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*Special Section on Drug Delivery Technologies—Minireview*

# Oral Drug Delivery Technologies—A Decade of Developments

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**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

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**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, Smartrix 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

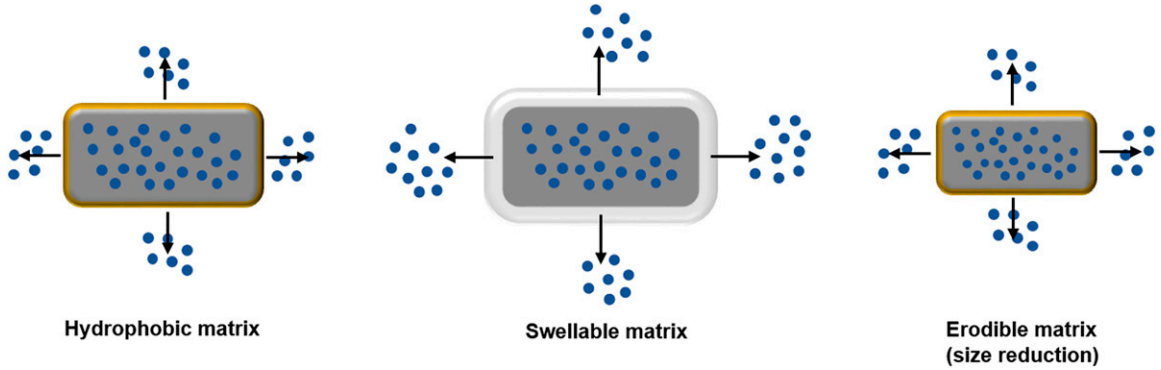


**Fig. 1.** Image showing drug release from the matrix tablets. Adapted and modified from Nokhodchi et al. (2012).

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 | Smartrix | 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) |
| Norfloxacin | 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

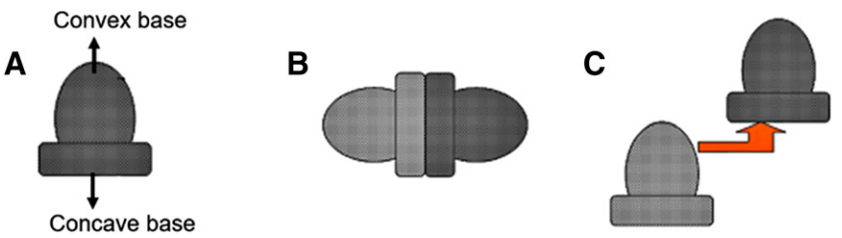


**Fig. 2.** (A) Dome matrix tablet module with void configuration (B) and piled configuration (C). Adapted and modified from Moodley et al. (2012).

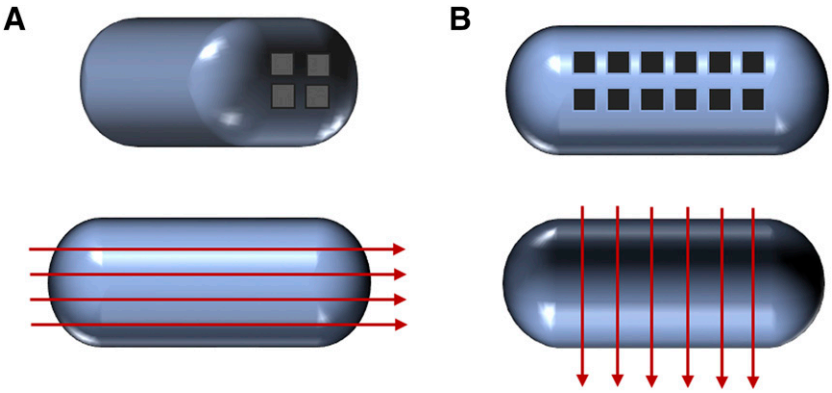


**Fig. 3.** Image showing perforated channels in 3D channeled tablet: (A) parallel and (B) at right angle to long axis. Adapted and modified from Sadia et al. (2018).

