CHAPTER 2

REVIEW OF RELATED LITERATURES

2.1 MEDICAL TEXTILE - AN INTRODUCTION

The term medical textile was defined as “structure composed of textile technology and medical science, designed for use in medical industry”. Medical textile is a new and fastest growing field of the textile technology with tremendous market potential (Czajka 2005; Hofer et al 2003). It includes everything from wound dressings, gauzes, bandages, surgical masks, fibrous implants, sutures, drug carrier, artificial organs, hospital linens, clothing used for rehabilitation and so on. In textiles context, cotton, silk, bamboo and wool are natural fibre groups, which are commonly used as biodegradable and biocompatible materials for medical applications across countries for wound dressing (Cao & Wang 2009; Sherif & Roedel 2011). The consumer demand for safe eco-friendly medical textile products has been growing day by day. At present mostly natural polymers are used to dress the wounds, which are biodegradable in nature. Biodegradable polymers have the advantage of delivering biological molecules at controlled rates and it reduces the number of repeated treatments (Determan et al 2006; Lopac et al 2009).

A recent study conducted in Poland Struszczyk & Olejnik (2012) assessed about different forms of textile medical devices and it is shown in Table 2.1 which evident the usage of textile based products in medical applications.
Table 2.1 Usage of textile based products in medical applications.

<table>
<thead>
<tr>
<th>Group of Technologies</th>
<th>Particular Technologies</th>
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<tbody>
<tr>
<td></td>
<td>1.2. Primary wound dressings (non – occlusive)</td>
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<td></td>
<td>1.2. Primary wound dressings (occlusive)</td>
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<tr>
<td></td>
<td>1.3.1. Resorbable wound dressings</td>
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<td></td>
<td>1.3.2. Advanced wound dressings incl. wound dressing designed from genetically modified raw sources containing bioactive substances and / or designed using bio technologies, etc.</td>
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<tr>
<td>2. Auxiliary textile medical devices</td>
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<tr>
<td>3. Fibrous Implants</td>
<td>3.1. Implants for hernia treatments</td>
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<td></td>
<td>3.2. Implants for vaginal reconstructions or urinary incontinence treatments</td>
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<td></td>
<td>3.3. Implants for the reconstruction of skull and facial bones</td>
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<td></td>
<td>3.4. Implants for vascular reconstructions</td>
</tr>
<tr>
<td></td>
<td>3.4.1. Components of endo vascular prostheses for less – invasive surgical procedures</td>
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<tr>
<td>4. Sutures</td>
<td>4.1. Resorbable</td>
</tr>
<tr>
<td></td>
<td>4.2. Non- Resorbable</td>
</tr>
<tr>
<td>5. Fibrous scaffolds for the tissue reconstructions</td>
<td></td>
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<tr>
<td>6. Advanced fibrous carriers for medicines</td>
<td></td>
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<tr>
<td>7. Artificial organs or fibrous components for artificial organ design</td>
<td></td>
</tr>
<tr>
<td>5,6,7 – Fibrous borderline products (medical devices containing bio active substances or incorporating, as an integral part, ancillary medicinal substances, ancillary human blood derivative, drug delivery scaffolds or carriers)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Struszczyk & Olejnik (2012)
2.2 SILK

Silk was discovered in China around 2700 B.C. and over years has spread to countries such as Japan, India and Iran. Silk fabrics have been of interest for over 5000 years due to its texture, strength, elasticity, and affinity for dyes. It was also being used commercially for years to make aesthetic fabrics such as the Japanese kimono and Indian sari. Recently, silk is used in cosmetics, powders, lotions, creams, makeup and pharmaceuticals (Sukigara et al 2003). Silk is an important natural protein based fibre that is produced by the spider and silkworm (Vepari & Kaplan 2007).

2.2.1 Life cycle of Bombyx mori silkworm

The silkworm is cultivated by sericulture. Silk filament produced by Bombyx mori, the mulberry silk moth, passes through different stages (egg, larva, feeding and pupa and moth). The first stage of silk production is the laying of silkworm eggs; this is done in a controlled environment, the female moth deposits 300 - 400 eggs at a time and newly laid eggs are creamy yellow in colour. The female moth dies almost with in a week immediately after depositing the eggs and the male moths live only a short period after that. In the second stage, the eggs are incubated for about 9 to 12 days until they hatch into larvae (caterpillars). The third stage is the feeding period; the larvae are fed with mulberry leaves for about six weeks (in order to store enough nutrients and to be able to shed their skins five times). As soon as the silkworms stopped eating, they are ready to spin silk cocoon. Figure 2.1 shows the production cycle of Bombyx mori silk by silkworm. In the last stage, silkworms spin its cocoon by continuously moving its head in the shape of S and for the construction of a cocoon it needs approximately 2 to 3 days. After it has finished spinning the cocoon, the silkworm sheds its skin and becomes a pupa.
A cocoon is made of a single continuous silk strand with a length in the range of 500–1200 m. The silk spun by the silkworm, *Bombyx mori* silk, consists mainly of two types of proteins, sericin and fibroin, the former forming a sheath around the latter (Zhao & Asakura 2001).

Source: Zhao & Asakura (2001)

**Figure 2.1** Life cycle of *Bombyx mori* silkworm

**2.2.2 Composition of *Bombyx mori* silk**

*Bombyx mori* type of silk fibre consists of two different protein based layers (Figure 2.2), fibroin in an inner layer and a sericin coating in an
outer layer (Wenk et al 2011). Every silk thread consists of fibroin filaments of 10 – 141 m, each embedded in the sericin coating, to bind the fibroins together. The composition of fibroin and sericin includes fats, wax and sand pigments plus minerals (Zhang 2002).

Sericin is water soluble protein and silk is degummed using anhydrous sodium carbonate solution at an appropriate temperature to obtain pure silk fibroin (Zhang 2002). The proportions of amino acids in *Bombyx mori* silk fibroin have been known for more than 60 years. Table 2.2 shows the Amino acid composition of *Bombyx mori* silkworm.

When silk has been converted into silk fibroin solution, the properties of the resulting construct can have tunable properties, and therefore
fibroin have more predictable degradation and biocompatible properties. It can be used as a biomaterial from the fact that they are made up of several different protein molecules and can be readily accepted and naturally degraded by the body without causing any inflammatory reactions if processed correctly.

