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Collagen-Based Drug Delivery Systems for Tissue Engineering

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1. Introduction

Biomaterials are considered those natural or artificial materials that can be used for any period of time, as a whole or as part of a system which treats, augments or replaces a tissue, organ or function of the human or animal body (Williams, 1999). In medicine a wide range of biomaterials based on metals, ceramics, synthetic polymers, biopolymers, etc. is used. Among biopolymers, collagen represents one of the most used biomaterials due to its excellent biocompatibility, biodegradability and weak antigenicity, well-established structure, biologic characteristics and to the way it interacts with the body, the latter recognizing it as one of its constituents and not as an unknown material (Friess, 1998; Lee et al., 2001). Irrespective of the progress in the field of biomaterials based on synthetic polymers, collagen remains one of the most important natural biomaterials for connective tissue prosthetic in which it is the main protein. Due to its excellent properties collagen can be processed in different biomaterials used as burn/wound dressings, osteogenic and bone filling materials, antithrombogenic surfaces, collagen shields in ophthalmology, being also used for tissue engineering including skin replacement, bone substitutes, and artificial blood vessels and valves. Biomaterials based on type I fibrillar collagen such as medical devices, artificial implants, drug carriers for controlled release and scaffolds for tissue regeneration have an important role in medicine, being widely used at present (Healy et al., 1999; Hubell, 1999; Wang et al., 2004). In this chapter, we attempted to summarize some of the recent developments in the application of collagen as biomaterial in drug delivery systems and tissue engineering field.

2. Collagen-based biomaterials

Collagen is the main fibrous protein constituent in skin, tendons, ligaments, cornea etc. It has been extensively isolated from various animals, including bovine (Renou et al., 2004; Doillon, 1992), porcine (Smith et al., 2000; Lin et al., 2011; Parker et al., 2006), equine (Angele et al., 2004), ovine (Edwards et al., 1992), shark, frog, bird (Limpisophon et al., 2009) and from marine origin such as: catfish (Singh et al., 2011), silver carp (Rodziewicz-Motowidło et al., 2008), marine sponge (Swatschek et al., 2002), jumbo squid (Uriarte-Montoya et al., 2010),

paper nautilus (Nagai & Suzuki, 2002), tilapia fish-scale (Chen et al., 2011), red fish (Wang et al., 2008). Among these types of sources the most used has been bovine hide. Although to date 29 different types of collagen have been identified (Albu, 2011), type I collagen is the most abundant and still the best studied. This work is focused on biomaterials based on type I collagen of bovine origin. Type I collagen consists of 20 amino acids, arranged in characteristic sequences which form a unique conformational structure of triple helix (Trandafir et al., 2007). Hydroxyproline is characteristic only for collagen and it confers stability for collagen, especially by intramolecular hydrogen bonds. The collagen structure is very complex, being organised in four levels, named primary, secondary, tertiary and quaternary structure. Depending on the process of collagen extraction, the basic forms of collagen are organized on structural level.

2.1 Process of collagen extraction

To obtain extracts of type I fibrillar collagen, fresh skin or skin technological waste from leather industry can be used as raw materials (Trandafir et al., 2007), extraction being performed from dermis. To minimize the exogenous degradation the skin has to be ready for immediate extraction. Yield of good extraction is obtained from skin of young animals (preferably younger than two years) due to weaker crosslinked collagen.

Figure 1 schematically shows the obtaining of collagen in different forms by the currently used technologies at Collagen Department of Leather and Footwear Research Institute, Bucharest, Romania.

As figure 1 shows, the bovine hide was used as raw material. After removal of hair and fat by chemical, enzymatic or mechanical process, the obtained dermis could undergo different treatment and *soluble* or *insoluble collagen* is obtained.

2.1.1 Process of extraction for soluble collagen

Depending on structural level the solubilised collagen extracts can be denatured (when 90% of molecules are in denatured state) or un-denatured (when 70% of molecules keep their triple helical structure) (Trandafir et al., 2007).

The process for obtaining of *denatured collagen* took place at high temperature, pressure or concentrated chemical (acid or alkali) or enzymatic agents. Following these critical conditions the collagen is solubilised until secondary or primary level of structure and *gelatine* or *partial* (polypeptide) and *total* (amino acids) *hydrolisates* are obtained.

The *undenatured collagen* can be isolated and purified by two technologies, depending on the desired structural level (Li, 2003): molecular and fibrillar. They allow the extraction of type I collagen from bovine hide in aqueous medium while maintaining the triple helical structure of molecules, of microfibrils and fibres respectively (Wallace & Rosenblatt, 2003).

Isolation and purification of collagen molecules from collagenic tissues can be performed using a proteolytic enzyme such as pepsin, which produces cleavage of telopeptides - places responsible for collagen crosslinking. Removing them makes the collagen molecules and small aggregates (protofibrils) soluble in aqueous solutions of weak acid or neutral salts.

Extraction of collagen soluble in neutral salts. Studies on the extraction of soluble collagen with neutral salt solutions were performed with 0.15 to 0.20 M sodium chloride at 5°C for 1-2 days (Fielding, 1976). Yield of this technology is low and the most collagenic tissues extracted with salts contain small quantities of collagen or no collagen at all.

