https://doi.org/10.31925/farmacia.2018.5.1 **REVIEW**

BIOCOMPATIBLE POLYMERS FOR 3D PRINTING

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Abstract

Biodegradable polymers have special particularities (e.g. can be transformed chemically or enzymatically in nontoxic, natural byproducts by hydrolysis) that make them suitable for medical applications and represent the best choice for patients' safety. In this article we review the most important characteristics of biodegradable polymers commonly used for 3D printing in two important health care fields, pharmaceuticals manufacturing and tissue engineering.

Rezumat

Polimerii biodegradabili prezintă proprietăți speciale pentru domeniul medical (la nivelul organismului sunt transformați prin hidroliză chimică sau enzimatică în produși netoxici, naturali) și reprezintă cea mai bună alegere pentru siguranța pacienților. În articol sunt prezentate proprietățile polimerilor biodegradabili care sunt frecvent utilizați pentru printare 3D în două domenii de maximă importanță pentru sănătate, domeniul farmaceutic și cel al ingineriei țesuturilor.

Keywords: 3D printing, biodegradable polymers, pharmaceutical products, tissue engineering

Introduction

In three dimensional (3D) printing, computer-aided design (CAD) virtual 3D archetypes are translated into physical 3D objects in a process that requires several steps like image acquisition and processing, printing of the desired object and post processing [1]. 3D printing can be performed by different technologies like contact printing, contactless printing and laser based techniques [2].

In the health care field, 3D printing technologies allow not only visualization and design of human body parts for complex surgery interventions, but also the design and artwork production of controlled release drugs and pharmaceutical forms for personalized treatments [3, 16]. Demanding requests of pharmaceutical field now a days are important aspects of drug formulation like those ones regarding efficacy, tolerability and adherence [4]. Production of controlled release drug delivery systems have numerous advantages in terms of key factors regarding successful therapy, patient safety and comfort (e.g. preservation and controlled pharmacokinetic profile of the active molecules, valorisation of drugs that are not usable in conventional pharmaceutical forms, drug variability control etc.) [5, 70]. 3D printing offers a huge opportunity for precision (personalized) medicine, an innovative way to prevent diseases and treat patients according to their individual characteristics (genetic background, external factors, diseases) by "Providing the right treatment to the right patient, at the right dose at the right time" (FDA) [6].

There is a continuous need for new methods for original medicines manufacturing with different pharmaceutical characteristics [7] and 3D printing technologies could be successfully used for production of pharmaceutical forms with different designs and dosages, in a short time, in health care units, at convenient prices [8, 13]. They are promising tools for precisely combining substances with complex release profiles and geometries [9] and offer the advantages of flexibility in terms of dose and treatment options for patients with individual needs like children [10].

3D Pharming, the direct printing of pharmaceutical tablets provide a feasible alternative to manufacture personalized drugs over conventional tablets' production

techniques [11]. In 2015, FDA approved Spritam® (Aprecia Pharmaceuticals), the first pill produced by 3D printing [12, 13, 14].

3D printing potential in healthcare has also already been proved by production and clinical applications of medical implants, body organs and living tissues. Biocompatible compounds, cells and scaffolds are assembled together in complex 3D structures like living tissues and organs [15]. A model without any defects, similar to the anatomical structure, is produced using high-quality 3D image acquired from the patient in order to produce data required for rapid prototyping of the desired structure [16]. Inks for 3D bioprinting have to be biocompatible, printable, biodegradable, to have the capacity to promote vascular and nerve regeneration and cellular differentiation and to be supplied in unlimited quantities in a cost-effective way [17]. Polymers have already gained a special place in 3D printing offering feasible solutions for inks manufacturing due to their particular properties.

Polymers used for 3D printing.

Polymers are natural or synthetic compounds with high molecular weights made up from small repetitive units. Polymers form micelles in diluted solutions. At higher concentrations of the polymer in solution occur gelation and three dimensional networks formation [18].

Polymers used in 3D printing for medical applications usually have two main characteristics: biocompatibility and printability. Biocompatibility refers to the capacity of a product to accomplish its role without development of any unwanted reactions on living organisms. Printability represents the capacity to adopt and maintain a structure as it was designed previously. This property relays on different parameters of the polymers used as printing material (first-layer formation, viscosity, shear thinning and cross linking mechanisms, etc.) [19].

Most polymers also possess a unique characteristic with great potential, "self-healing". Self-healing is an autonomic process that resembles the physiologic one. Damaged structures are rebuilded by reorientation of the polymer catena [20].

A special class of polymers extensively used for 3D printing is represented by biodegradable polymers. These compounds have special properties: they do not induce an inflammatory response, their mechanical properties are designed according to their function and are hydrolytically or enzymatically cleaved to soluble degradation products that are safely cleared from the body [21, 22].

Biodegradable polymers can be classified as synthetic polymers (e.g. polyglycolic acid (PGA), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), poly-β-hydroxybutyrate (PHB), poly-ε-caprolactone (PCL)) and natural polymers (e.g. gelatine and collagen) [23].

Biodegradable polymers can be designed in various shapes and complex 3D structures and do not necessitate their elimination from the organism [24].

In pharmaceutical technology, polymers are multi-functional and aside from primary function (as excipients) they display different attributes (enzyme inhibition, taste-masking ability, pharmacological action, the capacity to react with enzymes responsible for drug transformations etc.) [25, 71]. The drug release profile from polymers depends on the deteriorations of the polymer surfaces layer, break of chemical bonds inside the polymer and diffusion of entrapped drug [26].

Polyvinyl alcohol (PVA) is a linear polymer that forms copolymers of vinyl alcohol and vinyl acetate [27]. It is one of the very few vinyl polymers soluble in water, with a high melting temperature (190ºC) [28, 29]. PVA is considered GRAS (substances generally recognized as safe) by FDA [30]. PVA-based hydrogels are produced by various crosslinking processes such as physical, chemical and irradiation crosslinking [31]. PVA is obtained by the saponification of poly(vinyl ether), poly(vinyl acetate) or poly(vinyl pivalate) [32, 33]. Oral administration of PVA is devoided of toxic effects. PVA is absorbed in a small proportion at gastrointestinal level and does not agglomerate inside the organism [34].

Significant in this direction are the works of Tagami and Li. Tagami *et al* prepared by fused-deposition-modelling method tablets with PVA and investigated the effect of 3D printing settings. PVA-filaments were loaded with curcumin as active substance and fluorescent marker [35]. Li *et al* obtained by hot melt extrusion method thin strands of PVA loaded with glipizide, a drug used to treat type 2 diabetes. PVA drug-loaded filaments were used to print double chamber controlled release glipizide devices by fused deposition modelling (FDM) technology [36]. Goyanes *et al* used FDM to produce filaments of PVA loaded with paracetamol or caffeine in the form of caplets for oral administration [37].

