Expert Opinion

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Drug delivery strategies using polysaccharidic gels

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Hydrogels are hydrophilic polymeric networks, with chemical or physical crosslinks, that are capable of swell and can retain a large amount of water. Among the numerous types of macromolecules that can be used for hydrogel formation, polysaccharides show very attractive advantages in comparison to synthetic polymers. They are widely present in living organisms, are usually abundant and show a number of peculiar physicochemical properties; furthermore, these macromolecules are, in most cases, non-toxic, biocompatible and can be obtained from renewable sources. For these reasons, polysaccharides seem to be particularly suitable for different applications in the wide field of pharmaceutics. As examples of the studies that have been carried out on this topic, this review will focus on two polysaccharides, alginate and xyloglucan. Alginate has been, and still is, extensively investigated and has numerous industrial applications, whereas xyloglucan was chosen because, although it has been much less studied, it shows interesting properties that should find important practical uses in the near future. The possible advantages of physical gels over those that are chemically crosslinked are also discussed.

Keywords: alginate, drug delivery, hydrogel, polysaccharides, xyloglucan

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1. Introduction

Polymer networks can be classified into two main categories according to the type of crosslinking among the macromolecules: chemically crosslinked materials and entanglement (or physically crosslinked) networks; furthermore, numerous synthetic and natural products actually lie in between these two classes. Hydrogels are hydrophilic macromolecular networks that are capable of retaining a large amount of water. A precise description of these systems is quite complex and the practical use of hydrogels for drug delivery and biomedical applications is not often supported by a well-defined knowledge of the overall structure of the polymeric network; however, the remarkable usefulness of hydrogels is unquestionable and is supported by an almost exponential increase of publications and patents in the last 30 years.

Numerous macromolecules, in particular polysaccharides, have been proposed for the preparation of hydrogels. In fact, polysaccharides present very attractive advantages in comparison to synthetic polymers, which have been more extensively used in the pharmaceutical field. They are widely present in living organisms, are usually abundant and show a number of peculiar physicochemical properties. It is also important to note that polysaccharides are, in most cases, non-toxic, biocompatible and can be obtained from renewable sources such as algal and plant kingdoms, as well as from cultures of microbial-selected strains that have a large variety of compositions and properties that cannot be mimicked, even roughly, in a chemical laboratory.

As previously mentioned, in recent years many novel synthetic and/or polysaccharidic hydrogel systems have been developed and fundamental studies have greatly contributed to our present understanding of this unique class of materials. In terms of applications, a lot of progress has been made for hydrogels as matrices

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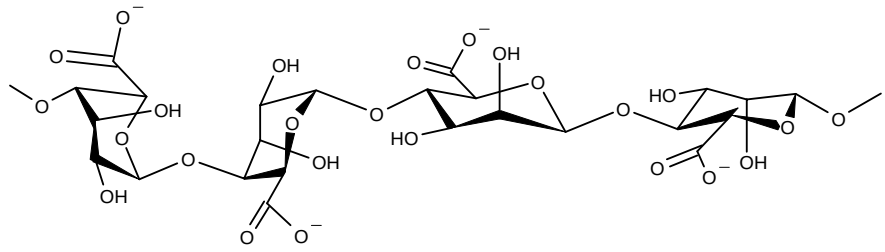

Figure 1. A schematic representation of the alginate chain.

for the encapsulation of living cells and for the controlled release of biologically active proteins. In this case, for the entrapment and encapsulation of labile, biologically active substances and living cells, physically crosslinked gels are of great interest, especially once the gel formation occurs under mild conditions and in the absence of organic solvents. It is hoped that the expanding research area of supramolecular chemistry will be applied to design novel type of hydrogels with tailored properties, which can preferably be prepared in an aqueous environment. In addition, protein engineering could contribute to the development of hydrogel systems with very precise control over their microstructure and, thus, over their properties. Furthermore, it can be foreseen that systems in which gel formation is induced by a specific trigger (temperature, pH, ionic strength, pathological stimuli and so on), will be further developed and applied for pharmaceutical and biomedical purposes; finally leading to an 'intelligent' drug delivery system that is capable of reacting to an external stimulus and delivering the drug only to a specific site and at the appropriate rate.

