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Review Paper

Oxygenation and Membrane Oxygenators: Emergence, Evolution and Progress in Material Development and Process Enhancement for Biomedical Applications

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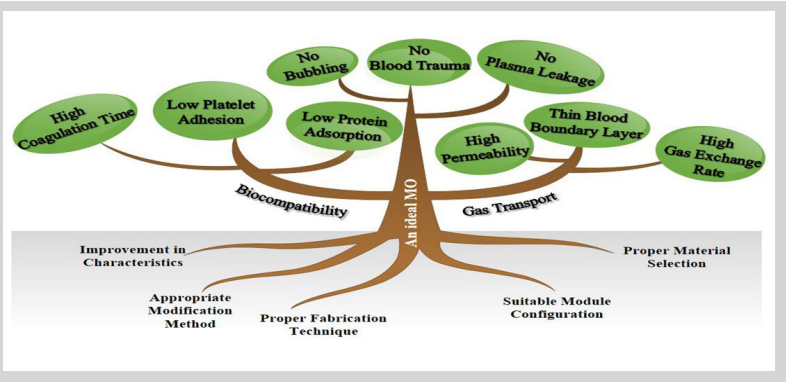

Highlights

- Emergence and evolution of oxygenation processes and oxygenators are described.
- Essential characteristics of membrane oxygenators and their functions are explained.
- Progress in development of materials and fabrication techniques is elaborated.
- Effect of modifications on the characteristics of membranes is discussed.
- Principles of transport phenomena for modeling membrane oxygenators are explained.

Abstract

Ever-increasing demands for high performance blood oxygenators have led to continuous advancements in this field. Despite the progresses made since their emergence, there still exist challenges that intimidate the reliability of membrane oxygenators. A promising approach for addressing these challenges and enhancing the overall process performance relates to the selection, development, and modification of materials with desirable characteristics. The main impetus for the present review is to bring forward important and yet less explored subjects by shedding light on the technological, design, and engineering aspects of oxygenators and the oxygenation process. Special attention is paid to membrane oxygenators and their essential characteristics such as gas transport, plasma leakage, and biocompatibility. Also, various practical configurations of membrane oxygenators are illustrated with their merits and limitations. From the materials perspective, a comprehensive range of polymeric materials with track records for applications as membrane oxygenators are surveyed and analyzed considering their physicochemical and biocompatibility properties in order to gain insights into the features of an optimal material. In addition to elaborations on the methods for fabrication of membrane oxygenators, various effective techniques that could be used for altering the microstructure and surface properties of the membranes are presented. Also, an in-depth overview is provided about the transport phenomena in membrane oxygenators aiming to provide a better understanding of the molecular and process aspects of the process. An overview of the state of the art is summarized along with points about the trends of future developments are provided at the end.

Contents

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1. Introduction

In living systems, respiration takes place based on the concept of delivering oxygen to the tissues and instead removing carbon dioxide (CO_2) produced during the cell metabolism. Considering human being, this process takes place in the lungs by capturing oxygen from the atmosphere and blood serves as the carrier for transporting them to the target tissues. The heart continuously pumps blood to the lungs in order to uptake the oxygen molecules by dissolving them in the blood's plasma with the aid of pulmonary capillaries of the lung. This is accomplished typically at the rate of about 0.3 $L.min^{-1}$. Red blood cells containing hemoglobins take up oxygen through the red cell's membrane. The blood with oxygen partial pressure of ~95 mmHg is then returned to the heart for further distribution into the vessels. The blood containing oxygen-rich hemoglobins flows inside arteries to oxygenate tissues and collect CO_2. According to this mechanism, the partial pressure of CO_2 in the blood is raised from ~41 to ~45 mmHg whilst the oxygen partial pressure drops to ~40 mmHg. In the final step of the cycle, the blood returns to the heart through the veins and then to the lungs to release CO_2 at the rate of ~0.25 $L.min^{-1}$ [1].

Essentially, human lungs have the main responsibility for oxygenation process. Each lung has a variety of air sacs at the end of respiratory tree called "*alveoli*". Typically, air with oxygen partial pressure of ~100 mmHg is received by these cells whereas CO_2 with the partial pressure of ~40 mmHg is released from them and the process is called "*ventilation"*. Subsequently, the gasses diffuse through the alveolar capillary membranes which are responsible to prevent direct contacts of gas and blood. Permeation of O_2 and CO_2 in the alveolar capillaries is proportional to the gas exchange area (ca. 100 m^2), the membrane diffusion distance (ca. 1 µm) as well as the total length of the air ways (ca. 2400 km). The rate of O_2 and CO_2 exchange in average adults can reach up to 2000-5000 $ml.min^{-1}$ [2]. Gas exchange through the alveolar-capillary interface is described by Fick's law according to equation (1):

$$Gas\ flow\ rate = A.D.(P_1 - P_2)l^{-1} \quad (1)$$

in which A is the surface area, l is the interface thickness, D is the diffusion coefficient and (P_1-P_2) is the pressure difference across the alveolar-capillary interface [3].

The characteristics of the lungs are unique and fascinating, enabling them to operate efficiently for the entire life [4]. However, their performance can be impaired by serious lung diseases. According to the official reports, by the end of 2017, large number of people suffered from lung diseases which contributed to the mortality rate of about 3.9 million per year [5]. One of the common diseases is caused by the rise of blood pressure in the lungs (called as *primary pulmonary hypertension*) in which the failure of the right heart leads to the blood shortage at the left heart ventilator and interrupting its function. Therefore, either the concentration of oxygen in the blood and tissues is decreased resulting in *hypoxemia* or the concentration of CO_2 is increased referred to as *hypercapnia*. Other typical culprits for the lungs failure are cystic fibrosis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and pneumonia (lung infection). In some patients, these disorders can even be more severe resulting in acute respiratory distress syndrome (ARDS) [6-10]. There are also certain disorders related to infants such as meconium aspiration syndrome and persistent fetal circulation [11]. Therefore, development of high performance oxygenators resembling the characteristics of natural lungs is of paramount interest and importance. Specially, considering the distinct anatomy of adults, kids and neonates, tuning the specification of oxygenators to meet the requirements for each category is essential [12].

In response to the need for blood oxygenation, some devices such as bubble and film oxygenators have been emerged over the years. Although they could oxygenate blood and remove carbon dioxide, none of them could compete with membrane oxygenators. This was partly due to the low blood trauma offered by the membrane oxygenators as well as their high

performance. In open heart surgery, heart and lung are on their minimum efficiency due to the lowered body temperature of the patient. In cardiopulmonary bypass (CPB), an artificial lung is required to constantly supply oxygen to the tissues and remove CO_2 from them in the course of the operation [13]. Extracorporeal membrane oxygenators (ECMO) are the devices that have been in use for this purpose and have been fairly successful [14,15]. Lately, they also have been examined for their potential in helping patients who suffer from the coronavirus (COVID-19) during its outbreak which that affected many people around the globe. Some results have demonstrated that the use of ECMOs has been helpful in reducing the mortality rate of infected patients further endorsed by the World Health Organization [16-18].

There exists number of review papers that have covered different aspects of membrane oxygenators especially in term of medical and operational experiences [19-31]. Based on a detailed literature survey and to the best of our knowledge, despite the significant importance of membrane and materials in governing the process performance, no comprehensive report could be found to include these aspects. On this basis, the main impetus for the present review is to fill this gap by exploring the advances in the development of membranes and materials for membrane oxygenators and the progresses made over the years from the chemical engineering and materials science points of view. The discussions made in different sections are intended to provide insights and a better understanding about the contributions of membrane, materials as well as transport phenomena in the process of oxygenation by scrutinizing their particular roles. The ultimate goal is to shape novel ideas for upcoming research activities that could potentially lead to the further enhancement of membrane oxygenators and oxygenation process.

2. Technological Evolution of Oxygenators

Due to the significance of blood oxygenation, many research investigations have been performed on the various aspects of this process. In a pioneering study carried out in 1666, Hooke [32] proposed an experimental procedure to keep a dog alive by blowing to his lungs with bellows. This was based on the notion that, in that era physicians believed that motion of lungs during inhalation and exhalation is the major cause of blood circulation within the body. However, Hook's observations in the experiments revealed that just the motion of lungs is not enough and supply of fresh air is also mandatory. In the course of another attempt, physiologist Legallois [33] proposed that arterial blood injection to a specific part of body, while detached from other parts, could keep the isolated organ alive. The validity of this hypothesis was examined by injecting arterial blood to a beheaded rabbit. However, this was not successful due to blood clotting. According to the review reports by Lim et al. [20] and Hewitt et al. [34], Prevost and Dumas had examined a method for defibrination of the blood that could address this problem. Since then many other researchers have contributed to the progress of this field. Nevertheless, none of these efforts could fulfill the acute need for appropriate oxygenation. A chronological summary of the major milestones and achievements is provided in Table 1. Progress in blood oxygenation technologies entered into a new era by the invention of extracorporeal oxygenators in the 19th century. According to Melrose [35], this breakthrough intended to serve three purposes: "*first: to carry temporarily a part of the cardio-respiratory function when the function of either or both of these organs is impaired, second: to provide a complete diversion of the blood stream away from the chambers of the heart in order to permit intracardiac surgery, and finally to perfuse isolated organs*".

2.1. Bubble oxygenators

According to a report [34], the first extracorporeal circulation device for blood oxygenation was devised by Ludwig and Schmidt in 1868 [39] comprising a balloon to shake blood and air together. This was followed by the introduction of the first bubble oxygenator by Schröder in 1882 [40]. This device was designed in such a way that venous blood was taken out from the body and after oxygenation with air returned to the arteries to reach an isolated organ. Another practical use of bubble oxygenators was carried out by Hooker in 1910 [43] and was aimed to investigate the effect of pulse pressure on the function of kidney. In order to supply oxygen to an isolated organ, Hooker designed a bubble oxygenator which could transfer oxygen to the circulation system. Other major improvements in bubble oxygenators are listed in Table 1.

Schematic representation of a typical bubble oxygenator is shown in Figure 1. Essentially, bubble oxygenators enable blood and oxygen to come into direct contacts. By having a large surface area, bubble oxygenators pose tremendous risk of blood trauma primarily. Blood trauma is often defined as the mechanical stresses causing serious damages to the blood cells. Another serious drawback of bubble oxygenator is embolism which takes place when gas bubbles are trapped inside the blood and then enter the vessels and block capillary pathways. To prevent embolism, usually a settling chamber is used [76,77].

On the basis of these drawbacks, evolution of the first generation of efficient bubble oxygenators was delayed until 1950 when Clark and colleagues [56] optimized the size and flow of bubbles to improve blood oxygenation rate and could remove the produced bubbles by flowing the blood over a methylpolysiloxane resin coated surface. This was breakthrough offered one of the most effective bubble oxygenators up to that time.

Bubble oxygenators remained in use for the next few decades because of their high performance and low priming volume. Their market, however, declined over time especially in competition to membrane oxygenators since problems such as embolism and trauma were not entirely solved. As of today, bubble oxygenators have no market values and are totally replaced by other oxygenators.

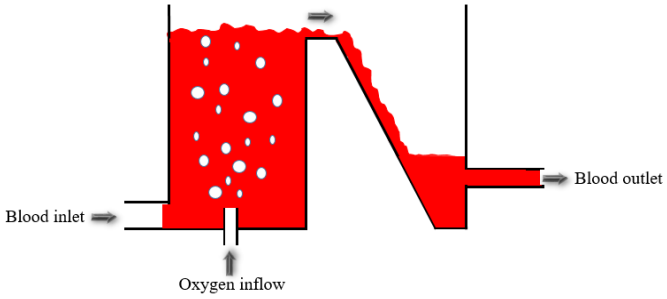


Fig. 1. Schematic representation of a typical bubble oxygenator.

2.2. Film oxygenators

The film oxygenator is another type of extracorporeal oxygenation device that was first introduced by von Frey and Gruber in 1885 [41]. It relied on the principle that a rotating inclined cylinder was employed to create a thin film of blood being oxygenated in contact with air. The contact between gas and blood was limited to the surface of the cylinder. Hence, blood trauma was expected to be lower than that of bubble oxygenators and instead a larger area was required to enable efficient gas exchange.

According to Table 1, film and disc oxygenators have undergone many improvements over time especially for use in cardiopulmonary bypass. In 1937, Gibbon [53], one of the pioneers in open heart surgery, used a vertical rotating disc oxygenator to take the responsibility of heart and lung. In which the cylinder and discs were all rotating. After many trials, in 1953, he finally announced the first successful operation of CPB using disc oxygenators. Later on, Melrose [35] suggested optimization of the contact period of blood cell and oxygen and the maximum rotation speed of discs as the crucial factors in the design of disk oxygenators. He also incorporated the roller pump developed by Henry and Jouvelet into the system [78]. Another major improvement was accomplished by Kay et al. and Cross et al. [68,69] in 1956 who used Teflon instead of silicone resin for coating of the stainless steel discs aiming to reduce trauma. However, hemolysis and foaming were observed in disc rotation rates beyond 120 r.min^{-1}. The mechanism of this device is displayed in Figure 2. The market for rotating disc oxygenators has been expanding in the last decades. However, suffering from some issues such as foaming, embolism and high priming volume severely hampered their widespread acceptance and eventually they lost the market to membrane oxygenators.

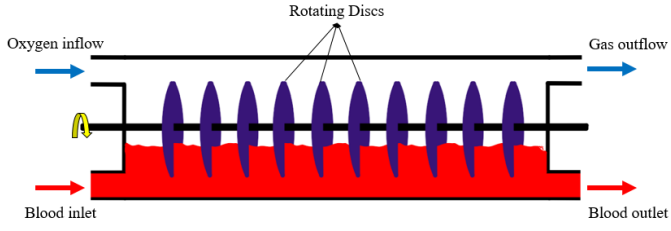


Fig. 2. The mechanism of a typical disc oxygenator.

Table 1
Chronological trend of progress in oxygenation process before the emergence of membrane oxygenators (*some data collected from Refs. [20,34]).

Researcher(s)	Year	Achievement
Hook [32]	1666	Blowing to a dog's lungs to keep the animal alive
Legallios et al. [33]	1812	Injection of arterial blood to a beheaded rabbit
Prevost et al. [36]	1821	Identification of a method of blood defibrination
Lobell [37]	1849	Isolated kidney perfusion
Porter et al. [38]	1855	Invention of roller pump
Ludwig et al. [39]	1868	Blood oxygenation by shaking the blood in an air balloon
Schroder [40]	1882	Introduction of the first extracorporeal bubble oxygenator
Von Frey and Gruber [41]	1885	Introduction of the first extracorporeal film oxygenator
Jacobj [42]	1890	Designing a new bubble oxygenator with a balloon pump
Hooker [43]	1910	Introduction of a new circulation system for isolated renal oxygenation
McLean [44]	1916	Discovery of heparin
Bayliss et al. [45]	1928	Using a series of truncated cones rotating inside a series of immobile plates to produce a thin film of blood
Dale and Schuster [46]	1928	Introduction of a double perfusion pump to achieve continues flow
Barcroft [47]	1933	Replacing a dog's heart by an electrically-driven rotary pump
De Burgh Daly and Thorpe [48]	1933	Employing a modified version of hooker's [49] and drinker's [50] oxygenators with Dale and Schuster pump
Cruickshank [51]	1934	Introduction of an efficient oxygenator using magnetic power for rotation with the minimum blood and oxygen leakage and foaming
Debakey [52]	1934	Modification of roller pumps for blood transfusion
Gibbon [53]	1937	Introduction of a film oxygenator with vertical revolving cylinder and Daly's pump for the purpose of total oxygenation of animal blood
Kolff et al. [54]	1944	Introduction of membrane oxygenators
Björk [55]	1948	Introduction of a novel rotating disc oxygenator
Clark et al. [56]	1950	Optimization of bubble oxygenator
Miller et al. [57]	1951	Development of a screen film oxygenator
Clowes [58]	1951	Definition of a simple method to bypass the left side of the heart with modified Dale-Schuster pump for the purpose of normal oxygenation of blood while the left side of heart is in rest
Dennis et al. [59]	1951	Failed attempt to perform the first CPB on human using a new effective disc oxygenator with modified Dale-Schuster pump
Karlson et al. [60]	1951	Introduction of the first cellulose membrane oxygenator
Dodrill [61]	1953	First successful right heart bypass using modified Dale-Schuster pump
Gibbon	1953	First successful CPB
Melrose and Aird [35]	1953	Investigation of a rotating disc oxygenator with Henry and Jouvelet pump
Clark et al. [62]	1953	Proposing a reliable method for measuring oxygen tension in the blood
Mustard et al. [63]	1954	Unsuccessful heart-lung bypass using monkey lung as an oxygenator
Clowes et al. [64]	1955	Measurement of gas transfer rate to the blood through different polymeric membranes
Lillehei et al. [65]	1955	"First controlled cross-circulation"
Clowes [66]	1956	Introduction of Teflon as a new membrane material
Dewall et al. [67]	1956	Introduction of a new efficient bubble oxygenator
Kay et al. [68] & Cross et al. [69]	1956	Using Teflon coated stainless steel film disc oxygenators
Clowes et al. [70]	1957	Evaluation of membrane oxygenators by total perfusion for 3 hours
Kirklin et al. [71]	1958	Modification of Gibbon type vertical screen oxygenator (Mayo-Gibbon pump-oxygenator)
Brown et al. [72]	1958	Introduction of an effective blood heat exchange unit
Osborn et al. [73]	1960	Modification of rotating disc oxygenators
Hopf et al. [74]	1962	Proof of membrane oxygenator capacity for a 10-hour-partial-heart-lung bypass by analyzing bubble, disc and membrane oxygenators
Kolobow et al. [75]	1963	Incorporation of Silastic (silicone rubber) membrane oxygenators

2.3. Liquid-liquid oxygenators

Beside gas-liquid contactors, new types of liquid-liquid contactors have been proposed to function as oxygenators though not economically and clinically comparable to membrane oxygenators [79,80]. In liquid-liquid oxygenators, oxygen is dissolved in a fluorocarbon as the carrier fluid and then comes in contact with venous blood to be exchanged with CO_2.