In another study, Goyanes *et al* printed capsules as drug delivery devices for oral administration of caffeine and paracetamol by FDM 3D printing using filaments of PVA loaded with desired drug. Pharmaceutical devices were designed as multilayer capsules (with each layer containing distinct drug) or as two-compartment systems comprising a caplet enclosed within a bigger caplet, each subdivision being loaded with a particular compound. The product was named DuoCaplet. The architecture of active substances influenced the release profile as follows: for multilayer capsules the release of active substances occurred synchronously and was not influenced by their solubility, while for DuoCaplet device the drug release profile was rapid or delayed according to the site of incorporation of the pharmaceutical substances [38].

Another study of Goyanes *et al* proved that 3D printing technology can be successfully used for tablet manufacturing with various architectures (printed-cube, pyramid, cylinder, sphere and torus). The tablets were obtained from filaments of PVA loaded with paracetamol [39].

Also, Goyanes used the 3D printing technology to produce tablets formed from PVA filaments loaded with 5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA). Both drugs are used in inflammatory bowel disease therapy [40].

Skowyra *et al* used a steroid drug, prednisolone and PVA to manufacture controlled release tablets by 3D printing method [41].

Poly(lactic acid).

PLA, is a biodegradable polymer that has been approved by FDA for multiple utilizations [42, 43]. It is one of the most widely used biocompatible material in 3D printing for preparation of drug-loaded nanoparticle drug carriers and for tissue engineering [43, 44].

PLA presents stereo isomers with different properties such as poly (l-lactide) acid (PLLA) and poly (d-lactide) acid (PDLA) [45]. Lactic acid has two isomers that can form three types of lactides: L-, D-, and meso. The chemical processing allows racemisation of small quantity of L-lactic acid to D-lactic acid. Proportion of D-lactic units and chirality can be controlled in order to obtain polymers with different properties [46].

For PLA synthesis are required both isomers of lactic acid [47]. PLA can be produced by direct polycondensation, azeotropic dehydrative condensation, ring-opening polymerization etc. [48].

The direct condensation of lactic acid leads to the formation of low molecular weight polymers. If high molecular weight products are desired, this reaction is followed by another polymerization reaction using PLA oligomers [49].

PLA production by ring-opening polymerization reaction was discovered by Carothers *et al* Low molecular weight oligomers are produced and are subject to depolymerization through internal trans-esterification to lactide, a cyclic dimer of lactic acid. This reaction occurs in the presence of heavy-metal-based catalysts. High molecular weight PLA is produced by opening the lactide ring [49].

Degradation of PLA polymer in water is accomplished through hydrolysis of ester bonds. The reaction is pro-autocatalysed by carboxylic acid end groups and occurs in a random manner.

In humans PLA is degraded *in vivo* in 2 or 3 years [50]. PLA is degraded by a hydrolytic process with formation of lactic acid that is eliminated as dioxide and water through the tricarboxylic acids cycle. PLA can be hydrolysed by two mechanisms: surface erosion (water action on the device is limited and degradation products are formed at the surface being dissolved in the surrounding media) and bulk erosion (amorphous phase is hydrolysed in the beginning without physical changes, followed by fragmentation of crystalline regions) [51].

3D printing was successfully used by Liu *et al* for fabrication of surgical implants from PLA scaffolds. After printing, PLA scaffolds were coated with hydroxyapatite which is known to increase osteo-conductivity of the implants and are loaded with mesenchymal stem cells suspended in Pluronic F-127 hydrogel. Evaluation of cell proliferation and osteogenesis *in vitro* and *in vivo* demonstrated once again that 3D printing is a feasible and economical solution for implant production [52].

Weisman *et al* obtained drug delivery systems with antibacterial activity (gentamicin) and cytostatic activity (methotrexate) with a 3D printing device. 3D-printed constructs were obtained from PLA filaments loaded with the desired drug [53].

Grayson *et al* designed biodegradable polymeric microchips that released four pulses of radiolabelled dextran, human growth hormone or heparin *in vitro* from PLA in combination with PLGA membranes [54].

Polyglycolic acid (PGA) is a biodegradable hydrophilic polymer. Glutamic acids molecules can be joined by γ or α linkages to produce γ -PGA and α-PGA [55]. γ -PGA can be obtained only in fermentative processes in bacteria (usually with *Bacillus microbes*). α-PGA is produced by chemical synthesis [56] via solution and melt/solid polycondensation [57]. γ -PGA can exist as L or D or both L/D isomeric forms. Different bacterial strains produce different isomers. Polymers can be soluble or insoluble in water [58].

pH influences dramatically the structure and molecular interactions of γ-PGA. γ-PGA acid form has a rod-like structure, while γ-PGA sodium adopts a sphere-like one [59].

PGA degrades *in vitro*, avoiding the accumulation of degradation products at the implantation locus, a process that can alter tissue reconstruction inducing fibrosis [60].

However, PGA has been reported to produce granulomatous inflammation after brain tumour resection. Foreign body granuloma at polyglycolic acid suture site was diagnosed after 10 months from resection of a cerebral glioblastoma [62].

Other studies proved that PGA can reduce local pH leading to local inflammation. Experimental results revealed that dispersion of titania nano particles into poly(lactide-co-glycolide acid) (PLGA) improved osteoblasts functions and limited the pH value modification at the site of the implant [61].

Poly(lactide-co-glycolide acid), PLGA, is a bio-degradable polymer extensively used for preparation by 3D printing technologies of tissue, organs and controlled release drug delivery systems [63].

PLGA is approved by FDA and the EMA (European Medicines Agency) for use in drug delivery systems

supplied *via* parenteral route [64]. The human body transforms PLGA through a hydrolytic process in lactic acid and glycolic acid which subsequently are metabolized and easily eliminated from the body [65]. PLGA nano-particles administered intravenously are rapidly eliminated from circulation in the blood due to opsonization [66]. PLGA is absorbed by human cells representing an ideal composite for biological scaffolds or extracellular matrix production [67].

PLGA produces a biocompatible by-product that can be eliminated through normal metabolic pathways [68]. The ratio between monomers in PLGA can vary and depends of the quantity of lactide and glycolide used in the polymerization reaction [69]. Polymer properties depend on the ratio between monomers of lactic and glycolic acid. A high proportion of glycolic acids increase the hydrophobicity of PLGA. A higher ratio of glycolic acid in PLGA polymer will lead to formation of a more crystalline matrix [70]. PLGA inhibits P-glycoprotein, an active transporter that pumps drugs out of the cells. Inhibition of P-glycoprotein can increase bioavailability of drugs [71].