The number of polysaccharides that have been proposed for the formulation of hydrogels that are suitable as delivery systems is extremely large and an exhaustive review on such a subject would be huge. Being aware of such a question, the authors of this report have chosen two polysaccharides as widely different examples of possible uses in the specific topic of pharmaceutics: the first one, alginate, has been extensively studied for many years and also has numerous other industrial applications, whereas the other, xyloglucan, has been much less investigated and has a reduced number of published papers. As well as the overview that is given here for alginate and xyloglucan, some references that are related to other important polysaccharides will also be reported.

2. Alginate

Alginate is a well-known polysaccharide (Figure 1); its advantages being due to its gelling properties in aqueous solutions due to the interactions between the carboxylic acid moieties and different counterions, especially calcium ions. It is also possible to obtain an alginic acid gel by lowering the pH. This polysaccharide can be extracted from marine brown algae or can be produced by bacteria. It exhibits a backbone of (1 → 4) linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues of widely varying composition and sequence. This polymer can be regarded as a true block copolymer that is composed of homopolymeric regions of M and G, called M- and G-blocks, respectively, interspersed with regions of alternating structure. It was found that the physicochemical properties of alginate are highly affected by the M/G ratio as well as by the structure of the alternating zone.

The kinetics of the gel formations is usually very fast and the resulting gels are strong enough to be suitable for many industrial and biomedical applications [1,2].

Traditionally, in the pharmaceutical field, sodium alginate has been used as a tablet-binding agent, whereas alginic acid is used as a disintegrant excipient in tablets that are designed for immediate drug release. On the other hand, many kinds of modulated drug delivery dosage forms were developed starting from the gelled forms of this natural biopolymer [3].

Although in the past most scientific work on alginate gels was devoted to the properties and the use of this polymer as a carrier for small molecules, in recent years attention has been focused on the delivery of proteins, on cell encapsulation and on tissue regeneration. This interest is strictly related to the intrinsic properties of alginate gels, such as biocompatibility, mucoadhesion, porosity and ease of manipulation. The specific interactions between alginate and macromolecular substances that are introduced in the gel network can also be exploited to modulate the overall properties of the matrix.

First, the use of calcium alginate gel beads for drug/protein delivery will be discussed, a topic that has been extensively studied in the last few years and that shows numerous applications. In particular, an interesting paper reviews the results up to 1998 on the release of proteins from alginate calcium gel matrices [4].

An important problem that was faced for the development of efficient delivery from an alginate calcium gel was the improvement of mechanical stability and resistance to the erosion of such a network. An approach to reach this result was the reinforcement of the matrix by the addition of chitosan or poly-L-lysine to alginate; the interactions between the alginate carboxylate ions and the positive charges carried on the two other polymers formed a shell around the alginate beads (or

microbeads) that became more resistant and suitable for numerous applications.

Recent papers discuss some innovations in this field: beads with a multilayer shell of chitosan crosslinked with tripolyphosphate were able to modulate the release of ampicillin in *in vitro* experiments, showing an improved mechanical resistance of the beads [5,6].

Microcapsules can be prepared by the interaction of alginate and poly-L-lysine. Such capsules have a core of calcium alginate gel covered by multiple shells of an alginate-polylysine coacervate. The obtained system showed an excellent resistance against acidic environments, thus it has been proposed for the oral delivery of live bacterial cells [7].

In fact, gastric resistance is an important goal that must be reached in order to allow the oral administration of drugs such as proteins and peptides. To this aim, numerous devices were prepared using calcium alginate gel beads that were reinforced with chitosan. These beads showed a resistance in simulated gastric fluid containing pepsine and pancreatine, thus protecting the model protein bovine serum albumin (BSA) loaded in the matrix; whereas, after suspension in simulated intestine fluid, the beads started to erode, releasing the entrapped BSA [8,9].

Similar systems were obtained preparing carboxymethylated chitosan/alginate microspheres by emulsion phase separation [10] or by mixing alginate and *N*,*O*-carboxymethyl chitosan, producing gel beads of physically crosslinked polymers [11].

Another way to prepare alginate beads that are suitable for an industrial scale up is accomplished by an internal gelation procedure: this preparation is based on the release of the counterions from a calcium salt that is soluble in acidic medium, dispersed in an emulsified sodium alginate solution. This is achieved by acidification, with an oil-soluble acid that partitions into the dispersed aqueous alginate phase: on the resulting beads a chitosan coating was then applied in order to favour protein encapsulation. The coated beads released the BSA in simulated gastric fluid to a lesser extent with respect to the beads without the chitosan layer. By doubling the chitosan-coating procedure, the release rate was reduced even further [12,13].

