The future of natural origin hydrogels in drug delivery and wound dressing systems.

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Abstract. Hydrogels are colloidal molecules that are made with polymer matrices and swollen by water. With the increasing global interest in more eco-friendly materials and the need to adopt more green chemistry ideals, natural polymers are a topic of interest for research. Hydrogels made with natural polymer are normally used in biomedicine because of their excellent qualities such as biocompatibility, non cytotoxicity and biodegradability, although they present poor mechanical strength as one of the biggest disadvantages. In this paper it is shown some of the most used natural polymers for hydrogel and their uses in medicine. It is also mentioned how they are normally used as hybrid hydrogels, being able to present even better qualities such as higher mechanical strength. Lastly, it is mentioned about how drug delivery and wound dressing systems work and some examples with the use of the natural polymer in their hydrogel matrices are shown. Despite having excellent qualities for use in medicine, outside of the wound dressing area it is hard and unlikely to see the use of only natural origin polymers as a hydrogel matrix, but their use in hybrid hydrogel matrices present a good future, with the increasing studies each year.

Keywords. Hydrogel, natural origin, drug delivery, wound dressing, biomedicine.

1. Introduction

Hydrogels are a type of colloid made with a polymer of natural or synthetic origin and swollen by water, with a characteristic 3D structure, and because of its high water content their properties tend to match the ones found in biological tissue, making them have a very good biocompatibility [1]. Hydrogels were first used for contact lenses, later being used for drug delivery systems [1,2] and wound dressing systems [3].

A hydrogel can be classified many ways like by its type of bond or polymer origin, in this case, being either natural or synthetic [1,4]. The most used natural polymers for biomedicine are: alginates, cellulose, gelatin, chitosan, hyaluronic acid. And, for biomedicine, the most used synthetic polymers used are: poly(vinyl alcohol)(PVA), poly(vinylpyrrolidone)(PVP), poly(lactic-co-glycolic acid) (PLGA) and poly(lactic acid) (PLA) [4]. In this paper, we will talk briefly about some natural hydrogels, hybrid hydrogels, and their uses as drug delivery systems and wound dressing systems.

2. Natural origin hydrogels

2.1 Alginate

Alginate is an anionic linear polysaccharide, represented in figure 1, found in brown seaweed or bacteria. As hydrogels, they present slow gelation time, are hydrophilic, have low toxicity, are water soluble, have low cost and are biodegradable. They are mostly used in wound dressing, burn treatment, drug delivery and bone/cartilage regeneration[2-5]. Its first registry of encapsulation was made in 1980, with insulin, since then, it is one of the most used materials for drug delivery. Its hydrogels can have a wide range of characteristics, according to the source of choice. Although, for wound dressing, the alginate is normally combined with synthetic polymers due to the lack of mechanical strength [5].

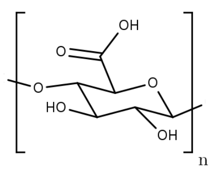

Fig. 1 - Alginate monomer.

2.2 Cellulose

Cellulose is a linear polysaccharide, represented in figure 2, and can be obtained from a wide range of sources, like trees, algae and cane sugar bagasse. Is non toxic, is relatively easy to extract, has a rigid structure, low cost and is biodegradable. As a hydrogel, it is used for wound healing and tissue regeneration, but it presents poor mechanical strength, limiting its uses [4,6]. Regarding its derivatives, like methylcellulose, they tend to have gelation temperatures that are too high, over 50 ºC [2], both this and its poor mechanical strength makes the use of cellulose without a synthetic hydrogel difficult. In particular, bacterial cellulose attracts lots of attention for their high mechanical strength, but also presents other advantages, like purity, high porosity, elevated water uptake and permeability to liquid and gases [3,6].

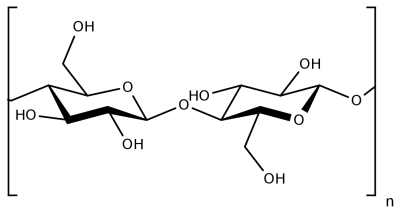

Fig. 2 - Cellulose monomer.

2.3 Chitosan

Chitosan is a cationic linear polysaccharide, represented in figure 3, that comes from chitin, found in the exoskeleton of shrimps, crabs, lobsters and other similar animals. They are hydrophilic, non-toxic, biodegradable, biologically adhesive, antimicrobial and anti-inflammatory and are being used for wound healing, bone/cartilage regeneration, antibiotic agents and for delivery of growth factors [2-4]. Since chitosan is insoluble under neutral conditions and presents solubility in acidic conditions, many studies focus on improving its solubility [2].

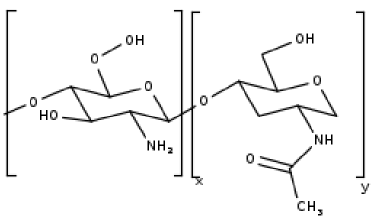

Fig. 3 - Chitosan monomer.