Shim *et al* fabricated by 3D printing slow-mode delivery systems for proteins loaded onto composite polymeric scaffolds. Systems for short-term delivery (within a week) were obtained from recombinant human bone morphogenetic protein-2 (rhBMP-2) in PCL/PLGA/gelatine scaffolds. For long-term delivery (up to 28 days) were constructed PCL/PLGA/collagen/ rhBMP-2 scaffolds [72].

Gupta *et al* produced by 3D printing stimuli-responsive capsules for programmable release of mixed gradients of substances within hydrogel structures. The capsules contained a hydrophilic center surrounded by a polymeric shell made from PLGA [73].

Gbureck *et al* used a PLA/PGA polymer to obtain 3D printed structures that delay the release of antibiotics (vancomycin, ofloxacin and tetracycline) printed on ceramic scaffolds (hydroxyapatite, brushite and monetite) [74].

Chitosan is generally used to produce different biomaterials in bone tissue engineering [75]. It is a polymer poorly soluble in water that contains *N*-acetyl glucosamine and glucosamine copolymer units. The major source for chitosan production is chitin that can be isolated from the crustacean exoskeleton (such as crab and shrimp), insects, fungi, plants and mushrooms [76]. Chitin and chitosan are biocompatible, biodegradable and non-toxic biopolymers. They have antimicrobial and hydrating properties [77].

Chitin, (β-(1–4)-poly-N-acetyl-D-glucosamine), is a natural polymer structured as a linear chain by the 2-acetoamido-2-deoxy-β-D-glucopyranose monomers. It exists as three forms (α-, β- and γ-) [78]. Chitin is processed by chemical or enzymatic deacetylation to produce chitosan. Deacetylation in alkali (NaOH) is the most conventional method for chitosan production. Chitin deacetylation can be performed in acidic or basic conditions but the last one is preferred due to susceptibility of glycosidic bonds to acids. Enzymatic deacetylation occurs in the presence of chitin deacetylases, enzymes responsible for the hydrolysis of *N*-acetamido links in chitin [79, 80].

Chitosan can be used to prepare drug delivery systems for acidic environment. Polymeric shell is degraded under acidic conditions allowing release of the drug [81].

Alginates are produced in brown algae where they have a structural role, or in gram-negative bacteria where they display protective functions. Alginates are copolymers of 1 4-linked β-d-mannuronic acid (M) and α-l-glucuronic acid (G) [82, 83]. They contain carboxylic acid functional groups, so they act as weak acidic cation exchanger compounds [84].

Alginates are often used for fabrication of drug delivery systems. They are biocompatible, biodegradable, readily available and low cost substances that do not induce unwanted reactions or immunogenic responses. Different drug delivery systems can be produced from alginates, such as hydrogels, microparticles and nanoparticles [85].

Alginates can function as biocompatible transporters in cartilaginous regeneration processes. Cells embedded in alginates are capable to crosslink with calcium ions to form hydrogels [86].

Kirillova *et al* used alginate, hyaluronic acid and mouse bone marrow stromal cells to produce auto assembled tubes with small diameters (20 μm) using 4D bio-fabrication technology [87].

Hyaluronic acid (HA) or hyaluronan is a linear polysaccharide (non-sulfated glycosaminoglycan) that contain N-acetyl-d-glucosamine and glucuronic acid [88, 89].

HA self-associates and interacts with water molecules changing its properties, resembling gelatine [90]. HA has important roles in cellular signalling and motility, wound repair, morphogenesis, matrix organization, embryogenesis and inflammation [91, 92].

HA-based hydrogels are often used to manufacture drug delivery systems and in tissue engineering applications [93]. Gels prepared from HA promote differentiation, growth and survival of neuronal cells displaying mechanical properties similar to brain tissue [94].

HA with high molecular weight inhibits angiogenesis. Low molecular weight fragments stimulate endothelial cell proliferation and migration [95].

HA is a hyaluronidase sensible polymer that is usually modified with functional groups like thiol groups (Extracel® and HyStem®), hexadecylamide (Hymovis®), tyramine (Corgel®), formaldehyde (Hylan-A®), divinyl-sulfone (Hylan-B®) [96]. Hyaluronan-based biodegradable polymers with different formulations like

HYAFF® 11 (produced by the esterification of the free carboxylic group of glucuronic acid), Hyalomatrix (is a bi-layered system made of HYAFF® 11 and silicone) and Hyalosafe are used as wound dressing to treat burns [97].

Acosta-Vélez *et al* printed tablets with a hydrophilic drug Ropinirole HCL loaded on a polymeric bioink obtained from hyaluronic acid modified with norbornene moieties. Polymerization was performed with visible light in the presence of poly(ethylene) glycol dithiol and Eosin Y as photo initiator. [11] Ropinirole is a non-ergoline dopamine agonist for the treatment of Parkinson's disease and restless legs syndrome [98].

Loebel *et al* used HA modified with adamantanes or with β-cyclodextrins to produce injectable hydrogels for 3D printing. These hydrogels act through non-covalent guest-host interactions, dissociate if are injected and then undergo a self-healing process [99].

Poly-ε-caprolactone (PCL) is a biodegradable, biocompatible aliphatic polyester suitable for fabrication of long-term delivery systems [100]. It is usually produced by polymerization to an open-loop structure of ε-caprolactone [101]. It was approved by FDA for biomedical applications [102]. PCL has a relative low melting point and received much attention in 3D printing of macroporous scaffolds for correction of bone defects [103].

Polyhydroxybutyrate (PHB) can be obtained by microbial synthesis (e.g. *Alcaligenes eutrophus*, *Bacillus spp*.) under nutrient limited conditions when acetyl CoA from tricarboxylic acid cycle is reoriented to polyhydroxybutyrate (PHB) biosynthetic pathway [104, 105].

Poly(propylene fumarate) (PPF) is a biocompatible and biodegradable polymer [106]. Due to the presence of a carbon-carbon double bond, PPF can be cross linked by itself or with cross linkers. This reaction occurs by radical polymerization [107, 108, 110]

Materials based on fumaric acid like poly(propylene fumarate), poly(propylene fumarate-co-ethylene glycol) and oligo(poly(ethylene glycol) fumarate) are non-toxic to cells and tissues and degrade in the body to various compounds that are excreted from the body [109].

Dean *et al* obtained poly(propylene fumarate)/β-tricalcium phosphate constructs that can be used as structural and osteogenic substrates for the repair of cranial defects [111].

