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Review

Medical applications of membranes: Drug delivery, artificial organs and tissue engineering

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Abstract

This paper covers the main medical applications of artificial membranes. Specific attention is given to drug delivery systems, artificial organs and tissue engineering which seem to dominate the interest of the membrane community this period. In all cases, the materials, methods and the current state of the art are evaluated and future prospects are discussed.

Concerning drug delivery systems, attention is paid to diffusion controlled systems. For the transdermal delivery systems, passive as well as iontophoretic systems are described in more detail. Concerning artificial organs, we cover in detail: artificial kidney, membrane oxygenation, artificial liver, artificial pancreas as well as the application of membranes for tissue engineering scaffolds and bioreactors.

This review shows the important role of membrane science and technology in medical applications but also highlights the importance of collaboration of membrane scientists with others (biologists, bioengineers, medical doctors, etc.) in order to address the complicated challenges in this field.

Keywords: Membranes; Medical applications; Drug delivery; Artificial organs; Tissue engineering

Contents

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1. Introduction

Membrane technology is of major importance in medical applications, in particular in a number of life saving treatment methods. Membranes are used in drug delivery, artificial organs, tissue regeneration, diagnostic devices, as coatings for medical devices, bioseparations, etc.

The total membrane area produced for medical applications almost matches all industrial membrane applications together [1]. In fact in fiscal terms, the value of medical membrane products is far larger than all other applications combined [1]. Only in the US for example, the medical membrane market approaches 1.5 billion dollars per year and grows steadily.

The biggest part of the medical market involves membranes in drug delivery, hemodialysis, other artificial organs (oxygenators, pancreas, etc.) and tissue engineering. These areas will be covered extensively in this review. In all cases, biocompatible and in some applications biodegradable materials are required for the membrane fabrication. Therefore, prior to the specific applications, we briefly discuss the issues of biocompatibility and biodegradability.

The presentation of detailed membrane production processes is beyond the scope of this review. The reader can find more on those in membrane text books [1,2].

1.1. Biomaterials: biocompatibility–biodegradability

Biomaterials can be defined as substances in therapeutic or diagnostic systems that are in contact with biological fluids [3]. Biomaterials require certain essential properties depending on the functionality of the final device. Properties such as blood compatibility, size, shape, and porosity must be controlled. For instance, for cardiovascular implants the devices have certain size requirements in order to avoid clotting; in drug delivery, the requirements are different: drug permeability, good release properties, etc.

Generally, biomaterial-based membranes that are in contact with biological fluids should prevent any type of infection and immune response, blood clotting and other biological responses that could affect the properties of the fluid and, therefore, the patient. For this reason, it is important to know both *host* and *material response* for a certain biomaterial. The host response is usually related to inflammation, fibrosis, coagulation and hemolysis. The material response focuses on fracture, wear, corrosion, dissolution, swelling and leaching.

Traditionally, biocompatibility has been related to the effect of the material on the biological system it is in contact with. However, this definition has been controversial for years. Initially, a consensus was reached in defining biocompatibility as 'the ability of a material to perform with an appropriate host response to a specific situation' [4]. Nowadays, some authors associate biocompatibility to biological performance or interaction between materials and living systems [5]. Since not always living systems but biological systems are taken into account, Black defines biocompatibility as 'the biological performance of a certain material in a specific application and its acceptance/suitability for such application if both host and material responses are optimal' [5].

Not all biomaterials have the same degree of biocompatibility. Often, surface properties have to be modified in order to enhance the interaction of such material with the host or biological fluid and suppress immune response [6]. Biomaterial surfaces can be modified either physically by methods such as plasma etching, corona discharge, UV irradiation or by covalent attachment [6,7]. For the latter, chemical grafting, photo-grafting, plasma polymerization, grafting with ionization radiation, self-assembled monolayer formation or biological modification are some of the strategies that can be used to control host response and increase biocompatibility of membrane surfaces.

In general, a wide range of natural and synthetic materials is used in biomedical membrane applications. Biocompatible polymers can be divided into several categories, based upon changes in host response [5]: (i) inert biomaterials that exhibit little or no host response; (ii) interactive biomaterials that are designed to trigger specific and beneficial responses such as cell growth, adhesion; (iii) viable materials that at implantation, for instance, incorporate or attract living cells that are considered as normal tissues by the host and are actively resorbed by the system; and (iv) replant biomaterials that consist of *in vitro* cultured tissue from the patient's cells.

One of the aspects with a great importance is *blood compatibility* in terms of reduced coagulation, platelet adhesion, protein adsorption and hemolysis [8]. This is of great relevance for applications where blood purification is involved like hemodialysis, plasmapheresis, blood oxygenation and others. Membranes that are in contact with blood often suffer from flux decline and lowered membrane selectivity (fouling) caused mainly by protein adsorption [9]. Protein adsorption can be affected by the membrane surface chemistry as well as protein size, shape, charge and isoelectric point. It is now generally accepted that for obtaining more biocompatible membranes, the membrane should not have surface nucleophils, should have low surface charge and a balanced distribution of hydrophilic and hydrophobic domains [10–12].

Membrane structure is also a relevant aspect to be taken into account for extracorporeal blood purification [13]. A certain pore size and narrow pore size distribution, high porosity, small tortuosity, high diffusion coefficient, smooth and hydrophilic surface, thin skin layer and asymmetric structure are some of the general characteristics of membranes used in blood-contacting devices [5,9,13].

Erosion (degradability) is also a key parameter for materials that are used as implants and/or in tissue regeneration. Degradation is directly linked to drug release; for instance, if a polymer degrades very fast, a much elevated drug concentration is released to the patient, which can be disadvantageous and even fatal. Swelling and leaching result from diffusion. Swelling involves transport of ions or fluid from the tissue into the biomaterial. As a consequence of swelling, the elastic limit of a material can be reduced leading to static fatigue or crazing [5]. Leaching takes place if, for instance, one component of the biomaterial dissolves into the surrounding fluid phase. This can cause local biological reactions to the released products, reduced fracture strength and elastic modulus of the material. Corrosion tends to occur to biomaterials of metallic origin, which are rarely used in membrane technology and, therefore will not be discussed here. However, dissolution of polymers and ceramics is a more frequent phenomenon. The most soluble ceramics are those that resemble calcium-based materials present in mammals (e.g. calcium hydroxyapatite, calcium phosphates) but also other substances like Bioglass. In case of polymers, the dissolution varies depending on the nature of the polymer (hydrophilic/hydrophobic). Hydrophobic polymers, for example, dissolve preferably in the amorphous regions, which results in increased surface area, integrity loss and release of small particles [5].

Some non-degradable polymers include polyethylene terephthalate (PET), nylon 6,6, polyurethane (PU), polytetrafluoroethylene (PTFE), polyethylene (PE), polysiloxanes and poly(methylmethacrylate) (PMMA), modified polyacrylonitrile (PAN) [14] and polyether imide (PEI) [15–17]. PEI seems to be an interesting material since it is sufficiently stable in physiological environment and can be functionalized easily [16,18,19]. Bioresorbable polymers are designed to degrade within the body and be absorbed naturally when its function

has been accomplished [20]. These degradation characteristics differ from polymer to polymer, and can vary from swelling to dissolution by hydrolysis, for instance, when being exposed to body fluids. Bioresorbable materials degrade products that are normal metabolites of the body. Some examples of degradable polymers are polylactide, polyglycolide, polycaprolactone and polyhyaluronic acid esters, but also natural polymers like collagen, chitosan. More examples of materials are given in the following sections where the specific medical membrane applications are discussed.

2. Drug delivery

2.1. General

The goal of an ideal drug delivery system is to deliver a drug to a specific site, in specific time and release pattern. The traditional medical forms (tablets, injection solutions, etc.) provide drug delivery with peaks, often above the required dose (Fig. 1). The constant drug level in blood or sustained drug release to avoid multiple doses and bypassing of the hepatic "first-pass" metabolism are the main challenges for every delivery system [21,22].

In this review, we will focus on membrane-based systems where basically a drug reservoir is contained in a membrane device. Two types of systems can be distinguished:

- Osmotic membrane systems.
- Diffusion controlled membrane systems.

Specific attention will be given to diffusion controlled systems which find broad commercial application.

2.2. Osmotic membrane systems

Fig. 2 shows a cross-section of an osmotic system. It consists of a reservoir made of a polymeric membrane permeable to water but not to the drug (semi-permeable membrane). The reservoir contains a concentrated drug solution. As water crosses the membrane due to osmotic pressure, the drug solution is released through the orifice. Using these devices one can deliver various types of drugs at relatively high fluxes. If the system does not contain an orifice, it can be used for one time dose by bursting of

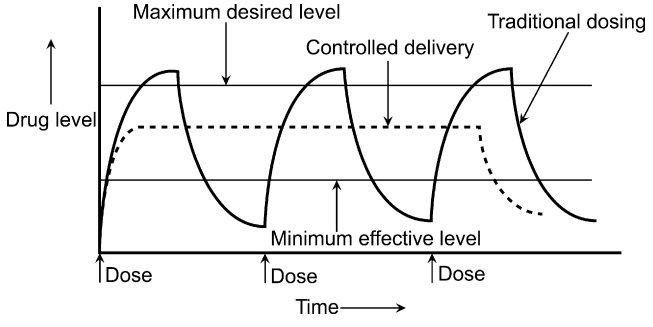

Fig. 1. Drug concentration in blood during drug delivery. The various cases; maximum, minimum, traditional dose and controlled delivery are indicated.

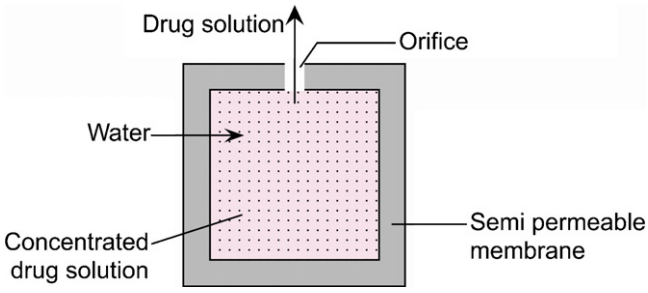

Fig. 2. Illustration of an osmotic drug delivery system.

the membrane when osmotic pressure is high [23]. Throughout the years, various osmotic system designs have been developed: the "Rose–Nelson" system in 1955, the "Higuchi–Leeper" and "Higuchi–Theeuwes" system in early 1970 or the "Theeuwes" elementary osmotic system in 1987. Recently, cellulose acetate asymmetric membrane capsules have been developed for osmotic delivery [24]. The system has no orifice and the influx of water and drug release is regulated by the membrane porosity. Commercial osmotic systems include OROS® (by Alza) for delivery of various drugs [1] or Procardia XL (by Pfizer) for the delivery of anti-anginals, anti-hypertensives.

2.3. Diffusion controlled membrane systems

In diffusion controlled membrane systems, the drug release is controlled by transport of the drug across a membrane. The transport is dependent on the drug diffusivity through the membrane and the thickness of the membrane, according to Fick's law. The membrane can be porous or non-porous and biodegradable or not. These systems find broad application in pills, implants and patches. (In this review, we will briefly discuss about pills and implants and draw specific attention to patches, which have been part of our research program.)

The design of a particular system often requires a tedious screening to select the specific polymer/drug pair which will satisfy the system criteria. Often predictive methods are used to estimate the drug permeability through the membrane from certain parameters characteristic of the drug and the polymer. For example, Michaels et al. [25] used the theories of Hildebrand's for solubility of solutes in solvents and of Flory-Huggins for solubility of solutes in polymers to derive a predictive correlation between the melting temperature of steroids (T_M) and their permeability through polymers. Fig. 3 presents their results (adapted from Ref. [25]). J_{max} corresponds to the maximum steroid flux through a membrane of thickness ℓ (given as $J_{max} = DC_A^o/\ell$, D is the diffusion coefficient of the steroid through the polymer and C_A^o is the concentration of steroid inside the polymer at equilibrium with saturated steroid solution in a solvent). χ is the interaction parameter between the steroid and the polymer (given as $\chi_{A-P} = V_A/RT(\delta_A - \delta_P)^2$, V_A is the molar volume of the steroid and δ_A, δ_P the solubility parameters of steroid and polymer, respectively). Michaels et al. showed that for various polymers (polydimethyl siloxane (Silastic®, $\delta_P = 7.6$), low-density polyethylene (LDPE, $\delta_P = 7.9$) and polyethylene vinyl acetate (EVA) containing 9, 18 or 40 wt%

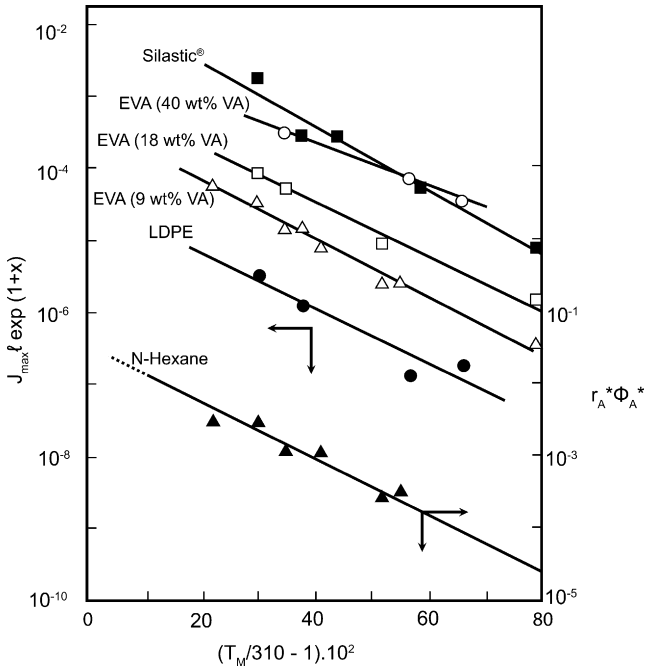

Fig. 3. Correlation of permeabilities of steroids in various polymers with steroid melting temperature (adapted from Ref. [25]).

VA, $\delta_P = 8.2$–8.5) a single linear plot is obtained with slope corresponding to $\Delta S_f/R$ (ΔS_f is the mean entropy of fusion of the steroid). In Fig. 3, the activities of various steroids in hexane at 310 K is also plotted (Γ_A^* is the activity coefficient of the steroid and ϕ_A^* the volume fraction of steroid in hexane).

2.3.1. Pills

The diffusion principle is applied to pills and tablets. The drug is pressed into tablet which is coated with a non-digestible hydrophilic membrane. Once this membrane gets hydrated, a viscous gel barrier is formed, through which the drug slowly diffuses. The release rate of the drug is determined by the type of membrane used [22,26].

2.3.2. Implants

Implants consist of a membrane reservoir containing a drug in liquid or powder form. The drug slowly diffuses through the semi-permeable membrane and the rate of diffusion depends on the characteristics of both the drug and membrane. The thickness of the membrane is constant to secure uniformity of drug delivery. If the membrane degrades, drug delivery should be accomplished prior to membrane degradation. If the membrane is made of non-degradable material, it should be surgically removed afterwards. A drawback of implants is the risk of membrane rupture resulting in drug-dumping: a sudden release of large amounts of drugs.

2.3.3. Patches

Patches are broadly used in drug delivery. The most characteristic examples are ocular (eye) and transdermal patches. Ocular patches are typical membrane-controlled reservoir systems. The drug, accompanied by carriers, is captured in a thin layer between two transparent, polymer membranes, which control the rate of the drug release (Fig. 4). An annular white-coloured border is surrounding the reservoir for handling of the device. The device is placed on the eye, where it floats on the tear film. Through diffusion, the drug is directly administered to the target area.

