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Review Article

Drug Loaded Porous Scaffold Films: Novel Method in Wound Healing

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ABSTRACT

From the ancient times, wound healing without infection has been main challenge in the field of medical science. For effective healing of a wound, a suitable material had to be used to cover the wound in order to prevent any infection. People have been trying various wound healing processes and material from natural extracts to synthetic implants. Various novel pharmaceutical preparations namely gels, hydrogels, spray, foams, composites and porous film membranes are available for better wound care and healing. Porous scaffolds have many advantages like hemostasis, absorbability, semi-permeability, conformability and scar free over the conventional wound healing materials. Porous scaffolds are easy to formulate and can also be easily sterilized depending upon the area of use. The current review emphasis on the use, method of preparation and advantages of various porous scaffolds fabrication techniques. With the continuous dedicated research in this field the future in near when prous scaffolds would be available as a simple film and would be in the reaches of every individual. This would improve the quality of wound healing with proper concern and care.

INTRODUCTION

From the ancient times, for effective healing of a wound, a suitable material had to be used to cover the wound in order to prevent any infection. Wounds characterized by loss of integrity of the skin and mortality are some basic challenges found in reconstructive surgery. A paradigm shift is taking place in medicine from using synthetic implants and tissue grafts to a tissue engineering approach that uses degradable porous material scaffolds integrated with biological cells or molecules to regenerate tissues. Historically, honey pastes, plant fibers, and animal fats were used as wound dressing materials [1]. Nowadays, with new biopolymers and fabrication techniques, a wound dressing material is expected to have extraordinary properties which enhance the healing process of a wound. For an effective design of a wound dressing, they provide the right environment to enhance and promote wound healing. Recently wound dressings are designed to decrease or eliminate pain, reduce the need for dressing changes, and provide autolytic debridement.

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Ultimately, the main purpose of wound dressing is to achieve the highest rate of healing and the best aesthetic repair of the wound.

Wound

A wound is defined as an injury or tear on the skin surface by physical, chemical, mechanical, and/or thermal damages. A more scientific definition of a wound is a disruption of normal anatomic structure and function of the skin [2]. Mainly two types of wounds are observed which are described as follow:

Acute wounds

These are caused by traumas, but the wounds are usually healable within 8 to 12 weeks. These wounds can be caused by mechanical damage induced by sheer, blunting, and/or stabbing action of hard objects. Cares for these wounds depend on the severity of the wounds [3].

Chronic wounds

These are those injuries which are produced as a result of specific diseases such as diabetes, tumors, and severe physiological contaminations. Healing of these wounds could take more than 12 weeks [4]. The vast majority of chronic wounds can be classified further into

three categories: venous ulcers, diabetic, and pressure ulcer's [5].

Management and Treatment of Wound

Management and treatment of Acute Wound Healing:

A key principle for the management of acute wounds is that the handling and treatment of tissue must be as a traumatic.

- For skin grafts, prevention of shearing is essential so that new blood vessels can grow between the skin graft and the wound bed [6].
- For flaps, support and maintenance of circulation is essential to ensure the survival of the mobilized tissue [6].
- Sutures and staples should be left in place long enough to ensure that there is sufficient tissue strength to hold the wound together without support.
- The time of the removal of sutures and stables varies with the stage of healing and the location and extent of the incision. Leaving sutures forprolonged period contributes to scarring and infection [7].
- If an acute wound fails to heal within six weeks, it can become a chronic wound.
- Acute wounds can result in significant changes to body image. Tissue reconstruction may be of benefit to improve cosmetic results for the patient.

Wound dressing

From old times people tried to heal wounds using wound dressing. They used crude drug extracts (mostly of plant origin), animal fat and honey to heal wounds. For example in Senegal, the people used the leaves of Guierasenegalensis to put on wound. In Ghana the people used extracts of Commelinadiffusa herb and Spathodeacampanulata bark to put on wound and heal it [8]. In order to specify optimal features of ideal wound dressing, several characteristics should be addressed such as:

An ideal material to be applied to wound should be

- Nontoxic
- Biocompatible
- Enhance cellular interaction and tissue development
- Be biodegradable and bioresorbable
-
- Provide a moist environment [9].
- Create a protective mechanical barrier and thermal isolation
- Protect against secondary infections
- Keep the wound environment moist
- Absorb the exudate and bacteria
- Promote debridement
- Contribute to simple gas exchange
- Decrease or removing trauma in the defected area
- Be acceptable for patient
- Should be non- toxic, non-irritant or neither any allergic properties
- Cost-effective

Classification of Wound Dressings Used In Wound Treatment

Materials used to cover wounds and burns are also called artificial skin, as they fulfill the functions of normal skin within areas with wounds and partly destroyed skin.Wound and burn covering materials are classified as follows [10].