Table 2.2 Amino acid composition of *Bombyx mori* silkworm

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Residue (%)</th>
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</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>44.7</td>
</tr>
<tr>
<td>Alanine</td>
<td>25.7</td>
</tr>
<tr>
<td>Serine</td>
<td>11.9</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>5.4</td>
</tr>
<tr>
<td>Valine</td>
<td>2.4</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>1.6</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>1.6</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>1.1</td>
</tr>
<tr>
<td>Threonine</td>
<td>1.0</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>0.6</td>
</tr>
<tr>
<td>Leucine</td>
<td>0.5</td>
</tr>
<tr>
<td>Proline</td>
<td>0.5</td>
</tr>
<tr>
<td>Arginine</td>
<td>0.5</td>
</tr>
<tr>
<td>Lysine</td>
<td>0.4</td>
</tr>
<tr>
<td>Histidine</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Source: (Neurath, 1953)

The silk construct can also be functionalized by embedding materials such as antibiotics, and growth factors into the material (Altman et al. 2003). Silk is stable at temperatures up to 170°C and as such, developed medical textile materials from silk as base have reduced
temperature sensitivity and can be easily sterilized by techniques such as autoclaving (Vepari & Kaplan 2007; Friedman 2013).

2.3 BASIC PROPERTIES OF BOMBYX MORI SILK FIBROIN

Drug loading, release kinetics and physico-chemical stability of a drug delivery system are features, which can be tailored by changing the properties of its silk fibroin matrix (Wenk et al 2011).

2.3.1 Molecular Properties of Silk

One of the best characterized silk is *Bombyx mori* silk fibroin fibres are about 10–25 mm in diameter and it consist of two proteins: a light chain (26 kDa) and heavy chain (390 kDa) which are present in a 1:1 ratio and linked by a single disulfide bond. These proteins are coated with a glue-like protein called sericin (20 kDa–310 kDa) (Vepari & Kaplan 2007). Sericin have been associated with immune response, but due to their higher hydrophilicity as compared to fibroin they can be easily removed by boiling silk in soap solution.

Silk fibroin consists of amino acid sequence that provides opportunities for chemical modification. Amines, alcohols, carboxyl groups, phenols, and thiols have been explored as potentially reactive side groups for the chemical modification of silk fibroin (Wenk et al 2011). With these chemical modifications of silk fibroin a variety of drugs in different compositions can be loaded and released with distinct kinetics, providing a wide range of adjustable drug release systems.

2.3.2 Molecular Weight

The molecular weight of a polymer strongly influences its mechanical properties, water uptake and biodegradability. The molecular
weights of silk fibroin heavy and light chains, extracted from the *Bombyx mori* pupae, are 370 and 25 kDa respectively (Tanaka et al 1999). These two chains occur in equal proportions and are connected at their C-terminus by a disulfide linkage. Increased degumming times and temperatures of the silk fibres correlated directly with a decrease in the average molecular weight of the protein (Partlowm 2012).

### 2.3.3 Solubility

Crystalline silk fibre is insoluble in most solvents that are widely used to dissolve polymers typical for drug delivery applications, as well as in water. The silk fibres can be dissolved in highly concentrated salt solutions of lithium bromide, calcium thiocyanate or calcium chloride (Sukigara et al 2003; Winkler & Kaplan 2000). Such electrolyte solutions are able to disrupt the hydrogen bonds that stabilize β-sheets. After solubilization, dialysis against water is performed to remove the electrolytes.

### 2.3.4 Swelling Properties

The release of drugs from matrices depends partially on the degree of swelling, which in turn depends on its degree of cross linking and its hydrophilic/hydrophobic balance (Peppas et al 1993). Blending of different polymer compositions can influence the degree of swelling (Haider et al 2005). This can potentially increase the cumulative amount and rate of drug to be delivered.

### 2.3.5 Mechanical Properties

Mechanical strength, however, is an important issue when a drug delivery device is used for load bearing function. Silk fibres exhibit high tensile strength, flexibility and resistance to compressive forces, which makes
them suitable for applications requiring considerable tensile strength such as sutures (Dattilo et al 2002; Omenetto & Kaplan 2013). *Bombyx mori* silk fibres demonstrate a remarkable tensile strength of 0.5 GPa at an elongation of 15% (Jin & Kaplan 2003). Removal of the water soluble sericin protein coat from the cocoon yields degummed silk fibres, which exhibit up to a 50% increase in tensile strength (Xie et al 2006). The excellent mechanical properties of silk fibroin make it well suited for load bearing biomedical applications.

2.3.6 Degradation

Degradation characteristic of polymeric matrices plays an essential role in determining the controlled release of entrapped bioactive agents. The control of degradation therefore delivers control of the transport properties of silk architectures, providing a pathway for drug delivery and controlled release applications (Mandal & Kundu 2008).

2.4 APPLICATIONS OF SILK FIBRE IN BIOMEDICAL/BIOTECHNOLOGY

In the recent years, the protein based materials have gained increasing research interest in biomedical and biotechnological field for their remarkable self-assembly behaviour, tunable porous structure, durability, elasticity, water uptake, excellent biocompatibility and biological activity. Silk is found to be an important natural polymeric protein biomaterial in the field of medical science (Zhang et al 2009) and tissue engineering (Baoyong et al, 2010; Tuzlakoglu & Reis 2009). This protein consists of a light chain at 26 kDa and a heavy chain at 390 kDa (Vepari & Kaplan 2007). The silk polymer, a representative fibrous protein, has been investigated as one of promising resources of biotechnology and biomedical materials due to its unique properties (Rajkhowa et al 2010, Wilz et al 2008). In medical textiles,
silk fibres find their effective application in the form of sutures and artificial ligaments due to its favorable properties like natural slow biodegradation, biocompatibility, processability and superior mechanical properties (Numata et al 2010; Mandal & Kundu 2008; Lawrence 2008). Due to these unique properties many researchers have used silk as an appropriate drug delivery tool in the form of films, hydrogels, fibres and 3D scaffolds in medical context (Khan et al 2009; Altman et al 2003; He et al 2012). Murphy & Kaplan (2009) summarized various literatures related to application of silk in wound healing arena.

A variety of silk protein modification chemistries has been reported and it is concluded that useful features of silk proteins including self-assembly, robust mechanical properties, biocompatibility and biodegradability properties can be enhanced through a variety of chemical modifications. These modifications provide chemical handles for the attachment of growth factors, cell binding domains and other polymers to silk, expanding the range of cell and tissue engineering applications attainable. Padol et al (2011), Pawar et al (2013), Sugihara et al (2000) and Vasconcelos et al (2012) found that the inherent features of silk make it as ideal material to be used as wound dressing material. A major advantage of these kind of genetically engineered polymers over their conventional synthetic counterparts have the ability to produce biopolymers with uniform composition, molecular weight, and amino acid sequence (Dinerman et al 2002).