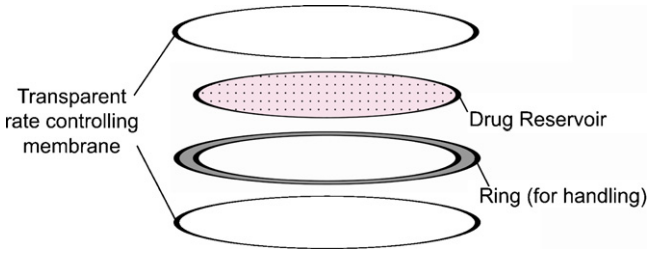

Fig. 4. Schematic illustration of ocular device.

In transdermal drug delivery (TDD), the drug is incorporated into a patch and delivered through the skin either due to the concentration difference or other driving forces (e.g. electrical current). The transdermal delivery will be described in more detail later.

2.3.4. Other systems

The deposition of "intelligent polymers" onto the surfaces of membrane pores can create permeation switches or gates. Such stimuli-responsive polymers react with relatively large property changes to small physical or chemical stimuli, such as temperature, pH or others [27–33]. For example, membrane pores can be blocked when swelling is stimulated, or open when surface polymers collapse. Drugs are released from inside the device or hydrogel as the surface polymers collapse. In other cases, the membranes have specific functionality to allow delivery of specific agent or drugs, for example glucose sensitive membranes to regulate insulin delivery [34,35].

Polymersomes are self assembled polymer shells composed of block copolymer amphiphiles [36] and can be used for encapsulation of biofunctional compounds and subsequent their release. Especially, biodegradable polymersomes can be potentially used for target delivery to specific sites of the body [37,38]. For example, Meng et al. [38] encapsulated the model compound carboxy fluorescein (CF) into polymersomes of amphiphilic copolymers based on polyethylene glycol (PEG) and biodegradable polyesters or polycarbonate. The release of CF at room temperature and 60 °C followed first order kinetics confirming a membrane-controlled reservoir system. In other cases, polymersomes have been used for encapsulation of haemoglobin [39] or anticancer cocktail drugs [40].

2.4. Transdermal drug delivery

Generally for drugs with short half-lives, TDD provides a continuous administration, rather similar to that provided by an intravenous infusion. However, in contrast to the latter, TDD is non-invasive and no hospitalization is required.

Skin is the largest organ of the human body (approximately 2 m^2 of surface area) and is a complicated multilayer organ. It

basically consists of two tissue layers: the dermis and the epidermis (Fig. 5, reprinted from Ref. [41] with permission from Elsevier). The dermis (thickness of 100–200 μm) forms the bulk of skin and consists of connective tissue elements [42]. The epidermis, the top layer of skin (thickness of 100–110 μm), is composed of epithelial cells held together by highly convoluted interlocking bridges which are responsible for the skin integrity. The epidermis comprises several physiologically active tissues and a physiologically inactive top layer: the stratum corneum (SC, 10 μm thick, Fig. 5 [41]). Drugs can potentially pass through the skin either via the intact SC and/or via hair follicles and sweat ducts (Fig. 5). However, both these appendages occupy only 0.1% of skin, therefore the SC is the main barrier to drug transport. The rate of penetration through the SC controls the drug delivery, since drug transport through the deeper layers as well as through the vessel walls is much faster. A detailed description of SC is presented well in Ref. [41].

In this review, we will focus on drug delivery via a patch, driven by drug concentration difference (passive diffusion) and by applying electric current. Both methods are commercially attractive.

2.4.1. Passive diffusion

The most popular TDD systems are based on passive drug delivery. In these systems, drug delivery through skin is due to the drug concentration difference between the patch and the skin. Technologies developed to provide controlled passive drug delivery can be classified into two main categories.

2.4.1.1. Membrane or reservoir systems. The drug is incorporated into a reservoir (liquid or gel) placed between a drug impermeable layer and a membrane (Fig. 6a). The device also includes an adhesive layer to achieve firm contact with the skin. Drug release can be controlled by varying the reservoir composition, drug permeability through the membrane (by tailoring the material, porosity or thickness) and/or through the adhesive layer. Several successful commercial TDD systems are based on this design (see Table 3, shown later).

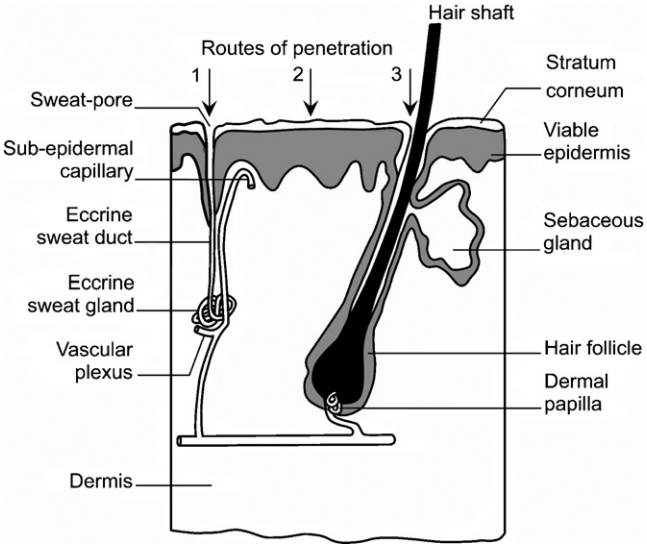

Fig. 5. Cross section of the human skin (reprinted from Ref. [41], with permission from Elsevier).

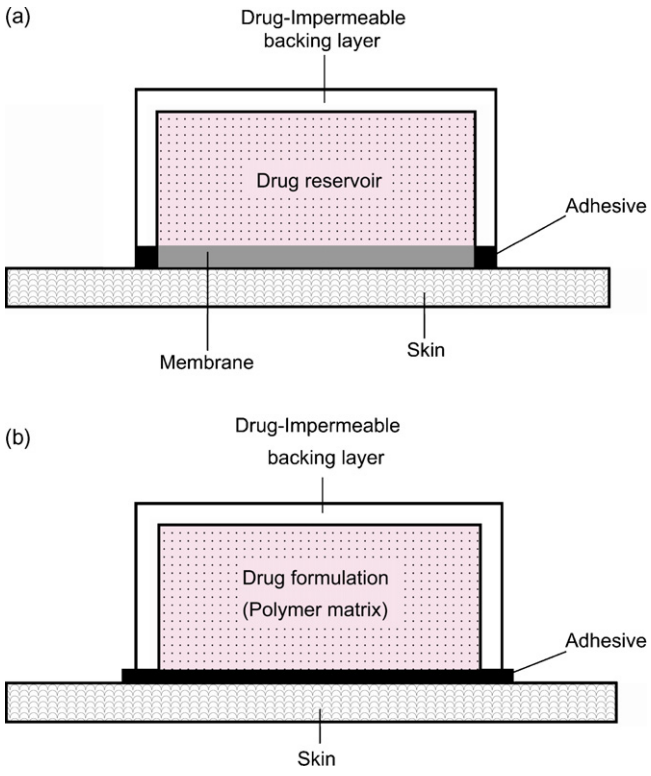

Fig. 6. Illustration of transdermal delivery systems: (a) membrane and (b) matrix system.

2.4.1.2. Matrix systems. The drug is incorporated (dissolved and/or distributed) into a polymer matrix (Fig. 6b). There is no membrane and the adhesive layer is added when the matrix itself is not adhesive.

The major parts of TDD systems such as the impermeable layer, the reservoir, the pressure adhesive layer, the membrane are all prepared from polymers. The range of the polymers used is broad; natural polymers (gelatin, starch, etc.), semi-synthetic (hydroxylpropyl cellulose, nitrocellulose, cellulosic, etc.), synthetic (polysiloxane, polybutadiene, polyisoprene, silicone rubber, polyesters, polyurethane, polyethylene vinyl acetate, polyacrylamide, polyvinyl alcohol, polysulfone, polymethyl methacrylate, etc.) [22,26,43,44].

The drug delivery through the skin due to the drug concentration difference between the patch reservoir ($C_{D,res}$) and the skin ($C_{D,skin}$) can be described by Fick's law:

$$J_D^{PD} = \frac{k_D D_D (C_{D,res} - C_{D,skin})}{\ell} \quad (1)$$

J_D^{PD} is the steady state drug flux through the skin, k_D is the drug partition coefficient in the skin, D_D is the diffusion coefficient of the drug through the skin and ℓ is the skin thickness. When $C_{D,res} \gg C_{D,skin}$, then Eq. (1) can be written as:

$$J_D^{PD} = \frac{k_D D_D C_{D,res}}{\ell} = K_D^{PD} C_{D,res} \quad (2)$$

K_D^{PD} is the passive drug permeability coefficient through the skin.

The drug passive diffusion increases by using the maximum drug amount that can be dissolved in the drug reservoir (the maximum solubility of the drug in the reservoir), $C_{D,S}$:

$$J_{D,max}^{PD} = K_D^{PD} C_{D,S} \quad (3)$$

Drugs with high partition into the skin and high diffusion coefficient are good candidates for a TDD system.

2.4.2. Iontophoresis

Iontophoresis applies small amounts of physiologically acceptable electric current to drive charged drug molecules into the body [42]. The device consists of two patches containing two electrodes – the anode and the cathode – and the power supply (Fig. 7). The drug formulation (drug dissolved in either liquid or gel reservoir) is placed in the patch–electrode which has the same charge as the drug (in Fig. 7, at the anode). The other patch contains only reference electrolyte or gel. The two patches are placed on the skin and connected to the power supply. The drug is driven into the skin by electrostatic repulsion. In addition, bulk fluid flow or volume flow occurs in the same direction as the flow of the counter ions. This phenomenon accompanying electro-migration is called electro-osmosis.

The steady state flux of a charged drug during iontophoresis comprises three parts: the flux due to passive diffusion (J_D^{PD}), the flux due to electro-migration (J_D^{EM}) and the flux due to electro-osmosis (J_D^{EO}):

$$J_D^{total} = J_D^{PD} + J_D^{EM} + J_D^{EO} \quad (4)$$

The electro-migration can be described [45] by the equation:

$$J_D^{EM} = \frac{i_D}{z_D A F} \quad (5)$$

where i_D denotes the drug ionic current flow, z_D the charge of the drug, A the surface area and F the Faraday constant. The drug current flow is related to the applied current, I, via the equation:

$$i_D = t_D I \quad (6)$$

where t_D is the transport number of the drug and represents the fraction of the total current transported by the drug. Since the total transport number of ions should equal 1, this shows the importance of the presence of competitive ions to the drug for

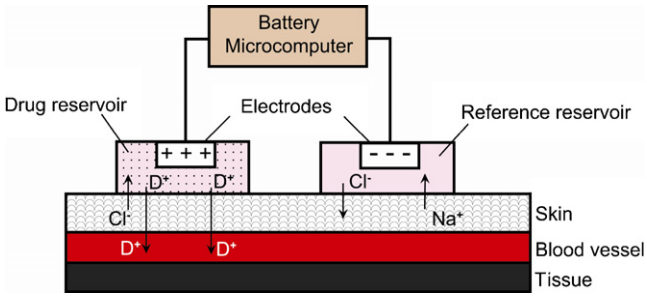

Fig. 7. Principle of iontophoresis (see more details in the text).

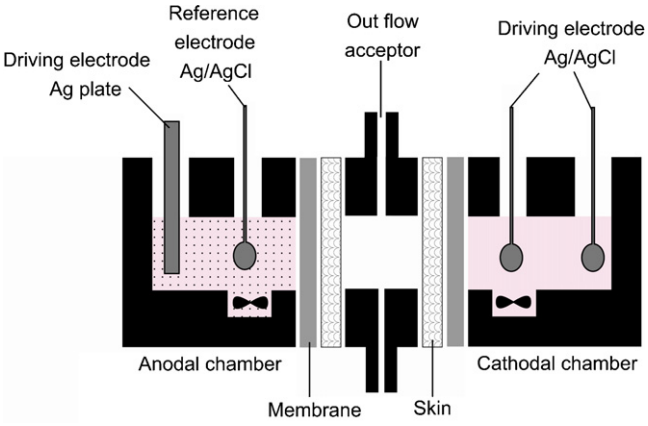

Fig. 8. Illustration of a continuous flow-through transport cell (adapted from Ref. [44]).

drug delivery—the higher the t_D, the higher the drug delivery efficiency. By combining the Eqs. (5) and (6), one gets:

$$J_D^{EM} = \frac{t_D}{z_D F} \frac{I}{A} \quad (7)$$

where the ratio I/A is the current density.

The electro-osmotic flux, J_D^{EO} (bulk drug flow occurring when a voltage difference is applied across the charged skin [46–50]) occurs always in the same direction as the flow of the counterion and may assist or hinder drug transport. For small ions, the drug flux increases mostly due to electro-migration and for bigger molecules (peptides and proteins) electro-osmosis might be the dominant transport mechanism [51].

Fig. 8 shows a continuous flow-through transport cell to measure the drug transport [52]. The drug is placed in the donor compartment (in Fig. 8, at the anodal chamber); the electric current is applied via the two electrodes connected to a power supply. The drug permeates through the skin and is collected by the flow-through solution which simulates the blood. The reference electrode compartment (in Fig. 8, the cathodal chamber) contains only the reference electrolyte. Under constant current density, the delivery increases when the drug concentration in the patch increases. However, the drug transport often reaches a plateau or even decreases at high concentrations due to the competition with other species of the background electrolyte for the current [45].

The iontophoretic drug flux is proportional to the applied current density (Eq. (7)). Fig. 9 shows some results of the delivery of timolol maleate (TM) through commercial artificial membranes [44] (timolol is a non-selective beta-adrenergic blocking agent that is used in the management of hypertension, angina pectoris, myocardial infraction and glaucoma). At the same drug concentration difference across the membrane, the TM transport increases at higher current densities. Current density of 0.5 mA/cm^2 is the maximum acceptable producing minimal skin irritation and/or damage [44,52,53]. Besides, the type of electrode has an important role as well. Conventional electrodes are classified as inert or reversible (Ag/AgCl, Fig. 8). Inert electrodes (stainless steel, platinum, carbon or aluminum) do not take part in the electrochemical reaction but they

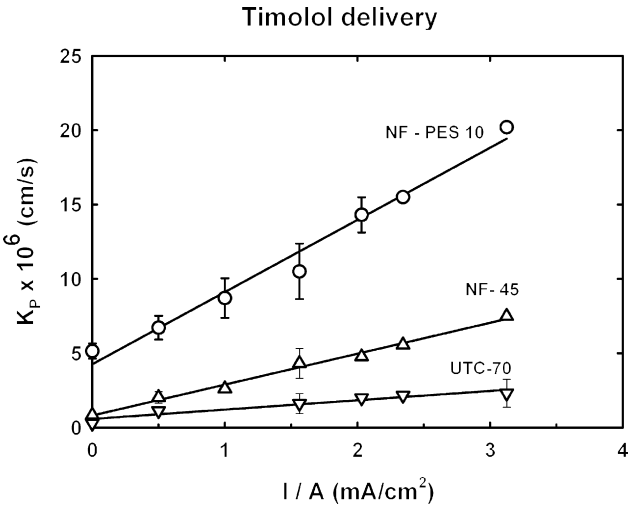

Fig. 9. Timolol (TM) delivery through artificial membranes versus the applied current density (adapted from Ref. [44]).

can cause water electrolysis, pH shifts and consequently skin irritation and perhaps variations in drug delivery and stability [42]. Reversible Ag/AgCl electrodes avoid these problems but require the presence of NaCl for the electrochemical reactions. These extra ions compete with the charged drug for electrical current.

Finally, the pH of the drug formulation is very important. One should select the pH such that the drug is highly charged to enhance the electro-migration. However, often a compromise should be achieved between the pH of the drug and the drug stability and solubility, and skin irritation. Besides, high amounts of H^+ and OH^- should be avoided to improve the drug current efficiency.

