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Review

Review on alginate based hydrogel biomaterials for biomedical application

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ABSTRACT

Alginate is a natural biopolymer based polysaccharide derived from brown seaweed and also be produced bacteria of *Azotobacter* sp. and *Pseudomonas* sp, its consisting different ratio of polymeric units such as β-1,4-linked D-mannuronic acid (M) and L-guluronic acid (G). Sodium alginate more attention in the field of textile, food, paper industries, pharmaceutical and biomedical applications of wound healing and tissue engineering due to its major properties of non-toxic, good biocompatibility, biodegradable and highly liquid absorption capacity. In moreover, unique physicochemical properties which are widely used for drug delivery applications. In this review, discussed on alginate based composite materials like hydrogel, fiber, bead and 3D-printed matrices for recent biomedical utilization in wound healing, tissue engineering and drug delivery applications.

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1. Introduction

Biomaterials either synthetic or natural based materials are widely used in various biomedical applications which to replacing damaged tissue or enhancing biological properties of human skeleton system. The past decade several researchers have been focused naturally derived biopolymer products with unique physicochemical properties and highly biocompatibility, biodegradability and non-toxic materials for drug delivery, biomedical and industrial applications (Raus et al., 2021; Reakasame and Boccaccini, 2018). Among them, the worldwide alginate is the abundant biopolymer major source of marine environmental and other cellulose materials. Sodium alginate is major contains of alginic acid, potassium, calcium, ammonium salts and propylene glycol alginate (Li et al., 2017). Those biomolecules is a very important biomedical application of wound healing, bone tissue engineering and cell culture. Alginates are mainly extracted from brown algae-cell membranes including *Macrocystis pyrifera*, *Lessonia, Ascophyllum nodosum*, *Laminaria Hyperborean*, *Sargassum*, *Durvillea Eclonia* and also be produced bacterial species of *Pseudomonas*, *Azotobacter vinelandii* (Szekalska et al., 2016). Which alginate contains up to 40% of their dry weights. Alginate is two disparate compositions contains of M-block and G-block, that major backbone of their physicochemical properties, such as transformation of the sol /gel and water absorption as well as viscosity. The alginate polymer is viscosity depending on the pH of the solution, if pH value increasing which causes of decreasing in the viscosity due to their protonation of the carboxylate groups in the alginate. In commercial molecular weight of the sodium alginates have average between 33, 000 and 400,000 g/mol (Watthanaphanit et al., 2018). The alginate is higher molecular weight based prepared materials had more viscous and an excellent gel forming properties. Alginates most considered due to the important biological properties of non-toxic, biocompatible and non-immunogenic (Fig.1). In this review, disused alginate based composite to be used for various recent biomedical applications in wound healing, tissue engineering and drug delivery.

