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Designing hydrogel particles for controlled or targeted release of lipophilic bioactive agents in the gastrointestinal tract

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ABSTRACT

Numerous lipophilic bioactive agents within the food and pharmaceutical industries need to be encapsulated within delivery systems to overcome problems associated with poor water-solubility, chemical instability, and/or low oral bioavailability. Hydrogel particles are finding increasing utilization for encapsulation, protection, and controlled release of lipophilic bioactives. These particles can often be fabricated from food-grade biopolymers (such as proteins and polysaccharides) using simple processing operations (such as complexation, antisolvent precipitation, homogenization, injection, shearing, and thermal processing). In this article, we review recent developments in the design and fabrication of food-grade hydrogel particles suitable for oral ingestion. In particular, we focus on the application of hydrogel particles for controlled or targeted release of lipophilic bioactive agents in the gastrointestinal tract including the mouth, stomach, small intestine, and colon.

1. Introduction

Many pharmaceuticals, nutraceuticals, and vitamins are highly lipophilic molecules that must be encapsulated within delivery systems to overcome physicochemical or physiological challenges that normally limit their efficacy, such as poor water solubility, chemical or biochemical instability, and low or variable oral bioavailability [1]. Numerous types of delivery systems have been designed to control the retention, stability, and release of bioactive components within the gastrointestinal tract (GIT) [2]. In particular, there has been a strong emphasis on developing delivery systems that can target or control the release of bioactives at specific locations within the GIT (such as mouth, stomach, small intestine, or colon) because this may improve their efficacy, as well as reduce any undesirable side effects. Emulsion-based delivery systems are one of the most suitable candidates for encapsulation and delivery of lipophilic bioactives because they are relatively simple and inexpensive to fabricate [3]. This category of delivery system includes nanoemulsions, emulsions, solid lipid nanoparticles, multiple emulsions, and filled hydrogel particles.

Filled hydrogel particles are one kind of emulsion-based delivery system that offers considerable scope for tailored functionality. Hydrogel particles contain biopolymer networks with a three-dimensional structure that is capable of trapping relatively large quantities of water [4]. A filled hydrogel particle typically contains oil droplets trapped within the biopolymer network [5]. Typically, lipophilic bioactives are first dissolved in an oil phase, and then an oil-in-water emulsion is formed by homogenizing this oil phase with an aqueous phase containing a suitable emulsifier. The resulting oil droplets are then trapped within the

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hydrogel particles during the preparation procedure. The ability to tune the composition, dimensions, shape, and internal structure of hydrogel particles has led to widespread interest in their utilization as delivery systems in the food, pharmaceutical, and personal care industries. A number of lipophilic bioactive components that have previously been encapsulated and delivered using hydrogel particles are summarized in Table 1 and shown schematically in Fig. 1.

There is already a huge body of knowledge on the design and fabrication of hydrogel particles reported in the literature, and it is not possible to cover all of this material in a single review article. Instead, we highlight current work related to the formation and design of food-grade hydrogel particles that can encapsulate lipophilic bioactive agents suitable for use in the food industry, such as oil-soluble vitamins and nutraceuticals. In particular, we focus on the application of hydrogel particles for controlled or targeted release of lipophilic bioactive agents in the GIT.

It is useful to start by highlighting some of the potential advantages of using filled hydrogel particles over other types of emulsion-based delivery systems for lipophilic bioactives:

- Hydrogel particles may be designed to protect a bioactive component from chemical degradation during storage of a food product. For example, the oxidation of polyunsaturated lipids may be retarded by using antioxidant biopolymers, such as proteins, to form the hydrogel matrix surrounding the bioactives [6,7].
- Hydrogel particles may be designed to protect bioactive components from metabolism or digestion during passage through specific regions of the GIT. For example, the digestion of triglycerides within the stomach and small intestine can be retarded by encapsulating them within hydrogel particles that remain impermeable and intact under these conditions, such as calcium alginate [8,9].
- Hydrogel particles may be designed to control the location of release of an encapsulated bioactive component within the GIT. For example, they may be designed to breakdown and release their cargo within the mouth, stomach, small intestine, or colon by careful selection of the biopolymer building blocks and the forces holding them together [10–12].
- Hydrogel particles may be designed to control the kinetics of the release of encapsulated bioactive components within the GIT. For example, they may be

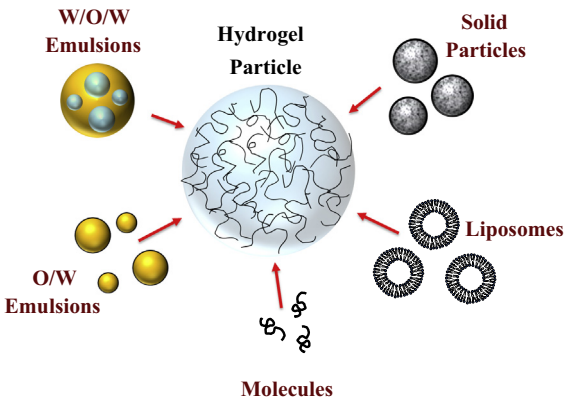

Fig. 1. A variety of bioactive molecules or particles can be trapped inside filled hydrogel particles to alter their physicochemical properties and delivery.

Table 1
Examples of lipophilic bioactive components that might need to be encapsulated, and some of the health claims and limitations made for them.

Name	Bioactive	Claimed function	Potential limitations	Potential delivery site	References
Fatty acids	$\omega-3$ fatty acids	Anti-inflammatory, anti-cancer, antioxidation	Strong odor, oxidant instable, water insoluble	Intestinal, colon	[7,14,15]
	Flavor oil	Flavor agent in food products	Volatile aroma prone to degradation or loss, water insoluble	Mouth	[16–18]
Polyphenols	Curcumin	Antioxidation, anti-inflammatory, anti-cancer	Chemical instability, water insoluble, low bioavailability	Intestinal, colon	[19–21]
	Resveratrol	Anti-carcinogenic, anti-inflammatory, anti-obesity	Chemical instability, water insoluble, low bioavailability	Intestinal, colon	[22,23]
Phytosterol	Stigmasterol	Anti-inflammatory, anti-cancer, antioxidation	Chemical instability, water insoluble, low bioavailability	Intestinal, colon	[24,25]
Drug	Lipophilic drugs	Therapeutical effect	Chemical instability, water insoluble, hardly to get targeted site	Stomach, intestinal, colon	[26–28]
Vitamins	α-tocopherol	Anti-atherogenic, anti-diabetic antioxidation, anti-cancer	Chemical instability, water insoluble, low bioavailability	Intestinal, colon	[29,30]
Carotenoids	β-carotene	Anti-cancer and antioxidation	Chemical instability, crystalline state exist, high melting point, water insoluble, low bioavailability	Intestinal, colon	[30,31]
	Lycopene	Anti-cancer, anti-inflammatory, antioxidation	Susceptible to oxidation and isomerization, water insoluble, low bioavailability	Intestinal, colon	[32,33]
	Lutein	Antioxidation, anti-atherogenic, anti-inflammatory	Chemical instability, water insoluble, low bioavailability	Intestinal, colon	[34,35]