Kallukalam *et al*, prepared a hydrogel with carboxyl terminated-poly(propylene fumarate)-co-ethylene glycol) and acrylamide with good mechanical strength and flexibility that allowed the adhesion of L929 fibroblast cells without proliferation or adherence and proliferation of cardiac fibroblast cells from new born rats [112].

Polyethylene glycols (PEGs) are non-immunogenic, non-toxic and water-soluble polymers without electric charge which contain repeating units of ethylene glycol. Different polymeric structures can be achieved by addition of initiator molecules during the polymerization process or by joining different linear PEGs. Insignificant fractions of PEGs are metabolized *in vivo*. PEGs are cleared from the body by renal or faecal routes [113].

PEGs were used for cell and organ preservation [114]. In transplantation procedures, PEGs might function as immuno-masking molecules that limit cellular infiltration of the graft [115].

PEGylation represents the covalent attachment of poly ethylene glycol (PEG) to proteins. PEGylation increases thermal and physical stability of proteins, confer stability to enzymatic actions and decrease the immunogenicity, antigenicity and toxicity of proteins. The apparent size of proteins is changed by PEGylation, increasing its half-life [116]. Due to large molecular sizes and to hydrophilic properties, PEGs retain water and decrease tissue oedema, act as free-radical detoxifiers, diminish lipid peroxidation and cell membrane damage. The "patch" injured cell membranes by reversible interactions with membrane lipids, support cell integrity and can interact with innate surfaces inducing changes of the physico-chemical properties of proteins [117].

Alhijjaj *et al* obtained by Fused Deposition Modelling technology a solid dispersion of felodipine (a drug used to treat high blood pressure) with PEG, PEO and Tween 80. Pharmaceutical preparations were compared with PVA based solid dispersion in order to evaluate the processability. Dissolution testing proved that rates of drug release were influenced by polymer used in formulations [118].

Agarose is a polysaccharide composed by alternating units of β-d-galactopyranose and 3,6-anhydro-α-l-galactopyranoside. It can be obtained from agaran, a linear galactan polysaccharide extracted from some seaweeds belonging to the *Rhodophyceae* class [119, 120].

Agarose-based hydrogels have properties that make them valuable bioinks for 3D printing, but do not contain proteins so the cellular adhesion process can be improved by addition of proteins [121].

Above the sol-gel temperature, agarose have a random-coil conformation in solution. At lower temperatures agarose adopt a double helix conformation. The gelling temperature vary with the concentration of the solution, the average molecular weight of the polymer and its structure [122].

Gu *et al* developed a method for production of human neural tissue by 3D printing, using a bioink composed from agarose, alginate and carboxy-methyl-chitosan [123].

Yang *et al* obtained by 3D printing a cartilage tissue with chondrocytes in a embedded in agarose/alginate matrix [124].

Fan *et al* produced scaffolds from agarose mixed with Matrigel that efficiently incorporated human intestinal cells and promoted cell activation and expansion [125].

Conclusions

In pharmaceutical field polymers are constantly used for creation of innovative drugs that will help patient to return to normal life by proper management of their conditions, even for those ones with unmet expectation now a days. One can mention many innovations cantered on polymers use in medical field like development of smart polymers, internal bleeding controlling, healing of injured tissues, artificial skin production, tumour growth control with thermo-responsive polymers etc.

3D printing technologies promise to overcome many of the present problems related to manufacturing of medical devices and drugs. Inevitable, modern medicine will focus on 3D printed products and privately held companies and universities will reunite their efforts to develop new methods for creating special pharmaceutical forms or medical tools in order to improve the patients' quality of life.

References

1. Vijayavenkataraman S, Fuh JYH, Lu WF, 3D printing and 3D bioprinting in pediatrics. *Bioengineering (Basel)*, 2017; 4(3): 1-11.
2. Müller M, Becher J, Schnabelrauch M, Zenobi-Wong M, Printing thermoresponsive reverse molds for the creation of patterned two-component hydrogels for 3D cell culture. *J Vis Exp.*, 2013; 77: 1-9.
3. Tellisi N, Ashammakhi NA, Billi F, Kaarela O, Three dimensional printed bone implants in the clinic. *J Craniofac Surg.*, 2018, 1. doi: 10.1097/SCS.0000000000004829.
4. Burcea Dragomiroiu GTA, Popa DE, Velescu BȘ, Andrieș A, Ordeanu V, Nicoale AC, Drăgoi CM, Barca M, Ghinghină O, Synthesis, characterization and microbiological activity evaluation of novel hard gelatin capsules with cefaclor and piroxicam. *Farmacia*, 2016; (64):6: 887-895
5. Park S, Han U, Choi D, Hong J, Layer-by-layer assembled polymeric thin films as prospective drug delivery carriers: design and applications. *Biomater Res.*, 2018; 22: 1-13.
6. https://www.fda.gov.
7. Dumitrescu IB, Lupuliasa D, Drăgoi CM, Nicolae AC, Pop A, Șaramet G, Drăgănescu D, The age of pharmaceutical 3D printing. Technological and therapeutical implications of additive manufacturing. *Farmacia*, 2018; 66(3): 365-389..
8. Rahman Z, Barakh Ali SF, Ozkan T, Charoo NA, Reddy IK, Khan MA, Additive manufacturing with 3D printing: Progress from bench to bedside. *AAPS J.*, 2018; 20(6): 1-14.
9. Charbe NB, McCarron PA, Lane ME, Tambuwala MM, Application of three-dimensional printing for colon targeted drug delivery systems. *International Journal of Pharmaceutical Investigation*, 2017; 7(2): 47-59. doi:10.4103/jphi.JPHI_32_17.
10. Preis M, Öblom H, 3D-printed drugs for children-Are we ready yet?. *AAPS PharmSciTech.*, 2017; 18(2): 303-308.
11. Acosta-Vélez GF, Linsley CS, Craig MC, Wu BM, PhotocurableBioink for the inkjet 3D pharming of hydrophilic drugs. *Bioengineering (Basel)*, 2017; 4(1): 1-11.
12. Hsiao W-K, Lorberb B, Reitsamerb H, Khinasta J, 3D printing of oral drugs: a new reality or hype? *Expert Opinionon Drug Delivery*, 2018; 15(1): 1-4.
13. Konta AA, García-Piña M, Serrano DR, Personalised 3D printed medicines: Which techniques and polymers are more successful?. *Bioengineering (Basel)*, 2017; 4(4): 1-16.
14. Alamán J, Alicante R, Peña JI, Sánchez-Somolinos C, Inkjet printing of functional materials for optical and photonic applications. Materials (Basel), 2016; 9(11): 1-47
15. Murphy SV, Atala A, 3D bioprinting of tissues and organs. *Nat Biotechnol.*, 2014; 32(8): 773-785.
16. Ozbolat IT, Yu Y, Bioprinting toward organ fabrication: Challenges and future trends. *IEEE Trans Biomed Eng.*, 2013; 60: 691-699.
17. You F, Eames BF, Chen X, Application of extrusion-based hydrogel bioprinting for cartilage tissue engineering. *Int J Mol Sci.*, 2017; 18(7): 1-26.
18. Agrawal SK, Sanabria-DeLong N, Bhatia SK, Tew GN, Bhatia SR, Energetics of association in Poly (lactic acid)-based hydrogels with crystalline and nanoparticle-polymer junctions. *Langmuir*, 2010; 26(22): 17330-17338.
19. Fuenmayor E, Forde M, Healy AV, Devine DM, Lyons JG, McConville C, Major I, Material considerations for fused-filament fabrication of solid dosage forms. *Pharmaceutics*, 2018;10(2): 1-27.
20. Hazekawa M, Kojima H, Haraguchi T, Yoshida M, Uchida T, Effect of self-healing encapsulation on the initial burst release from plga microspheres containing a long-acting prostacyclin agonist, ONO-1301. *Chem Pharm Bull. (Tokyo)*, 2017; 65(7): 653-659.
21. www.sigmaaldrich.com.
22. Ulery BD, Nair LS, Laurencin CT, Biomedical applications of biodegradable polymers. *Journal of polymer science Part B, Polymer physics*, 2011; 49(12): 832-864.
23. Debels H, Hamdi M, Abberton K, Morrison W, Dermal matrices and bioengineered skin substitutes: A critical review of current options. *Plast Reconstr Surg Glob Open.*, 2015; 3(1): 1-10.
24. Alhalafi AM, Applications of polymers in intraocular drug delivery systems. *Oman J Ophthalmology*, 2017; 10(1): 3-8.
25. Felton LA, Use of polymers for taste-masking pediatric drug products. *Drug Dev Ind Pharm.*, 2018; 44(7): 1049-1055.
26. Kamaly N, Yameen B, Wu J, Farokhzad OC, Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release. *Chemical reviews*, 2016; 116(4): 2602-2663.

