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E-mail: jzus_b@zju.edu.cn

**Review**

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# Microencapsulation and characterization of controlled-release intestinal drugs: a critical review

Weiguang SU[1,2]✉, Dawei WANG[1,2], Siegfried YEBOAH[3], Jinshen WANG[4], Chonghai XU[1,2], Li WANG[1,2]✉

[1]*School of Mechanical Engineering, Qilu University of Technology (Shandong Academy of Sciences), Jinan 250353, China*
[2]*Shandong Institute of Mechanical Design and Research, Jinan 250031, China*
[3]*School of Engineering and Design, London South Bank University, London, SE1 0AA, UK*
[4]*Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, China*

**Abstract:** Oral administration is associated with high patient adherence, as it is not only the route for primary site absorption of nutrients and peptide drugs but also is important for treating intestinal diseases. However, traditional oral intestinal drugs are limited by drug degradation and inactivation, particularly for proteins and peptides, due to gastric acid and digestive enzymes, making it difficult to effectively deliver drugs to target sites. To address these challenges, controlled-release microencapsulated intestinal drugs (MeIDs) have been developed and have attracted attention for their ability to protect drugs from degradation by gastric acid and digestive enzymes. In this study, we systematically reviewed research articles on the preparation methods, release mechanisms, and evaluation strategies of MeIDs using Google Scholar, Web of Science, and Science Direct databases. Our findings show that the preparation of emulsions, microencapsulation methods, shell material selection, and drug properties need to be considered comprehensively for MeID development. In addition, we found that coating, micro/nanocarriers, and absorption enhancers can be combined to enhance microcapsule performance. Beyond focusing on drug loading efficiency and microcapsule morphology, we also found that cell models, animal models, and spectroscopic analysis techniques can be used to evaluate drug biocompatibility, stability, and efficacy. Finally, the literature has shown that optimizing the preparation process can regulate drug release kinetics. For future research, we suggest that studies should focus on low-cost methods for producing monodisperse microcapsules, developing dynamic responsive shell materials, and using organ-on-a-chip technology for precise evaluation, as part of the theoretical support towards the development of microencapsulated drugs and targeted drug delivery.

**Key words:** Oral drug; Controlled release; Microencapsulated intestinal drug; Microencapsulation method; Response mechanism

## 1 Introduction

Oral drug administration is the main and preferred mode of drug delivery due to its comfort, non-invasiveness, and convenience (Drucker, 2020; Chu and Traverso, 2022). The intestinal system is the main absorption site for drugs due to its large absorption surface area and long residence time (Pinto, 2010; Durán-Lobato et al., 2020). In addition, drugs for treating intestinal diseases, such as inflammatory bowel disease (IBD), need to be locally released in the intestine to target the disease site (Durán-Lobato et al., 2020). Similarly, the absorption of vitamins like vitamin $B_{12}$ relies on binding to specific intestinal receptors, and anticancer drugs target M cells in the intestine to reduce systemic toxicity (Xu et al., 2020). However, traditional oral intestinal drugs, especially proteins, enzymes, and antibody-based drugs (Brown et al., 2019; Ahadian et al., 2020), are susceptible to degradation by gastric acid and digestive enzymes, and their penetration through mucus and cellular barriers is limited, resulting in low bioavailability (Xu et al., 2020; Ouyang et al., 2023a). To address this problem, encapsulating oral intestinal drugs within biocompatible shell materials with microencapsulation technologies can improve the stability, targeting capability, and bioavailability of oral drug delivery. This is because the shell from encapsulation protects drugs from degradation by enzymes and gastric acid, leading to targeted

✉ Weiguang SU, weiguang.su@qlu.edu.cn
Li WANG, liwang@qlu.edu.cn
Weiguang SU, https://orcid.org/0000-0003-1255-0440
Li WANG, https://orcid.org/0000-0002-5166-0397

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release in the intestine (Chen et al., 2019; Yao et al., 2020). Also, specific microencapsulation technologies can mask drug bitterness (Sarabandi et al., 2018), enhance intestinal absorption and adhesion, and reduce negative effects on other parts of the digestive system (Dos Santos et al., 2021).

Smart drug microcapsules can respond to specific physiological characteristics or disease biomarkers to achieve smart, controllable, and targeted drug release. The release and targeting mechanisms are commonly designed for encapsulation by different shell materials in microcapsules with appropriate thickness and structure (Wang R et al., 2022; Wang X et al., 2022; Zhang DX et al., 2023). Microencapsulated drugs can also regulate the intensity and duration of action, avoid adverse reactions caused by peak blood drug concentrations, and reduce the frequency of administration (Hoffman, 1998; Baek et al., 2016; Daly et al., 2020). Therefore, based on the customization of microcapsules, personalized drug therapy can be achieved with a specific release rate and residence time (Araújo et al., 2015; Dos Santos et al., 2021).

Currently, the preparation methods for microencapsulated intestinal drugs (MeIDs) include traditional methods for polydisperse particles and microfluidic technologies for monodisperse microcapsules. Traditional preparation methods, such as mechanical stirring and spray drying, are commonly used for industrial production. However, they are limited by poor control of particle size, shell thickness, encapsulation stability and efficiency, and chemical residues (Daly et al., 2020; Zhao et al., 2023). These limitations have been shown in the literature to lead to nonuniform drug distribution within microcapsules, unstable release rates, and challenges in the stability and release kinetics of drug microcapsules (Xu et al., 2009; Xuan et al., 2024). Microfluidic technologies have been shown to alleviate these shortcomings through the preparation of monodisperse emulsions as templates by solidifying monodisperse microcapsules through ionic crosslinking, solvent evaporation, and free radical polymerization methods (Li et al., 2018; Jo and Lee, 2020). During the fabrication of phycocyanin (hydrophilic drug) microcapsules (Wang X et al., 2022), monodisperse microcapsules have achieved an encapsulation efficiency (EE) as high as 98%, as well as a uniform particle size with a coefficient of variance (CV) of $<3\%$ (Li et al., 2018) and a controllable structure (Zhao, 2013; Jo and Lee, 2020). With monodisperse microcapsules, the drug release rate can be controlled by the drug content, surface area, volume, diffusion distance, or degradation rate of the microcapsules (Dos Santos et al., 2021). Therefore, the preparation of monodisperse MeIDs can provide insights into the release mechanism and pharmacokinetics of microcapsules (Xu et al., 2009; Wang et al., 2014).

To analyze and evaluate the current development of MeIDs, as well as future preparation and evaluation methods, we systematically reviewed the literature on the preparation methods and techniques for MeID development (Section S1 and Fig. S1). This review also focused on various methods for evaluating the biosafety, stability, response mechanisms, pharmacokinetics and drug release kinetics, in vitro action mechanisms, and in vivo pharmacological effects of drug microcapsules.

## 2 Preparation of microencapsulated intestinal drugs

The preparation of MeIDs is accomplished by using emulsion droplets as templates. The microencapsulation procedure typically includes two steps: (1) emulsification, in which the drug-containing solution is dispersed into another immiscible solution to form an emulsion, and (2) microencapsulation, where the droplets in the emulsion serve as templates to form microcapsules through physical or chemical methods (Zhao, 2013).

### 2.1 Preparation of emulsions

The droplets in emulsions directly affect the size, morphology, and internal structure of the microcapsules (Wang et al., 2014). Fig. 1 shows various methods for preparing microdroplets or emulsions using different devices.

#### 2.1.1 Mechanical stirring

Mechanical stirring can produce high shear stress and impact stress when a dispersed phase is dispersed into another immiscible continuous phase as tiny droplets (Fig. 1a) (Daly et al., 2020; Sastri et al., 2020). The size and dispersity of the droplets are influenced by the stirring speed and time, emulsifier

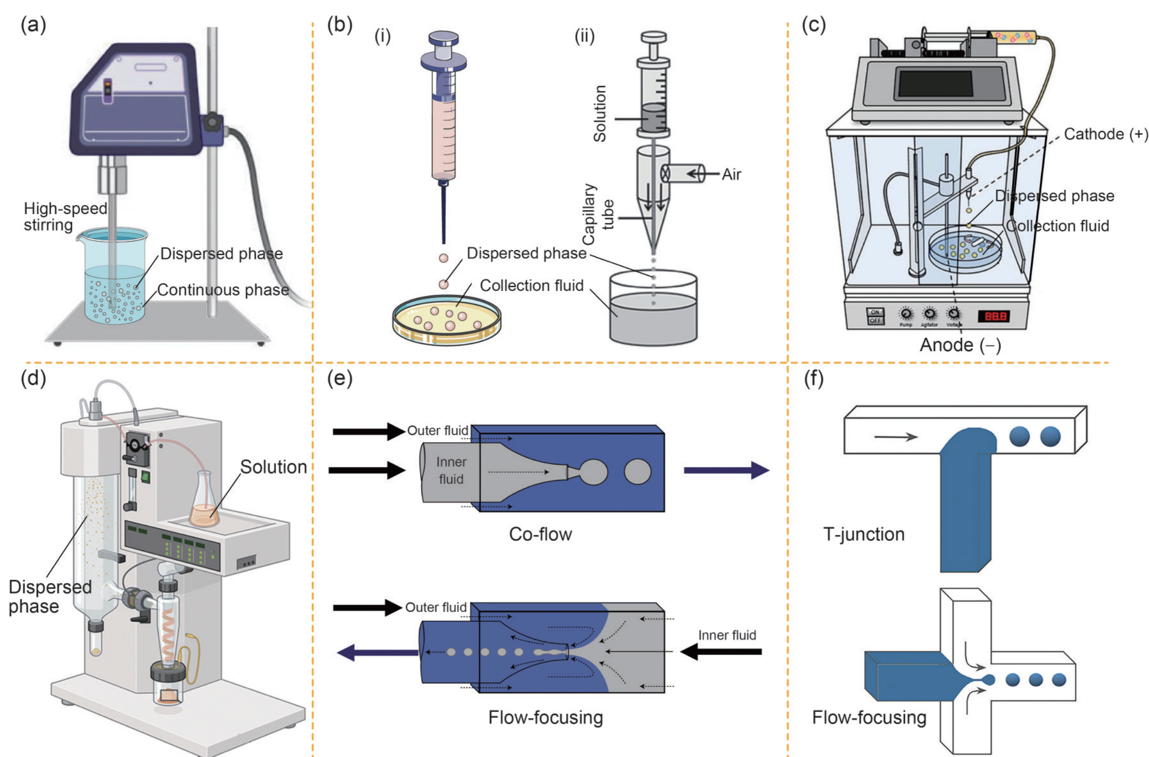


**Fig. 1 Dispersion methods for the preparation of microdroplets or emulsions. (a) Mechanical stirring. Adapted from Sastri et al. (2020). (b) Extrusion technique (i) and gas shearing technique (ii). Adapted from Ghaffarian et al. (2016) by permission of John Wiley and Sons. (c) Electrospray technique. Adapted from Yang K et al. (2024), Copyright 2023, with permission from Elsevier. (d) Spray drying. Adapted from Meola et al. (2024). (e) Three-dimensional (3D) capillary microfluidic device. Reprinted from Utada et al. (2007) with kind permission from Springer Nature. (f) Two-dimensional (2D) poly(dimethylsiloxane) (PDMS) microfluidic device. Reprinted from Su et al. (2021).**

type and concentration, material properties, and core-shell ratio (Wu et al., 2019; Daly et al., 2020). Mechanical stirring is a simple process with high efficiency in the generation of emulsions, but it leads to a non-uniform and polydispersed droplet size distribution (Li et al., 2018). Additionally, during a vigorous stirring process, large-molecule drugs (such as protein drugs) may be damaged and become inactivated by ultrasonic waves or mixed fluid shear stress (Ma, 2014; Li et al., 2022).

### 2.1.2 Extrusion and gas shearing techniques

The extrusion technique involves dissolving the drug in the shell material solution and then extruding the emulsion droplets through a syringe or pipette (Fig. 1b-i) (Uyen et al., 2020; How et al., 2022). The droplet size can be adjusted by the solution concentration, needle diameter, and extrusion speed (Uyen et al., 2020). This method does not need complex equipment, high temperature or pressure, and hence is commonly used to produce large droplets in the range of hundreds of micrometers to millimeters with a slow preparation speed (Uyen et al., 2020; How et al., 2022; Zhu et al., 2023). Also, the core-shell structure emulsion droplets can be prepared with a coaxial nozzle for extrusion, in which the core and shell materials are extruded through independent inner and outer feed channels, respectively (How et al., 2022).

Like the extrusion technique, the gas-shearing technique replaces the outer liquid phase with gas in a coaxial nozzle to form emulsion droplets (Fig. 1b-ii) (Ghaffarian et al., 2016; Tang et al., 2019). With this technique, the droplet size and production rate can be controlled by the gas and internal solution flow rates (Xuan et al., 2024). This method does not need surfactant or washing after solidification (Tang et al., 2019; Liu et al., 2021). Compared to the extrusion technique, the gas-shearing technique can produce much smaller droplets with a high production rate (Wang KY et al., 2022).