(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

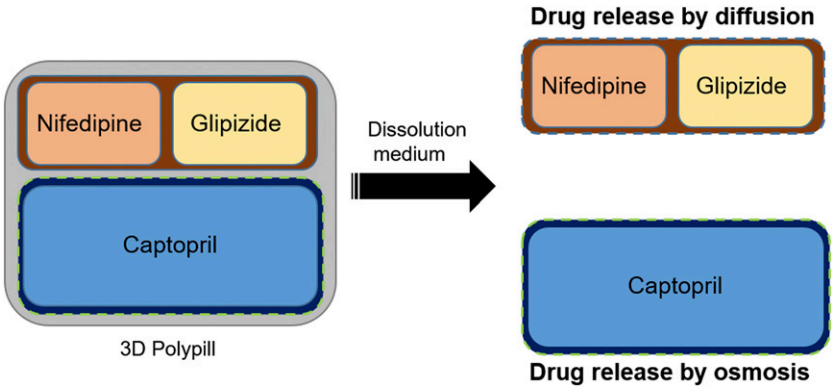


**Fig. 4.** Image showing 3D polypill containing three drugs, namely, captopril, nifedipine, and glipizide. Adapted and modified from Khaled et al. (2015).

TABLE 2
Summary of advanced capsule technologies

| Drug | Capsule | Purpose | Advantage | Reference |
|---|---|---|---|---|
| Ga-citrate | Gelatin capsules | To study the gastrointestinal transit time | Extended release | Wagner et al. (2017) |
| Tributyrin | Whey protein and γ-cyclodextrin | To study In vitro release of butyric acid for the treatment of intestinal disorder | Controlled release | 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 *N*-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 | Particle-in-particle | For effective colon cancer treatment | Targeted oral delivery | Ma et al. (2015) |
| Sodium salt of Furosemide | Microwells of poly-L-lactic acid with coating of Eudragit | To deliver the powdered drug to the target site throughout the GIT | Targeted oral delivery | 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) |

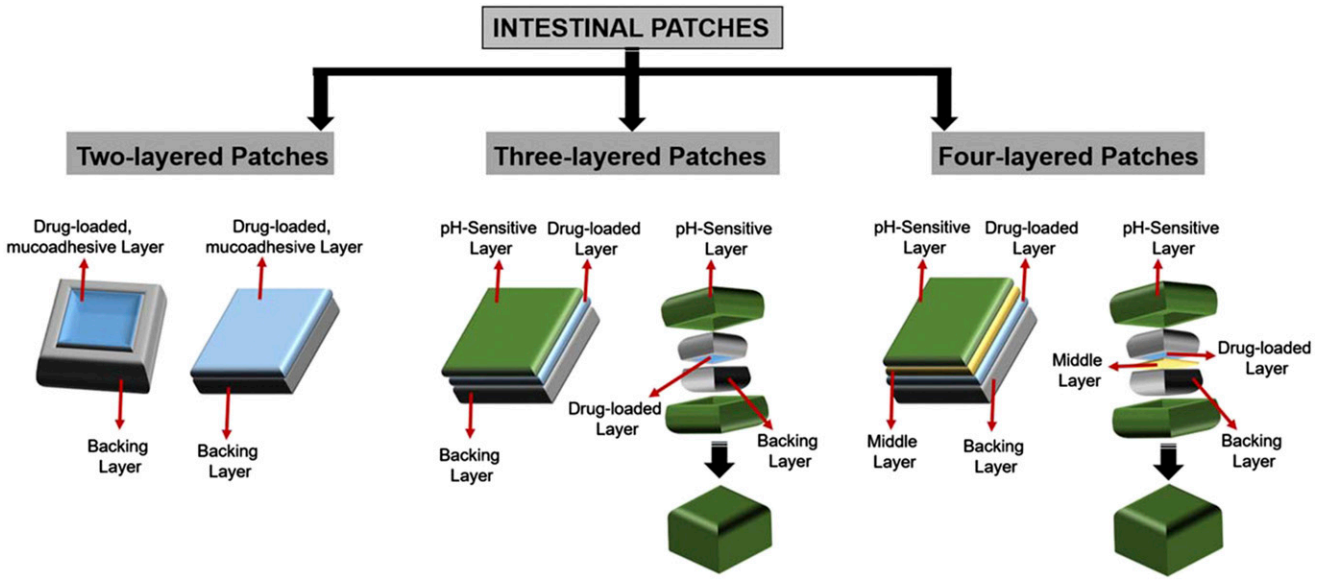


**Fig. 5.** Types of intestinal patches. Adapted and modified from Banerjee and Mitragotri (2017).

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 $\mu$m. 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 bioavailability. But still, for these patches to be used as oral delivery vehicles of insulin, they will require significant