The basic components of the iontophoresis patches are similar to those of the passive patches. Polymers are also used for the impermeable layers and skin contacting membrane. The basic drug formulation is a highly conductive gel. In almost all patches, an artificial membrane is used in direct contact with the skin which should be made of biocompatible material to avoid skin irritation and have low drug adsorption. In recent studies in our group, several membranes have been evaluated in transdermal patches containing TM [44,54–56] and salmon calcitonin (sCT) [57]. Tables 1 and 2 present some results of drug adsorption to commercial membranes [44,57]. Some of the membranes prepared from hydrophobic materials had high drug adsorption and therefore were not considered for the respective patches.

Table 1
Adsorption of TM to membranes (TM concentration = 25 mg/mL, adapted from Ref. [44])

Membrane	Material	TM adsorption (mg/cm^2)
Mill F-0.025 μm	Mixed cellulose acetate nitrate	2.9 ± 0.7
PSf-100 kDa	Polysulfone	0.3 ± 0.2
CT-10 kDa	Cellulose triacetate	0.2 ± 0.1
CA-10 kDa	Cellulose acetate	0.2 ± 0.1
NF 45	Aromatic polyamide	0.1 ± 0.0

2.4.3. Skin or device controlled delivery

The issue of skin or device controlled delivery has been discussed in the scientific community for a long time. In transdermal drug delivery by a patch (Fig. 6), the total permeability ($K_{D,total}$) of the drug through the membrane and skin is given by:

$$\frac{1}{K_{D,total}} = \frac{1}{K_{D,mem}} + \frac{1}{K_{D,skin}} \quad (8)$$

where $K_{D,memb}$, $K_{D,skin}$ represent the permeability of the drug through the membrane and the skin, respectively. Depending on the ratio of $K_{D,memb}$ and $K_{D,skin}$ the delivery may be primarily skin-rate controlled or primarily membrane-rate controlled. When the ratio $K_{D,memb}/K_{D,skin}$ is less than 0.2, the delivery is considered to be membrane controlled. When the ratio $K_{D,memb}/K_{D,skin}$ is larger than 5, it is considered to be skin-rate controlled. If the ratio $K_{D,memb}/K_{D,skin}$ is in between 0.2 and 5 the systematic dosage received is controlled by both the skin and the membrane.

Passive drug transport can have great intra- and inter-patient variability due to strong variations in skin permeability. To ensure that the drug delivery is invariant of the patient or patch position, the delivery rate should be membrane controlled. However, for most drugs passive TDD is very low, therefore great variability between patients cannot cause safety problems. The device is then designed to deliver as much drug as possible, and not impose any restriction or control to drug delivery. In iontophoresis, the inter- and intra-patient variability in drug–skin permeability is much lower in comparison to passive systems. Delivery can be mostly regulated via the applied current density. In a recent study [57], we have evaluated the transdermal delivery of sCT. For this drug the iontophoretic skin transport is generally very low. In addition, its price is high and only low drug concentrations can be included in the patch. For this system, it was found that the non-controlling, low drug binding

Table 2
Permeability of sCT through membranes during passive diffusion and iontophoresis ($I/A = 0.5$ mA/cm^2) and equilibrium adsorption of sCT to the membranes

Membrane	Material	$(K_P)_{memb} \times 10^6$ (cm/s)		sCT adsorption (μg/cm^2)
		Passive diffusion	Iontophoresis	
PES-30	Polyethersulfone	7.3 ± 3.0	6.9 ± 1.9	50.5 ± 9.9
Mill F-0.025	Mixed cellulose acetate nitrate	10.8 ± 1.2	12.5 ± 2.4	86.6 ± 4.6
PSf-100	Polysulfone	15.3 ± 1.5	15.4 ± 5.3	69.4 ± 1.6
Polyflux®	Polyaryl ether sulfone/polyamide	18.2 ± 3.4	20.0 ± 3.5	4.9 ± 0.4

Table 3
Some examples of commercial passive TDD systems

Trade name	Company	Type	Drug	Action
Nitroderm	Alza/Ciba	Reservoir	Nitroglycerin	Anti-anginal
Nitrodur	Key/Schering	Matrix	Nitroglycerin	Anti-anginal
Frandol-Tape	Nitto Electric Ind.	Matrix	Isosorbide dinitrate	Anti-anginal
Catapres	Alza/Boehringer Ing.	Reservoir	Clonidine	Anti-hypertensive
Duragesic	Alza/Ivers/Jansen	Reservoir	Fentanyl	Narcotic analgesic
Transderm-Scop	Alza/Ciba	Reservoir	Scoparamine	Anti-motion sickness
Estraderm	Alza/Ciba	Reservoir	Estradiol	Hormonal
Minitran	3M	Reservoir	Glyceryl trinitrate	Anti-anginal
Nicoderm	Alza	–	Nicotine	Anti-nicotinic
Nicotrol	Cygnus	–	Nicotine	Anti-nicotinic

Polyflux® ultrafiltration membrane would be the best option for a patch (see Table 2). The delivery can be well regulated with the applied current density and the low binging material ensures no losses of sCT and membrane fouling.

2.4.4. Commercial systems

In passive transdermal delivery, several companies have been active in the last 15–20 years (Alza, Merck, Ciba/Novartis, 3M and others, Table 3, adapted from Refs. [43,58]). Their products use a membrane which either exclusively controls drug delivery or partially controls drug transport together with other components (such as the adhesive layer).

In iontophoresis, the electrodes (Fig. 10) are connected to a relatively small ("walkman" or "discman" size) power supply. Iontophoresis is already approved in the USA, for delivery of lidocaine and epinephrine in local analgesia (Iomed, USA). Devices available on the market for delivery of local anesthetics and corticosteroids include Phoresor® II (Iomed), Empi® Dupel (Empi, USA), Life-Tech Iontophor (Life-Tech®, USA) and Henley Intl Dynaphor® (Henley Intl, USA). In addition, devices for iontophoresis of pilocaprine are on the market, including among others the CF Indicator® (Scandipharm, USA).

The passive TDD technology has "won the harts and minds" of the patients. The application and the market of the passive patches is expected to grow further the next years. New products easier to use having better quality materials will be developed. In our opinion, the main breakthrough in TDD would come from the active systems. Using active systems such as those based in iontophoresis, the transdermal delivery of more drugs with better patient compliance (reduced side effects, etc.) will become possible. Nowadays, one issue hindering the expansion of those systems is the need of rather bulky, heavy and complicated power supplies and other components. The miniaturization of the components and the development of suitable micro-computer for regulation and control of delivery will make these technologies safer and therefore available outside the hospital, too. Currently, the majority of active systems are more expensive than conventional drug delivery systems (although as the technology solves the technical problems, they become cheaper). Nevertheless, even if the costs are relatively high the patient benefits from those technologies may be able to justify the extra costs.

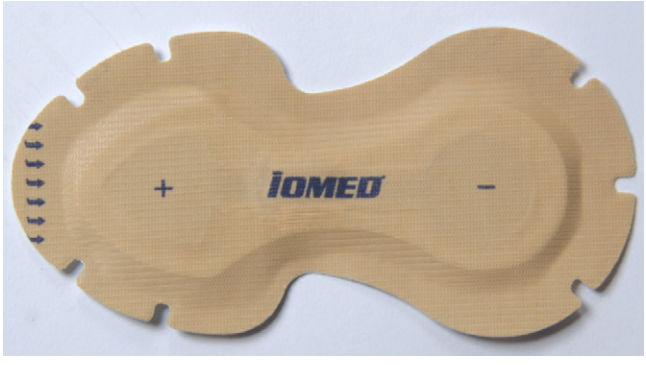

Fig. 10. Device containing electrodes on one patch, from Iomed (Salt lake City, UT, USA, ©2005, printed by permission).

3. Dialysis—artificial kidney

3.1. Natural kidney

In general, people have two kidneys of about 11 cm long and of about 160 g weight each. Healthy kidneys are essential part of metabolic processes of the body which involve:

- Accumulation of urine and disposal of it through the urinary tract.
- Regulation of the acid–base balance of the blood.
- Regulation of blood pressure by producing hormones, for example erythropoietin which controls the production of blood cells in bone marrow.
- Influence the amount of calcium in the blood and production of vitamin D which helps to provide bone stability.

Failure of the kidney results in building up of harmful wastes and excess fluids in the body. Kidney diseases can be due to infections, high blood pressure (hypertension), diabetes and/or extensive use of medication. The best form of treatment is the implantation of a healthy kidney from a donor. However, this is often not possible due to the limited availability of human organs. Chronic kidney failure requires the treatment using an artificial kidney called dialysis. Blood is taken out of the body and passes through a special membrane that removes waste and extra fluids. The clean blood is then returned to the body. The process is controlled by a dialysis machine which is equipped with a blood pump and monitoring systems to ensure safety.

Table 4
Daily waste production by a healthy person

Component	Concentration (g/day)
Water	1500
Urea	30
Creatinine	0.6
Uric acid	0.9
Sodium, Na^+	5
Chlorine, Cl^-	10
Potassium, K^+	2.2
Calcium, Ca^{2+}	0.2
Phosphates, PO_4^{3-}	3.7
HSO_4^-	8.2
Phenols	Traces

The machine can also administer drugs, for example heparin to avoid blood clotting during treatment. Table 4 presents the daily production of waste by the body which should be removed to maintain life. Waste removal is not necessary to happen on a daily basis, it can also occur every third day. Today, more than 1.8 million people worldwide require regular kidney therapy, and among them 1.5 million undergo dialysis. Most patients undergo this treatment three times a week, for 3–5 or more hours each visit. The yearly growth of dialysis patients is 7–8% [59].

Table 5 presents briefly the historic development in dialysis. The first attempt to purify blood with dialysis was reported in the beginning of the 20th century by Abel et al. [60] who used hand made collodium tubes (material based on cellulose). The first dialysis treatment on a patient was reported in 1925 by Haas [61], but it was in 1943 when Kolff and Berk developed their artificial kidney [62,63]. It consisted of a rotating drum dialyser equipped with a cellophane tubing membrane (Fig. 11). The cellophane tubes were filled with blood and wrapped around a wooden drum that rotated around a dialysate solution. This procedure required a large volume of blood circulation outside the body and priming with blood transfusions. Rotating water pumps permitted the drum to rotate, enabling the blood to flow through. Blood was "pumped" into the cellulose casing by using the patient's heart and blood pressure and was propelled from one end of the drum to the other by turning the drum. Blood was then collected in a glass cylinder which was connected by rubber tubing to the patient's venous access. By alternative lowering and raising the cylinder, blood was collected and drained back into the patient's vein.

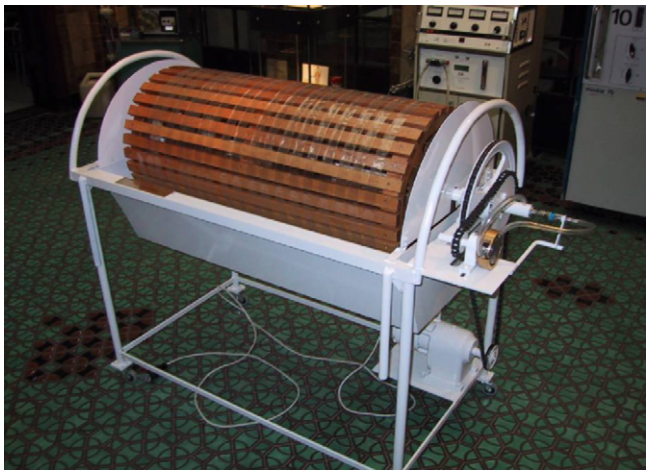

Fig. 11. The rotating drum developed in 1943 by Kolff and Berk.

Since then, dialysis has gone a long way to become a safe blood purification treatment (see Table 5). In 2006, more than 46,000 dialysis machines and about 150 million dialysers were sold.

3.2. Dialysis principle

The dialysis membrane contains pores that allow small molecules such as water, urea, creatinine, and glucose to pass through the membrane readily, but the red cells, white cells, platelets and the most plasma proteins are retained. Concerning the treatment, three modes are commonly used:

- Hemodialysis: solute removal is basically performed by diffusion alone.
- Hemofiltration: solute removal is performed by convection alone.
- Hemodiafiltration: solute removal is done by diffusion and convection.

In hemodialysis, the concentration difference across the membrane between blood and dialysis solution causes the small compounds to diffuse through the membrane while larger molecules like proteins and blood cells cannot pass. The dialysate is an electrolyte solution similar to the normal body fluid (purified water, sodium, potassium, calcium, magnesium, chloride and

Table 5
Historic development of the artificial kidney

Year	Event
1913	Abel et al. dialyse the blood of anesthetized animals by collodium membranes
1924	Haas performs dialysis to first patients using collodium membranes
1943	Kolff et al. use cellophane tubes in a rotating drum kidney to treat a 67-year-old patient
1947	Alwall develops a dialyser that combines dialysis and ultrafiltration
1948	Development of Skegg–Leonards parallel plate dialyser
1954–1962	The modified Kolff–Brigham "kidney" machines are placed in 22 hospitals worldwide
1960	Development of Kills' plate dialyser
1964	Stewart develops the hollow fiber dialyser
1964–1967	Dow chemical develops the technology to make hollow fiber dialyser at reasonable prices
2002	Scribner and Kolff awarded with the "A. Lasker award for Clinical medical research"

dextrose) and should be sterile and endotoxin-free. The concentration of these solutes regulates the net flow of substances from one side of the membrane to the other, by creating a concentration gradient, or osmolar gradient. In hemofiltration, the driving force for mass transport is a hydrostatic pressure difference rather than the concentration difference used for hemodialysis. The hemodiafiltration process makes use of a combination of pressure and concentration difference.

During hemodialysis, the fluid removal is equivalent to the fluid gained by the patient between treatments. However, in both hemofiltration and hemodiafiltration where the removal of bigger metabolites is achieved, the fluid removal exceeds that gained by the patient and is recovered by infusion of suitable substitution liquid.

3.3. Dialysis membranes

3.3.1. Materials

Membrane materials used in dialysis can be classified into two main categories:

- Cellulosic materials;
- Synthetic materials.

Most of the dialysers up to late 1960s were manufactured using regenerated cellulose. Later it was realized that free hydroxyl groups (–OH) have poor blood compatibility [64–68]. Therefore, the hydroxyl groups have been substituted by benzyl groups or acetylated [69], or the regenerated cellulose has been coated with polyethylene glycol (PEG) or vitamin E [70–72]. Initially, the cellulosic membranes were generally produced by extrusion to either tubes or sheets. The first hollow fiber dialyser was used in mid-1960s and contained cellulose acetate membranes [73].

The synthetic membranes are usually prepared from Refs. [64,74,75]

- Hydrophilic or hydrophilized copolymers (polyethylene vinyl alcohol, polymethyl methacrylate or modified polyacrylonitrile).
- Hydrophilic blends. These blends are mostly prepared by mixing high T_g hydrophobic polymers (polysulfone (PSf) or polyarylether sulfone (PES, PAES)) with hydrophilic polymers (polyvinyl pyrrolidone (PVP) [12] or aliphatic/aromatic polyamides) [76].

The major part of the synthetic membranes is produced from blends in a fiber spinning continuous process which involves phase separation or precipitation [2].

The blood compatibility of the materials is of outmost importance. It has been estimated that for a patient undergoing dialysis for 15 years, the blood will have contact with approximately 4000 m^2 of foreign surface [77]. This should not have clinical consequences for the patient and is generally assessed via five sets of biocompatibility parameters [78]. The material should have:

I. Low thrombogenicity and coagulation potential.
II. Low stimulation of the immune system (complement or cell activation).
III. No allergic or hypersensitivity reaction.
IV. No interaction with administrated drugs.
V. No hemodynamic affects (negatively charged surface can stimulate “contact phase” coagulation).

