ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 2(I), pp. 24384-24390, February, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

ADVANCEMENTS IN SKIN TISSUE ENGINEERING AREA WITH APPLICATION OF NANOTECHNOLOGY

Shikha Kumari[1]* and Pradeep Srivastava[2]

[1]C/54-A Shivani Vihar Kalyanpur, Lucknow
[2]Tissue Engineering Laboratory, School of Biochemical Engineering, IIT BHU Varanasi

DOI: http://dx.doi.org/10.24327/ijrsr.2018.0902.1651

ARTICLE INFO

Article History:

Received 20th November, 2017
Received in revised form 29th December, 2017
Accepted 30th January, 2018
Published online 28th February, 2018

Key Words:

Skin tissue engineering, nanotechnology, biomedical engineering, tissue replacement, scaffolds, nanomaterials, biomaterials

ABSTRACT

Skin tissue engineering is a vast field of research which aims at delivering people an efficient and effective way of skin replacement. It involves people from different research areas like material scientists, life scientists, biomedical engineers and also clinicians who give a combined effort in this field. This review helps elucidate the different fields of skin tissue engineering and it enables to understand the application of nanotechnology in the field of skin tissue engineering. Biomedical research involves the construction of scaffolds using different biomaterials and polymers inside which the cells are inserted and directed to form a new tissue or organ and application of nanotechnology in it allows changes at the material level. This can result in positive unpredictable variations inside the scaffold as well as also at the cellular level. Progress has been made in this area and it is being anticipated that more work and consideration at nano level can help in delivering a novel skin construct to the global healthcare market. In current scenario, if we start depending less over the factors like surgical techniques and wound bed preparation then it would ensure the success rate of recovery as well as tissue replacement.

INTRODUCTION

Background

Every day numerous surgeries are performed in order to restore or repair tissues that have been damaged due to ailment or trauma. Traumatic injuries and several diseases can cause damage to tissues and it could also result in the degeneration of tissues of the human body. Ultimately this entails treatment for facilitating repairing, substitution or regeneration of the damaged tissues. The developing field of tissue engineering is one of the solutions which aims to repair and regenerate the damaged tissues that ultimately helps in healing of organs and if required, growing full new organ. It involves three basic steps which state the requirement of base or primary cells; secondly a highly porous scaffold biomaterial that can act as a template for tissue regeneration; and finally applying the newly developed tissues or organ in tissue replacements and surgeries. The interdisciplinary field of tissue engineering started its way from the mid-1960s when the artificial skin was made using fibers for patients with severe burn (Spira, Fissette *et al*. 1969). Then in the early of 1970 strenuous efforts were made for treatment of the artificial surfaces, which were being applied in implants to mentor the blood coagulation, by the application of special heparin complex coatings (Leininger, Crowley *et al*. 1972). Several efforts were made in order to study the toxicological profiles and biocompatibility of numerous organic polymers that were being used as implants for the tissue engineering process. The collagen-based artificial skin was developed in the late 1970s for application in oral mucosal injuries (Levin, Tsaknis *et al*. 1979). Later in 1981, a skin equivalent was prepared that consisted of a silicone layer over a sponge of porous collagen cross-linked with chondroitin for treatment of severe burns (Burke, Yannas *et al*. 1981). This decade was continuously flourished by the development of different tissue engineered products.

Tissue engineering

Tissue engineering is a broad field of science which encompasses areas like chemistry, cell biology, molecular biology, material science, life science, medicine, and engineering*. It focus over the biomechanical, biophysical and biological parameters to develop new tissue and organ substitutes within the laboratory.* Tissue engineering involves scientific areas like chemistry, cell biology, molecular biology, material science, life science, medicine, and engineering. *Some of the engineered tissues include bone cartilage, artificial skin,*

Corresponding author:* **Shikha Kumari
C/54-A Shivani Vihar Kalyanpur, Lucknow

and artificial liver. Nowadays it is being extensively utilized by clinicians in cases of burns and even orthopedic cases. After being combined with the stem cells research, tissue engineering is also proving to be valuable in growing a new organ which naturally doesn't regenerate. Bladder being the first engineered organ used for transplantation was grown in a lab environment, using the patient's own cells, on a biodegradable scaffold. According to the standards, engineered tissue should be able to replace any soft or hard tissue which is damaged and needs to be replaced. Being an emerging field, tissue engineering is still developing and therefore it holds the potential for further development and various applications. Tissue engineering could be mainly categorized into two parts one is soft tissue engineering while the other is hard tissue engineering. Soft tissue engineering focuses mainly on the skin while hard tissue engineering refers to bones, cartilage tissues. This article is directed towards the skin tissue engineering which is presently dynamically active research field.

