Expert Opinion

Recent advances and perspectives on coated alginate microspheres for modified drug delivery

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Background: Alginate microspheres represent a useful tool for modified drug delivery. Their preparation is quite easy and is usually based on the gelling properties of the polysaccharide in the presence of divalent ions; nevertheless, microparticles prepared only with calcium alginate show several problems, mainly related to the mechanical stability and to the release that, in most cases, is too fast. To overcome such inconveniences, polymer-coated alginate microspheres and/or appropriately interpenetrating polymer network (semi-IPNs and IPNs) structures formed with alginate and other macromolecules were developed. *Objective*: This article reports a synthetic overview on the most recent searches carried out on coated alginate microspheres. *Methods*: After a section focused on the microsphere preparation, this article is divided into several main topics related to the specific polymer that was used as a coating material to provide a rationale in reporting literature data. In the last section, the advantages and disadvantages of the various approaches are discussed and the authors' opinion on perspectives for further studies and novel applications of coated alginate microspheres are reported. *Conclusion*: Ca^{2+}-alginate microparticles could experience a new era if scientists will increase their efforts in developing microparticles with smart properties.

Keywords: alginate, coating, drug delivery, hydrogel, microspheres, polysaccharides

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1. Introduction

Alginates represent a family of unbranched polysaccharides mainly extracted from brown algae (*Phaeophyceae*), where they play a structural role. They are copolymers of β-D-mannuronic acid (M) and α-L-guluronic acid (G) with 1→4 links, containing homopolymeric regions of M or G (M- and G-blocks, respectively) and alternated MG blocks, extremely various in composition and monomer sequences. Alginates are also present in the capsule of some soil bacteria in C_2 and/or C_3 *O*-acetylated forms. In M-blocks, mannuronic moieties are found to be in the $^4C_1$ conformation, whereas guluronic residues in G-blocks are in the $^1C_4$ conformation, and the stiffness of the chains is generally reduced by alternate MG sequences.

The main characteristic of alginates is their gelling properties in aqueous solutions in the presence of divalent counterions, such as calcium, due to the selective binding by the carboxylic groups of guluronate moieties in GG-sequences leading to a particular structure called the 'egg-box'. The gelation process is generally very fast and homogeneous hydrogels can be obtained only if the ions are introduced in a controlled manner by diffusion or by internal setting methods. The properties of the obtained gels are dependent on the alginate composition, in particular on the length of the G-blocks, but they are almost

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independent from the temperature. Different alginic acid-based hydrogels can be obtained by lowering the pH very slowly (i.e., by introducing lactones) [1,2].

Alginates are widely used in industrial applications because of their gelling and stabilising properties (i.e., as viscosifyers, plasticizers in the paper and printing industries, and as additives in the food industry). In the field of pharmaceutics, both sodium alginate and alginic acid are widely used as excipients in tablets as binding or as disintegrating agents [3]. Ca^{2+}-alginate hydrogels were found to be suitable in drug or protein delivery, as well as cell encapsulation or tissue regeneration, due to their biocompatibility, mucoadhesion and porosity properties; microspheres or microbeads are among the most commonly used drug delivery dosage forms.

Two major concerns about Ca^{2+}-alginate microbeads are: i) their stability in the release media because of the calcium leaching due to the complexation by other molecules (e.g., in phosphate buffer solutions) or because of salt exchange due to the mass effect; and ii) the high porosity of the hydrogel that can generally lead to a burst effect, or to drug or protein release that is too fast. The high porosity of the Ca^{2+}-alginate hydrogel is also responsible for the low drug loading of this drug carrier. To overcome these problems, alginate microspheres are generally coated with other polymeric systems to modify their surface properties, thus, improving both the dosage form stability and the release profile of the drug/protein payload. Coating is usually carried out exploiting the interaction among the negative charges present on the microspheres surface due to the carboxylic groups of the alginate monomers and the positive charges present on another polymer (e.g., chitosan, poly-lysine and poly-ornithine). The obtained microspheres can also be transformed in capsules using complexing agents (such as ethylendiamin tetraacetic acid [EDTA] or citrate), which remove the Ca^{2+} ions from the microspheres, destroying the egg boxes present in the inner part of the dosage form, while leaving the coacervate shell intact on the surface. The capsules show mechanical and drug-/protein-carrying properties different from those of the starting polymeric system and they usually find their application in the field of cell immobilization. Furthermore, the biocompatibility of the microspheres is also usually improved by the polymeric coating [4-9].