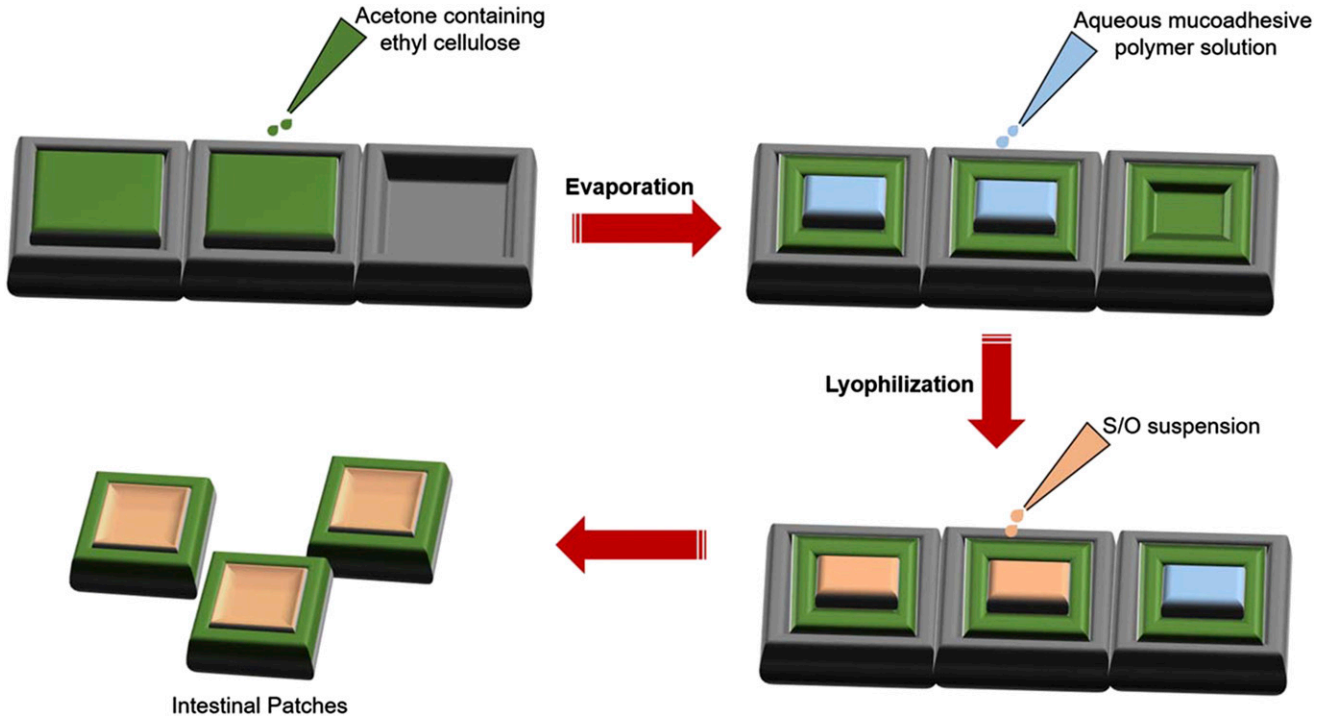


**Fig. 6.** Image showing the process of intestinal patch formation. Adapted and modified from Toorisaka et al. (2012).

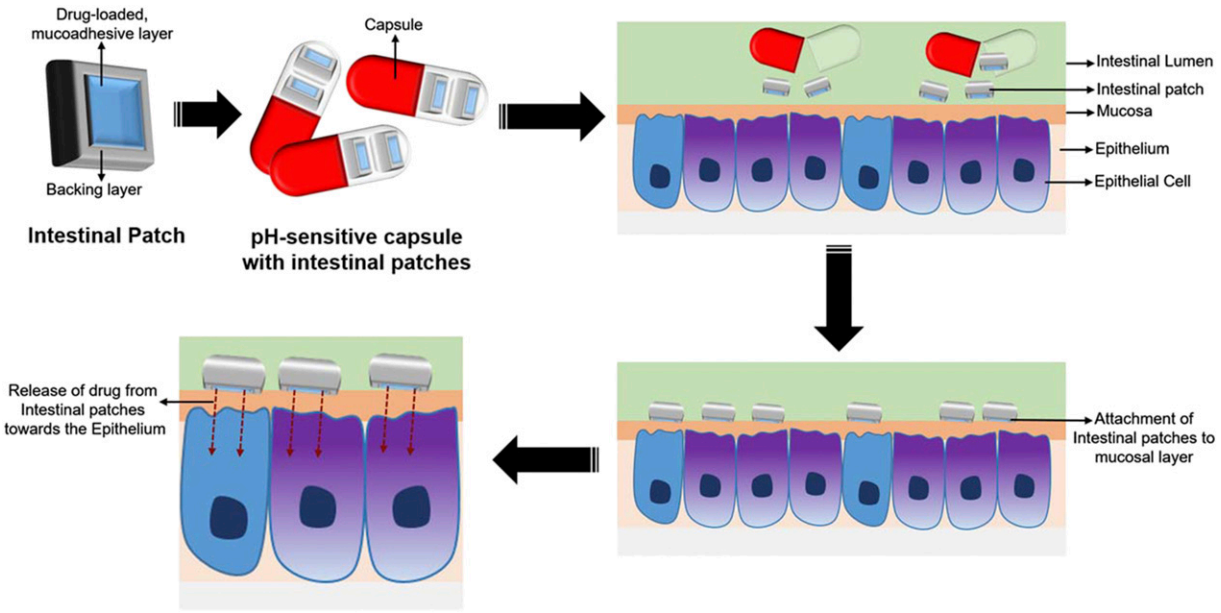


**Fig. 7.** Schematic representation of working of an intestinal patch. Adapted and modified from Banerjee and Mitragotri (2017).

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 synergetic 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,