Chronic wounds in case of skin could be treated by application of artificial skin substitutes however methodologies adopted for this should be performed easily over the wound area. Good adherence, non-antigenicity as well as good mechanical and physical properties are also important factors while designing a effective tissue engineered skin substitute (Liu and Cao 2007). Designing a novel skin substitute incorporated with all of these parameters is the current research demand among the researchers. Every clinician and engineer is aiming to develop a skin substitute which is manufactured using biomaterial. Therefore, material scientists have come to significance in finding out new and novel materials that are compatible for being used in a tissue engineered skin substitute. Skin tissue engineering requires an artificial extracellular matrix that could degrade once the new tissue starts regenerating. This biomimetic matrix thus needs to built from biodegradable polymers like collagen, chitosan, etc. Good vasculature and resorption properties provides significant potential in skin tissue regeneration. The strategy for developing any kind of tissue engineered skin substitute is firstly by identification of technique to manufacture the ECM and then finding apt source of cells for proper interaction and development of the cell-seeded scaffold.

Recently, some of the major advances in molecular biology have been applied to understand wound healing and the development and regenerative processes (Liu and Cao 2007). Suitable scaffold matrices application forms the basis of skin tissue engineering application.

Overview of tissue engineering strategies

Skin

Skin, the first line of defense in human body provides protection against the external environment as well as helps in thermoregulation (Nyame, Chiang *et al*. 2014). It comprises of two layers epidermis, the outer layer, and dermis, the inner layer. Both these layers serve important functions, like a traumatic barrier, synthesis of vitamin D, immune surveillance, prevention from dehydration, and sensory perception. Epidermis, composed of a primary layer which in turn is composed of keratinocytes which proliferates and forms the cornfield epidermal layer. Due to the presence of stem cells in this layer it forms the most regenerative layer of the skin. Stem cells present in this layer plays important role in homeostasis and thereby promoting the wound healing phenomenon. However both skin regeneration as well as wound healing are very well-coordinated processes and it depends on various factors. These factors include the type of wound like epidermal, deep dermal, full thickness or damage of tissue. The damage generally occurs either by the burn of different degrees, or by infections that includes secondary infections, inflammation and also the surrounding areas of wound (Mogoşanu and Grumezescu 2014). Wound healing comprises of three major steps which include the formation of extracellular matrix through fibroblast cells and then secondly proliferation of keratinocytes and finally their differentiation for development of epidermal layer.

Wounds turn into the chronic wounds once they take higher time duration for healing. Such wounds are also liable to higher risks for infection (Mogoşanu and Grumezescu 2014). Conditions like diabetes, the presence of foreign bodies, malnutrition, immuno-compromised body status, renal infections and older age could severely affect the normal wound healing phenomenon and thereby tissue restoration. Hence, it is tremendously significant to consider these factors while engineering various grafts for skin tissue regeneration (Mogoşanu and Grumezescu 2014).Development of certain novel skin tissue engineered products in last decades has shown promising future of tissue engineering. Various allografts, autografts, xenografts, and other grafts of the dermal, epidermal or dermo-epidermal source have been reported and are being used commercially (Nyame, Chiang *et al*. 2014). Such kind of grafts helps in restoring the skin structure by repairing the wounds efficiently. For engineering this kind of substitutes, several scaffold matrices have been developed for promoting the cell growth in a 3D structure. These types of scaffolds are quite biodegradable in nature as well as highly biocompatible with skin tissue thereby acts as a suitable dressing material for the wound healing application.

Tissue Engineering implies two major ways to produce an engineered tissue or a whole new organ. Main Components of skin tissue engineering of application of nanofibrous scaffold as an artificial extracellular matrix (O'brien 2011) are shown in Fig.1.

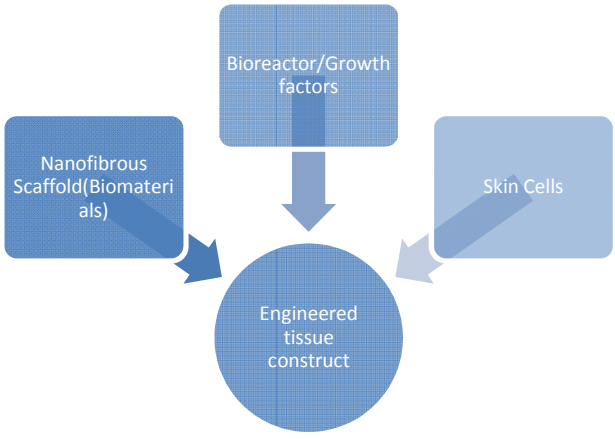

Figure 1 Main Components of skin tissue engineering of application of nanofibrous scaffold as an artificial extracellular matrix (Fergal J. O'Brien et.al., 2011)

Scaffolding is the approach for supporting the cells that are seeded over the scaffolds in-vitro. These cells are provided with several growth conditions which helps fixation of them over the matrix so that it generates the base for tissue regeneration. Combination of cells with the structure of scaffolds should be demonstrated vigilantly as it has been reported that structural architecture of the scaffold is essential in cells response and also the formation of tissue (Sundelacruz and Kaplan 2009). The composition of the material of scaffold, topography and also the design of the scaffold can alter the cell behaviour inside the body and it has also been reported by (Chan, Guzman *et al*. 2007) that even nano to microscale topography could posses variation in cells behaviour.

