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Biomaterials – Novel Advances in Nasal Medical Implants, 3D Printing Applications

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Mini-review Article

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ABSTRACT

The scope and applications of biomaterials have spread out throughout a broad spectrum. Particularly in pharmacy, biomaterials are an attractive choice because they can be modified to decrease toxicity, increase the targeting ability among many other aspects of drug delivery. Extensive studies have led to the development of many metal-based, ceramic, biocompatible and biodegradable biomaterials for medical purposes among many others. The utilization of 3D printing in this discipline is a very novel research subject with infinite potential. Personalized and customized nasal implants are a great option to increase patient compliance and 3D printed accurate anatomical structures are rendered to be effective tools of learning. One of the disadvantages of biomaterial-based implants is the formation of a thick fibrous capsule formation around the implant, others being breakage, soft tissue loss and so on. Regulatory aspects are less explored for nasal implants. 3D printing is a unique technique that allows for a high degree of customisation in pharmacy, dentistry and in designing of medical devices. Current research in 3D printing indicates towards reproducing an organ in the form of a chip; paving the way for more studies and opportunities to perfecting the existing technique.

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Keywords: Biomaterials; 3D printed biomaterials; 3D printed nasal implants; regulatory aspects; drug delivery.

1. INTRODUCTION

The concept of biomaterials can be found in the middle of various subjects like chemistry, materials science, surface science, biology, medicine and many more [1]. The field, since its discovery and introduction has been on a constant climb in terms of field of research interest, creating many branches, novel ideas and applications along the way.

Biomaterial is defined as "a non-viable material used in a medical device, intended to interact with biological systems" [1,2].

Biomaterials are a result of constant collaborative work between engineers, biologists, clinicians and physicists for more than sixty years [3,4].

1.1 Rationale for the Requirement of Biomaterials in Medicine

The need and applications of biomaterials in the field of pharmaceutical sciences are described in Fig. 1. [3,5-15].

1.2 Biomaterials in Implants

1.2.1 Brief historical background

Implants for medical use have evidence to have been in use for at least two thousand years. The modern era of implants started when a British ophthalmologist named Harold Ridley made an observation on spitfire fighter pilots in the 40s, when he observed that the accidental implantation of a plastic shard healed without complications [1]. This led to the invention of a lens for the eyes.

1.2.2 Mechanism of wound healing

In order to understand the process that occurs In vivo following implantation, it is important to understand the wound healing process. Wound healing is a complex process that involves many mechanisms. The main four phases of wound healing are represented in Fig. 2, and the other mechanisms occurring in between these phases are discussed [16].

