, these patches showed 2.2% increase in relative bio-availability. But still, for these patches to be used as oral delivery vehicles of insulin, they will require significant

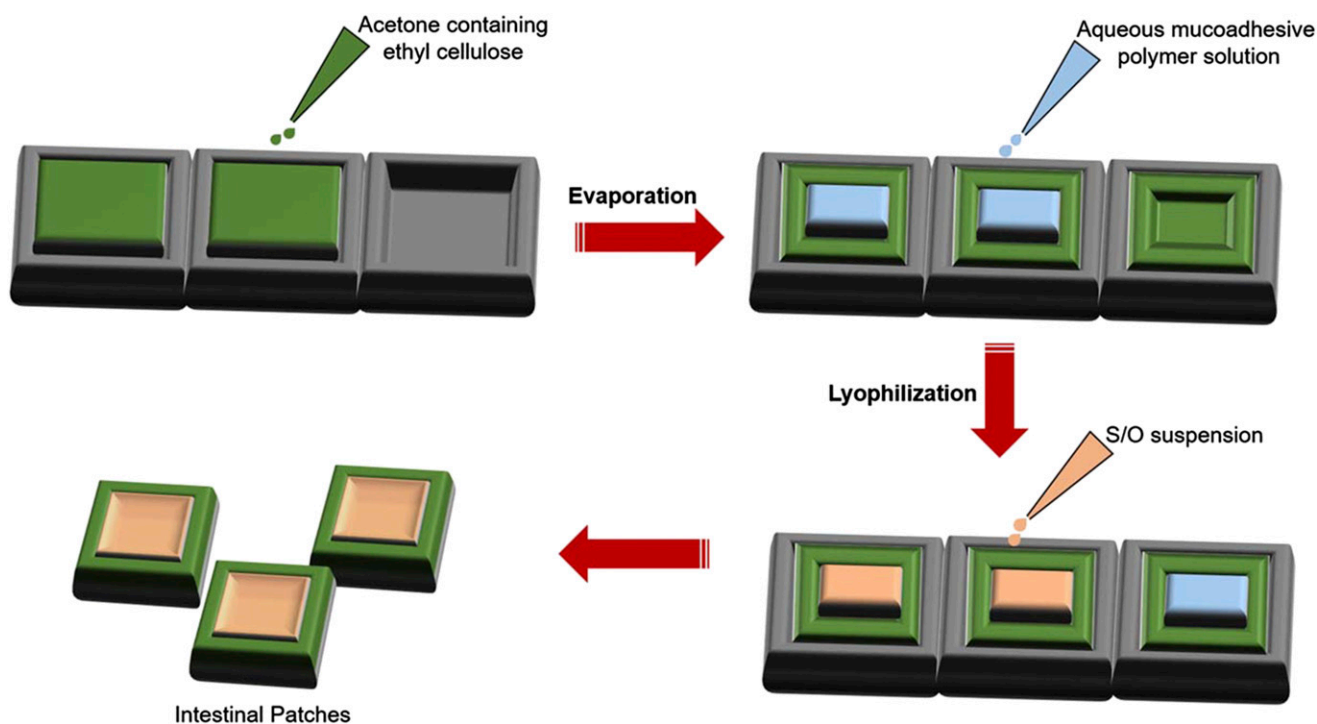


Fig. 6. Image showing the process of intestinal patch formation. Adapted and modified from Toorisaka et al. (2012).

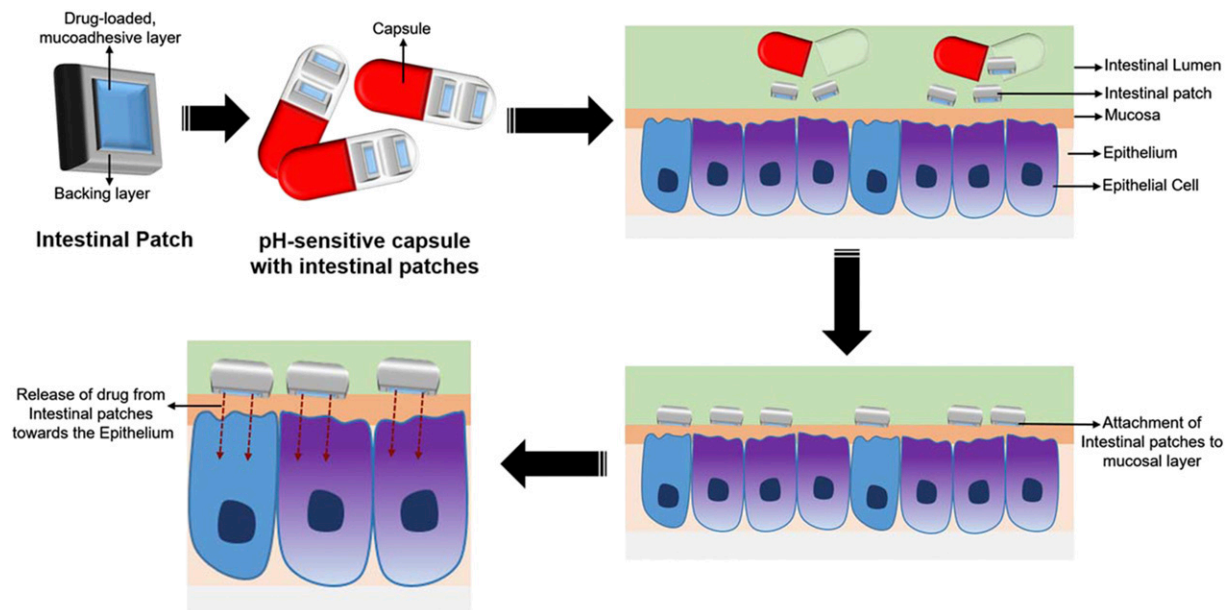


Fig. 7. Schematic representation of working of an intestinal patch. Adapted and modified from Banerjee and Mitragotri (2017).

improvements and considerations. Recently, Mitragotri and coworkers (Banerjee et al., 2016, 2017) prepared the insulin-dimethyl palmitoyl ammonio propanesulfonate micropatches for the efficient oral delivery of insulin. Propanesulfonate is considered to enhance paracellular drug uptake due to its involvement in the opening of intestinal tight junctions. The intestinal patches reduced glucose levels in nondiabetic rats, where serial dosing of the patches for every 30 min resulted in 41% lowering of glucose level in 8 hours.

Desai and coworkers (Ainslie et al., 2008) developed bioadhesive patches by using microfabrication techniques such as photolithography and etching. These bioadhesive patches contained multiple reservoirs for controlled drug release. The group had demonstrated the formation of multi-layered devices with up to three different drug layers for simultaneous controlled release in the Caco2 monolayer. These devices have been used for the synergistic effect of both insulin and camptothecin for controlled release in a simultaneous fashion. These devices have been tested in a Caco2 monolayer but are still under improvements and considerations for the intestinal conditions. Further details about similar devices can be found in

Chirra and Desai (2012), Fox et al. (2014, 2015), and Nielsen et al. (2018).

Microneedle Patches

The microneedle patches are like robotic pills or capsule-shaped devices containing needles that can be used for enhancing the bioavailability of the biologic drug class like proteins, hormones, growth factors, etc., across the GIT in a safe manner. The microneedle patches are generally fabricated from drug-loaded biocompatible polymers. The microneedle patches come in two types 1) hollow microneedle patch and 2) solid microneedle patch. In both types, microneedles are coated with pH-sensitive layer, which dissolves in appropriate site in GIT to release the drug-containing needles. In the case of a hollow microneedle patch, the drug release occurs due to peristaltic movement in the intestine, whereas, in solid microneedle patches, the microneedles break off from the pill and penetrate the intestinal walls and release the drug.

Rani Therapeutics (<https://www.ranitherapeutics.com/>) developed many microneedle patches that have the ability to deliver macromolecules like proteins and antibodies. Rani Therapeutics claims its Rani Pill is a low cost, safe, effective,

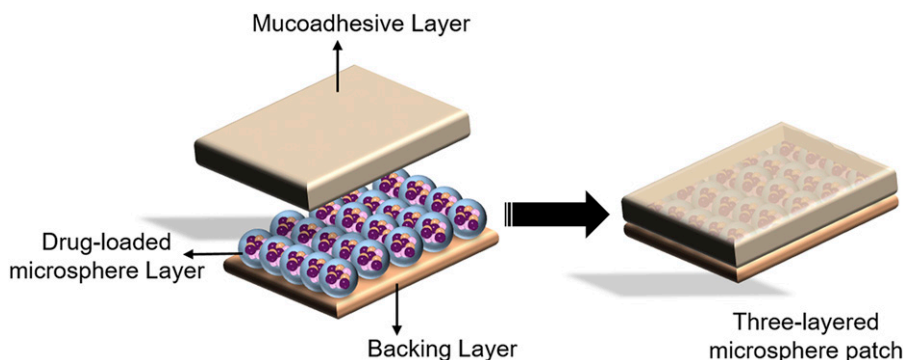


Fig. 8. Image showing a three-layered microsphere patch. Adapted and modified from Shen and Mitragotri (2002).