2.4 Gelatin

Gelatin is a linear polypeptide, represented in figure 4, obtained mostly from the skin and bones of bovines, it has as characteristics the following: hydrophilic, water soluble, soluble in various organic solvents, is cost efficient, biodegradable, non-antigenic and is similar to collagen. Is commonly used in wound healing, bone regeneration, drug delivery system and tendon tissue engineering [3, 4].

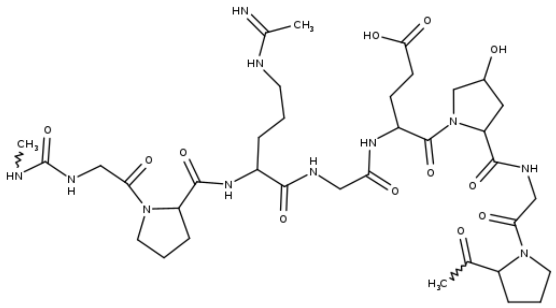

Fig. 4 - Gelatin molecule.

3. Hybrid hydrogels

The use of natural polymers is interesting to the global market because there is a need for eco-friendly materials [6] and hydrogel uses are increasing each year, including in the medicine field, as observed in figure 5 by the growth of papers published by year, as the excellent characteristics for its use in medicine are being explored, like biodegradability and biocompatibility. However, they present some downsides, such as low dimensional stability, susceptibility to immunogenic responses, possibility of pathogen transmission and inconsistency in composition depending on the natural source. To solve this problem, it is possible to either use only biodegradable synthetic polymers, which presents its own downsides, or make hybrid polymers. Hybrid polymers can be challenging when it comes to synthesis, but they can be used to enhance each other and commonly are useful to create smart hydrogels [3,4].

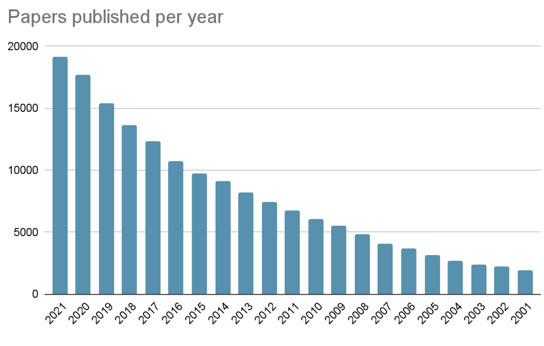

Fig. 5 - Papers published by year regarding the natural polymers mentioned in this paper, in the last two decades.

4. Drug delivery system

A drug delivery system consists of a technology that is made to enhance some of the drug characteristics, like its stability and cytotoxicity. It is also used for controlled release and localised therapy[7].

4.1 Drug delivery systems for controlled release

A controlled release system is designed to have a known release rate. One of the major benefits of this type of delivery system is that, with fewer doses, it can increase adherence of the patient to the treatment [7], a problem that occurs highly in treatments that include eye drops [8].

But, this method of delivery has its own problems, like needing a well known and desired release rate, the material cannot be toxic or have toxic byproducts, it has to degrade naturally, must maintain the drug concentration in a therapeutic window, load sufficient quantities of the drug, and reduce general discomfort for the patient. Because of those reasons, designing a controlled release system is very hard [7]. Even with the complications, there has been more and more research published regarding the topic, as seen in figure 6.

It is possible to have a controlled release system that releases the drug of choice when it is found in specific conditions and those are named smart response or stimuli-responsive. They work by changing the swelling rate in the hydrogel, and since the drug release is dependent on this rate, it also changes [4,7].

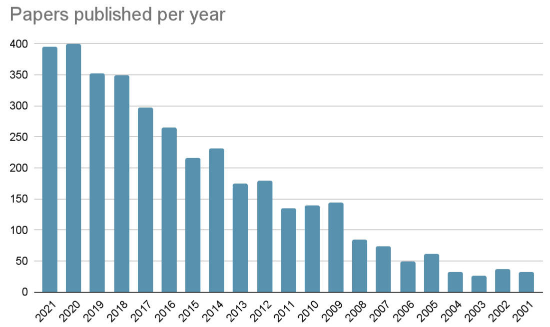

Fig. 6 - Papers published by year about controlled release systems made of hydrogel in the last two decades.

4.2 *In situ* forming hydrogels

Permanent hydrogels are advantageous for their creep deformation resistance, but they do possess a lot of disadvantages, such as having an elevated toxicity, since it is difficult to remove the unreacted reagents. So, *in situ* forming gels normally work by being liquid at room temperature and once injected in the human body, it starts sol-gel transformation at the body temperature, but they can also be solid and, once a shearing force is applied, turn into liquid [7, 9]. In figure 7 it is possible to see the number of papers published about those hydrogels.

In situ forming gels are normally used for cancer treatment, since they can be injected at the tumour site or used as prevention against recurring cancer after surgery. As an advantage, the method can reduce the toxicity of the chemotherapy drugs to healthy cells, can be used for insoluble drugs that are difficult to deliver in other ways and lower the overall dose needed [7, 10, 11]. They can also be used to improve the immune response of vaccines [7].