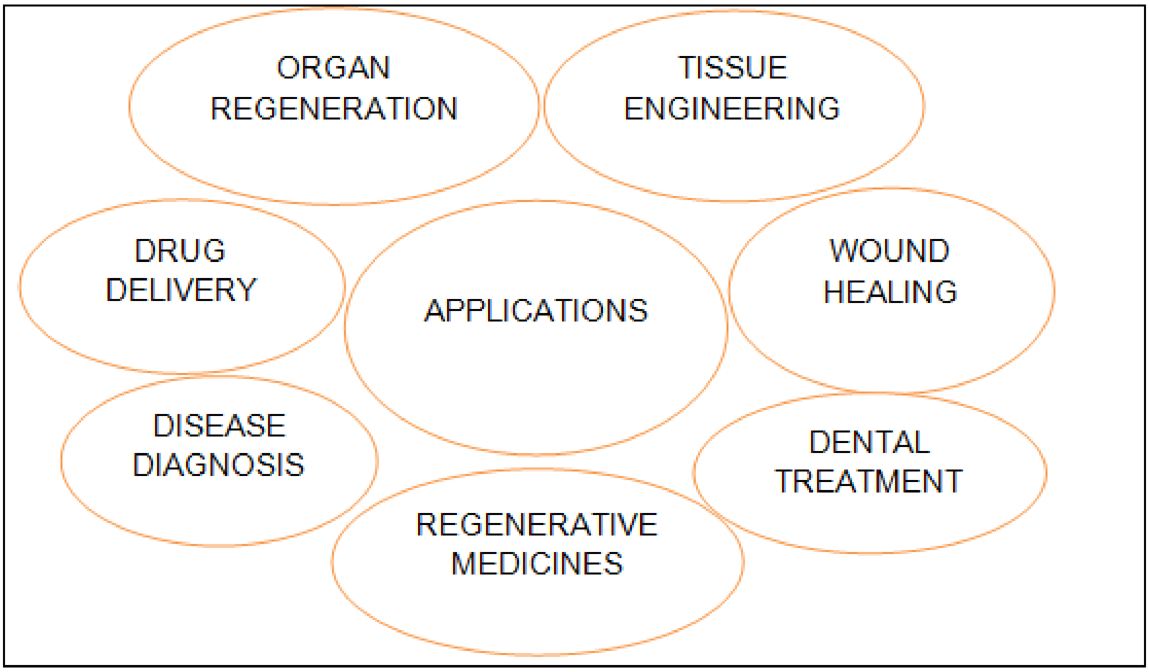

Fig. 1. Applications of biomaterials in pharmaceutical sciences

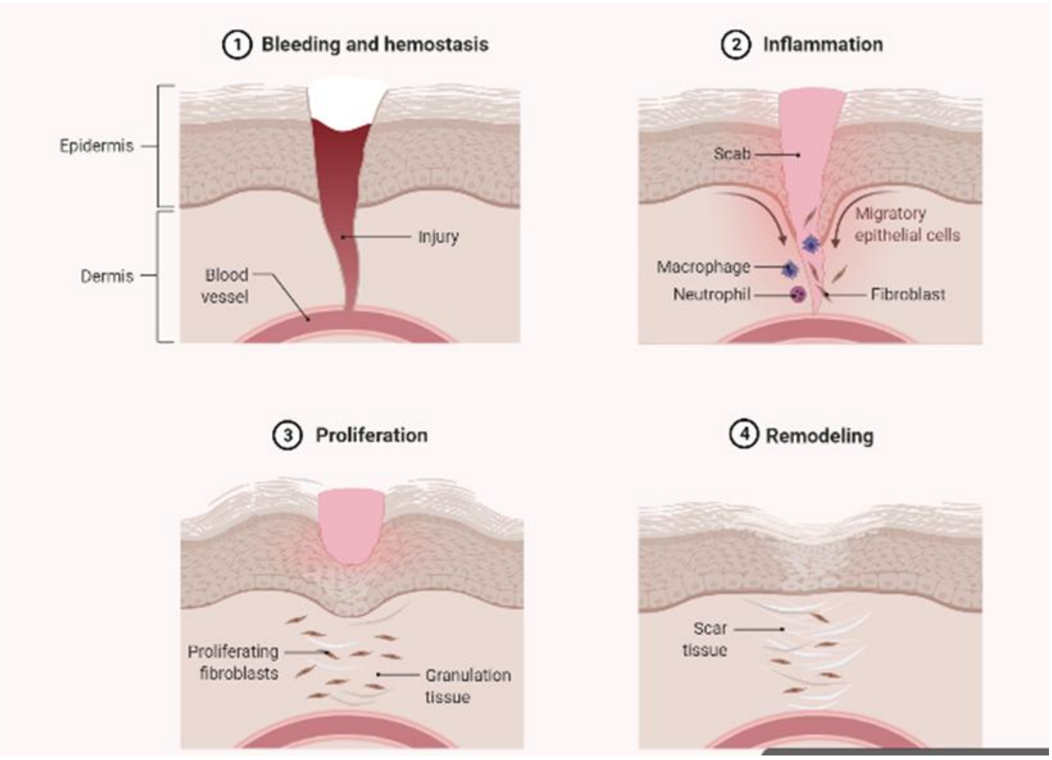

Fig. 2. Mechanism of wound healing

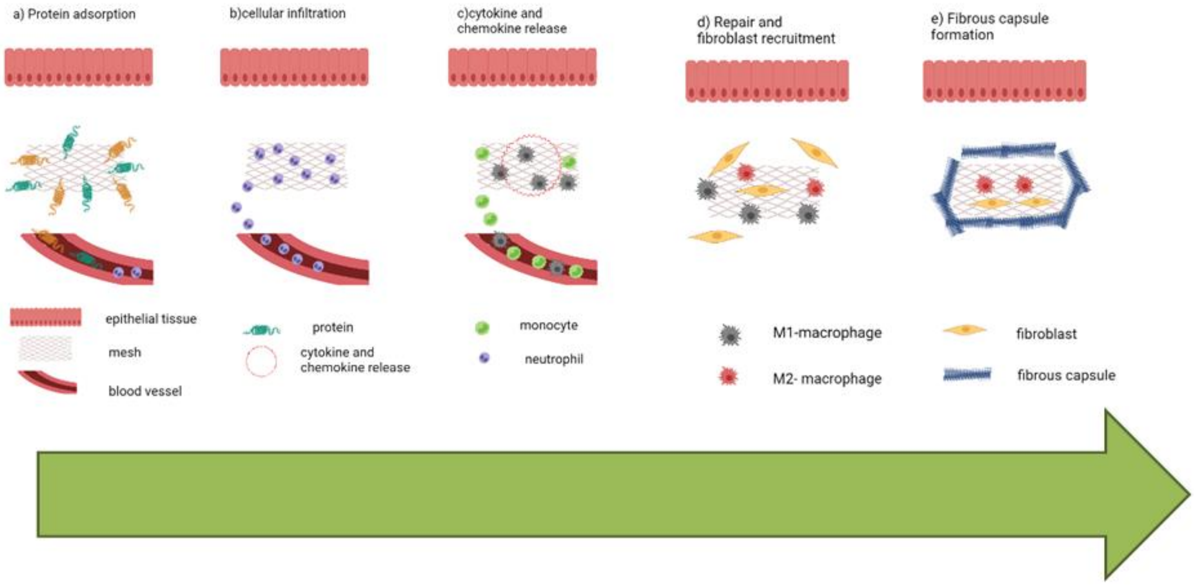

Fig. 3. Foreign body reaction to a biomaterial-based implant

1. An immediate surge in blood flow to the injured area. Blood clot formation due to the entrapment of platelets by activation of fibrinogen to mesh like fibrin network.
2. Cytokines and growth factors attract WBC's (White blood cells) and Neutrophils, monocytes differentiate into macrophages and accumulate at the site to clean out any bacteria, dead cells and other foreign materials and then the conversion of the blood clot into a highly vascularized granulation tissue occurs.
3. Extracellular matrix (ECM) replaces granulation tissue.

4. Either complete tissue architecture restoration; or replacement of granulation tissue with scar tissue occurs.

1.2.3 Foreign body reaction

Foreign body reaction, although a boon to protect the body from potential harmful foreign bodies, is rendered more harmful when it comes to implants. A fibrous capsule forms around the implant made of biomaterial which hinders the healing process. This points out the enormous amount of development that is needed in the designing of biomaterial implants. Foreign body reaction is slightly different than wound healing mechanism. The same is represented in Fig. 3. [16]

From Fig. 3,

a) Protein absorption.
b) Cellular infiltration.
c) Interrogation and attack by neutrophils, then macrophages.
d) Giant cell formation, Cytokine release.
e) Thick, Avascular capsule made of collagen- Around three weeks after implantation.

2. BIOMATERIALS IN IMPLANTS-CURRENT ADVANCES