2.4. Membrane oxygenators

Despite their shortcomings, commercial bubble and film oxygenators remained in use but not for long-term applications throughout 60s and 70s. Gas embolism, perfusion problems, hemolysis, platelet destruction, leukocyte response and leakage, and particularly damage to the blood components were among the complications reported for these devices [81]. Therefore, attempts to develop alternative devices began by Kolff et al [54] in order to eliminate direct contacts between blood and gas. In their study on artificial kidneys, they noticed that oxygen was quickly absorbed by blood and consequently the color of the blood changed from blue to red. This observation revolutionized the approaches to this issue by highlighting the potentials of membranes to be used similar to natural lungs as the means for gas exchange with blood [82]. Due to the prevention of direct contacts between the blood and gas in a membrane oxygenator, the risk of blood trauma could be considerably reduced compared to the bubble and film oxygenators [83,84]. Furthermore, membrane oxygenators encompass other benefits including high gas exchange rate, simplicity of design, flexibility and low risk of embolism. Nevertheless, one of the major limitations of membrane oxygenators is their resistance toward the transport of gas molecules. This implies that a large surface area would be required to achieve desirable performance. One idea to tackle this problem is the use of microporous membranes instead of fully dense microstructures. Other major drawbacks are related to the blood compatibility, large surface area and large operating volumes of the membranes. Today, the state of the art commercial membrane oxygenators such as Membrana, Oxyphan and Oxyplus are made of microporous hollow fiber polypropylene with sponge-like pore structure for cardiopulmonary bypass and polymethylpentene (PMP) with dense outer skin for long term applications. These membrane oxygenators have shown high gas exchange rate and good biocompatibility without causing plasma leakage.

Owing to the attractive features of membrane oxygenators, their use as ECMO has become more prevalent than bubble and film oxygenators especially during the past decade. The global market of ECMO, as the only oxygenator in use, has raised to USD 285 million in 2018 and it is anticipated to go beyond USD 370 million by 2025 [85]. Table 2 provides an overview and comparison among the prevailing oxygenation technologies.

2.5. Oxygenator circuits

As outlined earlier, oxygenators are used for CPB operations during cardiac surgery of patients suffering from lung failure. Oxygenators have also found applications as circulatory assist devices consisting of pumps and connecting tubes called extracorporeal circulation (ECC). Utilization of membrane oxygenators in such circulation system forms an ECMO device. ECC and ECMO are applied for both blood oxygenation and carbon dioxide elimination [86].

In 1978, Kolobow et al. [87] introduced a new extracorporeal gas exchange technique for patients with respiratory failure called extracorporeal carbon dioxide removal (ECCO2R). In contrast to ECMO which requires high gas exchange surface area, in ECCO2R the surface area of the natural lung is utilized for oxygenation and the membrane oxygenator is only used for the carbon dioxide removal [31]. Therefore, a smaller surface area is required which can lessen the risk of trauma. However, since it was not very efficient, a new carbon dioxide removal technique called arteriovenous CO_2 removal (AVCO2R) was developed by Brunston et al [88]. The desirable characteristics of AVCO2R such as low resistance and low priming volume made it very attractive and efficient for carbon dioxide removal.

Beside extracorporeal circuits, other devices have been designed to be implanted inside the chest for patients with ARDS. One of the popular ones is intravascular oxygenator (IVOX) devised by Mortensen [89,90] in which hollow fiber membranes are placed inside vena cavae (a head to heart vein) to remove carbon dioxide from the blood. Due to the limited surface area, CO_2 removal could not surpass 30% of the total amount. Hence, different modifications have been carried out to increase the efficiency [31,91]. Intravascular Membrane Oxygenator (IMO) is also attractive since it can exchange 50% of the gas [92]. However, the surface area in IMOs is limited because it can pose obstacles for blood flow in larger volumes [93].

3. Essential Characteristics of Membrane Oxygenators

3.1. Gas transport

In terms of gas exchange and permeability of membrane oxygenators, various progresses have been made over the past years. Early membrane oxygenators were dense and besides serving as a perfect barrier toward plasma leakage, this dramatically reduced the rate of gas exchange. This is due to the fact that in dense membranes, permeability is mainly governed by the inherent properties of membrane material than the microstructure [94]. To improve gas exchange across the membrane for efficient oxygenation of blood, microporous membranes have been extensively explored since they impose considerably less resistance toward the gas transport. Since their first trial for this purpose by McCaughan et al. [95]. In microporous membrane oxygenators, the resistance of membrane phase toward gas exchange is less than that in blood boundary layer [96].

However, the resistance in the blood boundary layer is still considerable. One proven approach for reducing this resistance is through applying a secondary flow patterns tangential to the primary flow so that besides diffusional flow, mass transfer convection is produced which contributes to the enhancement of gas exchange [97].

Controlling the liquid flow rate can also be a useful method for diminishing blood phase resistance through liquid velocity and Reynold's number. For example, increasing the rate of the blood flow reduces the thickness of the boundary layer and thus enhances the gas transfer rate in membrane oxygenator modules [98,99]. In addition, this enables faster displacement of the oxygenated blood resulting in the increased driving force [100]. Figure 3 demonstrates the effects of variation in liquid flow rate on oxygen and CO_2 exchange for various materials.

Another proposed method for enhancing the efficiency of gas exchange in the liquid side is through the application of an external energy force like vibration to the membrane module. This innovative method was firstly introduced by Krantz et al. [101] who vibrated the membranes axially during its operation which effectively reduced the blood boundary resistance and consequently increased overall gas exchange throughput.

According to various studies, the contribution of membrane microstructure on the gas exchange resistance should not be neglected. Typically, the governing mechanisms for the transport in microporous membranes are Knudsen-diffusion and Poisseuille flow. Considering transport across the membrane based on Poisseuille flow, gas molecules collide more to each other rather than to the pore walls and this is the case for the membranes having micropores larger than certain size. However, in the case of Knudsen diffusion, which happens in the case of membranes with smaller pore size, the transport occurs as a result of more collision of molecules with the walls than themselves. This is also dependent on the kinetic diameter of molecules and their molecular weight as well. Therefore, the contribution of Knudsen diffusion becomes more remarkable in the membranes having smaller pore size also resulting in reduced gas permeability [108,109]. It also should be noted that convective flow of gas will not play a role in a gas/liquid membrane contactor comprising a microporous membrane, unless the medium is used to produce gas bubbles in the liquid. Practically, to maintain the performance of membrane oxygenators, the pore diameter of the membranes should be less than 1 micrometer to prevent plasma leakage [12]. This can be achieved in practice through proper design, formulation and fabrication of membranes in the course of phase inversion to offer membranes with desirable morphology and microstructures [110]. In combination with the pore size, hydrophobicity of the membrane surface can influences the liquid entry pressure which can be estimated with the aid of Laplace equation [111].

3.2. Plasma leakage

Despite the distinctive advantages offered by the microporous membranes, one of the serious risks associated to them is with regards to plasma leakage so that upon several hours of operation blood plasma could penetrate through the membrane pores. Also called pore wetting, can adversely affect the gas exchange performance of membrane oxygenators due to the formation of additional resistance in pores toward the flow [112]. With these considerations, microporous membrane oxygenators are primarily used for short term surgical applications, whereas non-porous membranes are prescribed for the long-term surgical operations.

Various investigations have been carried out to gain a better understanding of plasma leakage in membrane oxygenators and the possible methods to tackle this issue. In 1992, Montoya et al. [113] discovered that adhesion of bipolar phospholipids present in the blood to the membrane surface results in the formation of a hydrophilic layer which in fact facilitates and accelerates intrusion of plasma into the membrane pores. Another hypothesis posed by Mottaghy et al. [114] who observed condensed vapor within the membrane pores caused by the temperature difference between gas and blood phases which could lead to plasma leakage. Accordingly, they suggested that heating the membrane and gas may lessen the tendency for leakage. Later on, Lund et al. [115] rules out this hypothesis both theoretically and experimentally.

Practically, one of the interim solutions to plasma leakage is frequent replacement of the used membrane oxygenator with a new one during open

heart surgery. However, beside its side effects for the interruptions, it is not considered very handy for long-term applications. One practical concept has been the integration of very thin skin layer on top of the microporous membrane with the notion of providing simultaneous benefits of both high exchange rate as well as reduced plasma leakage [93].

Bubbling is another crucial factor associated to membrane contactors and has often been neglected in membrane oxygenators. In a membrane oxygenator, if the gas pressure exceeds a certain limit, this can lead to bubbling in the blood phase resulting in embolism. Similarly, this can also happen due to sudden pressure drop at the blood side at any point along the fiber length.

Nevertheless, if liquid flows in the shell side of hollow fibers which is the case in membrane oxygenators, pressure drop is not significant. It is worth noting that the critical pressure of bubbling is highly dependent on the characteristics of membrane pores and the surface tension. So that the higher membrane porosity and wettability, the more the chance of bubbling.

Obviously, one strategy to reduce the chance of bubbling is through increasing the pressure at liquid side. However, this may be achieved at the expense of pore wetting. Both pore wetting and bubbling phenomena have negative effects on the membrane performance. Therefore, determination of an optimal pressure requires careful considerations of both membrane and system characteristics [116,117].

Table 2
The characteristics of various oxygenation technologies.

Oxygenator type	Risk of blood trauma	Risk of embolism	Rate of gas exchange	Application	Industrial predominance
Bubble oxygenator	High	High	High	Surgery	No-Limited
Film oxygenator	High	Medium	Medium	Surgery	No-Limited
Membrane oxygenator	Low	Low	High	Surgery / Respiratory failure	Yes

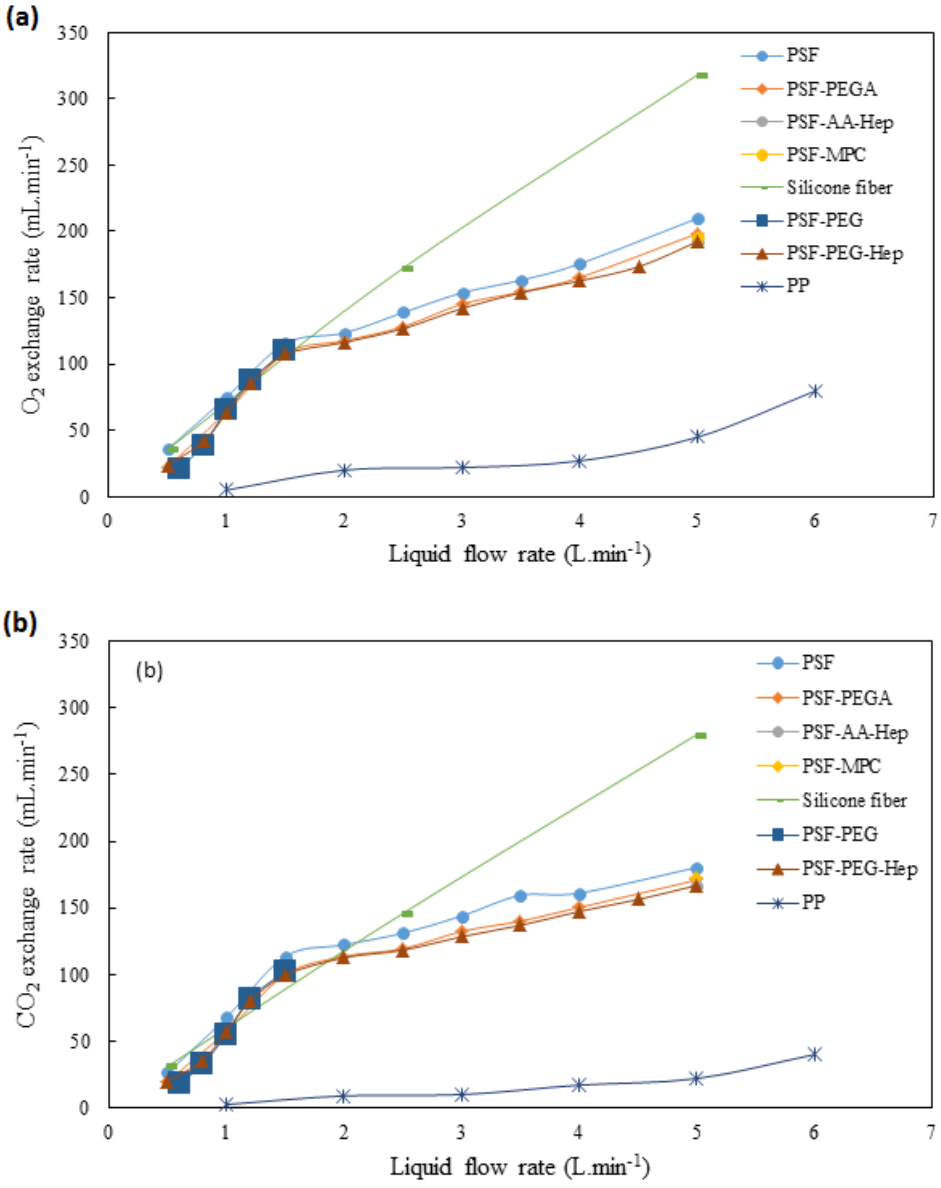


Fig. 3. Gas exchange rate for various materials as a function of liquid flow rate (a) O_2 and (b) CO_2 [102-107].

3.3. Biocompatibility

Biocompatibility is defined as the harmonious interaction between the blood and material without exerting any harmful effect neither on the blood components nor on the material [118,119]. Naturally, if blood is exposed to a synthetic polymer, especially when the contact surface area is large, a number of traumatic events such as hemolysis, immune reaction, and protein adsorption as well as platelet adhesion occur. All these can be traced by the formation of thrombus and also reduction of performance and gas permeability of the membranes [120,121]. For instance, one of the major issues associated to the use of hydrophobic membrane materials is the lack of biocompatibility. Therefore, the use of innocuous biocompatible materials or modification of the existing materials with certain additives or biocompatibilizing agents plays an important role in the progress of materials with desirable characteristics. Details on various aspects of biocompatibility in membrane oxygenators are provided in subsequent sections.

4. Module Configurations

Membrane oxygenator have been offered in various types of module configurations each possessing particular characteristics, performance and efficiency which are discussed in this section.

4.1. Spiral wound

The first blood membrane oxygenation device introduced by Kolff in 1944 was a spiral wound artificial kidney [54]. This module type, later named as *artificial coil lung*, underwent further investigations by other researchers and became more mature [56,122]. Generally, a typical spiral wound module consists of a single leaf comprising of two flat sheet membranes separated by a feed channel spacer as can be seen in Figure 4. To collect permeate flow, membranes are attached to the permeate spacers which is connected to a central tube. In the coil type membrane oxygenators, the blood flows over the surface of the membranes and parallel to the central tube. On the other side, oxygen enters the tube, passes the spiral envelope, then penetrates through the membrane pores and finally enters the blood phase. A spiral membrane oxygenator made by silicone rubber was analyzed by Kolobow et al. [123] and demonstrated a relative success for long-term usage in the range of ~6-7 days. This test was conducted on 18 animals with examination of 42 membranes each for less than 3 days on average. Finally, the first success of this device was announced in 1972 for adults and later in 1975 for newborns [21].

4.2. Plate and frame

Thanks to their simplicity, flat-sheet membranes are often made in laboratory and are used for the purpose of evaluating the performance of new materials. According to the reports, the first plate type membrane oxygenator was introduced by Clowes et al. [66] in 1956 based on Skeggs–Leonards plate dialyzer. This type of oxygenators is still widely employed in the laboratorial research trials. In plate and frame modules, typically two flat sheet membranes are attached together with a spacer in the middle for collecting the permeate fluid. In cross flow plate and frame membrane oxygenators, liquid flows over whereas oxygen flows inside the membranes. Accordingly, oxygen permeates through the membrane while carbon dioxide is released from blood to the gas phase. The schematic of a typical plate and frame membrane oxygenators is presented in Figure 5.

4.3. Hollow fibers

Hollow fibers are the most widely used type of modules for blood oxygenation. Hollow fiber membrane oxygenators were firstly proposed by Bodel et al. in 1963 [124] in which Silistic was employed in the form of cylindrical hollow membranes with the inner diameter of 0.012 inch (~0.3 mm). In this design, oxygen flowed in the lumen side of the membranes while blood flowed in the shell side. Hollow fiber membrane oxygenators bring several benefits in comparison to other oxygenation devices notably the provision of significantly larger surface area per unit volume which contributes to a more efficient gas exchange rate [125-127]. Nevertheless, the surface area provided by hollow fibers is at least 10 times less than that of alveoli of natural lungs and thus there are more rooms for improvement [2].

Hollow fiber membrane oxygenators are classified based on the mechanism of circulation. In the first type, the blood flows in the lumen side and the gas flows in the shell counter-currently. Bentley CM40 and Terumo Capiox Serie 300 fall in this category. The main disadvantage of this type is the risk of thrombosis in capillaries owing to the pressure gradient across the membrane wall which affects the membrane performance. Other disadvantages are occurrence of hemolysis and shear stress [128].

In the second type, as shown in Figure 6, gas flows in the fiber lumens and blood flows in the shell side counter-currently [129] and are more popular with advantages such as less pressure drop and larger surface area. Even so, the shell side should possess biocompatibility characteristics because of being in direct contact with the blood [130, 131].