Native silk fibres can be solubilized and reprocessed into an aqueous silk fibroin based protein solution, which can then be used to generate a multitude of new material formats or physical assemblies such as scaffolds (Karageorgiou et al 2006), films (Arai et al 2004), hydrogels (Ma et al 2013; Moreira et al 2009), foams (Kang et al 2009), micropheres (Wang et al 2007), mats (Jin et al 2004) and sponges (Roh et al 2006). These
new forms of SF are finding utility in drug delivery, cell culture and tissue engineering applications while providing programmable biodegradability.

Figure 2.3 shows a variety of physical assemblies and chemical approaches towards the formation of a diverse set of biomaterial architectures from the two silk proteins, sericin and fibroin.

Figure 2.3  Physical assemblies and chemical approaches of silk fibroin and sericin
2.5 BENEFITS WITH THE USE OF SILK FOR BIOMEDICAL APPLICATIONS (Altman et al 2003)

1. Novel mechanical property of silk that is superior to any other natural fibres

2. Natural fibre with a long standing history of use in clinical applications

3. The ability to process silk in aqueous solution for subsequent formation of films and other material formats, with relatively simple in solubilization via exposure to alcohols and other environmental factors

4. Simple chemical modifying procedures with regard to surface decorations, such as adhesion sites or cytokines, due to the availability of amine and acid side chains on some of the amino acids

5. Genetically tailor able composition and sequence to moderate specific features, such as molecular weight, crystallinity and solubility

6. Slow rates of degradation in case of in vitro and in vivo, this is particularly useful in biodegradable scaffolds in which slow tissue growth is desirable

7. No risk of bio burden

2.6 DRUG DELIVERY SYSTEM

The conventional method of drug delivery system such as oral administration and injection etc., has been depended on repeated doses for stipulated period of time. The improved approach that is named as controlled drug delivery approach used to deliver or release solute at controlled rate over
a prolonged period of time through a carrier device (Hines 2012; Bhowmik et al 2013). This technology is advantageous in terms of maintaining the drug levels within a desired range, minimizing the drug side effects through optimal use and increasing patient compliance. The rate of wound healing efficacy is higher in this kind of modern system. This technology has found commercial success since the 1950’s (Hines 2012). Further the conventional systems may not release the drug constantly or steadily as like advanced polymeric carrier devices or drug depots like scaffolds, sponges, hydrogel etc. The polymeric carrier devices or drug depots are cost effective (Daugherty & Mrsny 2006), convenient (Danckwerts & Fassihi 1991) higher wound healing efficacy and avoids unwanted side effects (Langer 1998).

2.7 WOUND AND ITS CLASSIFICATION

A wound is defined as an injury or tear on the skin surface by physical, chemical, mechanical, and/or thermal damages that disrupt the continuity of the tissue structure and its functions (Boateng et al 2008). Skin prevents water loss through evaporation and also prevents the penetration of exogenous substances from the environment. When there is a breach in the integrity of this tissue layer, a wound is created and the barrier is compromised.

On the basis of wound healing processes the wound is classified into acute and chronic is based upon the total healing time and repair process. Acute wounds are those that heal completely in a definite time frame, generally healable with in 8 to 12 weeks, leaving minimal scarring. Knife cuts, wounds caused by abrasion, surgical wounds, burns due to corrosive chemicals, and exposure to radiation are all acute wounds. Cares for these wounds depend on the severity of the wounds.
Chronic wounds may take a long time to heal (more than 12 weeks and longer), since healing does not go through the orderly set of stages (Zahedi et al 2010). Chronic wounds ultimately fail in wound closure. Wound healing is hindered due to poor treatment, physical and biological state, nutritional status and prolonged infections. Diabetic leg ulcers and sores, venous stasis, pressure ulcers and severe physiological contaminations are generally classed as chronic wounds (Kulkarni 2012; Babaei et al 2013).

2.8 WOUND HEALING PROCESS

The process of wound healing is a worldwide health problem and significantly increase healthcare costs. Wound healing is a complex and dynamic process of tissue repair that involves cells, local biochemical factors such as growth factors, components of extracellular matrix (ECM), neutrophils, and macrophages, and proteases interacting with each other. Wound healing begins when platelets contact a damaged blood vessel and begin to stick on to the exposed collagen.

Rovee (1991) states that wound healing process is a series of complex events which results in the restoration of the wounded tissue to the normal or quasi-normal state found prior to wounding. Some amphibians and reptiles can actually regenerate their lost parts but human beings have lost the ability for regeneration in most tissues.

The healing or repair can earn by cell migration, proliferation, differentiation and scarring (production of fibrous tissues) to re-establish a functional state. Based on the different literatures Zahedi et al (2010) shows the different stages of wound healing process hemostasis, inflammation, migration, proliferation, and maturation. The first stage includes hemostasis and inflammation which occurs soon after there is damage to the skin. Fibrinogen, which is one of the major components of the skin’s connective
tissues leads to the coagulation of exudates (blood without cells and platelets), and together with the formation of a fibrin network, produces a clot in the wound, which stops the bleeding.

Therefore, both hemostasis and inflammatory stages play an important role in the healing process of a wound. The inflammatory phase occurs simultaneously with the hemostasis phase usually takes more than 24 hours. At this stage, blood neutrophils followed by phagocytes enter the wound medium and penetrate inside the dead cells. In the migratory phase, the new and live cells called epithelial move towards skin injury to replace dead cells.

The proliferation stage consists of the complete coverage of wound by epithelium. At this stage, new stromas usually known as granulating tissues are formed after about 4 days. Microphages, fibroblasts, and blood vessels move toward the wound environment and form a single unit. The completion of this stage takes about 2 weeks. During the growth of migration phase, a reduction in the inflammatory phase of the wound is gradually observed.

The final stage in the healing process of a wound is tissue remodeling. At this stage fibroblasts completely cover the surface of the wound as a new layer of the skin and there is no evidence of the wound. This stage is also known as maturation phase in the healing process of wounds.

2.9 WOUND DRESSINGS

A number of wound dressing types are available for a variety of medical applications. The basic function of wound dressing is to provide some level of absorbency and wound protection, which is usually provided by the conventional or traditional wound dressings. The condition of the wound
bed and the desired dressing function determine the type of dressing needed (Capasso 2000). An ideal dressing has three key properties: (1) protects the wound, (2) is biocompatible, and (3) provides ideal hydration (moist environment). The traditional category of textile based wound dressing such as lint, gauze and wadding have limitations due to their inability to preserve a moist environment for effective wound healing. On the other hand, advanced category encompasses scaffolds, films, hydrocolloids, hydrogels and alginates achieve effective wound healing by providing an optimum moist microenvironment for healing (Pawar et al 2013).