Many people around the globe require prosthesis, implants and drug eluting devices due to trauma, external injury and to prevent oral intake of drug every day. Implants can also be designed to hold the drug and release at a constant rate for longer periods of time. The main reason for the failure of implants is the rejection due to foreign body response. Hence, extensive research is being carried out to make the biomaterials more biocompatible. Many studies are being undertaken to make the polymers biodegradable in order to avoid secondary procedure to take the implant out, e.g., in case if it is a drug eluting type, which requires to be in the body for only a short period of time. The Table 1 summarises usage of biomaterials in various disciplines in the medical field.

Table 1. Biomaterials and their intended use in various disciplines in the medical field

Sl No	Area of research	Biomaterials used	Uses/intended applications	Reference
1	Cardiovascular	Polypropylene, Polyamide, among others.	pacemakers, assisting device for left ventricle	[17] [18]
2	Orthopaedic	a.poly(aryl-ether-ether-ketone) (PEEK) Biomaterials. b. Metallic- cobalt alloys, titanium alloys, magnesium alloys among others. c. Biodegradable polymers: polylactic acid (PLA), poly3-caprolactone (PCL) and others. d. Ceramics-alumina, zirconia, bioactive calcium hydroxyapatite, bio glass and others. e. Biodegradable/ bioresorbable ceramics- tri calcium phosphate	a. Extending the longevity as compared to existing traditional biomaterial implants b. cobalt alloys show better strength and better resistance towards corrosion. Titanium alloys offer better biocompatibility and corrosion resistance whereas, magnesium alloys are third generation biomaterials designed to improve healing rate of fractured bone and are bioresorbable. c. PLA has a wide array of scope. From sutures to biodegradable implants. It is compliant with 3D printing. PCL can be stretched and pressed, it is biocompatible and biodegradable and is used as a drug delivery system.	[19-26] [27,28] [29,30]