The approach that is based on the technique of coating alginate calcium gel microspheres was also used to produce microcapsules. When the outer shell was made from a multilayer of poly(allylamine hydrochloride)/poly(styrene sulfonate), such microcapsules showed the peculiar behaviour of attracting positively charged macromolecules inside their structure. After the deposition of the outer layers, the inner core of alginate calcium gel was dissolved by a chelating agent for calcium ions (EDTA); in this way, the core of the microsphere became suitable for the peculiar loading procedure of macromolecular drugs as described above. This technique seems to be very promising for biomedical and biotechnological applications [14].

An interesting innovation of the alginate-chitosan delivery systems as described in the recent literature considers the use of a natural crosslinker (genipine) for a chitosan derivative. Genipine was used in the preparation of alginate chitosan beads; a chemical gel formation occurred in the core of the bead or onto the outer shell, according to the specific procedure that was followed for the preparation [15,16]. The resulting systems, loaded with indometacine, showed a modulated release that depended on the specific procedure that was followed.

Within the relevant number of studies on alginate, much attention was also focused on the application of alginate gels in the field of ocular drug delivery, due to the possible improvement of drug effects with respect to the use of solutions. The systems are based on the *in situ* gelling properties due to the high guluronic content in the polysaccharidic molecules; experiments were carried out both *in vitro*, with simulated lachrymal fluid and *in vivo* on rabbit eyes. A prolonged delivery of both of the investigated drugs pilocarpine [17] and carteolol [18] was observed in comparison to the same drugs instilled as simple solutions.

Recently, a new system based on alginate and Pluronic® (BASF Corporation), which is a vehicle that forms thermally reversible gels on warming to body temperature, has been developed to further improve on the ability of the dosage form to deliver pilocarpine in the eyes in a prolonged manner [19].

The modulation of the drug delivery profile was also studied as a function of the mechanical stimuli exerted on the gelled dosage forms. In particular, studies were focused on the effect of microwave irradiation on gel beads of calcium alginate, chitosan and calcium alginate-chitosan blends on sulfatiazole release. The authors observed a modulation of the effects that were related to the different stability to the temperature increase of the two polysaccharides, as well as to their different interactions and chain arrangements after irradiation [20,21].

Even if no release data were actually discussed, it is worth referring to a paper that discusses the behaviour of a suspension of gel particles or capsules of a synthetic polymer and of a calcium alginate-chitosan matrix as a function of the applied shear conditions. Strong shear-rate dependence of the particle shape and the amount of water that was squeezed out from the matrix was observed: at low-shear value, the deformation of the particles was reversible but above a critical value the process became irreversible; the solvent was definitively squeezed out from the particles and the particle shapes were permanently changed. It is, therefore, predictable that the release properties of such formulations can be deeply influenced by the shear [22].

Another interesting topic takes into account the ability of an electric stimulus to modulate the release of hydrocortisone from calcium alginate gels that contain increasing amounts of poly(acrylic acid) [23]. More recently, alginate was blended with carbopol gels and the resulting semi-interpenetrating polymer network was studied for an electrically modulated diclofenac release system [24].

As previously pointed out for ocular delivery, *in situ* gel formation represents another approach that was extensively studied for oral administration. The release of paracetamol or

cimetidine from an oral administration of an aqueous solution of alginate and drug plus a complex of calcium ions-citrate, was investigated. When the swallowed solution reached the stomach, the acidic environment allowed the calcium ions to interact with alginate, leading to the gel formation [25,26]. The authors showed that the bioavailability of paracetamol from the gels that formed in the stomach of rabbits was similar to that of a commercially available suspension containing an identical dose of paracetamol with the potential advantage to obtain a better patient compliance and to improve dosage uniformity.

A new interesting pH- and temperature-dependent drug delivery system was also obtained by mixing methylcellulose and alginate. This system allows an easy and a quantitative mixing/loading of the drug at room temperature; after mixing, the increase of temperature at the level of that of the human body turns the solution into a gel state because of the thermogelling properties of methylcellulose. When this system is in contact with a medium at a low pH, the acid gel of alginate is also formed; thus, it was demonstrated that in simulated gastric fluid, the system was able to release BSA at a lower rate with respect to the neutral environment or simulated intestine fluid [27].

