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Food-grade microgel capsules tailored for anti-obesity strategies through microfluidic preparation

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Microfluidics have been extensively used to investigate bubbles and droplets, and make uniform emulsions and foams; the benefit being that very monodisperse products are more stable. Besides, when used for encapsulate production, their size codetermines the payload, and allows accurate dosing of the component of interest. In this review, we specifically highlight the perspective of microfluidic production of microgel capsules for anti-obesity strategies that activate the intestinal brakes via controlled delivery of nutrients to the small intestine. We show various microgel capsule structures, their release characteristics, and discuss first results in human trials. We wrap up with recent progress made in up-scaling, which in our view is the key to bring the technology toward application in the food field.

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Introduction

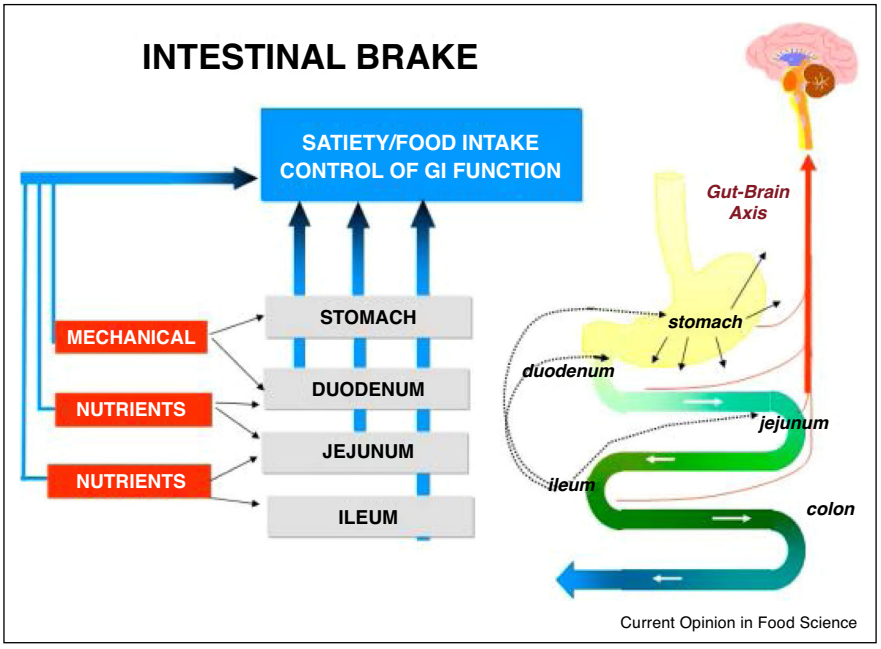
In a very recent review [1••], the ways for activating various intestinal brake mechanisms to reduce appetite have been summarized (see Figure 1). In the stomach pressure sensors are present that prevent people from overeating, and that also plays a role in the duodenum. But from the duodenum onward, digestion of nutrients starts playing a prominent role in controlling appetite. Nutrient sensing in the intestinal lumen leads to complex feed-back mechanisms that affect food intake. This natural brake on food intake is a promising target for a non-invasive anti-obesity strategy if it is activated by nutrients from ingested foods.

In the review of Wilbrink [1••] it is clearly pointed out that all macronutrients cause these effects, and the effect size is similar when administered in equicaloric amounts. This review addresses intubation, but if these effects were to be created by foods that pass through the gastro-intestinal tract, these components need to be protected against the early stages of our efficient digestive system. Although it is often suggested that reinforcement of, for example, the interface that covers an emulsion droplet can influence digestion, in practice that is often not a feasible strategy. In general the conditions in our gastro-intestinal system are thus harsh that, for example, the interface structure of emulsions can be readily replaced by bile salts, leading to proximal digestion and absorption [2,3]. Digestible structures (such as protein and starch that can be degraded by the enzymes in the human digestive tract) would mostly be digested by erosion, so be eten away from the outside [4,5••]. Depending on the chemical stability of the component of interest, this may even lead to loss of bio-activity [6••]. In general, it can be concluded that small food structures would be digested and absorbed relatively fast, unless properly protected. One of the options to do so is through the use of a gel-structure that reduces access of digestive components to components of interest [7••].

To have control over the release pattern of a component, the size of a food structure is an important parameter. Microfluidics are the ultimate tool to have precise control over the size and make these structures at such a size that they can be incorporated easily in a food without causing sensory effects that may make the food products less acceptable. More specifically, we will consider microgel-capsules made of protein or polysaccharide that may also contain small oil droplets. These capsules may erode during the digestion process, or remain intact with only the oil being digested or show combined behaviour. We focus on those examples that we consider relevant for delivery of components beyond the stomach, and ideally in the distal small intestine where feedback loops are most effective.