Sl No	Area of research	Biomaterials used	Uses/intended applications	Reference
			d. Alumina's inertness is attractive in the fabrication of orthopaedics, Zirconia is used in total hip prosthesis, Calcium hydroxyapatite shows better osseointegration and from bio glasses, microspheres and porous implants can be produced. e. Bone vacuum fillers show in a study by Cutright et al. showed good bone growth and reformation of bone marrow in rats after 48 days of surgically implanting a bone replacement.	[31-34] [35,36]
3	Plastic surgery	Silicone, polypropylene, polydimethylsiloxane, Polyethylene terephthalate and many others	Breast implants, lip implants, cheek, jaw and chin implants	[1]
4	Trauma, spinal	i) Nylon 6-10, polysulphone (PS), polybutylene terephthalate (PBT), poly(aryl-ether-ether-ketone) (PEEK) among others. ii) Polyaryletherketones (PAEK)	i) Because of their high biocompatibility and high-performance, they show good potential as fracture fixation devices and composite hip stem development. ii) For the treatment of back pain due to spinal instability or degenerative disc disease.	[19,37]
5	Dental implants	Polymethylmethacrylate, Titanium alloys	Dental implants, dentures.	[17,38]
6	Ear, nose, throat	Parylene, liquid crystal polymer, silicone, polylactic glycolic acid (PLGA) and others.	Nasal implants, cochlear implants, stapes implants and others.	
7	Orbital implants	a. Autologous-tissues b. Polymeric-Silicone, polyacrylamide hydrogel, Polyethylene, PMMA (poly (methyl methacrylat) among many others. c. Ceramic- Glass, Bioactive glass, Alumina and others. d. Composite- Teflon/ Carbon fibres, Silicone/Alumina and others. e. Magnetic	a. As a wrapping material to increase the implant biocompatibility. b. Highly biocompatible, inexpensive orbital implants. c. decreased complication, more mobile prosthesis. d. To increase the success rate of the implant. e. Integration of implant and prosthesis by sandwiching the conjunctiva between the two elements to impart better movement.	[39]
8	Hard tissue replacement	Hydroxyapatite (HAp) composites and ceramics.	Potential application in hard tissue replacement implants.	[40]

2.1 Biomaterials in Otorhinolaryngology

After discovering the enormous amount of personalisation potential offered by three-dimensional printing, the said technique has successfully made its way to Otorhinolaryngology. In addition to teaching anatomy, training for surgery using 3D printed prosthesis based on high resolution CT images which gives highly accurate anatomical structures, to overcome the otology related defects arising from defective ossicular chains, and to 3D printed scaffolds for correcting the septal perforation, 3D printing finds an enormous amount of application in otorhinolaryngology [41-46]. 3D replicas of the patient body structures in full scale facilitate the surgeons to fully understand the problem, even conduct a practice surgery to improve skills, and to decrease the error margin to get better results. An effort has been made to a 3D print for a splint in a lethal case of bronchomalacia was promising outcome [47,48]. 3D tissue printing has been a boon in the reconstruction of a damaged ear pinna due to a trauma or defects, e.g. postoperatively [49] and many other conditions such as anotia, in which the external ear pinna is completely absent. The Studies on various biomaterials used in ear, nose and throat for various purposes are listed in Table 2.

Table 2. Biomaterials for ear, nose and throat related complications

Sl No	Study	Intended target site	Biomaterial (s) utilised	3D Printing utilization	References
1	Creation of biomimetic microstructure of auricular tissues by proliferating the chondrocytes and perichondrial cells in a continuous flow bioreactor, shadowed by cultivation in an appropriate medium.	External ear	Polypropylene bioreactor wells for creating bi-layered constructs.	Not utilized	[50]
2	Printing of external ear shaped structure.	External ear pinna	Norbornene-modified poly (glycerol sebacate) (Nor-PGS)	Utilised	[51]
3	Model scaffold design for complete ear reconstruction using a three-dimensional printing method.	Auricular reconstruction	Polycaprolactone (PCL)	Utilised	[52]
4	Indirect utilisation of prototype for final prosthesis.	External ear	Powdered gypsum	Utilised	[53,54]
5	Custom 3D Printing of ear ossicular prosthesis	Middle ear	Not available	Utilised	[55]
6	Fabrication of biomimetic ceramic ossicles.	Middle ear	Hydroxyapatite and PCL	Utilised	[56]
7	Fabrication of human middle ear and potentially control the transmission behaviour.	Middle ear	White polyamide powder PA2200 (PA)	Utilised	[57]
8	Custom middle ear prosthesis.	Middle ear	Polycaprolactone	Utilised	[58]
9	Transparent temporal bone and vestibulocochlear organ fabrication.	Inner ear	White resin	Utilised	[59]