#### 2.1.3 Electrospray technology

Electrospray technology extrudes the polymer solution (microcapsule precursor) through a syringe at a high voltage at the needle tip (Alfatama et al., 2024). The droplet deforms into a "Taylor cone" due to the voltage. When the voltage exceeds a critical threshold, the electric field force overcomes the surface tension of the liquid phase at the needle tip, allowing the jet to break into tiny droplets before the droplets finally attach to the collection substrate (Fig. 1c) (Daly et al., 2020; Zhang XL et al., 2022; Yang K et al., 2024). The size and dispersibility of the droplets depend on the operational parameters (i.e., applied voltage, flow rate, needle diameter, and distance between the needle and the collection reservoir) (Alfatama et al., 2024) and the physical properties of the solution (i.e., viscosity, density, and conductivity) (Mehta et al., 2017). The uniformity of droplets (coefficient of variation (CV) range: 6%–23%) and the EE obtained via this method are better than those obtained via mechanical stirring (Qayyum et al., 2017).

#### 2.1.4 Spray drying

Spray drying involves atomizing a solution containing the drug into small droplets and then drying the droplets using hot air (Fig. 1d) (Ozkan et al., 2019; Meola et al., 2024; Xu YY et al., 2024). Usually, the droplet size, drying speed, and core material activity can be adjusted by the liquid feed rate, inlet and outlet drying air temperatures, and gas flow rate during spray drying (Gharsallaoui et al., 2007; Estevinho et al., 2013). This method has the advantages of low cost, high production efficiency, and good polydispersity powder characteristics (Xu YY et al., 2024). However, the high temperatures associated with this process may lead to degradation or damage of bioactive substances in the core material. Also, this method is unable to handle high-viscosity liquids (Jiang et al., 2022; Zhao et al., 2023).

Probiotic microcapsules can be prepared using coaxial spray drying, where sucrose is used as a protective agent to effectively protect *Lacticaseibacillus rhamnosus* GG (LGG) during spray drying to achieve a survival rate of about $1\times10^9$ CFU/g (CFU: colony-forming units) (Tan et al., 2022). In other cases, a low-temperature nitrogen-circulating spray-dryer has been used to prevent insulin degradation during the fabrication of microcapsules (Sun et al., 2017).

#### 2.1.5 Microfluidic methods

Microfluidic emulsification (Zhao et al., 2020) uses two-dimensional (2D) or three-dimensional (3D) microfluidic devices to introduce the dispersed liquid phase into another immiscible continuous phase liquid to generate shear forces to form monodisperse droplets at the junction of two microchannels (Zhao, 2013; Xuan et al., 2024). This process leads to the balanced interaction of the inertial, viscous, and interfacial tension forces in the flow of the two immiscible fluids (Li et al., 2018). The droplet size resulting from this process can be controlled by the geometry of the microfluidic device and the relative flow rates between the continuous and dispersed phases (Zhao, 2013; Daly et al., 2020). However, microfluidic emulsification cannot be used to disperse high-viscosity liquids (Daly et al., 2020; Jo and Lee, 2020). Additionally, the hydrophilicity or hydrophobicity of internal microchannel walls significantly affects the generation of droplets (Lee et al., 2016). For instance, to prepare water-in-oil (W/O) droplets, the walls should preferably be hydrophobic, whereas for oil-in-water (O/W) droplets, the walls should be hydrophilic (Li et al., 2018). Detailed information on 3D (Fig. 1e) and 2D (Fig. 1f) microfluidic devices is shown in Section S2.

Compared to the other dispersion methods, microfluidic emulsification can be used to fabricate droplets with precisely controllable structure and composition (Li et al., 2018; Jo and Lee, 2020). It also has the advantages of high EE, low reagent consumption (Araújo et al., 2015), and good reproducibility (Li et al., 2018; Jo and Lee, 2020; Wang R et al., 2022) for the preparation of monodisperse droplets (with CV<3%) (Li et al., 2018; Jo and Lee, 2020) in the size range of 5–500 μm (Daly et al., 2020). However, microfluidic devices are difficult to clean for re-use (Nabavi et al., 2017), and the low production efficiency of single-channel microfluidic devices limits their large-scale application. Some researchers have designed parallel multi-channel microfluidic devices for the mass production of monodisperse droplets, i.e., 128 cross-junctions or 128 co-flow microfluidic devices (Nisisako and Torii, 2008) and 15 dropmaker units (Romanowsky et al., 2012) integrated on a chip.

#### 2.1.6 Comparison of different emulsion methods

A double emulsion can be used to encapsulate single/multiple droplets within another droplet (Utada

et al., 2005). Double emulsions serving as templates for microcapsules can achieve more complex functionalities and reduce the cross-contamination of different materials (Zhao, 2013), as shown in Section S3 and Fig. S2.

As summarized in Table 1, mechanical stirring, spray drying, and electrospray methods are low-cost, highly efficient, and suitable for large-scale emulsion production. However, there are challenges associated with the non-uniform particle size distribution and low EE, particularly for the preparation of droplets with complex internal components. The extrusion technique needs only very simple equipment, as it is a low-cost emulsification method for large-particle-size droplet production. On the other hand, gas shearing technology does not require surfactants. Microfluidic dispersion technology has greater advantages for small-batch, high-value drugs, producing good monodisperse droplets, controllable structures, good batch-to-batch reproducibility, and high EE, especially for multilayer structures or specific morphologies. However, microfluidic emulsification faces challenges in terms of large-scale production and costs. Therefore, it is necessary to consider the objectives of the microcapsules and the characteristics of the drug when selecting an emulsification method. Theoretically, the smaller the particle size of the microcapsules is, the larger the surface area-to-volume ratio and hence the higher molecular diffusion (Wang KY et al., 2022). However, the preparation of monodisperse microcapsules with a diameter of 10 μm or less presents challenges (Champion et al., 2007; Zhao et al., 2021).

### 2.2 Microencapsulation methods

Microencapsulation methods for MeIDs are based on the physical and chemical properties of shell materials, which include ionic crosslinking, solvent evaporation, and free radical polymerization, as shown in Fig. 2.

#### 2.2.1 Ionic crosslinking

The ionically crosslinked gelation process is widely used for the preparation of biomedical microcapsules. Among the mild and simple ionic crosslinking gelation processes, sodium alginate with high biocompatibility is the most common shell material for the preparation of pH-responsive microcapsules (Gombotz and Wee, 2012; Lee and Mooney, 2012). Sodium alginate is a naturally occurring anionic polymer composed of β-D-mannuronic acid and α-L-guluronic acid (Smidsrød and Skjåk-Braek, 1990; Gombotz and Wee, 2012; Lee and Mooney, 2012;

**Table 1 Summary and comparison of various droplet dispersion methods**

| Dispersion method | Principle | Advantages | Disadvantages |
|---|---|---|---|
| Mechanical stirring | Mechanical shear and impact stress | Simple and highly efficient process | Difficult to control droplet size; low EE |
| Extrusion | Mechanical extrusion of solution into emulsion droplets | Easy operation with simple equipment | Slow preparation speed, large droplet size, and CV=15%–40% (Freitas et al., 2005) |
| Gas shearing | Shear force generated by gas to liquid phase | No surfactant | Polydisperse droplets |
| Electrospray | Voltage-induced formation and dispersion of droplets | High production efficiency | Non-uniform droplet size, CV=6%–23% (Qayyum et al., 2017) |
| Spray drying | Atomizing droplets and drying with high-temperature airflow | Low cost and high production efficiency | Polydisperse droplets; high temperatures not suitable for heat-sensitive biological materials |
| 2D PDMS microfluidics | Shear forces generated by two immiscible phases at junctions of 2D microchannels | High EE with controllable size and structure, and CV<3% (Li et al., 2018) | Incompatible with organic solvents, difficult for multiple emulsions, complex, and costly |
| 3D capillary microfluidics | Shear forces at junctions or apertures of immiscible phases | Easy for multiple emulsion preparation, and CV<2% (Yang XY et al., 2024) | Manually assembled, difficult to reproduce, and massively produced |

CV: coefficient of variance; EE: encapsulation efficiency; PDMS: poly(dimethylsiloxane).

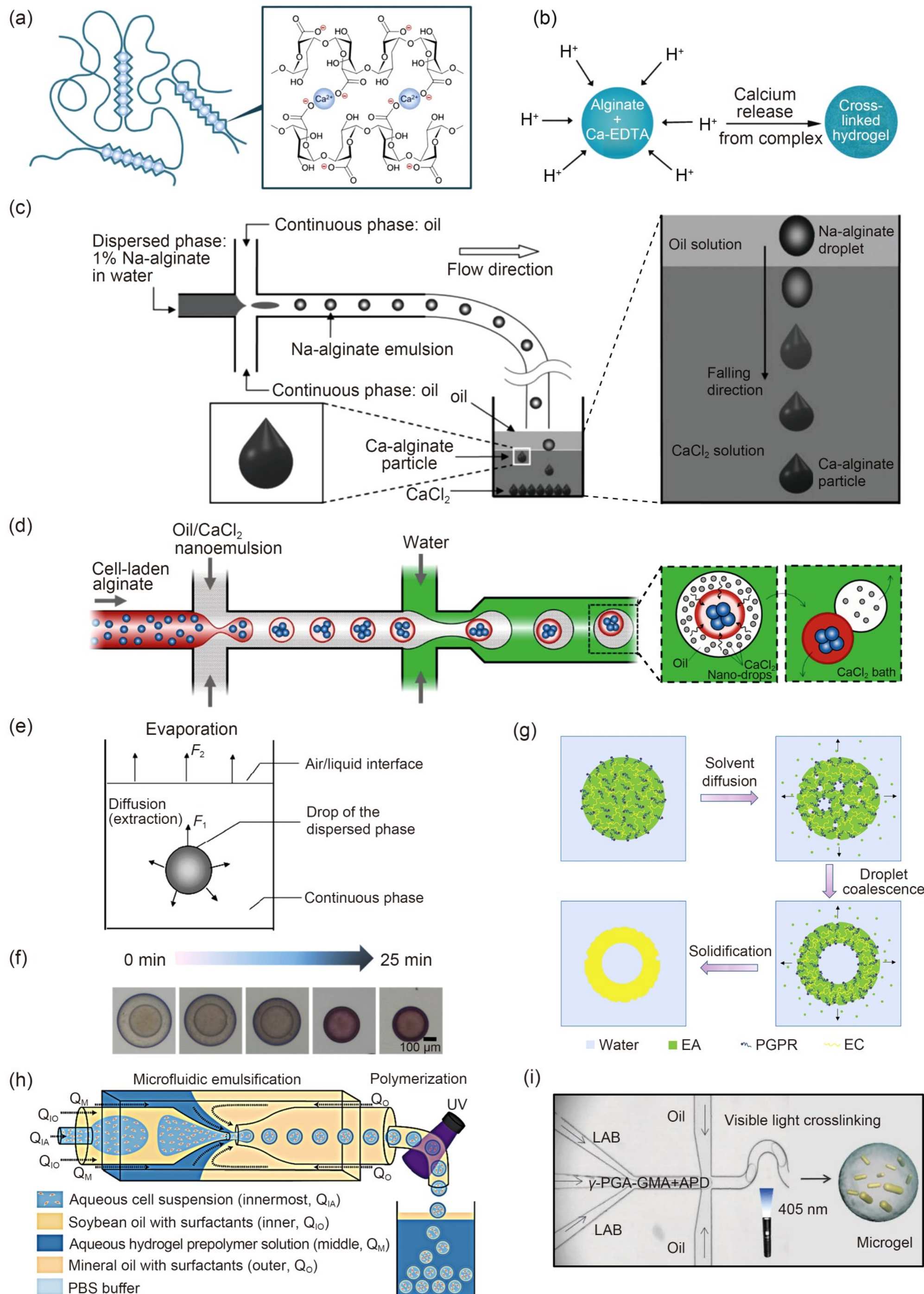


**Fig. 2 Microencapsulation methods. (a) $Ca^{2+}$ crosslinked with sodium alginate. Reprinted from Jo and Lee (2020) by permission of John Wiley and Sons. (b) Internal gelation. Adapted from Utech et al. (2015) by permission of John Wiley and Sons. (c) External gelation. Adapted from Lin et al. (2013) by permission of John Wiley and Sons. (d) Double emulsion microfluidic device for improved external gelation. Adapted from Samandari et al. (2019), Copyright 2019, with permission from Elsevier. (e) Schematic diagram of solvent evaporation. Reprinted from Li et al. (2008), Copyright 2008, with permission from Elsevier. $F_1$: solvent diffusion rate; $F_2$: solvent evaporation rate. (f) Particle size changes during solvent evaporation. Reprinted from Jiang et al. (2021) by permission of The Royal Society of Chemistry. (g) Hollow microcapsules fabricated by solvent evaporation. Reprinted from Song et al. (2022), Copyright 2022, with permission from Elsevier. EA: ethyl acetate; PGPR: polyglycerol polyricinoleate; EC: ethyl cellulose. (h) Initiation by ultraviolet (UV) light. Reprinted from Kim et al. (2022), Copyright 2022, with permission from Elsevier. PBS: phosphate-buffered saline. (i) Initiation by low-energy visible light. Reprinted from Wang R et al. (2022) by permission of John Wiley and Sons. LAB: lactic acid bacteria; γ-PGA: poly-γ-glutamic acid; GMA: glycidyl methacrylate; APD: *N*,*N*-(2-amino-1,4-phenylene) diacrylamide.**

Agüero et al., 2017). The ionic crosslinking of sodium alginate connects different polymer chains to form an egg-box structure due to the exchange of sodium ions in guluronic acid with divalent cations, as shown in Fig. 2a (Gombotz and Wee, 2012; Lee and Mooney, 2012; Jo and Lee, 2020).

