

# Perfluorocarbons as Oxygen Dissolving and Delivering Agent

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**Abstract:** Perfluorocarbons (PFCs) are a class of manufactured chemicals with a wide range of medical and pharmaceutical applications. PFCs are made up of carbon and fluorine atoms, and they have the unique property of being able to dissolve large amounts of oxygen. PFCs are insoluble in water. They have to be emulsified for administration. This property makes PFCs ideal for use in oxygen delivery systems and ultrasound contrast agents. In medical applications, PFC emulsions can be injected into the bloodstream or inhaled, delivering oxygen to tissues that are deprived of oxygen. PFC emulsions are used to treat a variety of medical conditions, including heart disease, stroke, and carbon monoxide poisoning. PFC emulsions can also be used as ultrasound contrast agents. Ultrasound contrast agents are used to improve the quality of ultrasound images by increasing the contrast between different tissues. PFC emulsions are used in various ultrasound procedures, including cardiac imaging, abdominal imaging, and prenatal imaging. PFCs are used as a drug carrier in pharmaceutical applications to deliver drugs to specific tissues or organs. PFCs can also be used to create sustained-release drug delivery systems.

**Keywords:** perfluorocarbons; oxygen dissolving and delivering agent.

**Abbreviation:** PFCs: Perfluorocarbons; C-F: carbon-fluorine; HC: hydrocarbon.

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## 1. Introduction

Perfluorocarbons (PFCs) are aliphatic [1], non-natural [2], manufactured class of synthetic organic fluorochemical compounds. PFCs are chemically stable and inert molecules that share a similar structure with hydrocarbons but with fluorine atoms replacing hydrogen atoms. This modification grants them unique properties that make them suitable for various applications in medicine, industry, and electronics [3]. PFCs contain only carbon atoms (4 to 16) surrounded by fluorine atoms [4]. It surprises me that replacing fluorine in place of entire hydrogen atoms in an organic molecule would result in significant behavioral alterations [5]. They are unique substances that repel oil, grease, and water. Carbon-fluorine (C-F) bonding molecules are considered absent from normal mammals, except as contaminants or metabolites from consumed manufactured items [2].

The C-F bonding is comparatively short and extremely strong. As a result, saturation of bonding positions on an organic molecule with fluorine prevents chemical attack, resulting in a very inert material. PFCs are hydrophobic and typically oelophobic, meaning they are

insoluble in fat and oil [6]. PFCs may appear as gases, liquids, or solids based on their molecular weight and chemical structure (Table 1).

**Table 1.** Applications of PFC Compounds in various states: gases, liquids, and solids.

State	PFC Compound	Molecular formula	Molecular weight	Examples of applications
Gases	Perfluoromethane	CF <sub>4</sub>	80.1	Semiconductor manufacturing, plasma etching gas
	Perfluoroethane	C <sub>2</sub> F <sub>6</sub>	138.01	Semiconductor manufacturing, chemical vapor deposition
	Perfluoropropane	C <sub>3</sub> F <sub>8</sub>	196.02	Electronics industry, plasma etching, gas-cooled nuclear reactors
Liquids	Perfluorohexane	C <sub>6</sub> F <sub>14</sub>	262.04	Ultrasound contrast agents, drug delivery vehicles, and lubricants
	Perfluorodecalin	C <sub>10</sub> F <sub>18</sub>	318.06	Oxygen carrier in medical applications, liquid ventilation, and blood substitutes
	Perfluorooctane	C <sub>8</sub> F <sub>18</sub>	370.06	Ophthalmic surgery, vitreous substitute
	Perfluorobutanesulfonic acid (PFBS)	C <sub>4</sub> F <sub>9</sub> SO <sub>3</sub> H	313.07	Surfactants, cleaning agents
Solids	Polytetrafluoroethylene (PTFE)	(CF <sub>2</sub> CF <sub>2</sub> ) <sub>n</sub>	Varies depending on the value of n	Nonstick coating in cookware (Teflon), various industrial applications
	Poly(perfluoropropylene oxide) (PFPO)	(CF <sub>3</sub> CF <sub>2</sub> O) <sub>n</sub>	Varies depending on the value of n	Optical coatings