An interesting way to achieve the *in situ* gel formation, tunable by the temperature, was obtained by hiding calcium ions into thermosensible liposomes. The calcium liposome/alginate mixture remained fluid when stored at 20°C, whereas gelation occurred after heating the system above the liposome-phase transition temperature due to the leakage of entrapped calcium. At room temperature, however, after only 1 day of storage, a gradual increase in viscosity was observed, which eventually led to a full gelation within 4 – 5 days. It was found that alginate triggered the slow release of calcium from the liposomes at 20°C. Although the lack of stability imposes constraints on the storage time of the mixture, it does not necessarily preclude the use of such a system, as the two components can be mixed just before the injection [28,29].

Naturally occurring macromolecules can be derivatised to modify their chemical and physicochemical properties to allow targeting to specific sites of the resulting material. Chemical crosslinking is an approach that is capable of producing hydrogels with predefined properties [30].

Alginate was chemically modified into low molecular weight oligomers, crosslinked with a biodegradable spacer (adipic dihydrazide) to form biodegradable hydrogels [31]. These systems were loaded with three model antineoplastic agents (methotrexate, doxorubicin and mitoxantrone) and their release behaviour was studied. Three different mechanisms were invoked to explain the observed delivery: diffusion-controlled, covalent bond degradation, and ionic dissociation-controlled mechanisms. This delivery system, which can be used for the controlled delivery of a variety of anticancer compounds, both sequentially or simultaneously, should lead to targeting that will reduce the side effects that are related to the systemic distribution.

Chemically introduced hydrophobic modifications (e.g., alkyl chains introduced by esterification of carboxylate groups) can dramatically vary the alginate behaviour, leading to a new type of physical gel [32] that is essentially based on the hydrophobic interactions among alkyl chains and reinforced by calcium ions. The release rates of model drugs from such gel matrices were remarkably affected by the presence of surfactants and enzymes that were capable of cleaving the ester linkages.

Hydrogels are interesting materials in wound dressing because of their advantages over a gauze dressing, such as homogeneous adhesion to the affected parts without wrinkling or fluting in the wound bed, easy removal without damage to renewed skin and a slightly faster rate of reconstruction of the injured skin, ease of application and improved patient compliance and comfort [33]. In particular, alginate hydrogels are extensively used in this field, especially for their ability to form gels with calcium ions that are present in the exudates. The polymer matrix can be loaded with antibiotics (e.g., vancomycin [34]) or mixed with other natural polymers, such as gelatine, leading to a physical gel. This last network was loaded with different drugs, such as silver sulfadiazine or gentamicin sulfate, which were slowly released for several days and were resistant to collagenase digestion *in vitro* for up to 3 days. Furthermore, an *in vivo* animal test showed an improvement on wound healing with respect to vaseline gauze [35]. A recent paper deals with a composite material that is based on alginate, gelatine and borax. This matrix shows the haemostatic effect of gelatin, the wound-healing promoting feature of alginate and the antiseptic property of borax that make it a potential wound-dressing material. The hydrogel was found to have a fluid uptake of 90% of its weight, which would prevent the wound bed from accumulation of exudates [36,37]. The alginate was previously oxidised with periodate to give a dialdehyde, which is able to react with gelatine in the presence of borax. The resulting system is a chemical gel that can be loaded with antiseptic substances or can be used as a scaffold for tissue regeneration.

A last topic that should be considered here is the possible use of alginate calcium hydrogels as scaffolds for tissue regeneration and as encapsulating matrices for secretory cells. Although numerous works have been published on this subject, an overview of the most significant papers that appeared on the release of specific bioactive molecules or macromolecules will be presented here.

