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REVIEW ARTICLE

TISSUE ENGINEERING BIOREACTORS: POTENTIAL APPLICATIONS AND SCALE UP STRATEGY

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Abstract

Tissue engineering bioreactors have been used in order to achieve production of artificial tissue, increasing cell proliferation capacity and yield and/or *in vitro* tissue/disease modelling. Although it is still discussing how to obtain functional and vascular tissue with these bioreactors, preclinical and clinical studies are ongoing. Tissue engineering bioreactors have been used as lab-scale bioreactors until now. Crucial potential application areas can be created by increasing the production capacity and bioprocess efficiency of these bioreactors. In this review, recent bioreactor technologies such as spinner flask, rotating wall/bed, hollow fiber membrane, perfusion and mechanical stimuli bioreactors are briefly presented in terms of their potential applications in medical field especially in the scope of scale-up approaches such as bubble column, stirred tank, membrane, air lift, fluidized packed and bed bioreactors.

Keywords: Bioreactors, modelling in pharmaceutical/biological research, tissue engineering, organ support systems, tailor made treatment.

INTRODUCTION

Cell culture has begun to use in medical sciences as 2D cell culture accompanying with many disadvantages such as not mimicking the *in vivo* environment, mass transfer, gas exchange, waste management, inability to real time monitoring of the culture medium, harvesting the cells by enzymatic methods and eliminating the cell products from the medium during replacement[1,2]. The 3D culture systems have been enhanced by using bioreactors in order to eliminate the disadvantages of the static culture. Bioreactor is a system that supports biological environment, which designed to gather cells/tissues in cell culture. They are developed to use in tissue, bioprocess/biochemical engineering. Bioreactors can be used for the tailor made treatment, the organ support systems, increasing the number of cells before autologous cell implantation, *in vitro* tissue/disease modelling in pharmaceutical research and producing recombinant human proteins, vaccines, drugs and tissue grafts[3,4]. There are different types of bioreactors; spinner flask, rotating wall/bed, hollow fiber membrane, perfusion and mechanical stimuli bioreactors[5]. In this review, recent bioreactor technologies for tissue engineering briefly presented in terms of their potential applications in medical field especially in the scope of scale-up approaches.

Tissue Engineering Bioreactors

Five types of bioreactors, which can be used for tissue engineering are currently in use and commercially available. These are; spinner flask, rotating wall/bed, hollow fiber membrane, perfusion and mechanical stimuli bioreactors[6]. Their mechanisms are briefly indicated as follows.

Spinner Flask Bioreactors

Spinner flasks are simple and frequently utilized bioreactor type. In this system; scaffolds are fixed the needles, magnetic bar mixes the medium. Along seeding, suspended cells into medium are transferred to scaffold throughout by convection. In this way, cell seeding performance is increased by 3D seeding medium[7].

Rotating Wall/Bed Bioreactors

First discovered rotating wall bioreactor has been originally projected by National Aeronautics and Space Administration (NASA) in order to gather stable cell culture research in space. At the same time, this is revealing a potential for culturing cells on Earth. Wall rotation rate allows the centrifugal force, hydrodynamic drag force and gravitational force[8,9].

Hollow Fiber Membrane Bioreactors

The bioreactors are frequently utilized for culturing sensitive and highly metabolic cells which are needed high mass transfer[10]. Hollow fiber membrane bioreactors have increased surface for cell attachment. Cells can be seeded inner/outer surface of fibers. Hollow fiber membrane bioreactors are utilized for several purposes; cell population expansion and creation of engineered tissues in the field of regenerative medicine, *in vitro* models for drug testing in pharmaceutical industry[11].

Perfusion Bioreactors

The perfusion bioreactors have continuous flow and oxygenated medium through seeded scaffold which is fixed part of bioreactor. These features enhance medium flow through scaffold pores also provide mechanical stimulus to cells with optimized shear stress. In this way, cell function and viability are improved[12].

Mechanical Stimuli Bioreactors

There are several types of mechanical stimuli bioreactors which are utilize static, dynamic or combined effect. Compression bioreactors utilized for development of cartilage tissue that are required mechanical stimulus for proliferation. In strain bioreactors; force applied to the construct is a tensile force. These systems are utilized for tendons and ligaments engineering[13].

Table 1: Application fields, types and examples of bioreactors in medical fields.

Applications Fields of Bioreactors	Types of Application	Application Examples
The tailor made treatment	Organ support systems	Bioartificial kidney system[4,18,19] Bioartificial liver support system[20,21,22,23] Bioartificial pancreas system[24,25]
	Increasing the number of cells before autologous cell implantation	Chondrocyte[26] Hepatocyte[27] Stem cell[28] Platelet rich plasma[29]
Modelling in pharmaceutical/biological researches	*In vitro* tissue modelling	Bone tissue[30] Cornealtissue[31] Skeletal muscle[32] Vascular smooth muscle tissue[33] Micro-Bioreactors, Lab-on-Chips, Organ-on-Chips[34-40]
	Disease modelling	Modelling fibrosis[41] Modelling colon cancer[42] Modelling acute liver failure[43] Modelling chronic obstructive pulmonary disease[44] Modelling lung tumor[45,46] Modelling malignant peripheral nerve sheath Tumor[47] Disease-on-Chips[48-50]
Human medicinal products bioprocess	Vaccines	Viral vaccine production (H1N1)[17] Monoclonal antibodies[51]
	Recombinant human proteins	Recombinant human serum albumin[52] Recombinant human insulin[53]
	Drugs	Antibiotics (phenoxymethyl penicillin)[54] Citric acid[55] Pyruvic acid[56] α-Cyclodextrin[57]
	Tissue grafts	Vascular tissue graft[58-62] Osteochondral graft[63,64] Bone graft[65-69]