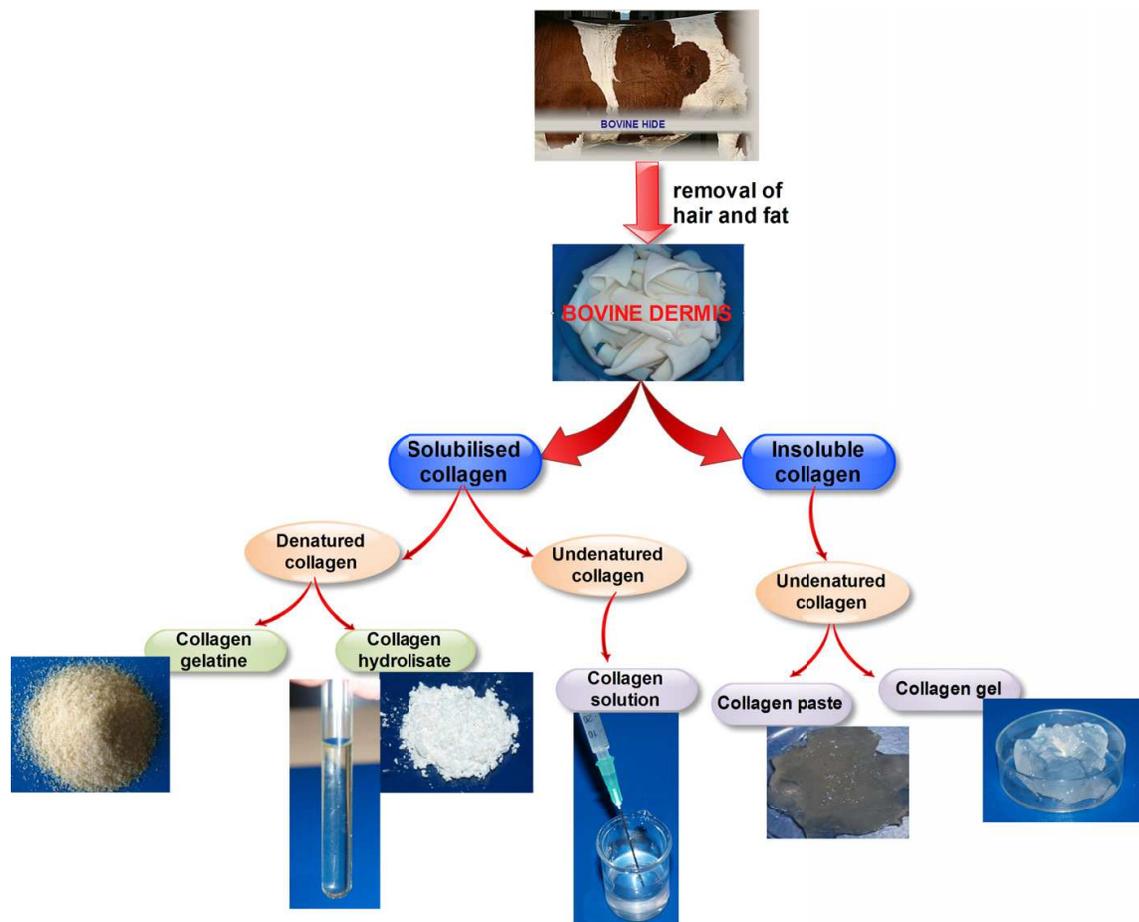


Fig. 1. Basic forms of collagen

Extraction of acid soluble collagen. Dilute acids as acetic, hydrochloric or citrate buffer solution with pH 2-3 are more effective for extraction of molecular collagen than neutral salt solutions. Type aldiminic intermolecular bonds are disassociated from dilute acids and by exerting forces of repulsion that occur between the same charges on the triple helix, causing swelling of fibril structure (Trelstad, 1982). The diluted acids do not dissociate keto-imine intermolecular bonds. For this reason collagen from tissues with high percentage of such bonds, such as bone, cartilage or tissue of aged animals is extracted in smaller quantities in dilute acids.

To obtain soluble collagen with diluted acids tissue is ground cold, wash with neutral salt to remove soluble proteins and polysaccharides, then collagen is extracted with acid solutions (Bazin & Delaunay, 1976). Thus about 2% of collagen can be extracted with salts or diluted acid solutions.

Enzymatic extraction is more advantageous, collagen triple helix being relatively resistant to proteases such as pronase, ficin, pepsin or chemotripsin at about 20°C (Piez, 1984). The efficacy of enzymatic treatment arises from selective cleavage in the terminal non-helical regions monomer and higher molecular weight covalently linked aggregates, depending on the source and method of preparation. Thus, telopeptidic ends are removed, but in appropriate conditions the triple helices remain intact. Solubilised collagen is purified by salt precipitation, adjusting pH at the isoelectric value or at temperature of 37°C (Bazin & Delaunay, 1976). Collagen extracted with pepsin generally contains higher proportions of intact molecules extracted with salts or acids.

2.1.2 Process of extraction for insoluble collagen

Collagen extraction by alkaline and enzymatic treatments. Alkaline pretreatment destroys covalent bonds resistant to acids. Collagen interaction with alkali shows the presence of certain specificities, hydrogen bonds being more sensitive to alkali. Degradation of the structure is more intense and irreversible if treatment is progressing on helicoidal structure (collagen → gelatin transition, alkaline hydrolysis).

Breaking of hydrogen bonds occurs by replacing the hydrogen atom from carboxyl groups with metal which is unable to form hydrogen bonds. Collagen can be extracted by treating the dermis with 5-10% sodium hydroxide and 1 M sodium sulphate at 20-25°C for 48 hours (Cioca, 1981; Trandafir et al., 2007). Thus, fats associated with insoluble collagen are saponified, the telopeptidic non-helical regions are removed, collagen fibers and fibrils are peptized. Size of resulted fragments of collagen depends on the time and concentration of alkali treatment (Roreger, 1995). The presence of sodium sulfate solution controlled the swelling of collagen structure, protecting the triple-helical native conformation. Alkaline treatment is followed by an acid one, which leads to total solubilization of collagen in undenatured state from the dermis of mature animals.

Thus technologies of molecular and fibrillar extraction are enabled to extract type I collagen from bovine hide in an aqueous medium keeping triple helical structure of molecules, microfibrils and fibrils (Wallace & Rosenblatt, 2003).

2.2 Obtaining of collagen-based biomaterials

Obtaining of collagen-based biomaterials starts from undenatured collagen extracts – gels and solutions – which are processed by cross-linking, free drying, lyophilization, electrospinning, mineralisation or their combinations. To maintain the triple helix conformation of molecules the conditioning processes must use temperatures not higher than 30°C (Albu et al., 2010a). Extracted as aqueous solution or gel, type I collagen can be processed in different forms such as hydrogels, membranes, matrices (spongy), fibers, tubes (Fig. 2) that have an important role in medicine today. Figure 2 shows some collagen-based biomaterials obtained at our Collagen Department.

Among the variety of collagen-based biomaterials, only the basic morphostructural ones will be presented: hydrogels, membranes, matrices, and composites obtained from undenatured collagen.

Collagen hydrogels are biomaterials in the form of tridimensional networks of hydrophilic polymeric chains obtained by physical or chemical cross-linking of gels. Chemical cross-linking consists in collagen reaction with aldehydes, diisocyanates, carboimides, acyl-azide, polyepoxydes and polyphenolic compounds which lead to the formation of ionic or covalent bonds between molecules and fibrils (Albu, 2011). Physical cross-linking includes the drying by heating or exposure at UV, gamma or beta irradiations. Their mechanical and biological properties are controllable and superior to the gels from which they were obtained.