Sl No	Study	Intended target site	Biomaterial (s) utilised	3D Printing utilization	References
10	Fabrication of nose shaped 3D printed structures.	Nose	Norbornene-modified poly (glycerol sebacate) (Nor-PGS)	utilised	[51]
11	3D printing and validation of osteomeatal complex and frontal sinus.	Sinus	Not available	utilised	[60]
12	Bioresorbable airway Splints for severe Tracheobronchomalacia.	Throat	Polycaprolactone, Hydroxyapatite	Utilised	[61]
13	Stent for tracheobronchial related complications.	Trachea	PCL, TPU (thermoplastic polyurethane) and others	Utilised	[62,63]

2.2 Nasal Drug Eluting Materials a Barely Explored RESEARCH Area with Infinite Potential

To increase the effectivity of the results in endoscopic sinus surgery (ESS), many absorbable and non-absorbable biomaterials have been introduced and studied in rhinology. These polymers are aimed to reduce postoperative inflammation as well as to increase the healing process. Some biomaterials like Hyaluronic acid, Chitosan, Fibrin glue, Collagen have been extensively studied for this purpose with no conclusive results of superiority in regards of e.g., inflammation, wound healing, or others [64].

The various applications of biomaterials in rhinology are represented in Table 3.'

Various studies are being undertaken in various fields of rhinology such as nasal reconstruction, nasal septum perforation reconstruction, reconstruction of nasal cartilages and subchondral bone and many more. Some of these studies are represented in Table 3.

Chronic sinusitis is a very pertinent chronic disease and nasal drug loaded implants are a novel application of biomaterials in rhinology, especially for endoscopic sinus surgery (ESS). The idea of nasal implants is that on addition to the existing treatment regimen, a novel implant loaded with a corticosteroid drug is implanted on the site of surgery, allowing a constant rate of release of drug at the site to decrease the inflammation, as well as the design is such that it prevents the closing up of the sinus again due to post-operative inflammation, polyp formation and scar tissue formation, which requires a secondary treatment or surgery. The drug eluting implant should stay at the site of implantation and it should biodegrade within a short span of time to avoid another procedure to take the implant back out. PROPELTM is one such promising drug eluting nasal implant. The main advantage of nasal implants is that they help overcome the adverse effects caused by oral steroids, as well as help prevent the need for secondary surgical intervention in the long term [70].

Table 3. Application and functions of biomaterials in rhinology in surgery [64]

SL. No	Applications	Functions
1	Rhinoplasty	cosmetic and functional sinonasal
2	Choanal Imperforation	Minimize the formation of granulation tissue
3	Balloon Sinuplasty	Dilation of obstructed ostia at the level of the maxillary, sphenoid and frontal sinuses
4	Endoscopic Dacryocystorhinostomy (DCR)	Formation of a large fibrous ring, to ensure a long lasting permeability of the lacrimal pathway

Table 4. Biomaterials in Rhinology related studies

Sl no	Study description	Biomaterial(s) Under study	3D printing	References
1	Examining the biocompatibility and absorption profile of a nasal implant using Ovine model.	Poly (L-lactide-co-D, L-lactide)(PLA)	No	Rippy et al. [65]
2	An implant for nasal augmentation and for nasal surgeries such as septoplasty and rhinoplasty.	Polycaprolactone (PCL)	Yes	Park et al. [66]
3	Developing a septal cartilage implant for the treatment of nasal septal perforations.	poly-L-lactic acid (PLLA)	Yes	Rajzer et al. [67]
4	Fabrication of electrospun scaffolds for nasal cartilages and subchondral bone reconstruction.	Layered gelatin/PLLA	Yes	Rajzer et al.[68]
5	Fabrication of customised nasal cartilage for augmentive rhinoplasty	Polycaprolactone (PCL)	Yes	Yi et al. [69]

3. RISKS AND DISADVANTAGES OF NASAL IMPLANTS [71]

As of now, no known implant has optimum characteristics. The effectiveness of the implant is decreased due to many factors. Some of the disadvantages and risks associated with nasal implants are represented in Fig. 4.