Currently, the majority of small and large molecules are delivered into patients systemically (e.g., by means of oral or intravenous delivery) without the use of a scaffold. Consequently, large doses are usually required for the desired site-specific effect because of enzymatic degradation of the drug and nonspecific uptake by other tissues. This is not only costly but can result in serious side effects. Thus, a vehicle or scaffold allowing the local and specific delivery to the desired tissue site is needed. At present, several hydrogel systems exist in which proteins are successfully incorporated into a scaffold

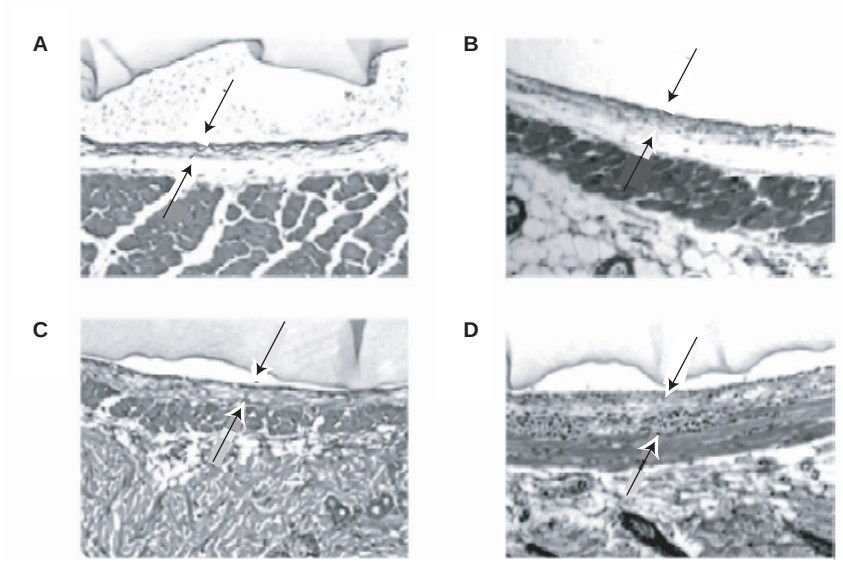

Figure 2. Photomicrographs of representative tissue sections surropunding alginate hydrogels containing: A) 0 (control), B) 10, C) 20 and D) 50 mg vascular endothelial growth factor/g alginate. Original pictures were taken at × 100 magnification. Arrows indicate the newly formed granulation tissue layer. Reproduced from LEE KY, PETERS MC, MOONEY DJ: Comparison of vascular endothelial growth factor and basic fibroblast growth factor on angiogenesis in SCID mice. *J. Control. Release* (2003) **87**:49-56 [43], with permission from Elsevier.

and then released. One of the most extensively studied proteins is the VEGF, which has been incorporated into ionically crosslinked alginate hydrogels [38-41] or within glutaraldehyde crosslinked collagen sponges [42]. VEGF was released from alginate scaffolds both by diffusion and by mechanical stimulation, whereas a hydrogel degradation occurred from collagen gels. It has been pointed out that the biological activity of VEGF delivered from alginate microspheres was greater than that obtained when VEGF was administered without the microspheres; such an effect was related to the stabilisation of the factor via an alginate interaction. The efficacy of this system [43] in driving the angiogenesis around the implant site has been demonstrated both *in vitro* and *in vivo* (Figure 2). The release of another angiogenesis-promoting protein, basic fibroblast growth factor, was also studied from heparin-alginate hydrogels [44]; enhanced angiogenesis was also observed in this case.

3. Xyloglucan

Xyloglucan is a polysaccharide that is derived from tamarind seeds and it is composed of a (1 → 4)-β-D-glucan backbone chain, which has (1 → 6)-α-D-xylose branches that are partially substituted by (1 → 2)-β-D-galactoxylose. The tamarind seed xyloglucan is composed of three units of xyloglucan oligomers with heptasaccharide, octasaccharide and nonasaccharide, which differ in the number of galactose side chains (Figure 3). The polymer that is used in the drug-release studies [28] is the one that is partially degraded by β-galactosidase to eliminate 44% of the galactose residues and is capable of forming thermoreversible gels in aqueous solution, whereas the native one does not gel. The gelation is similar to that of Pluronic, with a sol–gel transition that occurs when the system is heated (the so-called 'hot gelation') and the temperature of the gel transition is concentration dependent.

Gels of xyloglucan, loaded with a hydrophobic (indometacin) and a hydrophilic (diltiazem) drug were tested for drug release [45]. A more sustained *in vitro* release of indometacin was observed in comparison to commercial suppositories. A complete release from the suppositories was reported after 1 h, whereas, in the same time, only a low percentage of drug, depending on the gel concentration, was delivered from the hydrogel systems.