3.3.2. Membrane characteristics

The optimum characteristics of a dialysis membrane are [8,74,79]:

- Optimal biocompatibility—combination of hydrophilic/hydrophobic domains.
- A thin active separation layer to achieve high solute fluxes.
- High porosity to provide high hydraulic permeability.
- Narrow pore size distribution to achieve sharp molecular weight cut-off (MWCO).
- No back diffusion of components from the dialysate to the blood.
- Minimal surface roughness to reduce interaction with blood components.
- Sufficient mechanical stability to withstand the required pressure limits.
- Sufficient chemical and thermal stability to withstand the sterilization process.

It is finally important to note that sometimes the dialysate solution might contain bacteria and endotoxins such as lipopolysaccharides (LPS) [73]. The synthetic membranes contain hydrophobic domains and are charged. Both characteristics can enhance adsorption of the bacteria/endotoxins to the polymer and avoid their back diffusion into the blood stream. Recently, ceramic membranes have also been proposed for the purification of dialysis water and dialysate [80,81]. Ceramic membranes might be a good alternative to polymeric membranes. They can generally withstand better the rather harsh conditions at which membranes are heat sterilized and disinfected and perhaps be used for longer time after repeated disinfection cycles.

3.3.3. Membrane transport

Solute transport though the dialysis membrane is made up of two components: diffusion and convection. The solute flux (J_s) can be expressed as [73]:

$$J_s = -D_{S,M}\frac{dc}{dx} + C_{S,M}(1-\sigma)J_V \quad (9)$$

where $D_{S,M}$ is the diffusion coefficient of the solute in the membrane; dc/dx is the concentration gradient of the solute across the membrane; $C_{S,M}$ is the local solute concentration; J_v is the convective fluid flux through the membrane and σ is the Staverman reflection coefficient. The overall effectiveness of hemodialysis is determined by both the convective and diffusive transport of wide range of different molecular weight solutes. To effectively design and operate the dialyser, it is important to have accurate quantitative description of both solute diffusion and convection though the membrane. In the past, Langsdorf and

Zydney [82] evaluated both contributions using classical membrane transport theory to various dialysis membranes. Dialysis membranes are often characterized as:

- Low flux, having small pores (water permeability: 0.03–0.09 mL/(h m^2 Pa)) and mostly used in hemodialysis for removal of small solutes.
- High flux, having bigger pores (water permeability higher than 0.15 mL/(h m^2 Pa)) and mostly used in hemofiltration for removal of bigger solutes.

It is widely accepted that besides the small compounds (Table 4), larger molecules and small proteins such as β_2-microglobulin, parathyroid hormone (PTH) should also be removed [83,84]. For example, β_2-microglobulin (MW = 12 kDa) is produced during the body's cellular turnover and is primarily removed via the kidney. Its removal can be achieved by combination of convection and adsorption [85] (more on this issue is discussed later).

The membrane performance is generally determined by the sieving coefficient which represents the ability of the membrane to permit transport of a solute of given size [64]. The sieving coefficient varies from 1 (the solute molecule is small compared to the membrane pore size and therefore passes freely through the membrane) to 0 (the solute is big and thus fully retained by the membrane). Fig. 12 shows examples of the sieving coefficient of two dialysis membranes and the kidney itself.

The parameter of clinical interest is the solute clearance which represents the rate of solute removal from the blood divided by the incoming blood concentration ($C_{s,blood}$):

$$\text{Clearance} = \frac{\text{rate of solute removal}}{C_{s,blood}} \quad (10)$$

The clearance not only depends on the membrane (module) but also on the process design (for example, on hydrostatic pressure difference in hemofiltration and on volume flow rate in hemodialysis). Hydrodynamic boundary layer effects especially in the filtration mode may often dominate the entire process [8].

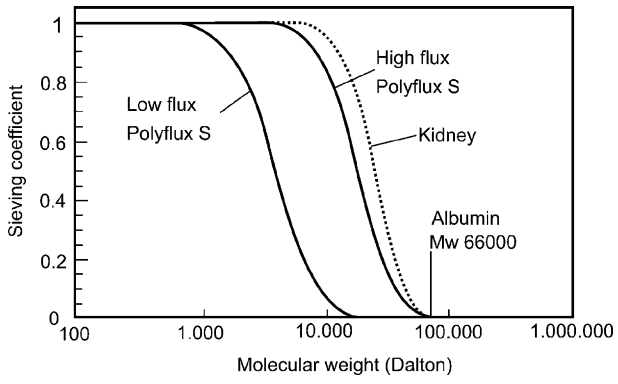

Fig. 12. Examples of sieving coefficients of two dialysis membranes in comparison to the natural kidney.

Fig. 13. Hollow fiber membrane dialyser.

3.3.4. Membrane module and process

The first dialysis modules were flat plate- and frame-modules containing sheets of cellophane or cuprophane membranes [64,73]. Later, coil type modules were introduced [73]. The membrane consisted of cellophane tubes which were flattened, placed on a nylon open mesh "spacer" material and rolled into a coil. The coil was then held in a cartridge which was open at each end. Both types of modules have been used for years.

Today, most dialysis modules are in hollow fiber configuration (Fig. 13) [64,74,86]. The modules are approximately 30 cm long and contain thousands of fibers (up to 15,000, membrane surface area up to 2.2 m^2). Typically the fibers have an inner diameter between 180 and 220 μm and wall thickness between 20 and 50 μm. To ensure even distribution of the dialysate, spacer yarns [87], fiber crossing [88] or undulated fibers are used [74]. The wavy shape of the undulated fiber prevents dense packing and ensures optimum dialysate circulation. The blood and dialysate always circulate in a counter-current configuration to ensure maximum driving force for solute removal.

Important elements of the module are also the potting and housing material. The housing should be transparent, mechanically stable and stable under different types of sterilization processes (steam, γ-radiation, etc.). Additionally, the material should be inert and should not interact with the blood or dialysate. Today, most housings are prepared from polycarbonate or polypropylene by injection molding. Potting material is used to glue together the membrane bundle ends and the housing. Polyurethane (PU) is probably the safest material for this application.

Nowadays, the technology for preparation of the dialysis modules has advanced very much and is fully automated [74]. Leading manufacturers are Fresenius AG, Gambro, Asahi medical, Nipro, Toray and others. (The reader can find in Ref. [64] an extensive overview of commercial dialysers and some details about their specifications.) The last years, hemodialytic treatment has improved the survival rates of patients with

acute or chronic renal failure. However, the membrane-based therapy is still not complete. Much progress is required to improve membranes and devices. The manufacturers often in collaboration with academia respond to this challenge and work towards improvement of their products. Membrane scientists work towards development of membranes with improved biocompatibility and/or sieving properties [89–93], as well as improved membrane modules and devices [94–97]. Besides, serious attempts have been focused to model hemodialysis and understand how the modification of the membrane can influence the performance and cost of dialysers [98]. The future challenge for membrane technologists will be the development of biohybrid devices using progenitor/stem cells and/or devices having active re-absorptive transport and metabolic activity [99]. For this, greater interaction with biologists, biomedical engineers and medical doctors is required. We believe that multi disciplinary teams have better chance of success in dealing with the issues.

Currently, hemoperfusion seems beneficial to the patients. In hemoperfusion (or plasmaperfusion), blood (or plasma) is purified by extracorporeal passage through a column containing the adsorbent which can remove or neutralize the substance of interest. The pioneering work of Yatzidis [100] reported an effective removal of creatinine, uric acid, phenols, organic acids and barbiraturates by direct hemoperfusion through uncoated activated charcoal. Hemoperfusion cannot fully substitute hemodialysis because it does not remove urea, excess of water or control fluid balances. Davankov et al. [101] suggested combining the strengths of dialysis membranes with the adsorption power of high surface area sorbent. Filtration through semi-permeable membranes should remove excess water together with urea and small toxins, whereas hemoperfusion should remove larger molecules such as β_2-microglobulin and pro-inflammatory cytokines. Hemoperfusion has recently been applied in the treatment of chronic uremia in adjunction to hemodialysis or hemofiltration [102]. Regular use of charcoal hemoperfusion as adjunct to hemodialysis in chronic uremia is capable to improve patient's clinical and laboratory condition as well as to reduce the weekly time of treatment [103].

In the last three decades, sorbent technology has been applied in treatment of severe intoxication and to increase the efficiency of hemodialysis, or replace it, in renal replacement therapy and fulminant hepatic failure [104]. Sorbent hemoperfusion is gaining ground as a valuable adjunct to dialysis, especially in regeneration of dialysate but also in the treatment of other disease states, such as sepsis, hepatic failure, cardiopulmonary bypass, intoxication of drug over doses and poisonous and multi organs failure [105].

Two kinds of sorbents are mostly used in medical treatments: (i) natural sorbents such as the activated carbon (charcoal) and (ii) synthetic sorbents. Activated carbon is an excellent sorbent for removing organic metabolic wastes, drugs and other undesirable components from the blood. Activated carbons and resins are the most widely used sorbent and these sorbent cartridges are commercially available (Table 6) [104,106–132]. Other sorbents, for example various immunosorbents and more complex sorbent systems; incorporated with biofunctional agents (e.g. antigens, antibodies, enzymes) are clinically applied [133]. Moreover, hemoperfusion has successfully been used to remove hypnotics and sedatives, analgetics, agricultural chemicals and cardiovascular agents. Many of these toxins are lipid-soluble or protein-bound in the blood stream and are not or poorly dialyzable [134].

Nevertheless, the poor biocompatibility of activated carbon is a challenge. High affinity of activated carbon to blood components such as platelets, partiality of activated carbon to fragment and create emboli formation requires avoiding direct contact with blood in a hemoperfusion circuit. Several attempts have been made to overcome these problems by coating the sorbent granular with a polymer solution and/or by encapsulating the activated carbon particles in polymeric hull [100,135]. However, the additional layer reduces the efficiency of hemoperfusion and the coated sorbents may still be involved in micro-emboli formation due to uniformity, not complete coverage of the coating, mechanical abrasion of the naked carbon surfaces prior casting and the fragility of the capsule.

4. Other blood purifications methods

4.1. Blood purification systems using affinity membranes

Affinity membranes are generally microfiltration membranes having selective affinity ligands attached on the membrane surface. Therefore, they combine the strengths of membrane filtration with the specificity of adsorption. Inside the membrane, the components of interest are complexed with the affinity ligands and separated from other components.

In blood purification, affinity membranes can be used for removal of various blood components. The configuration of the membranes is either hollow fiber or flat sheet spiral wound around a cylindrical core. Ideally, affinity membranes should have, besides biocompatibility, the following characteristics [136]:

- Macro-porosity, to allow access of biomolecules to the affinity site.
- Hydrophilicity, to avoid non-specific adsorption and denaturation of biomolecules.
- Suitable functional groups, to couple the affinity ligand.
- Chemical and physical stability, to withstand the derivatization, operation and regeneration conditions.
- Large surface area relative to membrane volume, to allow construction of small, integrated devices with high operational capacities.

Cellulose and cellulose acetate were among the first materials used for affinity separation. These materials are hydrophilic and biocompatible, and due to the presence of hydroxyl groups ligand coupling can be easily achieved. Polysulfones are also suitable materials due to their sufficient physical, chemical and biological stability. Other materials used for affinity membranes include polymethyl methacrylate (PMMA), poly(hydroxyl ethyl dimiethacrylate), polycaprolactam, poly(vinylidene difluoride), poly(ether-urethane urea), polyamide (nylon), polyvinyl alco-

Table 6
Applications of sorbent hemoperfusion

Name/system	Manufacturer	Functional group or sorbent type	Application	Reference
Adsorba 300C	Gambro	Charcoal (cellulose coating)	Non-specific	[106]
Amberlite®, Amberchrome®	Belco SpA	Amberlite XAD, Amberchrome	Non-specific	[107]
BetaSorb	Renal Tech.	Polystyrene resin (PVP coating)	Non-specific	[104]
Biocompatible System	Clark R&D	Charcoal (heparin coating)	Non-specific	[108]
Biologic DT, DTPF	Hemocleanse	Charcoal and cation exchange (no coating)	Non-specific	[109]
CytoSorb	Renal Tech.	Polystyrene	β_2-Microglobulin, leptin, retinol, angiogenin, IL-1β, TNF-α	[110]
DALI System	Fresenius	Anti-Apo antibodies	Lipoprotein	[111]
Hemosorba	Asahi Med.	Charcoal (poly-HEMA coating)	Non-specific	[112]
HELP system	B. Braun	Heparin	LDL cholesterol, lipoprotein, fibrinogen	[113]
Hemapur 260	Organon-Teknika	Norit extruded charcoal (cellulose acetate coating)	Non-specific	[114]
Immunosorba	Fresenius	Staphylococcal protein A (SPA)	nt-BNP, nt-ANP and Factor VIII antibodies	[115]
Liposorba	Kaneka	Dextran sulfate	Apolipoprotein B, LDL cholesterol, lipoprotein	[116]
Lixelle	Kaneka	Hexadecyl alkyl	β_2-Microglobulin	[117]
MARS	Teraklin	Active carbon and anion exchange resin (no coating)	Non-specific	[118]
MATISSE	Fresenius	Albumin	Endotoxins, cytokines, chemokines	[119]
Medisorba MG 50	Kuraray Med.	Anti-acetylocholine	Myasthenia gravis	[120]
Medisorba BL-300	Kararay Med.	Anion resin coated PHEMA	Bilirubin	[121]
Prosorba	Kaneka	Staphylococcal protein A (SPA)	IgG, low-density lipoproteins–cholesterol	[122]
PH-350	Asahi Med.	Phenylalanine	Anti-DNA antibody and immune components	[123]
Plasorba BR-350	Asahi Med.	Anion exchange resin (no coating)	Endotoxin	[124]
PMX-20R	Toray	Polymixin B	Endotoxins, cytokines, chemokines	[125]
REDY system	Renal solution	Charcoal and ion exchange (no coating)	Non-specific	[126]
Rheosorb	PlasmaSelect	Fibrinogen-binding pentapeptide	Fibrinogen, fibrin, fibrinogen	[127]
Selesorb	Kaneka	Dextran sulfate	Antibodies, immune complexes	[128]
Therasorb	Baxter	Anti-IgG antibodies	Inhibitors to Factor VIII	[129]
TR-350	Asahi Med.	Trypthophan	Myastenia, autoimmune polineuropathy, rheumatoid arthritis	[130]
Detoxyl 3	Belco SpA	Charcoal (no coating)	Non-specific	[131]
MDS	Univ. Krems	Neutral resin, charcoal and anion exchange (no coating)	Non-specific	[132]

Non-specific indicates: most hydrophobic and hydrophilic harmful substances are removed.

Table 7
Examples of affinity membranes used for the removal of IgG

Ligand	Membrane
Protein A	Hydroxyethyl cellulose treated blend of PES and PEO
Protein A/G	Methyl metacrylate base copolymer
Recombinant protein G	Regenerated cellulose
Protein A	Nylon based
Protein A	Poly(ether-urethane urea)
Protein A	Composite membrane
Recombinant protein A	PES, PSf
Recombinant protein A	Composite cellulosic membrane
Recombinant protein A/G	Polycaprolactam
Protein G	Nylon based
Protein A	Poly(vinylidene difluoride), PVA
Protein A	Poly(GMA-EDMA)
Recombinant protein G	Immobilon AV
Protein A formaldehyde-activated	Dextran coated
Protein A	Ultrabind-PrA
Protein A	Sartobind aldehyde-PrA, Sartobind epoxy-PrA

hol (PVA), polyethylene vinyl alcohol (EVAL) and silica glass. To fulfill all requirements, often composites of two or more materials are used [136].

Significant research efforts have been performed on adsorption of immunoglobulin (IgG). Proteins A and G can specifically bind IgG and therefore are used extensively as ligands in affinity membranes. Table 7 gives a selection of different combinations of membranes and ligands for the removal of IgG [137,138]. The Ultrabind-PrA, Sartobind Epoxy-PrA and Sartobind Aldehyde-PrA membranes are commercially available sorbents for human IgG purification [137].