a) Traditional dressing:

These are still the most commonly used materials for wound and burn dressings [11]. The traditional dressings, which are generally used during first intervention in wound treatment, prevent wound's contact with outer environment and bleeding [12]. The biggest advantage of these materials is their low cost [13].

b) Biomaterial-based dressings:

The most convenient method used in complete closure of wounds and burns is auto grafting. However, inadequate donor areas for large wounds led to the search for a new tissue source [14]. Biological dressings are natural dressings with collagen-type structures, generally including elastin and lipid. Such dressings can mainly be categorised as, Allografts, Xenografts, Tissue derivatives [15].

c) Artificial Dressings:

The usage of traditional dressing materials and biomaterial-based dressings is restricted due to factors such as their stability problems and risk of infection. These conditions brought up the use of wound and burn dressing materials being cheaper and more effective, and having long shelf-life. Much research is currently being undertaken studies to develop wound dressing materials that can provide optimum healing conditions, taking into account all of these factors and healing mechanisms (inflammation, tissue replacement, fibrosis, coagulation, etc. [16].

Pharmaceutical Formulations Used As Dressings for Wounds and Burns

a) Gels/ Hydrogels:

Gels are viscous semi-solid preparations formed by dispersion of inorganic or organic substances that have larger size than colloidal particles in a liquid phase. Hydrogels are semi-solid systems, formed by a combination of one or more hydrophilic polymer.They keep moisture at the application site and permit oxygen penetration [17]. Hydrogels have many advantages including patient compliance, treatment efficacy and ease of application. Natural polymers are generally preferred in the preparation of hydrogels. Hyaluronan is a biopolymer widely used in the treatment of wounds. Wounds treated with chitosan gel with silver sulfadiazine showed a higher fibroblast production and a better angiogenesis than that of commercially available silver sulfadiazine cream, which are important parameters on the evolution of the healing process [19].

b) Sprays and foams:

Sprays are pharmaceutical forms containing the solvent and polymer, forming a film layer on the surface of the wound when sprayed. The best example of a spray-based artificial wound and burn dressing is Hydron. It is prepared with polyhydroxyethyl methacrylate powder and liquid polyethylene glycol. When it is sprayed on the surface of the wound, it creates a thin and transparent film layer. In studies it was found that sprays reduce the pain of the wound, but have disadvantages including loss of integrity of the dressing and accumulation of sub membrane fluid. Researchers stated that Hydron provides an effective treatment when applied to small partial thickness wounds and to areas which are away from joints [20][21]. Another example of aerosol sprays is papain-pectin sprays. The spray-on topical wound debrider composition consisting of 0.1% papain immobilized in 6% pectin gel was formulated for skin wound healing.

c) Composites:

Composites developed for wound treatment may involve an elastic outer layer with high mechanical strength, which is resistant to the effects of the environment and provides moisture by preventing evaporation; in contrast, the inner layer provide adhesion of the composite to the surface of the wound. Telfa™ is a dressing material, including cotton, covered by polyester film and is used both for providing absorption and preventing dehydration of the wound surface. Clinical studies have been conducted of chitin nanofibrils/chitosan glycolate composites [22], salmon milt DNA/salmon collagen composites, polymer-xerogel composites and autologous cellular gel matrix systems [23].

d) Porous films/membranes:

These pharmaceutical dosage forms, which are available in thickness ranging from µm to mm, are prepared by different methods using one or more polymers. Films are ideal dressing materials and available in commercial. Films/membranes with a homogeneous polymeric network structure are used to treat the damaged area and generally protect the wound and burn area against external factors [24][25].The polymers used in the preparation of films include; polyurethane, polyvinylpyrrolidone, hyaluronic acid ,collagen , sodium alginate and chitosan and its derivatives, poly-N-acetyl glucosamine and fucoidan . In a clinical study, as a result of in vitro studies of polyurethane / poly (N-vinyl pyrrolidone) composite film combinations, it was reported that their water absorption capacity was high and water vapour permeability was between 1816-2728 g /m2 /day. It was seen that recovery in the injured area was significantly increased and a new epithelial tissue was formed in 15 day period following application of these prepared formulations to full-thickness wounds induced in a rat model [26].

Advantages of Porous Scaffold Film [27] [28]

1) Hemostasis:

Porous scaffold film as wound dressings with their small holes and high effective surface area can promote hemostasis phase

2) Absorbability:

Due to the high surface area to volume ratio of the films, they exhibit high water absorption whereas typical film dressings only show water absorption

3) Semi-permeability:

The porous structure of a dressing is excellent for the respiration of cells which does not lead the wound to dry up.

4) Conformability (3 D-dressing):

Conformability or the ability to conform to the contour of wound is one of the parameters that

need to be clinically assessed for the flexibility and resiliency of the medical dressings.