27. Panainte AD, Popa G, Pamfil D, Butnaru E, Vasile C, Tarțău Mititelu L, Gafițanu C, *In vitro* characterization of polyvinyl alcohol/chitosan hydrogels as modified release systems for bisoprolol. *Farmacia*, 2018; 66(1): 44-48.
28. Mohanty S, Larsen LB, Trifol J, Szabo P, Burri HV, Canali C, Dufva M, Emnéus J, Wolff A, Fabrication of scalable and structured tissue engineering scaffolds using water dissolvable sacrificial 3D printed moulds. *Mater Sci Eng C Mater Biol Appl.*, 2015; 55: 569-578.
29. Chiellini E, Corti A, D'Antone S, Solaro R, Biodegradation of poly (vinyl alcohol) based materials. *Progress in Polymer Science*, 2003; 28(6): 963-1014.
30. https://www.fda.gov.
31. Lee JM, Sultan MT, Kim SH, Kumar V, Yeon YK, Lee OJ, Park CH, Artificial auricular cartilage using silk fibroin and polyvinyl alcohol hydrogel. *Int J Mol Sci.*, 2017;18(8): 1-15.
32. Brough C, Miller DA, Keen JM, Kucera SA, Lubda D, Williams RO, Use of polyvinyl alcohol as a solubility-enhancing polymer for poorly water soluble drug delivery (Part 1). *AAPS Pharm Sci Tech.*, 2016; 17(1): 167-179.
33. Yang SB, Lee HJ, Sabina Y, Kim JW, Yeum JH, Novel poly(vinyl alcohol) nanofibers prepared by heterogeneous saponification of electrospun poly(vinyl acetate). *Colloids and Surfaces A: Physicochem Eng Aspects*, 2016; 497: 265-270.
34. DeMerlis CC, Schoneker DR, Review of the oral toxicity of polyvinyl alcohol (PVA). *Food and Chemical Toxicology*, 2003; 41(3): 319-326.
35. Tagami T, Fukushige K, Ogawa E, Hayashi N, Ozeki T, 3D printing factors important for the fabrication of polyvinylalcohol filament-based tablets. *Biol Pharm Bull.*, 2017;40(3):357-364.
36. Li Q, Wen H, Jia D, Guan X, Pan H, Yang Y, Yu S, Zhu Z, Xiang R, Pan W, Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. *Int J Pharm.*, 2017; 525(1): 5-11.
37. Goyanes A, Kobayashi M, Martínez-Pacheco R, Gaisford S, Basit AW, Fused-filament 3D printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. *Int J Pharm.*, 2016; 514(1): 290-295.
38. Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, Basit AW, 3D printing of medicines: Engineering novel oral devices with unique design and drug release characteristics. *Mol Pharm.*, 2015; 12(11): 4077-4084.
39. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S, Effect of geometry on drug release from 3D printed tablets. *Int J Pharm.*, 2015; 494(2): 657-663.
40. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW, 3D printing of modified-release amino salicylate (4-ASA and 5-ASA) tablets. *Eur J Pharm Biopharm.*, 2015; 89: 157-162.
41. Skowyra J, Pietrzak K, Alhnan MA, Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *Eur J Pharm Sci.*, 2015; 68: 11-17.
42. Markovic M, Van Hoorick J, Hölzl K, Tromayer M, Gruber P, Nürnberger S, Dubruel P, Van Vlierberghe S, Liska R, Ovsianikov A, Hybrid tissue engineering scaffolds by combination of three-dimensional printing and cell photoencapsulation. *Journal of Nanotechnology in Engineering and Medicine*, 2015; 6(2): 0210011-0210017.
43. Tyler B, Gullotti D, Mangraviti A, Utsuki T, Brem H, Polylactic acid (PLA) controlled delivery carriers for biomedical applications. *Adv Drug Deliv Rev.*, 2016; 107: 163-175.
44. Rosenzweig DH, Carelli E, Steffen T, Jarzem P, Haglund L, 3D-printed ABS and PLA scaffolds for cartilage and nucleus pulposus tissue regeneration. *Int J Mol Sci.*, 2015; 16(7): 15118-15135.
45. Prakasam M, Locs J, Salma-Ancane K, Loca D, Largeteau A, Berzina-Cimdina L, Biodegradable materials and metallic implants-A review. *J Funct Biomater.*, 2017; 8(4): 1-15.
46. National Research Council (US) Chemical Sciences Roundtable. Carbon Management: Implications for R&D in the Chemical Sciences and Technology: A Workshop Report to the Chemical Sciences Roundtable. Washington (DC): National Academies Press (US); 2001. 11, Commodity Polymers from Renewable Resources: Polylactic Acid. (Available at: www.ncbi.nlm.nih.gov)
47. Xiao L, Wang B, Yang G, Gauthier M, Poly(Lactic Acid)-based biomaterials: Synthesis, modification and applications, Biomedical Science, Engineering and Technology, www.intechopen.com.
48. Lopes MS, Jardini AL, Filho RM, Synthesis and characterizations of poly (lactic acid) by ring-opening polymerization for biomedical applications. *Chem Engineering Transact.*, 2014; 38: 331- 336.
49. Kanellakopoulou K, Kolia M, Anastassiadis A, Korakis T, Giamarellos-Bourboulis EJ, Andreopoulos A, Dounis E, Giamarellou H, Lactic acid polymers as biodegradable carriers of fluoroquinolones: An *in vitro* study. *Antimicrob Agents Chemother.*, 1999; 43(3): 714–716.
50. Rydz J, Sikorska W, Kyulavska M, Christova D, Polyester-based (bio)degradable polymers as environmentally friendly materials for sustainable development. *Int J Mol Sci.*, 2015; 16(1): 564-596.
51. Wuisman PIJM, Smit TH, Bioresorbable polymers: heading for a new generation of spinal cages. *European Spine Journal*, 2006; 15(2):133-148.
52. Liu A, Xue G, Sun M, Shao HF, Ma CY, Gao Q, Gou ZR, Yan SG, Liu YM, He Y, 3D printing surgical implants at the clinic: A experimental study on anterior cruciate ligament reconstruction. *Scientific Reports*, 2016; 6: 1-13.
53. Weisman JA, Nicholson JC, Tappa K, Jammalamadaka U, Wilson CG, Mills DK, Antibiotic and chemotherapeutic enhanced three-dimensional printer filaments and constructs for biomedical applications. *Int J Nanomedicine*, 2015; 10: 357-370.
54. Richards Grayson AC, Choi IS, Tyler BM, Wang PP, Brem H, Cima MJ, Langer R, Multi-pulse drug delivery from a resorbable polymeric microchip device. *Nat Mater.*,2003;2(11): 767-772.
55. Moraes LP, Brito PN, Alegre RM, The existing studies on biosynthesis of poly(ɣ-glutamic acid) by fermentation. *Food and Public Health*, 2013, 3(1): 28-36.