The bioavailability of the hydrophobic drug, obtained by rectal administration to rabbits in the gel, was compared with that achieved when this drug was administered in commercial suppositories. There was no significant difference of bioavailability between the two formulations but the gel preparations showed a higher residence time; therefore, in this case, the drug was effective for a longer interval of time. As the gel resides in the lower section of the rectum for quite a long time, the xyloglucan formulation can be important in the administration of a drug that, like diltiazem, is subject to first-pass metabolism.

The indometacin drug was also studied for sustained delivery when the xyloglucan gel was orally administered [46]. The *in vivo* experiments, carried out on rats, showed that a constant plasma level was maintained for at least 7 h and the presence of a soft gel was also observed after this period of time. The detected bioavailability was ~ 50% of that obtained after intravenous injection.

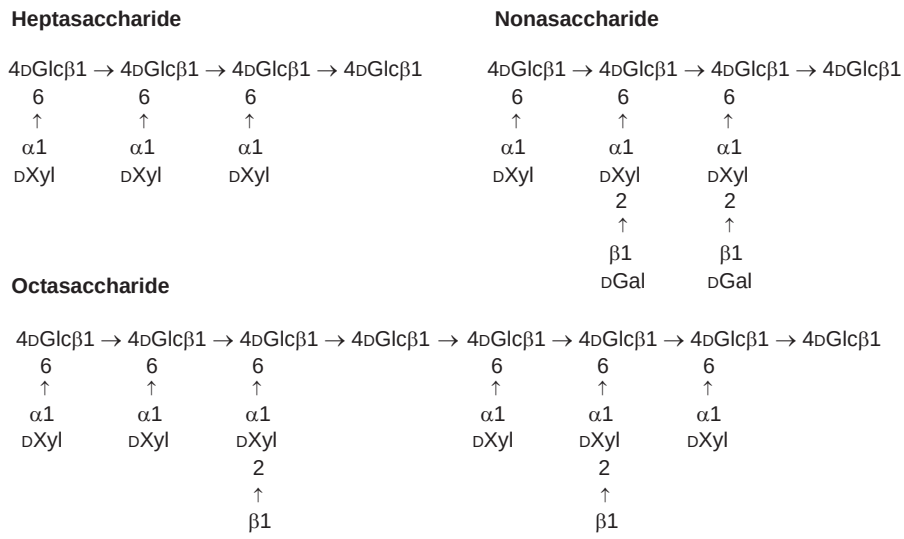

Figure 3. Three different types of monomer units of the tamarind seed polysaccharide xyloglucan.

Gels of xyloglucan have also been examined for intraperitoneal administration of mitomycin C [47]. An *in vitro* release study indicated that the process was diffusion controlled, as expected for a water-soluble drug, and that the diffusion coefficient decreased with increasing gel concentration. The corresponding *in vivo* study, performed on rats, showed a broad profile of plasma concentration during the time in both the ascites and the plasma, compared with a narrow peak and a rapid disappearance from both sites when the drug was administered via intraperitoneal delivery as a solution.

The oral delivery of cimetidine from *in situ* gelling formulations of xyloglucan, gellan and alginate has also been analysed and compared [48]. The *in vitro* release followed Fickian diffusion kinetics. *In vivo* studies showed that, despite the differences in the structure of the gels, the release curves from the three formulations were similar and resembled that of a commercial suspension used as a comparison. Among the studied preparations, xyloglucan results in the widest application in drug delivery as its gelation does not require the presence of protons, such as in the case of alginate, and its use is not restricted by the nature of the drug, as in the case of gellan.

The *in situ* gelling properties of xyloglucan have been investigated for the ocular delivery of pilocarpine hydrochloride [49]. Miotic studies were carried out on rabbits: the increase of pupil diameter was always greater for the gel formulation than for an aqueous buffer solution. As xyloglucan concentration in the gel increased, a decrease in the peak of the miotic response was monitored together with an increase in the duration of the response, indicating a more sustained release due to a greater diffusional resistance. Furthermore, the rapid gelation that occurred in the case of xyloglucan prevented the loss of formulation by drainage from the eye.