5) Scar-free:
Ultimately, scaffold film also holds a promise of healing wounds without leaving scars.

Scaffold Fabrication Technique [29][30][31]
A variety of techniques have been used for processing biodegradable polymers into 3-D porous scaffolds. The conventional methods include fiber bonding, melt molding, solvent casting/particulate leaching, gas foaming/particulate leaching and rapid prototyping etc. Some of the important techniques are described below:

1) Melt Moulding:
Scaffolds are prepared by melting polymers/ceramics in the presence of porogens (such as sodium chloride, sugar crystals) once the mixture is cooled, porosity is achieved by dissolving the porogens in water finally; the porous scaffolds are usually lyophilized.

2) Solvent-Casting:
Scaffolds are prepared by dissolving /suspending polymers /ceramics in the presence of porogens (such as sodium chloride or sugar crystals) , porosity is achieved by dissolving the porogens in water, after pouring the mixture into a mould, solvents are removed by either evaporation or vacuum/ freeze-drying.

3) Liquid/Liquid Thermally Induced Separation Technique:
Scaffolds are prepared by dissolving/ suspending polymers /ceramics in a solvent which freezes below the phase separation temperature of the polymer solution, porous structure is obtained by successively freeze-drying

4) Template Technique:
Scaffolds are prepared by dipping a poly-urethane sponge into a slurry of proper viscosity containing ceramic particles, the impregnation step and the removal of ,the surplus slurry should be adjusted to obtain, after the sponge removal, a defect-free porous three-dimensional scaffold, sometimes, in order to obtain mesoporous structures, surfactants may be added.

5) Sol–Gel:
Scaffolds are prepared by dissolving inorganic metal salts or metal organic compounds in a solvent where a series of hydrolysis and polymerization reactions allow the formation of a colloidal suspension (sol), after casting the 'sol' into a mould, a wet 'gel' is formed, with further drying and heat treatment, the 'gel' is converted into dense ceramic or glass articles.

6) Powder Compaction:
Scaffolds are prepared by compressing the polymers / ceramic using projectiles or punch and die the velocity of compaction of the projectile or punch and dies is adjusted to achieve powder consolidation and the desired porosity the process can include sintering an alternative is to use uniaxial or isostatic pressing.

7) Fiber Bonding:
3-D porous matrices can be constructed by bonding polymer fibers at their crosspoints using a secondary polymer. For example, PGA fibers have been bonded by embedding in PLLA solution, cooling, and subsequent removal of PLLA.

8) Supercritical Fluid Technology / High-Pressure Processing:
First disc shaped structures made of the desired polymer are prepared by means of compression molding using a heated mold. The discs are then placed in a chamber where are exposed to high pressure CO_2 for several days. During this procedure the pores are formed by the carbon dioxide molecules, resulting in a sponge like structure.

9) Electro-spinning:
A polymer solution or melt is drawn from a nozzle by applying a force of gravity or mechanical pressure combined with an electric field of high voltage (10–20 kV). When the electric charge overcomes the surface tension of the polymer solution droplet, a polymer jet is sprouted, followed by solvent evaporation which forms the solid nano fibers.

10) Rapid Prototyping/ Solid Free Form Fabrication:
This technique allows the production of scaffolds that are customized in size and shape according to specific requirement. Which highly reproducible. Biodegradable porous scaffolds can be fabricated directly by a melt–dissolution deposition process using fused deposition modeling (FDM) or by a particle bonding technique such as 3-D printing (3DP).

