REVIEW ARTICLE

Scaffold Mediated Carrier as Topical Drug Delivery System: A Review

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Received: 28th August, 2024; Revised: 30th Oct, 2024; Accepted: 25th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT

Background: The development of new pharmaceutical approaches and products based on fiber-based scaffold-mediated carriers for targeted drug delivery is crucial for managing acute and chronic ailments.

Objective: Past research has shown the potential of fiber-based scaffolds in biomedical scaffold design and skin tissue engineering for resorbing skin layers and regenerating skin appendages.

Method: Various fabrication methods, including fiber bonding, gas foaming, phase separation, freeze drying, and solid freeform manufacturing, are employed to create scaffolds.

Results: This review explores the use of different grades of polymers and their pharmacokinetic behavior in scaffold fabrication. It comprehensively discusses various sources of polymers for developing potent fibrous scaffolds, evaluation methods for scaffold physicochemical characteristics, and therapeutic applications in healthcare.

Conclusion: Overall, this review highlights fiber-based scaffold-mediated carriers as promising tools pharmaceuticals and healthcare applications, offering significant potential for targeted drug delivery and tissue regeneration.

Keywords: Scaffold, Nanocomposites, Bone tissue engineering, Tissue engineering, Fiber Technology, Drug Delivery system, Pharmaceuticals.

How to cite this article: Chaurasia L , Gaurav, Islam MU Scaffold Mediated Carrier as Topical Drug Delivery System: A Review International Journal of Drug Delivery Technology. 2024;14(4):2499-505. doi: 10.25258/ijddt.14.4.71

Source of support: IIMT College of medical Sciences, IIMT University Meerut, 250001, Uttar Pradesh, India

Conflict of interest: None

INTRODUCTION

As the past review and research studies throughout the several years, the development of using tissue engineering method made all of this possible and enabled the regeneration of tissue in practically all human tissues and organs. A crucial therapeutic approach for both current and future medicine is tissue engineering. Though conceptually basic and desirable, Regenerative medicine and tissue engineering have shown to be difficult technical tasks. Despite the quick development of this discipline, regenerative medicine and tissue engineering —to control, coordinate is the ultimate objective and direct tissue formation-remain difficult due to considerable information gaps. [1,2] Tissue engineering has become a crucial therapeutic approach for both current and future medicine, enabling tissue regeneration in almost all human tissues and organs. Despite its potential, regenerative medicine and tissue engineering remain challenging due to significant information gaps. The finalized tissue is transferred to the patient, where it continues self-repair remodeling and development. Tissue engineering is a promising replacement for existing therapies for illnesses and organ damage, and has potential in drug discovery and research. The interdisciplinary organization TERM (Tissue Engineering and Regenerative Medicine) aims to develop 3D cells composed of porous, biocompatible, and biodegradable material complexes for regenerative materials. TERM employs three main tactics: transplantation into the body, tissue integration, and cell delivery scaffolds. Scaffolds are beneficial for tissue engineering due to their properties such as tensile stresses, desired dimensions, form, mechanical strength, cell delivery, biocompatibility, and physical structure that supports cell adhesion.[3,4]

Classification of Scaffold Mediated Carrier

These structures fit into the following groups: The first four components are a typical 3D porous matrix, a nanofiber matrix, a sol-gel transition hydrogel that is thermosensitive, and a porous microsphere. Injectable versions include thermosensitive sol-gel transition hydrogel and porous microspheres, while regular 3D porous matrix and nano fiber matrix are available in implantable forms.[4,5] The core approaches or technologies being used tissue engineering and tissue regeneration that use naturally occurring materials, and encasing growth factors in hydrogels, microspheres, and porous scaffolds have been represented in the Figure 1.

Biomaterial used for Fabrication of Scaffold

B Using among these polymers straightforward technique in order to produce biomimetic materials because majority of naturally occurring substances, particularly Polymers based on proteins may, can imitate numerous extracellular matrix properties. Below, a quick overview of a few typical polymers that, in some cases, is the most often used for drug or cell administration in tissue engineering. [10-11]

EVALUATION PARAMETER OF SCAFFOLD

Physical examination

The uniformity and abrasiveness of a hydrogel are typically assessed visually and by tactile examination, running fingers through it to ensure consistency and smoothness.

