Review Article

Long Chain Polymeric Carbohydrate dependent nanocomposites in tissue engineering

Introduction

The use of nano-medicine has increased enormously especially in the field of gene delivery and targeted drug delivery. Ithas gained a lot of interest due to its wide application. Physical and chemical attributes of nanomaterials have lengthened its application in the field of biological science, and biomedical engineering such as biological imaging, drug delivery, bio-molecular sensing, and Infectious Diseases(X. Wang, Liu, Ramstrom, and Yan, 2009). There are different types of nanomaterials such as Inorganic nanomaterials (Graphene, mesoporous silica, gold, magnetic, quantum dots, and layered double hydroxides) and metal-organic frameworks (Zirconium-based metal-organic frameworks,Lanthanide-Based Metal-OrganicFrameworks,Oligonucleotide-Functionalized Metal-Organic Framework) (S. Wang *et al.*, 2017)(Pagis, Ferbinteanu, Rothenberg, and Tanase, 2016)(Liang, Wei, Evans, and Duan, 2014)(Schaate *et al.*, 2011). Inorganic nanomaterials possess intrinsically physicochemical properties and good biocompatibility, as a result, they are used in different applications such as bio imaging, targeted drug delivery and cancer therapies whereas Metal-organic framework is porous hybrid polymer-metal composites. They possess many biomedical applications due to its excellent porosity, high loading capacity, biodegradability and ease of surface modification when compared to among others (Beg *et al.*, 2016)(Keskin and Kızılel, 2011).

The selection of material depends upon biologically activity, biocompatibility and biodegradability. The materials provide analogous environment to the extra cellular matrix (ECM) and provide an induced rate of synthesis or growth of new tissues.Extracellular matrix consists of collagen fibril, glycoproteins such as fibronectin and laminin for attachment. In addition to the extracellular matrix, connective tissues are characterized by fibroblasts, and ground substance which are usually fluid in nature but it can also be mineralized and solid, as in bones(Kusindarta and Wihadmadyatami, 2018).

Polysaccharides offer a green alternative to synthetic polymers in the preparation of soft nanomaterials (Zheng, Monty, and Linhardt, 2015).These are Polymeric carbohydrate molecules consisting of long chains of monosaccharide or disaccharide units are linked together covalently by glycosidic linkages. In addition to monosaccharides, they may also contain other components such as methyl, sulfate and pyruvate. They may have a branched or linear molecular structure. The bacterial polysaccharides can be subdivided into the exopolysaccharides, capsular polysaccharides and the intracellular polysaccharide. Xanthan, dextran, alginate, gellan and hyaluronicacid (HA) are examples of exopolysaccharides which are synthesized extracellularly by cell wall-anchored enzymes(Mokhtarzadeh, Alibakhshi, Hejazi, Omidi, and Ezzati Nazhad Dolatabadi, 2016)(Mokhtarzadeh, Alibakhshi, Yaghoobi, *et al.*, 2016)(Rehm, 2010).

Ismail *et al.*, 2018 prepared gellan gum incorporated TiO_2 nanotubes using solvent casting method for skin tissue engineering. TiO_2 nanotubes are a promising tool for cell growth and proliferation for wound healing (Ismail, Mat Amin, and Razali, 2018). They are biocompatible inosseointegration(Awad, Edwards, and Morsi, 2017) and attenuate inflammatory mediators (Cimpean, Neacsu, Mazare, and Schmuki, 2015). Aadil*et al.*, 2019 formulate poly(vinyl) alcohol-gellan gum based nanofiber using electrospinning and found a promising 3D nanofibrous scaffolds for various tissue engineering applications (Aadil, Nathani, Sharma, Lenka, and Gupta, 2019). poly (d, l-lactide-co-glycolide acid) (PLGA) nanofiber is alternative biodegradable polymer when compared with polysaccharide based nanofiber, which used in medical devices and drug delivery applications (Stachewicz *et al*., 2015). Gellan and PVA crosslink nanofiber is prepared to enhance the physiochemical stability and made biocompatible to human dermal fibroblast (3T3L1) cells (Vashisth and Pruthi, 2016).