In our laboratory, extensive research has been performed on the preparation and application of mixed matrix affinity membranes. In this concept, porous particles with ion exchange functionality are incorporated into EVAL microfiltration membranes and used for the separation and recovery of bovine serum albumin (BSA) [139–142] or lysozyme (LZ) [143]. Alternatively BSA can be immobilized into the EVAL porous membrane and used for bilirubin removal [144,145]. Finally, it is important to note that affinity membranes find extensive application in protein purification, other bioseparations and production of biopharmaceuticals. Extensive review of these topics is beyond the scope of this paper. The reader, however, can find more in research [138,146–150] and patent literature [151–153].

4.2. Plasma treatment using membranes

Plasma is the liquid component of blood which serves as a source for many components such as albumin, IgG, plasma proteins and clotting factors. Plasma treatment usually involves as first step plasma separation from the blood cells using a centrifugal pump or a membrane filtration. Then, the cells can be returned to the patient while the plasma is replaced with donor plasma or albumin (treatment called "plasma exchange"). Alternatively, the patient's plasma flows along an adsorption column to selectively remove components and is then re-infused back to the patient (treatment called "plasmapheresis") [154,155].

During membrane plasma filtration, concentration polarization phenomena and pore plugging dominate the transport mechanism due to deposition of the red blood cells on the membrane surface. The membranes are operated in the mass transfer limited regime where the permeate flux is independent of transmembrane pressure and the maximum achieved filtration fluxes are about 1% of the clean water membrane flux [155]. As a result, the intrinsic membrane permeability may vary and does not present a significant mass transfer resistance. Membranes used in plasma treatment are made of biocompatible material and have pore diameters in the 0.2–0.65 μm range. The removal of cells occurs through augmented Brownian motion in the laminar flow at high shear rates [156].

Plasma treatment by membranes was first described by Solomon et al. in 1978 [157]. They fabricated a prototype filtration module and studied the effects of various operating conditions (blood velocity, transmembrane pressure or hematocrit) on the device performance. In 1989, Jaffrin [158] proposed alternative ways to improve process performance including superposition of large amplitude oscillations over the blood flow, generation of micro-vortices by circulating a pulsatile flow over a dimpled membrane and a combination of centrifugation and filtration. Burnouf et al. [159] used nanofiltration membranes (Planova® of 35 and 75 nm pore size) for filtration of normal human plasma as well as hepatitis C virus (HCV) positive plasma. Although some protein dilution or loss occurred, the filtered plasma met *in vitro* specifications for use in transfusion or fractionation. There were no signs of activation of the coagulation system and most importantly the HCV positive plasma became negative.

In severe sepsis and septic shock, the circulation of pro-inflammatory and anti-inflammatory mediators appears to participate in complex events which lead to cell and organ dysfunction and in many cases even to death. In the treatment of septic shock, a technique called "coupled plasma filtration adsorption" (CPFA), combining plasma filtration and plasma adsorption, has shown promising results [160]. First, the plasma is separated from the blood by filtration, then passed through a synthetic resin cartridge and returned back to the blood. If necessary, a second blood filtration follows to remove excess fluid and small toxins. The CPFA seems to attenuate the hypotension of septic shock and alter the immuno-paralytic toxicity of septic plasma [154,160]. More clinical research however, needs to be done to test whether the CPFA system can increase survival of patients suffering from blood sepsis.

The past years, efforts have been focused on improvement of life in patients with kidney disease as well as on reducing costs of treatment. Atkinson has recently summarized the results of three studies on blood filtration which were conducted in Europe and USA [161]. From these studies, it appears that dialysis and automated peritoneal dialysis (APD) performed at home can be an effective option for even high risk end stage renal disease patients. Moreover, wearable dialysis devices can improve the quality of patient's life as well as reduce hospital length stay and care unit utilization. In fact, Gura et al. carried out animal studies on the wearable ultrafiltration device from the US-brand

"National Quality Care Inc." [162]. This device has been shown to potentially remove excess salts and fluids in patients with congestive heat failure disease 24 h a day, 7 days a week.

4.3. Cell separation/fractionation using membranes

Separation of cells from tissue and/or cell fractionation are medical applications where membranes play important role. For example, Castino and Wickramasinghe [163] employed diafiltration process using hollow fiber microfiltration membranes to remove glycerol which is used as cryo-protectant for the cells, from frozen blood cell concentrates. Aoki et al. [164] used a cell filtration device (Stem Quick^{TM} E, Asahi, Japan) to isolate mononuclear cells from cord blood. Microfiltration membranes have been used for separation of mesenchymal progenitor cells [165], cells from peripheral blood [166] and human umbilical vein endothelial cells (HUVEC) from blood cells [167]. Membrane filtration has also been used in bone marrow processing to remove small clots, bone fragments, fat cells and fibrin followed by centrifugation to separate mononuclear cells [168].

5. Blood oxygenation

5.1. Natural lung

The lung is the organ responsible for oxygen (O_2) and carbon dioxide (CO_2) exchange between the blood and its environment. Each lung contains small air sacs suspended in a branching network of capillaries that allow one red blood cell to pass at a time. Each cell absorbs O_2 and excretes CO_2 through the sac membrane. The lung is a very efficient gas exchanger due to the large surface area generated by the capillary network. The total exchange membrane area is about 80 m^2 and the membrane thickness is about 1 μm. The total capacity of the lung is much larger than required; therefore, people with impaired lung capacity can generally live a normal life [1].

Blood oxygenators are used during surgery when the lung of the patient cannot function normally. The ideal oxygenator should perform efficient gas exchange and should be gentle to the blood. In specific, it should be able to:

- Oxygenate up to 5 L/min of venous blood to 95–100% haemoglobin saturation for periods between some minutes (20 min) till perhaps several hours.
- Simultaneously, remove a certain level of CO_2 to avoid respiratory acidosis (acidic blood) but also not too much to avoid alkalosis (alkaline blood). Generally, an outlet of 40 mmHg CO_2 is preferred.
- Have reasonable blood priming volume (1–4 L).
- Be gentle to blood and avoid hemolysis and protein denaturation.
- Be simple and safe to use, clean and sterilizable.

The first successful cardiopulmonary bypass operation was performed in 1953 [169]. There, the extracorporeal blood circuit device designed by Gibbon used a small tower filled with stainless steel screens to contact blood with counter flowing oxygen [1]. Over the years three types of oxygenators have been introduced [169]:

- *Film type oxygenators*: Gas exchange occurs on the surface of a thin blood film. For the treatment, a large surface area is necessary and therefore high priming volume is required.
- *Bubble oxygenators*: Gas bubbles are introduced directly into the blood. The oxygenation is effective due to the high surface area of the bubbles. However, the trauma is also high due to the mechanical stress on the blood by the bubbles. Additionally, extra care is required to ensure that all bubbles are removed.
- *Membrane oxygenators*: The blood is exposed to oxygen through a gas-permeable membrane. Today, membrane oxygenators are the only ones used and will be described in more detail below.

5.2. Membrane oxygenators

The membrane oxygenator represents a significant breakthrough in the development of blood oxygenation. There is no direct contact between the blood and the oxygen minimizing the risk of air embolism. There is good contact with the blood and there is no need to have a gas removal system [169].

Table 8 presents the most important historic developments concerning membrane oxygenators [170–177]. They were first introduced by the end of 1950s. By 1985, they represented more than half of the market and today they dominate the oxygenator market [1,169]. The first oxygenators used silicone rubber and Teflon membranes. Especially silicone has excellent advantages in terms of biocompatibility, gas permeability and low plasma leakage [178]. Nowadays, other materials such as polyolefin

Table 8
Main historic developments of membrane oxygenators

Year	Event
1956	Clowes et al. build the first plate type membrane oxygenator [170]
1956	Kolff et al. use coil polyethylene membrane in a oxygenation device [171,172]
1963	Kolobow and Bowman develop coil membrane oxygenator using a silicon rubber envelope reinforced with nylon knit [173]
1971	Kolobow et al. develop the coil oxygenator using a silicon rubber membrane [174]
1972–1981	Nosé and Malchesky develop at Monsanto microporous hollow fiber membrane oxygenator [175]
1981	First commercial hollow fiber membrane oxygenator (Capiox) using silicone coated microporous polypropylene [176]. In 1997, an improved version with no plasma leakage was introduced [177]
1980s	Menox oxygenator with a special polyolefin membrane was introduced

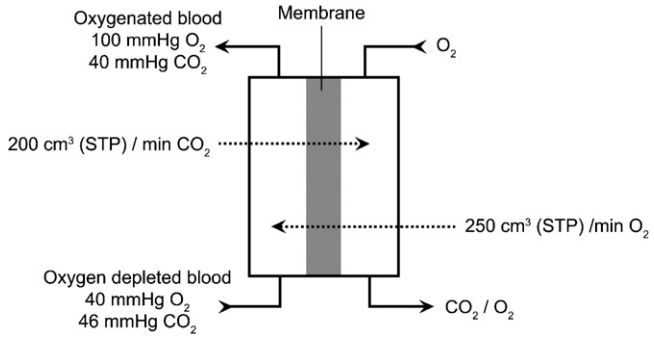

Fig. 14. Principle of the membrane blood oxygenation.

polymers are also used [1]. Especially, membranes from poly(4 methyl pentene-1) (TPX) have good properties for artificial lung devices [179–181]. Membrana GmbH (Germany) has developed asymmetric hydrophobic hollow fiber membranes based on TPX and/or mixtures with other polyolefines, such as poluethylene [182–184]. The membranes are prepared with thermally induced phase separation (TIPS).

Fig. 14 schematically shows the principle of membrane blood oxygenation. The oxygenator must deliver about 250 cm^3 (STP)/min O_2 and remove about 200 cm^3 (STP)/min CO_2. The solubility of these gases into the blood is limited; therefore high blood flow (2–4 L/min) through the device is required. In the oxygenator, the driving force for O_2 is 15 times that for CO_2. In the lung the ratio is about 13 times, but this organ is over 20 times more permeable to CO_2 than to O_2. Therefore, the key consideration in the design of a membrane oxygenator is the CO_2 transport.

The application of the membrane between blood and gas might add mass transfer resistance to the system depending on the membrane gas permeation properties (gas solubility and diffusivity through the membrane). Currently, the vast majority of oxygenators use hydrophobic hollow fiber membranes to avoid plasma leakage. The blood generally circulates on the outside of the fiber to maintain an optimal mass transfer and minimize the pressure drop through the device.

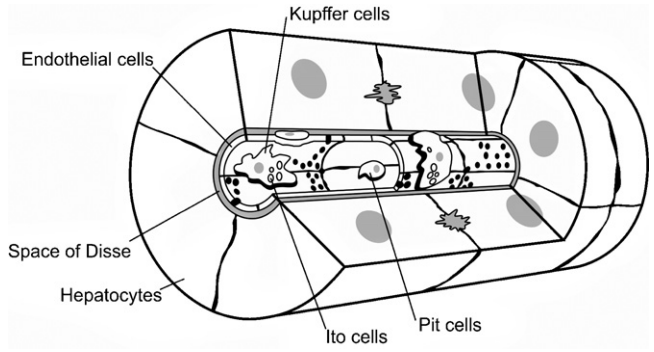

Fig. 15. Schematic drawing of liver tissue consisting of differentiated hepatocytes separated from fenestrated endothelial cells by the Space of Disse. Black filled circles in the endothelium depict fenestrae stellate or Ito cells are fat-storing cells. Kupffer cells function as liver-specific macrophages, while Pit cells are a type of natural killer cells [213].

Over the years extracorporeal membrane oxygenation (ECMO) therapy has seen impressive technical progress related to pumps, oxygenators and improved biocompatibility [185]. It seems, however, that the current marketed membrane oxygenators are adequate and the interest of most clinicians is focused on ease of use and pricing [186]. Nevertheless, significant efforts to develop new membrane materials [187–192] as well as optimized module configurations [192–201] have been performed. Only a few years ago, the first commercially available pump-less lung assist device has been introduced [202] (Novalung ILA, Novalung GmbH, Hechingen, Germany). It contains heparin coated fiber membranes and has been developed for temporary use in patients with maximum period of use of 29 days (more info at www.novalung.com).

6. Artificial liver

6.1. Natural liver

The liver is the central organ for many physiological functions, including protein synthesis, detoxification and metabolism of numerous endogenous substances and pharmacological agents. Most of these functions are performed by mature hepatocytes (parenchymal cells) which are in functional contact with non-parenchymal cells comprising bile duct cells, sinusoidal endothelial cells, Kupffer cells, stellate or fat storing cells and Pit cells (Fig. 15) [203].

Acute and chronic hepatic failure often occurs as a result of autoimmune and viral hepatitis, hepatocellular cancer, exposure to toxins such as alcohol and drugs, or trauma [204]. The loss of normal liver functions leads to life-threatening complications, including hepatic encephalopathy, cerebral edema, severe hypotension and multi-organ failure [205]. In most instances, liver function can only be restored by transplantation. However, there is a great shortage of organs, and significant numbers of patients with acute or chronic liver failure often die while waiting for a suitable organ for transplantation. Therefore, much attention has been paid to the development of a hybrid artificial liver support system that is capable of supporting the failing liver until the liver is regenerated or a donor organ is available [206].

6.2. Artificial liver systems using membranes

Earlier attempts to provide liver support comprised non-biological therapies based on detoxification (e.g. removal of bilirubin, bile acids, and toxins) of the patient's blood, such as hemodialysis, hemoperfusion, hemofiltration and plasmapheresis [207,208], but no impact on overall survival was observed [209]. These attempts included the use of the 'low' permeable membranes made of cellophane/cuprophane or polyacrylonitrile, allowing the removal of substances of small molecular weights [210]. From a medical point of view, the purely detoxifying and filtrating capacity of inorganic devices has been a relevant addition. Apart from charcoal and polymer based materials, the use of albumin as a potential acceptor molecule for toxins was also proven to be a successful treatment option which is currently in widespread use. Examples are such as the Molecu-

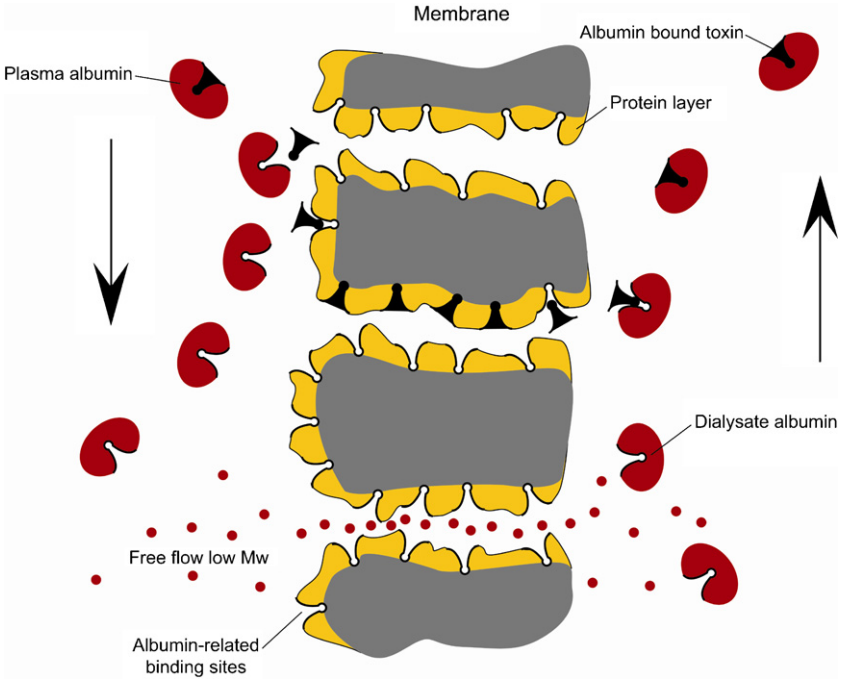

Fig. 16. The principle of MARS system.

lar Adsorbent Recirculation System (MARS) [118], Single-Pass Albumin Dialysis (SPAD) [211] and the Prometheus system [212]. The concept of these systems is based on the use of a high-flux hollow fiber hemodiafilter made of polysulfone for albumin dialysis. The filters in the MARS and SPAD systems are of the same membrane with a molecular weight cut-off (MWCO) of 50 kDa, thus not allowing albumin A sections to pass (Fig. 16). By contrast, the Prometheus system employs a specific albumin-permeable polysulfone membrane (with a cut-off of 250 kDa). Therapies with these non-biological liver support systems have shown some benefits for short-term liver support in patients with acute liver failure. However, most of the clinical studies conducted so far have been small and thus have provided limited clinical data. The limited success of these non-biological systems is probably due to their failure to replace a myriad of functions, including protein synthesis and biotransformation of the liver. For these reasons efforts have been made to develop various Bio-Artificial Liver Support (BALS) systems using a cellular hepatic component that can be fully exploited to support the patient's failing liver.