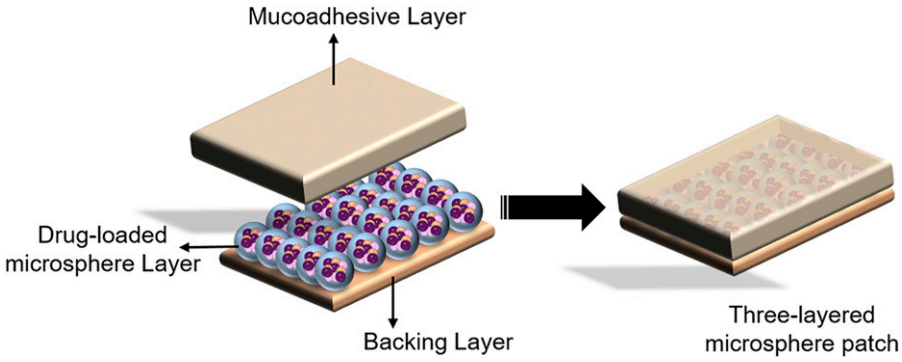


**Fig. 8.** Image showing a three-layered microsphere patch. Adapted and modified from Shen and Mitragotri (2002).

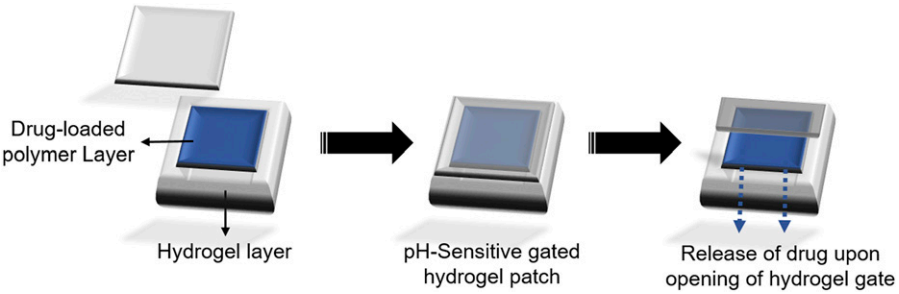


**Fig. 9.** Image showing working of a pH-sensitive gated hydrogel patch at appropriate pH. Adapted and modified from He et al., (2004).