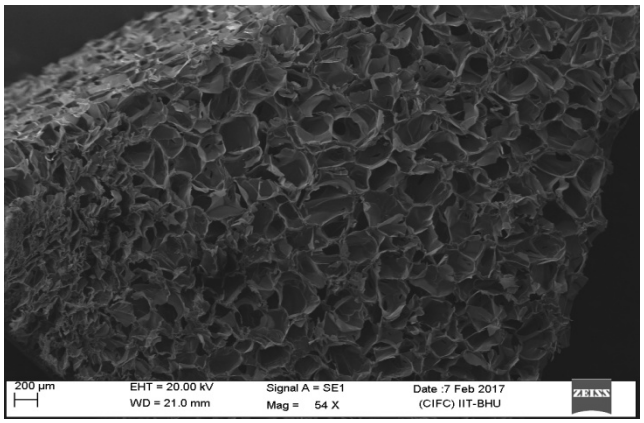

Figure 2 SEM of chitosan scaffold blended with gelatin

Scaffold

Tissue engineering is incomplete without a scaffold, that not only provides support for cell adhesion but it also acts as a relay station for numerous signaling molecules. One of its examples is shown in Fig.1. While the scaffold could be made from a natural or biosynthetic material, cells are generally obtained from the patient itself in order to avoid any kind of immunological reaction issues.

Scaffolds could be manufactured in form of a tissue structure that needs to be restored or replaced. Once the scaffold is developed after that certain growth factors are added along with cells. A scaffold must be biodegradable, biocompatible, biomimetic and also act as an artificial extracellular matrix on which cells could be seeded. Biocompatibility of scaffold material is a first and foremost criterion for tissue engineering purpose because adherence of cells and their normal functioning can be affected if the scaffold is non-biocompatible. The negligible immune reaction is also considered to be an important factor in order to prevent any severe inflammatory response by the body.

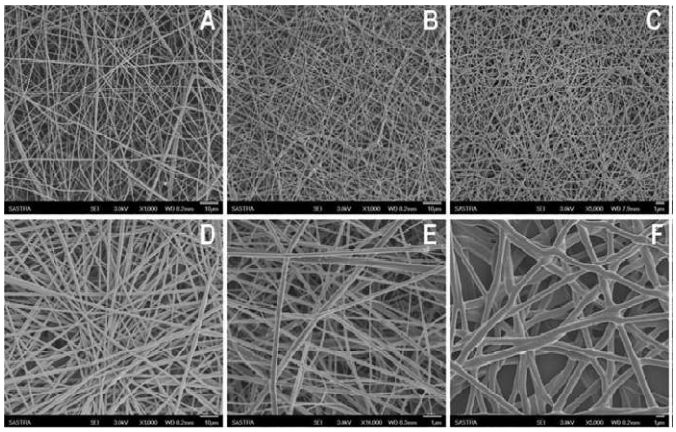

Figure 3 Distinct polymeric nanofibrous scaffolds studied for skin tissue engineering. (A) Poly(1,4 butylene succinate) (PBS); [B]PHBV-PBSu; [C] Chitosan-PVA; [D]PLGA; [E] PLA; [F] PHBV. *(Dhakshinamoorthy Sundaramurthi et al. 2014)*

Biodegradability is the second factor which is always taken into consideration while constructing a scaffold as it should allow the cells to generate their own extracellular matrix. Biodegradability refers to the solubility of the scaffold inside the body without generating any toxicity or interference with any other organ. Immunological response is also important while studying the scaffold's suitability.

Table 1 Different biopolymeric and synthetic composite scaffolds and their properties and applications.