The applications of alginate microspheres in drug delivery are very wide and it is possible to find many reviews on this topic in the recent literature [10-15]. For this reason, we discuss in this review the most recent and interesting results, focusing our attention mainly on drug and protein delivery from coated or reinforced microspheres. For an overview of the overall situation, cited literature is summarised in **Table 1**.

2. Microspheres preparation

Ca^{2+}-alginate microspheres are usually prepared by simply dropping an alginate aqueous solution into an aqueous $CaCl_2$ solution with the aid of a syringe, which immediately leads to the formation of the hydrogel with a spherical shape. The mean dimensions of the microspheres depend on several variables, such as the diameter of the needle used in the dropping procedure, on the polymeric solution extrusion flow rate, on the distance between the needle and the surface of the calcium solution, and on the polymer and salt concentrations. Several equipments have been developed with the aim of standardising the microsphere preparation procedure and to narrow their dimensional distribution. One of the most important and effective approaches reported is the electrostatic microbeads generator [16-18]: a high-voltage electrostatic field applied between a sharp needle and a $CaCl_2$ solution is exploited to overcome the surface tension of the droplets, thus, pulling the 'immature' droplets formed at the needle tip into the gelation solution, resulting in microspheres with micrometric size. The advantage of this technology includes high efficiency and easy control of dimension and size distribution of the microbeads.

The alginate microspheres can also be obtained by the emulsification technique [19]. In this case, droplets of a sodium alginate aqueous solution are dispersed in an organic solvent immiscible with water. Ca^{2+} ions are then added directly as $CaCl_2$ dissolved in water. In the internal gelation approach, a slight different procedure is followed: a $CaCO_3$ suspension or a Ca^{2+}-EDTA solution is added and, via a chemical reaction (e.g., by lowering the pH) the free Ca^{2+} ions are allowed to interact with alginate.

Recently, some new devices were developed to produce Ca^{2+}-alginate microspheres in a controlled manner; all of these are based on the internal gelation emulsification technique.

By means of a special T-junction equipment with appropriate dimensions, using $CaCO_3$ nanoparticles, Ca^{2+}-alginat microbeads with a controlled shape and a narrow distribution size are produced. Such a system is also useful for a large-scale production [20]. Because of its mild conditions, the process was developed for mammalian cell encapsulation, but it can also be applied for drug delivery when a strict control of the shape and the size of the microspheres must also be assured.

A new microfluidic device was also recently developed [21]. Exploiting a special array of microchannels and reaction chambers with a controlled shape and dimension, microparticles with various shapes (such as plugs, disks, microspheres, rods and threads) can be generated by choosing appropriate experimental conditions.

Another new microfluidic device used a silicon micronozzle array to obtain size-controlled Ca^{2+}-alginate microbeads [22] of 50 – 200 μM with a narrow size distribution. Alginate aqueous solution was extruded through a precisely fabricated thin and short micronozzle array and it was sheared by the viscous drag force of an oil flow, thus, forming alginate droplets. Such alginate droplets are immediately reacted with aqueous $CaCl_2$ droplets downstream of the oil flow to form the Ca^{2+}-alginate gel beads. This equipment was developed for the encapsulation

Table 1. Overview of the literature cited.