BALS incorporate freshly isolated xenogeneic (animal) or human primary hepatocytes or a human hepatoma cell line into a bioreactor in which the cells are cultured under different configurations: suspended as aggregates/spheroids, attached to a membrane in flat membrane or hollow fiber systems, and encapsulated in biomaterials [210,213]. The main challenge in the development of a functional BALS concerns the maintenance of differentiated hepatocyte functions for prolonged periods in such a system since hepatocytes lose their metabolic activities within a short period of time *in vitro* due to the deprivation of their original architecture and polarity [214].

The flat membrane bioreactor allows a high-density hepatocyte culture under sufficient oxygenation conditions closely corresponding to the *in vivo* microenvironment [215]. In this system, porcine hepatocytes are co-cultured with non-parenchymal cells between collagen layers (sandwich configuration) on a gas-permeable polytetrafluorethylene [216] membrane. In this way, the cells remain polarized *in vitro* and maintain constant liver-specific functions (Fig. 17). The use of a gas-permeable membrane in such system allows exchange of O_2 and CO_2, an indispensable requirement for optimal hepatocyte culture. Human primary hepatocytes have been successfully cultured on polyethersulfone membranes surface modified with a plasma-deposited acrylic acid coating [118] and a Arg-Gly-Asp (RGD) peptide covalently immobilized through a "spacer arm" molecule [217]. Novel modified polyether ether ketone membranes shave also been proposed as promising biomaterials for cell culture in biohybrid devices [218,219].

The use of a flat membrane bioreactor as an extracorporeal liver support system, however, is accompanied by some

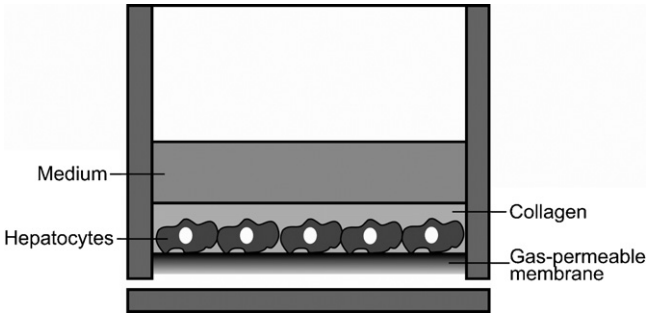

Fig. 17. Schematic drawing of hepatocyte culture: a PTFE membrane (25-μm thickness) is clamped between the scaffold and silicon seal of the small scale bioreactor and is coated with a thin collagen layer on which hepatocytes are placed. The cells are covered with a second collagen layer. The bioreactor is placed on a support which allows delivery of oxygen to the cells from the bottom.

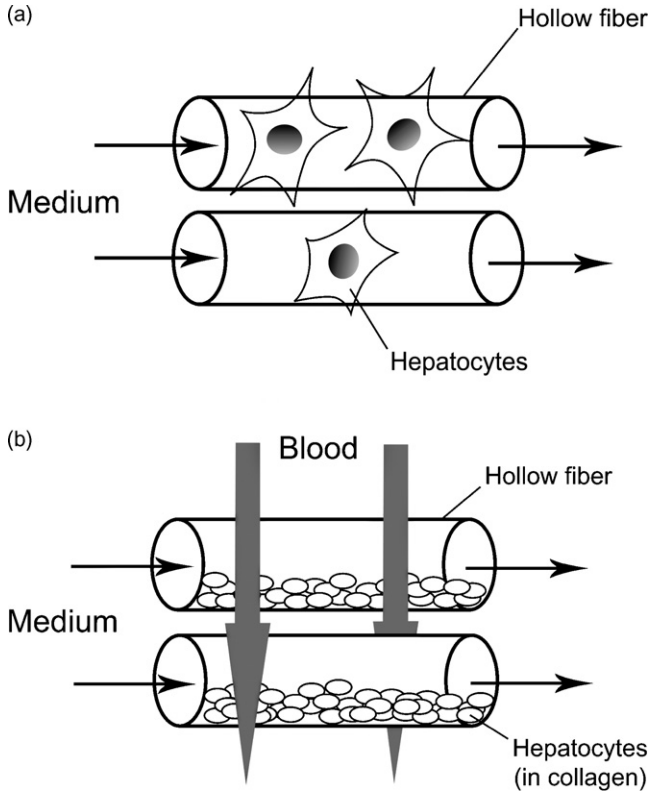

Fig. 18. (a) Hepatocytes are cultured on the outside while blood, plasma or medium flows through the fiber lumen. The scheme is based on a system described by Sussman et al. [220]; (b) hepatocytes are embedded in a gel injected into the intrafiber space of the hollow fibers [225]). Blood or plasma perfuse between the hollow fibers, while medium flows through the fiber lumen.

disadvantages. Examples are the potential large dead volume, exposure of the cells to shear stress and the complex up-scaling of large flat plates. Nonetheless, improvements of these factors will allow its use in a clinical setting in the near future. The development of hollow fiber technology using diverse polymeric membranes allows for human or animal hepatocytes to become an integral part of a BALS. Semi-permeable membranes in BALS function as scaffold for cell attachment and as permselective barriers allowing transfer of oxygen and nutrients. Most of the BALS, including Extracorporeal Liver Assist Device (ELAD) [220], HepatAssist [221], Bio-Artificial Liver Support System (BLSS) [222], MELS CellModule (Modular Extracorporeal Liver Support) [223], and AMC-Bio-Artificial Liver (AMC-BAL) [224], are currently being investigated in clinical trials. They composed of hollow fiber cartridges with different polymeric membranes, such as cellulose acetate in ELAD (MWCO: 70 kDa) and BLSS (MWCO: 100 kDa) or polyethersulfone (PES, MWCO > 400,000) in MELS. Hydrophilic membranes are used for cell attachment and mass exchange, while oxygenation membrane capillaries are hydrophobic (e.g. polypropylene in AMC-BAL). Mostly, hepatocytes are infused into the extra-luminal space of bioreactor cartridges and immobilized on the surface of the capillaries (Fig. 18a). In contrast, Nyberg et al. [225] suspended hepatocytes in a three-dimensional gel which was injected into the lumen of hollow fibers in a perfused bioreactor (Fig. 18b). Ideally, semi-

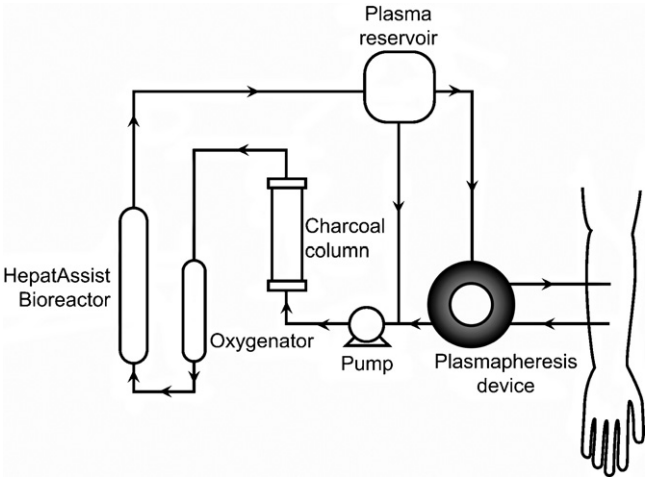

Fig. 19. Schematic illustration of the HepatAssist system (see more details in the text).

permeable membranes have a nominal MWCO that is large enough to allow diffusion of small molecules and proteins (e.g. albumin) but small enough to exclude cellular material, as well as immunoglobulins and viral pathogens when non-autologeous materials are used (membranes function as immunological and viral barriers) [226,227]. The HepatAssist system developed by Circe Biomedical contains a hollow fiber bioreactor containing primary porcine hepatocytes, two charcoal columns; membrane oxygenator and a pump (Fig. 19, adapted from [228]). The patient's plasma is first separated from the blood cells by plasmapheresis and is then pumped through the HepatAssist circuit. In the bioreactor, the porcine hepatocytes function similarly to a healthy human liver. The plasma is reconstituted with the blood cells and returned to the patient.

Despite the widespread use of hollow fibers in BALS, they have some inherent physical limitations with respect to total diffusion surface area and capacity for hepatocyte mass. BALS other than those using hollow fibers include the Radial-Flow Bioreactor (RFB) system employing hepatocytes entrapped within woven–non-woven polyester fabric [229], and the UCLA-BAL in which hepatocytes are encapsulated within a biomaterial a polymer [230].

7. Artificial pancreas

7.1. Natural pancreas

The beta cells (β-cells) are a type of cells in the pancreas which produce the protein hormone insulin and release it into the blood stream to regulate normal blood glucose levels. These cells are located in pancreatic areas called the islets of Langerhans.

Patients with diabetes have abnormal pancreas function and might require periodic injections of insulin for glucose regulation. In fact, almost all type I diabetics and some type II diabetics need insulin. Nonetheless, injection therapy can only mimic the pancreas function concerning insulin delivery but it cannot replace continuous sensing and regulation of glucose level or other pancreatic functions [228]. A long-term injection the-

rapy can result in the so called "diabetic complications" such as kidney failure. For patients, pancreas transplantation would be the best approach. However, scarce availability of donors and possible risk of rejection of implants limit this option [231].

7.2. Artificial pancreas systems using membranes

In the development of artificial pancreas, efforts have been focused on integration of islets of Langerhans into synthetic membranes. The membrane (flat sheet or hollow fiber) separates the cells from the blood stream and is permeable for glucose and insulin and absolutely impermeable to immunoglobulins and lymphocytes [232]. In 1970, Chick et al. [233] transplanted isolated islets protected from the blood stream by a hollow fiber polyacrylonitrile-vinyl chloride (PAN-*co*-VC) copolymer membrane (MWCO: 80 kDa) into dogs. Later, Sullivan et al. [234] designed a perfused artificial pancreas consisting of an annular shaped acrylic housing containing a coiled tubular membrane with nominal MWCO of 50 kDa and surface of 60 cm^2. The device was tested successfully *in vitro* and *in vivo* in diabetic dogs. Since then, different types of devices have been proposed using flat sheet or hollow fiber membranes, capsules or coatings [231]. In the case of hollow fiber membranes, the cells are loaded either on the outside or in the lumen of the fiber. The blood flows in the lumen or at the outside of the fiber, respectively. The hollow fiber configuration is a more attractive option due to the high membrane surface area [231] (Fig. 20). The devices can be [231]:

- Extravascular, when the cells are integrated into a membrane and implanted in an extravascular site.
- Intravascular, when the cells are integrated into a membrane and use the blood stream of the host.
- Microencapsulated, when the cells are encapsulated by polymer membrane which prevents contact with the host immune system and allows transplantation without immunosuppressive therapy.

Beck et al. [232] have highlighted the primal causes of failure of encapsulated islets: (i) hypoxia/limited diffusion at the transplantation site; (ii) non-optimum biocompatibility of the encapsulating material and (iii) insufficient immuno-protection. Recent research activities have been focused on addressing those issues and to the development of better membranes [235–237] and/or the optimization of devices for patients with pancreatic disease [238,239]. Recently, Ikeda et al. [240] have developed a new type of functional device composed of EVAL hollow fibers permeable to glucose and insulin and a poly(amino urethane) coated non-woven poly(tetra fluoroethylene) (PTFE) fabric that allows cells adhesion. (EVAL membranes were selected after screening of various polymers due to their very low insulin absorption.) Besides, Dulong and Legallais [241,242] estimated the relevant parameters of a bioartificial pancreas. Due to hypoxia and necrosis, the number of islets that needed to be implanted to obtain a correct response in terms of insulin secretion should be much higher than that of ultimately functional islets. They also demonstrated that compromise between reduction of the number of implanted islets and fiber length and diameter did not correspond to realistic hollow fiber systems. The alternative of using flat geometry was also envisaged with more optimistic feasibility assessments. Finally it is worth mentioning that Desai and co-workers [243–245] have manufactured capsules by etching nanometre sized pores in thin silicon membranes using microfabrication technology. The pores allow the transport of glucose, insulin and oxygen while blocking the larger immuno-compounds.

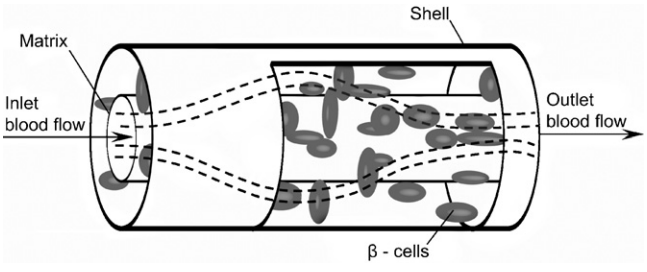

Fig. 20. Illustration of the principle of the hollow fiber system as artificial pancreas. The inner part of the system is shown via a section.

8. Membranes in tissue engineering

8.1. Tissue engineering—general

The replacement of organs since long has been the subject of debate, however, the field of engineering tissue *in vitro* to repair damaged tissue *in vivo* arose only two decades ago [246]. Tissue engineering originates from reconstructive surgery where direct transplantation of donor tissue is practiced to repair the function of damaged tissue. Many difficulties arise with direct transplantation due to insufficient donor organs, rejection of the donor organ and pathogen transmission. An autogenic tissue engineering transplant (using patient's own cells) would address most limitations of direct transplantation and avoid difficulties concerning rejection and pathogen transmission. Additionally, there would be no dependency on donors. Therefore, constructing a tissue-engineered replacement *in vitro* can be an excellent alternative to direct transplantation of donor organs [246,247]. Consequently, a large number of research groups focus on tissue engineering. One of the major research themes is the scaffold fabrication. A scaffold is a 3-D construct which serves as temporary support for isolated cells to grow into a new tissue before there are transplanted back to the host tissue (Fig. 21).

The design of the scaffold determines the functionality of the construct to a high extent. Although the final requirements are dependent on the specific purpose of the scaffold, several general characteristics need to be considered for all designs [248]. The scaffold should be highly porous with good pore connectivity to ensure sufficient nutrient transport towards the cells and removal of waste products [248–251]. Additionally, the scaffold should have suitable mechanical properties comparable to *in vivo* tissue at the site of implantation and should be easily connected to the vascularization system of the host [248,251]. The scaffold material should also be biocompatible and degrade in tandem with tissue regeneration and remodeling of the extracellular matrix

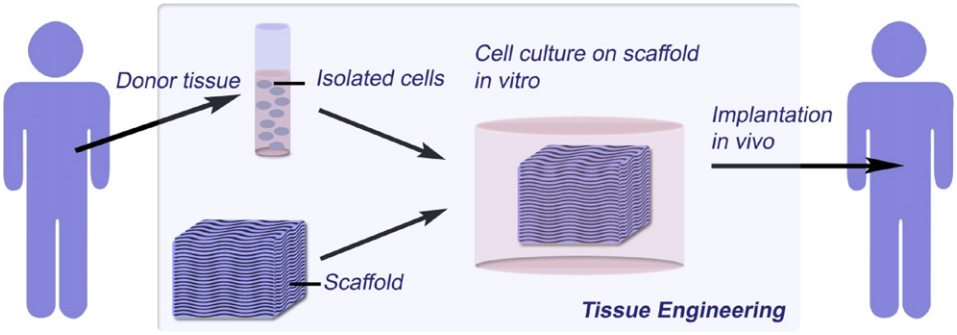

Fig. 21. The principle of tissue engineering.