In the current paper we specifically focus on the perspective of using microfluidics for the preparation of highly defined encapsulates that we expect can be used in anti-obesity strategies. We will highlight the differences with the much better understood droplet/bubble systems, also in the light of the required properties of the microfluidic devices. We will wrap-up with the newest developments in upscaling of micro/milli-fluidic devices for the production of encapsulates and give an outlook on applications that are within reach.

Figure 1



Overview of various intestinal brakes as they may occur in humans. Figure is published open access in Nutrients, and taken from Ref. [1••].

Microfluidic techniques

Microfluidic (and milli) fluidic devices consist of specifically designed channels that can serve a broad range of purposes, such as controlled flow of liquids in multi-phase systems (emulsions, foams), controlled supply of chemicals (reaction systems), or even separation of components, for example, based on their size, and so on [8,9]. For recent reviews please consult Zhu and Wang [10]; Liu *et al.* [11]; Shang *et al.* [12]; Venkatesan *et al.* [13] and Sohrabi *et al.* [14]. These devices have been applied in a number of fields such as chemical engineering, and medicine/pharma, but their use in the field of food is still rather limited due to their relatively low throughput compared to what would be required in food production (see upscaling section) and their price. One of us (KS) has recently contributed to a review on applications of droplet microfluidics for food and nutrition applications [7••], in which the interested reader will find an extensive overview of how droplets can be made using various devices, a number of examples of gel structures that have been successfully produced, and also the use of microfluidics for digestion studies.

Emulsions and foams, benefit from a uniform distribution, which makes these products inherently more stable in terms of Ostwald ripening (especially for foams), creaming, sedimentation and so on. Encapsulates could on top of that benefit from the fact that the payload of the 'active' component is extremely well defined, which allows very precise dosing, and maybe even more importantly, prevents overdosing. This may sound very medical, but also for (functional) foods, delivering exact amounts of components at specific positions in the gastrointestinal tract is of great importance (e.g. Ref. [6••]). Although often claimed, it is not often proven that this is indeed happening. Besides, it is good to mention that microfluidic tools have also been used as analysis tool of real-time digestion and bio-accessibility [15,16], which is an interesting way to investigate effectiveness early on in product development.

Microgel capsules made with microfluidics

Production of microgel capsules on chip would start from dispersing one phase into another to make microgel capsules of protein [17] or polysaccharide of which mechanical strength and shape can be adjusted [18,19]; see also Figure 2 left section. Besides, microgel capsules may also contain oil droplets [22,20]. The phases used may be all aqueous [23,24], but mostly consist of oil and water phases as reviewed in Refs. [25,26], also for medical applications. We have summarized recent developments in Table SI (In Supplementary material) that contains examples of microgels made with protein, polysaccharides, and in very limited cases also contain oil. A broad range of systems that can be considered can be found in this table, though often for application in the medical field and not food grade yet. To increase the resistance against digestive components, the encapsulates are solidified (gelled) on chip, or in a later stage [27], see also Table S1 (In Supplementary material).