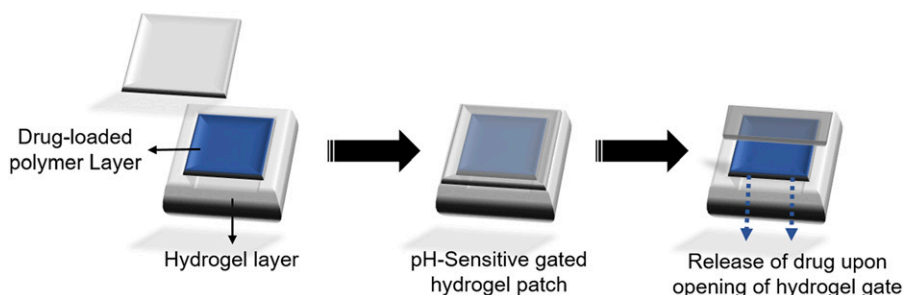


Fig. 9. Image showing working of a pH-sensitive gated hydrogel patch at appropriate pH. Adapted and modified from He et al., (2004).

and painless method to deliver various biologic molecules. A swallowable device capsule was designed containing a guide tube for tissue penetrating position, a delivery member, and a release element. The release element was designed to degrade in the intestinal conditions for enhanced absorption and delivery. The technology claims to enhance delivery of poorly absorbed drugs such as parathyroid hormone, interleukin-17, somatostatin, etc. (Imran, 2014).

The ability of these intestinal patches without/with micro-needles for the delivery of high-dose drugs or to modulate the release profiles needs to be further investigated.

Ionic Liquids

Ionic liquids are drug salts in the liquid state with low melting points. These liquids have charged particles that offer stronger interactions, thereby resulting in better stability as shown in Fig. 10. As ionic liquids form strong bonds with drug molecules and their salt counterparts, these can be useful in terms of drug repurposing and multiple drug dosing. Ionic liquids exhibited better permeability and bioavailability when acidic and basic drugs were used (Rogers and Seddon, 2003; Shamshina et al., 2015).

Porter and coworkers (Williams et al., 2014; Sahbaz et al., 2015, 2017; Williams et al., 2018) pioneered ILs for improving the oral delivery of poorly bioavailable drugs. In one of the examples, they demonstrated enhanced solubility of drugs such as danazol and itraconazole using 1-hexyl-3-hexyloxycarbonylpyridinium cation and dicyanamide $[\text{N}(\text{CN})_2]$ anion, resulting in almost ~ 100 times increased solubility. In another study, some weakly basic drugs such as itraconazole, cinnarizine, and halofantrine were converted to lipophilic ionic liquids using their hydrochloride salts and were combined with lipid systems for improved oral delivery (Sahbaz et al., 2015). Similar studies were conducted using various other high/low soluble or high/poor permeable drugs such as tolfenamic acid, meclofenamic acid, diclofenac, ibuprofen, amlodipine fexofenadine, ranitidine, and metformin (Sahbaz et al., 2017; Williams et al., 2018). Ionic liquids resulted in the possibility of higher dose administration in comparison with parent drugs, specially, in self-emulsifying drug delivery systems or using their lipophilic salts like lauryl sulfate, oleate, and docusate as counter ions. Assembling protic ionic liquids of diphenhydramine with commonly used analgesics naproxen and ibuprofen shows low diffusivity, high viscosity, poor ionic conductivity, and good wettability but exhibited low dissolution rates, which were improved with the use of silica mesoporous carriers. These protic ionic liquids carrier composites exhibited rapid dissolution and better bioavailability in capsule forms (Wang et al., 2018a). The

water-soluble acidic active pharmaceutical ingredients such as diclofenac, ibuprofen, ketoprofen, naproxen, sulfadiazine, sulfamethoxazole, and tolbutamide were converted into tetrabutylphosphonium ionic liquids and the results were quite encouraging compared with their respective free acid forms (Balk et al., 2015). A library of 36 counter ions as halide salts was prepared to map the pharmaceutical design space for ionic liquid of Selurampanel (Wiest et al., 2017).

Ionic liquids have been used to deliver macromolecules and proteins; like insulin, when mixed with choline and geranate ionic liquid, had shown a 45% decrease in blood glucose levels, even at low insulin doses of 3–10 IU/kg (accompanied by sustained release up to 12 hours) (Banerjee et al., 2018). The concept of vesicle synthesis in an aqueous medium was proposed using ionic liquids where anionic surfactant SDS was used for the cationic drug amitriptyline hydrochloride. These new amitriptyline hydrochloride-SDS ionic liquid had shown improved controlled release of the drug (Zhang et al., 2013).

While ionic liquids are proving beneficial in the effective delivery of a range of drug molecules that otherwise are poorly bioavailable, the safety of such delivery vehicles remains to be established.

Hydrogels

Hydrogels are 3D crosslink of synthetic and natural polymers, which can absorb considerable amounts of water without dissolving. The crosslinking network can be easily

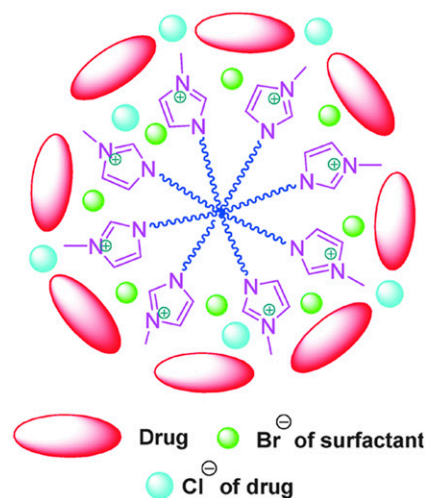


Fig. 10. Image showing possible adsorption of drug $[\text{C}_{14\text{mim}}][\text{Br}]$ micelles. Reproduced with permission from Mahajan et al. (2012).

TABLE 3
Summary of recent hydrogel technologies applied in drug delivery

Drug	Hydrogel	Purpose	Reference
Insulin	Methyl β -cyclodextrin in polymethacrylic acid (PMAA)	Improve intestinal transport upon oral delivery	Sajeesh et al. (2010)
Insulin	Hydroxyethyl methacrylate (HEMA)	“do”	Wang et al. (2018)
Insulin	Carboxymethyl cellulose/poly(acrylic acid)	“do”	Gao et al. (2014)
Insulin and porcine growth hormone	Terpolymer hydrogels P((MAA-co-NVP)-g-EG) composed of methacrylic acid (MAA), N-vinyl pyrrolidone (NVP), and poly(ethylene glycol) (PEG)	“do”	O'Connor et al. (2017)
Dexamethasone	Guar gum (GG), poly(acrylic acid) (PAA) and cyclodextrin (CD) and tetraethyl orthosilicate as linker	Enhanced drug delivery	Das and Subuddhi (2015)
Salmon calcitonin	poly(itaconic acid-grafted-poly(ethylene glycol)) (P(LA-g-EG))	Improve intestinal transport upon oral delivery	Koetting and Peppas (2014)
Hematological factor IX hFIX	poly(methacrylic acid)-grafted-poly(ethylene glycol) (P(MAA-g-EG)) (P(MAA-g-EG))	Improve intestinal transport upon oral delivery	Horava et al. (2016)
Lidocaine	Chitosan with catechols and genipin cross linker	Rapid onset of action via buccal route	Xu et al. (2015)
Propranolol	Carboxymethyl cellulose and ZnO nanoparticles using Fe ³⁺ ion as a crosslinking agent	Enhanced drug delivery	Zare-Akbari et al. (2016)

achieved via a variety of stimuli like pH sensitivity, stereo complexation, ionic interaction, condensation reaction, maturation, grafting, and enzymatic reaction. This 3D grid gives outstanding mechanical strength and adhesive properties to gels. Use of the biocompatible and biodegradable polymers with a stimulus responsive property offers the hydrogels as an alternate for oral drug delivery, in particular for enhancing the stability of drug in GI tract. Previous authors have endeavored to organize literature on oral administration, like buccal cavity administration (Yadav et al., 2009; Chaturvedi et al., 2013; Aminabhavi et al., 2014; Liu et al., 2017; Fonseca-Santos and Chorilli, 2018).

Chitosan and alginate hydrogels have been extensively used in biomedical applications (Du et al., 2015). For instance, in buccal delivery of lidocaine, chitosan with catechols using genipin cross linker has been tested in vitro and in vivo in rabbits (Xu et al., 2015). The pH-sensitive nanocomposite hydrogel beads of carboxymethyl cellulose and ZnO nanoparticles were prepared using a model drug propranolol and Fe³⁺ ion as a crosslinking agent (Zare-Akbari et al., 2016). Carboxymethyl cellulose with montmorillonite (modified chitosan with L-valine and phenylboronic acid) in a diabetic rat model showed better insulin levels even after 4 hours of dosing (Li et al., 2017). Alginate acts as a good encapsulating agent along with 3D network provider, e.g., oral delivery of doxorubicin-loaded liposomes for oral cancer (Shtenberg et al., 2018), emodin (Cong et al., 2018), insulin nano-emulsion was coated with alginate/chitosan using CaCl₂ as cross linkers (Li et al., 2013).