Liquid PFCs are generally harmless, but gaseous PFCs exhibit limited toxicity [4]. PFCs are primarily utilized as artificial blood substitutes. When it comes to dissolving gases in PFCs, oxygen (O<sub>2</sub>) can typically dissolve up to 50% by volume, while carbon dioxide (CO<sub>2</sub>) can dissolve 3 to 4 times more easily. This difference in solubility is due to the size of the gas molecules. Smaller molecules, like CO<sub>2</sub>, can fit more easily into the spaces between PFC molecules, making them more soluble. This relationship can be summarized by the following order of solubility: CO<sub>2</sub>>O<sub>2</sub>> N<sub>2</sub> [7]. Table 2 summarizes the relationship between gas, molecular volume, and solubility in PFCs.

**Table 2.** Summarizing the relationship between gas, molecular volume, and solubility in PFCs.

Gas	Molecular volume (Å <sup>3</sup> )	Solubility in PFCs	
		% volume	Grade
CO <sub>2</sub>	70	200-300	Highest
O <sub>2</sub>	54.6	40-50	Intermediate
N <sub>2</sub>	56.3	<10	Lowest

Since liquid PFCs are insoluble in water, they are unable to mix with water-based substances, such as blood and other bodily fluids [8]. PFCs are water-insoluble so that they can be converted into an emulsion form for further intravenous administration [9]. PFC liquids cannot be mixed with water-based substances like blood and other bodily fluids. However, they can be injected into the bloodstream as emulsions [7]. These emulsions are made up of tiny PFC droplets (about 0.1-0.2 μm in diameter) that are evenly spread out in a buffered, isotonic aqueous solution [7,10]. Two methods are commonly used to create these emulsions: Ultrasonic vibration (sonication): This method uses high-frequency sound waves to break up the PFC liquid into tiny droplets and disperse them in the aqueous solution. High-pressure homogenization: This method forces the PFC liquid through a narrow opening at high pressure, creating a fine mist of droplets that can then be mixed with the aqueous solution.

These emulsions are necessary because PFC liquids, on their own, would not mix with blood and would form globules that could block blood vessels. It can be injected intravascularly as an emulsion. The emulsions allow the PFCs to be transported throughout the bloodstream and deliver oxygen to tissues [7].

Fluosol-DA (Alpha Therapeutics, Los Angeles, CA) and oxygent (Alliance Pharmaceutical Corporation, San Diego, CA) are two PFCs that have advanced to clinical trials [11]. Fluosol-DA in 1989 was the first PFC emulsion approved to be used to enhance oxygen delivery to the heart muscle during percutaneous transluminal coronary angiography, a procedure that involves using a catheter to open up narrowed coronary arteries. However, Fluosol-DA usage was discontinued in 1994 because its oxygen delivery capacity was low under normal conditions, logistical challenges in preparation storage complex, and its limited application in angioplasty [11,12].

Oxygent is a (58% perfluorooctyl bromide and 2% perfluorododecyl bromide) [3] PFC emulsion that was approved by the FDA in 1998 for use as an oxygen carrier. Although Oxygent underwent human testing, it had not yet received FDA or other regulatory approval. After successfully finishing phase II trials, Oxycyte's funder discontinued its development in 2014 because of financial and patient enrollment difficulties. Oxygent progressed to phase III tests but was temporarily postponed due to safety concerns that subsequently turned out to be product-related and is presently undergoing clinical research in China [13].

Since the late 1970s, PFCs have also been investigated as contrasting agents for fluorine magnetic resonance imaging (MRI) and ultrasonography. The majority of contrasting agents used in ultrasonography are gaseous PFCs. However, liquid PFCs have been the research subject for the past 15 years. Liquid PFCs are recommended for fluorine MRI since they increase the fluorine concentration [4].