Figure 2

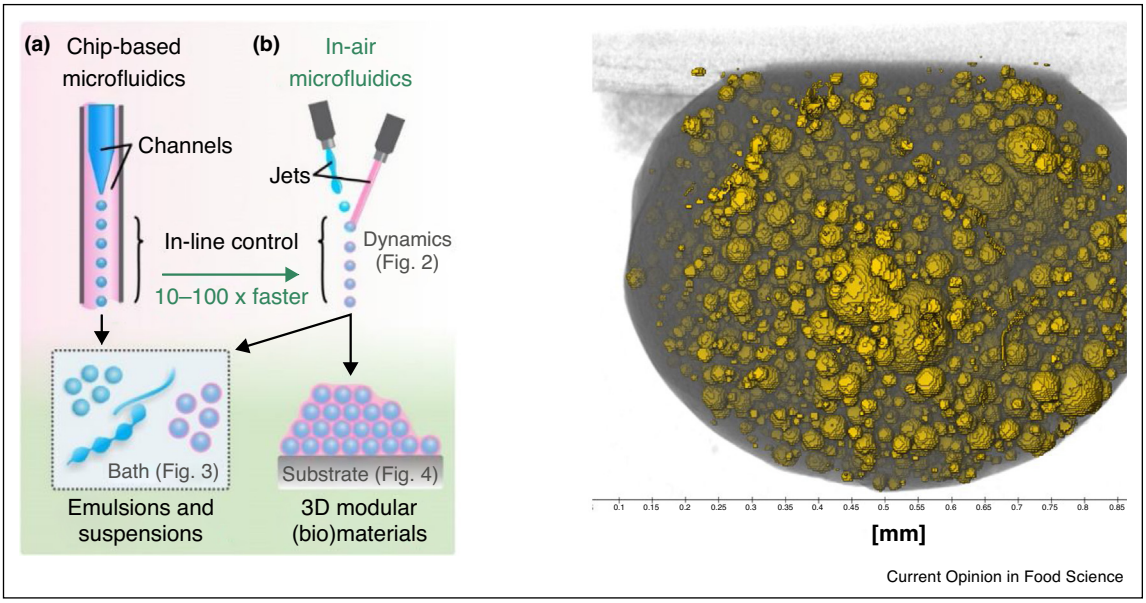


Illustration of **(a)** classic emulsion preparation with a microfluidic device followed by solidification in a bath, **(b)** in-air microfluidics in which both steps are combined [40••]. **(c)** Alginate microgel capsules with multiple oil droplets prepared with a gas-assisted nozzle [41].

Table 1

Dimensionless parameters used for the description of microfluidic droplet generation

Symbol	Name	Definition	Physical meaning
Re	Reynolds number	$\mathrm{Re} = \frac{\rho \cdot u \cdot L}{\eta}$	Inertial force/viscous force
Ca	Capillary number	$\mathrm{Ca} = \frac{\eta \cdot u}{\gamma}$	Viscous force/interfacial tension
We	Weber number	$\mathrm{Ca} = \frac{\eta \cdot u}{\gamma}$	Inertial force/interfacial tension
Bo	Bond number	$\mathrm{Bo} = \frac{\Delta\rho \cdot g \cdot L^2}{\gamma}$	Buoyancy force/interfacial tension
λ	Viscosity ratio	$\lambda = \frac{\eta_d}{\eta_d}$	Dispersed phase viscosity/continuous phase viscosity
φ	Flow rate ratio	$\varphi = \frac{Q_d}{Q_c}$	Dispersed phase flow rate/continuous phase flow rate

Symbols are: ρ density, u velocity, L typical dimension of the systems, viscosity η, interfacial tension γ, and density difference between the phases $\Delta\rho$, g the gravity constant, Q flow rate, and subscripts d and c referring to the dispersed and continuous phase, respectively.

Microgels made with microfluidic systems are well defined in terms of size. From Table S1 (In Supplementary material) it follows that protein microgels can be fabricated by acidification, thermal treatment and self-assemble property while polysaccharide microgels mostly rely on crosslinking between ions and polysaccharide, like Ca^{2+} and negative charged alginate (see also Figure 2). Microfluidic microgels have been produced from materials that are digestible (proteins) and undigestible (polysaccharides), see also last section on expected digestion effects. During fabrication using microfluidic devices, precipitation from protein and polysaccharides can occur. To avoid this and obtain uniform microgel, ultrasonic sound, filtration and other pre-treatments have been applied successfully.

Scaling relations used to describe droplet/bubble formation in microfluidics

The formation of droplets and bubbles in microfluidics is also the basis for preparation of microgel capsules, since underlying principles are expected to be the same, and scale in a similar way based on, for example, a force or torque balance. The typical dimensionless numbers used for droplets and bubbles are summarized in Table 1 [10]. These dimensionless numbers either revolve around interfacial, inertial, viscous, or buoyancy forces that are compared through a dimensionless number (Re, Ca, We, Bo), or the ratio of viscosity or flow rate of the two fluid phases used.

There are a number of general recent reviews that we mentioned before; for the food field, there are reviews on

the use of shear-based [28] and spontaneous systems [29], and upscaling of microfluidics systems [30]. It is good to point out that although interfacial tension is used in these equations, it is actually very difficult to measure it at the high interfacial expansion rates that occur in microfluidic devices. Mostly, dynamic interfacial tension effects take place, and since this influences the size of the encapsulates / droplets this would also be a point of attention [31].