Hydroxyethyl methacrylate nanogel via emulsion polymerization was developed for the oral delivery of insulin with improved bioavailability that controlled blood glucose levels for up to 12 hours (Wang et al., 2018). Insulin-loaded glucose responsive nanocarriers dispersed in hyaluronic acid hydrogel, offered better protection (almost 50% more protective than without hyaluronic acid gel nanocarriers) from harsh gastric environment in vivo in rats (Li et al., 2016).

To enhance the intestinal absorption of proteins, Sharma and coworkers reported the delivery of insulin-like proteins

using modified cyclodextrin as methyl- β -cyclodextrin and further encapsulated in polymethacrylic acid hydrogel (Sajeesh et al., 2010c). N-vinyl pyrrolidone (NVP) merged polymethacrylic acid-chitosan microparticles (Sajeesh and Sharma, 2011) and poly(methacrylic acid)-chitosan-poly(ethylene glycol) hydrogels (Sajeesh et al., 2010) and thiol modified polymethacrylic acid-polyethylene glycol-chitosan [poly(ethylene glycol)]-based hydrogel (Sajeesh et al., 2010). An intricate gel of guar gum, poly(acrylic acid), and cyclodextrin using tetraethyl orthosilicate as a linker has shown promise for the delivery of dexamethasone via oral route (Das and Subuddhi, 2015).

Peppas and coworkers (Betancourt et al., 2010; Koetting and Peppas, 2014; O'Connor et al., 2017) have pioneered to make hydrogels for the delivery of hydrophilic/hydrophobic and small/large molecule drugs incorporating a variety of polymers. The terpolymer hydrogels P[(MAA-co-NVP)-g-EG] composed of methacrylic acid (MAA), NVP, and poly(ethylene glycol) were prepared by varying poly(ethylene glycol) chain lengths, for protein delivery using model proteins such as insulin and porcine growth hormone (O'Connor et al., 2017). Similarly, pH responsive hydrogels such as poly[itaconic acid-grafted-poly(ethylene glycol)] for high isoelectric point biomolecules like salmon calcitonin (Koetting and Peppas, 2014), while poly(methacrylic acid)-grafted-poly(ethylene glycol) (P(MAA-g-EG)) has been used for oral delivery of hematologic factor IX hFIX (Horava et al., 2016). A substantial amount of work has been reported on the use of hydrophobic particle-trapped hydrogels for hydrophobic drug delivery (Schoener et al., 2013; Puranik et al., 2016). Over the years, this work has contributed toward a fundamental understanding of structure-function relationships of hydrogels and their application to drug delivery of diverse physicochemical attributes.

Superporous hydrogels are a new, upcoming field for nonconventional target drug delivery owing to their high swelling and high mechanical strength, making them a good candidate for the oral delivery of protein and peptides

TABLE 4
Summary of recent nanoparticle technologies applied in drug delivery

Drug	Nanosystems	Purpose	Reference
Insulin	L-valine and phenylboronic acid modified chitosan-based multifunctional nanocarrier PLGA and Pluronic F68 based nanoparticles	To overcome multiple barriers for oral insulin delivery	Li et al. (2017)
Insulin		To enhance the bioavailability using negatively charged nanoparticles for better absorption	Czuba et al. (2018)
Curcumin	Folic acid conjugated PLGA-PEG copolymer based nanosystem	To carryout site specific release of hydrophobic anti-cancer drugs	Pillai et al. (2015)
Curcumin	N-carboxymethyl chitosan based nanoparticles	To enhance the drug delivery to lymphatic system	Baek and Cho (2017)
Curcumin	Polyacrylamide-grafted-xanthan gum based nanoparticles	To improve the bioavailability of drug for colon targeting	Mutalik et al. (2016)
Paclitaxel and curcumin	Folate conjugated lipid nanoparticles	To co-deliver both drugs to enhance uptake and inhibit multidrug resistant	Liu et al. (2017)
Cisplatin prodrug [Asplatin, c,c,t-[PtCl ₂ (NH ₃) ₂ (OH) (aspirin)]	Cholesterol-asplatin-incorporated mPEG-PLGA nanoparticles	To improve the oral delivery with improved efficacy and reduced toxicity	Cheng et al. (2015)
Doxorubicin	HN-1 medicated PEGylated DOX	To improve the penetration efficiency to oral squamous cell carcinoma	Wang et al. (2017b)
Triclabendazole	Chitosan 70/5 and Miglyol 812	To develop oral nanoformulation for anti-parasitic drugs	Real et al. (2018)
Cyclosporine A	Lipid nanoparticles	To enhance drug delivery	Guada et al. (2016)
Betulinic acid	PLGA based nanoparticles	For improved anti-hepatocellular carcinoma activity than the parent compound	Kumar et al. (2018)
Olmesartan medoxomil	Lipid nanoparticles	To enhance oral bioavailability	Kaithwas et al. (2017)
Epirubicin	PLGA based nanoparticles with PEG modification	To improve permeability across the ileum of Rodent	Tariq et al. (2016)
Scutellarin	Nanosystem based on chitosan derivatives	To enhance oral bioavailability	Wang et al. (2017)
Resveratrol	Zein-based nanoparticles	Improved oral bioavailability and anti-inflammatory effects	Penalva et al. (2015)
Superoxide dismutase	Zein-alginate nanoparticles	For steady state release of drug to decrease endotoxicity of IP administration	Lee et al. (2016)
Quercetin	Modified chitosan and alginate nanoparticles	To reduce blood glucose levels in diabetic rats	Mukhopadhyay et al. (2018)
Hesperetin	Nanocrystals of drug using phytantriol and lecithin with Pluronic F-127 or mannitol as surfactant	To improve site targeting using 2D and 3D arrays of nanocrystals	Shete et al. (2015)
Paclitaxel	Eudragit-coated nanorods	For better therapeutic response by taking advantage of less macrophagial consumption of the polymer	Yilmaz et al. (2016)
Platinum complex drugs	B-lactoglobulin-pectin encapsulated nanoparticles	To protect the drug through GIT using natural coating of pectin	Izadi et al. (2016)

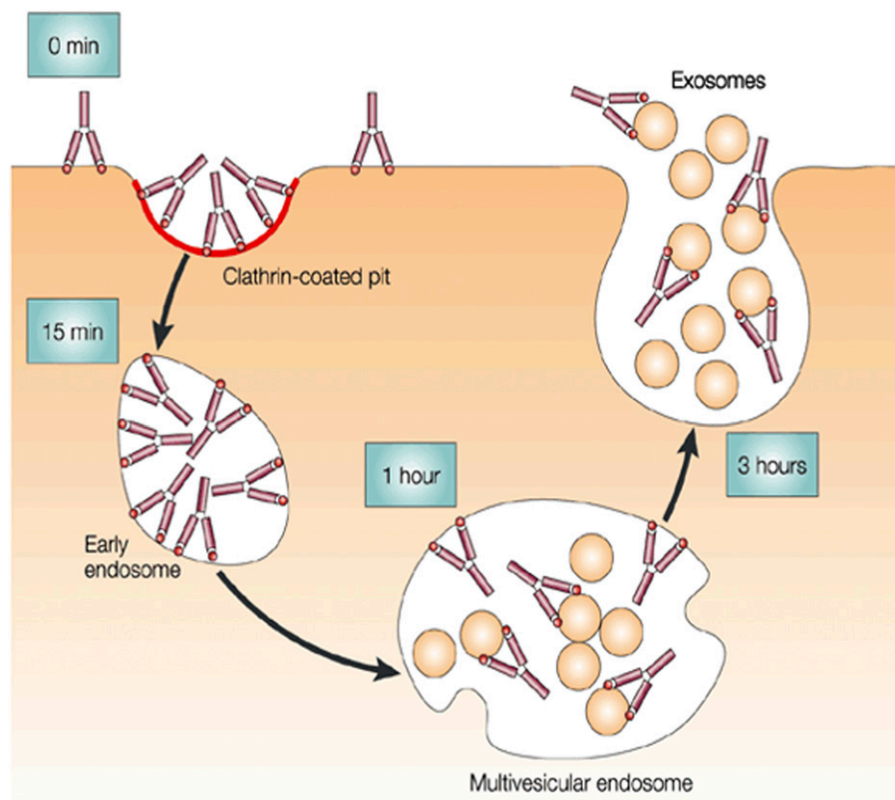


Fig. 11. Schematic representation of exosome formation. Reproduced with permission from Théry et al. (2002).

(Mastropietro et al., 2012). A summary of recent developments in hydrogel technologies is presented in Table 3.