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Ratios of moisture loss, porosity, and swelling

Moisture loss (%) = W2− W1/ W2 × 100 …(1)

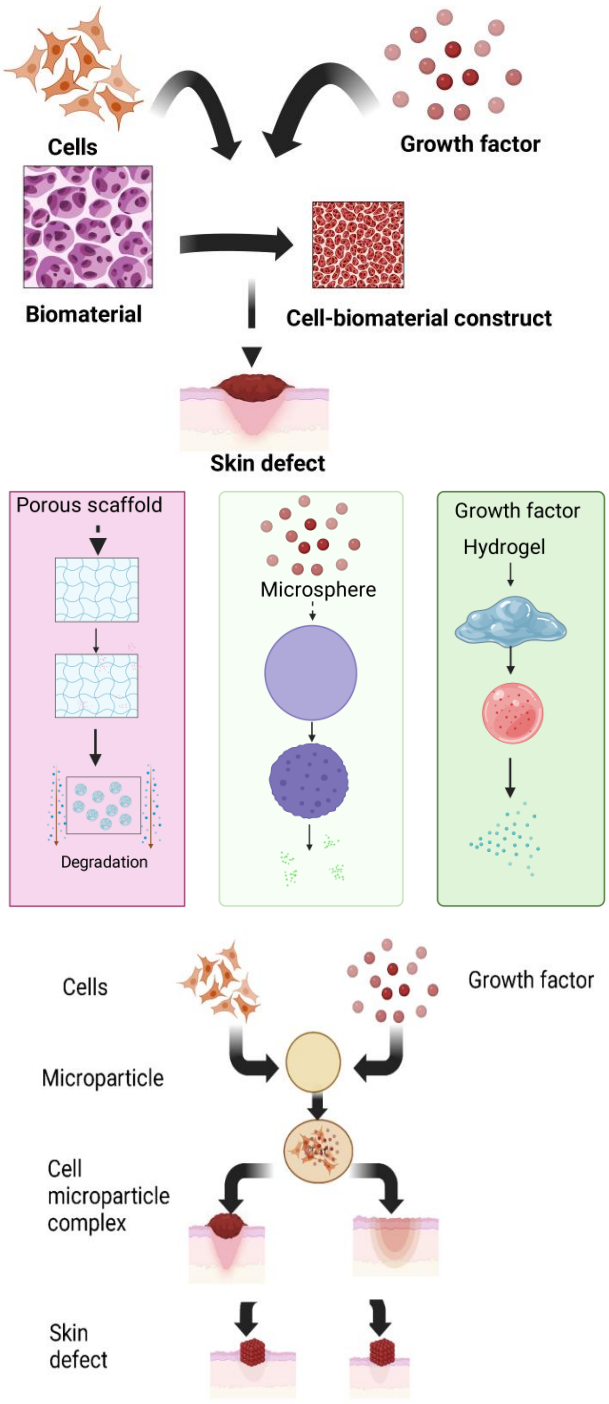

Figure 1: The essential techniques or technologies used in tissue engineering utilizing naturally produced materials (I) to promote in vivo tissue regeneration, a biomaterial scaffold made of organically generated materials is also used. (II) Other drug delivery methods include encasing growth factors in hydrogels, microspheres, and porous scaffolds. (III) The integration of controlled growth factor release into the same biopolymer may provide an enhanced versatile platform that might regulate and monitor the mechanism of tissue regeneration

Where W1 and W2 represent, respectively, the sample's weight before and after immersion

Porosity will then be calculated using Equation (2).

Porosity (%) = W2− W1/ρVs × 100…(2)

The swelling index is determined by immersing a sample at 37ºC for 48 hours. Afterward, excess water is removed, and the sample is accurately weighed. Equation (3) is then used to calculate the swelling ratio.

Swelling index (%) = Ww− Wd /Wd × 100…(3)

Where Wd is the scaffold's dry weight (before to submersion) and Ww is its wet weight (after immersion)

***In vitro* drug release**

The produced scaffold and formulation will go through in vitro drug release testing using the dialysis bag diffusion technique at pH 7.4 and 6.8.

Drug loading capacity

When referring to a carrier system, the amount of drug that can be loaded onto the system at one time is referred to as its drug-loading capacity. The ratio of an active pharmaceutical component to one or more excipients in a pharmaceutical carrier system is the definition of this term. To calculate the loading capacity of different scaffold compositions, the following formulas were utilized.

Drug loading (%) = Mass of drug/Mass of total polymers x 100

Diffusion studies

To prevent the receptor media from evaporating, the samples were first positioned on either human skin or a synthetic cellulose membrane, which was then positioned on a Franz diffusion cell and covered with parafilm. A phosphate buffer with a pH of 7.4 was added to the receptor medium to maintain a consistent temperature. [38,39]

THERAPEUTIC APPLICATION OF SCAFFOLD SYSTEM

Fiber-based scaffolds have a wide array of applications in the medical field, including tissue engineering, wound healing, medication delivery, and gene transfer. They're also utilized in filtration, affinity membranes, enzyme immobilization, and vascular graft implants. These applications extend beyond medicine into scientific, industrial, and military domains. Biomaterial scaffolds are indispensable in modern medical treatments for various diseases.