When sodium alginate is used as the shell material, its performance is influenced by the type of cation, the proportion of G units (α-L-guluronic acid), the crosslinking agent, and the crosslinking temperature (Smidsrød and Skjåk-Braek, 1990; Gombotz and Wee, 2012), as shown in Section S4. Ionic crosslinking can be accomplished by internal or external gelation (Qiao et al., 2024). Internal gelation usually involves the addition of water-insoluble calcium carbonate ($CaCO_3$) nanoparticles or calcium-ethylenediamine tetraacetic acid (EDTA) into the sodium alginate solution as a source of $Ca^{2+}$. Emulsion droplets are crosslinked by the release of $Ca^{2+}$ triggered by acid (Fig. 2b) (Tan and Takeuchi, 2007; Lee and Mooney, 2012; Utech et al., 2015). However, internal gelation may lead to the aggregation of gelling droplets, resulting in channel clogging in microfluidic devices (Samandari et al., 2019).

For external gelation, sodium alginate droplets are collected in calcium chloride solution, and the $Ca^{2+}$ ions diffuse into the sodium alginate droplets to accomplish crosslinking (Pawar and Edgar, 2012; Ghaffarian et al., 2016). Usually, the tail-shaped microcapsules, as shown in Fig. 2c (Lin et al., 2013; Samandari et al., 2019), result from uneven calcium gelation at the oil/water interface (Ling et al., 2019). However, this principle can be used to prepare microgels of different geometries by controlling the size, impact force, and concentration of sodium alginate droplets (Hu et al., 2012). Samandari et al. (2019) improved external gelation by preparing water-in-oil-in water (W/O/W) emulsion droplets by adding calcium chloride nanodroplets into the middle oil phase, which successfully avoided the formation of tail-shaped particles and did not require the use of acids or a chelator reagent (Fig. 2d). Song et al. (2013) compared the differences between internal and external gelation and found that microcapsules prepared by internal gelation achieved more regular morphology and narrower particle size distribution.

#### 2.2.2 Solvent evaporation

Solvent evaporation for microencapsulation preparation (Fig. 2e) involves (1) dissolving organic shell material in a volatile organic solvent, (2) emulsification to form tiny droplets, (3) diffusion of the solvent within the emulsion droplets slowly into the external continuous phase or evaporation into the surrounding air, and (4) increasing the concentration of the shell material and finally solidification as microcapsules (Freitas et al., 2005; Li et al., 2008; Lee et al., 2016).

The evaporation rate of the solvent determines the morphology, encapsulation, and release behavior of the microcapsules (Rosca et al., 2004; Sawalha et al., 2011). Compared to other microencapsulation methods, this technique requires emulsion droplets to have high stability due to long curing periods (Lee et al., 2016). A rotary evaporator can be used effectively to shorten the evaporation time. Moreover, during the solidification process, the volume of particles shrinks significantly, as shown in Fig. 2f (Jiang et al., 2021). At the same time, the drug usually accumulates on the surface of microcapsules, resulting in burst release at the initial decomposition stage (Rosca et al., 2004). Nevertheless, organic solvents may cause drug inactivation (Wang X et al., 2022).

Song et al. (2022) used ethyl acetate as a solvent to dissolve ethyl cellulose to prepare microcapsules with a hollow structure (Fig. 2g). They found that the interfacial mass transfer rate between ethyl acetate and water could be successfully controlled by adjusting the concentration of polyglycerol polyricinoleate in the oil phase.

#### 2.2.3 Free radical polymerization

Free radical polymerization usually adds shell monomers or oligomers to the dispersed phase to form emulsions (Li et al., 2018; Zhang XL et al., 2022). The thermal or photo initiators decompose to produce free radicals by heat or ultraviolet (UV) light, which initiates the polymerization and curing of the shell monomers to form microcapsules (Lee et al., 2016). The concentration of the initiator directly affects the solidification time and structure of the microcapsules (Wang R et al., 2022). Thermal initiation polymerization may damage the bioactivity of drug molecules and the stability of emulsions due to high temperatures, leading to coalescence of particles (Lee et al., 2016). The reaction speed of photoinitiated polymerization is relatively high, while emulsion stability has fewer negative effects (Li et al., 2018; Zhang XL et al., 2022). This method can be used to fabricate

microcapsules with response mechanisms and high drug loading capacity (Ma et al., 2023), but the generated free radicals may cause biological toxicity (Zhang XL et al., 2022).

To address the potential biocompatibility issues of radical polymerization, Kim et al. (2022) prepared triple emulsion droplets using a microfluidic approach as microcapsule templates, with polyethylene glycol diacrylate as the shell material, solidified through UV-induced free radical polymerization. The inner phase of the emulsion droplets was a cell solution, the outer phase was a prepolymer solution containing the photoinitiator and shell material, and the intermediate oil layer protected the cells from direct exposure to the photoinitiator (Irgacure 2959, 1%) and UV light during polymerization, achieving more than 98% cell viability within the microcapsules (Fig. 2h). In contrast, Wang R et al. (2022) grafted methacrylate groups (C=C double bond groups) onto the main chain of poly-γ-glutamic acid through an epoxy ring-opening reaction, resulting in the capability to polymerize. The study used *N*,*N*-(2-amino-1,4-phenylene) diacrylamide as a crosslinker, initiating polymerization to solidify the shell under low-energy visible light (405 nm) irradiation. This method effectively reduced the negative impact of UV light on cell viability and achieved a cell loading density as high as $6.0\times10^{8}$ cells/mL (Fig. 2i).

#### 2.2.4 Other microencapsulation methods

A phase change material as a shell can be used to form microcapsules by changing the temperature, i.e., by solidification of the shell material (Li et al., 2018). Fu et al. (2024) dissolved gelatin in water at 37 °C and then slowly dropped it into liquid paraffin with an emulsifier at 60 °C. The gelatin droplets were transferred and cooled down at 4 °C to form microcapsules.

The combination of different microencapsulation methods can improve the physicochemical properties of MeIDs. For example, Li YN et al. (2017) fabricated microcapsules sequentially through photopolymerization and solvent evaporation using W/O/W droplet templates (Fig. S3a). During the experiment, gelatin methacrylate was used as the core material to load the hydrophilic drugs, and poly(lactic-co-glycolic acid) (PLGA) solution was used as the shell material to load the hydrophobic drugs. By controlling the shell thickness, they achieved synergistic drug delivery and programmed drug release rates.

Gan et al. (2022) initially prepared sodium alginate microparticles using ionic crosslinking before forming a gelatin outer shell layer of the microparticles by freezing to construct core-shell-structured microcapsules. The gelatin required heating to maintain the fluidity before being solidified in an ice bath (Fig. S3b).

Li et al. (2022) modified sodium alginate as the microcapsule shell material by using water-in-water-in-oil (W/W/O) emulsion droplets as a template. The microcapsules were sequentially crosslinked through ionic and covalent crosslinking (Fig. S3c). This double crosslinking strategy reduced the mesh size of the solidified hydrogel, resulting in an elastic modulus roughly five times higher than that of the original sodium alginate gel.

#### 2.2.5 Comparison of microencapsulation technologies

The emulsion dispersion method, microencapsulation method, shell material selection, and drug characteristics are interrelated. When a microcapsule shell material is selected, the hydrophilicity and solubility of the drug must be considered. For drugs with good hydrophilicity and water solubility, sodium alginate is suitable. In contrast, for drugs that are soluble in organic solvents, it is more appropriate to prepare shell materials using a solvent evaporation method, as this helps to enhance the drug loading capacity and EE.

Different microencapsulation methods also vary in their compatibility with different emulsion dispersion methods. As shown in Table S1, ionic crosslinking is suitable for most emulsion dispersion methods, while solvent evaporation tends to favor mechanical stirring, spray drying, and microfluidic methods, as these facilitate solvent diffusion and evaporation. Note that due to the incompatibility of poly(dimethylsiloxane) (PDMS) microfluidic devices with organic solvents, solvent evaporation is typically used for 3D glass capillary microfluidic devices. Free radical polymerization tends to favor microfluidic methods, where the precise control of the droplet structure helps to avoid the potential toxicity of substances that may be generated during the free radical polymerization process.

Furthermore, the morphology and response mechanisms of the microcapsules need to be considered when choosing a microencapsulation method. Microcapsules prepared by ionic crosslinking typically have a wrinkled surface structure, while those prepared by solvent evaporation have a smooth surface. Due to the

limitations of biocompatible shell material types, the response mechanism of MeIDs with a solid homogeneous structure is generally based on physiological mechanisms in the human body, while microcapsules prepared by free radical polymerization allow for more flexible shell material designs that can respond to various release mechanisms.

Microcapsules prepared by composed microencapsulation multiple methods can exhibit a core-shell structure and can simultaneously load drugs with different hydrophilicities. However, the order of solidification of the core-shell materials needs to be considered to achieve different structures and shell materials for microcapsules, which directly affect drug release behaviors and mechanisms, such as diffusion-control, swelling-control, and erosion-control (Arifin et al., 2006).

### 2.3 Performance improvement of drug microcapsules

Conventionally prepared MeIDs face issues such as low drug loading, low EE, inadequate gastric protection, poor targeting, and uncontrollable drug release profiles. However, by incorporating coating methods, micro/nanocarriers, and absorption enhancers, these limitations can be effectively addressed, significantly improving the therapeutic efficacy of microcapsules.

#### 2.3.1 Coating methods

Fig. S4a shows a microcapsule coating method where the microcapsules are immersed in a polymer solution with opposite charges and then alternately polycations and polyanions are absorbed on the microcapsule surface to form a protective coating (Sato et al., 2011).

Yang et al. (2022) formed a coating on sodium alginate microcapsules and increased the drug loading capacity of the coated microcapsules from (9.2±2.3)% to (18.0±2.5)% (1%=0.01 g/mL) (Fig. S4b). However, the microcapsules showed insufficient protection in the stomach, releasing about 50% of the drug within 2 h during a simulated gastric fluid (SGF) experiment. Ling et al. (2019) added chitosan to the calcium chloride collection solution and simultaneously produced a chitosan coating with ionic crosslinking. This increased the retention efficiency of the loaded nanoparticles by 35% (Fig. S4c). Ghaffarian et al. (2016) also stabilized a chitosan shell by crosslinking the amino groups of chitosan with genipin after the microcapsules were coated with chitosan, to reduce the initial drug burst release by 25% within 1 h in simulated intestinal fluid (SIF) (pH=7.8). Hu et al. (2025) alternately deposited five layers of negatively charged sodium alginate-silver nanoparticles and positively charged aminocellulose-silver nanoparticles on the surface of chitosan microcapsules, forming a multilayer rigid coating that enhanced the mechanical stability and adsorption capacity of the microcapsules.

In addition to using electrostatic interactions to form a coating on the surface of microcapsules, Xu et al. (2025) used an oxidative polymerization method to coat the surface of porous PLGA microcapsules with pH-responsive polydopamine, achieving targeted delivery to disease sites. Additionally, Zhu et al. (2023) used a solvent evaporation-induced coating method by applying drug-containing sodium alginate droplets in an ethanol solution containing zein and calcium chloride. After the ethanol evaporated, the solubility of zein decreased, and it precipitated on the surface of the microcapsules to form a zein coating. Note that secondary growth of the coating can be achieved by repeating this process (Filippidi et al., 2014).

The coating of MeIDs can enhance their stability, drug loading capacity, and drug release time in low-pH environments (Agüero et al., 2017; Yang et al., 2021). The stability and performance of the coating are influenced by the pH of the solution, temperature, adsorption time, charge density, and molecular weight of the polyelectrolytes (Borges and Mano, 2014).

#### 2.3.2 Micro/nanocarriers

Low-cost and biocompatible natural bio-micro/nanoparticles have been highlighted for drug delivery in microcapsules (Iravani and Varma, 2021; Zhang DX et al., 2022; Seol et al., 2024). Microalgae cells are suitable for loading various drugs due to their surface containing carboxyl, amino, and phosphate groups and negative charges (Zhang DX et al., 2023; Zhang FY et al., 2024). Also, the fluorescence characteristics of the internal chlorophyll in microalgae cells are particularly suitable for drug distribution monitoring (Zhong et al., 2021). Polymers are also used to prepare drug-loaded nanoparticles, such as the commonly used PLGA, where the degradation rate of PLGA can be controlled by adjusting the ratio of lactic acid to glycolic acid (Rezvantalab and Keshavarz Moraveji, 2019).