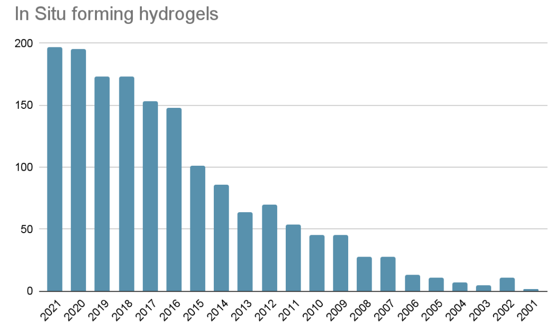

Fig. 7 - Papers published by year regarding *in situ* forming hydrogels in the last two decades.

5. Wound dressing

Wound dressings are used for protection of a wound by making a barrier between the affected area and the exterior. It is also important to maintain an adequate moisture level, absorb any extrudes, have oxygen permeability, difficult contact of bacteria and, in general, enhance the healing abilities of the body. For its design, it's important to have a material that won't adhere to the wound, but will still follow its shape. They can have just this purpose or they can also harbour molecules like antibiotics, growing factors, antioxidants, antimicrobics and painkillers [3-5,12,13]. Natural hydrogels, without the addition of synthetic polymers, are widely used because of their properties and their micro and nanospheres can be used as growth factors, like in the case of chitosan [3,14]. In figure 8 it is possible to see the growth of research in the area.

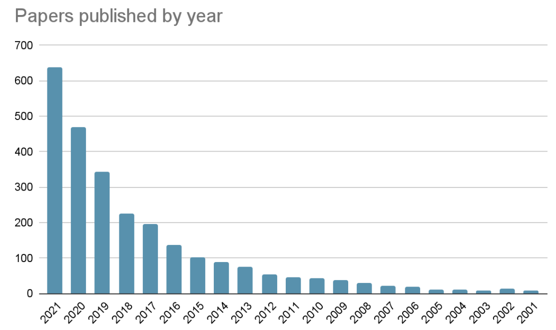

Fig. 8 - Paper published by year regarding wound dressing hydrogels, in the last two decades.

In the case of wound dressings with the presence of other molecules, one of the most common would be the usage of antibacterial hydrogels, since bacterial infections delay the healing process and could even cause sepsis. It's possible to obtain antibacterial effects with the use of antibiotics like amoxicillin and gentamicin or use metal nanoparticles, such as silver and copper and recently there has been studies about photothermal agents as antibiotics. Antioxidants and anti inflammatories are also used to maintain the inflammatory phase of the wound healing under control and there are a lot of antioxidant molecules that come from natural sources, like anthocyanins and flavonoids. It is also possible to use honey, aloe vera curcumin, acacia gum and many more. Lastly, they can present controlled release and stimuli responsiveness [13,14].

For diabetes, the design of wound dressing systems that enhances cell proliferation is very important, since patients will have a longer time of healing, being prone to develop chronic wounds that can lead to amputation [13].

6. Natural hydrogel usage

As mentioned in chapter 3, most hydrogels are not made exclusively from natural polymers, but instead of hybrid hydrogels. In the case of wound dressing, it is way more common to find hydrogel matrices based solely on natural polymers. In table 1 there are some examples of hydrogels developed for biomedicine

Tab. 1 - Uses of natural polymers in the hydrogel matrix for biomedicine.

Hydrogel Matrix	Use in biomedicine	Reference
CollagenGelatinAlginate-Lipo-MFX/DEX	Corneal infection treatment and healing	[8]
Nanofibrillar cellulose	Wound dressing in skin graft donor	[12]
Chitosan/MBP/DOX	Injectable hydrogel	[15]
Chitosan grafted Dihydro-caffeic acid	Injectable hydrogel for localised drug delivery	[16]
Alginate-Gelatin/Fe3O with DOX	Magnetic hydrogel for drug delivery	[17]
GlycolChitosan/CD/PTX	Injectable drug delivery for cancer treatment	[18]
alginate/polydopa-mine	Local delivery of chemotherapy	[19]
chitosan/gelatin/GP with Ferulic acid	Sustained release in corneal wound	[20]
sericin/chitosan and silver NP	Antimicrobial Wound dressing	[21]

7. Conclusion

Natural polymers have great characteristics and advantages as hydrogels for medicine since they are naturally biocompatible, resemble tissue, biodegrade and are non cytotoxic. But their disadvantages must be put in count, since they can be different based on batch and have poor mechanical strength. Since synthetic polymers tend to have high mechanical strength and tend to present poor characteristics where natural polymers exceed, the best solution for biomedicine is to make hybrid hydrogels with both the natural and synthetic polymers. Their uses can range from very simple wound dressings without any type of delivery to smart hydrogels used for drug delivery. While their use without the addition of synthetic polymers is uncertain, it is guaranteed that in the case of hybrid hydrogels there is only room for growth and more discoveries.

8. References

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