	Topic	Ref.
Chitosan-coated microspheres	Prednisolone loaded in microparticles prepared by a single- or double-step particle formation and coating	[24]
	5-Aminosalicilyc acid loaded in microparticles prepared by means of the spray-drying technique coupled with the polymer complexation/gelation method	[25]
	Stomach-specific delivery of metronidazole for *Helicobacter pylori* eradication using beads in different formulations with viscosity-imparting polymers	[26]
	Clarithromycin loaded in chitosan-coated alginate-ethylcellulose microparticles for a gastric floating-bioadhesive antibiotic anti-*H. pylori* delivery system	[27]
	Insulin loaded in microspheres reinforced by polyanionic additives	[28]
	Verapamil loaded in three different alginate/chitosan beads systems	[29]
	Studies of modulated releases of phenytoin, polymixyn B and artocarpin	[30-32]
	Beads tested for the immobilisation and stabilisation of the bioactive enzyme GOX	[33]
Poly-lysine and poly-ornithine-coated microspheres	Oral and nasal delivery of vaccines testing albumin or ovalbumin as model antigens	[35]
	Pectin-reinforced microparticles for the modified delivery of theophylline, chlorothiazide and indometacin	[36]
	Intestinal delivery of antisense oligonucleotides	[37]
	Novel modified APPPA microcapsules for oral drug delivery of *Lactobacilli*	[38]
	Pre-*in vivo* studies on alginate/PLL-encapsulated bifidobacteria	[39]
Layer by layer coating procedure	Poly(carboxy-*n*-propylacrylamide-*co*-dimethylacrylamide)-reinforced microcapsules of Ca^{2+}-alginate microbeads	[40]
	PMMA-coated alginate microspheres with different core:coating ratios synthesised using a liquid phase coating technique	[41]
	Alginate/chitosan-based microcapsules with a nanometric control of the thickness obtained on calcium carbonate microparticles templates	[42,43]
	Poly(allylamine hydrochloride)/poly(acrylic acid) coating of alginate microspheres for GOX enzyme encapsulation	[44]
	Ca^{2+}-alginate microspheres coated with a HSA-alginate membrane and PGA	[45]
	Ultra-thin nanoscale coatings obtained using *Bombyx mori* silk fibroin self-assembled on Ca^{2+}-alginate microspheres surface by a deposition techniques	[46]
pH and thermosensitive microbeads	Semi-IPN systems based on Ca^{2+}-alginate and poly-NIPAAM hydrogels	[47-50,54]
	Semi-IPN systems based on Ca^{2+}-alginate and methyl cellulose	[51]
	Systems obtained by means of covalent linkages between NH_2 derivatives of poly-NIPAAM and the carboxylic moieties of alginate	[52,53]
	Release of blue dextran as a model drug from Ca^{2+} cross-linked alginate-g-poly-NIPAAM beads	[55]
	Indometacin release from semi-IPN hydrogel beads composed of Ca^{2+}-alginate and poly-NIPAAM	[56]

APPPA: Alginate/poly-L-lysine/pectin/poly-L-lysine/alginate; GOX: Glucose oxidase; HSA: Human serum albumin; IPN: Interpenetrating polymer network; NIPAAM: N-isopropylacrylamide; PGA: Propylene glycol alginate; PLL: Poly-L-lysine; PMMA: Poly(methylmethacrylate).

of living cells into ~ 160 μM Ca^{2+}-alginate microbeads, but its use can also be proposed for drug delivery.

Similarly, a microfluidic device with improved performance was developed using a novel array of Teflon lines [23].

3. Chitosan-coated microspheres

Chitosan is a polysaccharide composed of randomly distributed β-(1→4)-linked D-glucosamine and *N*-acetyl-D-glucosamine, commercially produced by a partial deacetylation of chitin; therefore, it possesses free amino groups that are positively charged in acidic conditions (pK_a ~ 6.5), giving the polysaccharide a polycationic character. Chitosan is widely used for the coating of alginate microspheres by using the ionic interactions between its amino groups and the alginate carboxylic groups, resulting in surface-modified particles suitable for drug delivery.