The hydrogels have the capacity of hydration through soaking or swelling with water or biological fluids; hydrogels with a solid laminar colloidal or solid spherocolloidal colloidal frame are formed, linked by means of secondary valences, where water is included by swelling. One of the exclusive properties of hydrogels is their ability to maintain the shape during and after soaking, due to the isotropic soaking. Also the mechanical properties of the collagen hydrogels are very important for the pharmaceutical applications, the modification of the cross-linking degree leading to the desired mechanical properties. The spreading

ability of the different size molecules in and from hydrogels serves for their utilization as drug release systems. The development and utilization of collagen hydrogels in therapeutics is supported by some advantages contributing to patients compliance and product efficiency. Thus, the hydrogels are easy to apply, have high bioadhesion, acceptable viscosity, compatibility with numerous drugs (Albu & Leca, 2005; Satish et al., 2006; Raub et al., 2007).

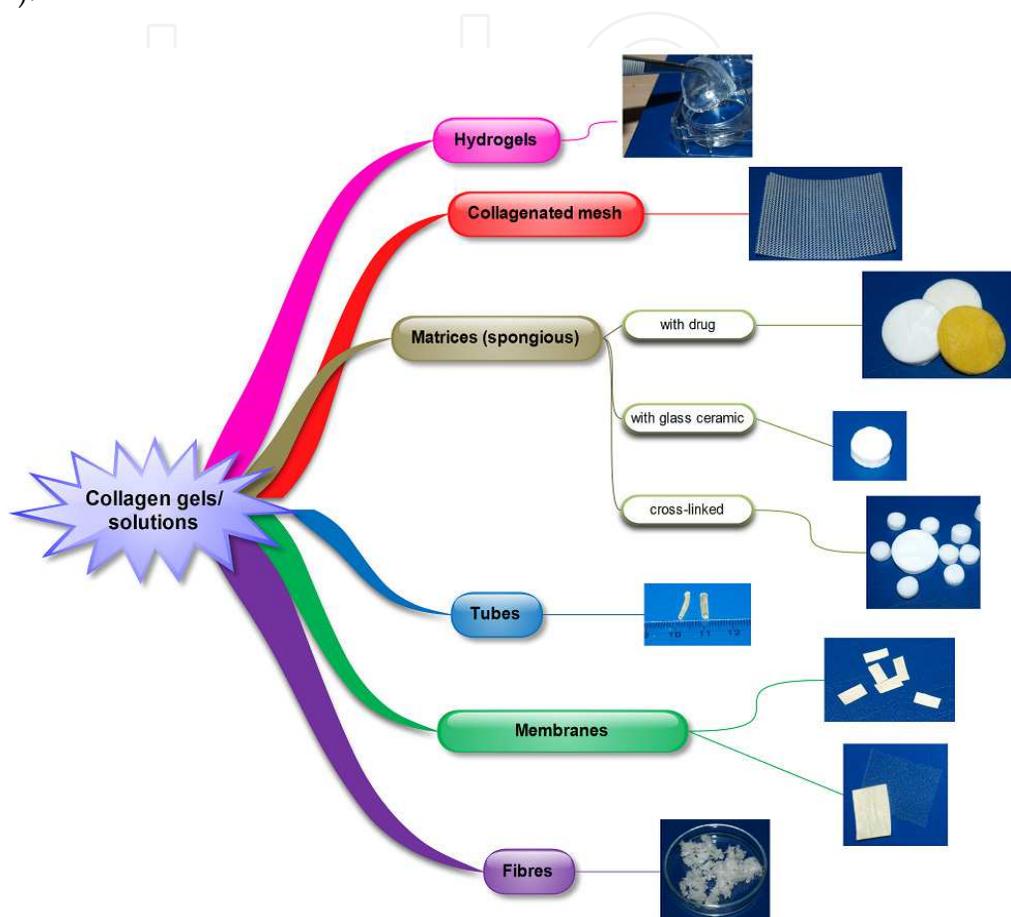


Fig. 2. Collagen-based biomaterials

Collagen membranes/films are obtained by free drying of collagen solution/gel in special oven with controllable humidity and temperature (not higher than 25°C) during 48-72 hours. These conditions allow the collagen molecules from gels to be structured and to form intermolecular bonds without any cross-linking agent. They have dense and microporous structure (Li et al., 1991).

Collagen matrices are obtained by lyophilisation (freeze-drying) of collagen solution/gel. The specificity of porous structure is the very low specific density, of approximately 0.02-0.3 g/cm³ (Albu 2011, Zilberman & Elsner, 2008; Stojadinovic et al., 2008; Trandafir et al., 2007). The matrix porous structure depends significantly on collagen concentration, freezing rate, size of gel fibrils and the presence or absence of cross-linking agent (Albu et al., 2010b). The collagen matrix morphological structure is important, influencing the hydrophilicity, drug diffusion through network, degradation properties and interaction with cells. Figure 3 shows characteristic pore structure with a large variation in average pore diameter in collagen matrices.

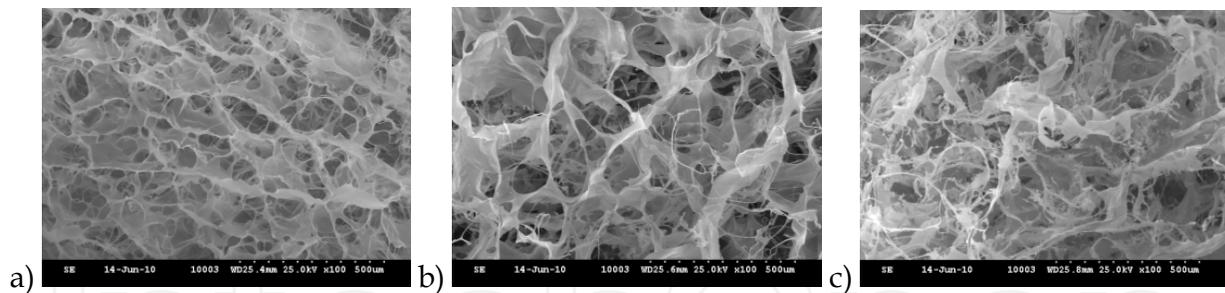


Fig. 3. SEM images of collagen matrices: (a) freeze at -40°C , (b) freeze at -10°C and (c) cross-linked with 0.25% glutaraldehyde.