Scaffold Material	Properties	Applications	References
Collagen	Reduce wound contraction	Skin substitute for full thickness burns, Implanted in full-thickness wound in athymic mice	Powell *et al*. 2008
Gelatin	Potential dermal-epidermal skin substitute	High cell infiltration suitable for dermal-epidermal skin substitute, In vitro using human skin fibroblasts	Powell *et al*. 2008
Silk fibroin	Cytocompatible for human keratinocytes and fibroblasts, Good wound dressing material	In vitro using normal human keratinocytes and fibroblasts	Min *et al*. 2004
Myoglobin and hemoglobin		Can prevent wound hypoxia and promote healing	Barnes *et al*. 2007
Poly(3–hydroxybutyrate– co–3–hydroxy valerate) (PHBV)	Promotes cell proliferation and topical administration of R-Spondin 1 enhances angiogenesis in vivo	In vitro using human skin fibroblasts and in vivo in rat model	Chong *et al*. 2007
Poly(lactide–co– glycolide) (PLGA),	In vitro compatible and possess anti-adhesive property thus favors healing	In vitro using normal human keratinocytes	Kumbar *et al*. 2008
Poly(ε– caprolactone) (PCL)-gelatin	3-D dermal substitute with enhanced cell infiltration for accelerated dermal wound healing	In vitro culture on both sides using normal human keratinocytes	Chong *et al*. 2007
Chitosan grafted PCL/PCL (Polycaprolactone	Cationic nanofibers promotes cell attachment and proliferation	Cell-scaffold interaction by culturing mouse fibroblast cells	Chen *et al*. 2011
Plasma-treated PLACE(poly(L–lactic acid)–co-poly (ϵ–caprolactone)) / gelatin	Promotes cell proliferation and collagen expression	In vitro using human foreskin fibroblast	Chandrasekaran *et al*. 2011
PVA-PHB (polyvinyl alcohol and polyhydroxybutyrate)	Supports HaCaT and fibroblast proliferation	In vitro using HaCaT (Keratinocytes) and fibroblast cells	Asran *et al*. 2011
Chitosan	Enables exudates removal, promotes healing in 14 days	Implanted in third-degree burns in patients	Kossovich *et al*. 2010
Silver sulfadiazine loaded polyurethane	Burn wound healing	Tested as scaffold for burns	Heo *et al*. 2013

The high porosity of the scaffold structure plays an essential role to ensure penetration of the cells and also ample of diffusion of nutrients required by the cells within the construct and the extracellular matrix formed by it. Mechanical properties of the scaffold, specifically its tensile strength should be consistent to the anatomical site for which the scaffold has to be built, otherwise, it could be a major problem for the clinicians to do the transplantation. These properties can be integrated by application of nanomaterials into the scaffolds. Fig.3 shows the distinct polymeric nanofibrous scaffolds studied for skin tissue engineering (Sundaramurthi, Krishnan *et al*. 2014).

All the above-mentioned characteristics of a genuine scaffold can only be met by choosing the right kind of biomaterial for the research purpose. Currently, research is more focused towards creating the scaffolds as it is becoming more complex with the technical developments that are transforming from a simple polymer to spectra of fibrous matrices. In table no.1 it is shown that how different biopolymeric and synthetic composite scaffolds are used in tissue engineering applications because of their unique properties.

Biomaterials for Soft tissue engineering applications

In the current scenario, various artificial skin tissue substitutes are available and it has been studied that lately they are using combination of dermal and epidermal layer together as skin graft (Huang, Zhang *et al*. 2004). These tissue engineered substitutes are comprised of natural as well as synthetic materials, but application of biomaterials like collagen and chitosan has been studied and is in application widely. These type of biomaterials generally possess low toxicity to the body. In table no.2, biomaterials and synthetic polymers have been shown along with their applications and drawbacks.

Other examples include polytetrafluoroethylene and polyethylene terephthalate. Matrices being used, often regularly, especially in healing applications are made up of polymers that are easily degraded in the body. Two basic challenges faced while obtaining bio-degradable polymers includes poor mechanical and degradation properties (Mohamed and Xing 2012). These kinds of challenges are being solved by developing a new class of materials. Another issue involves processing of this kind of polymers into the scaffolds that have a specific pore size and shape (Li, Liu *et al*. 2010). New nanotechnologies such as three-dimensional printing (Lee, Lee *et al*. 2007) and electro-spinning (Hsiao-Huei, THOMAS *et al*. 2000) are emerging that allows accurate manufacturing of materials with defined pore size.

Cell recognition signals which forms the major factor for interaction between the cell and material is not experienced by the synthetic materials being used widely. This has been reported lately and researchers are working on it. The results for it have been seen in form of the advancement in manufacturing techniques being developed for the construction of the scaffold.

Incorporation of cell-adhesion peptides inside the biomaterials and synthetic materials helps gaining the cellular interactions involved in skin tissue engineering methods. .

Nanotechnology and nanomaterials: biomimetic tools for tissue regeneration

In recent years, nanotechnology has become very popular for tissue engineering applications, because it has been observed that its applications have expanded into many areas which include material science, biomedical engineering as well as medicine.

Table 2 Biomaterials and Synthetic polymers along with their applications and drawbacks.