4.4. Microfluidics

Microfluidics are a type of membrane oxygenator modules in which the membrane thickness and blood flow channels are designed in the miniaturized scale with lumen size in the range of less than 100μm devoted to the transport of gas. Compared to hollow fiber oxygenators, microfluidic modules resemble natural lung in terms of their characteristic features and have benefits over commercial artificial lungs considering their higher surface area to volume (SAV) ratios which provides reduced priming volume and enhanced gas exchange. The microfluidic device developed by Potkay et al. [132] possessed SAV of 800 cm^{-1} which was higher in comparison to the commercial polypropylene hollow fiber membrane oxygenator with SAV of 74 cm^{-1}. Blauvelt et al. [25] compared SAV of different microfluidic oxygenators (ranging from 22 to 1026 cm^{-1}) and some state of the art hollow fiber oxygenators (ranging from 11 to 100 cm^{-1}) which corroborated the superiority of microfluidic oxygenators. Due to the lesser contact of blood with foreign substances in microfluidic modules, the chance of response in blood components is minimized. However, they suffer from some limitations such as the formation of thrombus which can block the flow path due to its tiny diameter [133].

5. Progress in Membrane Material Development

One of the crucial factors in the design and development of any type of membranes is the choice of material [134,135]. Especially considering membrane oxygenators, the membrane from the selected materials should be able to be processes as thin as possible and permeable enough to provide minimal resistance against the gas transport. Furthermore, blood compatibility with no plasma leakage is essential. Obviously, early membranes prepared from available materials did not exhibit good gas exchange performance and mechanical properties and this led to the wide range of investigations for the modification of existing materials or development of new materials with desirable features.

5.1. Pioneer materials

The early experiment on oxygenation of blood was accomplished in a membrane oxygenator made of cellophane. Over the years, other materials such as polyethylene, ethylcellulose, polytetrafluoroethylene (Teflon), polyvinyl chloride, polystyrene, cellulose acetate butyrate, mylar and chlorinate rubber were put into investigation [64,70,95,122,136,137].

However, despite the progress made, most of these materials suffered from drawbacks or limitations in terms of key performance indices for efficient operation. This has attracted many attentions for extensive research activities on tuning and modification of existing materials or synthesis of entirely new materials with enhanced features that can meet the expected requirements.

5.2. Silicones

Aside to the importance of increasing the transport of oxygen to the blood, removal of CO_2 has been trivial especially considering its low partial pressure as the driving force for transport across the membrane. Silicone, as hydrophilic polymer, has demonstrated high gas exchange rate with good CO_2 removal efficiency [138]. In 1963, Kolobow and Bowman [75] and Bodell et al. [124] explored gas exchange performance of silicone rubber and reported some success in partial ECMO [123]. This design due to provision of a non-porous surface is still in use for long-term life support applications.

Silicone elastomer was firstly patented in year 1943 and improved during the century [139]. One of the most popular silicone-based membrane materials is polydimethylsiloxane (PDMS) which is widely used for long-term applications [30,140]. PDMS is a rubbery hydrophobic polymer with a chemical formula of $(C_2H_6OSi)_n$. However, the use of this material is somehow hampered owing to its low mechanical stability and gas selectivity [141]. The results of recent investigations on silicone-based membrane oxygenators are illustrated in Table 3.

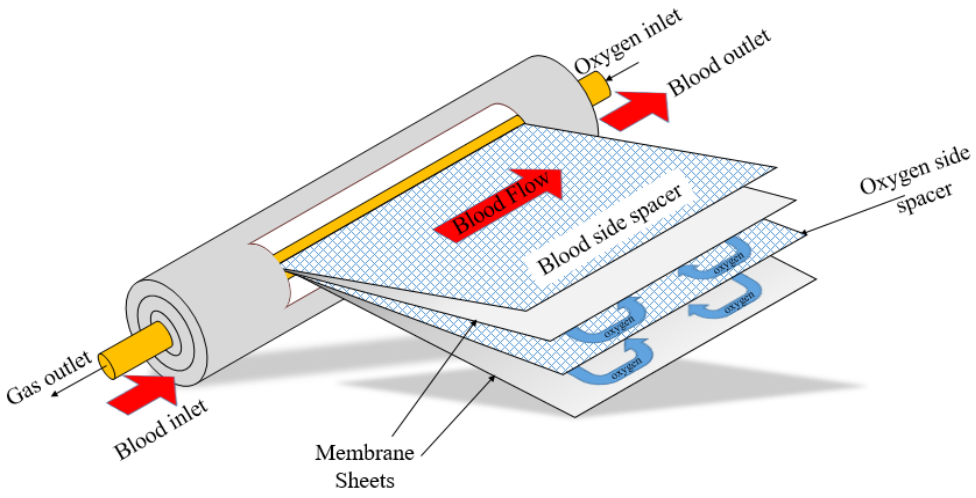


Fig. 4. A schematic of a typical spiral wound membrane oxygenator module and its components.

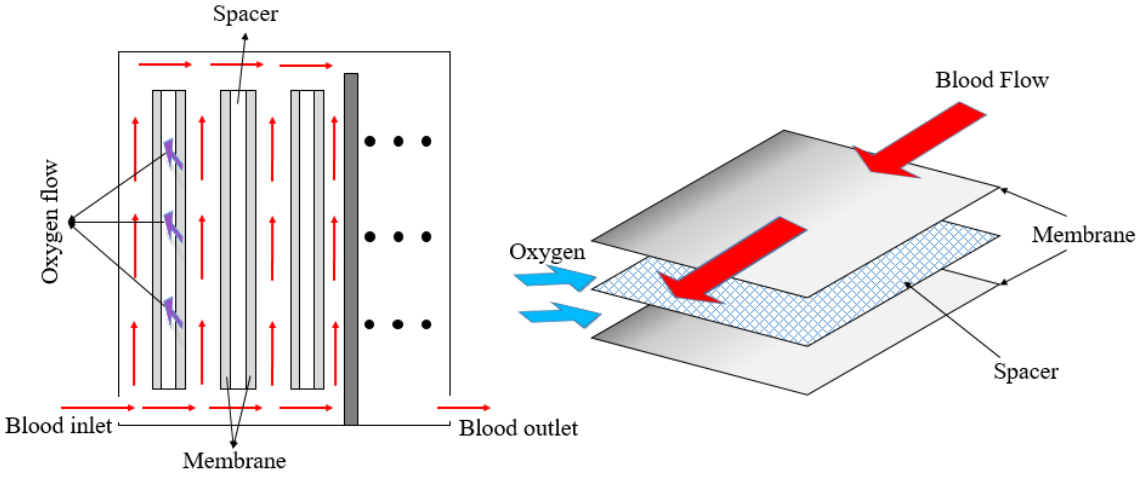


Fig. 5. Schematic illustration of a plate and frame membrane oxygenator module and its components.

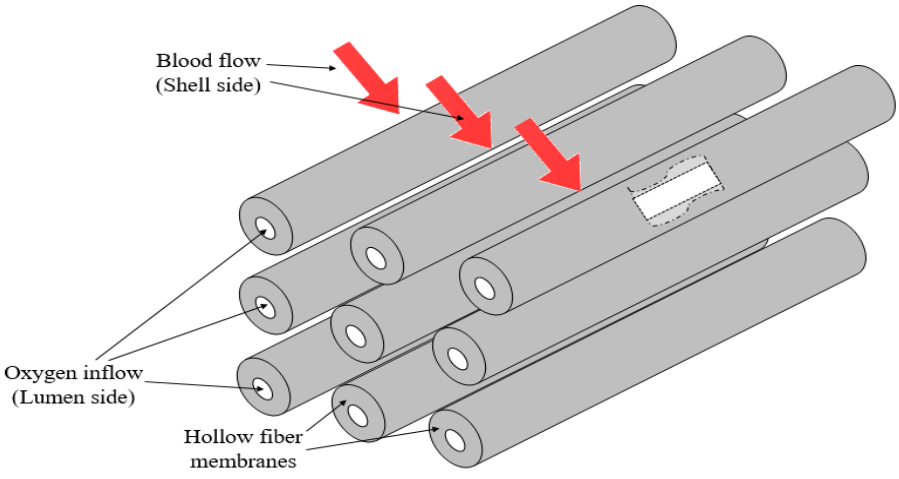


Fig. 6. A schematic representation of a bundle of a shell-side hollow fiber membrane oxygenator.

5.3. Polypropylenes

The origin of polypropylene (PP) with the chemical formula of $(C_3H_6)_n$ dates back to 1954 and is now considered as of the most popular materials for membrane oxygenators. Membrane oxygenators derived from PP offer several benefits such as simple manufacturing, affordability, non-toxicity, provision of high porosity, and chemical stability [142]. However, the hydrophobic nature of PP membranes make their surface susceptible be easily fouled by the blood proteins [143]. Accordingly, surface modification of PP membranes has been recommended to minimize the risks associated to fouling. Also, to prevent plasma leakage, the pores of PP membranes have been tuned to 0.02 micron through which blood penetration is prevented by surface tension forces [144].

5.4. Polymethylpentenes

Poly 4-methyl-1-pentene (PMP) is a biomaterial with good thermal and mechanical stability which has been examined as a high potential candidate for fabrication of membrane oxygenators. Thanks to the possibility of formation of a thin dense skin layer, PMP is found to be extremely resistant to plasma leakage while being highly gas permeable and recommended for long-term applications [145-147]. Asymmetric PMP membranes with dense skin layer can be fabricated by different methods such as thermal induced phase separation [148] and melt spinning-cold stretching [149].

5.5. Polyimides

Aromatic polyimides are high performance polymers with good thermal stability, high glass transition temperature and a low dielectric constant. These materials have been used in a vast variety of applications like as semiconductor devices, high-temperature adhesives and high performance composite membranes [150]. Membrane oxygenators made of fluorinated polyimides are not only biocompatible but exhibit attractive features of suppressing plasma protein adsorption, platelet adhesion, neutrophil adhesion and complement activation all together [151]. Matrimid is a glassy polyimide and widely used in gas separation studies due to its high permeability and selectivity [152,153]. Moreover, Matrimid possesses other favorable properties such as high thermal ability and solvent resistance [154]. On the basis of these characteristics, Khosravifard et al. [109] explored its potentials for membrane oxygenator applications and could improve the biocompatibility and gas permeation of Matrimid with the help of plasma modification.

5.6. Polyurethanes

Polyurethanes possess distinguished characteristics which has turned them very attractive for various applications. Different forms of polyurethanes such as polyether, polyester and polycarbonate based polyurethanes can be synthesized which have attracted attention due to their potential to be made biocompatible [155]. In a few studies, Faria et al. [156-159] investigated the performance of dense polyurethanes for membrane oxygenator applications. In one study, they synthesized polyester urethane urea (PEUU) with polycaprolactone (PCL) and showed the good biocompatibility of the membrane [156]. In another attempt, poly (urethane urea) bi-soft segment dense membranes using poly (propylene oxide) and PCL were prepared with increased CO_2 permeability [157]. They also fabricated an asymmetric PEUU membrane with dense surface layer for experimental analysis and applied modeling techniques to predict the gas exchange to the liquid phase [158]. All the synthesized membranes demonstrated high potentials for long-term operations. However, their use for short-term applications is yet debatable considering their low gas exchange rate.

5.7. Polysulfones

Polysulfones (PSF) have been in use for various medical applications such as hemodialysis and are considered among the relatively newer generations of materials extensively examined for membrane oxygenators [160,161]. This material has excellent properties including simple manufacturing process, reasonable cost, and good chemical, thermal and mechanical stability [162-164]. Despite these attractive features, its biocompatibility needs improvements to make it more suitable for membrane oxygenation applications [165]. Wang et al. [102] investigated the effect of grafting polyethylene glycol acrylate onto the surface of a PSF membrane. Their results showed the high capability of modified PSF for short-term applications. Efforts on the preparation of a biocompatible PSF membrane with high gas exchange rate were continued through modifications with polyethylene glycol and heparin [103,104]. In another study, Zheng et al. [105] fabricated hollow fiber PSF membranes modified by collagen and acrylic acid. The outcome of all these studies proved the high gas exchange and biocompatibility of modified PSF membranes as a perfect candidate for oxygenation applications.

5.8. Polyethersulfones

Similar to PSFs, polyethersulfones (PES) with excellent thermal, chemical and mechanical properties have regularly been used for various applications. This material also has other characteristics such as high glass transition temperature, and ability to be fabricated in different pore sizes. Nonetheless, the contact of membrane with blood can result in protein adsorption due to its weak antifouling properties [166,167]. The properties of PES could be tailored using appropriate modification techniques. Among the latest studies, Mostafavi and Hosseini [168] examined the capability of PES in membrane oxygenator applications. They successfully demonstrated fabrication of a high permeable membrane from PES which could easily become biocompatible through incorporation of TiO_2 nanoparticles or polyethylene glycol surface grafting imposed by plasma. The findings also suggested high potentials of PES as viable candidate for further explorations for such applications.

5.9. Considerations for material selection

Based on the analysis of various materials, important factors must be taken into consideration when selecting a polymeric material to be used for development of a high performance membrane oxygenator. Essentially, it is highly desirable for the material to be fully or even partially biocompatible. If not, it must be able to be made biocompatible through appropriate modification of functionalization methods. Since the process of tailoring is carried out on the membrane surface and subsequently affects the surface topography and functionalities, extra care must be taken on the extent of changes in the gas exchange properties.

PMP, polyurethane and silicone derivatives are among the popular polymers developed in asymmetric structure having a skin dense layer on top. The mechanism of gas transport in these membranes is mainly governed by the characteristics of the skin layer. According to the solution-diffusion mechanism, not only the interstitial spaces between the polymer chains (also known as d-spacing) and the kinetic diameter of gases control the diffusivity of the gas molecules, but also the affinity of each gas to the membrane material as well as their relative condensability have significant contribution in the overall transport. For instance, the presence of polar moieties in the repeating unit of the polymer is known to enhance the solubility of the polar gases. TPX, which is a type of PMP, has a non-polar structure due to the low cohesive energy density and this promotes higher solubility of oxygen and carbon dioxide as non-polar gases.

Another factor to be taken into consideration is the crystallinity of polymer. Since the permeability is accomplished through the amorphous sites, crystallites create impermeable sites in the membrane matrix [200]. On this basis, polymers such as TPX, PDMS and PU are among most widely used polymers for this purpose owing to their semi-crystalline structures.

Polymer chain mobility is another factor that that can greatly influence the gas exchange rate through the membrane. In fact, rubbery polymers such as silicone rubber are typically more permeable than glassy ones. Unlike the situation in the case of asymmetric membranes having dense skin layer, permeability in microporous membranes less dependent on the type and other mechanisms prevail in transport. Thus, in the case of microporous membranes, the method of fabrication and the ability and the rooms for controlling the internal microstructure are of prime importance. However, the influence of material type on the biocompatibility of microporous membranes cannot be underestimated. Common industrial microporous membrane oxygenators have been made of hydrophobic PP while this trend has changed in recent years, at least in lab-made studies, and more hydrophilic materials including PSF and PES have gained popularity. Nevertheless, the pore wetting phenomena which is associated to the hydrophilicity must be well controlled.

6. Methods of Membrane Fabrication

Since the emergence of wide ranges of membrane applications, several fabrication methods have been devised to address the needs for fabrication of various types of membranes [201]. Generally, membrane fabrication can be accomplished in few ways: non-solvent induced phase separation (NIPS), thermal induced phase separation (TIPS), vapor induced phase separation (VIPS), evaporation induced phase separation (EIPS), phase separation

micromolding (PSμM), electro spinning, track etching, sintering, imprinting/soft molding, manual punching and 3D printing [202-204].

Accordingly, different fabrication methods have been employed in the case of membrane oxygenators. Porous membranes can easily be fabricated by NIPS and has been widely used to produce asymmetric porous membranes from soluble polymers such as PES, PSF, and PI [195,205]. In this method, different parameters such as bath temperature, polymer material, solvent type, non-solvent, additives, and their concentration impress the resultant membrane characteristics (Table 4) [206,207]. The lab scale NIPS process involves preparation of a dope solution by dissolving the polymer in a solvent followed by casting in the case of flat sheet membranes. Then, the cast film is immersed in the coagulation bath containing a non-solvent and which results in phase separation into polymer rich and lean phases. In some cases, to make the surface denser, the polymeric film is exposed to air for a short period of time largely dependent to the characteristics and ingredients of the solution, before immersion into the coagulation bath. For the fabrication of hollow fiber membrane oxygenators according to phase inversion method, both dope solution and non-solvent flow concurrently through concentric nozzles within the spinneret in which the former creates the membrane walls and the latter forms the lumen channel. Similar to the casting of flat sheet membranes, the shaped dope solution exiting the spinneret is transferred to an external non-solvent coagulation bath. The inner and outer diameters of the hollow fiber depend on the spinneret geometries as well as the spinning process parameters. To ascertain desired morphology, appropriate concentrations of polymer, solvent and non-solvent in the dope solution must be selected. This is often accomplished with the aid of ternary phase diagrams [208-211].

Table 3
The characteristics and status of various materials and modules used in membrane oxygenators.