Wound dressings have a major role in wound management. The primary goals of wound care and dressing are rapid wound closure and to leave a minimal or aesthetically acceptable scar (Kurhade 2013). Lock & Webb (1980) states wounds require unique combination of therapy and dressing when the skin is absent or impaired because nutritious body fluids and their essential body fluids are continuously lost through the wound. The skin plays an important role in homeostasis and the prevention of invasion by microorganisms. Skin generally needs to be covered with a dressing immediately after it is damaged.

2.9.1 Properties of an Ideal Wound Dressing

The following are the properties of an ideal wound dressing:

- High exudates up-take
- It provides protective barrier from environmental contaminants
- Increases healing rate
- Reduces pain and
- Helps in decreasing infection rates.
2.9.2 Types of Wound Dressing

Proper wound management is a combination of understanding the wound healing process and a complete awareness of the properties of different available wound dressings. There are three categories of wound dressing such as biologic, synthetic and biologic-synthetic. Alloskin and pigskin are biologic dressings commonly used clinically, but they have some disadvantages, such as limited supplies, high antigenicity, poor adhesiveness and risk of cross contamination. Synthetic dressings have a long shelf life, induce minimal inflammatory reaction and carry almost no risk of pathogen transmission. Biologic-synthetic dressings are bilayered and consist of high polymer and biologic materials (Jayakumar et al. 2011).

The plan of wound care should always concentrate on using the appropriate wound dressing material and treatments to reduce dressing frequency. Zhao et al. (2009) also states that most suitable and useful tissue engineering scaffold materials should be biocompatible, porous and provide appropriate mechanical properties.

An ideal dressing material should maintain a moist environment at the wound interface, allow gaseous exchange, act as a barrier to microorganisms and remove excess exudates. It should also be nontoxic, non-allergenic, non adherent and easily removed without trauma. It should be made from a readily available biomaterial that requires minimal processing, possesses antimicrobial properties and promotes wound healing (Jayakumar et al. 2011). Figure 2.4 shows different phases of wound healing.
Figure 2.4 Phases of wound healing

2.10 NATURAL POLYMERIC MATERIALS USED IN WOUND HEALING

The natural origin polymer-based materials offer advantages such as the creation of new opportunities for mimicking the tissue microenvironment and can stimulate the appropriate physiological responses required for cellular regeneration. It seems that all these features associated with a controlled biodegradation rate and the biocompatibility of these naturally based-systems can be advantageous when compared to synthetic polymers (Silva et al 2010). However each polymeric material has its own advantages and disadvantages that have been detailed under Table 2.3.
<table>
<thead>
<tr>
<th>Polymer</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Polymer</td>
<td>Low toxicity, low manufacture and disposal costs, renewability, biological signalling, cell adhesion, cell responsive degradation and re-modeling</td>
<td>Low mechanical, thermal and chemical stability. Risk of immuno-rejection and disease transmission. Possible loss of biological properties during formulation.</td>
</tr>
<tr>
<td>Proteins</td>
<td></td>
<td>Low biomechanical stiffness and rapid bio degradation. Toxicity of some of the cross linking agents.</td>
</tr>
<tr>
<td>Collagen</td>
<td>Low antigenicity and good cell binding properties</td>
<td></td>
</tr>
<tr>
<td>Poly saccharides</td>
<td>Hydrophilic surface promoting cell adhesion, proliferation and differentiation. Good biocompatibility and acceptable host response. Anti bacterial activity.</td>
<td>Mechanical weakness and instability. Incapacity to maintain a predefined shape. Impurities affecting material properties.</td>
</tr>
<tr>
<td>Chitosan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Non immunogenic properties, ease of chain size manipulation. Interactions with cell – surface receptors. Production through large – scale microbial fermentation.</td>
<td>Water solubility. Its anionic surface does not thermodynamically promote cell attachment and tissue formation.</td>
</tr>
<tr>
<td>Alginates</td>
<td>Cross linking under very mild conditions. Gel injection avoiding an open surgical procedure.</td>
<td>Mechanical weakness, difficult to sterilize and to handle. Impurities affecting material properties.</td>
</tr>
<tr>
<td>Starch based materials</td>
<td>Inexpensive, suitable for processing by different techniques and into diverse shapes. High purity, nano fibrous structure, high tensile strength and good bio compatibility</td>
<td>In vivo degradation has not yet been fully assessed. Small pore size. Early stage of investigation as scaffold for tissue engineering. It need further investigation on in vivo behaviour</td>
</tr>
<tr>
<td>Bacterial cellulose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextrans</td>
<td>Chemical similarity to GAGs. Many hydroxyl groups amenable to chemical modification suitable for designing of scaffolds with specific sites for cell recognition.</td>
<td>Shortcomings typical of hydrogels. Needs modification to enhance cell adhesion. Early stage of investigation as scaffold for tissue engineering. It need further investigation on in vivo behaviour</td>
</tr>
<tr>
<td>Microbial Polymesters</td>
<td>Easy processability, broad range of mechanical and biodegradation properties</td>
<td>High cost of production compared to conventional plastics</td>
</tr>
<tr>
<td>Polyhydroxyalcanoates</td>
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</table>
Table 2.3 (Continued)