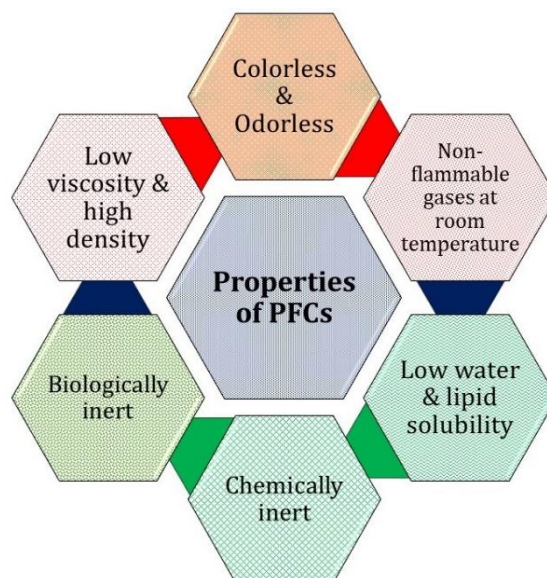
Compared to hydrocarbons (HCs), PFCs are typically much less reactive, have higher densities, are more easily compressed, flow more easily, spread out more easily, and dissolve gases more easily. They also have lower refraction indexes, surface tensions, dielectric constants, and water solubilities. The magnetic susceptibilities of PFCs are similar to those of water [5]. Here is Table 3 summarizes the key differences between HCs and PFCs.

**Table 3.** Differences between HCs and PFCs.

Property	Hydrocarbons (HCs)	PFCs
Reactivity	More reactive	Less reactive
Density	Lower	Higher
Compressibility	Less compressible	More compressible
Fluidity	Less fluid	More fluid
Spreading coefficient	Lower	Higher
Gas-dissolving capacity	Lower	Higher
Refraction index	Higher	Lower
Surface tension	Higher	Lower
Dielectric constant	Higher	Lower
Water solubility	Higher	Lower
Magnetic susceptibility	Higher	Similar to water

## 2. Properties of PFCs

The following properties of PFCs make them more interesting characteristics for clinical applications. They are colorless [14-17], odorless [15-18], non-flammable gases at room temperature [19], low water and lipid solubility [20,21], chemically inert [4,22,23], biologically inert [4,22], high density [14,17] and low viscosity [14,17,18].



**Figure 1.** Properties of perfluorocarbon.

### *2.1. Reason for colorless.*

PFC chemical structure consists of a carbon (C) backbone fully saturated with fluorine (F) atoms bonded together [24]. These molecules do not contain any aromatic or conjugated systems that typically absorb visible light, which is responsible for giving substances color. Because PFCs lack these light-absorbing structures, they appear colorless to the human eye [25].

### *2.2. Reason for odorless.*

Odors result from the interaction between specific odorant molecules and receptors in the human olfactory system [26]. Since PFCs do not contain molecules chemically configured to stimulate these receptors, they are perceived as odorless to the human nose. The lack of odor makes PFCs more acceptable to patients, particularly those sensitive to smells. The odorlessness of PFCs eliminates the potential for unpleasant odors that could discomfort patients during medical procedures or treatments. This is particularly important for patients with respiratory sensitivities or those already undergoing stressful procedures.

### *2.3. Reason for non-flammable.*

Pure PFCs are generally non-flammable because they do not contain hydrogen atoms. Hydrogen atoms are essential for combustion reactions; without them, PFCs cannot readily burn or support combustion. The strong carbon-fluorine bonds in PFCs further contribute to their non-flammability by making it difficult for them to break apart and release energy. Hydrogen is a clear gas, has no smell or taste, and can easily catch on fire. It is the lightest element and the simplest chemical substance. Once it starts burning, it produces a very light blue, almost invisible flame. The vapors from hydrogen are lighter than air. Hydrogen can burn in various concentrations when mixed with air [19].

### *2.4. Reason for low water and lipid solubility.*

Regarding organic compounds, PFCs are the most extreme hydrophobic ever synthesized. Compared to hydrocarbon (HC) oils, PFCs are far more hydrophobic because they

have low polarizability and large surface areas. This makes them less likely to interact with water molecules and more likely to interact with other molecules through van der Waals forces [5]. Even though the bonds between C-F are strong and have a strong positive and negative charge (polarity), this doesn't make the entire PFC molecule dissolve in water. This is because the symmetrical arrangement of the C-F bonds cancels out the polarity of each individual bond, making the overall molecule non-polar. A strong C-F bond makes it difficult for the PFC molecules to break apart and interact with water or lipid molecules. This high bond strength contributes to their low solubilities in water and lipids. The tight C-F bonds make PFC molecules bulkier, requiring more space in water, which increases the energy needed to hydrate them. This makes PFCs less soluble in water compared to similar HC molecules.