Although the matrices presented in Fig. 3a,b have the same composition, their structure is different. Therefore, the low temperature (e.g. -40°C) induces about 10 times smaller pore sizes than higher temperature (e.g. -10°C). It can be noticed that lower freezing temperature produces more homogeneous samples than those obtained at high freezing temperature. Major differences of pore size and shape appear between un-cross-linked and cross-linked samples, the most homogeneous matrix with the smallest and inner pores being the un-cross-linked obtained at lowest freezing temperature.

Hydrophilic properties expressed by absorbing water and its vapor, are characteristic for collagen matrices, which can absorb at least 1500% water. Permeability for ions and macromolecules is of particular importance for tissues which are not based only on the vascular transport of nutrients. Diffusion of nutrients into the interstitial space ensures survival of the cells, continued ability to grow and to synthesize extracellular matrix specifically for tissue.

The infrared spectra of collagen exhibit several features characteristic for the molecular organization of its molecules: amino acids linked together by peptide bonds give rise to infrared active vibration modes amide A and B (about 3330 and 3080 cm^{-1} , respectively) and amide I, II, and III (about $1629\text{-}1658\text{ cm}^{-1}$, $1550\text{-}1560\text{ cm}^{-1}$ and $1235\text{-}1240\text{ cm}^{-1}$, respectively) (Sionkowska et al., 2004).

Hydrothermal stability of collagen is characterized by its contraction when heated in water at a certain temperature at which the conformational transition of molecules from the triple helix statistic coil take place (Li, 2003).

Thermal behavior of collagen matrices depends on the number of intermolecular bonds. Generally, the number of bonds is higher, the shrinkage temperature is higher and the biomaterial is more stable *in vivo*.

Another method commonly used to assess the *in vivo* stability of collagen biomaterials, is the *in vitro* digestion of matrix with collagenase and other proteinases (trypsin, pepsin) (Li, 2003). Biodegradability of collagen matrices is dependent on the degree of cross-linking.

Collagen can form a variety of homogeneous collagen composites with ceramics, drugs, natural or synthetic polymers. The obtaining methods involve chemical cross-linking, physical loading and co-precipitation followed by free-drying, freeze-drying or electrospinning.

The most recent collagen composites used as medical devices, artificial implants, supports for drug release and scaffolds for tissue regeneration are presented in Table 1.

Collagen composites containing physiologically active substances acting as drug delivery systems (DDS) are discussed in Section 3.

Type of composite	Type of component from composite	Composite form
Collagen-natural polymer	Hyaluronic acid (Davidenko et al., 2010)	Matrix, membrane, hydrogel, fibers
	Silk fibroin (Zhou et al., 2010)	Membrane, fibers, matrix, microtubes
	Chondroitin-6-sulphate (Stadlinger et al., 2008)	Tube, matrix
	Elastin (Skopinska-Wisniewska et al., 2009)	Tube, film, fibers, matrix
	Alginate (Sang et al., 2011)	Spongy, filler for bone,
	Chitosan (Sionkowska et al., 2004)	Matrix, membrane, tubular graft, nanofibers, hydrogel,
	Heparin (Stamov et al., 2008)	Matrix
Collagen-synthetic polymer	Poly-L-lactide (PLLA) (Chen et al., 2006)	Coating for composite
	Poly-lactic-co-glycolic-acid (PLGA) (Wen et al., 2007)	Fibers, matrix, coated tube
	ϵ -caprolactone (Schnell et al., 2007)	Nanofibers
	Poly(ethylene-glycol) (PEG) (Sionkowska et al., 2009)	Films, fibers
Collagen-ceramic	Calcium phosphates (Hong et al., 2011)	Matrix, filler
	Hydroxyapatite (Zhang et al., 2010; Hoppe et al., 2011)	Matrix, filler
	Tricalciumphosphate (Gotterbarm et al., 2006)	Matrix, filler

Table 1. Collagen-based composites

3. Collagen-based drug delivery systems

Nowadays, the field of drug delivery from topical biopolymeric supports has an increased development due to its advantages compared to the systemic administration. These biopolymers can release adequate quantities of drugs, their degradation properties being adjustable for a specific application that will influence cellular growth, tissue regeneration, drug delivery and a good patient compliance (Zilberman & Elsner, 2008). Among the biopolymers, collagen is one of the most used, being a suitable biodegradable polymeric support for drug delivery systems, offering the advantage of a natural biomaterial with haemostatic and wound healing properties (Lee et al., 2001).

Studies with collagen as support showed that *in vivo* absorption and degradability on the one hand and drug delivery on the other hand are controlled by the collagen chemical or physical cross-linking performed in order to control the delivery effect (Albu, 2011).

Among the incorporated drugs in the collagen biomaterials various structures are mentioned: antibiotics and antiseptic (tetracycline, doxycycline, rolitetracycline, minocycline, metronidazole, ceftazidime, cefotaxime, gentamicin, amikacin, tobramycin, vancomycin, chlorhexidine), statines (rosuvastatin), vitamins (riboflavine), parasympathomimetic alkaloid (pilocarpine) etc. (Zilberman & Elsner, 2008; Goissis & De Sousa, 2009; Yarboro et al., 2007).

The most known collagen-based drug delivery systems are the hydrogels and matrices.

The literature in the field reveals the importance of modeling the drug release kinetics from systems with topical application. The topical preparations with antibiotics, anti-inflammatory, antihistaminics, antiseptics, antimicrobics, local anaesthetics must have a rapid release of the drug. The release kinetics has to balance the advantage of reaching a therapeutic concentration with the disadvantage of toxic concentrations accumulation (Ghica, 2010).

As far as the drug delivery kinetics from semisolid/solid systems generally is concerned, it has been widely studied only in the case of the hydrogels having quasi-solid structure (Lin & Metters, 2006; Albu et al., 2009b).

In the case of the matrices, there is scarce literature on the delivery and the delivery mechanism of the drug from such systems. In Fig. 4 the drug delivery from a spongy collagen support is schematically presented.

The delivery of the drug from polymeric formulations is controlled by one or more physical processes including: polymer hydration through fluid, swelling to form a gel, drug diffusion through the gel formed and eventual erosion of the polymeric gel. It is possible that, for the sponges, the swelling, erosion and the subsequent diffusion kinetics play an important role in the release of the drug from these systems upon contact with biological fluids (cutaneous wound exudate/gingival crevicular fluid). Upon contact of a dry sponge with the wet surface at the application site, biological fluid from that region penetrates the polymer matrix. Thus, the solvent molecules' internal flux causes the subsequent sponge hydration and swelling and the formation of a gel at the application site surface. The swelling noticed is due to the polymeric chains solvation that leads to an increase of the distance between the individual molecules of the polymer (Peppas et al., 2000; Boateng et al., 2008).