Nanosystems

Conventional delivery systems release the drug in the body at a specific site (e.g., tablets, capsules, patches, gels in the intestine) for a determined time, from where the drug has to be absorbed, except for the intravenous route. Oral administration remains the preferred route for drug delivery but numerous drugs are poorly bioavailable for reasons such as low mucosal permeability, restricted permeation to a region of the GIT, low solubility or stability of the compound, and elimination-degradation of a fraction of drug without absorption (Tibbitt et al., 2016). Nanoscale drug delivery systems hold the promise of novel clinical interventions because their minuscule size enables them to act *in vivo* at the subcellular level (Langer and Weissleder, 2015). During the gastrointestinal transit, the entrapped drug is believed to be protected from enzymatic degradation and the gastrointestinal milieu on account of absorption of the intact particulate form. The favored sites for nanoparticulate uptake appear to be the lympho-epithelial M cells of the Peyer's patches, because it has been shown that microparticles remain in the Peyer's patches while nanoparticles disseminate systemically (Jani et al., 1990). It is hypothesized that, following the binding of nanoparticles to the apical membrane of M cells, internalization and shuttling to lymphocytes occur, with particle distribution being dependent on particle size and surface charge (Hussain et al., 1997; Delie, 1998). However, only a fraction of the dose is absorbed from passive nanosystems (Lamprou et al., 2013). Receptor-mediated drug delivery using functional

nanosystems has been explored over the years to enhance the therapeutic index of drugs (Gref et al., 1994; Peer et al., 2007; Zhu et al., 2012; Mura et al., 2013; Cheng et al., 2015a). Cyclodextrins have been extensively used in drug delivery, in particular for small molecule delivery. The current advancement and potential future of cyclodextrin nanoparticulates was recently reviewed elsewhere (Adeoye and Cabral-Marques, 2017). The recent use of receptor-mediated uptake in the GIT presents an exciting opportunity for targeted and enhanced delivery of nanosystems via vitamin B12 (Petrus et al., 2009; Fowler et al., 2013), folate-receptor (Anderson et al., 2001; Roger et al., 2012), neonatal fc receptor (Pridgen et al., 2013), and transferrin receptor (TfR; Amet et al., 2010; Shofner et al., 2010; Du et al., 2013). A summary of recent developments in nanoparticle technologies applied in drug delivery is presented in Table 4.

While promising, the receptor-mediated drug-delivery approaches currently use endogenous ligands to modify the

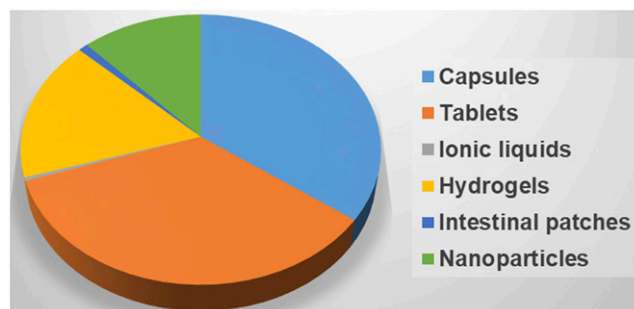


Fig. 12. Pie chart showing the distribution of patents for various oral drug delivery technologies.

particles that can be outcompeted by the physiologic ligands that are present in high concentrations (Lundquist and Artursson, 2016). To address this limitation, our laboratory recently reported the use of gambogic acid (GA), known for its affinity to transferrin receptors, independent of transferrin binding (Kasibhatla et al., 2005), as a noncompetitive ligand for TfR present in the small intestine (Saini et al., 2016; Ganugula et al., 2017a). The GA modified poly (lactic-co-glycolic acid) nanoparticles demonstrated noncompetitive transport in cellulo and improved oral bioavailability of encapsulated drugs or drug-like compounds (e.g., cyclosporine, curcumin, and insulin) in rodents (Saini et al., 2016; Ganugula et al., 2017a; Kaur et al., 2019). Our laboratory also observed that the ligand-receptor stoichiometry plays an important role in receptor-mediated drug delivery. Optimized ligand-receptor stoichiometry has been achieved through multiple coupling sites in newly formed polyester, which showed enhanced uptake and efficient drug delivery compared with benchmarking control, GA modified poly (lactic-co-glycolic acid) (Ganugula, et al., 2017b). It will be interesting to see if the improved bioavailability will subsequently lead to improved clinical outcomes, in particular chronic conditions on oral dosing.

Exosomes. Exosomes are saucer-shaped nanovesicles of biologic origin (Fig. 11) that participate in cell communication and act as cellular couriers to facilitate the transfer of lipids, proteins, and RNAs from one cell to another (Zomer et al., 2010).

Exosomes have been explored as nanocarrier to deliver macromolecules such as peptides, proteins, RNAs, etc., across the cell barriers (Alvarez-Erviti et al., 2011; Kamerkar et al., 2017; Wang et al., 2018). In general, exosomes are separated from dead cells and other debris by a series of centrifugations, followed by separation through flotation in sucrose gradients. The exosomes can be derived from bovine milk by removing the milk proteins (caseins) with hydrochloric acid through isoelectric precipitation followed by centrifugation to remove the debris (Yamauchi et al., 2019). As a cellular courier, the milk exosomes have been used as carriers for a variety of macromolecules such as proteins, microRNAs, anticancer drugs, etc. (Munagala et al., 2016; Samuel et al., 2017; Manca et al., 2018). These nanodevices are cost effective, scalable, and biocompatible and show enhanced drug bioavailability and cross species tolerance without any immune response. Moreover, the exosomes can be functionalized for targeted delivery of drugs. The milk exosome has been used to deliver flavonoids, like Anthos, as anticancer molecules for multiple cancer types (Munagala et al., 2017). Along with this, the milk exosomes have been used for the oral drug delivery of paclitaxel to enhance the efficacy and reduce the side effects associated with the drug (Agrawal et al., 2017).

Future Perspectives

Oral drug delivery technologies have come a long way from simple tablets to the most sophisticated nanoparticle technologies (Fig. 12). These developments are possible due to the better understanding of the intestinal barriers and the possible ports of entry to the systemic circulation via the portal vein and intestinal lymphatics. The significant body of literature describing the efforts of small and large

molecule delivery across the intestinal barriers only builds the confidence in nonconventional delivery strategies.

While delivery technology is as important as the active ingredient (drug) itself, it is important to realize that one technology does not fit all. It is very essential to understand the room for improvement when considering delivery technology; equally important is striking a balance between innovation and associated risk to ensure smooth translation. The success eventually lies in simplicity, and the focus should be in optimizing minimum effective therapeutic concentrations aided by delivery technologies. The application of nonconventional oral delivery strategies to repurpose the existing drugs should be reasonably straight forward, as we already understand the pharmacology and safety profiles that can greatly reduce the risk of attrition in drug development during clinical phases. This route of administration does not require the formulation to be sterile, an added advantage to run phase 0/I trials or, for that matter, conducting efficacy studies in higher order species, if adequate safety measures are established.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Kaur, Arora, Ravi Kumar.

References

- Adeoye O and Cabral-Marques H (2017) Cyclodextrin nanosystems in oral drug delivery: a mini review. *Int J Pharm* **531**:521–531.
- Agrawal AK, Aqil F, Jeyabalan J, Spencer WA, Beck J, Gachuki BW, Alhakeem SS, Oben K, Munagala R, Bondada S, et al. (2017) Milk-derived exosomes for oral delivery of paclitaxel. *Nanomedicine* **13**:1627–1636.
- Ainslie KM, Kraning CM, and Desai TA (2008) Microfabrication of an asymmetric, multi-layered microdevice for controlled release of orally delivered therapeutics. *Lab Chip* **8**:1042–1047.
- Alshehri SM, Al-Lohedan HA, Al-Farraj E, Alhokbany N, Chaudhary AA, and Ahamad T (2016) Macroporous natural capsules extracted from *Phoenix dactylifera* L. spore and their application in oral drugs delivery. *Int J Pharm* **504**: 39–47.
- Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhali S, and Wood MJ (2011) Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat Biotechnol* **29**:341–345.
- Amet N, Wang W, and Shen WC (2010) Human growth hormone-transferrin fusion protein for oral delivery in hypophysectomized rats. *J Control Release* **141**: 177–182.
- Aminabhavi TM, Nadagouda MN, Joshi SD, and More UA (2014) Guar gum as platform for the oral controlled release of therapeutics. *Expert Opin Drug Deliv* **11**: 753–766.
- Anderson KE, Eliot LA, Stevenson BR, and Rogers JA (2001) Formulation and evaluation of a folic acid receptor-targeted oral vancomycin liposomal dosage form. *Pharm Res* **18**:316–322.
- Andrews GP, Laverty TP, and Jones DS (2009) Mucoadhesive polymeric platforms for controlled drug delivery. *Eur J Pharm Biopharm* **71**:505–518.
- Baek JS and Cho CW (2017) Surface modification of solid lipid nanoparticles for oral delivery of curcumin: improvement of bioavailability through enhanced cellular uptake, and lymphatic uptake. *Eur J Pharm Biopharm* **117**:132–140.
- Bai JPF (2016) Pharmacodynamics and systems pharmacology approaches to repurposing drugs in the wake of global health burden. *J Pharm Sci* **105**: 3007–3012.
- Balk A, Wiest J, Widmer T, Galli B, Holzgrabe U, and Meinel L (2015) Transformation of acidic poorly water soluble drugs into ionic liquids. *Eur J Pharm Biopharm* **94**:73–82.
- Banerjee A, Ibsen K, Brown T, Chen R, Agatemor C, and Mitragotri S (2018) Ionic liquids for oral insulin delivery. *Proc Natl Acad Sci USA* **115**:7296–7301.
- Banerjee A, Lee J, and Mitragotri S (2016) Intestinal mucoadhesive devices for oral delivery of insulin. *Bioeng Transl Med* **1**:338–346.
- Banerjee A and Mitragotri S (2017) Intestinal patch systems for oral drug delivery. *Curr Opin Pharmacol* **36**:58–65.
- Banerjee A, Wong J, Gogoi R, Brown T, and Mitragotri S (2017) Intestinal micro-patches for oral insulin delivery. *J Drug Target* **25**:608–615.
- Bellinger AM, Jafari M, Grant TM, Zhang S, Slater HC, Wenger EA, Mo S, Lee YL, Mazdiyasi H, Kogan L, et al. (2016) Oral, ultra-long-lasting drug delivery: application toward malaria elimination goals. *Sci Transl Med* **8**:365ra157.
- Bernkop-Schnürch A (2005) Thiomers: a new generation of mucoadhesive polymers. *Adv Drug Deliv Rev* **57**:1569–1582.
- Betancourt T, Pardo J, Soo K, and Peppas NA (2010) Characterization of pH-responsive hydrogels of poly(itaconic acid-g-ethylene glycol) prepared by UV-initiated free radical polymerization as biomaterials for oral delivery of bio-active agents. *J Biomed Mater Res A* **93**:175–188.