(ECM). Furthermore, the surface should promote cell attachment and proliferation. Research suggests that the introduction of a micro-architecture into the scaffold improves tissue organization leading to increased tissue function [252–255]. The optimum scaffolds should have proper vascularization to be integrated efficiently to the host. The importance of angiogenesis is also highlighted later (see Section 8.4).

8.2. Materials

In 'soft' tissue applications, e.g. skeletal muscle or cardiovascular substitutes, mainly polymers are used whereas ceramics and metals are especially applied in 'hard' tissue replacements, e.g. bone substitutes. A wide scope of materials of natural as well as synthetic origin is used. It is beyond the scope of this review to discuss all cases in details, therefore, only a selection of widely used materials will be described. For in-depth information on materials used for scaffold fabrication, excellent reviews are available [249,251,256–258].

Polymers are the main source in scaffold fabrication for 'soft' tissue engineering applications. Extensively used polymers are listed in Table 9. Co-polymers of two or more polymers are commonly used as well (not listed). Scaffolds for hard tissue engineering applications are fabricated from a wider variety of classes of materials; polymers, ceramics, composites or metals are commonly used. The polymers used are similar to the polymers applied in soft tissue engineering (Table 9). However, due to low mechanical properties reinforcements are added frequently resulting in composites. By combining two or more classes of materials, improved mechanical properties can be achieved. Materials extensively used in hard tissue engineering are presented in Table 10.

Table 9
Materials frequently used in soft tissue engineering applications

Origin	Polymer (family)
Natural	Collagen (component of the extra cellular matrix-ECM) Fibrin Gelatin Poly(hydroxybutyrate) Polysaccharides (most common are hyaluronic acid, chitosan, starch and alginates)
Synthetic	Poly(esters) (most common are poly(α-hydroxy acids): poly(lactic acid) (PLA) and poly(glycolic acid) (PGA)) Poly(ε-caprolactones) Poly(propylene fumarates) Poly(anhydrides) Poly(orthoesters)

8.3. Fabrication methods

A great variety of well-known membrane fabrication techniques are used in tissue engineering applications; in particular, the scaffold fabrication. Those frequently used are described briefly in this section.

8.3.1. Polymer casting and hollow fiber fabrication

Several fabrication methods based on polymer casting are frequently applied to produce tissue engineering scaffolds, e.g. liquid induced phase separation (LIPS, immersion precipitation) [259–261], thermally induced phase separation (TIPS) [262–265], and evaporation [266–269]. These methods can be used for pure polymers as well as for composites of polymer–(bio)ceramic for application in "hard" tissue engineering [270].

In our laboratory, polymer casting is performed on a micropatterned mold. In this case, due to the solidification of the polymer on the mold, the inverse micropattern is imprinted in the polymer sheet. This technique is called phase separation micro-

Table 10
Materials frequently used in hard tissue engineering applications

Class of material	Type
Crystalline ceramics	Hydroxyapatite (most common since it is the inorganic component of natural bone) Tricalcium phosphate Calcium metaphosphate
Amorphous glasses	Silica Bioglass
Composites	Hydroxyapatite/poly(ε-caprolactone), chitosan, and/or collagen Titanium/calcium phosphate, polyvinyl alcohol, and/or boron Poly(lactic acid)/tricalcium phosphate, silica, and/or ceramic
Metals	Stainless steel Titanium Alumina

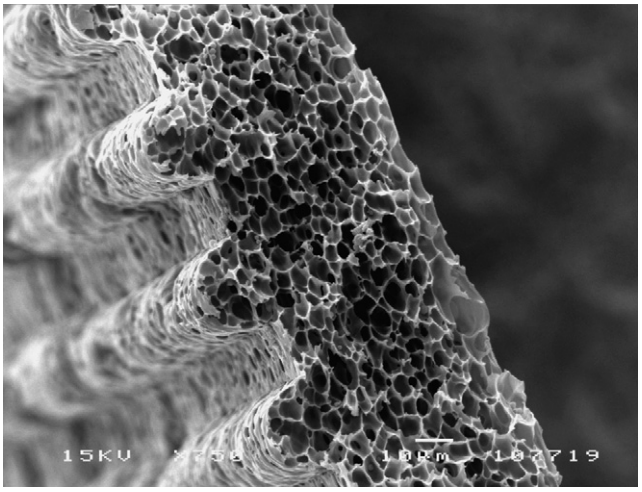

Fig. 22. SEM cross-section image of PLLA sheets prepared by PSμM. The sheet is prepared of a 5 wt% PLLA-dioxane solution using isopropanol at 4 °C as the non-solvent. The sheet was prepared on a mold featuring 20 μm wide continuous channels (bar: 10 μm).

molding (PSμM) [255,271–273]. The advantage of PSμM is the combination of micropatterning with porosity both in one fabrication step. The micropattern can be varied by the design on the mold where the porosity of the sheet can be tuned by the process parameters. Fig. 22 presents an example of a poly(L-lactic acid) (PLLA) sheet fabricated by PSμM.

Besides casting flat or micropatterned sheets from a polymer solution, the phase separation process can be used as well to produce hollow fiber membranes [2,274]. The advantage of polymer casting and hollow fiber fabrication is the creation of wide range of porosities, pore sizes and morphologies. The major drawback of these techniques, however, is the use of organic solvents, which may leave residues after processing and therefore possibly harm the cells. Thus, it is important to effectively wash the scaffolds prior to their contact with cells. This in fact is common praxis in the production of hemodialysis membranes [74].

8.3.2. Emulsion freeze-drying

In emulsion freeze-drying, an emulsion is prepared by homogenization of a polymer–solvent system and water [275,276]. The continuous phase consists of the polymer-rich phase, whereas water is the dispersed phase. The emulsion is cooled down quickly to freeze the solvent and water. This results in solidification of the polymer directly from the liquid state and the creation of porous polymer structure. Subsequently, the frozen solvent and water are removed by freeze-drying. The advantage of emulsion freeze-drying is that large pores can be created, as well as relatively thick scaffolds can be formed. Additionally, proteins can be incorporated during fabrication of the scaffold. The major drawback of freeze-drying is mainly a non-percolated morphology that is obtained which often limits cell in-growth and nutrient transport through the scaffold.

8.3.3. Foaming

In general, a soluble inert gas, e.g. CO_2 and N_2, in the supercritical region is used as blowing agent for foaming polymers via pressure quenching [277–279]. By varying the process conditions, the scaffold properties can be tuned [280]. Instead of using pure polymer, composites of polymer and (bio)ceramic can also be used for application in hard tissue engineering replacements [281].

The advantages of foaming are that no solvent has to be applied, eliminating the risk of remaining residues, and no high temperatures are needed that can cause degradation of the polymer. A drawback of the method is that generally closed skin and mainly non-percolated (cellular) pores are formed limiting nutrient transport through the scaffold. Open porous morphologies can be obtained in particular cases [282–284], but the pore size is often too small for tissue engineering applications. Through additional post-processing steps, interconnected pores can be introduced by, for example, pulsed ultrasound to break the walls of the cellular pores [277].

8.3.4. Particle leaching

Particle (or particulate, salt, porogen) leaching is applied in combination with various different techniques such as solvent casting [285,286], compression-molding [287] or foaming [279,281]. In particle leaching, particles, e.g. salt, sugar or specifically prepared spheres, are incorporated in a polymer sample. After processing the polymer sample into the final form, the particles are dissolved and washed out creating (additional) porosity in the scaffold.

The biggest advantage of particle leaching is the creation of scaffolds with well-controlled high interconnected porosity and pore morphology. The main drawbacks of this method are that it is not applicable for all materials such as soluble protein scaffolds, the time-consuming post-processing character of the method and the risk of remaining residues after processing.

8.3.5. Electrospinning

Electrospinning (ESP) is based on charging a polymer solution and ejecting this through a capillary tip or needle [288,289]. The jet coming from this needle is drawn towards a collector

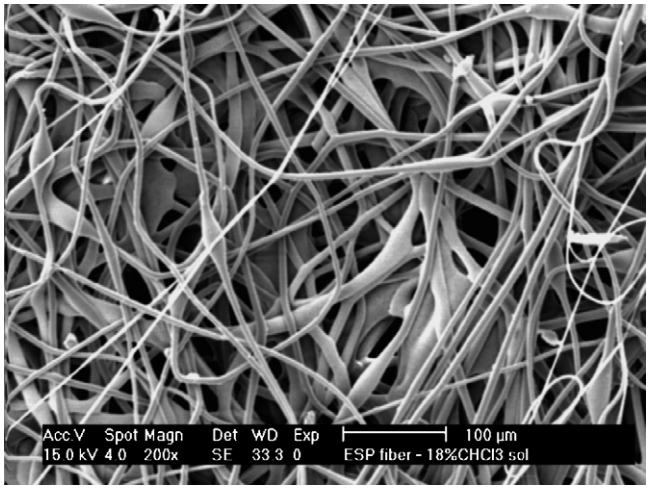

Fig. 23. SEM micrograph of a 300PEOT55PBT electrospun scaffold (printed from Ref. [291] with permission from Elsevier).

due to an electric field ranging from 10 to 30 kV. Evaporation of the solvent from the jet after leaving the needle results in fiber deposition on the collector. To obtain continuous fibers, solutions containing relatively high polymer concentrations are needed. By rotating the collector, a non-woven mesh with a preferential orientation of the fiber is created. The diameter of the fibers is within the range of nanometers to microns. By varying the process parameters, e.g. strength of the electric field, distance between needle–collector, polymer concentration, the diameter of the fibers can be tuned [290,291]. Fig. 23 presents an example of a electrospun scaffold from polyethylene oxide terephthalate–polybutyl terephthalate (PEOT–PBT) polymer (reprinted from Ref. [291] with permission from Elsevier). A major advantage of electrospinning is the high flexibility and good mechanical properties of the obtained scaffold. Additionally, the electrospun fibers can be aligned and used to induce cell and tissue alignment [292]. A drawback of electrospinning is that the fibers might break during fabrication, leading to inferior quality of the scaffold.

8.3.6. Sintering

The process of heat-treating a powder to make the particles adhere to each other is referred to as sintering. Scaffolds fabricated by sintering are mainly used in hard tissue engineering applications. Traditionally, this method is used for ceramic powders; however, also other materials such as metals, glasses and certain polymers as well as composites can also be processed. In the latter, during the heat-treatment the polymer is pyrolized and the ceramic particles are adhered taking over the porous design of the polymer sheet [256,293]. The main advantage of sintering is the possibility of creating controlled and graded porosity. The drawback of the method is the possible risk of low interconnectivity of the pores and the brittleness of the fabricated scaffold when using certain ceramics.

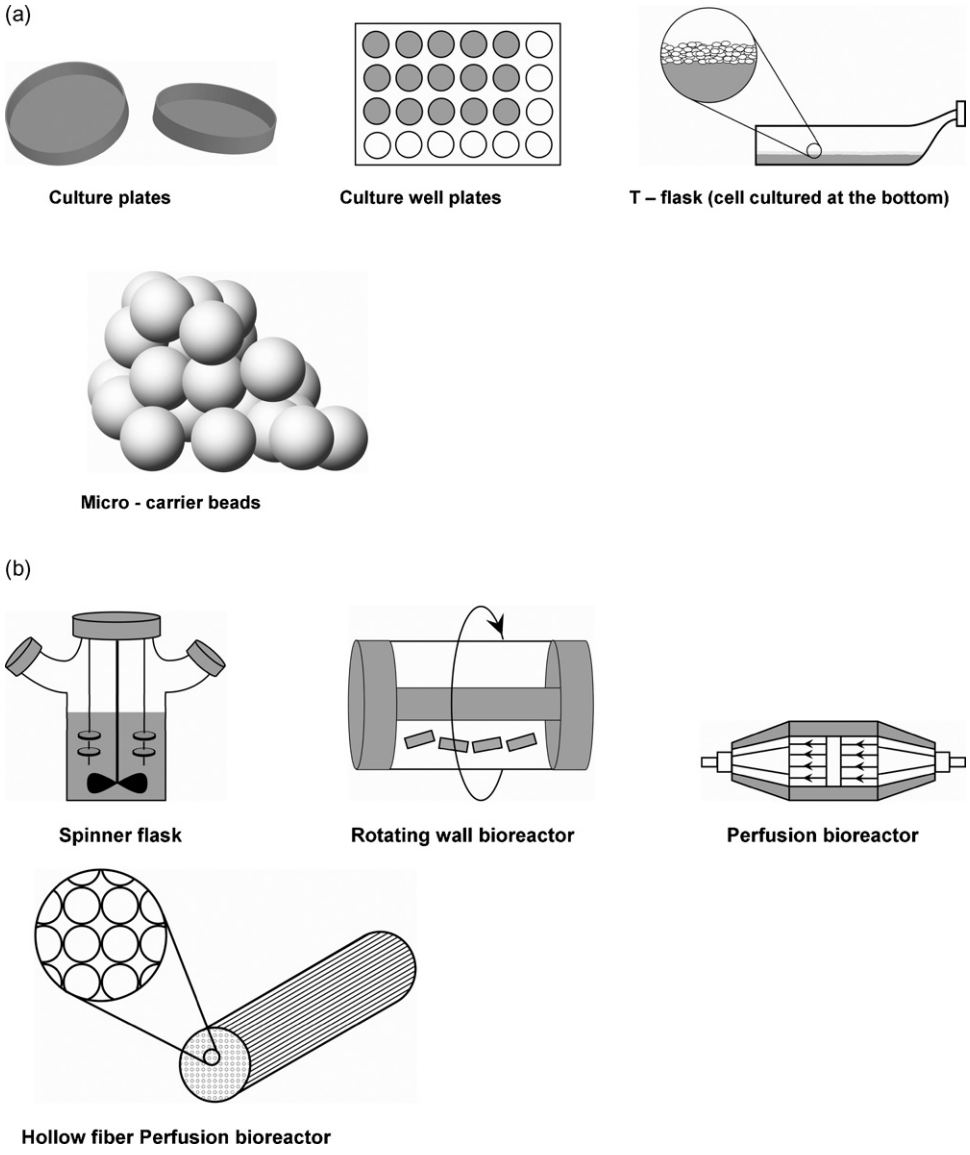

Fig. 24. Various types of (a) static and (b) dynamic bioreactors for tissue engineering.

8.4. Cell culture–bioreactors–scaffold design

8.4.1. Cell culture

Since the field of tissue engineering is still quite young, the broad clinical application of tissue engineering constructs is still premature. Nevertheless, a wide variety of materials have been tested as skin grafts and series of clinical products are available on the market (the reader can find a overview of those elsewhere [228,294]). Main issues to be addressed are optimal cell source and cell cultures performed under conditions that promote differentiation and growth of cells into viable and well functioning tissue for implantation [295]. Additionally, it is important to study the conditions that promote angiogenesis (development and in-growth of new blood vessels) to ensure good nutrient supply throughout the whole scaffold. To ensure efficient mass transfer through the cell cultured scaffold under aseptic conditions, complex bioreactors are required. Their design varies depending on requirements that correspond to the tissue growth.