Anti-inflammatory agents were loaded in alginate/chitosan microspheres with the aim to prepare solid dosage forms for colon targeting. A lipophilic drug (such as prednisolone) was loaded in mucoadhesive chitosan-coated alginate microparticles; microspheres were prepared starting from a drug dispersion of the alginate solution, using two different methods (i.e., by a single- or double-step particle formation and coating). Obtained results showed that the prednisolone release was not significantly affected by the preparation method. On the other hand, the microspheres prepared via the one-step method demonstrated higher mucoadhesive properties in comparison to those shown by the microspheres prepared with the two-steps method [24].

5-Aminosalicilyc acid, largely used in Crohn's disease and ulcerative colitis and also showing protective effects against colorectal cancer, was loaded in alginate/chitosan microparticles; the carriers were prepared by means of the spray-drying technique coupled with the polymer complexation/gelation method, leading to a heterogeneous distribution of chitosan chains, which were located predominantly on the surface of the particles [25].

The stomach-specific antibiotic delivery of metronidazole for *Helicobacter pylori* eradication has been studied using chitosan-coated alginate beads in different formulations with viscosity-imparting polymers (i.e., methylcellulose, carbopol 934P and κ-carrageenan) and with magnesium stearate as a floating agent. Histological analysis of the stomachs of mice and clearance tests were carried out after oral administration of the antibiotic-loaded beads at several doses. For *H. pylori* eradication, the treatment with the antibiotic in floating alginate beads was more efficient than that of the antibiotic administered as an oral suspension [26]. For the same purpose, clarithromycin has been loaded in chitosan-coated alginate-ethylcellulose microparticles, obtaining another gastric floating bioadhesive antibiotic anti-*H. pylori* [27] delivery system.

Insulin-loaded alginate microspheres reinforced by polyanionic additives (such as carboxylate or sulfate derivatives of cellulose and dextran, or polyphosphates or Eudragit®) have been prepared by emulsification/internal gelation. These are then coated with chitosan to protect insulin in the stomach and, at the same time, to improve the intestinal delivery of the protein [28]. Although several additive compositions and concentrations were tested, obtained results showed that these microspheres were not very successful at reducing the insulin release in the gastric environment; nevertheless, the presence of chitosan was important for the improvement of the intestinal absorption of insulin due to its mucoadhesive properties, which increased the residence time of the coated microspheres.

An antihypertensive drug, verapamil, was loaded in three polymeric systems [29]: alginate beads; alginate/chitosan beads; and chitosan-coated alginate beads. The drug-release kinetic was studied from both the wet beads and the beads dried at 40°C in air or by using ethanol. In all of the cases, the presence of chitosan significantly slowed down the verapamil release rate from the wet beads; on the other hand, the release from the dry alginate and alginate/chitosan mixed particles was not influenced by chitosan at the early stage of the release, but it increased at the later stage due to the higher swelling of chitosan-containing beads.

Other drugs (such as the antiepileptic agent phenytoin [30], the antibiotic polymixyn B [31] or artocarpin [32], a natural compound with a 5α-reductase-inhibitory effect) were successfully loaded in chitosan/alginate microparticles; in all of the cases, a modulated release was observed.

The chitosan/alginate beads were also tested for the immobilisation and stabilisation of bioactive enzymes, such as glucose oxidase (GOX, a protein that catalyses the oxidation of β-D-glucose into D-glucono-1,5-lactone, which then hydrolyses to gluconic acid, commonly used in biosensors to detect glucose levels). The encapsulation efficiency was found to depend on the pH of the medium, showing the maximum value at GOX pI. Furthermore, the loaded enzyme was shown to maintain 90% of its activity after lyophilisation of the microbeads and storage at -20°C [33].

4. Poly-L-lysine and poly-L-ornithine-coated microspheres

The cationic polyaminoacids poly-L-lysine (PLL) and poly-L-ornithine (PLO) have been used to coat alginate microparticles surface to reinforce the outer shell of the beads, thus, obtaining drug delivery devices with controlled permeability. Moreover, new alginate/PLL- and alginate/PLO-based microcapsules were obtained by the addition of EDTA to the coated microparticles: as pointed out in Section 1, such a procedure leads to the destruction of the inner template of the beads, leaving only the outer shell.