Nanoparticle carriers in microcapsules can also simultaneously load multi-type drugs with different physicochemical properties. The micro/nano co-delivery system combines the advantages of nano- and micro-scale particles (Araújo et al., 2015; Ahadian et al., 2020; Dos Santos et al., 2021). The use of nanoparticles as drug carriers dispersed and encapsulated within microcapsules can promote drug absorption (Zhang et al., 2014; Ghaffarian et al., 2016; Ling et al., 2019) and enhance targeting of the intestines (Yang et al., 2021) and disease sites (Fu et al., 2024). Interactions with biological systems can be enhanced by modifying the surface functionalization of nanocarriers (Zhang et al., 2014; Sun et al., 2022), thereby improving mucosal adhesion (Zhang et al., 2014; Liu et al., 2021) and promoting drug absorption (Araújo et al., 2015; Sun et al., 2022), as shown in Section S5 and Figs. S5a–S5f.

Recently, Janus-structured magnesium-based micro/nano self-propelled motors have been proposed as drug delivery carriers for MeIDs (Chen et al., 2024; Mundaca-Uribe et al., 2024). Magnesium particles are initially placed on a glass slide as a template, and then layers of a catalytic metal (or $TiO_2$) or drug are alternately deposited layer-by-layer on the surface of the magnesium particles by sputtering deposition technology, ultimately forming an onion-like layered structure (Fig. S5g) (Maric et al., 2022; Chen et al., 2024; Dutta et al., 2024; Ren et al., 2024). After microencapsulation, a tiny opening is formed at the particle–glass interface (Dutta et al., 2024), creating an asymmetric structure. The reaction of magnesium with water in the intestine then generates hydrogen bubbles that act as motors to promote drug release (Chen et al., 2016; Dutta et al., 2024), are delivered to the target intestinal region (Mundaca-Uribe et al., 2023), and extend the retention time by adhering to the intestinal wall (Wu et al., 2019). However, the lifespan of magnesium-based micromotor microcapsules is relatively short, and the drug can be completely released within 3 min (Maric et al., 2022). Therefore, the dissolution time required for the polymer layer needs to be controlled by adjusting the thickness of the enteric coating, thereby regulating the travel distance in the intestine before activation (Li et al., 2016). Wei et al. (2019) prepared microcapsules using magnesium-based micromotors, and managed to double the cellular uptake of antigen carriers compared to static microcapsules (Fig. S5h).

However, it is important to note that micro/nanocarriers occupy a certain amount of space in microcapsules and hence decrease their drug loading capacity (Sabu et al., 2019; Sun et al., 2022; Zhang FK et al., 2023). Also, defatting (Wang et al., 2024), chemical etching (Liu et al., 2014; Li W et al., 2017), and electrochemical anodizing (Zhang et al., 2014) of micro/nanocarriers increase the complexity of the microencapsulation process.

#### 2.3.3 Absorption enhancers

Enzyme inhibitors and intestinal permeation enhancers in microcapsules can improve the bioavailability of oral drugs (de Sousa and Bernkop-Schnürch, 2014; Negrulj et al., 2016; Twarog et al., 2019). Enzyme inhibitors can reduce enzyme activity, thereby reducing the degradation of drugs and increasing permeability across the intestinal epithelial monolayer (Liu et al., 2014). Permeation enhancers could increase the transport of peptide drugs by altering the structure and function of the intestinal epithelium (Maher et al., 2016). For example, Araújo et al. (2015) achieved a synergistic therapeutic effect by co-loading peptides and the enzyme dipeptidyl peptidase 4 inhibitor into microcapsules (Fig. S5f). Sun et al. (2017), on the other hand, used an ion pairing method to complex insulin with sodium deoxycholate, thereby reducing the accessibility of proteases to insulin to promote its absorption through paracellular and transcellular transport pathways. The bioavailability of insulin after microencapsulation increased from less than 0.5% to 16.1% compared to non-encapsulated insulin.

However, enzyme inhibitors and intestinal permeability enhancers may lead to negative effects, such as damage to and dysfunction of the cellular barrier and drug instability. Therefore, it is necessary to consider the concentration of intestinal permeability enhancers in microcapsules and the recovery time of the cellular barrier for oral drug administration (Bernkop-Schnürch, 1998; Maher et al., 2016).

#### 2.3.4 Sub-summary

During their preparation, coating microcapsules (Roque-Borda et al., 2023; Zhu et al., 2023), loading micro/nanocarriers (Liu et al., 2014; Li W et al., 2017; Jiang et al., 2021), adding absorption enhancers (Araújo et al., 2015), or combining these methods in an orderly manner (Ghaffarian et al., 2016; Yang et al., 2021;

Fu et al., 2024) can improve their controlled release effect, bioavailability, drug half-life, and stability.

Generally, coating can enhance the protective layer of the microcapsules in the stomach and increase their drug loading capacity. Micro/nanocarriers within microcapsules can provide a programmed control of drug release rates, retention of absorption advantages of nanoparticles in the intestines, and synergistic drug delivery of microcapsules. Absorption enhancers address the problems of poor absorption and easy degradation of the original drugs. By combining the above methods, the bioavailability and efficacy of MeIDs are expected to significantly improve.

## 3 Methods for evaluating microencapsulated intestinal drugs

Various standard instruments and methods have been used to evaluate the performance of oral drug intestinal microcapsules. For example, drug loading efficiency can be detected by high-performance liquid chromatography (HPLC) (Huang et al., 2024) and UV spectrophotometry (Wang X et al., 2022; Zhang FK et al., 2023). Microcapsule particle morphology and particle size distribution can be measured by optical microscopy (Jiang et al., 2021) and dynamic light scattering (Huang et al., 2024). The detailed morphology and structure of the microcapsules can be analyzed by scanning electron microscopy (SEM) (Li W et al., 2017), atomic force microscopy (AFM) (Li et al., 2022), and transmission electron microscopy (TEM) (Zhang FK et al., 2023). The components of the microcapsules can be analyzed by nuclear magnetic resonance (NMR) (Wang R et al., 2022), energy dispersive spectroscopy (EDS) (Ouyang et al., 2023b), Fourier transform infrared (FT-IR) spectroscopy (Chen et al., 2022), and X-ray diffraction (XRD) (Deng et al., 2021). In addition, some special evaluation methods are still required for the evaluation of biosafety, stability, response mechanisms, pharmacokinetics, and pharmacodynamics.

### 3.1 Biosafety

In vitro tests for the biosafety of drug microcapsules are carried out by detecting their cytotoxicity (leading to cell death) and cytostasis (preventing cell proliferation) (Liu et al., 2014; Adan et al., 2016; Li W et al., 2017; Wang R et al., 2022; Elmorshedy et al., 2023). For instance, the dye exclusion method is a cost-effective and easy-to-operate method that allows direct observation of cytotoxic effects in microcapsules (Ouyang et al., 2023b). However, it cannot distinguish between apoptosis and necrosis of cells, has low sensitivity (Adan et al., 2016), and is not suitable for high-throughput screening (Niles et al., 2008). The metabolic activity assay, on the other hand, assesses cell viability by detecting the activity of reductase enzymes during cell metabolism (Niles et al., 2008). For example, the 3-(4,5-dimethylthiazolyl)-2,5-diphenyltetrazolium bromide (MTT) assay is commonly used for high-throughput screening but requires dimethyl sulfoxide to dissolve formazan in cells (Niles et al., 2008) and also kills cells. This approach affects subsequent studies and has a long experimental cycle (Adan et al., 2016). In contrast, the cell counting kit-8 (CCK-8) assay does not require a dissolving solvent and is suitable for continuous monitoring of live cells (Niles et al., 2008). The adenosine 5'-triphosphate (ATP) assay can detect cell viability based on the reaction between intracellular ATP and exogenous luciferase (Niles et al., 2008; Liu et al., 2014; Adan et al., 2016). It has high sensitivity and speed but cannot distinguish between cytotoxicity and cytostasis (Adan et al., 2016), as well as being relatively expensive (Niles et al., 2008).

Compared to the limitations of in vitro models, in vivo biocompatibility assessment can provide a more comprehensive evaluation of the potential toxic effects of microcapsules by monitoring the complete physiological response and long-term effects. To assess liver and kidney damage after oral administration of drug microcapsules, some studies measured serum biochemical indicators of mice, i.e., alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflecting liver reactions, and blood urea nitrogen (BUN) and creatinine (CRE) reflecting kidney reactions (Kim et al., 2022; Elmorshedy et al., 2023; Du et al., 2024; Lin et al., 2024). After experimentation with drug microcapsules, histological examination of the major organs (i.e., heart, lungs, spleen, liver, and kidneys) of mice allows the visualization of organ toxicity effects (Gan et al., 2022; Fu et al., 2024). Ren et al. (2023) and Du et al. (2024) conducted long-term drug biosafety studies of MeIDs in mice over 30 and 50 d, respectively. They observed

pathological changes and abnormal inflammation in major organs through blood and biochemical testing and histological analysis.

In this review, in vitro cytotoxicity tests have been found to have the advantages of being simple to perform and having a low cost and fast screening speed, but they may lead to deviations in toxicity assessment results. In vivo biosafety tests, on the other hand, can accurately reflect actual physiological changes within the organism, especially in the evaluation of chronic toxicity during long-term treatment. For biosafety screening of microencapsulated drugs, it is therefore recommended to prioritize in vitro tests at early stages, combined with in vivo tests for in-depth evaluations. To select detection methods, the cell type, interactions, and culture conditions should be considered (Weyermann et al., 2005; Adan et al., 2016).

### 3.2 Stability

Optical microscopy can be used to observe and compare the morphological changes of MeIDs during long-term storage to evaluate their storage stability (Gan et al., 2022). This method is simple, but it cannot assess internal structure or drug activity changes in microcapsules. Thermogravimetric analysis (TGA) can be used to assess the gastric acid stability of microcapsules by measuring the residual weight of the microcapsules after digestion in SGF (Zhu et al., 2023). For probiotic microcapsules, the storage stability can be evaluated by measuring the number of viable cells under different storage conditions (i.e., 4 °C and 25 °C) at different storage times (Deng et al., 2021).

To precisely assess and analyze changes in the structure and bioactivity of protein drug microcapsules during digestion, Wang X et al. (2022) systematically evaluated the release of protein drugs from microcapsules after digestion in SGF and SIF. The released protein drugs retained their original structure according to the electrophoretic analysis of protein bands, FT-IR detection of protein secondary structure, and fluorescence spectroscopic analysis of the position and intensity of fluorescence emission peaks. Additionally, the biological activity of the released protein drugs was confirmed through experiments of free radical scavenging and macrophage activation. To investigate the stability of protein drugs after encapsulation and the release mechanism of microcapsules, Martínez-López et al. (2019) and Ma et al. (2023) analyzed the secondary structure of insulin after release from microcapsules using circular dichroism spectroscopy. They verified that the encapsulated and released insulin could maintain structural and biological stability through a reduction in blood glucose levels in mouse experiments.

### 3.3 Response mechanism of microcapsule shells

To achieve precise drug release at a predetermined location, intestinal microcapsules can be designed to respond to pH variation, microbiota, and intestinal peristalsis in the human body. For example, Liu et al. (2014) used hypromellose acetate succinate (HPMCAS) as the shell material and adjusted the ratio of acetate and succinate to prepare microcapsules with multistage pH responses. Their SGF and SIF experiments (Fig. 3a) proved that the shell can protect the microcapsules in the stomach and release drugs in the intestine. Yang XY et al. (2024) used dextran modified with glycidyl methacrylate and tannic acid as shell materials for microcapsules, with the dextran degraded exclusively by colonic bacteria-secreted dextranase to achieve targeted release in the colonic environment (Lu et al., 2022). Gastrointestinal fluid experiments showed that the microcapsules could remain intact in SGF and SIF, as well as respond to degradation and release in dextranase solution (15 U/mL), simulating the action of dextranase secreted by the intestinal microbiota (Fig. 3b) (Yang XY et al., 2024). Kim et al. (2022) designed a thin-shell microcapsule that can respond to intestinal peristalsis. They used a micropipette aspiration device to simulate mechanical stress in the intestine and observed the deformation and rupture of the microcapsules in the constriction region (Fig. 3c).