Delivery of drugs, cells, and genes via scaffolds

Drug delivery, cell and gene transport, and tissue engineering are among the most common applications for biomaterial-based scaffolds. These formulations can be administered through various routes such as intravenous, ophthalmic, peroral, topical, rectal, vaginal, transdermal, nasal, colonic, and breast administration. These formulations serve as attractive scaffolding materials by retaining cells within a three-dimensional gel matrix, enhancing tissue construct thickness and mechanical integrity

Tissue repairing

Cartilage tissue repair

The challenges associated with cartilage repair, especially in older individuals, stem from the weak matrix turnover, vasculature, and limited ability of mature chondrocytes to

Table 1: Classification and advantages of scaffold mediated carrier

S.no	Classification/type of scaffold mediated carrier	Advantages of different type of scaffold mediated carrier	References
1.	Hydrogel based system	Scaffolds based on hydrogel are a particularly significant class of scaffolds because it is possible to adjust their mechanical characteristics to make them closely mirror those who genuine tissues.	(6)
2.	Microsphere and micro particle based system	To control processes like angiogenesis and cell migration and to determine cell death, nanofabricated particles may provide improved delivery qualities.	(7)-(8)
3.	Membrane based systems	The observations subsequently recommended that GG-EGF/TEECM may enhance wound healing as seen by significantly earlier re-epithelialization and skin maturation.	(9)- (10)

regenerate tissue. Current therapeutic methods like autografts, allografts, and microfracturing often yield unsatisfactory results with low effectiveness rates and patient dissatisfaction

Tendon and ligament repair

The ligaments and tendons in our musculoskeletal system play a crucial role in joint mobility and stability. The most common connective tissue injuries involve ligament or tendon tears, affecting over 800,000 people annually. Shepherd, for instance, investigated collagen fiber-reinforced collagen-chondroitin-6-sulfate (C6S) constructs, aiming to create bioactive and biomechanically robust scaffolds for tissue regeneration.

Corneal tissue repair

Corneal diseases represent a significant cause of preventable blindness globally, affecting millions annually. With donor corneas in short supply, tissue-engineered corneas offer promise as alternatives. The microstructure and properties of the corneal extracellular matrix (ECM), primarily collagen fibrils and proteoglycans, are crucial for tissue-engineered corneas' success. Researchers have developed collagen-based membranes reinforced with silk fibroin to mimic the cornea's mechanical qualities.

Table 1: Different polymer used for fabrication of scaffold with their application

S.No	Polymer name with type	Specific consideration	Application	Reference
1.	Absorbing material (PLLA, PLGA etc) (Synthetic polymer)	scaffolds with a regulated porosity structure made of biodegradable polymers	Porous 3D scaffolds structures, bone and cartilage tissue engineering	(10)
2.	PLGA,PLLA,and PDLLA,PLAGA, PLGA/PPA/PPF (Synthetic polymer)	regulated pore size and porosity sponge with high cell density and have "transplant scaffold	Tissue engineering and drug delivery, Bone repair, Complex forms for applications in tissue engineering	(11)-(12) (13)-(14)
3.	Chitosan,HAP, Collagen, (Natural polymer)	Substantial mechanical stability, A flexible, 3D porous sponge structure	Engineering of bone and cartilage tissue	(13)
4.	HAp, TCP, BCP, and CP ceramics (Synthetic and natural polymer)	Porosity and bioresorbability	Porosity and bioresorbability	(15)
5.	Hydrophilic/ hydrophic di block triblock, PGA, PLGA, and PEG copolymers. PEO, PPO etc (Synthetic and natural polymer)	Biomimetically, exhibit minimal inflammatory response	Engineering of cartilage, bone tissue, and medication delivery	(15)
6.	PMMA,HA, PEG, PNIPAam,PAA, PAam,and PDMAEM (Synthetic polymer)	Microgel,biologically mechanical, Microrods, microbeads, pumps, and valves	Delivery of insulin with gene therapy and microreactors that employ cells, cell separation, controlled microreactors, and sensing	(16)
7.	Chitosan,fibronectin, Alginate (Natural polymer)	Microbeads, microrods, Microgel, biologically degradable	Insulin delivery, cell separation	(16)