On the other hand, the extreme polarity of PFCs prevents the formation of temporary dipoles, which are necessary for van der Waals interactions that allow molecules to dissolve in lipids. This makes PFCs unusual because they are both hydrophobic (water-repelling) and lipophobic (fat-repelling). PFCs are fully fluorinated, and fluorine is highly electronegative, which means it attracts electrons strongly away from the carbon atoms. This makes the PFCs extremely non-polar, making them highly hydrophobic (water-repellent) and lipophobic (fat-repellent) [13]. Hydrogen atoms are typically involved in hydrogen bonding and can enhance solubility in both water (which is polar) and lipids (which are non-polar). Hydrogen plays a significant role in acid-base reactions among water-soluble molecules. Since PFCs lack hydrogen atoms, they cannot be involved in hydrogen bonding, reducing their solubility in water and lipids [19].

#### *2.5. Reason for chemically inert.*

The C-F bond is one of the strongest chemical bonds known in organic chemistry [13]. The greater orbital fit between C-F than between carbon and hydrogen results in the strongest single bond in molecular compounds [5]. PFCs' extremely powerful C-F bonds, these bonds are highly resistant to chemical reactions with other substances, making them chemically inert [7]. Hydrogen atoms are often involved in chemical reactions. Still, in PFCs, their absence makes the molecules even more chemically stable because they lack the typical chemical reactivity associated with hydrogen-containing compounds [20].

PFCs are chemically non-reactive and stable substances that are not broken down by the body. They are eliminated through normal biological processes, such as being engulfed by cells in the reticuloendothelial system, and eventually removed from the body through exhalation and bowel movements. Most PFCs with a molecular weight between 460 and 520 Da are biologically inactive and do not pose significant health risks, including cancer or genetic damage. The inertness of most of these compounds makes them desirable for various applications [23].

#### *2.6. Reason for biologically inert.*

PFCs do not mix with either water or lipids, which helps to make them biologically inert. This means that PFCs don't react with living cells or tissues, which makes them less likely to cause harm to the body [5]. Pure PFCs have been considered biologically inert [27] because they are not recognized or metabolized by the body's natural biochemical processes. This is due to the very strong resistance to chemical reactions of C-F bonds in PFCs. When PFCs are introduced into biological systems, they are not broken down or modified by enzymes, other

biological molecules, or cellular components. This property makes them suitable for various medical applications, such as oxygen carriers in blood substitutes, without causing adverse biological reactions [23].

Hydrogen atoms often play a crucial role in chemical reactions and can make molecules more chemically reactive. Since PFCs lack hydrogen atoms, they do not engage in hydrogen bonding or other chemical interactions that could lead to biological reactivity. PFCs are not metabolized by enzymes in the body's metabolic pathways. Enzymes in living organisms typically recognize and process specific substrates or molecules, but PFCs are not recognized as substrates, so they are not metabolized or broken down by enzymes. Pure PFCs have been considered generally biologically inert. PFC toxicity arises when PFCs contain unsaturated carbon bonds and molecules containing hydrogen. The most dangerous impurities in PFCs are nitrogen-bonded molecules. Care should be taken while purifying PFC to eliminate these substances. Cell cultures, infrared spectroscopy, and hydrogen nuclear magnetic resonance (NMR) can all be used to detect the presence of these chemicals in PFCs [27].

### *2.8. High density.*

Pure PFCs are much denser than ordinary aqueous media, so they are much heavier for their volume. For example, the density of water is 1 gm/cm<sup>3</sup>, while the density of pure PFCs can range from 1.7 to 2.1 gm/cm<sup>3</sup>. This makes PFCs about 70% to 110% denser than water [28] and nearly two-fold that of the usual eye components [29]. The high density of PFCs is due to the strong bonds between C-F atoms in their molecular structure. These bonds make the PFC molecules tightly packed together, increasing their density. The high density of PFCs has several important implications, including medical imaging contrast agents (blood vessels, tumors, etc.), heat transfer fluids (electronics cooling and power generation), and lubricants (high-performance machinery).