For some of the spongy forms the drug release mechanism has been explained through the hydrolytic activity of the enzymes existing in biological fluids, different mathematical models of the collagen sponges' enzymatic degradation being suggested (Metzmacher et al., 2007; Radu et al., 2009).

It was shown that in an aqueous medium the polymer suffers a relaxation process having as result the direct, slow erosion of the hydrated polymer. It is possible that its swelling and dissolution happen at the same time as in the sponges' situation, each of these processes contributing to the global release mechanism. However, the quantity of the drug released is generally determined by the diffusion rate of the medium represented by biological fluid in the polymeric sponge. Factors such as polymeric sponge erosion after water diffusion and the swelling in other dosage forms are the main reason of kinetics deviation square root of time (Higuchi type, generally specific to the hydrogels as such) (Boateng et al., 2008).

Different methods have been suggested for the investigation of the drug controlled release mechanisms that combine the diffusion, the swelling and the erosion. It is assumed that the collagen sponge is made of a homogeneous polymeric support where the drug (dissolved or suspended) is present in two forms: free or linked to the polymeric chains. The drug as free form is available for diffusion, through the desorption phenomenon, for immediate release in a first stage, this being favored by the sponge properties behaving as partially open porosity systems. The drug amount partially immobilized in collagen fibrillar structure will be gradually released after the diffusion of the biologic fluid inside the sponge, followed by its swelling and erosion on the basis of polymers reaction in solution theory. This sustained release is favored by the matrix properties to act as partially closed porosity systems, as well as by the collagen sponge tridimensional structure, which is a barrier between the drug in the sponge and the release medium (Singh et al., 1995; Friess, 1998; Wallace & Rosenblatt, 2003; Ruszczak & Friess, 2003).

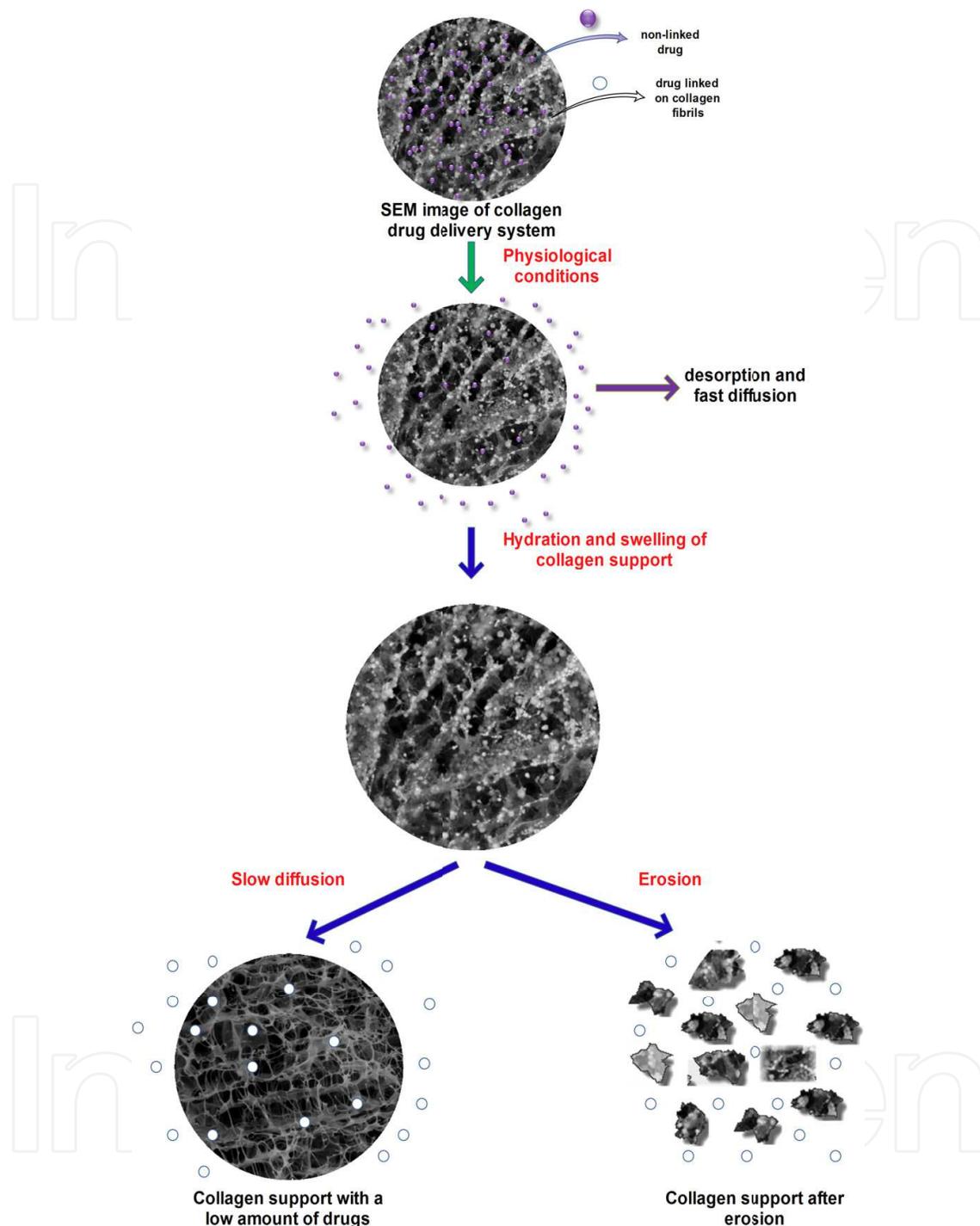


Fig. 4. Drug release from collagen matrix

In addition, the drug release kinetics can be influenced by the different chemical treatments that affect the degradation rate or by modifications of sponge properties (porosity, density) (M. Grassi & G. Grassi, 2005).

Among the chemical methods we can mention the cross-linking techniques. Thus, the different *in vivo* and *in vitro* behaviour, including the drug delivery profiles, can be obtained if the product based on collagen suffer in addition cross-linking with different

cross-linking agents. Among these agents, the most known and used is the glutaraldehyde that forms a link between the ϵ -amino groups of two lateral lysin chains. It was demonstrated that the treatment with glutaraldehyde reduces the collagen material immunogenicity, leading at the same time to the increase of resistance to enzymatic degradation (Figueiro et al., 2006).

