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Invited paper

# From macro to nano polysaccharide hydrogels: An opportunity for the delivery of drugs

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ABSTRACT

This overview follows the evolution of the studies carried out, mainly during last years, on polysaccharide hydrogels, with particular attention on the researches carried out in our department, often in collaboration with other groups in our country and abroad. The review points out the importance of this type of networks for the optimization of drug delivery and targeting in the various forms of macro, micro and nano systems. It is also shown that these materials are suitable for the culture of different types of cells. Release mechanisms are reported and explained by different physico-chemical approaches and by means of molecular dynamics simulations and the anomalous swelling behavior of a scleroglucan/borax hydrogel is thoroughly discussed. The role of polymer combinations forming interpenetrated structures is explained in terms of specific properties which significantly differ from those of the constituent polymers, thus allowing appropriate tailoring of the delivery rates. Finally the wide possibilities of applications of nanogel structures which allow combination therapies for cancer treatment and can be suitable for intracellular targeting are reported. The studies on polysaccharide hydrogels are still in progress and it is underlined that future researches, more focused on the passage from lab to market, should be further stimulated.

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## 1. Introduction

Together with the identification of new bioactive compounds, the release of drugs from appropriate dosage forms at prefixed time intervals, and at predetermined rates, as well as the targeting to specific sites represent the main challenges for scientists involved in pharmaceutical studies. It can be stated that a scientific approach to modified drug delivery studies dates back to the mid '60s [1] and in recent years significant advances, with an exponential trend of publications, have been achieved in the area of controlled/modified release. Nevertheless, much work is still needed to further improve the treatment of clinical pathologies. At the same time, the rapid evolution of tissue engineering stimulated innovative studies on biocompatible materials suitable for the culture of different types of cells. For all these purposes synthetic and natural polymers have been used and among them natural polysaccharides, and their derivatives, represent a class of macromolecules of particular interest. Furthermore, it is worth to point out how, throughout the years, three different periods can be identified which can be respectively called: macro-, micro- and nano-ages [2].

A similar trend was followed by the research team at the Faculty of Pharmacy at "Sapienza" University of Rome, often in collaboration with colleagues in Italy and abroad. Actually the studies on drug delivery carried out in our labs began in 1981 with one of the first published paper on smart polymers [3], while those related to the use of polysaccharides, our most studied polymers, started eight years later [4].

Anyhow, in this review we intend to give, within an international frame, an overview on researches, mainly recent, related to macro- micro- and nano-structures, with particular attention to hydrogels, a topic that will be discussed in more detail in the second part of this paper. Future perspectives of this type of research activities will also be given.

## 2. Why polysaccharides?

Among the wide variety of macromolecules that are actually used, or have been studied, for the formulation of conventional and

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modified release dosage forms, natural polysaccharides and their derivatives are indeed the most employed and versatile polymeric materials. It must be also pointed out that polysaccharides show an even wider variety of biomedical applications, ranging from their intrinsic biological activity to their ability in living cell encapsulation, from bone and cartilage repair to the preparation of friendly scaffolds for tissue engineering. Furthermore, looking at quite close areas of interest, polysaccharides are very often used as food additives and are also present in cosmetic formulations and personal care products. The peculiar and diversified properties of these macromolecules can be related to the different molecular weights (as well as their distributions) and chemical composition that these polymers may have and also to the presence of a large number of reactive groups. These properties allow numerous chemical modifications that can be appropriately tailored according to the specific use that is assigned to these multitasking materials. Polysaccharides are usually abundant and available from various renewable natural sources such as animals (e.g., chitosan, chondroitin), plants (e.g. pectin, guar gum, locust bean gum), algae (e.g. alginates, agar, carrageenans), microbes and fungi (e.g. dextran, xanthan gum, gellan, scleroglucan). Finally, but not less important, polysaccharides are, with only few exceptions, biocompatible and non-toxic products and can be classified as GRAS (Generally Recognized as Safe).

## 3. An overview on some polysaccharide hydrogels suitable as drug delivery matrices

Numerous polysaccharides are capable of forming gels in appropriate conditions: alginate (Alg) and gellan show gelling properties in aqueous solution in the presence of counterions (physical network) [Scheme 1 A]; the synergistic interaction between Locust Bean Gum and Xanthan leads to gel formation; the interaction of borax with the hydroxyl groups of polysaccharides allows the formation of stable hydrogels and numerous bi/multifunctional reagents behave as crosslinking agents for gel formation with many polymers (chemical network) [Scheme 1 B]. We shall report here some examples of polysaccharides that have been extensively studied as hydrogel matrices for drug delivery.