### *2.9. Low viscosity.*

Despite their high density, PFCs exhibit low viscosity. This is because the intermolecular forces between PFC molecules are relatively weak compared to other liquids. Fluorine atoms have a high electronegativity, which attracts electrons more strongly than other atoms. This strong electronegativity results in a partial negative charge on the fluorine atoms and a partial positive charge on the carbon atoms. These partial charges create weak dipole-dipole interactions between PFC molecules. The weak dipole-dipole interactions allow PFC molecules to slide past each other more easily, resulting in a low resistance to flow. This low resistance to flow is manifested as low viscosity.

The high density of PFC liquids is attributed to their compact molecular structure due to strong covalent bonds, while their low viscosity arises from weak dipole-dipole interactions between molecules [30]. This combination of high density and low viscosity makes PFC liquids valuable in various applications, including oxygen transport, ultrasound contrast agents, and drug delivery systems. Low-viscosity PFCs are useful in retinal surgery due to their unique optical properties and surface tension characteristics. They allow surgeons to support temporarily, hold in place, and move the retina effectively during delicate procedures [31].

### 3. Medical Application of PFCs

PFCs are a class of fluorinated hydrocarbons with unique properties that make them attractive for various medical applications. One of the most promising applications of PFCs is as an oxygen-dissolving and delivering agent.

#### 3.1. *Oxygen dissolving and delivering transport.*

In the 1960s, formulations with oxygen-carrying properties were created. Early on, it was noticed that a number of organic compounds with fluorine substitutes showed a strong attraction for oxygen [2]. PFCs are being studied as a potential alternative as an oxygen carrier to blood in 1966. PFCs can dissolve more oxygen than other liquids, making them promising candidates for use as oxygen carriers and delivering oxygen to tissues. In situations where traditional blood transfusions are not feasible or practical, such as during surgery or in cases of extreme blood loss, PFCs can be used as oxygen carriers. These PFC-based oxygen carriers are known as "blood substitutes" [3].

##### 3.1.1. Reason for PFCs able to dissolve more amount of oxygen.

PFCs are made up of carbon chains where fluorine atoms replace all the hydrogen atoms. This complete fluorination makes PFCs more biocompatible and able to dissolve a significant amount of oxygen because fluorine is highly electronegative. At standard temperature and pressure, oxygen can dissolve in water up to 2.2 mM (millimoles). This value can be much higher for PFCs, reaching up to 44 mM [32]. This represents a 20-40-fold increase in oxygen solubility compared to water [32,33].

PFCs readily absorb and dissolve oxygen due to their non-polar. Non-polar molecules do not have any positive or negative charge areas, making them more soluble than other non-polar molecules. Oxygen is also non-polar, so it is more soluble in PFCs than in polar molecules such as water [34].

In addition, PFCs have a very low surface tension. Surface tension is the force that acts at the surface of a liquid, causing it to resist being broken. The lower the surface tension, the easier it is for molecules to dissolve in the liquid. PFCs have a very low surface tension, making it easier for oxygen molecules to dissolve. PFCs can dissolve large amounts of gases because of their non-polar nature. PFCs have low polarity and polarizability, which means they can easily dissolve non-polar gases like noble gases, oxygen, nitrogen, and carbon dioxide [35].

The other reason for PFCs' dissolved gases being more effective than any other solvent is that PFCs cannot chemically bind gases; instead, they dissolve them, much like water or HCs do. Fluorine has an extremely low polarizability, which results in weak van der Waals force between PFC molecules. Van der Waals interactions are directly dependent on variations in the polarity of the electronic cloud. Van der Waals interactions are the only intermolecular forces that can keep non-polar molecules together. As a result, liquid PFCs behave almost exactly like perfect, gaseous fluids. So, PFCs have an incredibly high gas-dissolving capability. In particular, gases like O<sub>2</sub>, CO<sub>2</sub>, N<sub>2</sub>, NO, etc., which have poor cohesivity, are easily dissolved by PFC [5].