Targeted microcapsules can be designed to respond to abnormal secretions caused by diseases. For example, Regmi et al. (2019) designed microcapsules responsive to reactive oxygen species (ROS) to treat inflammation resulting from a significant increase of ROS and observed the ROS-dependent in vitro release of the microcapsules in a simulation experiment (Fig. 3d). Wang R et al. (2022) proposed a novel nitric oxide (NO)-responsive poly-γ-glutamic acid hydrogel microcapsule strategy based on a droplet microfluidic technology platform. During intestinal inflammation, the expression of NO significantly increased, and NO auto-oxidized to dinitrogen trioxide ($N_2O_3$). When the microcapsules were exposed to $N_2O_3$, the crosslinked bonds of the shell were broken down and the microcapsules disintegrated. The researchers

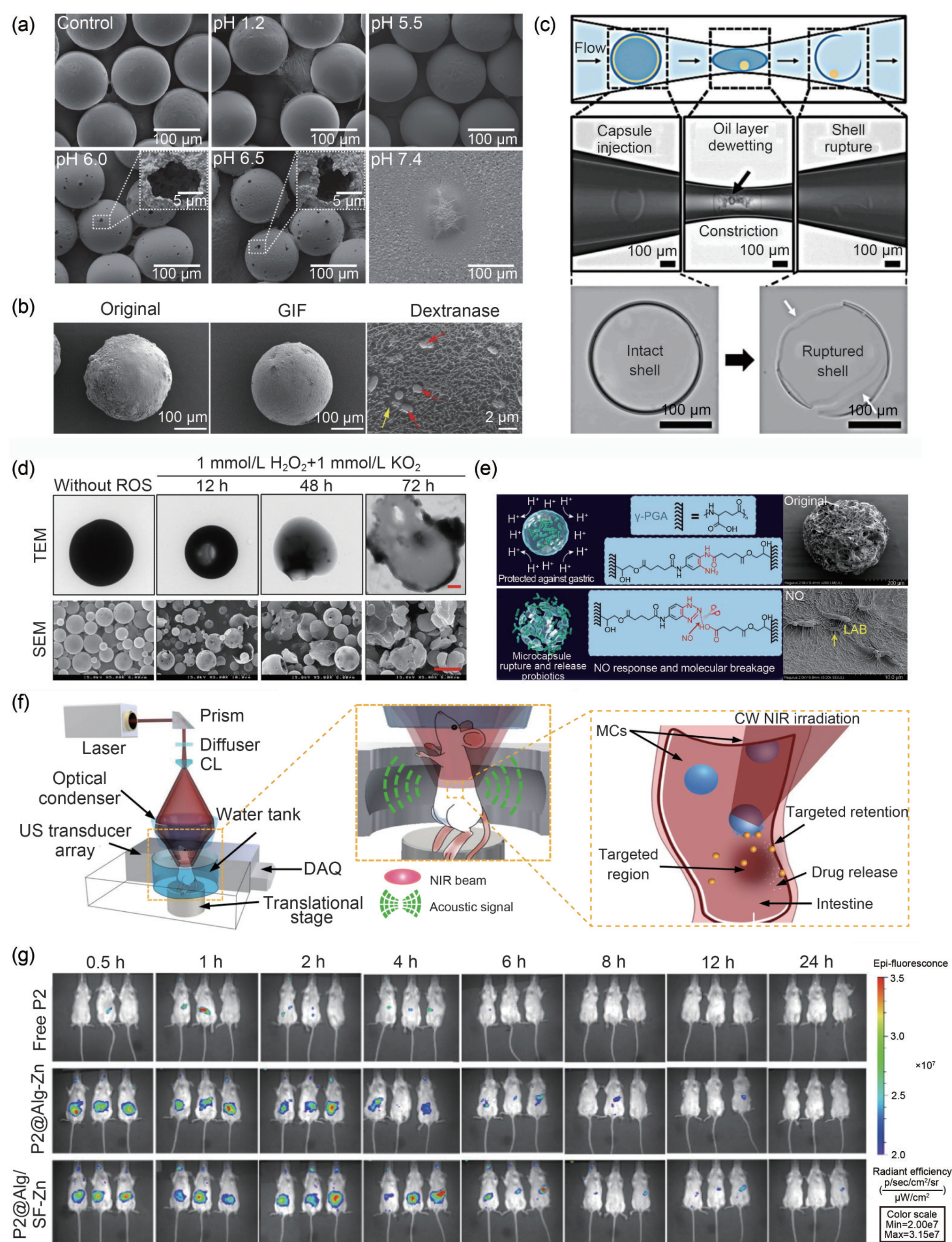


**Fig. 3 Response mechanism of the microencapsulated intestinal drugs (MeIDs). (a) Simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) experiments with pH-responsive microcapsules. Reprinted from Liu et al. (2014) by permission of John Wiley and Sons. (b) Dextranase-responsive microcapsules. Reprinted from Yang XY et al. (2024), Copyright 2024, with permission from Elsevier. GIF: gastrointestinal fluid. (c) Microcapsules with release responsive to intestinal peristalsis. Reprinted from Kim et al. (2022), Copyright 2022, with permission from Elsevier. (d) Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) images of reactive oxygen species (ROS)-responsive microcapsules (scale bars: 500 nm for TEM and 6 μm for SEM images). Reprinted from Regmi et al. (2019), Copyright 2019, with permission from Elsevier. (e) Comparison of microcapsules before and after release in response to nitric oxide (NO). Reprinted from Wang R et al. (2022) by permission of John Wiley and Sons. LAB: lactic acid bacteria. (f) Near-infrared (NIR) light-induced microcapsule release. Reprinted from Wu et al. (2019) with the permission of The American Association for the Advancement of Science. US: ultrasound; CL: conical lens; DAQ: data acquisition system; MCs: micromotor capsules; CW: continuous-wave. (g) In vivo imaging system of the microcapsule distribution in mice. Reprinted from Du et al. (2024), Copyright 2024, with permission from Elsevier. Alg: alginate; SF: silk fibroin.**

also found that, as a result of the cytoprotective effects of the microcapsule, there was high viability in the SGF (89.67%) and SIF (93.67%) environments (Fig. 3e).

Fig. 3f shows a photoacoustic computed tomography system capable of real-time in vivo monitoring of microcapsule migration in mouse tissues (Wu et al., 2019). Wu et al. (2019) developed a gold layer inside microcapsules that effectively converts near-infrared (NIR) light into heat. They observed that the moment the microcapsules reached the targeted intestinal location, continuous-wave NIR irradiation triggered the release of the core material of the microcapsules.

Several studies (Kim et al., 2022; Du et al., 2024; Yang K et al., 2024) have also shown that after the oral administration of fluorescently labeled drug microcapsules in mice to directly observe the distribution and retention time of microcapsules using the in vivo PerkinElmer IVIS Spectrum Series imaging system, the stability and release behavior of MeIDs can be observed (Fig. 3g).

### 3.4 Pharmacokinetics and drug release kinetics

For MeID development, understanding the mechanisms of drug release, absorption, distribution, metabolism, and excretion is crucial (Uyen et al., 2020). By combining in vitro and in vivo models in the evaluation system, the drug release and pharmacokinetic properties of microcapsules can be optimized for more accurate performance assessment. Usually, the concentration of the drug in the blood circulation is measured to plot the blood concentration–time curve to obtain parameters from the area under the curve (AUC), as well as peak concentration ($C_{max}$), peak time ($t_{max}$), and bioavailability. The other method involves placing intestinal microcapsules in SGF and SIF and then extracting the samples to plot drug–time release curves (Paarakh et al., 2018; Ouyang et al., 2023b). Pharmacokinetics and drug release kinetics models are shown in Section S6.

The drug release kinetics of microcapsules include diffusion-controlled, swelling-controlled, and erosion-controlled systems (Arifin et al., 2006). The rate of drug release from microcapsules is usually influenced by the shell thickness (Rosca et al., 2004; Wang X et al., 2022), particle size (de la Vega et al., 2013; Zhao, 2013), particle size distribution (Wang et al., 2014), shell material solution concentration (Mandal et al., 2010), swelling properties (Yang et al., 2022; Ouyang et al., 2023a), and drug solubility and dosage (Ghaffarian et al., 2016) of the microcapsules. Drug release kinetics models can be used to analyze and optimize the formulation of microcapsules (Huang et al., 2006; Trucillo, 2022), and to guide the design of microcapsule structure and drug loading (Arifin et al., 2006; Paarakh et al., 2018).

The mathematical models of drug release from microcapsules can be used to predict drug release behavior based on the parameters of the diameter, shell material, drug loading, and solubility in microcapsules (Siepmann and Peppas, 2012), as shown in Table S2.

However, the drug release kinetics of microcapsules is still affected by the uniformity of the particle size and the drug distribution in the microcapsules. To this end, the drug release kinetics, the structure–activity relationship between the drug and the shell material, and the theoretical design of various monodisperse microcapsules need to be explored.

### 3.5 Pharmacodynamics

#### 3.5.1 In vitro simulation

In vitro simulation models constructed by cell culture technology are commonly used to study the absorption and mechanisms of MeIDs. For instance, mouse intestinal epithelial cells (IEC-6) have been used to simulate intestinal epithelial cells to study the release of insulin from microcapsules and the endocytosis of the released insulin (Ren et al., 2023). Ren et al. (2023) used human colon cancer cells (Caco-2) and mouse macrophages (RAW264.7) to simulate M cell-mediated endocytosis and macrophage phagocytosis, to verify the drug absorption ability of microcapsules. Ma et al. (2023) used the Transwell model to simulate the small intestinal epithelium in Caco-2 cells. They analyzed the transmembrane mechanism of the microcapsules by pre-treating with betaine or L-tryptophan to block proton-coupled amino acid transporter 1 (PAT1).

In recent years, organ-on-chip technology based on cell culture and microfluidic technology has shown great potential due to its high physiological relevance (Macedo et al., 2023; Xu XM et al., 2024). This technology provides new possibilities for in vitro simulation of MeIDs and is expected to significantly

advance the drug development process (Ahadian et al., 2020; Shin et al., 2020). In vitro models can quickly and cost-effectively help in the evaluation of the toxicity and efficacy of drug microcapsules. However, they cannot fully simulate the complex physiological processes of drugs in the human body, especially where there are significant differences in pH, transit time, mucus, and intestinal fluid volume as a result of various disease states (Hua, 2020).

### 3.5.2 Animal models

Animal disease models are expensive, although they can accurately provide evaluation of the actual effects and biological responses of drugs (Yao et al., 2020). Disease models for mice can be induced using some specific methods. For instance, streptozotocin (STZ) is used to induce a diabetic mouse model (Ren et al., 2023), and 1,2-dimethylhydrazine (DMH) to induce a mouse colon cancer model (Elmorshedy et al., 2023). An arthritis (AIA) rat model can be established in rats by induction with complete Freund's adjuvant (CFA) (Zhang FK et al., 2023). Using the unilateral ureteral obstruction (UUO) rat model, renal fibrosis can be simulated (Sun et al., 2022), while a mouse metabolic syndrome (MetS) model can be induced by a high-fat high-sugar (HFHS) diet (Zhao et al., 2021).

The evaluation of drug performance in animal disease models is usually carried out by comparing the biomarker levels (Elmorshedy et al., 2023) and histopathology (Li et al., 2022). For instance, a dextran sulfate sodium (DSS) solution can be used to induce a colitis model to simulate IBD treatment (Kim et al., 2022; Zhu et al., 2023). Therapeutic effects are then evaluated through the disease activity index (DAI), colon length, histopathology, intestinal tissue repair (Ouyang et al., 2023b), and levels of inflammatory factors (Du et al., 2024). In a murine model of colitis, Liu et al. (2021) used orally administered microcapsules loaded with thiolated hyaluronic acid for treatment. Immunohistochemical analyses revealed that, in the treatment group, the proportion of myeloperoxidase-positive neutrophils was significantly reduced, indicating that the microcapsules effectively inhibited the infiltration of inflammatory cells. Simultaneously, the expression level of proliferating cell nuclear antigen was significantly elevated, suggesting that the proliferation of intestinal epithelial cells was enhanced, thereby promoting the repair of intestinal tissue. Du et al. (2024) treated subjects with orally administered microcapsules containing bornyl acetate. Immunofluorescence staining results showed that this treatment significantly restored the expression levels of MUC-2 mucin and the tight junction protein ZO-1 in the colonic tissues, indicating that the microcapsules were capable of repairing the mucus layer and the tight junctions between epithelial cells, thereby reestablishing colonic barrier function. Ouyang et al. (2023b) used microcapsules containing orally administered selenium nanoparticles modified with hyaluronic acid for treatment. Immunofluorescence staining results showed that the fluorescence intensity of pro-inflammatory factors interleukin-6 (IL-6) and IL-1β in mouse colon tissues was significantly reduced, effectively inhibiting the inflammatory response.

## 4 Conclusions and outlook

This review has covered an in-depth and critical analysis of the development, application, and progress of various MeIDs. It shows that the controlled drug release of microcapsules offers significant support for precision medicine. The outcomes are expected to provide support for the MeID development, precise control of drug dosage, and delivery and evaluation methods.

For the preparation of MeIDs, drug hydrophilicity and solubility provide the basis for selecting shell materials that should also be compatible with specific microencapsulation methods. In addition, modifying the emulsion dispersion process enhances the monodispersity, size, and structure of the microcapsules. Furthermore, the review has shown that coating, micro/nanocarriers, and absorption enhancers can be used to achieve the multifunctional and intelligent release of microcapsules.