Concerning the preparation of sponges with different porosities, those can be obtained by modifying the temperature during the collagen sponges lyophilization process (Albu et al., 2010a).

To understand the release process, both from hydrogels and from collagen sponges, and to establish the drug release mechanism implicitly, a range of kinetic models is used (Peppas, Higuchi, zero order). The general form of the kinetic equation through which the experimental kinetic data are fitted is the following: (eq. 1)

$$\frac{m_t}{m_\infty} = k \cdot t^n \quad (1)$$

where m_t is the amount of drug released at time t , m_∞ is the total drug contents in the designed collagen hydrogels, m_t/m_∞ is the fractional release of the drug at the time t , k is the kinetic constant, reflecting the structural and geometrical properties of the polymeric system and the drug, and n is the release exponent, indicating the mechanism of drug release.

If $n=0.5$ the release is governed by Fickian diffusion (the drug diffusion rate is much lower than the polymer relaxation rate, the amount of drug released being proportional to the release time square root, corresponding to Higuchi model). If $n=1$ the release is controlled by surface erosion (the drug diffusion rate is much higher than the polymer relaxation rate, the amount of drug released being proportional with the release time, corresponding to zero order model). If $0.5 < n < 1$, the drug release mechanism is of non-Fickian type diffusion, the drug diffusion rate and the polymer relaxation rate being roughly equal. In this case the release is not based only on diffusion, being also associated with other release mechanisms due to the complex processes previously described (Teles et al., 2010; Higuchi, 1962; Peppas et al., 2000; Singh et al., 1995; Ho et al., 2001).

The studied literature shows that Peppas, Higuchi and zero order models do not explain the mechanisms involved in the kinetic processes in the case of sponge forms, because the value of the apparent release order value (n) does not fit between the limits imposed by these aforesaid models, having values much lower than 0.5. This is why an extension of Peppas model to the Power law model ($0 < n < 1$) is generally applied in order to elucidate the complex kinetic mechanisms involved in the drug release from such natural supports. Practically, n value includes characteristics of each particular model previously described (Ghica et al., 2009; Albu et al., 2009a; Albu et al., 2010b; Phaechamud & Charoenteeraboon, 2008; Natu et al., 2007).

Our studies showed values of n equal to 0.5 for different collagen-based hydrogels with doxycycline, uncross-linked or cross-linked with glutaraldehyde, which confirms the respect of Higuchi model concerning the drug release from semisolid supports (Albu et al., 2009b). On the contrary, n values for doxycycline release from spongy supports were inferior to 0.5 (Ghica et al., 2009; Albu et al., 2010a; Albu et al., 2010b).

4. Collagen-based scaffolds for tissue engineering

It is known that collagen is the major component of the extracellular matrix of most tissues. As a natural molecule, collagen possesses a major advantage in being biodegradable, biocompatible presented low antigenicity, easily available and highly versatile. Collagen provides structural and mechanical support to tissues and organs (Gelse et al., 2003) and fulfils biomechanical functions in bone, cartilage, skin, tendon, and ligament. For this reason, allogenic and xenogenic collagens have been long recognized as one of the most useful biomaterials. Collagen can be prepared in a number of different forms with different application: shields used in ophthalmology (Rubinstein, 2003; Yoel & Guy, 2008) matrices for burns/wounds (Keck et al., 2009; Wollina et al., 2011), gel formulation in combination with liposomes for sustained drug delivery (Wallace & Rosenblatt, 2003; Weiner et al., 1985; Rao, 1996), as controlling material for transdermal delivery (Rao, 1996; Thacharodi & Rao, 1996), nanoparticles for gene delivery (Minakuchi et al., 2004) and basic matrices for cell culture systems. Therefore thin sheets and gels are substrates for smooth muscle (Dennis et al., 2007; Engler et al., 2004), hepatic (Hansen & Albrecht, 1999; Ranucci et al., 2000), endothelial (Albu et al., 2011; Deroanne et al., 2001; Titorencu et al., 2010), and epithelial cells (Haga et al., 2005), while matrices are often used to engineer skeletal tissues such as cartilage (Stark et al., 2006; Schulz et al., 2008), tendon (Gonçalves-Neto et al., 2002; Kjaer, 2004) and bone (Guille et al., 2005).

It is known that the goal of tissue engineering (TE) is to repair and restore damaged tissue function. The three fundamental “tools” for both morphogenesis and tissue engineering are responding cells, scaffolds and growth factors (GFs - regulatory biomolecules, morphogens), which, however, are not always simultaneously used (Badylak & Nerem, 2010; Berthiaume et al., 2011) (Fig. 5).

In tissue engineering, matrices are developed to support cells, promoting their differentiation and proliferation in order to form a new tissue. Another important aspect for the generation of 3D cell matrix constructs suitable for tissue regeneration is represented by cell seeding. Besides the seeding technique, the cellular density is a crucial factor to achieve a uniform distribution of a number of cells which is optimal for new tissue formation (Lode et al., 2008). Such strategies allow producing of biohybrid constructs that can be implanted in patients to induce the regeneration of tissues or replace failing or malfunctioning organs.

The advantage of tissue engineering is that small biopsy specimens can be obtained from the patient and cells can be isolated, cultured into a structure similar to tissue or organs in the living body, expanded into large numbers (Bruder & Fox, 1999; Levenberg & Langer, 2004; Mooney & Mikos, 1999; Service, 2005) and then transplanted into the patients.

The recent advances in collagen scaffold biomaterials are presented as follows:

Wound dressing and delivery systems

In the treatment of wounds the collagen-based dressings are intensely used. There are many studies which attest the benefits of topical collagen matrices on the wound healing (Inger & Richard, 1999; Ruszczak, 2003; Shih-Chi et al., 2008).

It is known that collagen matrices absorb excess wound exudate or sterile saline, forming a biodegradable gel or sheet over the wound bed that keeps the balance of wound moisture environment, thus promoting healing (Hess, 2005). Also, collagen breakdown products are chemotactic for a variety of cell types required for the formation of granulation tissue. Nowadays, many types of skin substitutes using living cells have been used clinically (Table 2).