Physicochemical studies showed that PLL binding was strongly influenced by the alginate M:G ratio (preferential interaction with mannuronic-rich alginate blocks) and the concentration of the two polymers [34].

Several studies were carried out for the oral and nasal delivery of vaccines by testing albumin or ovalbumin as model antigens [35], which were encapsulated in PLL-coated alginate microspheres. *In vivo* experiments showed that the formulations induced immunity in mice, rabbits and cattle.

Pectin-reinforced PLL-alginate microparticles have been also synthesised and characterised for the modified delivery of theophylline, chlorothiazide and indometacin, which were used as model drugs. Obtained results showed an improved strength and resistance of the particles to the acidic environmental pH values, which are related to the presence of pectin. Mannitol was also used to evaluate the paracellular absorption of drugs, which was enhanced by the use of alginate and pectin [36].

PLL-alginate microparticles were successfully used for the intestinal delivery of antisense oligonucleotides, which are new promising therapeutic agents that show several problems in oral administration (such as degradation due to the gastric environmental conditions, to enzymatic metabolism in the lumen and to first-pass hepatic clearance) [37].

Novel modified microcapsules (such as alginate/poly-L-lysine/pectin/poly-L-lysine/alginate (APPPA) microcapsules [38]) have been used for oral drug delivery of *Lactobacilli* because of their improved stability in the gastrointestinal tract. In fact, it has been shown that 90% of microcapsules were stable both in gastric- and intestinal-simulated environments. Recently, pre-*in vivo* studies have been carried out on human volunteers by administering free and alginate/PLL encapsulated bifidobacteria for a period > 1 month [39].

5. Layer-by-layer coating procedure

A strategy to obtain reinforced microcapsules is to build up layer-by-layer (LbL) shells on Ca^{2+}-alginate microbeads by a two-step polyelectrolyte coating. This was achieved, for example, using the copolymer poly(carboxy-*n*-propylacrylamide-*co*-dimethylacrylamide), obtaining a coating thickness ranging from 25 to 125 μM. Release of fluorescein isothiocyanate-labelled dextrans of various molecular weights was studied, obtaining a time-programmed pulsatile release from the multilayer-coated Ca^{2+}-alginate microspheres with different coating thicknesses [40].

Poly(methylmethacrylate) (PMMA)-coated alginate microspheres with different core:coating ratios were synthesised using a liquid phase coating technique, which minimises the contact between the alginate microsphere cores and the solvent used for the coating, thus, reducing the loss of drug loaded within the core. This approach is based on a modified solvent-evaporation technique and it is obtained by preparing an emulsion with liquid paraffin and the subsequent dispersion of the alginate microspheres. This technique was useful in reducing drug loss during the coating and for the preparation of microparticles with a prolonged drug release [41].

Other microgel-based nanostructures have also been obtained by the LbL technique. Biocompatible nanotubes were obtained, for example, by alternate adsorption of alginate and chitosan onto the pores of a polycarbonate template with subsequent removal of the template. The thickness of the wall of such nanotubes was controlled by appropriately modulating the number of assembled layers. Biological experiments showed good biodegradability and low cytotoxicity of these alginate/chitosan nanotubes, and the confocal microscopy images showed that the assembled alginate/chitosan nanotubes were easily internalised into the cells, leading to a good system that is suitable as a drug carrier or a biomedical device [42].

Other alginate/chitosan-based microcapsules with a nanometric control of the thickness were obtained by a two-step polyelectrolyte coating followed by the LbL adsorption technique on calcium carbonate microparticles used as templates. The alginate inner shell of the microcapsule represents the matrix for protein/drug encapsulation, while the outer shell modulates the wall properties and provides a nano-engineered diffusion barrier for the encapsulated substances [43].

The LbL self-assembly technique was successfully used for the ultra-thin film coating of Ca^{2+}-alginate microspheres using various polyelectrolytes. The GOX enzyme was encapsulated within these alginate microspheres [44] and its leaching was studied using different polyelectrolyte multilayers. The application of multilayer thin films was effective in reducing the loss of the encapsulated enzyme, with the cross-linked poly(allylamine hydrochloride)/poly(acrylic acid) coating being more effective than the coating obtained with other uncross-linked polymers. No significant reduction of enzyme activity was observed.