Cellulose nanocrystals offers aggrandize Cytocompatibility and improved mechanical properties as compared to carbon or metallic nanotubes (Habibi, Lucia, and Rojas, 2010). Nanocellulose reinforced gellan-gum hydrogels is helpful in Annulus fibrosus (AF) defects such as annular tears, herniation and discectomy (Pereira *et al*., 2018).Nanocellulose Composite for also useful in the tumor-targeted gene delivery. Anirudhan and Rejeena have developed a novel nonviral gene vector consist of aminated b-cyclodextrin modified carboxylated magnetic cobalt/nanocellulose composite, which is helpful in reducing the toxicity but also increased the transgene expression level (Anirudhan and Rejeena, 2014). Yvette and co-researcher also worked on nanocellulose based gene delivery and designed polyelectrolyte layer assembly of bacterial nanocellulose whiskers with plasmid DNA (Pötzinger *et al*., 2018). Nguyen *et al*., developed nanocellulose/alginate Bioink for 3D Bioprinting of iPS Cells. The result suggests to support cartilage production in co-cultures with irradiated chondrocytes (Nguyen *et al*., 2017). The other researcher also supports the evidence for the development of 3D bio printing using nanocellulose such as 3D bioprinting of human chondrocyte-laden nanocellulose hydrogels for patient-specific auricular cartilage regeneration (Martínez Ávila, Schwarz, Rotter, and Gatenholm, 2016), wood-based nanocellulose and bioactive glass modified gelatin–alginate bioinks for 3D bioprinting of bone cells (Ojansivu *et al*., 2019) and development of nanocellulose-based bioinks for 3D bioprinting of Soft Tissue. The problem in all above research is lacking pre-clinical and clinical trials. This leads to motivation for researchers to design randomized double blind clinical trial for future commercial prospective.

Dextran based hydrogel is a popular in different kind of tissue repair such as cartilage tissue engineering (Xiaoyu Wang *et al*., 2017), vascular tissue engineering (Y. Liu and Chan-Park, 2009), bone tissue engineering(Ding *et al*., 2019), skin tissue engineering , (Pan, Liu, Sun, and Xu, 2014), wound repair (Ribeiro, Morgado, Miguel, Coutinho, and Correia, 2013). Nikpour and their co researcher developed dextran based bioactive glass-ceramic nanocomposite scaffold. They synthesized nano bioactive glass ceramic particles (nBGC) by sol–gel method whereas chemical cross linked technique is used for the preparation of nanocomposite scaffold. They identify silicon dioxide improves surface reaction to contact with body fluids and develops active surface area for *in vitro/*vivo bone tissue engineering (Nikpour *et al*., 2018). Some important Polysaccharide-based Nanocomposites for tissue engineering and gene delivery are mentioned in table 1. The researcher excluded a number of nanocomposite as of lack of available literature on *in-vitro* or *in-vivo* evaluation.

Chitosan based biomaterial has been well known for the preparation of nontoxic, biodegradable, and biocompatible polysaccharide of β(1-4)-linked d-glucosamine and N-acetyl-d-glucosamine (Riva *et al*., 2011). Chitosan have been used to prepare collagen/chitosan porous scaffolds (Ma, 2003), injectable chitosan-based hydrogels (R. Jin *et al*., 2009), chitosan-nanohydroxyapatite composite scaffolds (Thein-Han and Misra, 2009), chitin-based tubes (Freier, Montenegro, Shan Koh, and Shoichet, 2005), chitosan-alginate hybrid scaffolds (Z. Li, Ramay, Hauch, Xiao, and Zhang, 2005) and chitosan/carbon scaffolds (Martins *et al*., 2014).

Table 1: Long Chain Polymeric Carbohydrate dependent nanocomposites in tissue engineering

No.	**Material Composition**	**Characterization Techniques**	**Application**	***In-vitro/in-vivo* Testing relevant to TE and GD**	**Reference**
1.	Gellan gum incorporated TiO_2 nanotubes	FTIR, XRD and SEM	Skin tissue engineering	Cell viability and proliferation testing	(Ismail *et al.*, 2018)
2.	Poly(vinyl) alcohol-gellan gum based nanofiber	SEM and FTIR	3D nanofibrous scaffold.	*In-vitro* embryonic stem cells (ESCs)	(Aadil *et al.*, 2019)
3.	Crosslinked gellan/PVA nanofibers	FESEM	Human dermal fibroblast (3T3L1) cells in tissue engineering application	Cell proliferation behaviour of human dermal fibroblast cells (3T3L1)	(Vashisth and Pruthi, 2016)
4.	Nanocellulose reinforced gellan-gum hydrogels	TEM	Annulus fibrosus tissue regeneration	Bovine annulus fibrosus culture	(Pereira *et al.*, 2018)
5.	Dextran and sol–gel derived bioactive glass ceramic nanoparticles	FESEM, SEM	Bone tissue engineering	Normal human osteoblasts (HOB) Cells, Cell viability assay	(Nikpour *et al.*, 2018)
6.	Aminated β-Cyclodextrin-Modified-Carboxylated Magnetic Cobalt/Nanocellulose Composite	FTIR,XRD,SEM,ESR	Tumor Targeted Gene delivery	DNA Binding Studies, MTT Cytotoxicity Assay, *In vitro*Gene Transfection and Gene Expression Experiments.	(Anirudhan and Rejeena, 2014)
7.	3D Bioprinting of iPS Cells in a Nanocellulose/Alginate Bioink	Confocal images, Fluorescence	BioprintingiPSCs to support cartilage production in co-	Immunohistochemical analysis,	(Nguyen *et al.*, 2017)