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Polymers</td>
<td>Physical, Chemical and mechanical properties tailorable to the specific needs, thanks to the wide variety of copolymers, polymer blends and composites with other materials. Easily processable into desired shape and size. Low risks of toxicity, immunogenicity and infections.</td>
<td>Lack of biological cues.</td>
</tr>
<tr>
<td>Short chain saturated aliphatic polyesters</td>
<td>FDA approval for various medical applications. Degradation rate, physical and mechanical properties, adjustable by changing the copolymer ratio.</td>
<td>Possible premature fail of scaffold due to bulk hydrolysis. Adverse tissue reactions caused by acidic degradation products. Poor wetability and lack of cellular adhesion and interaction.</td>
</tr>
<tr>
<td>Poly (E-caprolactone)</td>
<td>FDA Approval for various medical applications</td>
<td>Slow degradation rate (years). Release of acidic degradation products (slower than short chain saturated aliphatic polyesters). Poor wetability and lack of cell adhesion and interaction.</td>
</tr>
<tr>
<td>Bioresorble poly (urethane)</td>
<td>Broad range of mechanical, biological and physical properties. High elasticity.</td>
<td>Acidic degradation products in poly (Esther urethanes) causing autocatalyzed degradation.</td>
</tr>
<tr>
<td>Poly (propylene fumarate)</td>
<td>Mechanical properties and degradation rate tunable by varying the polymer Mw or the cross linking content. Suitable mechanical properties for load bearing tissue applications.</td>
<td>Toxicity of cross linking agents. Acidic degradation products can elicit in vivo inflammatory response.</td>
</tr>
<tr>
<td>Poly phosphazenes</td>
<td>Selective substitution of side groups used for controlling polymer degradation and enhance bio compatibility and bio activity.</td>
<td>Early stage of investigation as scaffold for Tissue engineering: need further investigations on mechanical properties, in vivo behaviour, etc.</td>
</tr>
<tr>
<td>Poly(1, 4 - butylene succinate)</td>
<td>Good mechanical properties and melt processing characteristics</td>
<td>Acidic degradation products. Early stage of investigation as scaffold for Tissue engineering: needs further investigations on both in vitro and in vivo performances.</td>
</tr>
</tbody>
</table>


Malafaya et al (2007) states that natural protein-based polymers have the advantage of mimicking many features of extra cellular matrix and thus have the potential to direct the migration, growth and organization of
cells during tissue regeneration and wound healing and for stabilization of encapsulated and transplanted cells.

The commonly used polymeric materials that are used by many researchers for medical applications such as collagen, gelatin, hyaluronic acid, chitosan, alginate, silk fibroin, fibrin (fibrinogen) and other proteins such as elastin or soybean. Collagen and gelatin have been studied for various medical applications. However impurity and high cost have limited their medical applications (Cheung et al 2008).

Chitosan found to have the disadvantages like instability, mechanical weakness, low capability of maintaining a predefined shape and impurities associated with it. Similarly, Hyaluronic acid also had the drawbacks like water solubility and shorter residence time on the tissues (Puppi et al 2010; Pritchard 2011).

2.11 SILK SCAFFOLDS

Natural and synthetic polymers have been utilized for fabricating scaffolds. They must be inherently biocompatible, biodegradable, and highly cell adhesive. Additionally, they must have a porous, mechanically stable, and dimensional structure with facile manufacturing processes. Scaffolds made from synthetic materials have also been widely investigated, but they do not elicit biological cues similar to native extracellular matrix and they do not have mechanical properties similar to that of skin. Many cases synthetic scaffolds are not biodegradable (Har-el et al 2014). Natural polymers are low toxic, low disposal cost, renewable, biological signalling, cell adhesion, cell responsive degradation and re-modeling. There are variety of techniques have been used for developing biodegradable polymers into porous scaffolds. The conventional methods include fibre felts, fibre bonding, melt molding, solvent casting/particulate leaching, gas foaming/particulate leaching, phase
separation, and high-pressure processing. In order to produce porous silk fibroin scaffolds, a diversity of methods have been used, such as salt leaching, gas foaming, freeze-drying and rapid prototyping (Yan et al 2012).

Scaffolds developed from natural protein polymer like silk have received increasing interest and it has been considered as an alternative option for medical applications (Mandal et al 2012). Silk scaffolds are versatile material for tissue engineered scaffolding as its degradability and mechanical properties can be tailored by chemical cross-linking or by the introduction of beta sheet conformation (Chang et al 2007). The rapid rate of biomaterial degradation represented as a key point in scaffold form (Gomez et al 2012). Cao & Wang (2009) emphasis that an ideal biomaterial is one that is non-immunogenic, biocompatible and bio degradable which can be functionalized with bioactive proteins and chemicals. In particular biodegradability is one of the essential properties of the biomaterials.

Hong & Madihally (2011) also emphasized that biomaterial should be a biodegradable, biomimetic ability, which is essential for cell colonization, attachment, migration, tissue regeneration and diffuse vital cell nutrients. Silk found to have excellent biodegradability and biomimetic ability (Malafaya et al 2007; Silva et al 2010). Zhao et al (2009) also highlights that silk based scaffolds established bio compatibility, impressive mechanical properties and slow degradability. Specifically silk based scaffolds lose its tensile strength with in one year in vivo, and can be completely degraded with in two years (Chang et al 2007). Therefore silk based scaffolds can be act as a pharmacologically active and ideal medical device to provide rapid pharmacological action.

Wang et al (2006) composed various reviews related to silk based biomaterials in the grounds of stem cell based tissue engineering. The synthesis of various research studies shown that ideal scaffold are supporting
cell attachment, migration, cell–cell interactions, cell proliferation and differentiation. It should be biocompatible to the host immune system and biodegrade at a controlled rate to match the rate of neo tissue growth and facilitate the integration of engineered tissue into the surrounding host tissue. It should provide structural support for cells and tissues formed in the scaffold during the initial stages of post-implantation and also have versatile processing options to alter structure and morphology related to tissue-specific needs. All the research studies granted that wide range of molecular structures, remarkable mechanical properties, morphology control, versatile process ability and surface modification options make silk fibroin an attractive polymeric biomaterial for design, engineering and processing into scaffolds for applications in controlled drug delivery, guided tissue repair and functional tissue engineering.

Minoura et al (1990) have investigated the insolubility of silk fibroin in water by methanol treatment and also tested the physico-chemical properties such as oxygen permeability, water vapour permeability, transparency, mechanical properties and enzymatic degradation through in vitro behavior of the wet membrane in biomedical application. These physico-chemical properties changed according to the condition of the methanol treatment. The result shows that silk fibroin membrane has promising oxygen permeability, water vapour permeability, transparency and biodegradability and hence it can be used as a biomaterial in medical applications.

She et al (2008) developed silk fibroin/chitosan scaffold by freeze-drying method and tested its efficacy on cell survival and cell proliferation context. Fourier Transform Infrared (FTIR) spectra and X-Ray diffraction curves has been used to confirm the different structure of scaffolds from both chitosan and silk fibroin. The porosity was found through the pore sizes of the
scaffolds range from 100 µm to 150 µm. This result shows Silk fibroin/chitosan scaffold as a suitable candidate for tissue engineering.

Kim et al (2005) developed a three-dimensional porous silk fibroin scaffolds from silk fibroin aqueous solutions by a salt leaching method without any organic solvents or chemical cross linking. The functional and morphological properties of these scaffolds can be controlled by the concentration of the silk and the particle size of NaCl used in the process. The mechanical properties of porous biodegradable polymeric scaffolds offer favorable properties. From his study it was observed that the mechanical features of these scaffolds are considered along with their biocompatibility, biodegradability and versatility in processing and chemistry, these silk fibroin based biomaterials offer new and important options to the needs related to tissue repair and tissue engineering in biomedical field.