Year	Material	Thickness (μm)	Module type	Membrane structure	Surface area (m^2)	Priming volume (mL)	Manufacturing scale	Ref.
1989	PP	- -	Flat sheet Hollow Fiber	Porous	2.3 4	-	Commercial	[128]
1992	Silicone	100	Hollow Fiber	Non-porous	0.5 0.8	35 50	Commercial	[169]
1994	PMP	30-40	Flat sheet	Non-porous	-	-	Laboratory	[170]
1995	PP	-	Hollow Fiber	Porous	0.8	500	Commercial	[171]
1996	PI	-	Flat sheet	Porous	10^{-4}	-	Laboratory	[172]
1996	Silicone	50	Hollow Fiber	Non-porous	2	230	Laboratory	[173]
1998	Silicone	50	Hollow Fiber	Non-porous	1 1.1	208 209	Laboratory	[174]
2000	PP	60	Hollow Fiber	Porous	-	-	Commercial	[175]
2000	Silicone	50	Hollow Fiber	Non-porous	0.8	140	Laboratory	[176]
2001	PI	50	Hollow Fiber	Porous	-	-	Laboratory	[177]
2002	Silicone	50	Hollow Fiber	Non-porous	0.8 1	140 200	Laboratory	[178]
2002	PI	50	Flat sheet	Porous	-	-	Laboratory	[151]
2002	PMP	-	Hollow Fiber	Non-porous	-	-	Commercial	[145]
2002	PE	27	Flat sheet	Porous	0.019	-	Commercial	[179]
2003	PI	70	Hollow Fiber	Porous	0.03	-	Laboratory	[180]
2003	Silicone	35	Hollow Fiber	Non-porous	1	220	Commercial	[181]
2004	PI	74	Hollow Fiber	Porous	0.6	95	Laboratory	[182]
2005	PMP	-	Hollow Fiber	Non-porous	0.31	55	Commercial	[183]
2005	PMP	-	Hollow Fiber	Non-porous	1.3	120	NA	[146]
2006	PMP	-	Hollow Fiber	Non-porous	0.67	90	Commercial	[184]
2007	PP	60	Hollow Fiber	Porous	0.17	-	Commercial	[185]
2008	PMP	-	Hollow Fiber	Non-porous	1.8	250	Commercial	[186]
2009	Silicone	50	Hollow Fiber	Non-porous	0.45	50	Laboratory	[187]
2010	PMP	180	Hollow Fiber	Non-porous	-	-	Commercial	[121]
2011	PEUU	40-65	Flat sheet	Non-porous	-	-	Laboratory	[156]
2012	PMP	180	Hollow Fiber	Non-porous	-	-	Commercial	[188]
2012	Silicone	11-117	Microfluidic	Non-porous	-	-	Laboratory	[189]
2013	PMP	-	Hollow Fiber	Non-porous	1.35	190	Commercial	[190]
2013	Silicone	110 90 75 100 50	Hollow Fiber	Non-porous	0.0203 0.0200 0.0197 0.0208 0.0204	4.72 4.40 1.74 5.70 1.87	Laboratory	[191]
2014	PP	50	Hollow Fiber	Porous	-	-	Commercial	[192]
2014	Silicone	20	Microfluidic	Non-porous	0.0153	4.8	Laboratory	[193]
2014	PP	100	Hollow Fiber	Porous	-	-	-	[194]
2015	PI	-	Flat sheet	Porous	-	-	Lab-made	[195]

Table 3 (Continued)

2015	PSF	80	Flat sheet	Porous	0.0064	-	Lab-made	[102]
2016	PP	-	Hollow Fiber	Porous	-	-	commercial	[196]
2016	PMP	150	Hollow Fiber	Non-porous	0.005	-	commercial	[197]
2016	PSF	80	Flat sheet	Porous	0.0064	-	Lab-made	[104]
2016	PSF	150	Flat sheet	Porous	0.0064	-	Lab-made	[103]
2016	PUU	300-450	Flat sheet	Non-porous	0.0028	-	Lab-made	[157]
2017	Silicone	66	Microfluidic	Non-porous	0.66	0.0027	Lab-made	[198]
2018	Silicone	50	Microfluidic	Non-porous	0.0222	10	Lab-made	[133]
2018	PSF	200	Hollow Fiber	Porous	0.005	-	Lab-made	[105]
2018	Silicone	-	Hollow Fiber	Non-porous	-	215	Lab-made	[107]
2018	Silicone	3-5	Parallel Plate	Non-porous	0.0006	-	Lab-made	[199]
2018	PU	-	Flat sheet	Non-porous	0.006	-	Lab-made	[158]
2019	Matrimid	-	Flat sheet	Porous	-	-	Lab-made	[109]
2020	PES	130	Flat sheet	Porous	-	-	Lab-made	[168]

Table 4
Parameters and the characteristics of membrane oxygenators fabricated using non- solvent induced phase separation process.

Membrane material	Solvent	Non-solvent	Polymer conc. (%)	Porosity (%)	Thickness (µm)	Pore size (nm)	Ref.
PES	NMP	water	17	74	130	-	[168]
Matrimid	NMP-THF	Water-EtOH	15-20	-	-	210-378	[109]
PSF	DMAc	water	-	60	200	100	[105]
PSF	-	-	-	60	80	-	[104]
PSF	DMAc	water	15	60	80	100	[102]
PI	NMP	air	10	-	-	-	[195]
PI	MC-TCE-Butanol	methanol	17-20	-	74	-	[182]
PI	MC-TCE-Butanol	methanol	12	-	70 70 70	0.85 2.7 6.8	[180]

Another method for fabrication of membrane oxygenators is melt-spinning cold-stretching (MSCS) which is dedicated to non-soluble and high crystalline polymers such as polypropylene, polyethylene, etc. [212]. This process also enables formation of microporous membranes by which the polymer is firstly heated beyond its melting point and then extruded through a die to form a thin film in the case of flat sheets. If hollow fiber membrane is intended, the melt is extruded and spun through a hollow spinneret. Then the annealing process begins with the aid of air or water to shape the internal microstructure. The process is governed with the aid of different parameters such as crystallinity, melting point and tensile strength. According to a study by Liu et al. [213], the longer the annealing time, the higher would be the flux and permeability of the resultant membrane.

Another procedure for the fabrication of membranes from hardly soluble polymer is TIPS which has been in use for production of commercial PP and PMP membrane oxygenators such as Oxiphan™ and Oxiplus™. In this method, a low molecular weight diluent is required with a high boiling point to be mixed with the solvent. The temperature should then rises about 25-100 °C more than the melting point of the polymer while still being lower than the boiling point of the solvent. The solution is then extruded with the aid of a spinneret to shape the ultimate hollow fiber membrane. Afterwards, the temperature falls steadily below the dissolution temperature in order to enable phase transition. Different parameters such as polymer concentration, viscosity and solvent properties can affect the final geometry and microstructure of the membrane [214].

7. Progress in Tailoring of Membrane Characteristics

Although a diverse range of materials has been explored for membrane oxygenators, so far none of them completely meets the ideal characteristic requirements envisioned for this application. Thus, various strategies and modification techniques have been employed to improve the characteristics including grafting through common plasma treatment [215], low temperature plasma treatment [105], irradiation [216], surface chemical reaction [103], incorporation of additives and nanoparticles [168], use of non-solvent and solvent additives [109], and coating [188]. These modifications have been examined on the prevailing materials and the progresses made for each characteristic and its effect on the overall membrane properties and performance are elaborated in this section. Table 5 provides an overview of various membrane materials and modification methods used in this respect.

7.1. Biocompatibility

Biocompatibility in membrane oxygenators is important to prevent or to minimize the protein adsorption onto the membrane surface. This can be accomplished through four methods described as follows [220]:

Introduction of negatively charged surface groups: This method is based on the fact that blood proteins and cells often carry the net negative charge. Therefore, to avoid their adsorption, the membrane surface can be tuned through introduction of negatively charged groups to enable repelling forces. Anionic surfactants such as sodium di-2-ethylhexyl sulfosuccinate are viable candidates for this purpose [221].

Introduction of hydrophilic agents: This method involves introduction of a hydrophilic agent to the membrane surface through molecular grafting, coating, plasma treatment, chemical modification, photochemical modification and UV irradiation. It has been demonstrated that all these

techniques can effectively diminish protein adsorption [222]. This is accomplished through formation of a very thin protein layer on the outermost surface of the membrane which prevents subsequent adsorptions by blood components. Furthermore, upon addition of hydrophilic agents to the dope solution the overall contact angle of the membrane is also reduced. Another successful method has been the introduction of hydrophilic additives such as TiO_2 nanoparticles into the dope solution since they can migrate to the membrane surface during the phase inversion process due to their high tendency to a hydrophilic non-solvent such as water. It is shown that accumulation of nanoparticles on the membrane surface significantly improved the hydrophilicity of the membrane while simultaneously reduced protein adsorption [223].

Table 5
A summary of materials and modification techniques used for improvement of the characteristics of membrane oxygenators.

Membrane material	Modification technique	Modification agent(s)	Ref.
PES	Mixed matrix membranes	TiO_2	[168]
PES	Grafting through O_2 plasma treatment	PEG	[168]
Matrimid	Grafting through CF4 plasma treatment	Fluorine	[109]
PSF	Grafting through argon LTPT	AA[1]-Heparin MPC[2] Collagen	[105]
TPX[3]	Grafting through O_2 plasma treatment	MeOEGMA[4] HEMA[5] HPMA[6] PCMA[7] SBMA[8] CBMAA[9]	[217]
PSF	Grafting by chemical agent(PDA[10])	NMEG5[11]	[218]
PSF	Grafting by chemical reaction(chloromethyl)	PEG-Heparin	[103]
PSF	Grafting through O_2, CO_2 and Ar plasma treatment	PEG-Heparin	[104]
PMP	Grafting through O_2 and N_2 plasma treatment	MPC Heparin	[197]
PP	Coating	PMBT[12] zwtterionic copolymer	[196]
PSF	Grafting through argon LTPT	PEGA	[102]
PP	Coating	PMB[13] copolymer PMBT copolymer	[192]
PP	Grafting through H_2 and O_2 plasma treatment	PEG	[144]
PMP	Grafting through water plasma treatment	CA	[188]
PP	Grafting through NH_3 plasma treatment	PELG[14] PSLG[15]	[219]
PP	Grafting through γ-rays irradiation	EPMA[16]	[216]

[1] Acrylic acid
[2] 2-methacryloyloxyethyl phosphorylcholine
[3] poly(4-methyl-1-pentene)
[4] oligo(ethylene glycol) methyl ether methacrylate
[5] 2-hydroxyethyl methacrylate
[6] N-(2-hydroxypropyl) methacrylamide
[7] 2-(methacryloyloxy) ethyl phosphorylcholine
[8] N-(3-sulfopropyl)-N-methacroyloxyethyl-N,N-dimethylammonium betaine
[9] (3-methacryloylamino-propyl)-(2-carboxy-ethyl) dimethylammonium carboxybetaine methacrylamide
[10] polydopamine
[11] 5-mer 2-methoxyethyl
[12] poly(MPC-co-BMA-co-TSMA)
[13] poly(MPC-co-BMA)
[14] poly(γ-ethyl L-glutamate)
[15] poly(γ-stearyl L-glutamate)
[16] 2,3-epoxypropyl methacrylate

Imposing steric hindrance: In this method, a hydrophilic polymer with long chains and high surface density like PEO is attached to the membrane forming a hydrophilic "brush" which reduces the chance for proteins to come in close proximity of the membrane surface. Several investigations have performed on the characteristics and effects of attachment of PEO to the membrane surface all demonstrating the effectiveness of this approach [224-227].

Biomimetic modifications: This is an efficient method for improving the membrane biocompatibility and has been widely utilized in development of other artificial organs [22]. In this method, a phospholipid membrane such as MPC which imitates the red blood cell membrane is introduced to the surface of the synthesized membrane. This phospholipid conserves the membrane from protein adsorption and platelet adhesion due to its unique intrinsically biocompatible nature [145].

Table 6 shows the biocompatibility status of various membrane materials and the achievements in improving their characteristics by modification.

Platelet adhesion is another major factor that should be minimized to avoid functional problems in membrane oxygenators. One solution is through systemic heparinization which was first introduced by Jay McLean in 1916 [44]. Although it has been used in ECMO for whom undergo cardiac surgery, heparinization may be followed by a high risk of bleeding in patients [229]. Thus, total heparinization cannot help to reduce adsorption of proteins such as fibrinogen or von Willebrand factor which is the protein used for anti-bleeding [230]. Number of investigations has been carried out to tackle this problem by grafting heparin to the membrane surface [103-105]. Urokinase is also another enzyme used to break down fibrin (a protein that causes clot formation) and to dissociate thrombi [216].

Figure 7 compares the effect of application of different modification agents on membrane biocompatibility. As can be seen, the decrease in the extent of protein adsorption and platelet adhesion follows a similar trend for different modification techniques whereas coagulation time has significantly increased by incorporation of heparin and MPC. Moreover, it can be found from the collected data in Table 7 and Figure 7 that most of studies concentrated on the introduction of PEG to the membrane surface while only a few studies were devoted to other modification agents. This can be regarded as an opportunity for future research in this field by exploring other agents and may lead to notable discoveries.

For determination of the degree of protein adsorption, typically membrane samples are immersed in a solution of protein in phosphate buffered saline (PBS). After a certain period, the membrane is removed from the solution after which the amount of adsorbed protein on the membrane surface can be determined using BCA assay kit with the aid of UV–visible spectrophotometry [102]. On the other hand, to determine the degree of platelet adhesion, platelet-rich plasma (PRP) with the concentration of 5×10^5 count.ml^{-1} is poured onto the surface of the membrane under examination. Then, the membrane is immersed in the solution of glutaraldehyde in PBS in order to immobilize blood components. In the next step, dehydration of samples in ethanol/water solutions having different compositions should be accomplished. Finally, number of platelets can be measured using SEM analysis [231-234]. For determination of the coagulation time, membranes are placed in the blood treated by normal saline and incubated, and then citrate is added. The coagulation time can be evaluated by activated partial thromboplastin time (APTT) and prothrombin time (PT) obtained by a semi-automated coagulometer .

7.2. Surface roughness

Membrane surface roughness is one of the effective factors that can largely determine membrane characteristics and performance. According to the modified Young's equation, membrane roughness directly affects the membrane hydrophilicity and contact angle [235]. Accordingly, increasing the hydrophilicity of membrane oxygenators can reduce protein adsorption and platelet adhesion at the membrane surface; also giving rise to an enhanced biocompatibility and reduced fouling [109,156]. The popular methods for tailoring membrane roughness are grafting by plasma treatment and UV irradiation, both enhancing surface roughness.

The effect of use of hydrophilic additives in dope solution on the membrane roughness relies on its contribution in the course of membrane formation [168]. In fact, the presence of hydrophilic additives accelerates the inflow rate of non-solvent (e.g., water) during the phase inversion process. Accordingly, demixing and crystallization rates are enhanced resulting in creation of a more rough membrane surface [236-240]. However, if the hydrophilic additives are not miscible with the coagulating agent (e.g., nanoparticles), the chance of blockage of surface pores by the additives is increased which creates a more smooth surface [99]. Also, use of hydrophobic

additives causes delayed demixing and consequently surface roughness is declined [241]. In many studies membrane roughness has been examined with the aid of atomic force microscopy (AFM) [242]. Membrane surface porosity and surface pore size also can be determined by this method [243].

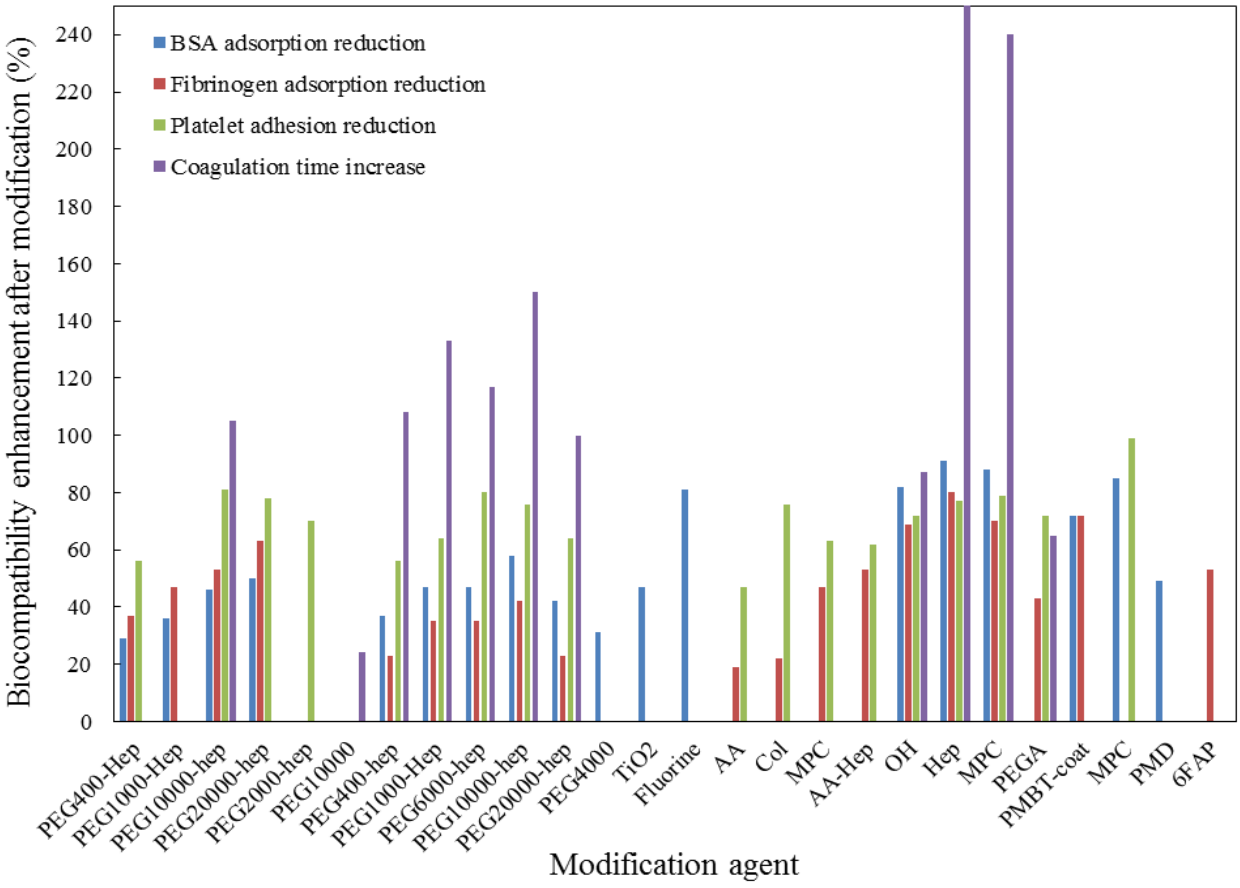


Fig.7. The effectiveness of various modification agents in improving the biocompatibility of membrane materials [102-105,109,168,179,192,197].