Table 1: Merits and Demerits of Scaffold Fabrication Techniques

S.NO	Technique	Merits	Demerits
1.	Solvent casting	• Useful for controlling shape of scaffolds. • Control over porosity, pore size and crystallinity • Very simple, easy, and inexpensive and there is no need for specialized equipment.	• It uses highly toxic solvents which can denature proteins and other incorporated molecules. • There is also the possibility for retention of toxic solvent within the scaffold.
2.	Freeze drying	• Control the pore size of the scaffolds. • Highly interconnected pores with high porosity. • Applied for many biocompatible natural and synthetic polymers. • It does not require an extra washing/leaching step	• Single most costly process. • Small pore size and long processing time. • It has stability problem associated with single drug. • Long process time.
3.	Phase separation	• Compatible with many bioresorbable and non-resorbable polymers, ceramics, and biologic materials. • Simple, efficient, and cheap method for scaffolds fabrications. • No decrease in the activity of the molecule.	• Variation in cooling rate and the melting temperature of the solvent may affect the porosity and structure of porous scaffolds. • Poor control over internal architecture, and limited range of pore sizes.
4.	Gas foaming	• Bioactive molecule is not loss from scaffold matrix. • Free of harsh organic solvents. • Extremely useful for the fabrication of the highly porous PLGA scaffolds for the delivery of growth factors	• Poor interconnectivity of the pores. • Scarce pore inter connectivity, relatively low pore volume and limited production rate.
5.	Electro spinning	• Suitable for growth of the cell and subsequent tissue organization. • Long continuous fibers can be produced. • Cost effective	• Main problem of the electro spinning method is cell seeding. • Low mass production rate.Limited mechanical property, pore size decrease with fiber thickness
6.	Fiber bonding	• Desirable for its simplicity, the retention of the fibers original properties. • High porosity, large surface area is available for cell attachment and regeneration of ECM	• Shortage of control over porosity and pore size, the availability of suitable solvents, immiscibility of the two polymers in the melt state. • Poor mechanical integrity,difficulties in controlling the porosity or choice of solvents.
7.	Melt Molding Technique	• Control the porosity, pore interconnectivity geometry, pore size and macro shape. • Easily controls the porosity, pore size, pore interconnectivity, geometry, and macro shape	• Method required is the high temperature required for non-amorphous polymers and residual porogen. • This method required extra leaching step for the formation of PLGA scaffolds
8.	Rapid Prototyping	• Customized in size and shape according to specific requirements. • Excellent control over geometry, porosity, no supporting material required	• Limited polymer type, highly expensive equipment. • Expensive technique as it require computer based instrument for the scaffolds fabrication
9.	Fiber Mesh	• Formation of large surface area, favorable conditions is produce for cell survival and high cell attachment.	• Lack of structural stability.
10.	Supercritical Fluid Technology (SFT)	• Produces macroporous structure with higher mechanical strength	• Inter connectivity of pores within the matrix is not sufficient.
11.	Porogen leaching	• Control over porosity and pore geometry. • Simple, versatile and easy to control the pore size and geometry.	• Inadequate pore size and pore interconnectivity. • Difficult to design the scaffolds with accurate pore inter- connectivity

Table 2: Commercialized scaffold products and their major research application in the

S.NO.	Commercialized Scaffold Products	Current Major Research Application
1	Apligraf®	An artificial skin product
2	Revitix™	Topical cosmetic product
3	VCTO1™	Bilayered bio-engineered skin
4	Forta-Derm™	Anti-microbial wound dressing
9	Gelfoam®	Used as a hemostatic device
10	Gelfilm®	In neurosurgery, thoracic and ocular surgery
11	CultiSpher-G®	Used as microcarrier cell culture
12	CryoSeal®	The production of autologous fibrin sealant components from a single unit of a patient's blood plasma
13	Vivostat®	Platelet-rich fibrin
14	HemCon®	Forming a blood clot
15	Nu-Derm®,AlgiSite®, Curasorb®	Wound dressings
17	Bionect® , Jossalind®	Used as a viscoelastic gel for surgery and wound healing
18	Orthovisc®,OpeganR®, Opelead®, Healon®	Used for implantation of artificial intraocular lens.
19	EmbryoGlue®	Use in vitro fertilization
20	Hyaff®	Used as a biomaterial for biomedical applications
21	Integra®	Dermal regeneration
22	Viscoat®	Used as a surgical aid in anterior segment procedures including cataract extraction and intraocular lens implantation

11) Gas Foaming:

Effervescent salts (ammonium bicarbonate) are used as porogens and mixed with an organic viscous Solution / suspension of polymer/ceramic, after solvent evaporation, porosity is achieved by placing scaffolds into hot water or an aqueous solution of citric acid to dissolve the salts.

12) Freeze-Drying:

Scaffolds are prepared by dissolving /suspending polymers/ceramics in water or in an organic solvent followed by emulsifications with a water phase, after pouring the mixture into a mould, solvents are removed by freeze-drying and porous structures are obtained.

Merits And Demerits Of Scaffold Fabrication Techniques [32][33][34]

Merits and demerits of scaffold fabrication techniques are illustrated in Table1 and are given as follow;

Commercial Status Of Scaffold Formulations [35][36]

Commercialized scaffold products and their major research application described in Table 2

CONCLUSION

People have been trying various wound healing processes and material from natural extracts to synthetic implants. Various novel pharmaceutical preparations namely gels, hydrogels, spray, foams, composites and porous film membranes are available for better wound care and healing. Porous scaffolds have many advantages like hemostasis, absorbability, semi-permeability, conformability and scar free over the conventional wound healing materials. Porous scaffolds are easy to formulate and can also be easily sterilized depending upon the area of use. The preparation of porous scaffolding films is as easy as any conventional dosage form also it has advantages of wound healing over the conventional dosage forms. With the continuous dedicated research in this field the future in near when porous scaffolds would be available as a simple film and would be in the reaches of every individual

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