S.No.	Natural Materials	Drawbacks	Applications	References
1.	Collagen	Low mechanical strength, Less stable, low melting point, nanofiber fusion in aqueous environment	Spinal cord healing, scar formation, and tendon regeneration	Nam J *et al*.2011, Minton AP *et al*.1992
2.	Gelatin	Poor mechanical strength, Requires chemical cross-linking, less stable	Bioprinting, Bone, cartilage, cardiac and vascular tissue regeneration	Kuijpers, Alma J., *et al*.2000, Li, Mengyan, *et al*. 2006
3.	Chitosan	Poor mechanical strength, Immunogenic, difficult to electrospun	Bone and cartilage regeneration wound healing	Kim, In-Yong, *et al*.2008
4.	Hyaluronic acid	High surface tension and viscosity make it hard to electrospun	Bone and cartilage regeneration wound healing	Kogan, Grigorij, *et al*. 2007
5.	Fibrinogen	Less stable in aqueous environment, requires chemical cross-linking	Wound healing, bone regeneration, urinary tract tissue regeneration	McManus, Michael C., *et al. 2007*
	Synthetic Materials			
1.	Poly-α-hydroxy esters	Acid degradation products	Develop tubular nerve guides	Ishaug-Riley, *et al*.1997
2.	Poly-glycolic acid (PGA)		Bone regeneration	Athanasiou, Kyriacos A., *et al*. 1998
3.	Poly-lactide acid (PLA)		Orthopedic applications	Herrmann JaRK, *et al*.2007
4.	Poly L-lactic acid (PLLA)	Slow degradation, mechanical stiffness, hydrophobic	Sternal Bone Healing, drug delivery in wound bed	Collet JaJB, *et al*.2002, Derman A, *et al*.1993
5.	Poly L-lactic acid-caprolactone (PLLA PCL)	Hydrophobic, less cytocompatible	Wound healing mediators, growth factors	Derman A, *et al*.1997, Stewart E, *et al*.1998
6.	Poly D,L-lactide-co-glycolide (PLGA)	Acid degradation products	Anti-adhesive property	Lü, Jian-Ming, *et al*.2009
7.	Poly ε caprolactone (PLGA/PCL)	Acid degradation products, Highly elastic, slow degrading	Wound healing in diabetic foot ulcers	Chong, *et al*.2007, Kim, *et al*.2009
8.	Hydrogels		Empty tubular nerve prosthesis, infarcted myocardia	Davis ME, *et al*.2005
9.	RADA16-I	Large aggregation propensity	Neural regeneration in optic nerve lesions	Ellis-Behnke RG, *et al*.2006

The nanomaterials especially nanofibers (such as collagen fibers) being used in the field of biomedical engineering mimics the nanofibrous components of the native extracellular matrix (ECM). The core of this new technology is the creation and utilization of large surface area, a wide range of materials and devices at the molecular level (Ellis-Behnke, Liang *et al*. 2006). Applications of nanotechnology are now not limited to medicine but it is widely accepted in fields like tissue engineering, delivery of drugs as well as diagnosis. Addition of a small nano-sized material into the matrix constructed from polymers could also be of great advantage for enhancing the performance of the system.

The applications of nanomaterials in the field of biomedical engineering is quite impressive and can be seen in Fig.4 where hybrid scaffold template incorporated with nanoparticles have been shown for tissue engineering application.

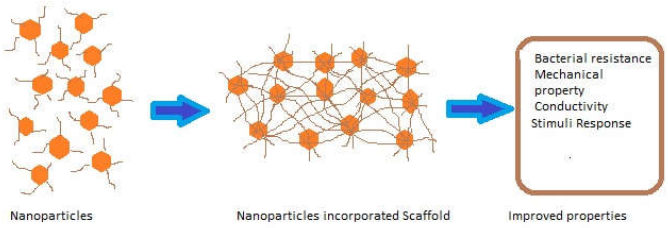

Figure 4 Diagram of Hybrid Scaffold template for tissue engineering incorporated with nanoparticles

Nanomaterials are composed just like conventional micron structured material. They are usually made from metals, polymers, polymer composites, organic matters, and ceramics. Several methodology from top- down approach to bottom-up approach are employed for construction of these nano structured materials. Fabrication techniques like electrospinning, phase separation, chemical vapor deposition, thin film deposition, nano-imprinting, etc. are now coming into light. These methods help in obtaining desired topogrophy of materials and also synthesizing self- assembled even nano topographies. The nanomaterials have a great spectra from nano wires to nano-rods and from nano- films to nano- tubes. Increased surface area and sourface roughness of these nano materials imparts enhanced physicochemical properies and hence they have made a huge place in the biomedical sciences and regenerative medicines.

Skin tissue engineering implies the conventional methods of replacements which comprises of allografts, autografts, etc. But they cause lots of immunological rejections and severe complications and hence implementation of nanotechnology has become a great and promising approach for obtaining desirable skin tissue equivalents. High market demands of artificial skin tissue substitutes as well as grafts can only be accomplished if these materials are being used for replenishing the current demand of tissue engineered products. Scientists working over fabrication of cytocompatible biomimetic scaffolds made from nanomaterials that encapsulates stem cells are currently opening a new array for research in biomedical field.