Table 6
Biocompatibility status of various membrane materials and the achievements in improving their characteristics by modification.

Membrane material (s)	Additive concentration	BSA adsorption reduction	Fibrinogen adsorption reduction	Platelet adhesion reduction	Coagulation time (APTT) enhancement	Ref.
PES/TiO_2	0.25% 0.5%	30% 47%	-	-	-	[168]
PES-PEG	GD=1.4%	31%	-	-	-	[168]
Matrimid-F	-	81%	-	-	-	[109]
PSF-AA-Hep	-	-	53%	75%	-	[105]
PSF-MPC	-	-	47%	63%	-	[105]
PSF-Col	-	-	22%	62%	-	[105]
PSF-PEG-Hep	-	46%	53%	81%	105%	[103]
PSF-PEG-Hep	GD=2%	47%	46%	76%	105%	[104]
PMP-OH	-	82%	69%	72%	87%	[197]
PMP-Hep	-	91%	80%	77%	430%	[197]
PMP-MPC	-	88%	70%	79%	240%	[197]
PSF-PEGA	GD=6.7%	-	43%	72%	65%	[102]
PP-PMBT	1.0 mg mL^{-1}	72%	72%	-	-	[192]
PES/CA-PU	8wt%	79%	95%	>99%	≈200%	[223]
PP-PVP	GD=1.49%	29%	-	69%	-	[228]
PSF/MPC	10 wt%	85%	-	99%	-	[220]
PE-PMD	-	49%	-	-	-	[179]
6FDA–6FAP	-	-	53%	-	-	[177]

7.3. Porosity and pore size

Membrane porosity and pore size also play crucial roles in the performance of membrane oxygenators. Higher porosity and pore size are favorable for membrane permeability. Typically, adding hydrophilic additives can increase membrane porosity thanks to the faster demixing during the phase separation process while adding hydrophobic additives and non-solvents generally contribute to delayed demixing and consequently reduced porosity [244, 245]. Nevertheless, the influence of addition of some materials on the viscosity increment should not be ignored. For example, adding bath-immiscible additives, including solid or viscous liquids, can increase solution viscosity and reduce membrane porosity. Surface porosity and pore size can also be affected by membrane roughness. As outlined earlier, the surface pore size and porosity of membranes can be obtained by AFM, SEM or gas permeability measurements. The overall porosity of the membrane is often evaluated by displacement techniques.

7.4. Contact angle

In addition to the inherent material characteristics, contact angle depends on various physical properties of the membrane as pore size, surface roughness and porosity. Essentially, decrease in contact angle which is equivalent to increase in hydrophilicity in membrane oxygenators has improving effects on its biocompatibility features. This is why modification of the surface to increase hydrophilicity is of prime importance in the case of membrane oxygenators. There are several methods for hydrophilicity enhancement among which grafting hydrophilic agents to the surface and incorporation of additives to the dope solution are most widely used. Upon grafting, a very thin hydrophilic layer is formed on the membrane surface which contributed to the reduced contact angle. It is worth mentioned that grafting is often accomplished by plasma treatment in which operational conditions and parameters can play roles [246]. In addition, the presence of additives such as hydrophilic polymers and hydrophilic nanoparticles in the dope solution has shown great effects in the hydrophilicity enhancement of membrane oxygenators. During the phase separation process, due to the high affinity of hydrophilic additives to water, they migrate to the interface and decrease the interfacial energy and contact angle of the membranes [247,248].

Figure 8 demonstrates a general trend of variation in contact angle of different membrane oxygenators before and after modification. In fact, the points located lower the reference line belongs to the materials in which contact angle has been reduced after modification. It can be noted that, almost in all cases, the membrane hydrophilicity increased by different extents, showing the high potentials of this method for improving hydrophilicity features.

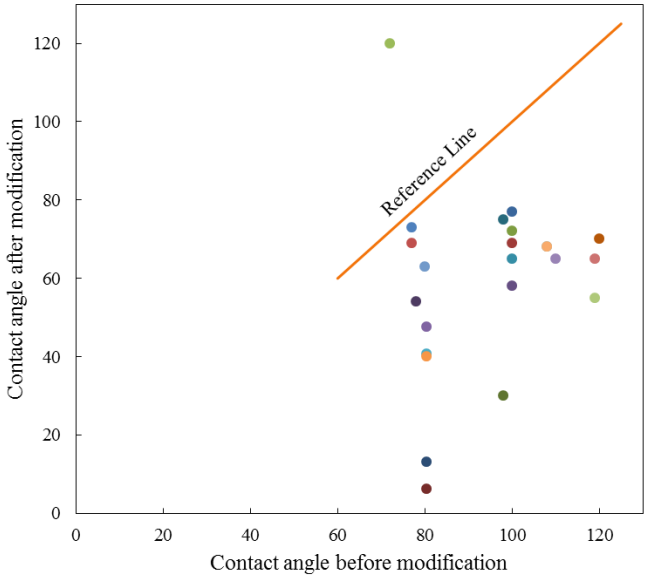


Fig. 8. Contact angle of membranes before and after different modifications [102,104,109,144,168,192,196, 216-219].

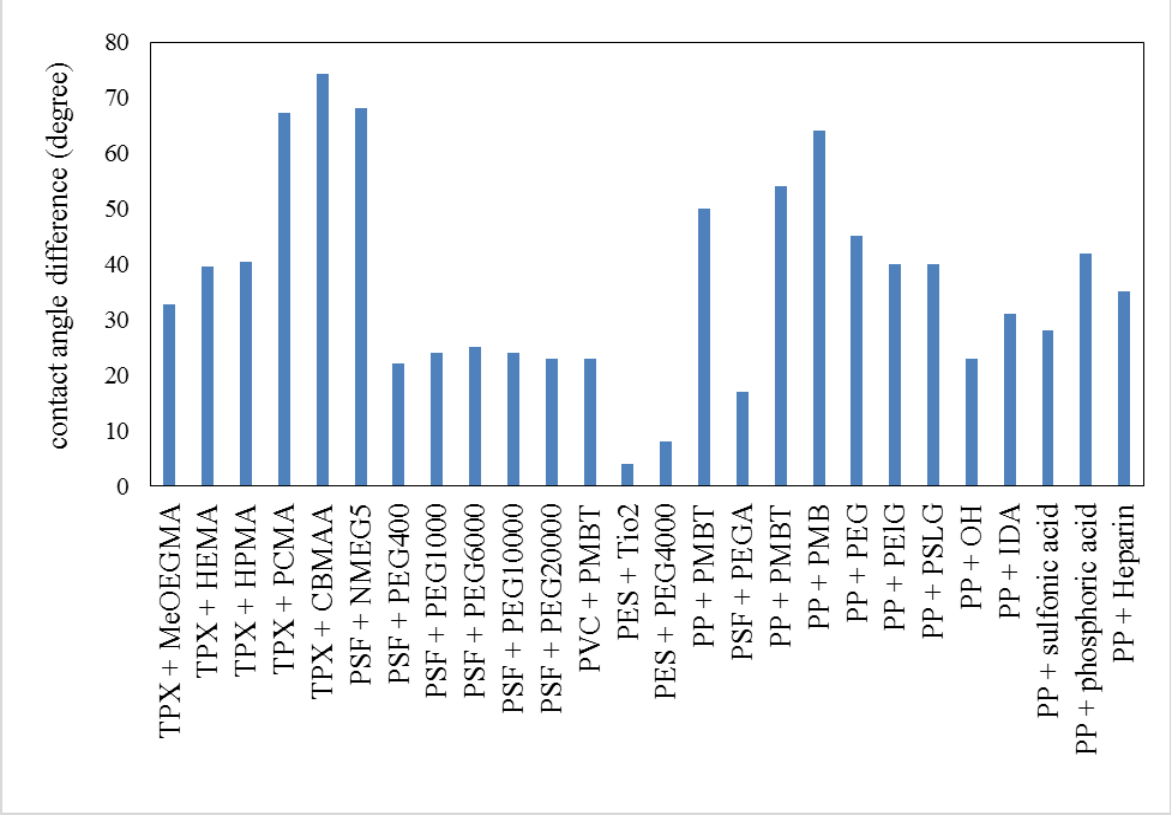


Fig. 9. The net difference in contact angle of membranes before and after modification for diverse materials [102,104,109,144,168,192,196,216-219].

Also, Figure 9 also shows the net difference in contact angle of membranes before and after modification. It can be noted that in general, application of modification techniques has been more effective in reducing the contact angle of PSF membranes than PP which stems from the their inherent properties. Different ways to determine the membrane contact angle are described elsewhere [249]. Among them, the sessile drop is more practiced for membranes in which a drop of DI water is placed onto the surface of the membranes with a syringe and the contact angle is measured using a goniometer.

7.5. Permeability and gas exchange

Depending on the membrane modification technique, the permeability and gas exchange properties of membranes can undergo distinctive changes. The main goal for modification of membrane oxygenators is to increase membrane biocompatibility which is often accomplished at the expense of reduction in gas transfer rate. Figure 10 clearly demonstrate how O_2 exchange rate has been affected considerably upon modification. In dense membranes, the rate of transport of oxygen through the membrane decreases due to the non-polar properties of oxygen molecules [250]. However, since the majority of commercial membrane oxygenators are microporous, the rate of gas transfer to the blood still remains in the reasonable range. In modifications by grafting, the decrease in the permeability may be noticed due to the formation of the grafting layer at the membrane surface. Moreover, enhancement of the membrane hydrophilicity can increase the probability of pore wetting. It has been demonstrated that pore wetting or plasma leakage phenomena to negatively affect gas flux and membrane performance [251-253].

From another point of view, the trend of changes in O_2 permeability and reduction in protein adsorption is illustrated in Figure 11. As it can be observed, in the cases of PSF and PES, modification led up to about 55% reduction in protein adsorption at the expense of about 10% reduction in O_2 permeability. In contrast, modification of PMP and Matrimid simultaneous improvements in both membrane permeability and protein adsorptions were achieved.

To measure the permeability of the neat and modified membranes, two different modes including constant-pressure/variable-volume and constant-volume/variable-pressure are often employed. In the first mode shown in Figure 12(a), gas flows over the membrane surface and permeates through the membrane on account of the pressure difference gradient between the two sides while the pressure of the downstream is kept atmospheric. The volumetric flow rate of gas in the downstream is measured when the steady state condition is reached. The second mode is more suitable for dense and less permeable membranes in which vacuum is applied in the downstream to enhance the driving force (Figure 12(b)). A pressure transducer is used for monitoring the rate of pressure increase in the downstream in the course of gas permeation. Table 7 provides the permeability data for the various membrane oxygenators made from different materials. Also, Figure 13 shows the typical values for the O_2 and CO_2 permeability of various neat and modified membrane oxygenators. Considering the reference line that corresponds to the identical permeability of the gases, it is evident that O_2 permeability in membranes is in overall higher than CO_2 permeability.

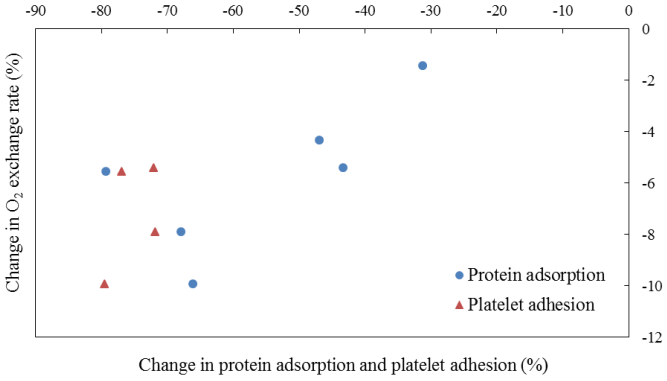


Fig. 10. The changes in O_2 exchange rate and protein adsorption and platelet adhesion of membranes upon modification [102,168,197].

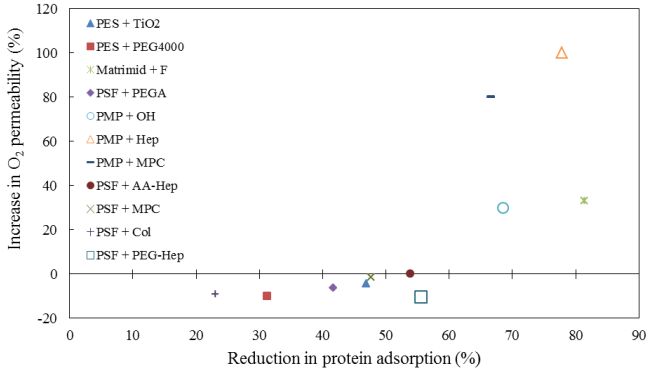


Fig. 11. The permeability change after undertaking modifications as a function of protein adsorption reduction [102,103,105,109,168,197].

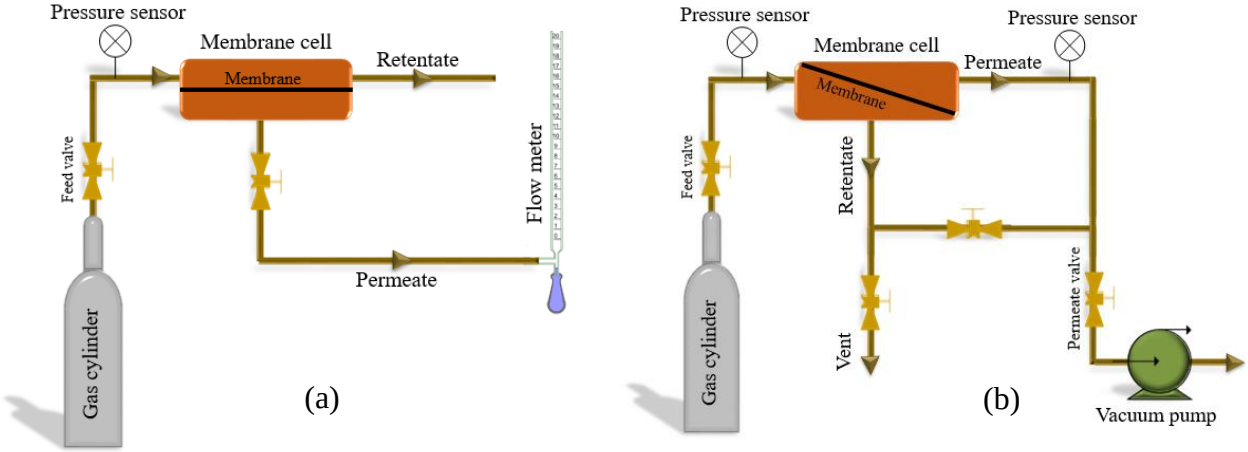


Fig. 12. Schematics of permeability measurement set-ups (a) constant-pressure/variable-volume (b) constant-volume/variable-pressure modes.

Table 7
The permeability values for diverse ranges of materials used in membrane oxygenators.