8.	PGS,PEG,andPDMS (Synthetic polymer)	Microrods, microbeads, pumps, and valve	Sensing, cell separation, microreactors that use cells, and controlled microreactors	(17)
9.	Calcium alginate, silicon (Natural polymer)	Microrods, microbeads, pumps, and valves	Sensing, cell separation, microreactors that use cells, and controlled microreactors	(17)
10.	Collagen, gelatin, and HA (Natural polymer)	Cell diagnostic, Microgels, and Microsensors	Drug delivery methods that are sustainable and under your control	(18)
11.	Keratin (Natural polymer)	Biocompatibility	coatings for implants, and scaffolds for tissue engineering	(19)
12.	PGA,PLA,PLGA,PCL (Synthetic polymer)	biomechanical, biocompatible, and high surface area	Soft tissue artificial skin, as well as tissue engineering scaffolds	(19)-(20)
13.	PCL, PLA, and PLGA (Synthetic polymer)	fibers that are biocompatible and have strongmechanical qualities	scaffolds for tissue, non wetting textile surfaces, and vascular grafts	(20)
14.	PDO, PGA, and polyesters (Synthetic polymer)	Size of submicron fiber	Filtration, membrane separation, bandages, and tissue engineering scaffolds	(21)
15.	Alginate, chitosan, gelatin, collagen, and fibrin (Natural polymer)	Particles, microspheres, foams, hydrogels, and membranes	Bone regrowth, angiogenesis, and wound healing	(22)
16.	PLA, PEG, and PLGA (Synthetic polymer)	Particles, microspheres, foams, hydrogels, and membranes	Angiogenesis, boneregeneration,and wound healing	(22)
17.	Sodium alginate (Natural polymer)	To create complex tissues made up of several cell types (Hydrogel scaffold)	Active proteins are microdeposited on cellulose, biochips, and acellular polymeric scaffolds.	(18)–(23)
18.	Biodegradeable polymers or blends (Natural polymer)	Complex, mechanically strong, 3D solid item	Hard-tissue scaffolds and honey comb structure scaffolds	(24)

Table 2: Current scenario of scaffold as therapeutic regimen for acute and chronic disease

S.no	Scaffold type Drug loaded with Effective dose	Animal model/ Experimental trial	Tentative or possible mechanism or Biomolecular approch	Reference
1.	Chitosen based biomaterial(4–5 ng/day)	*In-vitro and In- vivo*	Periodontics, orthopedics, and plastic surgery reconstructive treatment.	(25)-[37]
2.	scaffolds that are three dimensional	*both in-vivo and in-vitro*	Plans for identifying adverse outcomes and clinical follow-up.	(27)
3.	Polymerized heparin(L-lactide-co-glycolide) at (Zero order release rate)	*both in-vivo and in-vitro*	Enhance angiogenesis	[40]-(28)
4.	• Gelatin–chondroitin–hyaluronan tri-co polymer scaffold(5cmtri-copolymer scaffold disc)	*In- vivo*	Cartilage tissue engineering	(29)
5.	collagen/chitosan/ glycosaminoglycan scaffold(Scaffold 10 ng)	*both in-vivo and in-vitro*	Proliferation and cartilage tissue engineering scaffolds	(30)
6.	Glycosaminoglycan based hydrogel (250 ng of bFGF per 0.25 ml hydrogel)	*both in-vivo and in-vitro*	hydrogels for controlled release	(31)

7.	Alginate based non-woven scaffold(20 µm diameter)	*In- vivo*	cartilage tissue engineering	(32)
8.	hyaluronic acid (HA) and alginate based hydrogel (5×10^4 cells/sponge)	*In- vivo*	cartilaginous tissue during the repair process	(33)
9.	PLGA,NMP based injectable scaffold Dose of (25 kGy)	*both in-vivo and in-vitro*	cartilage scaffold	(34)
10.	Alginate Hydrogels (Alginate at 2%)	*In-vivo*	Articular Cartilage Regeneration	(35)
11.	3D-Bioprinted Scaffolds bioinks with viable cells	*both in-vivo and in-vitro*	Wound Healing	(36)
12.	Agarose-Based Buccal Gels Scaffold Agarose and carbopol (0.5–1.25% w/v)	*both in-vivo and in-vitro*	Pharmacokinetic estimation of mucoadhesive property	(37)
13.	Nano composite scafolds	*both in-vivo and in-vitro*	Chronic wound healing	(38)-(39)
15.	Porous Scaffold & Three dimensional bioprinting Collagen:HA: Gelatin (2:1:3) and 2% collagen-2%polyethylene oxide (PEO)	*both in-vivo and in-vitro*	Skin Regeneration & Muscle tissue engineering	(40)- (41)
17.	Herbal Extracts based Scaffolds (1.5% centella asiatica)	*In-vitro*	Wound healing therapy	(42)

CONCLUSION

This article discusses remarkable breakthroughs in regenerative medicine and tissue engineering, particularly focusing on advanced 3D scaffolds designed to sustain regenerated and transplanted cells while facilitating the local release of regulatory or medicinal chemicals. These scaffolds, which need to meet various biochemical and functional requirements, are typically created by combining biomaterials with supportive properties conducive to local regeneration. This article highlights that while the designed structures of these complex scaffolds enhance their biological impacts; this often comes with the challenge of rapidly evolving technologies. Advanced composite scaffolds may feature multiple layers with distinct variations in chemical or physical characteristics. These variations play crucial roles in organizing, guiding, and stabilizing multiple cellular phenotypes and heterogeneous extracellular matrix morphogenesis.[40-42]

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