56. Tong Z, Chen Y, Liu Y, Tong L, Chu J, Xiao K, Zhou Z, Dong W, Chu X, Preparation, characterization and properties of alginate/poly(γ-glutamic acid) composite microparticles. *Marine Drugs.*, 2017; 15(4): 1-14.
57. Ayyoob M., Lee DH, Kim JH, Nam SW, Kim YJ, Synthesis of poly(glycolic acids) *via* solution polycondensation and investigation of their thermal degradation behaviors. *Fibers and Polymers*, 2017; 18(3): 407-415.
58. Khalil IR, Irorere VU, Radecka I, Burns ATH, Kowalczuk M, Mason JL, Khechara MP, Poly-γ-glutamic acid: Biodegradable polymer for potential protection of beneficial viruses. *Materials (Basel)*, 2016; 9(1): 1-13.
59. Wang LL, Chen JT, Wang LF, Wu S, Zhang GZ, Yu HQ, Ye XD, Shi QS, Conformations and molecular interactions of poly-γ-glutamic acid as a soluble microbial product in aqueous solutions, Sci Rep. 2017; 7(1): 1-11.
60. Wang Y, Wang W, Wang X, Wang Y, Wang J, Fu Q, Shi G, Tissue-engineered sling with adipose-derived stem cells under static mechanical strain. *Experimental and Therapeutic Medicine*, 2017; 14(2): 1337-1342.
61. Liu H, Slamovich EB, Webster TJ. - Less harmful acidic degradation of poly(lactic-co-glycolic acid) bone tissue engineering scaffolds through titania nanoparticle addition. *Int J Nanomed.*, 2006; 1(4): 541-545.
62. Munteanu RM, Eva L, Dobrovăţ BI, Iordache AC, Pendefunda L, Dumitrescu N, Mihăilă D, Gavrilescu CM, Şapte E, Poeată I, Longer survival of a patient with glioblastoma resected with 5-aminolevulinic acid (5-ALA)-guided surgery and foreign body reaction to polyglycolic acid (PGA) suture. *Rom J Morphol Embryol.*, 2017; 58(2): 671-680.
63. Reinbold J, Hierlemann T, Urich L, Uhde AK, Müller I, Weindl T, Vogel U, Schlensak C, Wendel HP, Krajewski S, Biodegradable rifampicin-releasing coating of surgical meshes for the prevention of bacterial infections. *Drug Des Devel Ther.*, 2017; 11: 2753-2762.
64. Ortega-Oller I, Padial-Molina M, Galindo-Moreno P, O'Valle F, Jódar-Reyes AB, Peula-García JM, Bone Regeneration from PLGA micro-nanoparticles. *Biomed Res Int.*, 2015; 2015: 1-19.
65. Chen S, Jian Z, Huang L, Xu W, Liu S, Song D, Wan Z, Vaughn A, Zhan R, Zhang C, Wu S, Hu M, Li J, Mesoporous bioactive glass surface modified poly(lactic-co-glycolic acid) electrospun fibrous scaffold for bone regeneration. *International Journal of Nanomedicine*, 2015; 10: 3815-3827.
66. Sah H, Thoma LA, Desu HR, Sah E, Wood GC, Concepts and practices used to develop functional PLGA-based nanoparticulate systems. *Int J Nanomed.*, 2013; 8: 747-765.
67. Xiang H, Lin Y, Shen N, Wang Y, Wu X, Zhang G, Ma X, Chen B, Construction and assessment of bio-engineered intervertebral discs. *Experimental and Therapeutic Medicine*, 2017; 14(3): 1929-1934.
68. Wang H, Liu J, Tao S, Chai G, Wang J, Hu FQ, Yuan H, Tetracycline-grafted PLGA nanoparticles as bone-targeting drug delivery system. *Int J Nanomed.*, 2015; 10: 5671-5685.
69. Gentile P, Chiono V, Carmagnola I, Hatton PV, An overview of poly(lactic-co-glycolic) acid (PLGA)-based biomaterials for bone tissue engineering. *Int J Mol Sci.*, 2014; 15(3): 3640-3659.
70. Hines DJ, Kaplan DL, Poly (lactic-co-glycolic acid) controlled release systems: experimental and modeling insights. *Crit Rev Ther Drug Carrier Syst.*, 2013; 30(3): 257-276.
71. Karolewicz B, A review of polymers as multifunctional excipients in drug dosage form technology. *Saudi Pharm J.*, 2016; 24(5): 525-536.
72. Shim J-H, Kim SE, Park JY, Kundu J, Kim SW, Kang SS, Cho DW, Three-dimensional printing of rhBMP-2-loaded scaffolds with long-term delivery for enhanced bone regeneration in a rabbit diaphyseal defect. *Tissue Engineering Part A.*, 2014; 20(13-14): 1980-1992.
73. Gupta MK, Meng F, Johnson BN, Kong YL, Tian L, Yeh YW, Masters N, Singamaneni S, McAlpine MC, 3D printed programmable release capsules. *Nano letters*, 2015; 15(8): 5321-5329.
74. Gbureck U, Vorndran E, Müller FA, Barralet JE, Low temperature direct 3D printed bioceramics and biocomposites as drug release matrices. *J Control Release.*, 2007; 122(2): 173-180.
75. Dong L, Wang SJ, Zhao XR, Zhu YF, Yu JK, 3D-printed poly(ε-caprolactone) scaffold integrated with cell-laden chitosan hydrogels for bone tissue engineering. *Sci Rep.*, 2017; 7(1): 1-9.
76. Husain S, Al-Samadani KH, Najeeb S, Zafar MS, Khurshid Z, Zohaib S, Qasim SB, Chitosan biomaterials for current and potential dental applications. *Materials (Basel)*, 2017; 10(6): 1-20.
77. Elieh-Ali-Komi D, Hamblin MR, Chitin and chitosan: production and application of versatile biomedical nanomaterials. *Int J Adv Res. (Indore)*, 2016; 4(3): 411-427.
78. Rasti H, Parivar K, Baharara J, Iranshahi M, Namvar F, Chitin from the mollusc Chiton: Extraction, characterization and chitosan preparation. *Iran J Pharm Res.*, 2017; 16(1): 366-379.
79. Younes I, Rinaudo M, Chitin and chitosan preparation from marine sources. structure, properties and applications. *Marine Drugs*, 2015; 13(3): 1133-1174.
80. Kafetzopoulos D, Martinou A, Bouriotis V, Bioconversion of chitin to chitosan: purification and characterization of chitin deacetylase from *Mucor rouxii*. *Proc Natl Acad Sci. USA*, 1993; 90(7): 2564-2568.
81. Oryan A, Alidadi S, Bigham-Sadegh A, Moshiri A, Comparative study on the role of gelatine, chitosan and their combination as tissue engineered scaffolds on healing and regeneration of critical sized bone defects: An *in vivo* study. *J Mater Sci Mater Med.*, 2016; 27(10): 1-14.
82. Kaklamani G, Cheneler D, Grover LM, Adams MJ, Anastasiadis SH, Bowen J, Anisotropic dehydration of hydrogel surfaces. *Prog Biomater.*, 2017; 6: 157-164.
83. Arlov Ø, Skjåk-Bræk G, Sulfated alginates as heparin analogues: A review of chemical and functional properties. *Molecules*, 2017; 22(5): 1-16.