		microscopy	cultures with irradiated chondrocytes	Microscopy,Gene expression assays	
8.	Chitosan-chitin nanocrystal composite scaffolds	SEM, XRD	Bone tissue engineering	Cell adhesion and proliferation	(M. Liu *et al.*, 2016)
9.	Sodium alginate-xanthan gum based nanocomposite scaffolds	FESEM	Bone tissue engineering	Cell viability	(Kumar, Rao, and Han, 2017)
10.	Nano-hydroxyapatite Pullulan/dextran polysaccharide composite	ESEM	Orthopaedic and maxillofacial surgical applications.	Experimental models performed in rat and goat	(Fricain *et al.*, 2013)
11.	Chitosan/Carbon nanofibers Scaffolds	SEM	Cardiac Tissue Engineering	Culture of Neonatal Rat Cardiomyocytes, Gene Expression	(Martins *et al.*, 2014)
12.	Nano-bio composite scaffold of chitosan–gelatin–alginate–hydroxyapatite	ESEM	Bone tissue-engineering	*In vitro* cell culture using osteoblast cell line,Cell viability, proliferation and attachment over the scaffold,Gene expression study, RNA extraction study	(Sharma, Dinda, Potdar, Chou, and Mishra, 2016)
13.	Alginate/gelatin scaffolds with homogeneous nano apatite coating	SEM, EDS	Bone tissue engineering.	Proliferation and differentiation of cells on scaffolds The	(Luo, Li, Qin, and Wa, 2018)
14.	Nano-hydroxyapatite-alginate-gelatin microcapsule as		Modular bone tissue engineering	Osteogenesis activity	(Nabavinia, Khoshfetrat, and Naderi-Meshkin, 2019)

15.	Poly(ε-caprolactone)/keratin nanofibrous mats	SEM	Vascular tissue engineering	Fibroblast viability assay, Cell attachment	(Y. Li, Wang, Ye, Yuan, and Xiao, 2016)
16.	Keratin nanoparticles-coating electrospun PVA nanofiber	SEM	Neural tissue applications	Cell morphology, adhesion and proliferation	(Guo *et al.*, 2019)
17	Nano-hydroxyapatite/chitosan/chondroitin sulfate/hyaluronic acid	SEM	Bone tissue engineering	Cell biocompatibility	(Hu *et al.*, 2017)
18	Chitosan/chondroitin sulfate/nano-bioglass	XRD, FT-IR, FE-SEM and TEM.	Bone tissue engineering	*In-vivo* bone regeneration study, *In-vitro* cell study	(Singh *et al.*, 2019)

2. Medicinal herbs incorporated into long chain polymeric carbohydratebased Nano-composites

Plants are the essential foundation of medicine. Some important drugs that are still in use today are derived from traditional medicinal herbs (Aslam and Ahmad, 2016). Functional polysaccharides have a wide variety of application in the field of biomedical engineering and tissue repair (Q. Li, Niu, Xing, and Wang, 2018). A number of medicinal herbs such as *Indigoferaaspalathoides*, *Azadirachtaindica*,*Memecylonedule* and *Myristicaandamanica* along with a biodegradable polymer, polycaprolactone has been used in combination for skin tissue engineering (G. Jin *et al*., 2013). Table 2 represent some of the medicinal herbs that is used in combination with polysaccharides based Nano-composites. *Lycium barbarum* polysaccharides has encapsulated Poly lactic-co-glycolic acid Nanofibers is indicated for peripheral nerve tissue engineering (J. Wang *et al*., 2018).*Elaeagnus angustifolia* is traditionally indicated in osteoarthritis (Mahboubi, 2018).*Elaeagnus angustifolia* extract was loaded in poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL/EA) nanofibers for bone tissue engineering (Hokmabad *et al*., 2019). Aloe vera is incorporated in poly(ε-caprolactone)/gum tragacanth nanofibers to develop the wound dressing (Ranjbar-Mohammadi, 2018).*Stryphnodendron adstringens* is indigenous to Brazil and a well-known wound healing herb in the eastern coast of South America (Hernandes, Pereira, Palazzo, and Mello, 2010). It has been used in combination with Polyvinyl alcohol and pineapple nanofibers for medical applications (Costa *et al*., 2013) .