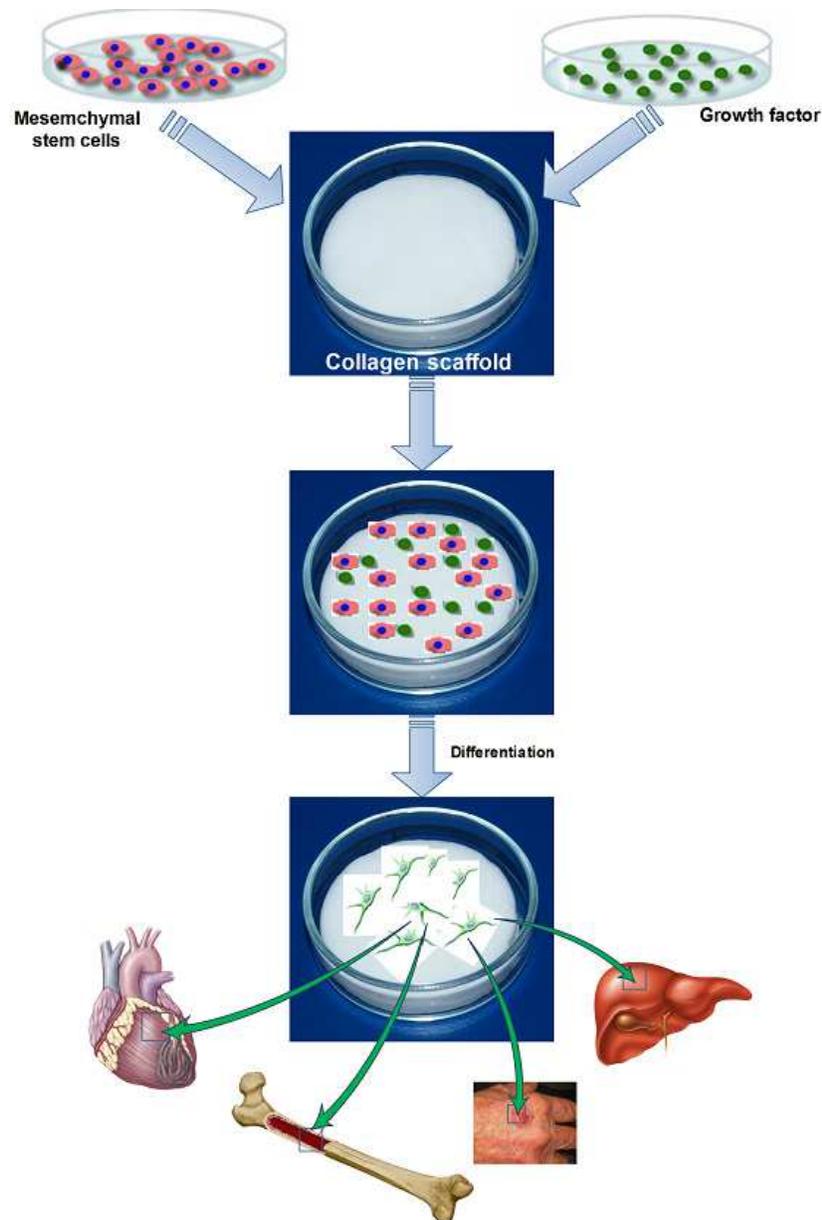


Fig. 5. Strategies for tissue engineering

Classification	Tissue replaced	Layers
TranCyte®	Epidermal	Silicone Nylon mesh Collagen seeded with neonatal fibroblasts
PermaDerm™	Dermal	Autologous fibroblasts in bovine collagen matrix with autologous keratinocytes
Apligraf®	Epidermal and dermal	Neonatal keratinocytes Collagen seeded with neonatal fibroblasts
OrCell™	Epidermal and dermal	Collagen (bovine type I) seeded with allogenic fibroblasts and keratinocytes

Table 2. Classification of collagen substitutes with living cells

These biomaterials can be divided into three groups depending on the type of layer cells which are substituted. The first type consists of grafts of cultured epidermal cells with no dermal components. The second type has only dermal components. The third type is a bilayer containing both dermal and epidermal elements.

Bone defects

Bone development and regeneration occurs as a result of coordinated cell proliferation, differentiation, migration, and remodeling of the extracellular matrix. In bone tissue engineering collagen scaffolds play an essential role in supporting bone regeneration. The implantation of these 3D biomaterials is necessary when osteochondral defects reach an important volume or when autografts have to be avoided for practical or pathological reasons. In order to promote bone healing scaffolds must have some properties: to promote the differentiation of immature progenitor cells into osteoblasts (*osteoinduction*), to induce the ingrowth of surrounding bone (*osteoconduction*) and to be integrated into the surrounding tissue (*osseointegration*) (Dickson et al., 2007). However there is still some ambiguity regarding the optimal porosity and pore size for a 3D bone scaffold. A literature review indicates that a pore size in the range of 10–400 μm may provide enough nutrient and osteoblast cellular infusion, while maintaining structural integrity (Bignon et al., 2003; Holmbom et al., 2005; Woodard et al., 2007).

Collagen scaffolds have the advantage of facilitating cell attachment and maintaining differentiation of cells (Fig. 6). Resorbable collagen sponges have been successfully used as carriers of BMP-2, BMP-4 and BMP-7 but they have the disadvantages of a fast degradation rate and low mechanical strength (Bessa et al., 2008; Higuchi et al., 1999; Huang et al., 2005; Huang et al., 2005; Kinoshita et al., 1997;).

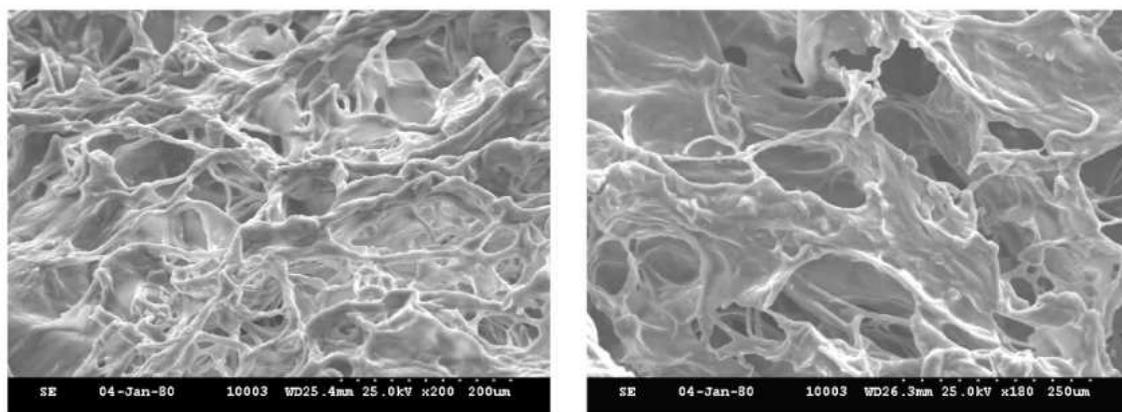


Fig. 6. Human osteoblast precursor cells (hFOB1.19) grown seven days on collagen scaffolds

In order to increase mechanical strength and to improve the release of growth factors a combination between collagen and other natural polymer has been used such as chitosan (Arpornmaeklong et al., 2007), dextran (Fig. 7) or glycosaminoglycans (Harley & Gibson, 2008; Wang et al., 2010).