The field of nanotechnology has recently boomed in the past decade and as the next frontier in biomedical and tissue engineering field, toxicity caused by application of these materials should be covered. A study showed that cells attach, grow and organize well on nano-fibrous structures even though the fiber diameter is smaller than that of the cells. Therefore considering all the above examples steps can be taken to diversify the applications of nanotechnology in skin tissue engineering.

The promise of nanomaterials for skin tissue engineering applications

Skin injury can occur due to accidents, injuries, trauma, especially thermal trauma. Skin tissue re-engineering can be helpful in such cases. The integrity of the re-engineered skin should be maintained. Earlier, autografts and allografts were used to treat skin burns. But autografts cannot be used if there is extensive skin injury and allografts have rejection problems. Tissue re-engineering uses cells such as keratinocytes and fibroblasts were grown in a scaffold with the use of growth factors. Melanocytes are used for repopulating cells in the burn scars. The cell interacts and organizes to form the final structure (Metcalfe and Ferguson 2007). The re-engineered graft is then transplanted onto the site of injury where new skin is gradually generated (Groeber, Holeiter *et al*. 2011). Scaffold materials of natural origin include polypeptides, hydroxyapatite, hyaluronan, alginate (Metcalfe and Ferguson 2007). Synthetic materials include polyglycolide, polylactide, polylactide coglycolide. A newer approach uses polyethylene oxide-based macromer substrate. They can incorporate biologically active ligands. Growth factors are critical for the regeneration of skin. Platelet-derived growth factor activates the mesenchymal cells and stimulates chemotaxis and proliferation. TGF-β is the most potent growth factor in wound healing. β1 and β2 show cutaneous scarring, whereas β3 shows an anti-scarring effect. BMP, FGF and vascular endothelial growth factor are the other growth factors which can be used for improved efficiency and growth of skin substitutes. The recent advancements show that mechanical stretching fastens the skin regeneration by upregulating the gene expression of mesenchymal stem cells (MSC) related to vascularization and cell proliferation. This MSC expression provides homing to the expanded skin and transdifferentiation into epidermal and endothelial cells (Liang, Huang *et al*. 2016). In burns where only the upper epidermal lining is lost and dermal layer is intact, the epidermis can be grown from the epidermal keratinocytes lining the dermis layer. But if both, the epidermis and dermis are lost, then there is no formation of epithelium by the body and tissue re-engineering is required. In such cases either the cells are allowed to generate their own extracellular matrix or the scaffolds are used. Epidermal cover, dermal replacement, and epidermal/dermal replacement can be provided as per the degree of skin injury (MacNeil 2008). Dermal replacement is used when both the epidermal and dermis layer is to be replaced. Dermal vascularization has to be provided in such cases (Metcalfe and Ferguson 2007). An alternative to split-skin graft is known as the epidermal/dermal replacement which is the most advanced and also a sophisticated construct. But re-vascularization and adequate blood supply to skin grafts are still being resolved by the researchers. Anatomosis between graft vessels and natural blood vessels undergoing angiogenesis can be done for re-vascularization. The other problem is of scars which are formed due to the application of the skin graft that is not constructed from the original skin. This can be aesthetically problematic. A technique known as the fetal wound repair is characteristic for

its scar-free and fibrosis-free regenerative nature; this is because the wound healing in fetal tissue takes place by a different mechanism and hence less scarring is observed. Re-engineered skin substitutes do not mimic the functional normal skin perfectly. It does not control the temperature nor does it have sebaceous and sweat glands. All these factors when incorporated into the skin constructs will result in a better functioning of the construct. Also, keratinocytes cannot be delivered as small sheets because they are too fragile. Hence they can be grown on a temperature sensitive polymer sheet, incorporated on a carrier which collapses as temperature decreases and thus releases the cell sheet.

Nanomaterials have also been used for other soft tissues, such as the bladder. As emerging bladder tissue engineering materials, nanomaterials provide a promising approach for efficient bladder tissue regeneration. In table no.3 various applications of presently available artificial skin substitutes and their features have also been shown.

Significance of nanomaterials is not limited to all the above areas but also it needs in-depth research in treatment of wounds and acceleration of wound healing phenomenon and skin tissue regeneration. A study was done where biodegradable nanofiber scaffolds were enriched with bone marrow-derived mesenchymal stem cells and that has accelerated the rate of wound-healing phenomenon (Ma, Liao *et al*. 2011).

CONCLUSIONS

Applications of nanomaterials in several fields including biological sciences as well as chemical sciences have allowed scientists to undergo profound research on them. This is due to the effective and remarkable physical and chemical properties possessed by the nanomaterials. Due to the successful biological interaction of the nanomaterials within the system makes them the suitable candidate for application in the biomedical field.

Table 3 Applications of presently available artificial skin substitutes and their features.