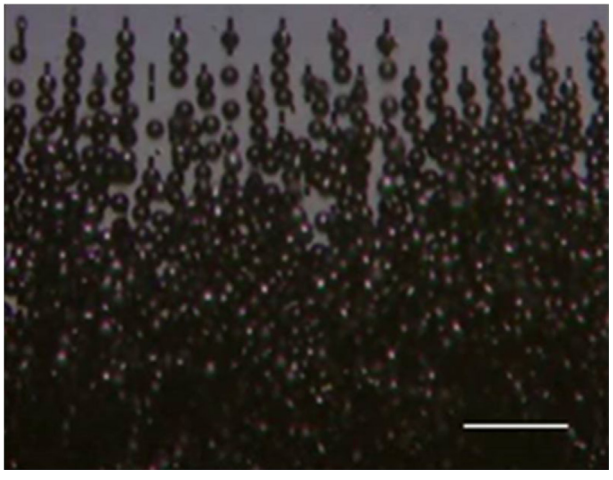
Upscaling microfluidic systems for microgel production: key steps to take

Although many microfluidic tools have been presented in literature, not that many can be used to make considerable amounts of product. For this a number of aspects need to be considered: wettability of the device, parallelisation of droplet formation units to increase productivity, and the design of the droplet formation unit to thus have control on the droplet size (as described in the previous section) (Figure 3).

Wettability of the microfluidic systems needs to be guarded very carefully, which can be done through surface modification to prevent adsorption of surface active components, or in some case by an in-situ layer formed that warrants appropriate wettability (as demonstrated for proteins in combination with so-called EDGE emulsification devices) [32,33].

Ideally, the microgel capsules are in the micrometre range in order to prevent undesired sensory side-effects. This implies that the productivity of the individual microfluidic channels will be low, and that many would need to operate in parallel to increase overall productivity. Some examples in the field of emulsification have been described in literature, such as microchannel emulsification (group of Nakajima and Kobayashi, Tsukuba, Japan [34]), STEP in the Weitz group in Harvard [35,36], and EDGE for the Wageningen group [37,38]. To the best of our knowledge, these systems have not yet been used for large(r) scale production of microgel capsules, and this could quite well be the result of undesired interactions between the constituent materials and the construction material of the microfluidic system. It is still an ongoing challenge to go from milli-fluidics [39], to smaller sizes, as well as higher throughput using microfluidics. A system that circumvents these issues is the one in Figure 2, in-air microfluidics. With this system relatively large amounts of microgel capsules have been made [40••] and that in general consist of an oil core surrounded by a gel shell with thickness 20–300 micron.

Figure 3



Upscaled grooved microfluidic system, picture courtesy of Dr Kobayashi, Food Research Institute, Tsukuba, Japan.

Structure and expected delivery profile

As mentioned in the introduction, intestinal delivery of oil, protein or polysaccharide can induce satiety. Various microgel capsules made with microfluidics using these components have been presented, but the question is whether they are able to resist digestive conditions sufficiently long enough to induce the strongest feed-back signals that originate from the distal small intestine and be suitable for an effective anti-obesity strategy.

Microgels of digestible materials are expected to be subjected to rapid digestive abrasion, and controlled delivery in the distal parts of the GI tract is expected to be a complex matter [4]. Some interesting results have been achieved with hierarchically structured gels that contain oil droplets [5••], creating a controlled boost that can be tailored between half an hour to four hours. Although these gels are rather big (centimetres) and have not been prepared with microfluidic systems, the release mechanism is of great interest.

Microgels of indigestible polysaccharide may be used as protective matrix to encapsulate a digestible component from early digestion, and are an interesting option if they subsequently allow controlled delivery in the distal small intestine to reduce food intake (see Figure 2 for examples). Alginate microgels with encapsulated oil did show effective release profiles due to the pH-dependent swelling behaviour of alginate to fit with release in the distal part of the small intestine [41,42]. These encapsulates have been used in a human test, and first indications on food intake reduction have been reported [42]. Amongst others, the effect of the size of the capsules, and their mesh size of the gel were investigated, although it is good to point out that these capsules used were still relatively large (~1 mm).

To make the capsules unnoticeable in food products, the size of the capsules would need to become considerably

smaller. The mesh size of the capsule, and the size and number of oil droplets in the microgel capsule can in principle be used to tune the release, which is part of ongoing research in our lab. An interesting new development is the use of so-called in-air microfluidics to make core shell capsules from undigestible polysaccharides [40••], which has been demonstrated to circumvent a number of the drawbacks of 'classic' microfluidics (wettability issues, difficult upscaling).

Conclusions

Current developments in the field of microfluidics make us hopeful that food-grade microgel capsules tailored for anti-obesity strategies will become a reality soon. The current state of affairs is that microgel capsules can be made at very high precision, both capsules that are digested fully, and capsules that are made of undigestible hydrogel thus allowing efficient dosing. Especially the undigestible microgel capsules that contain digestible oil hold great promise since it has been demonstrated that they reduce food intake in humans. For actual application in food products, the size of the capsules still needs to be reduced while productivity of the microfluidic systems needs to be increased. To address both aspects, considerable research efforts are currently done.

Conflict of interest statement

Nothing declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cofs.2022.100816.

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