- Biederman J, Quinn D, Weiss M, Markabi S, Weidenman M, Edson K, Karlsson G, Pohlmann H, and Wigal S (2003) Efficacy and safety of Ritalin LA, a new, once daily, extended-release dosage form of methylphenidate, in children with attention deficit hyperactivity disorder. *Paediatr Drugs* 5:833–841.
- Binkley N, Bolognese M, Sidorowicz-Bialynicka A, Vally T, Trout R, Miller C, Bubon CE, Gilligan JP, and Krause DS; Oral Calcitonin in Postmenopausal Osteoporosis (ORACAL) Investigators (2012) A phase 3 trial of the efficacy and safety of oral recombinant calcitonin: the Oral Calcitonin in Postmenopausal Osteoporosis (ORACAL) trial. *J Bone Miner Res* 27:1821–1829.
- Cárdenas-Bailón F, Osorio-Revilla G, and Gallardo-Velázquez T (2015) Microencapsulation of insulin using a W/O/W double emulsion followed by complex coacervation to provide protection in the gastrointestinal tract. *J Microencapsul* 32:308–316.
- Cha Y, Erez T, Reynolds IJ, Kumar D, Ross J, Koytiger G, Kusko R, Zeskind B, Risso S, Kagan E, et al. (2018) Drug repurposing from the perspective of pharmaceutical companies. *Br J Pharmacol* 175:168–180.
- Chaturvedi K, Ganguly K, Nadagouda MN, and Aminabhavi TM (2013) Polymeric hydrogels for oral insulin delivery. *J Control Release* 165:129–138.
- Cheng CJ, Tietjen GT, Saucier-Sawyer JK, and Saltzman WM (2015a) A holistic approach to targeting disease with polymeric nanoparticles. *Nat Rev Drug Discov* 14:239–247.
- Cheng Q, Shi H, Huang H, Cao Z, Wang J, and Liu Y (2015b) Oral delivery of a platinum anticancer drug using lipid assisted polymeric nanoparticles. *Chem Commun (Camb)* 51:17536–17539.
- Chirra HD and Desai TA (2012) Emerging microtechnologies for the development of oral drug delivery devices. *Adv Drug Deliv Rev* 64:1569–1578.
- Choonara BF, Choonara YE, Kumar P, Bujukumar D, du Toit LC, and Pillay V (2014) A review of advanced oral drug delivery technologies facilitating the protection and absorption of protein and peptide molecules. *Biotechnol Adv* 32:1269–1282.
- Cipolla DC and Gonda I (2012) Formulation technology to repurpose drugs for inhalation delivery. *Drug Discov Today Ther Strat* 8:123–130.
- Cong Z, Shi Y, Wang Y, Wang Y, Niu J, Chen N, and Xue H (2018) A novel controlled drug delivery system based on alginate hydrogel/chitosan micelle composites. *Int J Biol Macromol* 107 (Pt A):855–864.
- Czuba E, Diop M, Mura C, Schaschok A, Langlois A, Bietiger W, Neidl R, Virgilio A, Auberval N, Julien-David D, et al. (2018) Oral insulin delivery, the challenge to increase insulin bioavailability: influence of surface charge in nanoparticle system. *Int J Pharm* 542:47–55.
- Das S and Subudhi U (2015) pH-Responsive guar gum hydrogels for controlled delivery of dexamethasone to the intestine. *Int J Biol Macromol* 79:856–863.
- Del Curto MD, Maroni A, Palugan L, Zema L, Gazzaniga A, and Sangalli ME (2011) Oral delivery system for two-pulse colonic release of protein drugs and protease inhibitor/absorption enhancer compounds. *J Pharm Sci* 100:3251–3259.
- Delie F (1998) Evaluation of nano- and microparticle uptake by the gastrointestinal tract. *Adv Drug Deliv Rev* 34:221–233.
- Donovan JD, Bauer L, Fahey GC Jr, and Lee Y (2017) In vitro digestion and fermentation of microencapsulated tributyrin for the delivery of butyrate. *J Food Sci* 82:1491–1499.
- Du H, Liu M, Yang X, and Zhai G (2015) The design of pH-sensitive chitosan-based formulations for gastrointestinal delivery. *Drug Discov Today* 20:1004–1011.
- Du W, Fan Y, Zheng N, He B, Yuan L, Zhang H, Wang X, Wang J, Zhang X, and Zhang Q (2013) Transferrin receptor specific nanocarriers conjugated with functional 7peptide for oral drug delivery. *Biomaterials* 34:794–806.
- Eiamtrakarn S, Itoh Y, Kishimoto J, Yoshikawa Y, Shibata N, Murakami M, and Takada K (2002) Gastrointestinal mucoadhesive patch system (GI-MAPS) for oral administration of G-CSF, a model protein. *Biomaterials* 23:145–152.
- El-Aassar MR, Hafez EE, El-Deeb NM, and Fouda MM (2014) Microencapsulation of lectin anti-cancer agent and controlled release by alginate beads, biosafety approach. *Int J Biol Macromol* 69:88–94.
- Elder DP, Holm R, and Diego HL (2013) Use of pharmaceutical salts and cocrystals to address the issue of poor solubility. *Int J Pharm* 453:88–100.
- Fleming AB, Carlson DR, Varanasi RK, Grima M, Mayock SP, Saim S, and Kopecky EA (2016) Evaluation of an extended-release, abuse-deterrent, microsphere-in-capsule analgesic for the management of patients with Chronic Pain With Dysphagia (CPD). *Pain Pract* 16:334–344.
- Fonseca-Santos B and Chorilli M (2018) An overview of polymeric dosage forms in buccal drug delivery: state of art, design of formulations and their in vivo performance evaluation. *Mater Sci Eng C* 86:129–143.
- Fowler R, Vilasaliu D, Trillo FF, Garnett M, Alexander C, Horsley H, Smith B, Whitcombe I, Eaton M, and Stolnik S (2013) Nanoparticle transport in epithelial cells: pathway switching through bioconjugation. *Small* 9:3282–3294.
- Fox CB, Chirra HD, and Desai TA (2014) Planar bioadhesive microdevices: a new technology for oral drug delivery. *Curr Pharm Biotechnol* 15:673–683.
- Fox CB, Kim J, Le LV, Nemeth CL, Chirra HD, and Desai TA (2015) Micro/nanofabricated platforms for oral drug delivery. *J Control Release* 219:431–444.
- Ganugula R, Arora M, Guada M, Saini P, and Kumar MNVR (2017a) Noncompetitive active transport exploiting intestinal transferrin receptors for oral delivery of proteins by tunable nanoplateform. *ACS Macro Lett* 6:161–164.
- Ganugula R, Arora M, Saini P, Guada M, and Kumar MNVR (2017b) Next generation precision-polyesters enabling optimization of ligand-receptor stoichiometry for modular drug delivery. *J Am Chem Soc* 139:7203–7216.
- Gao X, Cao Y, Song X, Zhang Z, Zhuang X, He C, and Chen X (2014) Biodegradable, pH-responsive carboxymethyl cellulose/poly(acrylic acid) hydrogels for oral insulin delivery. *Macromol Biosci* 14:565–575.
- Gref R, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V, and Langer R (1994) Biodegradable long-circulating polymeric nanospheres. *Science* 263:1600–1603.