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 microneedles 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 $[N(CN)_2]$ 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 ibuprophen 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

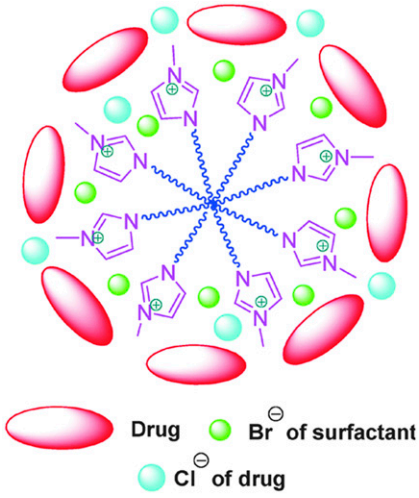


**Fig. 10.** Image showing possible adsorption of drug $[C_{14mim}]$ [Br] micelles. Reproduced with permission from Mahajan et al. (2012).

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(IA-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 $Fe^{3+}$ 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 $CaCl_2$ 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-$\beta$-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 | To overcome multiple barriers for oral insulin delivery | Li et al. (2017) |
| Insulin | PLGA and Pluronic F68 based nanoparticles | To enhance the bioavailability using negatively changed 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) |

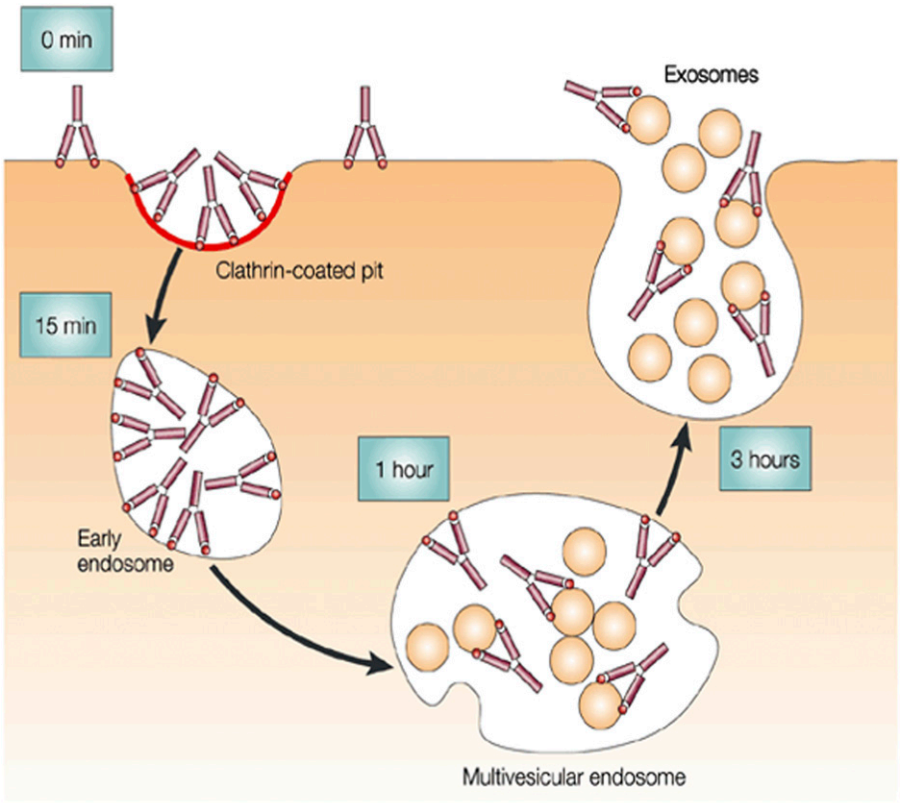


**Fig. 11.** Schematic representation of exosome formation. Reproduced with permission from Théry et al. (2002).

(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 miniscule 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 nanopaticles 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

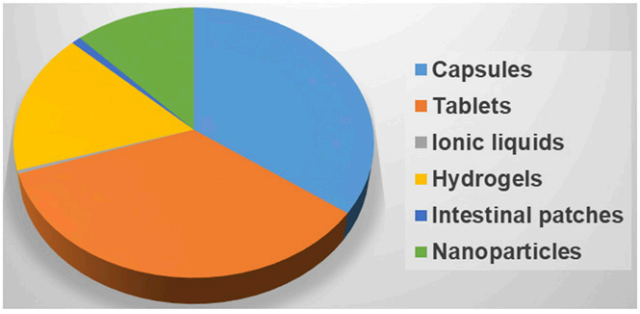


**Fig. 12.** Pie chart showing the distribution of patents for various oral drug delivery technologies.

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.

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