Besides standard methods, in vitro cell and animal models were used to evaluate the biosafety and efficacy of microencapsulated drugs. Structural stability and drug activity, on the other hand, were typically analyzed using microscopic and spectroscopic techniques. Response mechanisms, however, were investigated under simulated physiological conditions, with fluorescence tracing used to study the in vivo distribution of microcapsules.

From this review, it appears critical that preparation processes are optimized to regulate drug release kinetics and enhance therapeutic efficacy. This is

because the current MeID preparation faces challenges, including the high cost of monodisperse microcapsules, difficulties in large-scale production, and suboptimal targeted release performance. In addition, existing in vitro cell models lack dynamic physiological simulations, and studies on the in vitro–in vivo correlation of drug release kinetics remain insufficient. Therefore, future research should focus on developing low-cost, scalable methods for producing monodisperse drug microcapsules.

Also, to achieve active and precise targeted release, novel shell materials or carriers with excellent biocompatibility and dynamic responsiveness (e.g., dual responses to disease biomarkers or enzymes) must be explored and integrated with functionalities for biological targeting and external stimuli (e.g., magnetic fields or infrared radiation). Meanwhile, organ-on-chip technologies have been proposed for evaluating the biocompatibility and pharmacological efficacy of microcapsules, which is expected to accelerate drug development and reduce associated costs. Furthermore, monodisperse drug microcapsules can be used as standardized research objects to establish a database of structure–activity relationships between drugs and shell materials, enabling rapid screening of suitable materials and processes, to accelerate drug development.

Through interdisciplinary collaborative innovation, the field of MeID will transition from laboratory technology to clinical application in the future, thereby advancing the development of personalized precision medicine.

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## Author contributions

Weiguang SU: conception, supervision, funding acquisition, investigation, formal analysis, validation, and writing – original draft. Dawei WANG: writing – original draft, data curation, investigation, and visualization. Siegfried YEBOAH, Jinshen WANG, and Chonghai XU: writing – review & editing. Li WANG: supervision, funding acquisition, and writing – review & editing. All authors have read and approved the final manuscript.

## Compliance with ethics guidelines

Weiguang SU, Dawei WANG, Siegfried YEBOAH, Jinshen WANG, Chonghai XU, and Li WANG declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

## Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

## References

Adan A, Kiraz Y, Baran Y, 2016. Cell proliferation and cytotoxicity assays. *Curr Pharm Biotechnol*, 17(14):1213-1221.
https://doi.org/10.2174/1389201017666160808160513

Agüero L, Zaldivar-Silva D, Peña L, et al., 2017. Alginate microparticles as oral colon drug delivery device: a review. *Carbohydr Polym*, 168:32-43.
https://doi.org/10.1016/j.carbpol.2017.03.033

Ahadian S, Finbloom JA, Mofidfar M, et al., 2020. Micro and nanoscale technologies in oral drug delivery. *Adv Drug Deliv Rev*, 157:37-62.
https://doi.org/10.1016/j.addr.2020.07.012

Alfatama M, Shahzad Y, Choukaife H, 2024. Recent advances of electrospray technique for multiparticulate preparation: drug delivery applications. *Adv Colloid Interface Sci*, 325: 103098.
https://doi.org/10.1016/j.cis.2024.103098

Araújo F, Shrestha N, Shahbazi MA, et al., 2015. Microfluidic assembly of a multifunctional tailorable composite system designed for site specific combined oral delivery of peptide drugs. *ACS Nano*, 9(8):8291-8302.
https://doi.org/10.1021/acsnano.5b02762

Arifin DY, Lee LY, Wang CH, 2006. Mathematical modeling and simulation of drug release from microspheres: implications to drug delivery systems. *Adv Drug Deliv Rev*, 58(12-13):1274-1325.
https://doi.org/10.1016/j.addr.2006.09.007

Baek JS, Choo CC, Qian C, et al., 2016. Multi-drug-loaded microcapsules with controlled release for management of Parkinson's disease. *Small*, 12(27):3712-3722.
https://doi.org/10.1002/smll.201600067

Bernkop-Schnürch A, 1998. The use of inhibitory agents to overcome the enzymatic barrier to perorally administered therapeutic peptides and proteins. *J Controlled Release*, 52(1-2):1-16.
https://doi.org/10.1016/s0168-3659(97)00204-6

Borges J, Mano JF, 2014. Molecular interactions driving the layer-by-layer assembly of multilayers. *Chem Rev*, 114(18): 8883-8942.
https://doi.org/10.1021/cr400531v

Brown TD, Whitehead KA, Mitragotri S, 2019. Materials for oral delivery of proteins and peptides. *Nat Rev Mater*, 5(2):127-148.
https://doi.org/10.1038/s41578-019-0156-6

Champion JA, Katare YK, Mitragotri S, 2007. Particle shape: a new design parameter for micro- and nanoscale drug delivery carriers. *J Controlled Release*, 121(1-2):3-9.
https://doi.org/10.1016/j.jconrel.2007.03.022

Chen CR, Karshalev E, Li JX, et al., 2016. Transient micromotors that disappear when no longer needed. *ACS Nano*, 10(11):10389-10396.
https://doi.org/10.1021/acsnano.6b06256

Chen CR, Ding SC, Wang J, 2024. Materials consideration for the design, fabrication and operation of microscale robots. *Nat Rev Mater*, 9(3):159-172.
https://doi.org/10.1038/s41578-023-00641-2

Chen GP, Yu YR, Fu X, et al., 2022. Microfluidic encapsulated manganese organic frameworks as enzyme mimetics for inflammatory bowel disease treatment. *J Colloid Interface Sci*, 607:1382-1390.
https://doi.org/10.1016/j.jcis.2021.09.016

Chen L, Gnanaraj C, Arulselvan P, et al., 2019. A review on advanced microencapsulation technology to enhance bioavailability of phenolic compounds: based on its activity in the treatment of Type 2 Diabetes. *Trends Food Sci Technol*, 85:149-162.
https://doi.org/10.1016/j.tifs.2018.11.026

Chu JN, Traverso G, 2022. Foundations of gastrointestinal-based drug delivery and future developments. *Nat Rev Gastroenterol Hepatol*, 19(4):219-238.
https://doi.org/10.1038/s41575-021-00539-w

Daly AC, Riley L, Segura T, et al., 2020. Hydrogel microparticles for biomedical applications. *Nat Rev Mater*, 5(1):20-43.
https://doi.org/10.1038/s41578-019-0148-6

de la Vega JC, Elischer P, Schneider T, et al., 2013. Uniform polymer microspheres: monodispersity criteria, methods of formation and applications. *Nanomedicine*, 8(2):265-285.
https://doi.org/10.2217/nnm.12.210

Deng ZY, Li J, Song R, et al., 2021. Carboxymethylpachymaran/alginate gel entrapping of natural pollen capsules for the encapsulation, protection and delivery of probiotics with enhanced viability. *Food Hydrocolloids*, 120:106855.
https://doi.org/10.1016/j.foodhyd.2021.106855

de Sousa IP, Bernkop-Schnürch A, 2014. Pre-systemic metabolism of orally administered drugs and strategies to overcome it. *J Controlled Release*, 192:301-309.
https://doi.org/10.1016/j.jconrel.2014.08.004

Dos Santos AM, Carvalho SG, Meneguin AB, et al., 2021. Oral delivery of micro/nanoparticulate systems based on natural polysaccharides for intestinal diseases therapy: challenges, advances and future perspectives. *J Controlled Release*, 334:353-366.
https://doi.org/10.1016/j.jconrel.2021.04.026

Drucker DJ, 2020. Advances in oral peptide therapeutics. *Nat Rev Drug Discov*, 19(4):277-289.
https://doi.org/10.1038/s41573-019-0053-0

Du YY, Jiang YT, Song YJ, et al., 2024. Alginate/silk fibroin/$Zn^{2+}$ composite microspheres for site-specific delivery for enhanced ulcerative colitis therapy. *Chem Eng J*, 495:153441.
https://doi.org/10.1016/j.cej.2024.153441

Durán-Lobato M, Niu ZG, Alonso MJ, 2020. Oral delivery of biologics for precision medicine. *Adv Mater*, 32(13):1901935.
https://doi.org/10.1002/adma.201901935

Dutta S, Noh S, Gual RS, et al., 2024. Recent developments in metallic degradable micromotors for biomedical and environmental remediation applications. *Nano-Micro Lett*, 16:41.
https://doi.org/10.1007/s40820-023-01259-3

Elmorshedy YM, Teleb M, Sallam MA, et al., 2023. Engineered microencapsulated lactoferrin nanoconjugates for oral targeted treatment of colon cancer. *Biomacromolecules*, 24(5):2149-2163.
https://doi.org/10.1021/acs.biomac.3c00037

Estevinho BN, Rocha F, Santos L, et al., 2013. Microencapsulation with chitosan by spray drying for industry applications – a review. *Trends Food Sci Technol*, 31(2):138-155.
https://doi.org/10.1016/j.tifs.2013.04.001

Filippidi E, Patel AR, Bouwens ECM, et al., 2014. All-natural oil-filled microcapsules from water-insoluble proteins. *Adv Funct Mater*, 24(38):5962-5968.
https://doi.org/10.1002/adfm.201400359

Freitas S, Merkle HP, Gander B, 2005. Microencapsulation by solvent extraction/evaporation: reviewing the state of the art of microsphere preparation process technology. *J Controlled Release*, 102(2):313-332.
https://doi.org/10.1016/j.jconrel.2004.10.015

Fu YJ, Zhao X, Wang LY, et al., 2024. A gas therapy strategy for intestinal flora regulation and colitis treatment by nanogel-based multistage NO delivery microcapsules. *Adv Mater*, 36(19):2309972.
https://doi.org/10.1002/adma.202309972

Gan JJ, Sun LY, Chen GP, et al., 2022. Mesenchymal stem cell exosomes encapsulated oral microcapsules for acute colitis treatment. *Adv Healthc Mater*, 11(17):2201105.
https://doi.org/10.1002/adhm.202201105

Ghaffarian R, Pérez-Herrero E, Oh H, et al., 2016. Chitosan-alginate microcapsules provide gastric protection and intestinal release of ICAM-1-targeting nanocarriers, enabling GI targeting in vivo. *Adv Funct Mater*, 26(20):3382-3393.
https://doi.org/10.1002/adfm.201600084

Gharsallaoui A, Roudaut G, Chambin O, et al., 2007. Applications of spray-drying in microencapsulation of food ingredients: an overview. *Food Res Int*, 40(9):1107-1121.
https://doi.org/10.1016/j.foodres.2007.07.004

Gombotz WR, Wee SF, 2012. Protein release from alginate matrices. *Adv Drug Delivery Rev*, 64:194-205.
https://doi.org/10.1016/j.addr.2012.09.007

Hoffman A, 1998. Pharmacodynamic aspects of sustained release preparations. *Adv Drug Deliv Rev*, 33(3):185-199.
https://doi.org/10.1016/s0169-409x(98)00027-1

How YH, Lai KW, Pui LP, et al., 2022. Co-extrusion and extrusion microencapsulation: effect on microencapsulation efficiency, survivability through gastrointestinal digestion

and storage. *J Food Process Eng*, 45(3):e13985.
https://doi.org/10.1111/jfpe.13985

Hu BX, Wang YQ, Yu L, et al., 2025. Biomimetic wrinkled prebiotic microspheres with enhanced intestinal retention for hyperphosphatemia and vascular calcification. *Sci Adv*, 11(3):eads5286.
https://doi.org/10.1126/sciadv.ads5286

Hu YD, Wang Q, Wang JY, et al., 2012. Shape controllable microgel particles prepared by microfluidic combining external ionic crosslinking. *Biomicrofluidics*, 6(2):026502.
https://doi.org/10.1063/1.4720396

Hua SS, 2020. Advances in oral drug delivery for regional targeting in the gastrointestinal tract – influence of physiological, pathophysiological and pharmaceutical factors. *Front Pharmacol*, 11:524.
https://doi.org/10.3389/fphar.2020.00524

Huang D, Wang YM, Xu CL, et al., 2024. Colon-targeted hydroxyethyl starch-curcumin microspheres with high loading capacity ameliorate ulcerative colitis *via* alleviating oxidative stress, regulating inflammation, and modulating gut microbiota. *Int J Biol Macromol*, 266:131107.
https://doi.org/10.1016/j.ijbiomac.2024.131107

Huang HJ, Yuan WK, Chen XD, 2006. Microencapsulation based on emulsification for producing pharmaceutical products: a literature review. *Dev Chem Eng Mineral Process*, 14(3-4):515-544.
https://doi.org/10.1002/apj.5500140318

Iravani S, Varma RS, 2021. Plant pollen grains: a move towards green drug and vaccine delivery systems. *Nano-Micro Lett*, 13:128.
https://doi.org/10.1007/s40820-021-00654-y

Jiang JJ, Xiao JC, Zhao ZX, et al., 2021. One-step prepared nano-in-micro microcapsule delivery vehicle with sequential burst–sustained drug release for the targeted treatment of inflammatory bowel disease. *Mater Chem Front*, 5(16): 6027-6040.
https://doi.org/10.1039/d1qm00589h