An interesting method for the encapsulation of peptides was developed using a LbL procedure. Ca^{2+}-alginate microspheres were coated with a human serum albumin (HSA)-alginate membrane prepared by the emulsification of an aqueous solution of sodium alginate and propylene glycol alginate (PGA), followed by the addition of $CaCl_2$ [45]. The resulting microspheres were transferred into an aqueous solution of HSA. The addition of NaOH induced the reaction between PGA and HSA, producing amide bonds and thereby forming a membrane around the particles. An oligopeptide was encapsulated and the *in vitro* release was slower than that observed for uncoated microspheres. The microcapsules formed by treatment with citrate were shown to be biocompatible and were proposed as peptide containers to be combined with prosthetic materials for the improvement of osteointegration.

Ultra-thin nanoscale coatings were also obtained using *Bombyx mori* silk fibroin self-assembled on the Ca^{2+}-alginate microspheres surface by deposition techniques [46]. The silk fibroin penetrated into the alginate gel matrix and survived EDTA treatment, suggesting the possible use of such a system as a template to form silk microcapsules. Silk coatings on alginate microspheres provide mechanically stable shells as well as a diffusion barrier for the encapsulated proteins.

Horseradish peroxidase and tetramethylrhodamine-conjugated BSA as model proteic drugs were encapsulated in the Ca^{2+}-alginate microspheres. The drug release rate was significantly reduced by the silk coating when compared to the uncoated microspheres that were used as a control. This coating technique has potential for biosensor and drug delivery applications due to the aqueous process used, the ability to control coating thickness and crystalline content, and the biocompatibility of the silk fibroin protein used in the process.

6. pH and thermosensitive microbeads

A Ca^{2+}-alginate hydrogel is intrinsically pH responsive because of the carboxylate groups, whereas it is quite temperature insensitive, at least in the temperature range of the potential biomedical and pharmaceutical applications. Many efforts have been made to impart stimuli-responsive properties to alginate hydrogels and the interpenetration with a thermosensitive polymer is the strategy generally adopted. Semi-IPN systems based on Ca^{2+}-alginate and poly-N-isopropylacrylamide (NIPAAM) hydrogels [47-50] or methyl cellulose [51] were developed.

Other systems were developed in which the thermosensitive properties were obtained by means of covalent linkages between NH_2 derivatives of poly-NIPAAM and the carboxylic moieties of alginate [52-53]. Poly-NIPAAM was grafted to alginate chains and the resulting comb-type grafted hydrogel showed a pH and temperature-responsive behaviour. Swelling dependence from temperature was studied; this behaviour was compared with that of the semi-IPN prepared by simply mixing Ca^{2+}-alginate and poly-NIPAAM NH_2-terminated All of the resulting hydrogels showed mechanical and drug delivery properties that depend on temperature and the pH of the medium.

Few examples are reported in the literature of pH- and temperature-responsive Ca^{2+}-alginate beads or microbeads. Thermoresponsive alginate beads based on a semi-IPN with poly-NIPAAM were developed and their behaviour was compared with that of poly-NIPAAM beads [54]. These beads exhibited apparent reversible formation of a core-shell structure by raising the temperature above the lower critical solution temperature (LCST). The temperature-induced formation of a poly-NIPAAM-rich core and an alginate-rich shell layer was fully reversible with the variation of temperature. At 25°C, the release rate of model drugs from the microbeads was slower than that from the poly-NIPAAM beads, while the drug release rate at 37°C from the IPN beads was much faster than that from the poly-NIPAAM microbeads.