Membrane material	Gas	Upstream pressure (bar)	Measurement mode	Permeability	Ref.
PES	O_2	1	Constant-pressure/	884 GPU	[168]
		2	Variable-volume	941 GPU	
		3		988 GPU	
PES/TiO_2	O_2	1	Constant-pressure/	820 GPU	[168]
		2	Variable-volume	889 GPU	
		3		947 GPU	
PES-PEG	O_2	1	Constant-pressure/	808 GPU	[168]
		2	Variable-volume	851 GPU	
		3		889 GPU	
Matrimid	O_2	2	Constant-pressure/	103 GPU	[109]
	CO_2	2	Variable-volume	251 GPU	
	N_2	2		83 GPU	
Fluorinated Matrimid	O_2	2	Constant-pressure/	137 GPU	[109]
	CO_2	2	Variable-volume	295 GPU	
	N_2	2		103 GPU	
PSF	O_2	-	Constant-pressure/	660 GPU	[105]
	CO_2		Variable-volume	580 GPU	
PSF-AA-Hep	O_2	-	Constant-pressure/	660 GPU	[105]
	CO_2		Variable-volume	580 GPU	
PSF-MPC	O_2	-	Constant-pressure/	650 GPU	[105]
	CO_2		Variable-volume	570 GPU	
PSF-Col	O_2	-	Constant-pressure/	600 GPU	[105]
	CO_2		Variable-volume	550 GPU	
PEUU	O_2	-	Constant-volume/ Variable-pressure	11 Barrer	[158]
PDMS	O_2	-	Constant-volume/ Variable-pressure	1.71 cm^3 STP $(m^2.min.cmHg)^{-1}$	[199]
PSF	O_2	0.5	Constant-pressure/	250 GPU	[102]
		1	Variable-volume	310 GPU	
		1.5		370 GPU	
		2		480 GPU	
	CO_2	0.5		210 GPU	
		1		260 GPU	
		1.5		310 GPU	
		2		380 GPU	
PSF-PEGA	O_2	0.5	Constant-pressure/	210 GPU	[102]
		1	Variable-volume	280 GPU	
		1.5		350 GPU	
		2		450 GPU	
	CO_2	0.5		200 GPU	
		1		250 GPU	
		1.5		300 GPU	
		2		360 GPU	
PSF	O_2	-	Constant-pressure/	290 GPU	[103]
	CO_2	-	Variable-volume	200 GPU	
PSF-PEG-Hep	O_2	-	Constant-pressure/	250-270 GPU	[103]
	CO_2	-	Variable-volume	170-180 GPU	
PUU	O_2	-	Constant-volume/	10-11 barrer	[157]
	CO_2		Variable-pressure	113-337 barrer	
PP	Air	2	Constant-pressure/ Variable-volume	30-85 $(m^3/h.m^2)$	[213]
PMP	O_2	0.66	Constant-pressure/	1700 GPU	[254]
	CO_2	0.66	Variable-volume	1460 GPU	
PMP	O_2	0.66	Constant-pressure/	346 GPU	[254]
	CO_2	0.66	Variable-volume	272 GPU	
TMCTS	O_2	0.66	Constant-pressure/	548 GPU	[254]
	CO_2	0.66	Variable-volume	592 GPU	
Siloxane	O_2	0.66	Constant-pressure/	496 GPU	[254]
	CO_2	0.66	Variable-volume	1200 GPU	
Siloxane	O_2	0.66	Constant-pressure/	954 GPU	[254]
	CO_2	0.66	Variable-volume	1620 GPU	
PMP	O_2	0.2	Constant-volume/	13 $ml(cm^2.min.bar)^{-1}$	[197]
		0.4	Variable-pressure	10 $ml(cm^2.min.bar)^{-1}$	
		0.6		11 $ml(cm^2.min.bar)^{-1}$	
		0.8		10 $ml(cm^2.min.bar)^{-1}$	
	CO_2	0.2		1.5 $ml(cm^2.min.bar)^{-1}$	
		0.4		2 $ml(cm^2.min.bar)^{-1}$	
		0.6		2 $ml(cm^2.min.bar)^{-1}$	
		0.8		2 $ml(cm^2.min.bar)^{-1}$	

Table 7 (Continued)

PMP-OH	O_2	0.2	Constant-volume/	16 ml(cm^2.min.bar)$^{-1}$	[197]
		0.4	Variable-pressure	13 ml(cm^2.min.bar)$^{-1}$	
		0.6		17 ml(cm^2.min.bar)$^{-1}$	
		0.8		18 ml(cm^2.min.bar)$^{-1}$	
	CO_2	0.2		3 ml(cm^2.min.bar)$^{-1}$	
		0.4		3 ml(cm^2.min.bar)$^{-1}$	
		0.6		4 ml(cm^2.min.bar)$^{-1}$	
		0.8		4 ml(cm^2.min.bar)$^{-1}$	
PMP-Hep	O_2	0.4	Constant-volume/	20 ml(cm^2.min.bar)$^{-1}$	[197]
	CO_2	0.4	Variable-pressure	3 ml(cm^2.min.bar)$^{-1}$	
PMP-MPC	O_2	0.4	Constant-volume/	18 ml(cm^2.min.bar)$^{-1}$	[197]
	CO_2	0.4	Variable-pressure	4 ml(cm^2.min.bar)$^{-1}$	
PP-Silicone	O_2	1	Constant-volume/	750 GPU	[182]
	CO_2	1	Variable-pressure	500 GPU	
	N_2	1		800 GPU	
Polyolefin	O_2	1	Constant-volume/	590 GPU	[182]
	CO_2	1	Variable-pressure	500 GPU	
	N_2	1		600 GPU	
PI	O_2	1	Constant-volume/	6900 GPU	[182]
	CO_2	1	Variable-pressure	6000 GPU	
	N_2	1		7500 GPU	
PE	O_2	-	Electrode	2.48 cm^3(STP)cm(cm^2.s.cmHg)$^{-1}$	[179]
PE-MPC	O_2	-	Electrode	1.53-3.33 cm^3(STP)cm(cm^2.s.cmHg)$^{-1}$	[179]

For evaluation of gas exchange rate between blood and gas, a membrane contactor set-up is needed (Figure 14). In this method, the liquid phase (e.g., blood or water) flows over the membrane surface and the oxygen gas flows on the opposite side. The gas permeates through the membrane duo to the chemical potential difference between two sides and diffuses through the liquid boundary layer. This method is typically the same for membrane oxygenators while there are some differences in the details [255]. According to Kim et al. [106], the use of auxiliary vibration can improve the gas transport up to about 52%. Table 8 provides the typical ranges of gas exchange rates obtained for diverse ranges of materials used as membrane oxygenator.

7.6. Plasma leakage

Plasma leakage is one of the main characteristics of membrane oxygenators which can be tailored by membrane modification. In fact, since most modification methods give rise to hydrophilicity and consequently affect membrane surface tension, the probability of pore wetting is increased especially in the case of microporous membranes [113]. The critical water permeability pressure (CWPP) test is carried out to identify the propensity of pore wetting. In this test, DI water is added to the upstream membrane cell and the pressure is increased by 0.02 MPa in every 5 minutes. The process is continued until the first water droplet is appeared in the downstream for which the pressure is considered as the critical water permeability pressure [104]. According to the investigations, CWPP value should be higher than 0.053 MPa in clinical membrane oxygenators [104,259].

8. Transport Phenomena in Membrane Oxygenators

Transport phenomena and mathematical modeling in membrane separation has been widely studied to gain more insights about the process performance [260-262]. Likewise, several studies have been devoted to transport in membrane oxygenators. Essentially in membrane oxygenators, total mass transfer rate is often derived by using mass transfer coefficient to evaluate both diffusion and convection terms [263].

$$N = K\Delta C \tag{2}$$

where N is the total molar flux, ΔC is the overall concentration difference and K is the overall mass transfer coefficient. The overall mass transfer coefficient also can be obtained using Eq. (3) as follows:

$$K = \frac{Q}{A}\ln\left(\frac{C_0 - C^*}{C - C^*}\right) \tag{3}$$

where Q is the water flow rate, A is the membrane surface area, C^* is the oxygen concentration at gas-liquid equilibrium, and C_0 and C are the inlet and outlet oxygen concentrations in the fluid flow, respectively [264]. In Eq. (3), K is the overall mass transfer coefficient which is dependent on the gas, liquid and membrane phases in membrane oxygenators and can be calculated using Eq. (4):

$$\frac{1}{K} = \frac{1}{k_L} + \frac{1}{k_M} + \frac{1}{k_G} \tag{4}$$

where k_L, k_M, and k_G are individual mass transfer coefficients in liquid, membrane, and gas phases, respectively [265].

In membrane oxygenators, the resistance of gas phase is often considered negligible regardless of the type of the membrane used. While, in microporous membrane oxygenators, only the liquid phase is considered as the resistance layer, in dense membranes the contribution of membrane phase is also taken into consideration [115]. In this section, the conditions governing all the phases including gas, membrane and liquid are discussed and the corresponding equations are presented which could be used for developing mathematical modeling of a membrane oxygenator device.

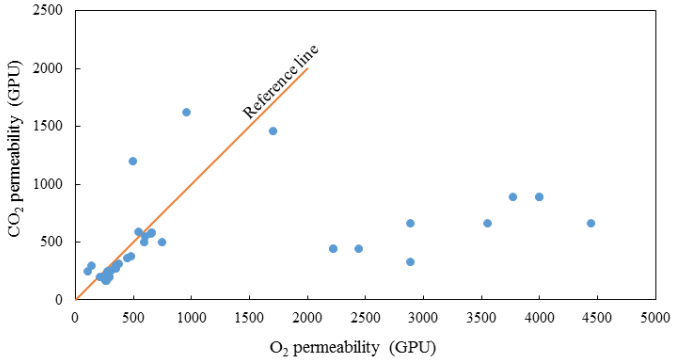


Fig. 13. Oxygen and carbon dioxide permeability of different neat and modified membrane oxygenators [102,103,105,109,168,182,197,199,254].

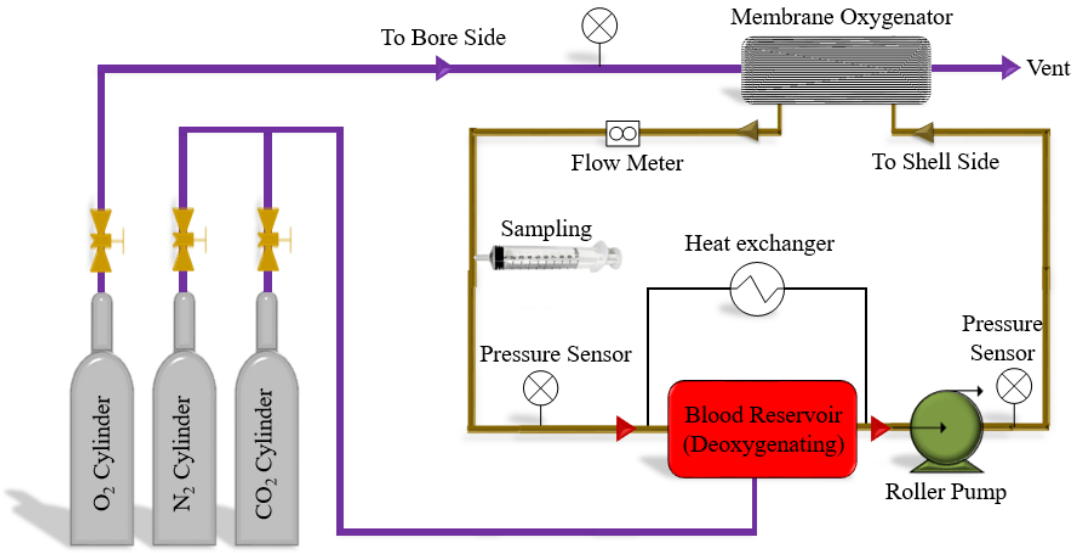


Fig. 14. Schematic representation of a testing set-up for analysis of the performance of membrane contactor.

Table 8
The gas exchange rates reported for diverse ranges of membrane oxygenators.

Membrane	Liquid flow rate ($L.min^{-1}$)	Liquid	O_2 exchange rate	CO_2 exchange rate	Ref.
PES	1-2.5	Water	484-927 mL m^{-2} min^{-1}	-	[168]
PES/TiO_2	1-2.5	Water	363-887 mL m^{-2} min^{-1}	-	[168]
PES-PEG	1-2.5	Water	376-914 mL m^{-2} min^{-1}	-	[168]
PSF-AA-Hep	5	Blood	192.6 mL min^{-1}	166.9 mL min^{-1}	[105]
PSF-MPC	5	Blood	196.3 mL min^{-1}	172.5 mL min^{-1}	[105]
PSF-Col	5	Blood	148.1 mL min^{-1}	120.2 mL min^{-1}	[105]
Silicone fiber	0.5 2.5 5	Blood	28.5-35.7 mL min^{-1} 140-172.5 mL min^{-1} 271.7-318.3 mL min^{-1}	27.7-31.2 mL min^{-1} 112.5-145.8 mL min^{-1} 228.3-280 mL min^{-1}	[107]
PEUU	2 2.5 3	Water	25.5 mL m^{-2} min^{-1} 25.5 mL m^{-2} min^{-1} 26.9 mL m^{-2} min^{-1}	-	[158]
PDMS	0.5-4 E-03	Blood	45-140 mL m^{-2} min^{-1}	-	[133]
PDMS	0.4-1.6 E-03	Blood	60-140 mL m^{-2} min^{-1}	300-350 mL m^{-2} min^{-1}	[256]
PDMS	5-40 E-03	Blood	25-104 mL m^{-2} min^{-1}	40-100 mL m^{-2} min^{-11}	[193]
PDMS	0.005	Blood	25 mL m^{-2} min^{-1}	30 mL m^{-2} min^{-1}	[257]
PDMS	0.5-6.3 E-03	Blood	41 mL min^{-1}	40-190 mL min^{-1}	[258]
PSF	0.5-5	Blood	35.82-210 mL min^{-1}	26.34-180.3 mL min^{-1}	[102]
PSF-PEGA	0.5-5	Blood	22.54-198.6 mL min^{-1}	19.9-170.9 mL min^{-1}	[102]
PSF-PEG	0.6-1.5	Blood	21.35-110.52 mL min^{-1}	18.27-102.41 mL min^{-1}	[103]
PSF-PEG-HEP	0.5-5	Blood	23.69-192.6 mL min^{-1}	19.82-166.9 mL min^{-1}	[104]
PMP	0.06	Blood	935 mL m^{-2} min^{-1}	103 mL m^{-2} min^{-1}	[197]
PMP-OH	0.06	Blood	861 mL m^{-2} min^{-1}	95 mL m^{-2} min^{-1}	[197]
PMP-HEP	0.06	Blood	883 mL m^{-2} min^{-1}	96 mL m^{-2} min^{-1}	[197]
PMP-MPC	0.06	Blood	842 mL m^{-2} min^{-1}	88 mL m^{-2} min^{-1}	[197]
PI	1-4	Water	3-9 mL min^{-1}	35-100 mL min^{-1}	[182]
Polyolefin	1-4	Water	3-10.5 mL min^{-1}	25-80 mL min^{-1}	[182]
PP	1-6	Blood	5-80 mL min^{-1}	2.5-40 mL min^{-1}	[106]
PP	1-6	Blood	8-125 mL min^{-1}	3-60 mL min^{-1}	[106]
PMP	0.06	Blood	-	80 mL m^{-2} min^{-1}	[188]
PMP-CA	0.06	Blood	-	110 mL m^{-2} min^{-1}	[188]
PDMS	0.1-1 E-03	Blood	0.08-027 mL min^{-1}	-	[189]

8.1. Transport in the gas phase

As outlined earlier, the contribution of the resistance of gas phase in transport is often negligible. This is similar to the membrane contactors used for CO_2 absorption. However, it should be noted that, in contrast to membrane oxygenators, the flow of gas in CO_2 absorption contactors is usually in the shell side. Accordingly, the continuity equation for gas flow in the lumen side of hollow fiber membrane oxygenators can be written as follows:

$$2u\left[1-\left(\frac{r}{R_f}\right)^2\right]\frac{\partial C}{\partial z}=D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right)\right] \quad (5)$$

where r is the radial distance, R_f is the fiber radius, u is the lumen average velocity, C represents the concentration of the diffusing component (in a gas mixture), z is the axial distance and D is the diffusion coefficient of the diffusing component. This equation can be solved numerically by using appropriate boundary condition by which the concentration variation in the lumen side of membrane oxygenators can be obtained [266].

8.2. Transport in the membrane phase

As discussed in the earlier parts, the gas transfer rate through the membranes strongly relies on the porosity and pore size of the membrane. In fact, the membrane phase resistance is not significant in porous membranes in contrast to what it can be in the case of dense membranes. Gas transport through non-porous membranes is often examined by solution-diffusion method described by Eq. (6) [108]:

$$P=D.S \quad (6)$$

where P is the permeability, and D and S are diffusion and solubility coefficients of permeating molecules, respectively.

The solubility of gasses in dense polymeric membranes can be obtained either experimentally or by different equations of state with the aid of non-athermal and athermal models [267]. For asymmetric membranes, the effect of porous substructure can be neglected and the strategy for the dense thin surface layer is similar to the symmetrically dense membranes. Also in asymmetric membranes, the contribution of the membrane phase is of less importance than in the case of dense membranes since the effective thickness of membrane is less. This is followed by enhancement of the membrane gas transfer rate and consequently the reduction of the membrane phase resistance [254]. In microporous membrane oxygenators, the effect of membrane phase resistance is often ignored considering the high gas flux. In these cases, especially when the gas pressure is not high, the flow in the membrane is governed by Knudsen law and can be calculated using Eq. (7) [108]:

$$J=\frac{\pi.n.r^2.D_k.\Delta p}{R.T.\tau.l} \quad (7)$$

where r is the pore radius, D_k is the Knudsen-diffusion coefficient, ΔP is the pressure gradient across the membrane, T is the temperature, τ is the tortuosity and l is the thickness. To determine the Knudsen diffusion coefficient, Eq. (8) is used:

$$D_k=0.66\,r\sqrt{\frac{8\,R.T}{\pi.M_W}} \quad (8)$$

in which M_W stands for the molecular weight of gas.

The gas transfer through the membrane also depends on the membrane module. In order to develop a mathematical model for HFM microporous and dense membranes, the velocity inside the membrane is considered negligible. Hence, the following continuity equation can be written for each gas in the membrane side:

$$D_{gas-mem}\left[\frac{\partial^2 C_{gas-mem}}{\partial r^2}+\frac{1}{r}\frac{\partial C_{gas-mem}}{\partial r}+\frac{\partial^2 C_{gas-mem}}{\partial r}\right]=0 \quad (9)$$

where $D_{gas\text{-}mem}$ is the diffusion of gas in the membrane effective layer, $C_{gas\text{-}mem}$ is the concentration of gas in the membrane-gas interface (within the membrane phase) and r is the membrane thickness. Eq. (9) can be solved by taking proper boundary conditions. The results obtained from these equations can show the concentration variation in the membrane phase [268]. Equation (9) also can be derived in rectangular coordination to be used for flat sheet membranes.

8.3. Transport in the liquid phase

The key resistance for the transport in membrane oxygenators is imposed by the liquid boundary layer. Therefore, a thorough understanding about the details involved is of great importance especially for high accuracy mathematical modeling and simulation of the oxygenation process. In the following sub-sections, some of the key contributing factors are introduced and their roles in mathematical modeling are discussed.