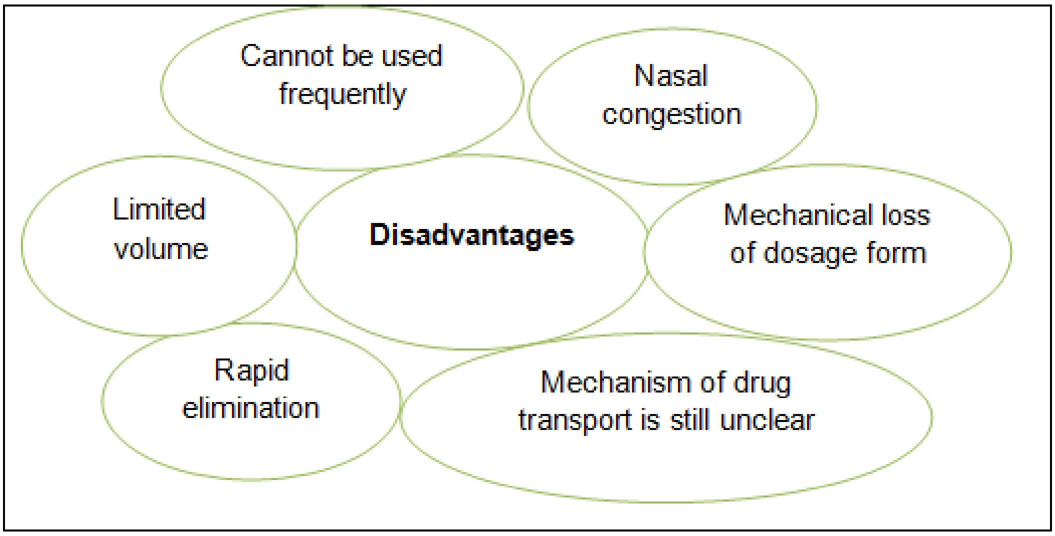

Fig. 4. Disadvantages and risks related to nasal implants

4. FUTURE PROSPECT OF 3D PRINTING IN OTORHINOLARYNGOLOGY

4.1 Regulatory Aspects

With a new application, comes a need for stringent regulatory requirements and Good Manufacturing Practices guidelines. There is a need for a control process for 3D printed medical devices. Some attempts have been made by various regulatory bodies of the world, such as the EU and USFDA in this aspect, which still needs a lot of refinement [47].

4.2 Integration of Electronics into 3D Printed Implants [72]

Using additive manufacturing processes, electric components and sensors may be combined into complex parts. According to studies, 3D printed sensors have been used to assess a range of things, including pressure, ultrasounds, gas detection, food quality, biosensors, and even brain activity.

In the form of bionics, a group from Princeton has attempted to create a coil antenna by the integration of chondrocytes of the cartilage as well as silver nanoparticles.

4.3 Tissue Engineering

The idea behind tissue engineering is to impregnate 3D printed scaffolds with living cells in order to build a very complicated microarchitecture, which is still in the phase of ongoing research and not clinical practice [73].

The demonstration of cartilage growth by nasal and ear scaffolds in a swine model has been done by Zopf and co-workers. Many studies have pointed towards the excellent cell viability of bio-ink extruded by inkjet or extrusion techniques [74].

5. CONCLUSION

Biomaterials find numerous applications in various fields of science. They are especially attractive in the field of medicine and pharmaceutical sciences due to their adaptability, biocompatibility and biodegradability. Combining 3D printing with biomaterials makes way for increased patient compliance, thus helping in the betterment of the said fields by increasing the degree of personalisation and customisation. One of the main issues to be tackled with biomaterial implants is the formation of a fibrous capsule around the implant which forms as a result of natural foreign body reaction. 3D printing in otorhinolaryngology is an attractive research area and clinical topic and will lead to further guidelines developments and regulations with ongoing research and usage. As attractive the 3D printing in otorhinolaryngology is, there is a need for more defined guidelines and stringent regulatory requirements for the success of this approach. Although some ideas appear to be only theoretically feasible, it is only a matter of time before the most futuristic-looking possibilities become a reality.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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