Jiang JY, Ma C, Song XN, et al., 2022. Spray drying co-encapsulation of lactic acid bacteria and lipids: a review. *Trends Food Sci Technol*, 129:134-143.
https://doi.org/10.1016/j.tifs.2022.09.010

Jo YK, Lee D, 2020. Biopolymer microparticles prepared by microfluidics for biomedical applications. *Small*, 16(9): 1903736.
https://doi.org/10.1002/smll.201903736

Kim DW, Jeong HS, Kim E, et al., 2022. Oral delivery of stem-cell-loaded hydrogel microcapsules restores gut inflammation and microbiota. *J Controlled Release*, 347:508-520.
https://doi.org/10.1016/j.jconrel.2022.05.028

Lee KY, Mooney DJ, 2012. Alginate: properties and biomedical applications. *Prog Polym Sci*, 37(1):106-126.
https://doi.org/10.1016/j.progpolymsci.2011.06.003

Lee TY, Choi TM, Shim TS, et al., 2016. Microfluidic production of multiple emulsions and functional microcapsules. *Lab Chip*, 16(18):3415-3440.
https://doi.org/10.1039/c6lc00809g

Li B, Li X, Chu XD, et al., 2022. Micro-ecology restoration of colonic inflammation by in-situ oral delivery of antibody-laden hydrogel microcapsules. *Bioact Mater*, 15:305-315.
https://doi.org/10.1016/j.bioactmat.2021.12.022

Li JX, Thamphiwatana S, Liu WJ, et al., 2016. Enteric micromotor can selectively position and spontaneously propel in the gastrointestinal tract. *ACS Nano*, 10(10): 9536-9542.
https://doi.org/10.1021/acsnano.6b04795

Li M, Rouaud O, Poncelet D, 2008. Microencapsulation by solvent evaporation: state of the art for process engineering approaches. *Int J Pharm*, 363(1-2):26-39.
https://doi.org/10.1016/j.ijpharm.2008.07.018

Li W, Liu DF, Zhang HB, et al., 2017. Microfluidic assembly of a nano-in-micro dual drug delivery platform composed of halloysite nanotubes and a pH-responsive polymer for colon cancer therapy. *Acta Biomater*, 48:238-246.
https://doi.org/10.1016/j.actbio.2016.10.042

Li W, Zhang LY, Ge XH, et al., 2018. Microfluidic fabrication of microparticles for biomedical applications. *Chem Soc Rev*, 47(15):5646-5683.
https://doi.org/10.1039/c7cs00263g

Li YN, Yan D, Fu FF, et al., 2017. Composite core-shell microparticles from microfluidics for synergistic drug delivery. *Sci China Mater*, 60(6):543-553.
https://doi.org/10.1007/s40843-016-5151-6

Lin SC, Han SW, Wang X, et al., 2024. Oral microto-nano genome-editing system enabling targeted delivery and conditional activation of CRISPR-Cas9 for gene therapy of inflammatory bowel disease. *ACS Nano*, 18(37):25657-25670.
https://doi.org/10.1021/acsnano.4c07750

Lin YS, Yang CH, Hsu YY, et al., 2013. Microfluidic synthesis of tail-shaped alginate microparticles using slow sedimentation. *Electrophoresis*, 34(3):425-431.
https://doi.org/10.1002/elps.201200282

Ling K, Wu HX, Neish AS, et al., 2019. Alginate/chitosan microparticles for gastric passage and intestinal release of therapeutic protein nanoparticles. *J Controlled Release*, 295:174-186.
https://doi.org/10.1016/j.jconrel.2018.12.017

Liu DF, Zhang HB, Herranz-Blanco B, et al., 2014. Microfluidic assembly of monodisperse multistage pH-responsive polymer/porous silicon composites for precisely controlled multi-drug delivery. *Small*, 10(10):2029-2038.
https://doi.org/10.1002/smll.201303740

Liu H, Cai WZ, Wang F, et al., 2021. Colon-targeted adhesive hydrogel microsphere for regulation of gut immunity and flora. *Adv Sci*, 8(18):2101619.
https://doi.org/10.1002/advs.202101619

Lu IL, Yu TW, Liu TI, et al., 2022. Microfluidized dextran microgels loaded with cisplatin/SPION lipid nanotherapeutics for local colon cancer treatment via oral administration. *Adv Healthc Mater*, 11(20):2201140.
https://doi.org/10.1002/adhm.202201140

Ma GH, 2014. Microencapsulation of protein drugs for drug delivery: strategy, preparation, and applications. *J Controlled Release*, 193:324-340.
https://doi.org/10.1016/j.jconrel.2014.09.003

Ma YH, Li QH, Yang JR, et al., 2023. Crosslinked zwitterionic microcapsules to overcome gastrointestinal barriers for oral insulin delivery. *Biomater Sci*, 11(3):975-984.
https://doi.org/10.1039/d2bm01606k

Macedo MH, Dias Neto M, Pastrana L, et al., 2023. Recent advances in cell-based in vitro models to recreate human intestinal inflammation. *Adv Sci*, 10(31):2301391.
https://doi.org/10.1002/advs.202301391

Maher S, Mrsny RJ, Brayden DJ, 2016. Intestinal permeation enhancers for oral peptide delivery. *Adv Drug Deliv Rev*, 106:277-319.
https://doi.org/10.1016/j.addr.2016.06.005

Mandal S, Kumar SS, Krishnamoorthy B, et al., 2010. Development and evaluation of calcium alginate beads prepared by sequential and simultaneous methods. *Braz J Pharm Sci*, 46(4):785-793.
https://doi.org/10.1590/S1984-82502010000400021

Maric T, Atladóttir S, Thamdrup LHE, et al., 2022. Self-propelled janus micromotors for pH-responsive release of small molecule drug. *Appl Mater Today*, 27:101418.
https://doi.org/10.1016/j.apmt.2022.101418

Martínez-López AL, Carvajal-Millan E, Sotelo-Cruz N, et al., 2019. Enzymatically cross-linked arabinoxylan microspheres as oral insulin delivery system. *Int J Biol Macromol*, 126:952-959.
https://doi.org/10.1016/j.ijbiomac.2018.12.192

Mehta P, Haj-Ahmad R, Rasekh M, et al., 2017. Pharmaceutical and biomaterial engineering via electrohydrodynamic atomization technologies. *Drug Discov Today*, 22(1): 157-165.
https://doi.org/10.1016/j.drudis.2016.09.021

Meola TR, Elz A, Wignall A, et al., 2024. Inulin-lipid core–shell microcapsules target the gut microbiota and mimic the pharmaceutical food effect for improved oral antipsychotic delivery. *Adv Funct Mater*, 34(40):2403914.
https://doi.org/10.1002/adfm.202403914

Mundaca-Uribe R, Holay M, Abbas A, et al., 2023. A microstirring oral pill for improving the glucose-lowering effect of metformin. *ACS Nano*, 17(10):9272-9279.
https://doi.org/10.1021/acsnano.3c00581

Mundaca-Uribe R, Askarinam N, Fang RH, et al., 2024. Towards multifunctional robotic pills. *Nat Biomed Eng*, 8(11): 1334-1346.
https://doi.org/10.1038/s41551-023-01090-6

Nabavi SA, Vladisavljević GT, Bandulasena MV, et al., 2017. Prediction and control of drop formation modes in microfluidic generation of double emulsions by single-step emulsification. *J Colloid Interface Sci*, 505:315-324.
https://doi.org/10.1016/j.jcis.2017.05.115

Negrulj R, Mooranian A, Chen-Tan N, et al., 2016. Swelling, mechanical strength, and release properties of probucol microcapsules with and without a bile acid, and their potential oral delivery in diabetes. *Artif Cells Nanomed Biotechnol*, 44(5):1290-1297.
https://doi.org/10.3109/21691401.2015.1024845

Niles AL, Moravec RA, Riss TL, 2008. Update on *in vitro* cytotoxicity assays for drug development. *Expert Opin Drug Discov*, 3(6):655-669.
https://doi.org/10.1517/17460441.3.6.655

Nisisako T, Torii T, 2008. Microfluidic large-scale integration on a chip for mass production of monodisperse droplets and particles. *Lab Chip*, 8(2):287-293.
https://doi.org/10.1039/b713141k

Ouyang J, Zhang ZY, Deng B, et al., 2023a. Oral drug delivery platforms for biomedical applications. *Mater Today*, 62: 296-326.
https://doi.org/10.1016/j.mattod.2023.01.002

Ouyang J, Deng B, Zou BH, et al., 2023b. Oral hydrogel microbeads-mediated in situ synthesis of selenoproteins for regulating intestinal immunity and microbiota. *J Am Chem Soc*, 145(22):12193-12205.
https://doi.org/10.1021/jacs.3c02179

Ozkan G, Franco P, de Marco I, et al., 2019. A review of microencapsulation methods for food antioxidants: principles, advantages, drawbacks and applications. *Food Chem*, 272: 494-506.
https://doi.org/10.1016/j.foodchem.2018.07.205

Paarakh MP, Jose PA, Setty CM, et al., 2018. Release kinetics–concepts and applications. *Int J Pharm Res Technol*, 8(1): 12-20.

Pawar SN, Edgar KJ, 2012. Alginate derivatization: a review of chemistry, properties and applications. *Biomaterials*, 33(11):3279-3305.
https://doi.org/10.1016/j.biomaterials.2012.01.007

Pinto JF, 2010. Site-specific drug delivery systems within the gastro-intestinal tract: from the mouth to the colon. *Int J Pharm*, 395(1-2):44-52.
https://doi.org/10.1016/j.ijpharm.2010.05.003

Qayyum AS, Jain E, Kolar G, et al., 2017. Design of electrohydrodynamic sprayed polyethylene glycol hydrogel microspheres for cell encapsulation. *Biofabrication*, 9(2):025019.
https://doi.org/10.1088/1758-5090/aa703c

Qiao DL, Hu WT, Wang Z, et al., 2024. Food structuring using microfluidics: updated progress in fundamental principles and structure types. *J Food Eng*, 360:111703.
https://doi.org/10.1016/j.jfoodeng.2023.111703

Regmi S, Pathak S, Nepal MR, et al., 2019. Inflammation-triggered local drug release ameliorates colitis by inhibiting dendritic cell migration and Th1/Th17 differentiation. *J Controlled Release*, 316:138-149.
https://doi.org/10.1016/j.jconrel.2019.11.001

Ren A, Hu JR, Qin CW, et al., 2024. Oral administration microrobots for drug delivery. *Bioact Mater*, 39:163-190.
https://doi.org/10.1016/j.bioactmat.2024.05.005

Ren CJ, Zhong DN, Qi YC, et al., 2023. Bioinspired pH-responsive microalgal hydrogels for oral insulin delivery with both hypoglycemic and insulin sensitizing effects. *ACS Nano*, 17(14):14161-14175.
https://doi.org/10.1021/acsnano.3c04897

Rezvantalab S, Keshavarz Moraveji M, 2019. Microfluidic assisted synthesis of PLGA drug delivery systems. *RSC Adv*, 9(4):2055-2072.
https://doi.org/10.1039/c8ra08972h

Romanowsky MB, Abate AR, Rotem A, et al., 2012. High throughput production of single core double emulsions in a parallelized microfluidic device. *Lab Chip*, 12(4):

802-807.
https://doi.org/10.1039/c2lc21033a

Roque-Borda CA, de Mesquita Souza Saraiva M, Macedo Junior WD, et al., 2023. Chitosan and HPMCAS double-coating as protective systems for alginate microparticles loaded with Ctx(Ile[21])-Ha antimicrobial peptide to prevent intestinal infections. *Biomaterials*, 293:121978.
https://doi.org/10.1016/j.biomaterials.2022.121978

Rosca ID, Watari F, Uo M, 2004. Microparticle formation and its mechanism in single and double emulsion solvent evaporation. *J Controlled Release*, 99(2):271-280.
https://doi.org/10.1016/j.jconrel.2004.07.007

Sabu C, Raghav D, Jijith US, et al., 2019. Bioinspired oral insulin delivery system using yeast microcapsules. *Mater Sci Eng C*, 103:109753.
https://doi.org/10.1016/j.msec.2019.109753

Samandari M, Alipanah F, Haghjooy Javanmard S, et al., 2019. One-step wettability patterning of PDMS microchannels for generation of monodisperse alginate microbeads by in situ external gelation in double emulsion microdroplets. *Sens Actuators B Chem*, 291:418-425.
https://doi.org/10.1016/j.snb.2019.04.100

Sarabandi K, Sadeghi Mahoonak A, Hamishekar H, et al., 2018. Microencapsulation of casein hydrolysates: physicochemical, antioxidant and microstructure properties. *J Food Eng*, 237:86-95.
https://doi.org/10.1016/j.jfoodeng.2018.05.036