8.3.1. Mass transfer correlations

Wickramasinghe et al. [269-272] have put considerable efforts to develop mass transfer correlations for prediction of gas exchange performance in membrane oxygenators. They suggested that momentum transfer can be obtained using Eq. (10) as follows:

$$F=A_w(0.5\rho v^2)f \quad (10)$$

where F is the friction force, A_w is the wetted area, ρ is the liquid density, f the friction factor and υ is the liquid velocity

The driving force for the liquid flow can be obtained with the aid of Eq. (11) as follows:

$$F=\varepsilon\left(\frac{\pi}{4}(D_0^2-D_i^2)\right)\Delta P \quad (11)$$

where ε is the porosity of the void fraction expressed as the ratio of the void space to the total volume of the mass transfer chamber.

By combining Eqs. (10) and (11), the friction factor can be obtained:

$$f=\frac{d_e\Delta P}{4L_0(1/2)\rho v^2} \quad (12)$$

Also for determination of the friction factor, Chilton-Colburn analogy was used as follows:

$$St_{mass}Sc^{2/3}=\frac{f}{2} \quad (13)$$

where St_{mass} is the Stanton number and Sc is the Schmidt number.

In this method, the pressure drop can be calculated experimentally. Consequently, by drawing relative diagrams, Sherwood and friction factor correlations are obtained according to the following equations:

$$\begin{aligned} &Sh=0.8Re^{0.59}Sc^{0.33}\\ &\frac{f}{2}=130Re^{-1.1},\quad 0.1<Re<5\\ &\frac{f}{2}=50Re^{-0.5},\quad 5<Re<100 \end{aligned} \quad (14)$$

To solve Eq. (14), the blood pressure drop (ΔP) should be obtained experimentally. Finally, by finding the Sherwood number, mass transfer coefficient can be obtained.

Matsuda et al. [273] aimed to investigate the effect of the number of tied fibers on the performance of oxygenation (Figure 15). They found that by increasing the number of tied fibers, the total membrane surface area also increased while void fraction and flow path diameter decreased. According to the findings, when the number of tied hollow fibers reduced, the friction factor, which is directly related to the void fraction, increased at a constant Reynold's number. As a result, a more effective blood contact could be achieved despite having less surface area which gave rise to the oxygen transfer rate [273]. They also established the relationship between Sherwood coefficient and void fraction as follows:

$$\begin{aligned} &f=Re^{-0.496}\exp(7.36\varepsilon-3.33)\\ &Sh=Re^{0.67}Sc^{0.33}\exp(3.29\varepsilon-4.27) \end{aligned} \quad (15)$$

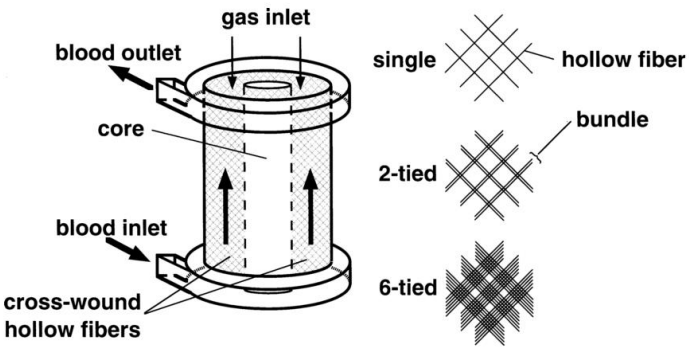


Fig. 15. Schematic illustration of the hollow fiber membrane oxygenator module comprising a single hollow fiber and tied bundles [273].

For the examination of the effect of fiber arrangement, Nagase et al. [265] used different arrangements including parallel and crossed hollow fibers (Figure 16). For the mathematical modeling, the theory of bank tube was utilized in which the maximum velocity and outer diameters were involved expressed as Eq. (16):

$$\frac{k_L d_0}{D_L} = a\left(\frac{d_0 u_{max}}{v}\right)^b \left(\frac{v}{D_L}\right)^{0.33} \tag{16}$$

where d_0 (m) is the outer diameter of the hollow fibers, D_L ($m^2.s^{-1}$) is the diffusion coefficient of oxygen in liquid, v ($m^2.s^{-1}$) is the kinematic viscosity and u_{max} ($m.s^{-1}$) is the maximum fluid velocity calculated by Eqs. (17) or (18):

$$u_{max} = \frac{S_T}{S_T - d_0} u_0 \tag{17}$$

$$u_{max} = \left(\frac{S_T}{2\left[\left(S_L^2 + \left(\frac{S_T}{2}\right)^2\right)^{0.5} - d_0\right]}\right) u_0 \tag{18}$$

where S_T is the transverse pitch of hollow fibers, u_0 is the superficial velocity of fluid ($m.s^{-1}$) and S_L (m) is the longitudinal pitch of hollow fibers. Finally, they established the following Sherwood correlation for their system:

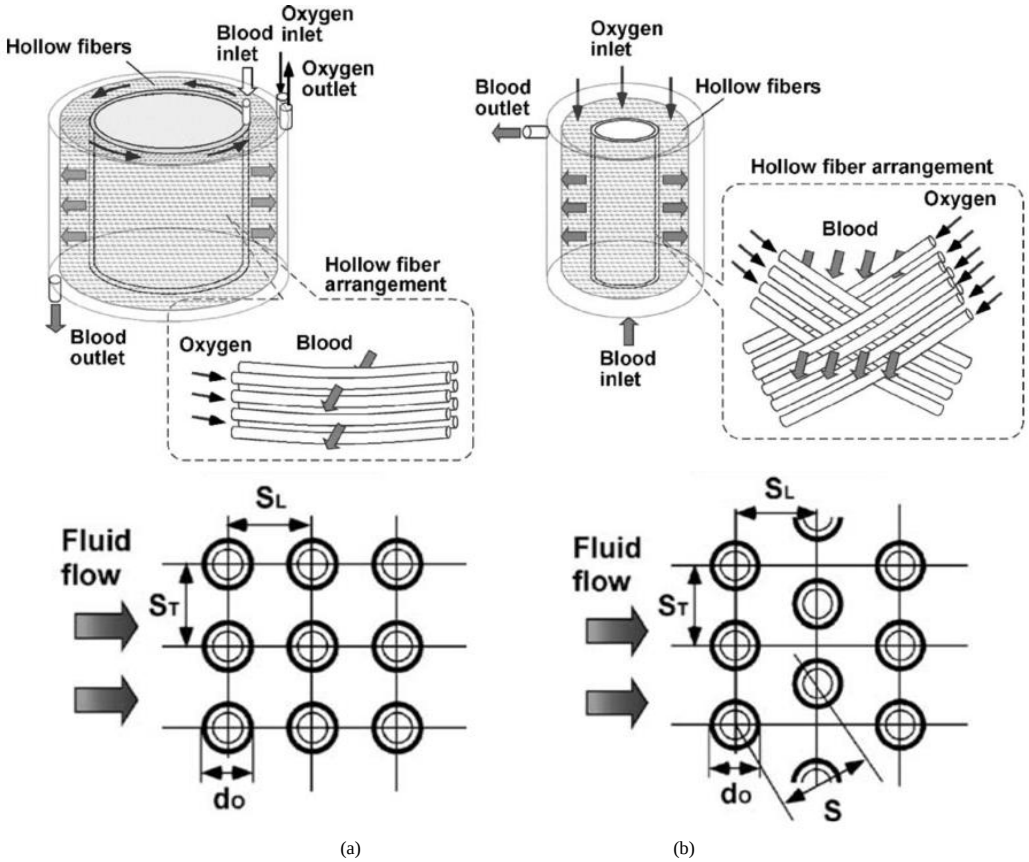
$$Sh = 0.46 Re_{max}^{0.76} Sc^{0.33} \quad \text{for parallel hollow fiber}$$
$$Sh = 0.14 Re_{max}^{0.90} Sc^{0.33} \quad \text{for crossed hollow fiber} \tag{19}$$

The findings revealed that crossed hollow fibers are more efficient than parallel in term of mass transfer rate for higher maximum Reynolds numbers [265].

For the assessment of the effect of fiber arrangement angles, Catapano et al. [97] examined different fiber angles to derive a correlation that can describe the effect of fiber arrangements. They used the following Eqs. for Sherwood and friction factor:

$$f = bRe^c (1-\varepsilon)^d e(\varphi) \tag{20}$$

$$Sh = b'\left(Re\frac{d_h}{L}\right)^{c'} h'(\varepsilon) Sc^{1/3} e'(\varphi) \tag{21}$$



(a) (b)

Fig. 16. Illustration of (a) parallel and (b) crossed hollow fiber membrane oxygenator modules [265].

where φ is the membrane angle with respect to the main direction of liquid flow and L is the module length. They found the pressure drop experimentally for the angles from 0 to 20 degrees and achieved the following formulae for Sherwood and friction factors [97]:

$$f = Re^{-0.43}(1-\varepsilon)^{-1.22}(1.75+0.049\varphi) \tag{22}$$

$$Sh = \left(Re\,\frac{d_h}{L}\right)^{0.15}\left(\frac{\varepsilon}{1-\varepsilon}\right)^{-0.13} Sc^{1/3}\,(1.1+1.2e^{-0.1\varphi}) \tag{23}$$

The method of finding the correlations for flat sheet membrane oxygenators is quite similar to hollow fiber membrane oxygenators although the considerations about the geometry should be applied. For instance, to find a correlation for flat sheet membrane oxygenator, Sherwood number and friction factor are calculated as functions of Graetz and Reynolds numbers respectively through the Eqs. (24) and (25) for a laminar flow regime:

$$Sh = 6.4Gr^{0.33} \tag{24}$$

$$f = \frac{24}{Re} \tag{25}$$

8.3.2. Oxygen solubility

In membrane oxygenators, because of the high purity of oxygen, low operating pressure and low solubility of gasses in the water, often the Henry's law is applied as follows [168]:

$$C_{O_2}k = P \tag{26}$$

where C_{O_2} is the oxygen concentration in the liquid at the interface, k is the Henry's constant and P is the gas pressure.

However, in the blood the situation is more complicated since beyond physical solubility, a chemical reaction with hemoglobin is also involved:

$$\mathrm{Hb} + n\mathrm{O_2} \underset{k_{-1}}{\overset{k_1}{\Leftrightarrow}} \mathrm{Hb(O_2)}_n \tag{27}$$

where Hb stands for the hemoglobin of the blood and n is 2.7 for human blood and 2.85 for bovine blood.

Accordingly the equilibrium constant can be written as:

$$K_E = \frac{k_1}{k_{-1}} = \frac{[\mathrm{Hb(O_2)_n}]}{[\mathrm{Hb}][\mathrm{O_2}]^n} \tag{28}$$

Hill [274] proposed the following relation for determination of the degree of oxygen saturation:

$$S = \frac{[\mathrm{Hb\,(O_2)_n}]}{[\mathrm{Hb}]_t} = \frac{(P_{O_2}/P_{50})^n}{1+(P_{O_2}/P_{50})^n} \tag{29}$$

in which P_{O_2} is oxygen partial pressure and P_{50} is oxygen partial pressure at 50% hemoglobin saturation which can be calculated using Eq. (30) [275]:

$$P_{50} = 29.0\times 10^{(-.041\,(pH-7.4)+0.024\,(T-37))} \tag{30}$$

Equation (28) also can be transformed to the following form:

$$[\mathrm{Hb\,(O_2)_n}] = \frac{\mathrm{K_E}[\mathrm{Hb}]_t[\mathrm{O_2}]^n}{1+\mathrm{K_E}[\mathrm{O_2}]^n} = \frac{[\mathrm{Hb}]_t[\mathrm{O_2}]^n}{\mathrm{K_D}+[\mathrm{O_2}]^n} \tag{31}$$

where $\mathrm{K_D} = 1/\mathrm{K_E}$ and K_E is the equilibrium constant based on Freundlich-Langmuir isotherm.

$$\frac{1}{n}\frac{d[\mathrm{O_2}]}{dt} = k_{-1}[\mathrm{Hb(O_2)_n}] - k_1[\mathrm{Hb}][\mathrm{O_2}]^n \tag{32}$$

$$\frac{d[\mathrm{Hb}]}{dt} = k_{-1}[\mathrm{Hb(O_2)_n}] - k_1[\mathrm{Hb}][\mathrm{O_2}]^n \tag{33}$$

$$\frac{d[\mathrm{Hb(O_2)_n}]}{dt} = -k_{-1}[\mathrm{Hb(O_2)_n}] + k_1[\mathrm{Hb}][\mathrm{O_2}]^n \tag{34}$$

According to the film theory and by combining Eqs. (32) to (34), the following relations can be obtained:

$$D_{\mathrm{O_2}}[\mathrm{O_2}] + nD_{\mathrm{Hb(O_2)}_n}[\mathrm{Hb(O_2)_n}] = a_1x + a_2 \tag{35}$$

$$D_{\mathrm{Hb}}[\mathrm{Hb}] + D_{\mathrm{Hb(O_2)}_n}[\mathrm{Hb(O_2)_n}] = a_3x + a_4 \tag{36}$$

Due to the fact that there exist four constants, four boundary conditions are considered as follow:

- At the gas-liquid interface ($x=0$):

$$[\mathrm{O_2}] = [\mathrm{O_2}]_0 \tag{37}$$

- At the outer edge of the liquid boundary layer ($x=\delta$):

$$[\mathrm{O_2}] = [\mathrm{O_2}]_\delta \tag{38}$$

$$[\mathrm{Hb}] = [\mathrm{Hb}]_\delta \tag{39}$$

- Hemoglobins remain in the liquid phase and thus their total flux is zero:

$$D_{\mathrm{Hb}}\frac{d([\mathrm{Hb}])}{dx} + D_{\mathrm{Hb(O_2)}_n}\frac{d([\mathrm{Hb(O_2)_n}])}{dx} = 0 \tag{40}$$

- The flux of oxygen to the liquid is calculated by following Eq.:

$$J = -D_{\mathrm{O_2}}\frac{d[\mathrm{O_2}]}{dx} - nD_{\mathrm{Hb(O_2)}_n}\frac{d[D_{\mathrm{Hb(O_2)}_n}]}{dx} = -a_1 \tag{41}$$

Now, with the help of equations (28), (36)-(40) and (41), Eq. (42) can be derived:

$$J = \frac{D_{\mathrm{O_2}}}{\delta}([\mathrm{O_2}]_0 \tag{42}$$

$$-[\mathrm{O_2}]_\delta)\left[1+\frac{nD_{\mathrm{Hb(O_2)}_n}}{D_{\mathrm{O_2}}}\frac{K_E[\mathrm{Hb}]_\delta}{1+\frac{D_{\mathrm{Hb(O_2)}_n}}{D_{\mathrm{Hb}}}K_E[\mathrm{O_2}]_0^n}\frac{[\mathrm{O_2}]_0^n-[\mathrm{O_2}]_\delta^n}{[\mathrm{O_2}]_0-[\mathrm{O_2}]_\delta}\right]$$

If case of assumption of no reaction with the blood hemoglobin, this can be simplified as:

$$J_0 = \frac{D_{\mathrm{O_2}}}{\delta}([\mathrm{O_2}]_0 - [\mathrm{O_2}]_\delta) = k_0([\mathrm{O_2}]_0 - [\mathrm{O_2}]_\delta) \tag{43}$$

where k_0 is the mass transfer coefficient in the absence of chemical reaction.

By dividing Eq. (42) over (43), the following relationship is obtained:

$$k = k_0\left[1+\frac{nD_{\mathrm{Hb}(\mathrm{O_2})_n}}{D_{\mathrm{O_2}}}\frac{K_E[\mathrm{Hb}]_\delta}{1+\frac{D_{\mathrm{Hb}(\mathrm{O_2})_n}}{D_{\mathrm{Hb}}}K_E[\mathrm{O_2}]_0^n}\frac{[\mathrm{O_2}]_0^n-[\mathrm{O_2}]_\delta^n}{[\mathrm{O_2}]_0-[\mathrm{O_2}]_\delta}\right] = k_0E \quad (44)$$

where E is the enhancement factor, defined is a difference between the presence and absence of hemoglobin. Accordingly, the presence of hemoglobin should result in increased mass transfer coefficient [272].

According to the report by Matsuda et al., total dissolved oxygen can be calculated using the following formula [273]:

$$C = C_C + C_P = \beta(\mathrm{Ht}/100)S + \alpha P_{O_2} \quad (45)$$

in which C_C is the oxygen concentration bound to hemoglobins, C_P is the dissolved oxygen in the plasma, β is the maximum amount of oxygen combined with a unit volume of red blood cells, S is the degree of oxygen saturation of hemoglobin, α is the physical solubility of oxygen in blood, H_t (%) is the hematocrit (the volume percentage of red blood cells (RBC) in blood) and P_{O_2} is the oxygen partial pressure. Therefore, the mass transfer equation can be expressed as:

$$K = \frac{Q}{A}\int_{C_{P,I}}^{C_{P,O}}\frac{dC}{(C^*-C_P)} = \frac{Q}{A}\int_{C_{P,I}}^{C_{P,O}}\frac{d[\beta(Ht/100)S+\alpha P_{O_2}]}{(C^*-C_P)} \quad (46)$$

where $C_{P,I}$ andare the concentration of dissolved oxygen in the $C_{P,O}$ plasma at the inlet and outlet streams, respectively. Also, K is the overall average mass transfer coefficient and C^* is the oxygen concentration of gas-liquid equilibrium.