Potential application fields and scale up strategy

Tissue engineering bioreactors are lab-scale bioreactors based on tissue production or modeling. In addition to the works carried out to achieve the goal of tissue production, other outcomes of these systems were also benefited. Scale-up approaches and techniques are coming with problems to overcome. These problems are also parameters that need to be optimized such as operating time, production efficiency and capacity, temperature, pH, oxygenation, continuous monitoring, mass transfer, gas exchange, obtaining products and control of secondary processes. If repeatable and reproducible systems are obtained by optimizing scale-up conditions, potential applications of bioreactors in the medical field can be better succeded[5-13].

Considering the usage areas of tissue engineering bioreactors and gains, it is seen that these bioreactors have potential application capacity. Potential applications arise due to the needs for them. Recent potential applications of bioreactors in the medical field can be listed as; i. taylor made treatment, ii. *in vitro* tissue/disease modelling in pharmaceutical /biological research, iii. producing recombinant human proteins, vaccines, drugs and tissue grafts[4,14-17]. Although not in the near future; there is a potential that tissue/organ printing and personal bioreactor producing.

The Tailor Made Treatment

Conventional treatment methods include generalized protocols based on common indications. On the other hand in some clinical scenarios, patients' individual feature and medical charts of patients may vary from patient to patient. The tailor made treatment with bioreactors can be achieved as application of organ support systems and increasing the number of cells before autologous cell implantation. Some organs have synthesis, filtration, metabolization and detoxification function such as kidney, liver and pancreas. In this point, the extracorporeal organ supporting systems is beneficial, especially on the cell based therapy for example; stem cell, platelet rich plasma, autologous cell implantation, etc., cell proliferation capacity and harvested cell number differ with patient to patient by cell origin, age and gender. Because of these individual changes, the tailor made treatment has been gained importance[14,15].

Modelling in Pharmaceutical Research

Animal studies and their outcomes are naturally piece of development of therapeutic systems. However; there are some ethical concern come from 3R approach. In this point *in vitro* tissue, disease and physiological system modelling are preferable because of saving animals and also avoid consuming time, budget and working power. Scientists have been still working on tissue modelling such as cardiac, liver, pancreas, breast and bone tissue modelling in order to work targetted organ. On the other way, there are some studies as to disease modelling such as bone fracture, damaged tissue, cancer tissue in order to work disease based therapeutical agents[16]. Multicellular spheroid, hollow fiber and multicellular layer are utilized for modelling pharmaceutical research such as understanding cytotoxicity, drug metabolism and pharmacokinetics[4].

Producing Human Medicinal Products

The batch processing is conventionally utilized in order to gather human medicinal products such as vaccine, drug and recombinant proteins. In this point, there are some concerns about Good Manufacturing Practices (GMP) requirements, yield performance, process management requirements, monitoring, which also must be evaluated in a standardized manner to ensure quality control. Some critical parameters such as proteomics,surface marker analysis,sterility testing and functional assays can be used toensure the quality control[15,70,71]. In spite of the mentioned concerns, the bioreactors seem to be a good a solution with acoustic settlers, hollow fiber bioreactors and hollow fiber based perfusion systems including tangential flow filtration or alternating tangential flow technologies[17].

CONCLUSIONS

The results obtained with tissue engineering bioreactors are promising. These systems increase cell number and efficiency, cell transplantation performance through tissue scaffolds, largely eliminate the disadvantages of the 2D cell culture medium, ensure real-time monitoring of the cell culture medium and achieve graft production. However; there are some problems such as lack of repeatability/reproducibility in production performance, standardizing treatment protocols for transplantation and achieve the same efficiency due to patients' different age, gender and health status. It is also seen from the studies in the literature that functional and vascular structures cannot be obtained. On the other hand, GMP requirements and legislative infrastructure should be developed in advanced therapy medicinal products. Additionally; scale-up approaches and techniques are coming with problems to overcome. These problems are also parameters that need to be optimized such as operating time, production efficiency and capacity, temperature, pH, oxygenation, continuous monitoring, mass transfer, gas exchange, obtaining products and control of secondary processes. If repeatable and reproducible systems are obtained by optimizing scale-up conditions, potential applications of bioreactors in the medical field can be better succeeded. From the perspective of the future, it is anticipated by the related studies that while the developments in bioreactor systems continue, there will be significant developments regarding the use of plants as bioreactors in drug development.

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AUTHOR'S CONTRIBUTION

ALADAĞ S: writing, review, and editing. **ALGIN YAPAR E:** methodology, data curation, formal analysis. All authors revised the article and approved the final version.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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