84. Inoue K, Parajuli D, Ghimire KN, Biswas BK, Kawakita H, Oshima T, Ohto K, Biosorbents for removing hazardous metals and metalloids. *Materials*, 2017; 10(8): 1-33.
85. Spadari C de C, Lopes LB, Ishida K, Potential use of alginate-based carriers as antifungal delivery system. *Front Microbiol.*, 2017; 8: 1-11.
86. Ewa-Choy YW, Pingguan-Murphy B, Abdul-Ghani NA, Jahendran J, Chua KH, Effect of alginate concentration on chondrogenesis of co-cultured human adipose-derived stem cells and nasal chondrocytes: a biological study. *Biomater Res.*, 2017; 21: 1-11.
87. Kirillova A, Maxson R, Stoychev G, Gomillion CT, Ionov L, 4D biofabrication using shape-morphing hydrogels. Adv Mater., 2017; 29: 1-8.
88. Aduba DC, Yang H, Polysaccharide fabrication platforms and biocompatibility assessment as candidate wound dressing materials. *Bioengineering*, 2017; 4(1): 1-16.
89. Zhang J, Skardal A, Prestwich GD, Engineered extracellular matrices with cleavable crosslinkers for cell expansion and easy cell recovery. *Biomaterials*, 2008; 29(34): 4521-4531.
90. Fakhari A, Berkland C, Applications and emerging trends of hyaluronic acid in tissue engineering, as a dermal filler, and in osteoarthritis treatment. *Acta Biomater.*, 2013; 9(7): 7081-7092.
91. Burdick JA, Prestwich GD, Hyaluronic acid hydrogels for biomedical applications. *RSC Adv.*, 2018; 8(56): 31934-31942.
92. Serban MA, Prestwich GD, Modular extracellular matrices: Solutions for the puzzle. *Methods*, 2008; 45(1): 93-98.
93. Jha AK, Hule RA, Jiao T, Teller SS, Clifton RJ, Duncan RL, Pochan DJ, Jia X, Structural analysis and mechanical characterization of hyaluronic acid-based doubly cross-linked networks. *Macromolecules*, 2009; 42(2): 537-546.
94. Zhong J, Chan A, Morad L, Kornblum HI, Fan G, Carmichael ST, Hydrogel matrix to support stem cell survival after brain transplantation in stroke. *Neurorehabil Neural Repair.*, 2010; 24(7): 636-644.
95. lia R, Fuegy PW, VanDelden A, Firpo MA, Prestwich GD, Peattie RA, Stimulation of *in vivo* angiogenesis by in situ crosslinked, dual growth factor-loaded, glycosaminoglycan hydrogels. *Biomaterials*, 2010; 31(17): 4630-4638.
96. Datar A, Joshi P, Lee M-Y, Biocompatible hydrogels for microarray cell printing and encapsulation. *Biosensors*, 2015; 5(4): 647-663.
97. Longinotti C, The use of hyaluronic acid based dressings to treat burns: A review. *Burns & Trauma*, 2014; 2(4): 162-168.
98. Nashatizadeh MM, Lyons KE, Pahwa R, A review of ropinirole prolonged release in Parkinson's disease. *Clinical Interventions in Aging*, 2009; 4: 179-186.
99. Loebel C, Rodell CB, Chen MH, Burdick JA, Shear-thinning and self-healing hydrogels as injectable therapeutics and for 3D-printing. *Nat Protoc.*, 2017; 12(8): 1521-1541.
100. Sinha VR, Bansal K, Kaushik R, Kumria R, Trehan A, Poly-epsilon-caprolactone microspheres and nanospheres: an overview. *Int J Pharm.*, 2004; 278(1): 1-23.
101. Yu HS, Park J, Lee HS, Park SA, Lee DW, Park K, Feasibility of polycaprolactone scaffolds fabricated by three-dimensional printing for tissue engineering of *tunica albuginea*. *World J Mens* Health, 2018; 36(1): 66-72.
102. Cardoso GB, Machado-Silva AB, Sabino M, Santos Jr AR, Zavaglia CA, Novel hybrid membrane of chitosan/poly (ε-caprolactone) for tissue engineering. *Biomatter.*, 2014; 4(1): 1-10.
103. Tsai K, Lin H, Chen Y, Lin C, Hsu T, Kao C, Laser sintered magnesium-calcium silicate/poly-ε-caprolactone scaffold for bone tissue engineering. *Materials*, 2017; 10(1): 1-14.
104. Hankermeyer CR, Tjeerdema RS, Polyhydroxybutyrate: plastic made and degraded by microorganisms. *Rev Environ Contam Toxicol*, 1999; 159: 1-24.
105. Patel SKS, Singh M, Kalia VC, Hydrogen and polyhydroxybutyrate producing abilities of *Bacillus spp.* from glucose in two stage system. *Indian Journal of Microbiology*, 2011; 51(4): 418-423.
106. Melchiorri A, Hibino N, Best C, Yi T, Lee YU, Kraynak CA, Kimerer LK, Krieger A, Kim P, Breuer CK, Fisher JP, 3D Printed Biodegradable Polymeric Vascular Grafts. *Advanced health care materials*, 2016; 5(3): 319-325.
107. Wang S, Lu L, Yaszemski MJ, Bone tissue-engineering material poly(propylene fumarate): Correlation between molecular weight, chain dimensions, and physical properties. *Biomacromolecules*, 2006; 7(6): 1976-1982.
108. Kasper FK, Tanahashi K, Fisher JP, MikosAG, Synthesis of poly(propylene fumarate). *Nature protocols*, 2009; 4(4): 518-525.
109. Temenoff JS, Kasper FK, Mikos AG, Fumarate-based macromers as scaffolds for tissue engineering applications. *Topics in Tissue Engineering*, 2007; (3): 1-16.
110. He S, Timmer MD, Yaszemski MJ, Yasko AW, Engel PS, Mikos AG, Synthesis of biodegradable poly(propylene fumarate) networks with poly(propylene fumarate)–diacrylatemacromers as crosslinking agents and characterization of their degradation products. *Polymer*, 2001; 42(3): 1251-1260.
111. Dean D, Topham NS, Meneghetti SC, Wolfe MS, Jepsen K, He S, Chen J, Fisher JP, Cooke M, Rimnac C, Mikos AG, Poly(propylene fumarate) and Poly(DL-lactic-co-glycolic acid) as Scaffold Materials for Solid and Foam-Coated Composite Tissue-Engineered Constructs for Cranial Reconstruction. *Tissue Engineering*, 2004; 9(3): 495-504.
112. Kallukalam BC, Jayabalan M, Sankar V, Studies on chemically crosslinkablecarboxy terminated-poly (propylene fumarate-co-ethylene glycol)–acrylamide hydrogel as an injectable biomaterial. *Biomedical Materials*, 2008; 4(1): 015002.
113. Pasut G, Panisello A, Folch-Puy E, Lopez A, Castro-Benítez C, Calvo M, Carbonell T, García-Gil A, Adam R, Roselló-Catafau J, Polyethylene glycols: An effective strategy for limiting liver