Uebersax et al (2006) studied the effect of scaffold design on bone morphology through *in vitro* method. The three dimensional biomaterial matrices were fabricated from silk fibroin with controlled pore diameter and pore interconnectivity it was also used to engineer bone starting from human stem cells. The result shows that scaffolds proved slow degradation and preserved their initial morphology and provided a stable template during the mineralization phase of stem cells progressing through osteogenic differentiation and new extra cellular matrix formation. The slow degradation feature also facilitated transport throughout the 3D scaffolds to foster improved homogeneity of new tissue, avoiding regions with decreased cellular density. The capability to direct bone morphology via scaffold design suggests new options in the use of biodegradable scaffolds to control *in vitro* engineered bone tissue outcomes.
Gupta et al (2011b) studied about the treatment of a tissue defect post tumor resection by using silk fibroin and chitosan blended scaffolds to provide therapeutic and filling of the defected site. The scaffold emodin nanoparticle composites were fabricated and characterized for drug entrapment and release, mechanical strength and efficacy against breast cancer cells in vitro and in vivo in a rat tumor model was also tested. There was no significant difference in tumor size was observed between the in vivo tested groups, tumors treated with emodin loaded silk fibroin and chitosan scaffolds had decreased in size and similar regeneration of new tissue as compared to no emodin silk fibroin/chitosan scaffolds.

Tungtasana et al (2010) investigated tissue responses and biodegradation, both in vitro and in vivo, of four different types of Bombyx mori silk fibroin based scaffolds were fabricated using salt leaching, dehydrothermal chemical cross linking and an alternate soaking technique for mineralization. Among the four different types of scaffolds, the biodegradability of the gelatin blended silk scaffold in a collagenase solution appeared to be slowest. From in vivo biodegradation studies, all scaffolds observed after 12 weeks of implantation in subcutaneous tissue of Wistar rats. At 2 and 4 weeks of implantation the four types of Thai silk fibroin based scaffolds were classified as non-irritant to slight irritant. All implanted scaffolds, at 2 and 4 weeks showed slight irritation. It was found that these naturally-modified materials may have future potential for clinical applications.

Vasconcelos (2012) developed silk based scaffold for the treatment of burn wounds. The silk fibroin was combined with elastin protein to produce scaffolds with the ability to mimic the extra cellular matrix. Porous scaffolds were acquired by lyophilization and were further cross linked with genipin. Genipin cross linking induces the conformational transition from
random coil to beta sheet of silk fibroin chains, yielding scaffolds with smaller pore size and reduced swelling ratios, degradation and release rates. It was observed from the results, composition of the scaffolds had a significant effect on their physical properties, and that can easily be tuned to obtain scaffolds suitable for biological applications.

Wound healing was assessed through the use of human full thickness skin equivalents and standardized burn wounds were induced by a cautery and the best re-epithelialization and the fastest wound closure was obtained in wounds treated with scaffolds and these contain the highest amount of elastin after 6 days of healing in comparison with other dressings and controls. Moreover, silk fibroin blended with elastin scaffolds showed no cytotoxicity and are able to support cell proliferation in vitro in human skin fibroblasts. Dermal burn healing experiments using human skin equivalents have shown that the application of silk fibroin with elastin scaffolds containing higher amount of elastin accelerates re-epithelialization and wound closure.

Yeo et al (2008) developed silk scaffold amalgamating collagen through electro spinning method for tissue engineering. The morphology of prepared scaffold was observed by scanning electron microscopy and average diameters of collagen based silk scaffold was ranged from 320 to 360 mm. The cyto compatibility, cellular behaviour, spreading with normal human epidermal keratinocytes and fibro blasts seeded on the scaffolds was assessed. The results showed a higher level of cell attachment and spreading of normal human epidermal keratinocytes in collagen and silk blended scaffolds with compare with pure silk and collagen scaffolds. This result indicates that collagen and silk blended scaffolds would act as a good wound dressing material in tissue engineering ground.
Wang et al (2008) studied about *in vivo* degradation of silk fibroin scaffolds and its effectiveness on cell culture and tissue engineering applications. It investigate how processing method (aqueous vs. organic solvent) and processing variables (silk fibroin concentration and pore size) affect the short-term (up to 2 months) and long-term (up to 1 year) *in vivo* behavior of the protein scaffolds in both nude and Lewis rats. The scaffolds were examined for morphological changes, tissue growth and immune responses. During the period of implantation, all scaffolds were well tolerated by the animal and immune responses to the implants were mild. The scaffolds prepared from aqueous process degraded to completion between two and six months, while those prepared from organic solvent hexafluoro isopropanol (HFIP) process persisted beyond 1 year. The results validate that the *in vivo* behavior of the three dimensional silk fibroin scaffolds is related to the morphological and structural features that resulted from different scaffold preparation processes.

2.12 SILK HYDROGELS

Hydrogels have been used for the management and care of wounds. This form has all the characteristics required for ideal wound dressing. Hydrogels are made of cross-linked polymer networks that have a high number of hydrophilic groups or domains. These networks have a high affinity for water, but are prevented from dissolving in exudates, due to the chemical or physical bonds formed by the polymer chains (Petrini et al 2003). Water uptake through these networks cause swelling and giving the hydrogel its form. Fully swollen hydrogels have some physical properties common to living tissues, including a soft and rubbery consistency, and low interfacial tension with water or exudates (Ribeiro et al 2013; Bhattarai et al 2010). The complex three-dimensional giant hydrophilic structures make the hydrogels to absorb aqueous solution and undergo degradation via erosion, hydrolysis,
solubilization, and other biodegradation mechanisms (Ghose 2004). Generally hydrogels are highly absorbent natural or synthetic polymers. Hydrogels exhibit tissue like elastic properties making them ideal aspirant for creating environment that promote cell and tissue growth (Bryant et al 2008). Naturally derived materials have been used to form hydrogels but also natural polymer based hydrogels have been reported to be more biocompatible for hosting cells and bioactive molecules (Lee et al 2012). A great advantage of hydrogel type wound dressings is that they can usually be applied and removed without greatly interfering on wound beds. In addition, these dressings are flexible, non-antigenic, and permeable to water and oxygen.

There are many research studies that support silk based hydrogels can be act as a supreme medical device to provide rapid therapeutic action on diabetic patient’s wounds and also in normal wounds that are presented as follows.