Fibrous Scaffolds (Skin Substitutes)	Characteristics	References	Applications
Terudermis®	Combination with Collagen sponge	Nyame *et al*.,2014	Good adhesion and reduces pain, applicable to deep wounds, prevent infection and control moisture flux like exudates.
Pelnac®	Combination with Collagen sponge	Suzuki, Shigehiko, *et al*.2000	Helps reducing surface irregularities, used for chronic wounds, reducing donor site injuries, minimal skin contracture
Biobrane®	Acellular	Lal, Sophia, *et al*.2000	Ultrathin, semi-permeable silicone membrane, good adherence, maintains moisture, reduce pain, flexible
Integra®	Acellular, porous matrix of collagen, GAG and a silicone layer	Kim, P. J., *et al*. 2014	immediate wound coverage, highly conformable, exceptional strength and flexibility, for deep wounds
Apligraf®	Cellular (Autologous)	Falanga, *et al*.1998	Thin, piece of real skin, diabetic foot ulcer and venous leg ulcers treatment
Epicel®	Cellular, cultured epidermal autograft	King, Stephen, *et al*. 2004	Deep burns
Transcyte®	Cellular, human cells, and silicone layer	Noordenbos, *et al*. 1999	Second-degree burns
Permaderm®	Cellular, autologous epidermal and dermal cells	Poinern, G. E. J., *et al*.2010	Decreases infection, lower risk of rejection stretches and grows with patient, reduced healthcare cost
Dermagraft	Acellular, human fibroblast-derived dermal substitute with bioabsorbable polyglactin mesh	Hart, Charles E., *et al*.2012	Diabetic foot ulcers treatment
Acticoat	Wound dressing with antimicrobial properties containing silver, epidermal or surface application	Yin *et al*., 1999	Diabetic ulcers, venous ulcers

The use of nanoparticles provides several advantages such as biologically inspired roughness, selective adsorption of protein and increased surface energy. Studies have been done on surface modification wherein nanofibers with cell-adhesive peptides are coated over the PGA scaffolds (Harrington, Cheng *et al*. 2006). A series of the linear and branched self assembling peptides were used by them to coat the traditional scaffold and provide it better cell compatibility. The progress is also being made in bladder tissue engineering where electrospun nanofibers of polystyrene scaffolds have been aligned with bladder muscle cells to obtain a nanostructured bladder tissue (Baker, Atkin *et al*. 2006). Smooth muscle cell attachment was also improved by them because of the application of argon plasma treated polymer nanofibers. Nanomaterials vast application is also seen in neural tissue engineering wherein scientists fabricated nanofibrous scaffolds of PLLA and PCL with improved cytocompatibility (Koh, Yong *et al*. 2008). Application of nanomaterials in orthopedic are well substantiated but in vascular tissue regeneration is also being widely studied by the scientists for healing damaged nerves.

Electrochemical properties as well as magnetic and optical properties of the nanomaterials have opened up a wide spectra of opportunities in the field of drug delivery for the scientists. Researchers working over the design of the materials are considering the possibilities of controlling and altering the materials at nanoscale so that it can deliver better material performance and process efficacy.

Elucidating newer technologies for making the nanotechnology more effective to biomaterial science has turned to be a naive frontier in skin tissue engineering. Still, significant progressions are required for realizing the potential of nano biomaterials in the clinical applications. Nanotechnology has currently offered great solutions for mimicking complex structure of the subjected tissue. Taking everything into account, current trends in nanotechnology suggests a bright future in the skin tissue domain through the use of nanobiomaterials.

Scaffolds constructed from nanofibers play essential role in the wound healing process and also they help in regeneration of skin. Numerous scaffolds made from natural and synthetic materials developed from nanofibers are being studied

intensively due to the cons associated with the current scaffolding technology. New techniques and biocompatible materials usage for this process possess equivalent potential in tissue engineering field. Therefore, studies are being done to obtain desired physicochemical properties and improved biocompatibility along with reduced scar formation and good vasculature system.

Stem cell technology applications in this field also has a great future if combined together to obtain novel skin substitutes for present market scenario. techniques like electrospinning, 3D printing have come into observation for the attainment of desired characteristics within the artificial skin equivalents. Enhanced dermal wound healing and better structural and mechanical integrity is still a challenge for upcoming biomedical scientists who are trying to design an ideal tissue engineering strategy.

Hence, it can be elucidated that by the application of such multi-functional nanomaterials, skin regeneration could be achieved easily. Incorporation of nanoparticles with properties like antimicrobial activity and anti-inflammatory activity can be an appealing approach for upcoming generation skin replacements.