### 3.1.2. Mechanism of PFC oxygen delivering.

Within PFCs, oxygen can be dissolved via the Van der Waals interactions [3]. Once the oxygen-rich PFC solution is introduced into the body through various means, depending on the medical application. Once the oxygenated PFCs are circulated through the bloodstream, the oxygen-enriched PFC solution contacts tissues requiring oxygen and delivers oxygen to the tissues. The gas exchange occurs at the tissue level, where oxygen molecules dissolved in the PFC diffuse into surrounding tissues, effectively delivering oxygen to cells. This release occurs through diffusion gradients as oxygen moves from regions of higher concentration (dissolved in the PFC) to regions of lower concentration (in the cells) [36].

PFC is a promising material for improving oxygen delivery to tissues, especially when oxygen levels are low (hypoxia). PFCs can effectively carry oxygen at normal temperature and pressure and release oxygen when they come into contact with lower oxygen concentrations, similar to how red blood cells work. This makes PFCs a promising tool for treating hypoxia-related conditions [37].

### 3.1.3. The advantages of PFCs include oxygen dissolving and delivering substances.

**High oxygen-carrying capacity:** PFCs are promising candidates for artificial oxygen carriers (AOCs) because they can dissolve large amounts of oxygen. This property makes them well-suited for carrying oxygen to tissues in the body. PFCs can dissolve up to 80 times more oxygen than blood. This high oxygen-carrying capacity makes them useful in patients with anemia or other conditions that make it difficult for them to get enough oxygen. Also, in situations where enhanced oxygen delivery to tissues is needed, such as in critical care settings or during medical procedures [38].

**Non-toxic:** PFCs are considered non-toxic, which means they are unlikely to cause harm to the body [39].

**Superior oxygen storage capacity:** PFCs have gained significant interest from scientists due to their exceptional ability to store oxygen and their potential to replace red blood cells in artificial blood. Their nanoscale size allows them to deliver oxygen to the tiniest capillaries, directly reaching the hypoxic tumor environment and alleviating oxygen deficiency. Recent research has demonstrated that PFCs can transport oxygen to generate a substantial amount of reactive oxygen species, enabling them to overcome hypoxia treatment resistance and enhance the effectiveness of tumor radiotherapy, immunotherapy, and photodynamic therapy [40].

**Biologically inert:** PFCs are biologically inert, meaning they do not interact with or affect biological processes in the body. This biocompatibility reduces the risk of adverse reactions, making them suitable for medical applications without causing harm to the patient [5,23,27].

**No blood typing required:** Unlike traditional blood transfusions, which require compatibility matching based on blood types (ABO and Rh factors), PFCs do not require blood typing. They can be used universally without the need for donor matching [41].

**Improved tissue oxygenation:** PFCs can enhance tissue oxygenation in situations where there is inadequate oxygen delivery to vital organs. This is particularly important in cases of trauma, surgery, or conditions like acute respiratory distress syndrome [42].

**Stability at room temperature:** PFCs remain stable at room temperature for more than one year and do not require refrigeration, making them easy to store and transport [43].

Low vapor pressure: PFCs have a low vapor pressure (~10-20 mm Hg), meaning they evaporate slowly at room temperature [44]. This is because the strong C-F bonds in PFCs make it difficult for the molecules to escape from the liquid phase. The low vapor pressure of PFCs makes them useful in various applications, such as lubricants, coolants, insulators, etc.

Chemical and thermal stability: PFCs are chemically stable and can withstand high temperatures, making them suitable for various industrial applications, such as heat transfer fluids and lubricants [44].

#### 3.1.4. Disadvantages of PFCs as oxygen dissolving and delivering substance.

Gas embolism risk: One of the significant drawbacks of PFCs is the risk of gas embolism. If PFCs are not properly degassed and administered, they can release gas bubbles in the bloodstream, potentially leading to embolisms, which can block blood vessels and cause serious health complications [45].

Insufficient stability: The emulsions were not stable for long periods [45] and tended to break down over time. This required careful handling and storage to maintain their effectiveness [9].

Retention time: PFCs are not easily broken down by the body. As a result, they can accumulate in tissues such as the liver and spleen. The amount of time that PFCs remain in the body depends on their molecular weight. Larger PFC molecules tend to have a longer retention time than smaller PFC molecules [7]. PFCs can have a relatively long organ retention time [45]. Prolonged exposure of organs to PFCs can lead to adverse effects. The accumulation of PFCs in organs can disrupt their normal function and interfere with essential metabolic pathways.