Ribeiro et al (2013) developed a dextran based hydrogel containing chitosan microparticles loaded with growth factors to be used in wound healing. The in vitro assessments found that the hydrogel loaded with microparticles both with and without the growth factors is non cytotoxic. The in vivo assessment suggested that dextran hydrogel and chitosan microparticles with the two growth factors encapsulated promote faster wound healing with no signs of local or systemic provocative response. The results obtained here support the simultaneous application of the two growth factors, with synergic roles in wound healing mechanism. Moreover, chitosan microparticles were considered good vehicles to deliver the growth factors studied, since a unique application helps to reduce the wound area faster.

Gil et al (2013) studied about silk based biomaterial with epidermal growth factor and silver sulfadiazine by means of mouse wound model. Three different material designs and two different drug incorporation techniques
were deliberated to compare wound healing responses. One of the material designs is silk hydrogels. The application of drug loaded hydrogels shows outstanding wound healing efficacy through the changes in wound size and assessments of wound tissues showed that the functionalized silk biomaterial wound dressings increased wound healing rate, including re-epithelialization, dermis proliferation, collagen synthesis and reduced scar formation, when compared to a commercial wound dressing.

Ma et al (2013) developed a silk based hydrogel by blending calcium carbonate crystal for wound dressing applications. The study reports that calcium carbonate (CaCO$_3$) crystal growth in the silk fibroin hydrogel with different concentrations by a simple ion diffusion method. The experimental results indicate that the CaCO$_3$ crystals obtained from silk fibroin gels with low and high concentrations are all calcites with unusual morphologies. Time-dependent growth study was carried out to investigate the crystallization process. It is found that silk hydrogel boost the process of crystallization and that may influence the wound healing process.

Zhong et al (2011) fabricated three dimensional hydrogel blended with chitosan and poly (e-caprolactone) PCL for tissue engineering applications. A modified emulsion lyophilisation technique was developed to produce 3D chitosan/PCL hydrogels. The accumulation of 25 and 50 wt% of PCL into chitosan substantially enhanced the compressive strength of composite hydrogel of 160 % and 290 %, respectively, compared to pure chitosan hydrogel. The Attenuated Total Reflectance-FTIR test shows that PCL and chitosan were well mixed and physically co-existed in the composite structures. The composite hydrogels were constructed of homogenous structure had average pore size. The SEM and confocal laser scanning microscopy images confirmed that fibroblast cells were attached and proliferated on the 3D structure of these composite hydrogels. The composite
hydrogels acquired in this study found to have high potential for the production of 3D hydrogels for tissue engineering applications.

Lee et al (2012) prepared a layered hydrogel composing of alginate, chitosan and poly glutamic acid. The hydrogel was characterized that comprising the swelling ratio, water vapor transmission rate, the release of Ca\(^{2+}\) and blood coagulation activity. In vitro evaluation of cell migration and proliferation were assessed on electric cell-substrate impedance sensing. The hydrogels effect on wound healing was examined in type 1 diabetic rat model induced by streptozotoxin. It was observed that hydrogels contains alginate, chitosan and poly glutamic acid exhibited higher rate of wound healing than conventional alginate based hydrogels. Epithelialization and collagen deposition were examined histologically and hydroxyproline levels also were assessed in the wound skin. The results indicated that hydrogels that contains alginate, chitosan and poly glutamic acid exhibited increased collagen regeneration and epithelialization.

2.13 SILK FILMS

Generally, silk films are prepared by casting solutions of silk fibroin onto a substrate and allowing the evaporation of the solvent. Once the solvent has evaporated, the films can be peeled off for further use, modified chemically (e.g. cross-linked), or modified structurally via treatment with another solvent (Hardy et al 2008). Silk fibroin offers a number of advantages in tissue regeneration arena. Silk films provide a mechanically robust and simplified architecture for developing different tissue regeneration devices. Silk films have also been used for improved cell attachment and bone formation when they are chemically modified with cell binding domains (Sofia et al 2001). In addition, silk film processing is a straightforward and highly scalable production process. In case of other biopolymer materials such as collagen and fibrin require more intense purifying and processing
steps, and are more difficult to form into robust structures when compared to silk (Lawrence 2008). Silk films blends of silk fibroin and recombinant human-like collagen were seeded with hepatocytes and showed higher cell viability (Hu et al 2006). Silk fibroin blend films can also be used as a wound dressing and artificial skin because of its good mechanical properties and water vapor and oxygen permeability (Kweon et al 2001). Silk fibroin molecules could self-assemble into films with less β-sheet content.

Sugihara et al (2000) investigated about healing full thickness skin wounds in rats using silk films validate that the wounds healed in seven days faster with a lower inflammatory response than traditional porcine-based wound dressings.

Bai et al (2012) investigated about tissue repair process through the application of silk fibroin films by implantation on the hypo dermal tissue of rats, arteriole development and the morphogenesis of smooth muscle cells were histologically monitor and micro anthropogenesis is quantitatively analyzed. After the implantation the arteriolar density was reached its maximum and the arterioles junction tissues appeared in a matured state. This result shows the application feasibility of silk films in bio medical context.

Lu et al 2010 study silk fibroin processed into film formats provided efficient and highly effective carriers for the long term stabilization of entrapped enzymes. Based on this mechanism, a promising protein drug delivery system with high materials stability, controllable release of drug, and sustained release of protein/drug was achieved by changing hydrophilic/hydrophobic interactions and structures of enzyme-loaded silk fibroin films via various post-processing strategies.

Lawrence (2012) conducted a study about in vivo characterization for cornea related applications. Silk biomaterial was processed for high
resolution surface patterns, controllable film thickness, porosity and sterility. Developed silk film found to support corneal fibroblast growth, cell guidance and assembled to form three dimensional corneal tissue constructs.

Padol et al (2011) studied about irritation of acute dermal toxicity in rats by using silk films. In the assessment and evaluation of the dermal safety of a substance, acute dermal toxicity and the determination of irritant and sensitization effects on skin are important initial tests. The rats were witnessed for clinical croons and mortality after the silk film application. The maximum level of irritation of silk film was analyzed using Draize test. In the test patches were applied for 3 minutes, 1 hour and 4 hours and skin reaction was classified. It can infer from the study that the materials used in the study are safe under acute dermal toxicity, acute dermal irritation and skin sensitization.

Srisuwan et al (2012) established silk film loaded chlorhexidine drug model for hydrophilic drug release. The release of the chlorhexidine depended on the polarity of each polymer and it is inferred that the releasing pattern of the model drug could be controlled by adjusting the ratio of the blend polymer.