The release profiles from calcium cross-linked alginate-g-poly-NIPAAM beads using blue dextran as a model drug was also evaluated [55]. The release studies showed that the percentage of the blue dextran released from the beads was higher at 40°C than at 25°C. The difference in the release rate between the two temperatures became more detectable when the content of poly-NIPAAM in the beads was higher. Below the LCST, the expanded poly-NIPAAM should close the pores of the beads, leading to a lower release rate. Above LCST, the thermally contracted polymer should open the pores, leading to a faster release. These trends were found to be reproducible when the temperature was repeatedly shifted between 25 and 40°C. As a result, a step-wise response to the temperature alteration was obtained.

Finally the release behaviour of indometacin from the semi-IPN hydrogel beads composed of Ca^{2+}-alginate and poly-NIPAAM was analysed as a function of both pH and temperature [56]. A drastic change in drug release, attributed to the different ionisation of the ionisable groups within the semi-IPN beads, was achieved by alternating the pH of the buffer solution. The release rate was found to be much faster at 37°C than at 25°C due to the squeezing-out effect originating from the precipitation of the poly-NIPAAM. Above the LCST, a tendency was also observed for an increase in drug release rate with increasing poly-NIPAAM content. These studies indicate that alginate-g-poly-NIPAAM hydrogels could be useful as a rapid stimuli-responsive drug delivery system or as a biomimetic actuator.

7. Expert opinion and conclusions

The mechanical stability and the fast drug release of Ca^{2+}-alginate microparticles can be improved by modifying the microsphere surface using polycations, such as chitosan, poly-L-lysine and poly-L-ornithine, or by applying LbL strategies. The main advantages of the proposed coating strategies are the reduced use of toxic chemicals and the ease of preparation. Many efforts have been made to develop procedures for the preparation of microspheres with small dimensions and narrow size distributions. The literature evaluation may convince the readers that this field can be considered mature and that new publications can only add information on the use of this type of drug carriers with a slight innovation content.

Despite this impression, we believe that Ca^{2+}-alginate microparticles could enter a new era if scientists increase their efforts in developing systems of microparticles with smart properties. Knowledge in stimuli-responsive Ca^{2+}-alginate microbeads is still limited and only a few studies were devoted to the development of thermoresponsive carriers.

Ca^{2+}-alginate microparticles showing stimuli-responsive properties, and in particular thermoresponsive or even magnetic behaviour, could represent a great improvement. Smart microbeads showing these properties could lead to drug-release applications where it could be possible to control the accumulation of the drug-loaded carrier at a specific target site by the application of external stimuli (e.g., applying a gradient of temperature or an electric field using external probes).

Another possibility could be to impart a lipophilic character to the microbeads to obtain completely new properties of the drug carrier. The hydrophobic character of the Ca^{2+}-alginate microspheres could be exploited to carry and to control the delivery of hydrophobic drugs. The liphophilic properties could also be useful in improving the adhesion of microparticles to human tissues.

Numerous approaches could be used to develop smart microbeads and in particular thermosensitive or lipophilic microbeads: the first one could include semi-IPNs or IPNs between alginate chains and thermosensitive polymers. The second approach could be based on the derivatisation of alginate with thermosensitive moieties, such as poly-NIPAAM chains. A third could be the derivatisation of the microsphere surface with polymers with specifically tailored properties. In particular, this last approach could exploit the interactions among the negative charges of the carboxylate groups of the chains on the surface of the microbeads and polycations that possess stimuli-responsive properties. Furthermore, surface coating with lipophilic polymers could represent a new strategy to improving the stability of microbeads.

Another field where Ca^{2+}-alginate microbeads should be involved more deeply is enzyme delivery as the loading procedures can be very mild and preservative of the enzyme activity, but the direct enzyme loading is not developed as it could be mainly because of the poor loading/carrying properties of these microspheres. A new surface modification with synthetic chains can modulate the release of the enzyme, thereby obtaining a carrier that is suitable for therapeutic applications. It was recently demonstrated that the coating the alginate microsphere surfaces with a hydrophobic polymer can improve the carrier properties of the system by modulating the release of the protein.

We can conclude that Ca^{2+}-alginate microspheres certainly have many new opportunities still to offer in the field of modified drug delivery.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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