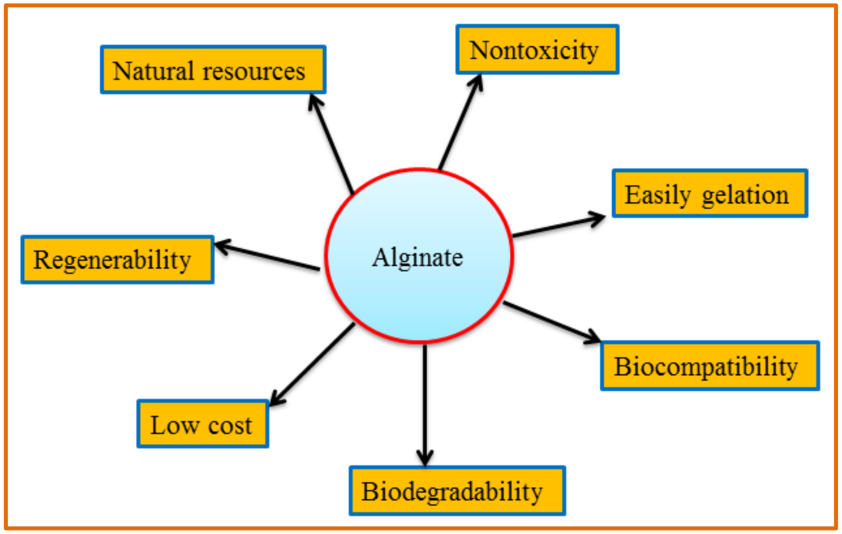

Figure 1 Advantage of alginate

2. Biomedical applications

2.1. Wound healing

In human skeleton has largest sensor system of skin and its play an important role of protection from the microbes, environmental factors, and also maintains electrolytes, body fluid and nutritional components. Wounds are defined based on the disruption of skin integrity and their function which leads to different causes such as surgery, trauma, burns and diabetes (Xu et al., 2015). Wound healing process is common in human life. But in current scenario healing process is difficult based on wound is acute or chronic. Moister based wound healing materials are potentially enhancing, the cells and enzymes, and also accelerates the proliferation of tissue its leads to promote wound healing. Wound healing dressing materials should be exhibiting the following characteristics: (1) fist stop blood bleeding and relief the pain; (2) absorb exudate body fluid and maintain wound moister environment; (3) easily to rejoining of health tissues; (4) gas permeability and good water vapor; (5) reduce the infection from the microbial contamination; (6) enhancing the formation of re-epithelialization and granulation rate; (7) most important of nontoxic and biocompatible of the prepared materials (Liang et al., 2019; Miguel et al., 2019). Most promising material of alginate is potential used for wound dressing development in the form of hydrogel, film, beads and forms, in this based materials good biological and physicochemical properties such as nontoxicity, biodegradability, excellent water absorption capacity, non-immunogenicity and hemostatic property (Rajpooot and Jain, 2020; Niu et al., 2019; Okur et al., 2019). Table 1 revealed recent literature of alginate based biomaterials for wound healing activity.

2.2. Tissue engineering

Tissue engineering is more important in biomedical field its tool for restoring or improving tissue or organs at specific defective area. Alginate based hydrogel can be synthesized different cross-linking techniques such as covalent crosslinking, ionic crosslinking, cell crosslinking, phase transition and free radical polymerization and its structure similar to extracellular matrices of living tissues (Costa et al., 2018; Lee et al., 2012; Tan and Marra, 2010). In currently more research emphasis is given in the field of tissue engineering, towards the healing of the damaged or injured tissues. Naturally bone tissue has greater ability to reconstruct of small damage, but large bone defects are required some additional treatment. Several critical bone diseases like bone cancer, osteoarthritis, osteoporosis, bone infection and major bone fracture it’s also needed extra treatment for complete

Table 1 Alginate based composite materials for wound dressing

Composite materials	Function	Reference
Alginate + gelatin	Antibacterial activity	Diniz et al., 2020
Alginate + Chitosan	Hemolytic activity Antibacterial activity Blood clotting	Wrona et al., 2016
Alginate + Activated charcoal	Moisture absorbent wound	Osmokrovic et al., 2019
Alginate + Vancomycin	Drug delivery	Kurczewska et al., 2017
Alginate + Nano - hydroxyapatite (nHAP)	Reinforced composite	Zhang et al., 2017
Alginate + Natural polyols (polypropylene glycol)	Enhancing physicochemical properties of dressing sheets	Namviriyachote et al., 2019
Alginate + Collagen @ polyacrylamide (PAM-Col)	Mix with oxidized sodium alginate as a new cross linker (COA) to form composite hydrogel	Bai et al., 2018
Alginate + Chinese nutgall	Drug delivery	Xue et al., 2019
Alginate + Zinc ions (Zn2+)	Antimicrobial activity	Osmokrovic et al., 2019
Alginate + Poly (lactic-co-glycolic acid) Manuka honey	Properly release of oxygen to cells and tissues	Nanm, et al., 2018
Alginate + Silver nanoparticles (Ag NPs) and asiaticoside (AS)	Antimicrobial activity	Namviriyachote et at., 2019
Alginate + Halloysite nanotubes	Drug encapsulation	Kurczewska et al., 2017
Alginate + gelatin + polyvinyl alcohol	Maintain wound moist environment and absorb exudates and enhance interaction with the tissues	Satish et al., 2019
Alginate + PVA + PVP	Proliferation and adhesive properties	Jin et at., 2016