2.14 CACTUS IN MEDICAL APPLICATIONS

Cactus, containing large numbers of vitamin, polysaccharide, protein and amino acid and widely used for biomedicine, pharmaceuticals, cosmetics, food stuff and chemical product (Xu et al 2011). The cactus Opuntia (genus Opuntia, subfamily Opuntioideae, family Cactaceae) is a xerophyte producing about 200–300 species and is mainly growing in arid (less than 250 mm annual precipitation) and semi-arid (250–450 mm annual precipitation) zones. Due to their remarkable genetic variability, Opuntia plants show a high ecological adaptivity and can therefore be encountered in
places of virtually all climatic conditions (Stintzing & Carle 2005). Cactus is rich in a variety of alkaloids, flavones, glycosides and polysaccharides.

Cactus has therapeutic potential in a variety of tissue injuries. Traditionally such extracts are used for wound healing and skin regeneration. Nowadays the traditional usage is replaced by cosmetic and pharmaceutical applications. It has been used in the traditional folk medicine and said to be beneficial in the treatment of skin, burns, edema, and wounds across cultures (Chithra et al 1998). Cactus has been extensively used in Chinese traditional medicine for treatments of lung disorders, skin diseases and blood circulation diseases. Cactus fruit has also been found to promote proliferation of normal fibroblasts thereby promoting wound healing (Chen 2004). The usage of cactus plant encouraged in the public health policy of the Thailand government as inscribed in the 5th National Economic Development Plan. Further, Chang (2007) invented a nutritional supplement prepared with cactus powder and other beneficial ingredients that are permitted for human consumption. This study evident the medical value of cactus. Chen (2004) also invented a cactus based product that deliver vitamins and other skin care nutrients by topical application.

2.15 HONEY IN MEDICAL APPLICATIONS

Honey is the oldest remedy for treating wounds and dates back to the 6th century A.D. The religious texts such as Bible and Quran have written about the healing power of honey. Ancient Egyptians, Greeks and people all over the world used honey for curing wounds for centuries. It has recently been rediscovered by the healthcare professionals and used as a therapeutic agent in New Zealand, Australia, Germany, Austria, United Kingdom, Hong Kong, India and many other countries (Biglari et al 2013). Gupta (2011a) found that honey dressings make the wound sterile in less time, enhanced
wound healing and had better outcome in terms of hyper tropic scars and post burn contractions as compared to silver sulfadiazine dressings.

Khoo et al (2010) also found the wound contraction effect and antibacterial properties of Tulang honey that is a type of honey produced locally in Malaysia. It was found the positive effect of Tualang honey as a sound topical dressing for full thickness burn wounds in an animal model (Sukur et al 2011). Honey had better results with regard to its control of Pseudomonas aeruginosa bacterial infection and its wound contraction effects on burn wounds.

2.16 DEXTRIN IN MEDICAL APPLICATIONS

Dextrin is a glucose polymer, which produced by the hydrolysis of starch, obtained from various natural products such as wheat, rice, maize and tapioca. Therefore any dextrin is a mixture of polyglucose molecules of different chain length (Brown 2012). Dextrin found to have excellent biocompatibility, hydrophilicity and availability hence it is an ideal material for clinical applications. Indeed, several researchers described dextrin based biodegradable materials are not designed for wound healing applications (Chakravarthy & Smith 1995). Dextrin is widely used as adhesives in food, textile and medical industry (Carvalho et al 2010; Moreira et al 2009).

Dextrins are readily degraded by alpha-Amylase (α-amylase). This rate of degradation decreases with increased biodegradability and reabsorption are highly desirable features for tissue engineering and for other biomedical applications to avoid further surgery. Dextrin constructs can therefore be tailored to satisfy a variety of drug delivery objectives (Hreczuk-Hirst et al 2001). The dextrin-rhEGF combined matrix was able to stimulate in vitro proliferation and migration of normal dermal fibroblasts, chronic wound fibroblasts and keratinocytes, provides further evidence to
support the treatment for chronic wounds (Hardwicke et al 2011). This dextrin combination scaffolds has been found to have excellent biocompatibility and degradability.

2.17 ALGINATE IN BIOMEDICAL APPLICATIONS

The natural polymer group of alginate is used in the fabrication of wound dressing material due to its promising biocompatibility and biodegradation properties (Thu et al 2012). Alginate based dressing materials have been used clinically to absorb excess exudates from the wound (Smitha et al 2005). The degree of alginate cross linking will significantly reduce the hydrogel swelling in the presence of water that delays the delivery of drugs. The delayed release makes the alginate as a promising vehicle for controlled delivery drugs. In addition to that, alginate hydrogels can retain and create a moist environment around the wound to promote wound healing (Boateng et al 2008).

2.18 CHITOSAN

Biopolymer like chitosan is a nontoxic, biocompatible, and biodegradable polysaccharide derived from naturally occurring chitin that has been widely used in biomedical and pharmaceutical field (Hansson et al 2012; Lee et al 2012; Murakami et al 2010). Chitosan has the properties such as wound healing ability, to reduce the scars, and antimicrobial growth and inhibition of a wide variety of bacteria which is an advantage in wound healing. Its antibacterial and acceleration of healing wounds of characteristics make it as wound healing material in various forms like beads, powders, gels, sponges, tubes, fibres and films (Sionkowska & Anna 2013; Alemdaroglu et al 2006; Ribeiro et al 2013; Seol et al 2004; Jayakumar et al 2011).
2.19  EPIDERMAL GROWTH FACTOR (EGF) IN MEDICAL APPLICATIONS

Human EGF (hEGF) was first isolated in 1975 and has been shown to contain 53 amino acids it has been identified in various human tissues and fluids including urine, saliva, plasma and breast milk. Human EGF has recently been synthesized using recombinant DNA techniques, which has provided sufficient quantities of rhEGF for preclinical and clinical evaluation (Brazzell at al 1991). Recombinant human epidermal growth factor (rhEGF) is known to stimulate cell proliferation and accelerate wound healing. Direct delivery of rhEGF at the wound site in a sustained and controllable way without loss of bioactivity would enhance its biological effects (Zhou et al 2011). Ryu et al (2009) also confirm that many researchers attempt various growth factors to study the environment of wounds and to enhance wound healing. The results found that key elements in wound healing, includes platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), keratinocyte growth factor (KGF), and epidermal growth factor (EGF) which can trigger tissue regeneration and the remodeling wound healing process.