Cost: The raw materials used to produce PFCs are expensive, making the production process costly. However, mass production could potentially make it a more cost-effective alternative to traditional blood transfusions, particularly in developing countries [9].

Labor-intensive management: Preparing the emulsions for use was a complex and time-consuming process. It involved freezing the emulsion for shipping and storage, thawing it, and combining it with other components under specific conditions [9].

#### 3.1.5. Applications of PFCs as oxygen-carrying agents.

##### 3.1.5.1. For hypoxia/cancer.

Lan *et al.* [40] researched PFC carrying oxygen (PFC@O<sub>2</sub>) targets Hypoxia Inducible Factor-1 $\alpha$  (HIF-1 $\alpha$ ) to reverse the immunosuppressive hypoxic tumor microenvironment (TME) in oral squamous cell carcinoma (OSCC). Their research concluded that PFC@O<sub>2</sub> has established promising potential in treating OSCC by reversing the immunosuppressive TME. By alleviating hypoxia, PFC@O<sub>2</sub> effectively downregulates the expression of HIF-1 $\alpha$ , a key regulator of the immunosuppressive TME. This reduction in HIF-1 $\alpha$  expression leads to a decrease in the number of M2-like macrophages, which are known to suppress antitumor immune responses. Additionally, PFC@O<sub>2</sub> treatment increases the infiltration of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, further boosting the antitumor immune response. These findings suggest that PFC@O<sub>2</sub> could be a valuable therapeutic approach for OSCC, particularly in combination with immunotherapy, to overcome immunosuppression and enhance tumor control.

Nguyen *et al.* [33] research aims to develop PFC-nanoemulsion (NE) with a photosensitizer (PS) dissolved in the fluorine phase for antitumor photodynamic therapy in hypoxia. They are designed to target and destroy tumor cells in hypoxic conditions,

which are environments with low oxygen levels. Hypoxia is a common feature of tumor microenvironments and can make cancer cells more resistant to traditional therapies. The PS in the PFC-NEs absorbs light and generates reactive oxygen species (ROS), which can damage tumor cells. The fluorous phase helps to stabilize the PS and deliver it to the tumor cells. Their new nanoformulations effectively killed normoxic (oxygen-rich) and hypoxic (oxygen-poor) cancer cells through photonecrosis.

Huang *et al.* [37] made an oxygen-carrying nano platform made up of photosensitizer (IR780), an immune stimulant (R837), liposome formulation (LIP) loaded with perfluorooctyl bromide (PFOB, a second-generation of PFC-based blood substitute) for synergistic cancer photothermal therapy (PTT) and immunotherapy. The obtained oxygen-carrying nanoplatfroms were shortened as IR-R@LIP/PFOB. The IR-R@LIP/PFOB that they had developed was able to effectively accumulate in 4T1 tumor cells, particularly in the mitochondria. In combination with laser irradiation, the IR-R@LIP/PFOB showed a strong ability to generate immunogenic cell death in the 4T1 tumor-carrying mouse species at the level of cells. In the meantime, the IR-R@LIP/PFOB proved effective in oxygen delivery due to the high oxygen loading volume of PFOB, reducing cancer hypoxia in situ. Significantly, combination treatments of immunogenic PTT and immune checkpoint blockade treatment might efficiently suppress cancer development by prompting potent anti-cancer immune response and reversing cancer immunosuppression. IR-R@LIP/PFOB nanoplatfroms are promising for cancer therapy with extremely effective therapeutic efficiency, outstanding biosafety, and biocompatibility.

Xiaona *et al.* [46] made a biocompatible, amphiphilic tetraphenylporphyrin–lysophospholipid conjugate (PPNH<sub>2</sub>-PC) and then assembled it with perfluorooctyl bromide (PFOB) to form PFOB-encapsulated porphyrin–lipid nanoparticles as for cancer therapy. The PFOB@PPNH<sub>2</sub>-PC NPs were able to make more reactive oxygen species (ROS) when exposed to light than PPNH<sub>2</sub>-PC NPs without PFOB, and they also killed more cells. The scientists found that PFOB@PPNH<sub>2</sub>-PC NPs caused about 12 times more pyroptosis bubbles than PPNH<sub>2</sub>-PC NPs after 5 minutes of light exposure. Further analysis showed that pyroptosis was caused by caspase 3-mediated cleavage of gasdermin E. Therefore, their PFOB-encapsulated lipid NP has the potential to be developed further as a pyroptosis inducer that can be activated by light to treat cancer.