Table 2 Alginate based composites for tissue engineering

Organ/Cells	Function	Reference
Vascular of adipose tissue	Enhancing revascularization of adipose tissue when combination of VEGF + alginate with adipocytes.	Ding et al., 2015
Heart	Good development of left ventricular function in rats, Alginate hydrogel form.	Rocca et al., 2016
Vascular	Improvement of stromal vascular function. 3D alginate spheroid combined with with human fat-derived stromal vascular.	Williams et at., 2013
Cornea	Propagating of epithelial therapeutic in cornea	Wright et al at., 2012
Liver	Proliferation of encapsulated HepG2/C3A liver cells for *in vivo* implantation	Capone et al., 2013
Chondrocytes	Promotes and proliferation of chondrocyte and chondrogenic phenotype.	Mhanna et al., 2014
Testis	Improved testicular tissue, the grafted combined with alginate hydrogel.	Poels et al., 2016

Table 3 Alginate based composites for drug delivery

Composite materials	Function	Reference
Alginate + **Alginate-g-Poly (N isopropylacrylamide) (alginate-g-PNIPAAm)**	Anticancer drug delivery	Liu et al., 2017
Alginate- Cyclodextrin	Enhance chemotherapeutic for colon cancer	Hosseinifar et al., 2018
Alginate + **Magnetic Alginate/Chitosan**	Sustained drug release and enhancing cytotoxicity against Human breast cancer.	Sang et al., 2018
Alginate + **Folate conjugated hyaluronic acid coated alginate**	Antitumor and apoptosis activity against on colon cancer therapy.	Shad et al., 2019
Alginate-keratin composite	Potential anti-tumor agent for breast cancer.	Sun et al., 2017

Alginate nanogel platform	Inhibit tumor growth of breast cancer and improved life of cancer patients.	Mirrahimi et al.,2019
Hybrid alginate/liposomes	Enhance chemotherapeutic for Human tongue carcinoma.	Shtenberg et al., 2018
Alginate-PAMAM (G5) hybrid nanogel	Reduced toxic and improvement of anticancer activity against Human breast cancer	Matai et al., 2016
Dual crosslinked methacrylated alginate (Alg-MA)	Best anticancer activity of Human lung epithelial carcinoma cells.	Chen et al 2014
Chitosan-alginate polyelectrolyte multilayer capsule filled with bovine serum albumin gel (BSA gel-capsule	An excellent efficacy of drug resistant breast cancer.	Shen et al 2018
Lectin-conjugated chitosan–Ca–Alginate	Potential improves against for colon cancer.	Dodov et al 2013

recovery of bone tissue (Kurowiak et al., 2020; Urtuvia et al., 2017). Alginate incorporated biomaterials are commonly used as a potential therapeutic agents for pain relieving, anti-inflammatory and along with anti-microbial. Alginate based hydrogels are attractive in wound healing, drug delivery and tissue engineering because of chemical structural similarity to the extracellular matrices in human tissues.

2.3. Drug delivery

Ensuring lowest therapeutic dosing molecules reaching to specifically targeted tissue or organ with minimum side effects and maximum effectiveness of the drug it's the major objective of the drug delivery system (Chawla et al. 2017). The generally drug delivery method has been through the oral route, administered orally, prolonged-release drug, face two challenges, an unpredictable rate of gastric emptying and short gastric residence time. Several method and material have been developed and tested for drug delivery applications. Among them, alginate based hydrogel has been most attractive because the easily gelation process it's mainly used for sustained drug release and cell encapsulation. In current researchers have been reported several alginate based hydrogel drug delivery system for wound dressing applications (Tsujimoto et al., 2018). Table 3 showed current research reported of alginate based hydrogel or composite for drug delivery applications.

3. Conclusions

Alginates are natural biopolymer derived from various biological resources of marine algae and some other microbial sources, which have been traditionally, used many industrial applications of pharmaceutical, wound dressing, tissue engineering and drug delivery. Alginate based hydrogel materials possess good physicochemical properties such as nontoxicity, biocompatibility, biodegradability and excellent viscosity. In moreover, alginate incorporated films, beads, fibers, forms and hydrogel are also to be performed *in vitro* and *in vivo* studies its revealed exhibit cell proliferation of tissue, hemostatic and antibacterial activity have been reported pervious several researchers. In this review suggested alginate based hydrogel biomaterials are currently developed many promise materials and thus need to provide new approaches for treatment of biomedical applications in future options.

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