Sastri KT, Radha GV, Pidikiti S, et al., 2020. Solid lipid nanoparticles: preparation techniques, their characterization, and an update on recent studies. *J Appl Pharm Sci*, 10(6):126-141.
https://doi.org/10.7324/JAPS.2020.10617

Sato K, Yoshida K, Takahashi S, et al., 2011. pH- and sugar-sensitive layer-by-layer films and microcapsules for drug delivery. *Adv Drug Deliv Rev*, 63(9):809-821.
https://doi.org/10.1016/j.addr.2011.03.015

Sawalha H, Schroën K, Boom R, 2011. Biodegradable polymeric microcapsules: preparation and properties. *Chem Eng J*, 169(1-3):1-10.
https://doi.org/10.1016/j.cej.2011.02.078

Seol Y, Ganguly K, Kim H, et al., 2024. Stimuli-triggered pollen-inspired micro/nanorobots for advanced therapeutics. *Nano Today*, 57:102337.
https://doi.org/10.1016/j.nantod.2024.102337

Shin YC, Shin W, Koh D, et al., 2020. Three-dimensional regeneration of patient-derived intestinal organoid epithelium in a physiodynamic mucosal interface-on-a-chip. *Micromachines*, 11(7):663.
https://doi.org/10.3390/mi11070663

Siepmann J, Peppas NA, 2012. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Delivery Rev*, 64:163-174.
https://doi.org/10.1016/j.addr.2012.09.028

Smidsrød O, Skjåk-Braek G, 1990. Alginate as immobilization matrix for cells. *Trends Biotechnol*, 8:71-78.
https://doi.org/10.1016/0167-7799(90)90139-o

Song HY, Yu WT, Gao M, et al., 2013. Microencapsulated probiotics using emulsification technique coupled with internal or external gelation process. *Carbohydr Polym*, 96(1):181-189.
https://doi.org/10.1016/j.carbpol.2013.03.068

Song XC, Yu YL, Yang GY, et al., 2022. One-step emulsification for controllable preparation of ethyl cellulose microcapsules and their sustained release performance. *Colloids Surf B Biointerfaces*, 216:112560.
https://doi.org/10.1016/j.colsurfb.2022.112560

Su Y, Zhang BL, Sun RW, et al., 2021. PLGA-based biodegradable microspheres in drug delivery: recent advances in research and application. *Drug Deliv*, 28(1):1397-1418.
https://doi.org/10.1080/10717544.2021.1938756

Sun J, Xu ZS, Hou Y, et al., 2022. Hierarchically structured microcapsules for oral delivery of emodin and tanshinone IIA to treat renal fibrosis. *Int J Pharm*, 616:121490.
https://doi.org/10.1016/j.ijpharm.2022.121490

Sun SP, Liang N, Gong XF, et al., 2017. Multifunctional composite microcapsules for oral delivery of insulin. *Int J Mol Sci*, 18(1):54.
https://doi.org/10.3390/ijms18010054

Tan LL, Mahotra M, Chan SY, et al., 2022. In situ alginate crosslinking during spray-drying of lactobacilli probiotics promotes gastrointestinal-targeted delivery. *Carbohydr Polym*, 286:119279.
https://doi.org/10.1016/j.carbpol.2022.119279

Tan WH, Takeuchi S, 2007. Monodisperse alginate hydrogel microbeads for cell encapsulation. *Adv Mater*, 19(18):2696-2701.
https://doi.org/10.1002/adma.200700433

Tang GS, Xiong RH, Lv D, et al., 2019. Gas-shearing fabrication of multicompartmental microspheres: a one-step and oil-free approach. *Adv Sci*, 6(9):1802342.
https://doi.org/10.1002/advs.201802342

Trucillo P, 2022. Drug carriers: a review on the most used mathematical models for drug release. *Processes*, 10(6):1094.
https://doi.org/10.3390/pr10061094

Twarog C, Fattah S, Heade J, et al., 2019. Intestinal permeation enhancers for oral delivery of macromolecules: a comparison between salcaprozate sodium (SNAC) and sodium caprate ($C_{10}$). *Pharmaceutics*, 11(2):78.
https://doi.org/10.3390/pharmaceutics11020078

Utada AS, Lorenceau E, Link DR, et al., 2005. Monodisperse double emulsions generated from a microcapillary device. *Science*, 308(5721):537-541.
https://doi.org/10.1126/science.1109164

Utada AS, Chu LY, Fernandez-Nieves A, et al., 2007. Dripping, jetting, drops, and wetting: the magic of microfluidics. *MRS Bull*, 32(9):702-708.
https://doi.org/10.1557/mrs2007.145

Utech S, Prodanovic R, Mao AS, et al., 2015. Microfluidic generation of monodisperse, structurally homogeneous alginate microgels for cell encapsulation and 3D cell culture. *Adv Healthc Mater*, 4(11):1628-1633.
https://doi.org/10.1002/adhm.201500021

Uyen NTT, Hamid ZAA, Tram NXT, et al., 2020. Fabrication of alginate microspheres for drug delivery: a review. *Int J Biol Macromol*, 153:1035-1046.
https://doi.org/10.1016/j.ijbiomac.2019.10.233

Wang KY, Ni JL, Li HL, et al., 2022. Survivability of probiotics encapsulated in kelp nanocellulose/alginate microcapsules on microfluidic device. *Food Res Int*, 160:111723. https://doi.org/10.1016/j.foodres.2022.111723

Wang R, Guo K, Zhang WJ, et al., 2022. Poly-γ-glutamic acid microgel-encapsulated probiotics with gastric acid resistance and smart inflammatory factor targeted delivery performance to ameliorate colitis. *Adv Funct Mater*, 32(26): 2113034. https://doi.org/10.1002/adfm.202113034

Wang W, Zhang MJ, Chu LY, 2014. Functional polymeric microparticles engineered from controllable microfluidic emulsions. *Acc Chem Res*, 47(2):373-384. https://doi.org/10.1021/ar4001263

Wang X, Zhu MM, Wang KY, et al., 2022. Preparation of core-shell microcapsules based on microfluidic technology for the encapsulation, protection and controlled delivery of phycocyanin. *J Drug Delivery Sci Technol*, 72:103361. https://doi.org/10.1016/j.jddst.2022.103361

Wang XY, Qiu HY, Chu CN, et al., 2024. Dual-responsive microsphere based on natural sunflower pollen for hemostasis and repair in inflammatory bowel disease. *ACS Appl Mater Interfaces*, 16(24):30658-30670. https://doi.org/10.1021/acsami.4c02408

Wei XL, Beltrán-Gastélum M, Karshalev E, et al., 2019. Biomimetic micromotor enables active delivery of antigens for oral vaccination. *Nano Lett*, 19(3):1914-1921. https://doi.org/10.1021/acs.nanolett.8b05051

Weyermann J, Lochmann D, Zimmer A, 2005. A practical note on the use of cytotoxicity assays. *Int J Pharm*, 288(2):369-376. https://doi.org/10.1016/j.ijpharm.2004.09.018

Wu ZG, Li L, Yang YR, et al., 2019. A microrobotic system guided by photoacoustic computed tomography for targeted navigation in intestines in vivo. *Sci Robot*, 4(32): eaax0613. https://doi.org/10.1126/scirobotics.aax0613

Xu QB, Hashimoto M, Dang TT, et al., 2009. Preparation of monodisperse biodegradable polymer microparticles using a microfluidic flow-focusing device for controlled drug delivery. *Small*, 5(13):1575-1581. https://doi.org/10.1002/smll.200801855

Xu QJ, Zhao Y, Yuan PP, et al., 2025. Functionalized microsphere platform combining nutrient restriction and combination therapy to combat bacterial infections. *ACS Appl Mater Interfaces*, 17(2):2966-2976. https://doi.org/10.1021/acsami.4c16610

Xu XM, Cheung S, Jia XM, et al., 2024. Trends in organ-on-a-chip for pharmacological analysis. *TrAC Trends Anal Chem*, 180:117905. https://doi.org/10.1016/j.trac.2024.117905

Xu YN, Shrestha N, Préat V, et al., 2020. Overcoming the intestinal barrier: a look into targeting approaches for improved oral drug delivery systems. *J Controlled Release*, 322:486-508. https://doi.org/10.1016/j.jconrel.2020.04.006

Xu YY, Dong MS, Xiao HM, et al., 2024. Advances in spray-dried probiotic microcapsules for targeted delivery: a review. *Crit Rev Food Sci Nutr*, 64(30):11222-11238. https://doi.org/10.1080/10408398.2023.2235424

Xuan LY, Hou YY, Liang L, et al., 2024. Microgels for cell delivery in tissue engineering and regenerative medicine. *Nano-Micro Lett*, 16:218. https://doi.org/10.1007/s40820-024-01421-5

Yang D, Gao KY, Bai Y, et al., 2021. Microfluidic synthesis of chitosan-coated magnetic alginate microparticles for controlled and sustained drug delivery. *Int J Biol Macromol*, 182:639-647. https://doi.org/10.1016/j.ijbiomac.2021.04.057

Yang K, Han HS, An SH, et al., 2024. Mucoadhesive chitosan microcapsules for controlled gastrointestinal delivery and oral bioavailability enhancement of low molecular weight peptides. *J Controlled Release*, 365:422-434. https://doi.org/10.1016/j.jconrel.2023.10.021

Yang KL, Wang XC, Huang RK, et al., 2022. Prebiotics and postbiotics synergistic delivery microcapsules from microfluidics for treating colitis. *Adv Sci*, 9(16):2104089. https://doi.org/10.1002/advs.202104089

Yang XY, Nie WM, Wang C, et al., 2024. Microfluidic-based multifunctional microspheres for enhanced oral co-delivery of probiotics and postbiotics. *Biomaterials*, 308:122564. https://doi.org/10.1016/j.biomaterials.2024.122564

Yao MF, Xie JJ, Du HJ, et al., 2020. Progress in microencapsulation of probiotics: a review. *Comp Rev Food Sci Food Safe*, 19(2):857-874. https://doi.org/10.1111/1541-4337.12532

Zhang DX, Zhong DN, Ouyang J, et al., 2022. Microalgae-based oral microcarriers for gut microbiota homeostasis and intestinal protection in cancer radiotherapy. *Nat Commun*, 13:1413. https://doi.org/10.1038/s41467-022-28744-4

Zhang DX, He J, Cui JR, et al., 2023. Oral microalgae-nano integrated system against radiation-induced injury. *ACS Nano*, 17(11):10560-10576. https://doi.org/10.1021/acsnano.3c01502

Zhang FK, Du YW, Zheng JC, et al., 2023. Oral administration of multistage albumin nanomedicine depots (MANDs) for targeted efficient alleviation of chronic inflammatory diseases. *Adv Funct Mater*, 33(9):2211644. https://doi.org/10.1002/adfm.202211644

Zhang FY, Li ZX, Chen CR, et al., 2024. Biohybrid microalgae robots: design, fabrication, materials, and applications. *Adv Mater*, 36(3):2303714. https://doi.org/10.1002/adma.202303714

Zhang HB, Liu DF, Shahbazi MA, et al., 2014. Fabrication of a multifunctional nano-in-micro drug delivery platform by microfluidic templated encapsulation of porous silicon in polymer matrix. *Adv Mater*, 26(26):4497-4503. https://doi.org/10.1002/adma.201400953

Zhang XL, Qu QL, Zhou AY, et al., 2022. Core-shell microparticles: from rational engineering to diverse applications. *Adv Colloid Interface Sci*, 299:102568. https://doi.org/10.1016/j.cis.2021.102568

Zhao C, Chen GP, Wang H, et al., 2021. Bio-inspired intestinal scavenger from microfluidic electrospray for detoxifying lipopolysaccharide. *Bioact Mater*, 6(6):1653-1662. https://doi.org/10.1016/j.bioactmat.2020.11.017

Zhao CX, 2013. Multiphase flow microfluidics for the production of single or multiple emulsions for drug delivery. *Adv Drug Deliv Rev*, 65(11-12):1420-1446.
https://doi.org/10.1016/j.addr.2013.05.009

Zhao D, Li ZB, Xia JY, et al., 2023. Research progress of starch as microencapsulated wall material. *Carbohydr Polym*, 318:121118.
https://doi.org/10.1016/j.carbpol.2023.121118

Zhao QL, Cui HQ, Wang YL, et al., 2020. Microfluidic platforms toward rational material fabrication for biomedical applications. *Small*, 16(9):1903798.
https://doi.org/10.1002/smll.201903798

Zhong DN, Zhang DX, Chen W, et al., 2021. Orally deliverable strategy based on microalgal biomass for intestinal disease treatment. *Sci Adv*, 7(48):eabi9265.
https://doi.org/10.1126/sciadv.abi9265

Zhu YL, Wang YW, Xia GG, et al., 2023. Oral delivery of bioactive glass-loaded core-shell hydrogel microspheres for effective treatment of inflammatory bowel disease. *Adv Sci*, 10(18):2207418.
https://doi.org/10.1002/advs.202207418

**Supplementary information**

Sections S1–S6; Tables S1 and S2; Figs. S1–S5