- Guada M, Lana H, Gil AG, Dios-Viéitez M del C, and Blanco-Prieto MJ (2016) Cyclosporine A lipid nanoparticles for oral administration: pharmacodynamics and safety evaluation. *Eur J Pharm Biopharm* 101:112–118.
- Guarascio AJ and Slain D (2015) Review of the new delayed-release oral tablet and intravenous dosage forms of posaconazole. *Pharmacotherapy* 35:208–219.
- Gupta V, Hwang BH, Doshi N, Banerjee A, Anselmo AC, and Mitragotri S (2016) Delivery of exenatide and insulin using mucoadhesive intestinal devices. *Ann Biomed Eng* 44:1993–2007.
- Gupta V, Hwang BH, Lee J, Anselmo AC, Doshi N, and Mitragotri S (2013) Mucoadhesive intestinal devices for oral delivery of salmon calcitonin. *J Control Release* 172:753–762.
- Hasciöcek K, Rossi A, Colombo P, Massimo G, Strusi OL, and Colombo G (2011) Assemblage of drug release modules: effect of module shape and position in the assembled systems on floating behavior and release rate. *Eur J Pharm Biopharm* 77:116–121.
- He H, Cao X, and Lee LJ (2004) Design of a novel hydrogel-based intelligent system for controlled drug release. *J Control Release* 95:391–402.
- Hong Y, Liu G, and Gu Z (2016) Recent advances of starch-based excipients used in extended-release tablets: a review. *Drug Deliv* 23:12–20.
- Horawa SD, Moy KJ, and Peppas NA (2016) Biodegradable hydrophilic carriers for the oral delivery of hematological factor IX for hemophilia B treatment. *Int J Pharm* 514:220–228.
- Hoyer H, Greindl M, and Bernkop-Schnürch A (2009) Design and in vivo evaluation of a patch system based on thiolated polymers. *J Pharm Sci* 98:620–627.
- Huang L, Injac SG, Cui K, Braun F, Lin Q, Du Y, Zhang H, Kogiso M, Lindsay H, Zhao S, et al. (2018) Systems biology-based drug repositioning identifies digoxin as a potential therapy for groups 3 and 4 medulloblastoma. *Sci Transl Med* 10:ea01150.
- Hussain N, Jani PU, and Florence AT (1997) Enhanced oral uptake of tomato lectin-conjugated nanoparticles in the rat. *Pharm Res* 14:613–618.
- Imran M (2014) inventors. Swallowable drug delivery device and methods of drug delivery. U.S. Patent 8,721,620. Assignee: Rani Therapeutics LLC.
- Izadi Z, Divsalar A, Saboury AA, and Sawyer L (2016) β -Lactoglobulin-pectin nanoparticle-based oral drug delivery system for potential treatment of colon cancer. *Chem Biol Drug Des* 88:209–216.
- Jani P, Halbert GW, Langridge J, and Florence AT (1990) Nanoparticle uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency. *J Pharm Pharmacol* 42:821–826.
- Kaithwas V, Dora CP, Kushwah V, and Jain S (2017) Nanostructured lipid carriers of olmesartan medoxomil with enhanced oral bioavailability. *Colloids Surf B Biointerfaces* 154:10–20.
- Kamerkar S, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, Lee JJ, and Kalluri R (2017) Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature* 546:498–503.
- Kasibhatla S, Jessen KA, Maliartchouk S, Wang JY, English NM, Drewe J, Qiu L, Archer SP, Ponce AE, Sirisoma N, et al. (2005) A role for transferrin receptor in triggering apoptosis when targeted with gambogic acid. *Proc Natl Acad Sci USA* 102:12095–12100.
- Katsuma M, Watanabe S, Takemura S, Sako K, Sawada T, Masuda Y, Nakamura K, Fukui M, Connor AL, and Wilding IR (2004) Scintigraphic evaluation of a novel colon-targeted delivery system (CODES) in healthy volunteers. *J Pharm Sci* 93:1287–1299.
- Kaur G, Arora M, Ganugula R, and Kumar MNVR (2019) Double-headed nano-systems for oral drug delivery. *Chem Commun* 55:4761–4764.
- Khaled SA, Alexander MR, Wildman RD, Wallace MJ, Sharpe S, Yoo J, and Roberts CJ (2018) 3D extrusion printing of high drug loading immediate release paracetamol tablets. *Int J Pharm* 538:223–230.
- Khaled SA, Burley JC, Alexander MR, Yang J, and Roberts CJ (2015) 3D printing of tablets containing multiple drugs with defined release profiles. *Int J Pharm* 494:643–650.
- Kim S, Diab R, Joubert O, Canilho N, and Pasc A (2016) Core-shell microcapsules of solid lipid nanoparticles and mesoporous silica for enhanced oral delivery of curcumin. *Colloids Surf B Biointerfaces* 140:161–168.
- Kirsch K, Hanke U, and Weitschies W (2017) An overview of intestinal wafers for oral drug delivery. *Eur J Pharm Biopharm* 114:135–144.
- Knipe JM, Chen F, and Peppas NA (2015) Enzymatic biodegradation of hydrogels for protein delivery targeted to the small intestine. *Biomacromolecules* 16:962–972.
- Koetting MC and Peppas NA (2014) pH-Responsive poly(itaconic acid-co-N-vinylpyrrolidone) hydrogels with reduced ionic strength loading solutions offer improved oral delivery potential for high isoelectric point-exhibiting therapeutic proteins. *Int J Pharm* 471:83–91.
- Kumar P, Singh AK, Raj V, Rai A, Keshari AK, Kumar D, Maity B, Prakash A, Maiti S, and Saha S (2018) Poly(lactic-co-glycolic acid)-loaded nanoparticles of betulinic acid for improved treatment of hepatic cancer: characterization, in vitro and in vivo evaluations. *Int J Nanomedicine* 13:975–990.
- Kyobula M, Adediji A, Alexander MR, Saleh E, Wildman R, Ashcroft I, Gellert PR, and Roberts CJ (2017) 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. *J Control Release* 261:207–215.
- Lamb YN, Garnock-Jones KP, and Keam SJ (2016) Oxycodone DETERx[®] ER capsules: a review in severe, chronic pain. *Drugs* 76:1759–1769.
- Lamprou DA, Venkatpurwar V, and Kumar MNVR (2013) Atomic force microscopy images label-free, drug encapsulated nanoparticles in vivo and detects difference in tissue mechanical properties of treated and untreated: a tip for nanotoxicology. *PLoS One* 8:e64490.
- Langer R and Weissleder R (2015) Nanotechnology. *JAMA* 313:135–136.
- Lee S, Kim YC, and Park JH (2016) Zein-alginate based oral drug delivery systems: protection and release of therapeutic proteins. *Int J Pharm* 515:300–306.
- Leonard TW, Lynch J, McKenna MJ, and Brayden DJ (2006) Promoting absorption of drugs in humans using medium-chain fatty acid-based solid dosage forms: GIPET. *Expert Opin Drug Deliv* 3:685–692.
- Li L, Jiang G, Yu W, Liu D, Chen H, Liu Y, Huang Q, Tong Z, Yao J, and Kong X (2016) A composite hydrogel system containing glucose-responsive nanocarriers for oral delivery of insulin. *Mater Sci Eng C* 69:37–45.