8.3.3. Carbon dioxide desorption

It might be interesting to note that the process of CO_2 removal from blood is even more complicated than oxygen transfer. This mainly stems from the fact that almost 90% of CO_2 exists as bicarbonate (HCO_3), and almost 5% is bound to hemoglobin while the rest 5% is dissolved. Because of the presence of the enzyme carbonic anhydrase, CO_2 and bicarbonate can easily be converted to each other. The equilibrium reaction of CO_2 and bicarbonate can be represented as below [276]:

$$\mathrm{CO_2} + \mathrm{H_2O} \overset{\text{Carbonic Anhydrase}}{\underset{1}{\Longleftrightarrow}} \mathrm{H_2CO_3} \overset{2}{\Longleftrightarrow} \mathrm{H^+} + \mathrm{HCO_3^-} \quad (47)$$

A mathematical model is needed to determine the amount of both CO_2 and bicarbonate in the blood. Consequently, Sherwood number for CO_2 is defined by the following Eq.:

$$Sh_{CO_2} = \frac{k_{CO_2}d_h}{\alpha_{CO_2}D_f} \quad (48)$$

where d_h is the hydraulic diameter, α_{CO_2} is the solubility of CO_2 in blood and D_f is the facilitated diffusion coefficient calculated by:

$$D_f = D_{CO_2} + \frac{D_{HCO_3}}{\alpha_{CO_2}}\frac{\partial C_{HCO_3}}{\partial P_{CO_2}} \quad (49)$$

where D_{CO_2} and D_{HCO_3} are the diffusivity of CO_2 and HCO_3 in the blood, respectively and $\partial C_{HCO_3}/\partial P_{CO_2}$ is the change in bicarbonate ion concentration with respect to the change in P_{CO_2}, which can be calculated by the following equation [276, 277]:

$$\frac{\partial C_{HCO_3}}{\partial P_{CO_2}} \cong \frac{\partial C_{CO_2}}{\partial P_{CO_2}} \cong 12.81\times 0.3692P_{CO_2}^{0.3692-1.0000} \equiv \lambda_{CO_2} \quad (50)$$

where λ is an effective solubility that incorporates both dissolved and the chemically bound CO_2.

The Schmidt number for CO_2 can be expressed by:

$$Sc = \frac{v_b}{D_{\mathrm{eff}}} \quad (51)$$

where D_{eff} is an effective diffusivity calculated by:

$$D_{\mathrm{eff}\_CO_2} = \frac{D_{\mathrm{eff}}}{1+\frac{1}{\alpha_{CO_2}}\overline{\lambda_{CO_2}}} \quad (52)$$

where $\overline{\lambda_{CO_2}}$ is the constant slope of CO_2 dissociation curve. As a result, the mass transfer correlation can be calculated by the following equation:

$$k_{CO_2} = a\alpha_{CO_2}d_h^{b-1}\left(\frac{Q}{2\pi rL}\right)^b + \left(D_{CO_2}+\frac{D_{HCO_3}}{\alpha_{CO_2}}\overline{\lambda_{CO_2}}\right)^{\frac{2}{3}}\left(1+\frac{1}{\alpha_{CO_2}}\overline{\lambda_{CO_2}}\right)^{\frac{1}{3}}v^{1/3-b} \quad (53)$$

In a similar procedure, the mass transfer coefficient for oxygen is determined as follows:

$$k_{O_2} = a\alpha_{O_2}d_h^{b-1}\left(\frac{Q}{2\pi rL}\right)^b + D_{O_2}^{2/3}\left(1+\frac{C_T}{\alpha_{O_2}}\lambda_{O_2}\right)^{1/3}v^{1/3-b} \quad (54)$$

On the other hand, the mass balance of O_2 or CO_2 in the fiber bundle is written as:

$$Q\frac{dC}{dr} = 2\pi rLka_v\Delta P \quad (55)$$

where Q is the blood flowrate through the fiber bundles, C is the gas concentration comprising dissolved and chemically bound in the blood, r is the radial coordinate, L is the bundle thickness, a_v is the surface area per volume of the fiber bundle, k is the mass transfer coefficient and ΔP is the gas partial pressure difference at fiber lumen and the blood.

The above equation can be shown by the following expression based on partial pressure:

$$\frac{dP}{dr} = -\frac{2\pi rLka_v}{Q\lambda}\Delta P \quad (56)$$

By inserting Eqs. (53) and (54) in the above Eq., the concentration profile of carbon dioxide and oxygen can be obtained. Then, with the help of experiments, oxygen transfer rate is calculated and the following estimation for both O_2 and CO_2 is determined:

$$Sh = 0.54Re^{0.42}Sc^{1/3} \quad (57)$$

There are a number of other methods for approximating the gas exchange rates in membrane oxygenators. Table 9 shows some of the correlations proposed in the literature.

8.3.4. Conservation equations

Another method for prediction of mass transfer in membrane oxygenators is through incorporation of mathematical models in which velocity and concentration profiles can be obtained using Navier-Stokes and continuity equations. The Navier-Stokes equation is represented as follows [279]:

Table 9
The correlations proposed in the literature for approximation of O_2 and CO_2 transfer to liquids.

Sherwood/ Mass transfer coefficient	Gas	Module type	Flow characteristics	Ref.
$Sh = 1.38Re^{0.34}Sc^{0.33}$	O_2 CO_2	HFM	Water outside in cross flow	[278]
$Sh = 0.8Re^{0.47}Sc^{0.33}$	O_2	HFM	Water flow	[264]
$Sh = Re^{0.67}Sc^{0.33}\exp(3.29\varepsilon - 4.27)$	O_2	HFM	Blood flow	[273]
$Sh = \left(Re\frac{d_h}{L}\right)^{0.15}\left(\frac{\varepsilon}{1-\varepsilon}\right)^{-0.13}Sc^{1/3}(1.1 + 1.2e^{-0.1\varphi})$	O_2	HFM	Water flow, effect of membrane angle	[97]
$Sh = 1.62Gr^{0.33}$	O_2	HFM	Flow inside fiber- 1<Gr<100	[263]
$Sh = 3.0Gr^{0.33}$	O_2	Thin channels	1<Gr<100	[263]
$Sh = 0.8Re^{0.59}Sc^{0.33}$	O_2	HFM	Flow across fibers	[269]
$Sh = 0.46Re_{max}^{0.76}Sc^{0.33}$ parallel $Sh = 0.14Re_{max}^{0.9}Sc^{0.33}$ crossed	N_2	HFM	Water flow	[265]
$Sh = 0.54Re^{0.42}Sc^{0.33}$	O_2 CO_2	HFM	Blood flow	[276]
$K_{O_2} = 0.004Re^{0.76}Sc^{0.33}(1+\theta)^{0.33}$ $K_{CO_2} = 0.128Re^{1.31}Sc^{0.33}(1+\theta)^{0.33}$	O_2 CO_2	HFM	Water flow	[275]

$$\rho\left(\frac{D\vec{\mathbf{V}}}{Dt} + \vec{\mathbf{V}}.\vec{\nabla}\vec{\mathbf{V}}\right) = -\vec{\nabla}p + \rho g + \mu\nabla^2\vec{\mathbf{V}} \quad (58)$$

and the continuity equation is written as:

$$\frac{\partial C_A}{\partial t} = -\vec{\mathbf{V}}.\vec{\nabla}C_A + D_{AB}\nabla^2 C_A + R_A \quad (59)$$

For simplification, the following assumptions are made:

1) The liquid flow is laminar,
2) Gravity is considered only in vertical direction,
3) System is at steady state,
4) Velocity changes in parallel to the membrane is negligible,
5) No reaction takes place in the system,
6) Concentration polarization is negligible,

By solving Eqs. (58) and (59), local velocity profile is obtained in conjunction with simplified continuity equations. For instance, in the Cartesian coordination, the velocity and oxygen concentration profiles are obtained by Eqs. (60) and (61):

$$(y) = \frac{\Delta P}{2\mu X}(y^2 - Yy) \quad (60)$$

$$0 = -u(y).\left(\frac{\partial C_{O_2}}{\partial x}\right) + D_{O_2-liquid}\left(\frac{\partial^2 C_{O_2}}{\partial y^2}\right) \quad (61)$$

Eq. (61) can be solved analytically or numerically. In case of microporous membranes, oxygen concentration at the membrane-liquid interface can be equal to the liquid saturation concentration, but in case of dense membranes, in which the resistance of membrane phase cannot be neglected, the oxygen flux through the membrane active layer can be obtained by the Fick's first law as follows [158].

$$J_{O_2} = \frac{D_{O_2 m}}{l}\left(C_{O_2 0(m)} - C_{O_2 l(m)}\right) \quad (62)$$

The solubility of oxygen in the membrane bulk and membrane active layer is calculated by:

$$S_1 = \frac{C_{O_2 0(m)}}{p_{O_2}} \quad (63)$$

$$S_2 = \frac{C_{O_2 l(m)}}{C_{O_2 l}} \quad (64)$$

where S_1 is the solubility of oxygen in the membrane phase and S_2 is the solubility coefficient at the membrane-liquid interface. Consequently, the flux is given by:

$$J_{O_2} = \frac{D_{O_2 m}.S_1}{l}(p_{O_2} - HC_{O_2 l}) \quad (65)$$

8.4. Prediction of pressure drop

Another vital factor that should be taken into account in membrane oxygenator modules is the pressure drop at the liquid phase. It is known that larger pressure drops in the blood side can increase the risk of hemolysis and also more energy would be needed for pumping [19]. The pressure drop in hollow fiber membrane oxygenators can be calculated with the aid of Darcy's law [280]:

$$\nabla p = -\frac{\mu}{\alpha}\mathrm{v} \quad (66)$$

where p is the static fluid pressure, μ is the dynamic fluid viscosity, α is the fiber bed permeability and v is the superficial velocity which is the volumetric flow rate divided by fiber bundle cross-sectional area.

In order to predict the pressure drop in porous media, momentum balance should be written:

$$\frac{\partial}{\partial t}(\rho v_i) + \frac{\partial}{\partial x_j}(\rho v_i v_j) = -\frac{\partial p}{\partial x_i} + \frac{\partial \tau_{ij}}{\partial x_j} + \rho g_i + S_i \quad (67)$$

where ρ is the fluid density, x_i and x_j are directional coordinates respectively, τ_{ij} is the stress tensor and S_i is determined by the following equation [280]:

$$S_i = -\frac{\mu}{\alpha}v_i \quad (68)$$

In this equation, the fiber bed permeability (α) can be linked to experimental pressure drop by the following relation [281].

$$\alpha = \frac{\mu . Q . L}{A . \Delta P} \tag{69}$$

where *A* is the transversal cross-section of the fiber bundle, *Q* the flow rate and *L* is the length of the hollow cylinder.

8.5. Analysis of pore wetting

In the porous membrane contactors and specifically membrane oxygenators, membrane pores are being filled with the blood after few hours of operation. This phenomenon is called pore wetting, which ends in the reduction of membrane permeability. Under such circumstances, the modeling of the membrane gas exchange does not follow the established models requiring certain adjustments. The following formula describes the mass transfer coefficient in case of wetted and non-wetted pores:

$$k_m = \frac{1}{\frac{1}{k_{m,g}}(1-\varphi) + \frac{1}{k_{m,l}}(\varphi)} \tag{70}$$

where φ is the wetting ratio of membrane pores, $k_{m,g}$ and $k_{m,l}$ are membrane mass transfer coefficients for non-wetting and wetted conditions, respectively. $k_{m,g}$ and $k_{m,l}$ can be obtained from the following equations:

$$k_{m,g} = \frac{D_{g,m}\varepsilon_m}{\delta_m \tau_m} \tag{71}$$

$$k_{m,l} = \frac{D_{g,l}\varepsilon_m}{\delta_m \tau_m} \tag{72}$$

where ε_m is the membrane porosity, δ_m is the membrane thickness, τ_m is the membrane tortuosity. Also, $D_{g,m}$ and $D_{g,l}$ are the CO_2 diffusion coefficients in the non-wetted and wetted conditions, respectively [282].

It is worth noting that the difference of equations (71) and (72) lies in the nature of diffusion through wetted and non-wetted pores. As described before, the diffusivity through the non-wetted membrane oxygenators follows Knudsen-diffusion mechanism. However, under pore wetting condition, the diffusivity through the wetted pores is mainly influenced by the pore-filler liquid.

8.6. Effect of vibration

As discussed earlier, vibration of membranes can reduce the blood phase resistance as the main resistance for the gas transfer. According to Krantz et al. [101] vibration can increase the gas transfer rate by considerably and up to 5 folds. The following equations apply for mathematical modeling of vibration effects:

$$\rho \frac{\partial V_z}{\partial t} = \frac{\mu}{r}\frac{\partial}{\partial r}\left(r\frac{\partial V_z}{\partial r}\right) + \frac{P_0 - P_L}{L} - \rho g \tag{73}$$

Eq. (73) requires three boundary conditions as follows:

$$\begin{aligned} &V_z = 0 \text{ at } t = 0 \\ &\frac{\partial V_z}{\partial r} = 0 \text{ at } r = 0 \\ &V_z = A\omega \sin(\omega t) \text{ at } r = R_i \end{aligned} \tag{74}$$

By making the boundary condition homogenous, the dimensionless equations and the following boundary conditions can be obtained.

$$\frac{\partial V_z^*}{\partial t^*} + \Pi_v \Pi_\omega \cos(\Pi_\omega t^*) = \frac{1}{r^*}\frac{\partial}{\partial r^*}\left[r^*\frac{\partial V_z^*}{\partial r^*}\right] + 8 \tag{75}$$

$$\begin{aligned} &V^* = 0 \text{ at } t^* = 0 \\ &\frac{\partial V_z^*}{\partial r^*} = 0 \text{ at } r^* = 0 \\ &V_z^* = 0 \text{ at } r^* = 1 \end{aligned} \tag{76}$$

where $V_z^* \equiv \tilde{V}_z/\bar{V}$, $\tilde{V}_z = V_z - A\omega\sin(\omega t)$, $t^* \equiv tv/R_i^2$, $r^* \equiv r/R_i$, $\bar{V}$ is average velocity $= (P_0 - P_L - \rho g L)R_i^2/(8\mu L)$, $\Pi_v = A\omega/\bar{V}$, $\Pi_\omega = \omega R_i^2/v$ and V_z is the velocity of vibration.

On the other hand, like the equations illustrated in section 8.3.4, conversation equations should be written in order to obtain the velocity and concentration profiles. Then, by using Eqs. (2) and (3), the mass transfer correlations can be determined. Finally by using experimental methods and Sherwood plots, the Sherwood number of a vibrating membrane module can be obtained.

9. Summary and Concluding Remarks

Development of high performance oxygenators in order to help the patients suffering from lungs failure and those undergoing open cardiac surgery has been one of the primary goals for scientists active in the fields of chemical and biomedical engineering as well as materials and medical sciences. Membrane oxygenators have succeeded the early generation oxygenators by far by offering several benefits and as of today commercial hollow fiber membrane oxygenators made of polymeric materials are widely available in the market. Nevertheless, despite their attractive features, more progresses are still needed for overcoming some shortcomings and improvements in gas exchange rate, plasma leakage, and biocompatibility. One of the promising avenues to address these issues is through advancement in membrane materials and adoption of modification techniques. Materials such as silicone and PMP have shown attractive performance for mitigating plasma leakage in long-term applications while other biomaterials such as microporous PSF, PES and polyimides are still under further examinations especially in terms of biocompatibility. Also, microporous PP membranes due to provision of better gas exchange rates have been recommended for short-term applications. These membranes can be fabricated through different phase separation techniques including NIPS for soluble polymers and melt-spinning cold-stretching for non-soluble polymers. Progresses in the membrane materials for gas separation applications can also help in parallel by introduction of novel attractive materials.

Considering material modification, methods such as surface treatment with the aid of grafting heparin, polyethylene glycol and other suitable biomimetic materials have shown promising results for enhancing biocompatibility. Due to the attractive features of these modifying agents, it is expected that their use for modification of upcoming novel materials will be attractive. However, extra care must be taken for not negatively affecting other characteristics of the membrane. Since in most cases, by giving a rise to the biocompatibility, membrane gas transfer rates are severely affected.

Among the new trends is the design of new microfluidic membrane oxygenators due to resembling natural lungs. Further improvements in maturation of microfluidic membranes may potentially lead to breakthroughs in the field of membrane oxygenators. Trials have shown that by using these novel devices instead of conventional hollow fiber membrane oxygenators, the resistance of blood boundary layer to gas transfer and priming volume to decline dramatically. In between, further investigations on the methods for minimization of clot formation and pressure drop would also be essential.

Besides the progresses made by experimental research, mathematical modeling and simulations have also been able to provide insights about the process details and to identify the points for further improvements in the performance of membrane oxygenators. This includes establishing relationships for prediction of oxygen transfer to and carbon dioxide removal from the liquid phase. Also use of useful methods such as computational fluid dynamics, artificial intelligence and machine learning are among the untouched areas for research. For instance, artificial intelligence can be used for membrane preparation, membrane fouling control, analysis of gas permeation among others. Also, evolutionary computations like particle swarm intelligence or genetic algorithms can be used for optimization purposes.

Despite all these improvements, the progress in the membrane oxygenators is to be continued. In terms of materials, several novel materials

yet to be investigated. In fact, except a few commercially available materials such as PP and PMP, many other materials have been subjects of studied in the lab-scale. Also benchmarking studies for the materials seems to be very useful for providing better visions and directions for future research. This is especially important in the case of biocompatibility due to the wide ranges of methods, procedures and conditions used for its determination which makes comparison unfair and complex. Also, it seems more efficient biocompatibility assessment methods are needed in order to provide more accurate about the real interaction of membrane material to the blood components. Furthermore, adoption of innovative modification ideas such as nanoparticle additives, block copolymerization, molecular blending and surface functionalization may lead to breakthroughs in the field. Translation of research activities within the scope of chemical engineering and materials science into clinical research and further steps is still a serious gap that necessitates establishment of systematic collaborations between scientists from diverse disciplines involved in the subject. This also would help in smoother upscaling of laboratory results into commercial scales which itself requires further research.

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