8.4.2. Bioreactors

Bioreactors can be generally divided into (a) static and (b) dynamic bioreactors (Fig. 24). Sub-classification of bioreactors depends on geometry and/or special functions customized for the particular tissue growth. Bioreactors designed for tissue engineering are built to suit different applications such as (i) small and large scale cell proliferation (e.g. experiments for organ therapy), (ii) *in vitro* development of 3D tissue constructs from isolated and proliferated cells (e.g. skin, blood vessel) and (iii) organ support devices (e.g. artificial liver, kidney) [296–298]. The common critical design aspect of bioreactors is providing controlled environmental conditions such as oxygen tension, pH, temperature and mechanical simulation (mimicking *in vivo* situation). Bioreactors should also allow aseptic and automated feeding and sampling operations.

A new type of culture system has recently been developed and investigated, the flow perfusion culture bioreactor also known as hollow fiber membrane bioreactor (Fig. 25) [299–301]. The flow perfusion culture offers several advantages. They can reduce both external and internal diffusion limitations as well as apply mechanical stresses to the cultured cells. Such system finds application in for example, biopsy cell expansion and bone tissue engineering [299–301].

The vascular construct perfusion bioreactor is an important tool in vascular cell biology and tissue engineering to investigate cell–cell and cell–extracellular matrix interactions [302,303]. Small diameter tissue-engineered vascular grafts are grown using the pulsatile flow of the nutrient media which is generated by periodical expansion of a highly elastic membrane, de- and inflated by an air pump [304]. The pulsatile nutrient flow within the engineered vessels mimics the *in vivo* blood flow. There are many techniques which facilitate the development of micro- (<6 mm) or macro-vascular blood vessels by using biodegradable vascular scaffolds, on which smooth muscle cells and endothelial cells are co-cultured in flow perfusion bioreactors [304,305].

Although perfusion bioreactors can induce limited mechanical stimulation, many experiments have shown an increased tissue growth when additional mechanical contraction or stretching was performed. Skin [306–308], cardiovascular valves [309–311] and other "soft" tissues have been cultured on porous flat sheets in novel bioreactors with incorporated stress and strain based conditioning [312]. On the other hand, bone cartilage and other "hard" tissue constructs have been cultured in bioreactors with direct mechanical stress/load based [216] conditioning [300].

Polymeric membranes have also been investigated for successful long-term primary hepatocyte cultures. This allows the prediction of *in vitro* drug screenings with the aim of reducing the number of animal experiments and interspecies differences

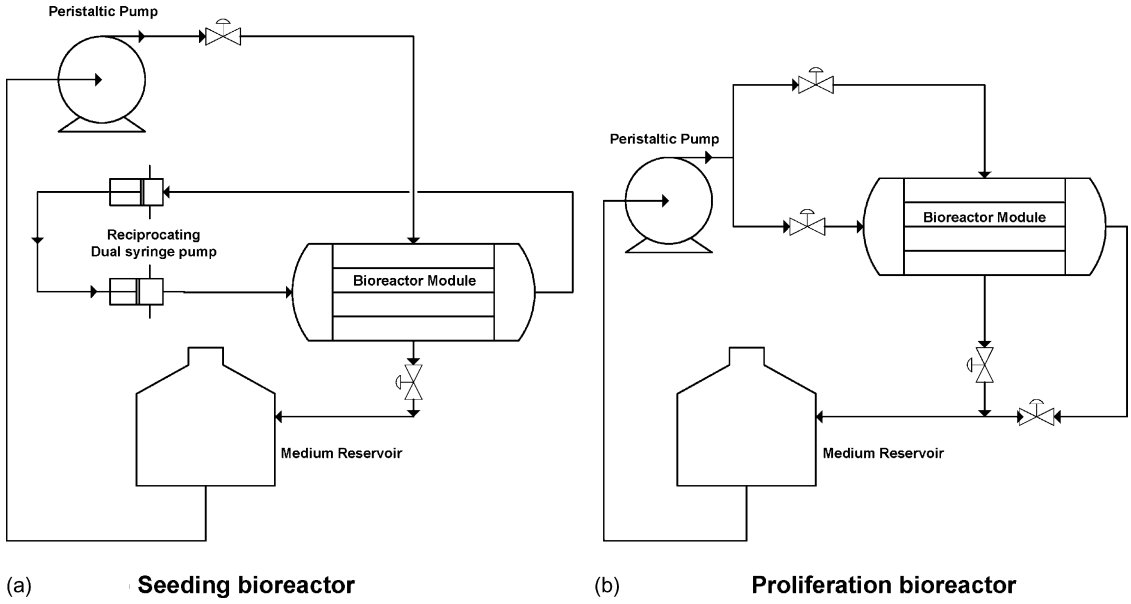

Fig. 25. Schematic illustration of flow perfusion bioreactors: (a) seeding and (b) proliferation bioreactors.

with respect to drug metabolism, as well as providing a faster and more cost-effective way of analysis. Primary hepatocytes are known to lose liver-specific functions rapidly when maintained under standard *in vitro* cell culture conditions [313]. Therefore, it is of great importance for drug metabolism and toxicity studies to maintain *in vivo*-like liver-specific functions of primary hepatocytes in culture. Various *in vitro* testing models using animal and human hepatocytes have been developed, allowing predictive screens for drug metabolism, enzyme induction and hepatotoxicity [314–318]. Bader et al. have established long-term primary rat hepatocyte sandwich cultures in petri dishes with an oxygen-permeable fluorocarbon film (PTFE) at the bottom [216]. This system is a forerunner model of a novel small scale bioreactor described by Schmitmeier et al. [317] (Fig. 17). Primary human hepatocytes directly cultured on a gas-permeable membrane bioFolie (company: IVSS, Germany) could be successfully cultured up to one month in a bioreactor connected to a recirculation perfusion system [316]. Additionally, these types of bioreactor have the advantage of serving as a device to test novel membranes for their biocompatibility with respect to culture hepatocytes as well as for tissue engineering.

8.4.3. Scaffold design

The design of a scaffold ultimately determines the functionality of the grown tissue. It comprehends the material and method used to fabricate the scaffold, and additionally the appearance of the construct, i.e. shape, size and micropattern. A micropattern can be applied to control the behaviour of attached cells; tuning the architectural design of the micropattern can impact on tissue organization [319,320]. By mimicking the *in vivo* micro-architecture around cells, the functionality of the growing tissue can be improved [321]. Fig. 26a presents schematically the culture of cells on micropatterned sheet and Fig. 26b shows example of culturing C2C12 mouse pre-myoblast cells on PLLA membrane sheets. The cells align well within the micropatterned channels.

For some of the fabrication methods the final shape and size can be fixed during processing. In others, the scaffold structure is obtained in a post-processing step. One way is a layer-based design; the final 3D shape and size is obtained via lamination of stacked 2D layers [322,323]. First 2D sheets are fabricated using one of the methods described previously. Subsequently, these sheets are stacked together and laminated using heat or chemical adhesion products, e.g. solvent of the material [255,273]. Fig. 27a shows a stack of three layers laminated through rolling up a micropatterned sheet with continuous channels directly after casting. Lamination can be applied either only at specific points, e.g. corners of the construct, or throughout the full construct. An optimum scaffold should be sufficiently vascularized. The interaction between the material and the surrounding tissue requires sufficient capillary and vessel growth to ensure transport between the implant and the tissue [324]. After lamination, the micropattern can be used to grow cells and create blood vessels (see illustration in Fig. 27b) and/or as perfusion microfluidic channels for nutrient supply throughout the scaffold. This concept seems to be interesting approach to induce nutrient delivery and vascularization.

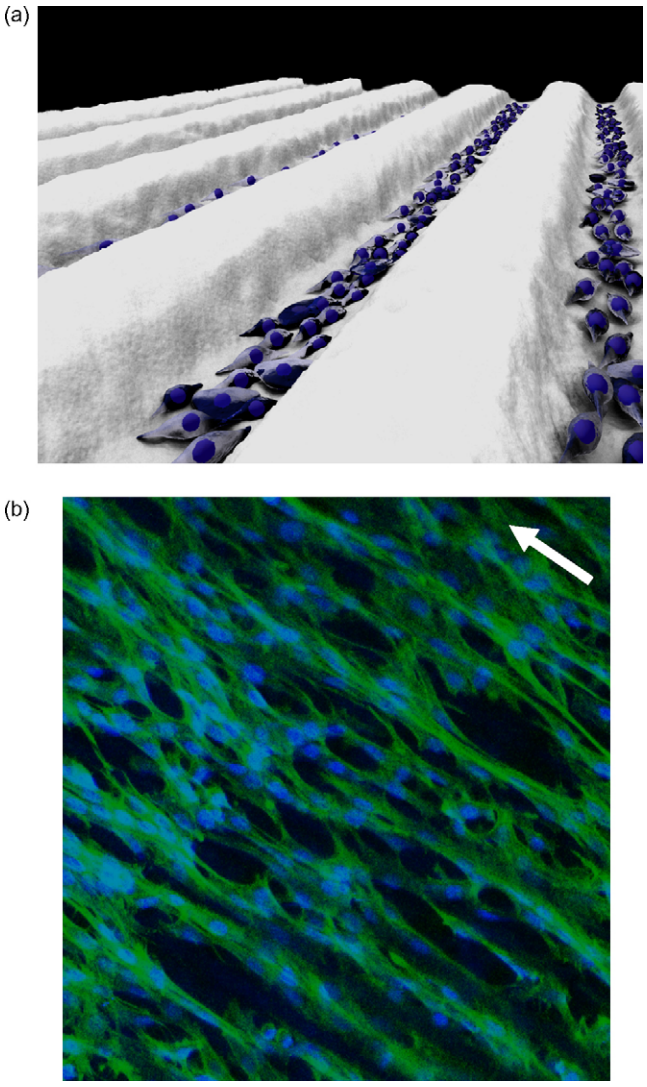

Fig. 26. (a) Schematic illustration of cells cultured on micropatterned membrane sheets. (b) Confocal fluorescence microscopy images of 4 day C2C12 cell cultures on porous PLLA sheets featuring 20 μm wide channels (cell density 25,000 cells/cm^2). Magnification 63×, cytoskeleton labeled with Bodipy-phallacidine (green) and nucleus labeled with Hoechst (blue). The direction of the channel is indicated by the arrow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

Successful clinical trials of tissue engineering constructs has been reported in literature [325]. Nowadays, major areas of tissue-engineered replacements in clinical trials and applications are skin, cardiovascular, bone and cartilage. One example is the work performed by Matsumura et al. [326] who reported application of tissue-engineered autografts in cardiovascular surgery on children with various complex heart diseases. They applied a tissue engineering technique where patients own cells were isolated, cultured and subsequently seeded on a biodegradable polymer scaffold fabricated by freeze-drying. The first operation was performed in May 1999, and over 40 patients have been treated by then. During post-operative analysis no complications related to the tissue engineering autograft were observed.

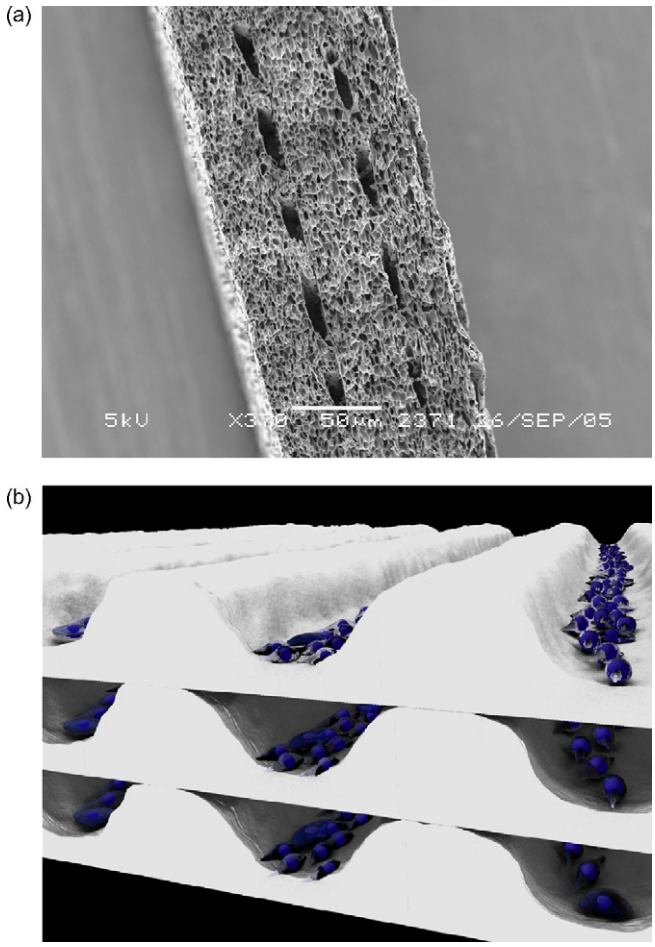

Fig. 27. (a) SEM cross-section image of a stack of three layers fabricated from a micropatterned sheet featuring 20 μm wide channels prepared from a 5 wt% PLLA-dioxane solution using ethanol at 4 °C as the non-solvent (taken from ref [255] with permission from Elsevier). (b) Schematic illustration of cell culturing on stacked micropatterned sheets.

In the past 10–15 years, there has been an increased interest in the use of microfluidics in tissue engineering. The so called "Lab on a chip" approach allows scientists to control the accuracy of the tests, perform high throughput screening of biomaterials in contact with cells, of biological reactions and/or processes [327–331]. In several microfluidics papers, PDMS is used as material because its fabrication process is simple, cheap and can be performed outside the clean room. Besides, in cell experiments the high gas permeability of PDMS is mostly exploited for O_2 supply and CO_2 removal. PSμM offers the possibility to process various biomaterials outside the clean room and most importantly introduce and tune material porosity [6,255,272,332]. This is a crucial issue for tissue engineering where the nutrient transport limitations within the scaffold limit the survival of the cells. In the future, we think that PSμM can find broad application in tissue engineering and generally on cell-on-chip applications.

9. Conclusions and outlook

This paper covered extensively the most important medical applications of membranes.

9.1. Drug delivery with membranes

Membranes are used extensively in drug delivery systems; especially in osmotic and diffusion controlled systems. Here, the discussion concerning transdermal drug delivery systems was focused on passive and iontophoretic systems which find broad commercial application. The market for both systems is expected to grow steadily in the future.

9.2. Artificial kidney–blood purification

Dialysis membranes and modules are used daily all over the world for the treatment of patients. The technology is mature and grows steadily. New developments towards membranes with improved biocompatibility for longer time periods as well as better sieving properties should be the focus in the future.

9.3. Membrane oxygenators

The extracorporeal membrane oxygenation therapy has seen impressive technical progress the last years. The marketed oxygenators are adequate and the interest of the clinicians seems to be focused on ease of use and pricing.

9.4. Membranes for artificial liver

The membrane can play a pivotal in the artificial liver support systems. Most of these systems contain flat sheet or hollow fiber membranes (prepared from various polymers) where hepatocytes are cultured. The main challenge concerns the maintenance of differentiated hepatocyte function for prolonged periods. Here the development of new scaffolds and efficient bioreactors would be the future challenge of membranologists.

9.5. Membranes for artificial pancreas

Most of efforts have been focused on integration of islets of Langerhans into synthetic membranes. Although significant progress has been made there are still challenges to be resolved; encapsulation of islets often fails due to hypoxia/limited diffusion of the transplantation site, insufficient biocompatibility of the encapsulation material or insufficient immunoprotection.

9.6. Membranes for tissue engineering

The field has not been explored sufficiently by membrane scientists. There is need for design and construction of better scaffolds for cell culture. Especially the optimum design of cell culture bioreactors, using mainly hollow fiber membranes, for delivery of nutrients and oxygen is an important challenge for membrane scientists.

Membrane science and technology play – and will continue to play – an important role in medical applications. Nevertheless, membrane scientists cannot solve the issues alone. They need to get more contacts and improve interaction with biologists, bioengineers, medical doctors and others. We hope that

this review will stimulate such contacts and interactions. Multidisciplinary teams could certainly deal better with the issues and have higher chance of success.

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