- Li L, Jiang G, Yu W, Liu D, Chen H, Liu Y, Tong Z, Kong X, and Yao J (2017) Preparation of chitosan-based multifunctional nanocarriers overcoming multiple barriers for oral delivery of insulin. *Mater Sci Eng C* **70**:278–286.
- Li X, Qi J, Xie Y, Zhang X, Hu S, Xu Y, Lu Y, and Wu W (2013) Nanoemulsions coated with alginate/chitosan as oral insulin delivery systems: preparation, characterization, and hypoglycemic effect in rats. *Int J Nanomedicine* **8**:23–32.
- Liu L, Yao W, Rao Y, Lu X, and Gao J (2017) pH-Responsive carriers for oral drug delivery: challenges and opportunities of current platforms. *Drug Deliv* **24**:569–581.
- Lundquist P and Artursson P (2016) Oral absorption of peptides and nanoparticles across the human intestine: opportunities, limitations and studies in human tissues. *Adv Drug Deliv Rev* **106** (Pt B):256–276.
- Ma G (2014) Microencapsulation of protein drugs for drug delivery: strategy, preparation, and applications. *J Control Release* **193**:324–340.
- Ma Y, Fuchs AV, Boase NRB, Rolfe BE, Coombes AGA, and Thurecht KJ (2015) The *in vivo* fate of nanoparticles and nanoparticle-loaded microcapsules after oral administration in mice: evaluation of their potential for colon-specific delivery. *Eur J Pharm Biopharm* **94**:393–403.
- Mahajan S, Sharma R, and Mahajan RK (2012) An investigation of drug binding ability of a surface active ionic liquid: micellization, electrochemical, and spectroscopic studies. *Langmuir* **28**:17238–17246.
- Makary P (2014) Principles of salt formation. *UK J Pharm Biosci* **2**:1–4.
- Malewar N, Avachat M, Kulkarni S, and Pokharkar V (2015) Design and evaluation of novel barrier layer technologies for controlling venlafaxine hydrochloride release from tablet dosage form. *Pharm Dev Technol* **20**:588–597.
- Manca S, Upadhyaya B, Mutai E, Desaulniers AT, Cederberg RA, White BR, and Zempleni J (2018) Milk exosomes are bioavailable and distinct microRNA cargos have unique tissue distribution patterns. *Sci Rep* **8**:11321.
- Mappara SS and Patravale VB (2017) Medical capsule robots: a renaissance for diagnostics, drug delivery and surgical treatment. *J Control Release* **261**:337–351.
- Mastropietro DJ, Omidian H, and Park K (2012) Drug delivery applications for superporous hydrogels. *Expert Opin Drug Deliv* **9**:71–89.
- Mathavan S, Chen-Tan N, Arfuso F, and Al-Salami H (2016) The role of the bile acid chenodeoxycholic acid in the targeted oral delivery of the anti-diabetic drug glimepiride, and its applications in type 1 diabetes. *Artif Cells Nanomed Biotechnol* **44**:1508–1519.
- Mignani S, El Kazzouli S, Bousmina M, and Majoral JP (2013) Expand classical drug administration ways by emerging routes using dendrimer drug delivery systems: a concise overview. *Adv Drug Deliv Rev* **65**:1316–1330.
- Moes JJ, Koolen SLW, Huitema ADR, Schellens JHM, Beijnen JH, and Nuijen B (2011) Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001). *Int J Pharm* **420**:244–250.
- Moodley K, Pillay V, Choonara YE, du Toit LC, Ndesendo VMK, Kumar P, Cooppan S, and Bawa P (2012) Oral drug delivery systems comprising altered geometric configurations for controlled drug delivery. *Int J Mol Sci* **13**:18–43.
- Mooranian A, Negrulj R, Mikov M, Golocorbin-Kon S, Arfuso F, and Al-Salami H (2015) Novel chenodeoxycholic acid-sodium alginate matrix in the microencapsulation of the potential antidiabetic drug, probucol. An *in vitro* study. *J Microencapsul* **32**:589–597.
- Mukhopadhyay P, Maity S, Mandal S, Chakraborti AS, Prajapati AK, and Kundu PP (2018) Preparation, characterization and *in vivo* evaluation of pH sensitive, safe quercetin-succinylated chitosan-alginate core-shell-corona nanoparticle for diabetes treatment. *Carbohydr Polym* **182**:42–51.
- Mulugeta LY, Yao L, Mould D, Jacobs B, Florian J, Smith B, Sinha V, and Barrett JS (2018) Leveraging big data in pediatric development programs: proceedings from the 2016 American College of Clinical Pharmacology Annual Meeting Symposium. *Clin Pharmacol Ther* **104**:81–87.
- Munagala R, Aqil F, Jayabalan J, Agrawal AK, Mudd AM, Kyakulaga AH, Singh IP, Vadhanam MV, and Gupta RC (2017) Exosomal formulation of anthocyanidins against multiple cancer types. *Cancer Lett* **393**:94–102.
- Munagala R, Aqil F, Jayabalan J, and Gupta RC (2016) Bovine milk-derived exosomes for drug delivery. *Cancer Lett* **371**:48–61.
- Mura S, Nicolas J, and Couvreur P (2013) Stimuli-responsive nanocarriers for drug delivery. *Nat Mater* **12**:991–1003.
- Mutalik S, Suthar NA, Managuli RS, Shetty PK, Avadhani K, Kalthur G, Kulkarni RV, and Thomas R (2016) Development and performance evaluation of novel nanoparticles of a grafted copolymer loaded with curcumin. *Int J Biol Macromol* **86**:709–720.
- Nielsen LH, Keller SS, and Boisen A (2018) Microfabricated devices for oral drug delivery. *Lab Chip* **18**:2348–2358.
- Nielsen LH, Nagstrup J, Gordon S, Keller SS, Østergaard J, Rades T, Müllertz A, and Boisen A (2015) pH-triggered drug release from biodegradable microwells for oral drug delivery. *Biomed Microdevices* **17**:9958.
- Nokhodchi A, Raja S, Patel P, and Asare-Addo K (2012) The role of oral controlled release matrix tablets in drug delivery systems. *Bioimpacts* **2**:175–187.
- O'Connor C, Steichen S, and Peppas NA (2017) Student Award for Outstanding Research Winner in the Undergraduate Category for the 2017 Society for Biomaterials Annual Meeting and Exposition, April 5–8, 2017, Minneapolis, Minnesota: development and characterization of stimuli-responsive hydrogel microcarriers for oral protein delivery. *J Biomed Mater Res A* **105**:1243–1251.
- Oliveira PR, Bernardi LS, Strusi OL, Mercuri S, Segatto Silva MA, Colombo P, and Sonvico F (2011) Assembled modules technology for site-specific prolonged delivery of norfloxacin. *Int J Pharm* **405**:90–96.
- Omer ME, Alkatheri A, Yassin AEB, Albagami AM, and Al Bekairy AM (2017) Modified geometry three-layered tablet as a platform for class II drugs zero-order release system. *Trop J Pharm Res* **16**:1773–1778.
- Paulmurugan R, Bhethanabotla R, Mishra K, Devulapally R, Foygel K, Sekar TV, Ananta JS, Massoud TF, and Joy A (2016) Folate receptor-targeted polymeric micellar nanocarriers for delivery of orlistat as a repurposed drug against triple-negative breast cancer. *Mol Cancer Ther* **15**:221–231.
- Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, and Langer R (2007) Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol* **2**:751–760.
- Penalva R, Esparza I, Larraneta E, González-Navarro CJ, Gamazo C, and Irache JM (2015) Zein-based nanoparticles improve the oral bioavailability of resveratrol and its anti-inflammatory effects in a mouse model of endotoxic shock. *J Agric Food Chem* **63**:5603–5611.
- Peska L, Buza K, and Koller J (2017) Drug-target interaction prediction: a Bayesian ranking approach. *Comput Methods Programs Biomed* **152**:15–21.
- Petrus AK, Fairchild TJ, and Doyle RP (2009) Traveling the vitamin B12 pathway: oral delivery of protein and peptide drugs. *Angew Chem Int Ed Engl* **48**:1022–1028.
- Pillai JJ, Thulasidasan AKT, Anto RJ, Devika NC, Ashwanikumar N, and Kumar GSV (2015) Curcumin entrapped folic acid conjugated PLGA-PEG nanoparticles exhibit enhanced anticancer activity by site specific delivery. *RSC Adv* **5**:25518–25524.
- Preis M (2015) Orally disintegrating films and mini-tablets-innovative dosage forms of choice for pediatric use. *AAPS PharmSciTech* **16**:234–241.
- Pridgen EM, Alexis F, Kuo TT, Levy-Nissenbaum E, Karnik R, Blumberg RS, Langer R, and Farokhzad OC (2013) Transepithelial transport of Fc-targeted nanoparticles by the neonatal Fc receptor for oral delivery. *Sci Transl Med* **5**:213ra167.
- Puranik AS, Pao LP, White VM, and Peppas NA (2016) Synthesis and characterization of pH-responsive nanoscale hydrogels for oral delivery of hydrophobic therapeutics. *Eur J Pharm Biopharm* **108**:196–213.
- Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Williams T, Latimer J, McNamee C, et al. (2018) Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov* **18**:41–58.
- Real D, Hoffmann S, Leonardi D, Salomon C, and Goycoolea FM (2018) Chitosan-based nanodelivery systems applied to the development of novel trichlabendazole formulations. *PLoS One* **13**:e0207625.
- Roger E, Kalscheuer S, Kirtane A, Guru BR, Grill AE, Whittum-Hudson J, and Panyam J (2012) Folic acid functionalized nanoparticles for enhanced oral drug delivery. *Mol Pharm* **9**:2103–2110.
- Rogers RD and Seddon KR (2003) Chemistry. Ionic liquids—solvents of the future? *Science* **302**:792–793.
- Roy S, Pal K, Anis A, Pramanik K, and Prabhakar B (2009) Polymers in mucoadhesive drug-delivery systems: a brief note. *Des Monomers Polym* **12**:483–495.
- Sadia M, Arafat B, Ahmed W, Forbes RT, and Alhnan MA (2018) Channelled tablets: an innovative approach to accelerating drug release from 3D printed tablets. *J Control Release* **269**:355–363.
- Sahbaz Y, Nguyen TH, Ford L, McEvoy CL, Williams HD, Scammells PJ, and Porter CJH (2017) Ionic liquid forms of weakly acidic drugs in oral lipid formulations: preparation, characterization, *in vitro* digestion, and *in vivo* absorption studies. *Mol Pharm* **14**:3669–3683.
- Sahbaz Y, Williams HD, Nguyen TH, Saunders J, Ford L, Charman SA, Scammells PJ, and Porter CJH (2015) Transformation of poorly water-soluble drugs into lipophilic ionic liquids enhances oral drug exposure from lipid based formulations. *Mol Pharm* **12**:1980–1991.
- Saini P, Ganugula R, Arora M, and Kumar MNVR (2016) The next generation non-competitive active polyester nanosystems for transferrin receptor-mediated peroral transport utilizing gambogic acid as a ligand. *Sci Rep* **6**:29501.
- Sajeesh S, Bouchemal K, Marsaud V, Vauthier C, and Sharma CP (2010) Cyclodextrin complexed insulin encapsulated hydrogel microparticles: an oral delivery system for insulin. *J Control Release* **147**:377–384.
- Sajeesh S, Bouchemal K, Sharma CP, and Vauthier C (2010c) Surface-functionalized polymethacrylic acid based hydrogel microparticles for oral drug delivery. *Eur J Pharm Biopharm* **74**:209–218.
- Sajeesh S and Sharma CP (2011) Mucoadhesive hydrogel microparticles based on poly (methacrylic acid-vinyl pyrrolidone)-chitosan for oral drug delivery. *Drug Deliv* **18**:227–235.
- Sajeesh S, Vauthier C, Gueutin C, Ponchel G, and Sharma CP (2010) Thiol functionalized polymethacrylic acid-based hydrogel microparticles for oral insulin delivery. *Acta Biomater* **6**:3072–3080.
- Samuel M, Chisanga D, Liem M, Keerthikumar S, Anand S, Ang CS, Adda CG, Versteegen E, Jois M, and Mathivanan S (2017) Bovine milk-derived exosomes from colostrum are enriched with proteins implicated in immune response and growth. *Sci Rep* **7**:5933.
- Scannell JW and Bosley J (2016) When quality beats quantity: decision theory, drug discovery, and the reproducibility crisis. *PLoS One* **11**:e0147215.
- Schoener CA, Hutson HN, and Peppas NA (2013) pH-responsive hydrogels with dispersed hydrophobic nanoparticles for the oral delivery of chemotherapeutics. *J Biomed Mater Res A* **101**:2229–2236.
- Serajuddin ATM (2007) Salt formation to improve drug solubility. *Adv Drug Deliv Rev* **59**:603–616.
- Shamshina JL, Kelley SP, Gurau G, and Rogers RD (2015) Chemistry: develop ionic liquid drugs. *Nature* **528**:188–189.
- Shen Z and Mitragotri S (2002) Intestinal patches for oral drug delivery. *Pharm Res* **19**:391–395.
- Shete G, Pawar YB, Thanki K, Jain S, and Bansal AK (2015) Oral bioavailability and pharmacodynamic activity of hesperetin nanocrystals generated using a novel bottom-up technology. *Mol Pharm* **12**:1158–1170.
- Shofner JP, Phillips MA, and Peppas NA (2010) Cellular evaluation of synthesized insulin/transferrin bioconjugates for oral insulin delivery using intelligent complexation hydrogels. *Macromol Biosci* **10**:299–306.
- Shtenberg Y, Goldfeder M, Prinz H, Shainsky J, Ghantous Y, Abu El-Naaj I, Schroeder A, and Bianco-Peled H (2018) Mucoadhesive alginate pastes with embedded liposomes for local oral drug delivery. *Int J Biol Macromol* **111**:62–69.
- Silber BM (2010) Driving drug discovery: the fundamental role of academic labs. *Sci Transl Med* **2**:30cm16.