The xyloglucan gels that were formed *in situ* by dilute aqueous solutions of the polymer have also been tested as a vehicle for a sustained release of percutaneous administration of NSAIDs [50]. The topical delivery of this kind of drugs is important as a method capable to avoid the first-pass effect and the gastric irritation that occurs when they are orally administered. Xyloglucan was also tested for many topical preparations and its drug delivery behaviour was compared with that obtained using Pluronic. It is well known that the vehicle composition can affect drug release and skin permeability properties: the influence of the gel vehicle was investigated comparing the permeation rates of two bioactive molecules through cellulose membranes. The cumulative permeation of ibuprofen and ketoprofen, when released from xyloglucan gels and Pluronic, followed a diffusion process with an initial lag time; however, the diffusion coefficients were remarkably higher when the drugs were released from xyloglucan gels in comparison to the release from Pluronic. The *in vivo* release of the two drugs from xyloglucan and Pluronic gels to a defined area of the abdominal rat skin was monitored: the release from xyloglucan gels showed considerably higher bioavailability when compared with that from Pluronic gels. The observed difference in behaviour of the two gels has been ascribed to the prevention of water loss from the skin, which is exhibited to a different extent by the two polymers. Finally, it must be pointed out that xyloglucan gels are non-toxic and present a lower gelation concentration if compared with that of Pluronic.

4. Other polysaccharides

Numerous other polysaccharides have been studied for applications in the field of pharmaceutics. Below is a list of the most important ones together with some related references: carrageenan [51-52], chitosan [53-56], dextran [57-62], gellan

[25,63-65], guar gum [66,67], hyaluronic acid [68-74], scleroglucan [75-77] and xanthan [78].

5. Expert opinion and conclusions

Since the pioneering work of Wichterle and Lim in 1960 on crosslinked 2-hydroxyethyl methacrylate hydrogels [79], these types of polymeric networks have been of great interest for their possible applications in the field of pharmaceutics due to their hydrophilic character and potential biocompatibility, and the attention of biomaterial scientists towards this topic is continually increasing. Both chemically and physically crosslinked hydrogels have been extensively studied and numerous applications have been proposed; nevertheless, as pointed out, the physical gels (such as those reported as typical examples in this review) present numerous advantages over those that are chemically crosslinked. Chemical gels, depending on the nature of the chemical bonds, usually need relatively long degradation times; furthermore, the entrapped substance can be damaged, leading to a loss of activity. Most crosslinking agents are toxic and removal needs to be ensured before *in vivo* application. On the other hand, physical gels, where gel formation is not instantaneous but occurs at a certain time after mixing the components, can be administered (e.g., by injection, as oral solution or as eye drops) as a liquid formulation that forms the gel *in situ*. Furthermore, as outlined above, a number of possible applications can be foreseen, such as the controlled delivery of pharmaceutically active proteins and the entrapment of living cells for tissue engineering.

The examples reported here demonstrate the importance of the role of polysaccharides in the field of hydrogel devices: together with their wide presence in living organisms, they usually show low toxicity and, often, the possibility to be produced in abundance and at low costs. Furthermore, they show a number of peculiar physicochemical properties that give them great versatility.

For all these reasons, polysaccharides look to be very appealing candidates for the next generation of intelligent drug delivery systems, including the nanotechnologies. The important results collected so far allow us to hope that, in the near future, it will be possible to overcome the limits that still affect the actual systems. The study to develop new routes to produce chemical networks that avoid organic solvents; the understanding of the relaxation behaviour during dynamic swelling; and the modelling of the dissolution and biodegradation processes are only a few of the aspects that still need to be clearly understood in order to design the ideal drug delivery system. The desirable carrier needs to offer many functionalities in a single device. The aim would be the fabrication of intelligent materials into a single assembled device that is responsive to the individual therapeutic requirements of the patient, and is able to deliver a certain amount of drug in response to a physio-pathological state. Such smart therapeutic system should possess one or more properties, such as a proper drug protection, local targeting, precisely controlled release, self-regulated therapeutic action, permeation enhancement and enzyme inhibition. This is clearly a highly challenging task and it is difficult to add all of these functionalities in a single device that should also have good biocompatibility and functionality serving as a drug delivery carrier for oral, buccal, rectal, vaginal, ocular, epidermal and subcutaneous applications.

In conclusion, reading the most recent literature about hydrogels (and in particular polysaccharide hydrogels), it can be asserted that the foundations of this complex building are already well established; it is now up to the scientists of the next generation to improve the basic knowledge that has already been acquired and to find the best and most feasible solutions to the problems that are still faced.

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