ischemia reperfusion injury. *World Journal of Gastroenterology*, 2016; 22(28): 6501-6508.
114. Puts CF, Berendsen TA, Bruinsma BG, Ozer S, Luitje M, Usta OB, Yarmush ML, Uygun K, Polyethylene glycol protects primary hepatocytes during supercooling preservation. *Cryobiology*, 2015; 71(1): 125-129.
115. Dutheil D, Underhaug Gjerde A, Petit-Paris I, Mauco G, Holmsen H, Polyethylene glycols interact with membrane glycerophospholipids: is this part of their mechanism for hypothermic graft protection?. *Journal of Chemical Biology*, 2009; 2(1): 39-49.
116. Akbarzadehlaleh P, Mirzaei M, Mashahdi-Keshtiban M, Shamsasenjan K, Heydari H, PEGylated human serum albumin: Review of PEGylation, purification and characterization methods. *Advanced Pharmaceut Bull.*, 2016; 6(3): 309-317.
117. Valuckaite V, Seal J, Zaborina O, Tretiakova M, Testa G, Alverdy J, High molecular weight polyethylene glycol (PEG 15–20) maintains mucosal microbial barrier function during intestinal graft preservation. *The Journal of Surgical Research.*, 2013; 183(2): 869-875.
118. Alhijjaj M, Belton P, Qi S, An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared *via* fused deposition modeling (FDM) 3D printing. *Eur J Pharm Biopharm.*, 2016; 108: 111-125.
119. Zucca P, Fernandez-Lafuente R, Sanjust E, Agarose and its derivatives as supports for enzyme immobilization. *Molecules*, 2016; 21(11): 1-25.
120. Souza BWS, Cerqueira MA, Bourbon A, Pinheiro A, Martins J, Texeira J, Coimbra M, Vicente A, Chemical characterization and antioxidant activity of sulfated polysaccharide from the red seaweed *Gracilariabiridiae*. *Food Hydrocolloid*, 2012; 27: 287–292.
121. Fan R, Piou M, Darling E, Cormier D, Sun J, Wan J, Bio-printing cell-laden Matrigel–agarose constructs. *Journal of biomaterials applications*, 2016; 31(5): 684-692.
122. Gasperini L, Mano JF, Reis RL, Natural polymers for the microencapsulation of cells. *Journal of the Royal Society Interface.*, 2014; 11(100): 20140817.
123. Gu Q, Tomaskovic-Crook E, Wallace GG, Crook JM, Engineering Human Neural Tissue by 3D Bioprinting. *Methods Mol Biol.*, 2018; 1758: 129-138.
124. Yang X, Lu Z, Wu H, Li W, Zheng L, Zhao J, Collagen-alginate as bioink for three-dimensional (3D) cell printing based cartilage tissue engineering. *Mater Sci Eng C Mater Biol Appl.*, 2018; 83: 195-201.
125. Fan R, Piou M, Darling E, Cormier D, Sun J, Wan J, Bio-printing cell-laden Matrigel-agarose constructs. *J Biomater Appl.*, 2016; 31(5): 684-692.