### 3.1. Scleroglucan

Among the numerous polysaccharides that have been proposed for biomedical applications, Scleroglucan (Sclg) is undoubtedly a particularly versatile polymer which is studied since many years, both in its native form and after different types of chemical modifications [3,4]; and a quite recent review summarizes the most important results obtained during the first twenty years [5].

Several approaches have been followed for the formation of three-dimensional networks capable of swelling and suitable as drug delivery systems. After the first studies based on chemical crosslinking strategies, of particular interest and of peculiar behavior is the gel formed with borax. This gel can be very easily prepared by addition, to a Sclg solution, of an appropriate amount (best: moles of borax = moles of repeating unit of Sclg) of a borax solution. For delivery experiments, the drug was preliminary dissolved in the polymer solution before the addition of borax, and the obtained gel was freeze-dried and then compressed for tablet preparation [6]. The release studies, carried out with model molecules of different steric hindrance; i.e., Theophylline (TPH), Vitamin B12 (VitB12) and Myoglobin (MGB), showed that, as expected, delivery rates decreased as the van der Waals radius of the loaded molecule increased, but, at the same time, a totally unexpected and almost bizarre behavior was observed: when the tablets, obtained from the Sclg/borax freeze-dried hydrogel, were soaked in a water medium an anisotropic swelling takes place, as it is possible to visualize in Fig. 1, where the unidirectional increase of thickness with respect to the original tablet can be observed (the color is due to the presence of VitB12), while the increase of tablet diameter is almost negligible.

Molecular dynamics simulations allowed shedding some light on the anomalous swelling of this hydrogel. According to this approach, an ordered configuration of parallel bundles of the Sclg triple helices, hold together partially by covalent linkage and partially by physical interactions with borate ions, was proposed [7,8].

In Fig. 2 such structures, in the presence of the tested model drugs, are reported. From these simulations it was also evidenced that the ordered configuration is kept during swelling but is rapidly lost in the absence of borax.

Furthermore, from the same Fig. 2 it can be evidenced that the interaction between Sclg and borax leads to the formation of nanochannels with different sizes, according to the steric hindrance of the loaded molecule, thus allowing the diffusion and delivery also of the larger tested molecule such as MGB. In this sense it is also interesting to point out that the anisotropic effect above described was more relevant in the case of the tablet prepared with MGB because, in this case, a looser, but still ordered, structure is formed (Fig. 2, c).

As a consequence of the anisotropic solvent uptake, also the dynamo-mechanical and drug diffusion properties of the swelled tablets were significantly different when detected along the two directions (i.e., parallel and perpendicular with respect to the compression force applied for the preparation of the tablets) [9,10].

More recently it has been evidenced, by means of NMR studies, that the peculiar nanochannel structure together with the anisotropic swelling induced also a difference in water diffusion. In fact, for the first time in a polysaccharide hydrogel, a significantly enhanced diffusion of water molecule (superdiffusive behavior) was detected along the swelling direction [11].

Finally, it should be pointed out that all the reported behaviors are peculiar and specific of that particular Sclg/borax hydrogel: in fact, it was shown that while this polysaccharide is capable of forming gels also with trivalent ions, such as Al (III) and Fe (III), tablets obtained from these hydrogels never evidenced these type of features [12].

### 3.2. Guar gum and locust bean gum

Just like Sclg, also Guar Gum (GG), both in its native form and after chemical modifications, has been proposed, since numerous years, for the formulation of modified release oral dosage forms, and in particular for colon targeting [13,14].

More recently, GG was crosslinked with glutaraldehyde (GA) and the release of guest molecules of different molecular weight (TPH, VitB12, MGB), from tablets prepared by compression of the freeze dried derivative, was evaluated and compared with that from tablets obtained from the corresponding derivative of Sclg and Locust Bean Gum as well as from the native polysaccharides.

Experimental data showed, quite unexpectedly, that, in the case of the smaller molecules (TPH and VitB12), the presence in the matrix of a well defined network, increased the delivery rate of the guest molecules in comparison with the release profiles obtained when no crosslinker was present. Actually, the introduction of a spacer among the macromolecular chains, led to the formation of meshes with sizes wide enough for a rather easy diffusion of small molecules. On the other side, when the drugs diffuse only trough the polymeric network, the chain entanglements hinder significantly the free movement of the molecules, which showed an appreciable decrease in rate of delivery [15].

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