Another combination of collagen scaffolds is represented by mineralization with calcium phosphate (Du et al., 2000; Harley et al., 2010) and/or on cross-linking with other substances like hydroxyapatite (Dubey & Tomar, 2009; Liao et al., 2009.) or bushite (Tebb et al., 2006).

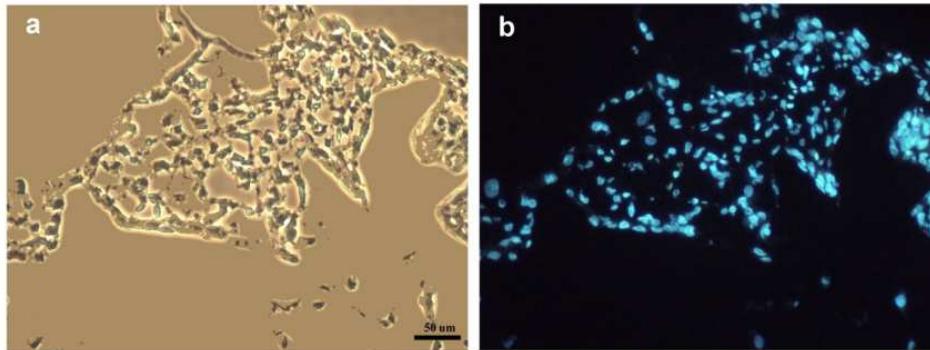


Fig. 7. Osteosarcoma cells (MG 63) grown on collagen-dextran scaffold: a – phase contrast, b – Hoechst nuclear staining

Urogenital system

Injuries of the genitourinary system can lead to bladder damage. Treatment in most of these situations requires eventual reconstructive procedures that can be performed with native non-urolologic tissues (skin, gastrointestinal segments or mucosa), heterologous tissues or substances (bovine collagen) or artificial materials (Atala, 2011). Acellular collagen scaffolds were used in the treatment of bladder augmentation (Akbal et al., 2006; Liu et al., 2009; Parshotamet al., 2010) and urethral stricture (el-Kassaby et al., 2008; Farahat et al., 2009). Also collagen-composite scaffolds populated with the patient's own urothelial and muscle cells or self-assembled fibroblast sheets represent a promising strategy for bladder augmentation (Bouhout et al., 2010; Magnan et al., 2006). Trials of urethral tissue replacement with processed collagen matrices are in progress, and bladder replacement using tissue engineering techniques are intensely being studied (Atala et al., 2006).

Scaffolds for hepatic cells

Recent new strategies for treating liver diseases, including the extracorporeal bioartificial liver device and hepatocyte transplantation represent the future in hepatic diseases treatment. Recent advances in the field of tissue engineering have demonstrated that type I collagen matrices induced the differentiation of hepatic stem-like cells into liver epithelial cells and that biodegradable collagen matrices provide an appropriate microenvironment for hepatocytic repopulation (Uneo et al., 2004; Ueno et al., 2005.); also, a combination between collagen-chitosan-heparin scaffolds was used in order to obtain bioartificial liver (Xing et al., 2005).

Cornea and neural cells

Bioengineered corneas are substitutes for human donor tissue that are designed to replace part or the full thickness of damaged or diseased corneas. Collagen has been used successfully in reconstruction of artificial cornea alone by delivery of limbal epithelial stem cells to damaged cornea (Builles et al., 2010; De Miguel et al., 2010) or in combination with glycosaminoglycan (GAG) molecules (Auxenfans et al., 2009). The combination of collagen biomaterials and stem cells could be a valuable strategy to treat corneal defects also. Other strategies in collagen-based corneal scaffolds include the utilization of recombinant human collagen (Dravida et al., 2008; Griffith et al., 2009), the secretion of collagen by the fibroblasts themselves (Carrier et al., 2008) and surface modification to reduce extensive endothelialization (Rafat et al., 2009).

Nerve repairing

One of the major challenges in neurology is to be able to repair severe nerve trauma. It was observed that collagen scaffolds is a suitable nerve guidance material (Han et al., 2010) Most collagen nerve guides are engineered from crosslinked collagen with tubular shape such as commercially available NeuraGen® from Integra™. Recent tissue engineering strategies involve addition of neurotrophic factors into collagen scaffolds (Sun et al., 2007; Sun et al., 2009) and cell delivery (Bozkurt et al., 2009; Kemp et al., 2009) in order to attempt to enhance nerve guides.

5. Conclusion

Collagen biomaterials as matrices, hydrogels, composites have already been proved to be effective in tissue repairing, in guiding functional angiogenesis and in controlling stem cell differentiation. Also, collagen-based drug delivery systems were studied and their mechanisms of release were determined. Based on such good results, the promising next generation of engineered tissues is relying on producing scaffolds which can prolong the release rate of growth factors or cells in order to increase their therapeutic effect. This justifies the importance of drug delivery in tissue engineering applications.

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7. References

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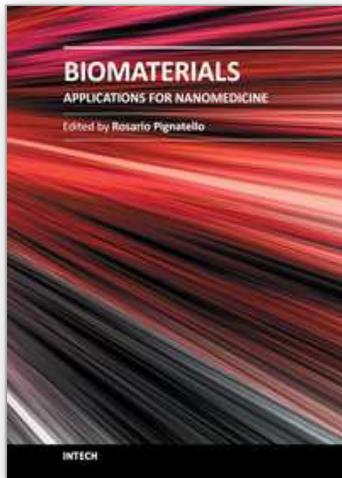
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