Table 2: Some medicinal herbs incorporated into long chain polymeric carbohydratebased Nano-composites for Tissue Regeneration

Medicinal Herb	**Polysaccharides based Nano-composites**	**Application**	**Reference**
Lycium barbarum	*Lycium barbarum* polysaccharide encapsulated Poly lactic-co-glycolic acid Nanofibers	Peripheral nerve tissue engineering	(J. Wang *et al*., 2018)
Elaeagnus angustifolia	EA extract was loaded onto poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL/EA) nanofibers	Bone tissue engineering	(Hokmabad *et al*., 2019)
Aloe barbadensis miller	Aloe vera incorporated poly(ε-caprolactone)/gum tragacanth nanofibers	Wound dressing	(Ranjbar-Mohammadi, 2018)
Stryphnodendron adstringens	PVA/pineapple nanofibers/*Stryphnodendron adstringens*	Medical Application	(Costa *et al*., 2013)

3. Clinical trials of long chain polymeric carbohydratebased Nano-material

Limited available literature on clinical trial of polysaccharides based Nano-material. Although a number of material is available and examined *in-vitro* or *in-vivo* but a very few materials went for clinical trial. Most of available literature does not able to proceed further for clinical trials. A Pilot randomized clinical trial of a customized nanotextile wet garment treatment were performed on moderate and severe atopic dermatitis and found good in the treatment of eczema (He, Koh, Lee, and Ang, 2020). A couple of randomized double blind clinical trial have been performed on nano-hydroxyapatite toothpaste and nano-hydroxyapatite plus 8% Arginine in dentine hypersensitivity intervention (Vano *et al.*, 2018)(Anand *et al.*, 2017). Table 3 represent clinical trials with polysaccharides based Nano-material.

Table 3: Clinical trials with long chain polymeric carbohydratebased Nano-material

Product	Clinical trial	Application	Reference
Nano-Hydroxyapatite Toothpaste	Double Blind Randomized Clinical Trial	Dentine hypersensitivity	(Vano *et al.*, 2018)
Nano-hydroxyapatite and 8% Arginine	Double Blind Randomized Clinical Trial.	Dentine hypersensitivity	(Anand *et al.*, 2017)
Nanofibrillar cellulose wound dressing	Preliminary Clinical trial	Wound healing	(Hakkarainen *et al.*, 2016)
Tinidazole functionalized homogeneous electrospun chitosan/poly (-caprolactone) hybrid nanofiber membrane	Preliminary Clinical trial	Chronic periodontitis	(Khan *et al.*, 2017)

Conclusion

Polymeric carbohydrate molecules consist of long chains of monosaccharide or disaccharide units, that are linked together covalently by glycosidic linkages.These are abundantly available and have potential to be used for synthesis, fabrication and structure. Their application ranges from biomaterials to electronics and other industrial uses. Polysaccharides also offer a “green” alternative to oil-based synthetic polymers.Formation ofnanoparticles from polysaccharides is achieved by ionic or covalent crosslinking, ion-complex andself-assembly after grafting of hydrophobic segments to the polymer backbone.In this regard, the choiceof the most suitable technique for nanoparticle production depends on the nature of the materials such ascharges and polymer chain lengths. In coming days these will become potential candidatesfor the precisely targeted delivery of drugs and genes in treatment of different diseases.

List of abbreviations

ECM= Extra cellular matrix

ESCs= Embryonic stem cells

HOB= Normal human osteoblasts

TiO_2= Titanium dioxide

iPSCs= Induced pluripotent stem cells

FTIR= Fourier-transform infrared spectroscopy

XRD= X-ray crystallography

SEM= Scanning electron microscope

ESR= Electron Spin Resonance (ESR) Microscopy

FESEM= Field Emission Scanning Electron Microscope

PVA= Polyvinyl alcohol

TEM=Transmission electron microscopy

PCL-PEG-PCL/EA=poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone)

nBGC= nano bioactive glass ceramic particles

HA= hyaluronicacid

PLGA= poly (d, l-lactide-co-glycolide acid)

AF= Annulus fibrosus

Reference

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