References

1. Baker, S. C., N. Atkin, *et al*. (2006). "Characterisation of electrospun polystyrene scaffolds for three-dimensional in vitro biological studies." *Biomaterials* 27(16): 3136-3146.
2. Burke, J. F., I. V. Yannas, *et al*. (1981). "Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury." *Annals of surgery* 194(4): 413.
3. Chan, C. S., J. N. Guzman, *et al*. (2007). "'Rejuvenation'protects neurons in mouse models of Parkinson's disease." *Nature* 447(7148): 1081.
4. Ellis-Behnke, R. G., Y.-X. Liang, *et al*. (2006). "Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision." Proceedings of the National Academy of Sciences of the United States of America 103(13): 5054-5059.
5. Groeber, F., M. Holeiter, *et al*. (2011). "Skin tissue engineering-in vivo and in vitro applications." Advanced drug delivery reviews 63(4-5): 352-366.
6. Harrington, D. A., E. Y. Cheng, *et al*. (2006). "Branched peptide-amphiphiles as self-assembling coatings for tissue engineering scaffolds." *Journal of Biomedical Materials Research* Part A 78(1): 157-167.
7. Hsiao-Huei, W., J. A. THOMAS, *et al*. (2000). "p53 protein oxidation in cultured cells in response to pyrrolidine dithiocarbamate: a novel method for relating the amount of p53 oxidation in vivo to the regulation of p53-responsive genes." *Biochemical Journal* 351(1): 87-93.
8. Huang, Z.-M., Y. Zhang, *et al*. (2004). "Electrospinning and mechanical characterization of gelatin nanofibers." Polymer 45(15): 5361-5368.
9. Koh, H., T. Yong, *et al*. (2008). "Enhancement of neurite outgrowth using nano-structured scaffolds coupled with laminin." *Biomaterials* 29(26): 3574-3582.
10. Lee, W., T. G. Lee, *et al*. (2007). "Grafting of Poly (acrylic acid) on the Poly (ethylene glycol) Hydrogel Using Surface-initiated Photopolymerization for Covalent Immobilization of Collagen." *Journal of Industrial and Engineering Chemistry* 13(7): 1195-1200.
11. Leininger, R., J. Crowley, *et al*. (1972). "Three Years'experience In Vivo And In Vitro With Surfaces And Devices Treated By The Heparin Complex Method." *ASAIO Journal* 18(1): 312-315.
12. Levin, M. P., P. J. Tsaknis, *et al*. (1979). "Healing of the oral mucosa with the use of collagen artificial skin." *Journal of periodontology* 50(5): 250-253.
13. Li, S., X. Liu, *et al*. (2010). "Removal of Cationic Dye from Aqueous Solution by a Macroporous Hydrophobically Modified Poly (acrylic Acid-acrylamide) Hydrogel with Enhanced Swelling and Adsorption Properties." CLEAN-Soil, Air, Water 38(4): 378-386.
14. Liang, X., X. Huang, *et al*. (2016). "Mechanical stretching promotes skin tissue regeneration via enhancing mesenchymal stem cell homing and transdifferentiation." *Stem cells translational medicine* 5(7): 960-969.
15. Liu, W. and Y. Cao (2007). "Application of scaffold materials in tissue reconstruction in immunocompetent mammals: our experience and future requirements." *Biomaterials* 28(34): 5078-5086.
16. Ma, K., S. Liao, *et al*. (2011). "Effects of nanofiber/stem cell composite on wound healing in acute full-thickness skin wounds." Tissue Engineering Part A 17(9-10): 1413-1424.
17. MacNeil, S. (2008). "Biomaterials for tissue engineering of skin." Materials today 11(5): 26-35.
18. Metcalfe, A. D. and M. W. Ferguson (2007). "Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration." *Journal of the Royal Society Interface* 4(14): 413-437.
19. Mogoşanu, G. D. and A. M. Grumezescu (2014). "Natural and synthetic polymers for wounds and burns dressing." *International journal of pharmaceutics* 463(2): 127-136.
20. Mohamed, A. and M. M. Xing (2012). "Nanomaterials and nanotechnology for skin tissue engineering." *International journal of burns and trauma* 2(1): 29.
21. Nyame, T. T., H. A. Chiang, *et al*. (2014). "Clinical applications of skin substitutes." *Surgical Clinics* 94(4): 839-850.
22. O'brien, F. J. (2011). "Biomaterials & scaffolds for tissue engineering." Materials today 14(3): 88-95.
23. Spira, M., J. Fissette, *et al*. (1969). "Evaluation of synthetic fabrics as artificial skin grafts to experimental burn wounds." *Journal of Biomedical Materials Research* Part A 3(2): 213-234.
24. Sundaramurthi, D., U. M. Krishnan, *et al*. (2014). "Epidermal differentiation of stem cells on poly (3-hydroxybutyrate-co-3-hydroxyvalerate)(PHBV) nanofibers." *Annals of biomedical engineering* 42(12): 2589-2599.
25. Sundelacruz, S. and D. L. Kaplan (2009). Stem cell-and scaffold-based tissue engineering approaches to osteochondral regenerative medicine. Seminars in cell & developmental biology, Elsevier.