- Svagan AJ, Kusic A, De Gobba C, Larsen FH, Sassene P, Zhou Q, van de Weert M, Mullertz A, Jørgensen B, and Ulvskov P (2016) Rhamnogalacturonan-I based microcapsules for targeted drug release. *PLoS One* **11**:e0168050.
- Tao SL and Desai TA (2005) Gastrointestinal patch systems for oral drug delivery. *Drug Discov Today* **10**:909–915.
- Tariq M, Alam MA, Singh AT, Panda AK, and Talegaonkar S (2016) Surface decorated nanoparticles as surrogate carriers for improved transport and absorption of epirubicin across the gastrointestinal tract: pharmacokinetic and pharmacodynamic investigations. *Int J Pharm* **501**:18–31.
- Teutonico D and Ponchel G (2011) Patches for improving gastrointestinal absorption: an overview. *Drug Discov Today* **16**:991–997.
- Thanou M, Verhoef JC, and Junginger HE (2001) Oral drug absorption enhancement by chitosan and its derivatives. *Adv Drug Deliv Rev* **52**:117–126.
- Théry C, Zitvogel L, and Amigorena S (2002) Exosomes: composition, biogenesis and function. *Nat Rev Immunol* **2**:569–579.
- Tibbitt MW, Dahlman JE, and Langer R (2016) Emerging frontiers in drug delivery. *J Am Chem Soc* **138**:704–717.
- Toorisaka E, Watanabe K, Ono H, Hirata M, Kamiya N, and Goto M (2012) Intestinal patches with an immobilized solid-in-oil formulation for oral protein delivery. *Acta Biomater* **8**:653–658.
- Wagner RH, Savir-Baruch B, Halama JR, Venu M, Gabriel MS, and Bova D (2017) Proof of concept: design and initial evaluation of a device to measure gastrointestinal transit time. *J Nucl Med Technol* **45**:230–235.
- Wang C, Chopade SA, Guo Y, Early JT, Tang B, Wang E, Hillmyer MA, Lodge TP, and Sun CC (2018a) Preparation, characterization, and formulation development of drug-drug protic ionic liquids of diphenhydramine with ibuprofen and naproxen. *Mol Pharm* **15**:4190–4201.
- Wang J, Tan J, Luo J, Huang P, Zhou W, Chen L, Long L, Zhang LM, Zhu B, Yang L, et al. (2017a) Enhancement of scutellarin oral delivery efficacy by vitamin B12-modified amphiphilic chitosan derivatives to treat type II diabetes induced-retinopathy. *J Nanobiotechnology* **15**:18.
- Wang Q, Yu J, Kadungure T, Beyene J, Zhang H, and Lu Q (2017b) ARMMs as a versatile platform for intracellular delivery of macromolecules. *Nat Commun* **9**:960.
- Wang X, Cheng D, Liu L, and Li X (2018c) Development of poly(hydroxyethyl methacrylate) nanogel for effective oral insulin delivery. *Pharm Dev Technol* **23**:351–357.
- Wang Y, Wan G, Li Z, Shi S, Chen B, Li C, Zhang L, and Wang Y (2017b) PEGylated doxorubicin nanoparticles mediated by HN-1 peptide for targeted treatment of oral squamous cell carcinoma. *Int J Pharm* **525**:21–31.
- Wiest J, Saedtler M, Balk A, Merget B, Widmer T, Bruhn H, Raccuglia M, Walid E, Picard F, Stopper H, et al. (2017) Mapping the pharmaceutical design space by amorphous ionic liquid strategies. *J Control Release* **268**:314–322.
- Wilding IR, Davis SS, Sparrow RA, Ziemniak JA, and Heald DL (1995) Pharmacoscintigraphic evaluation of a modified release (Geomatrix®) diltiazem formulation. *J Control Release* **33**:89–97.
- Williams HD, Ford L, Lim S, Han S, Baumann J, Sullivan H, Vodak D, Igonin A, Benameur H, Pouton CW, et al. (2018) Transformation of biopharmaceutical classification system class I and III drugs into ionic liquids and lipophilic salts for enhanced developability using lipid formulations. *J Pharm Sci* **107**:203–216.
- Williams HD, Sahbaz Y, Ford L, Nguyen TH, Scammells PJ, and Porter CJH (2014) Ionic liquids provide unique opportunities for oral drug delivery: structure optimization and in vivo evidence of utility. *Chem Commun (Camb)* **50**:1688–1690.
- Wong TW (2010) Design of oral insulin delivery systems. *J Drug Target* **18**:79–92.
- Xu J, Strandman S, Zhu JX, Barralet J, and Cerruti M (2015) Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery. *Biomaterials* **37**:395–404.
- Yadav N, Morris G, Harding SE, Ang S, and Adams GG (2009) Various non-injectable delivery systems for the treatment of diabetes mellitus. *Endocr Metab Immune Disord Drug Targets* **9**:1–13.
- Yamauchi M, Shimizu K, Rahman M, Ishikawa H, Takase H, Ugawa S, Okada A, and Inoshima Y (2019) Efficient method for isolation of exosomes from raw bovine milk. *Drug Dev Ind Pharm* **45**:359–364.
- Yehia SA, Elshafeey AH, and Elsayed I (2011) Pulsatile systems for colon targeting of budesonide: in vitro and in vivo evaluation. *Drug Deliv* **18**:620–630.
- Yilmaz C, Sarisozen C, Torchilin V, and Busnaina A (2016) Novel nanoprinting for oral delivery of poorly soluble drugs. *Methodist DeBakey Cardiovasc J* **12**:157–162.
- Yu F, Li Y, Liu CS, Chen Q, Wang GH, Guo W, Wu XE, Li DH, Wu WD, and Chen XD (2015) Enteric-coated capsules filled with mono-disperse micro-particles containing PLGA-lipid-PEG nanoparticles for oral delivery of insulin. *Int J Pharm* **484**:181–191.
- Zare-Akbari Z, Farhadnejad H, Furughi-Nia B, Abedin S, Yadollahi M, and Khorsand-Ghayeni M (2016) PH-sensitive bionanocomposite hydrogel beads based on carboxymethyl cellulose/ZnO nanoparticle as drug carrier. *Int J Biol Macromol* **93** (Pt A):1317–1327.
- Zhang L, Liu J, Tian T, Gao Y, Ji X, Li Z, and Luan Y (2013) Pharmaceutically active ionic liquid self-assembled vesicles for the application as an efficient drug delivery system. *ChemPhysChem* **14**:3454–3457.
- Zhu Q, Talton J, Zhang G, Cunningham T, Wang Z, Waters RC, Kirk J, Eppler B, Klinman DM, Sui Y, et al. (2012) Large intestine-targeted, nanoparticle-releasing oral vaccine to control genitoretal viral infection. *Nat Med* **18**:1291–1296.
- Zimmer L, Kasperek R, and Poleszak E (2014) [Modern polymers in matrix tablets technology]. *Polim Med* **44**:189–196.
- Zomer A, Vendrig T, Hopmans ES, van Eijndhoven M, Middeldorp JM, and Pegtel DM (2010) Exosomes: fit to deliver small RNA. *Commun Integr Biol* **3**:447–450.

Address correspondence to: Dr. M.N.V. Ravi Kumar, Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M University, Mail Stop 1114, College Station, TX 77843. E-mail: mnvrkumar@tamhsc.edu