Wang *et al.* [47] have developed a new type of oxygen carrier called O<sub>2</sub>@PFC@FHA NPs to increase radiotherapy. These oxygen carriers are made up of nanoparticles (NPs) by encapsulating oxygen (O<sub>2</sub>) saturated PFC in fluorinated hyaluronic acid (FHA). Radiation therapy is a common treatment for cancer, but it is often limited by the presence of hypoxia in tumors. Hypoxia, or low oxygen levels, can make tumors more resistant to radiation therapy. One way to overcome this limitation is to use PFC-based oxygen carriers to deliver oxygen directly to the tumor. However, these oxygen carriers can also cause systemic oxidative stress and toxicity during hyperoxic respiration. FHA is a targeting molecule that can bind to CD44 receptors found on tumor cells. This allows the O<sub>2</sub>@PFC@FHA NPs to accumulate in tumors and deliver oxygen directly to tumor cells. In this study, researchers found that O<sub>2</sub>@PFC@FHA NPs significantly relieved tumor hypoxia and enhanced the therapeutic efficacy of radiation therapy. The nanoparticles were also well-tolerated and did not cause any obvious systemic toxicity. Their findings suggest that O<sub>2</sub>@PFC@FHA NPs have great potential to improve the effectiveness of radiation therapy for cancer.

Lee *et al.* [48] developed a new injectable hydrogel to treat hypoxic tumors with low oxygen levels. They prepared their hydrogel with different components, including indocyanine green (ICG), paclitaxel (PTX) albumin bounded nanoparticles, polyethylene glycol (PEG), bovine serum albumin (BSA), chlorin e6 (Ce6), PFCs, as a nanoparticle (NPs) named ICG/PTX/BSA-Ce6-NPs. Their hydrogel was able to kill tumor cells in three ways: a) Photothermal therapy: The hydrogel is able to heat tumor cells when exposed to light. This heat can kill the tumor cells. b) Photodynamic therapy: The hydrogel is able to generate reactive oxygen species (ROS) when exposed to light. These ROS can kill the tumor cells. c) Oxygen-supplying activity: The hydrogel is able to deliver oxygen to tumor cells. This oxygen can help to overcome the hypoxia and make the tumor cells more sensitive to photothermal and photodynamic therapy. When the hydrogel was tested in mice, it significantly shrinks hypoxic tumors. The hydrogel was also able to ablate the tumors, which means that it was able to destroy them completely. The researchers believe that their hydrogel has the potential to be a new treatment for hypoxic tumors.

#### 3.1.5.2. For strokes.

Kline *et al.* [49] investigated the effectiveness of two treatment approaches for ischemic strokes: isovolemic hemodilution with a PFC emulsion or dextran PO. In a study using a cat stroke model, researchers compared the effects of two treatment methods: hemodilution with a PFC emulsion (FDA) or dextran PO (NR). The study found that isovolemic hemodilution with a PFC emulsion, a substance that can carry oxygen, resulted in reduced brain edema, increased mitochondrial metabolic activity in the peri-infarct cerebral tissue, and higher levels of oxidation of cytochrome as a marker of cellular oxygenation, compared to isovolemic hemodilution with dextran PO, a glucose polymer. Their findings suggested that isovolemic hemodilution with a PFC emulsion may be a promising treatment option for ischemic strokes.

Deuchar *et al.* [50] evaluated the therapeutic potential of Glasgow Oxygen Level Dependent (GOLD) technology, a PFC emulsion-based oxygen carrier, in combination with normobaric hyperoxia (50% O<sub>2</sub>) for the treatment of acute stroke. Neuronal cell cultures were subjected to oxygen-glucose deprivation (OGD) to mimic ischemic stroke conditions. The effects of GOLD and normobaric hyperoxia on cell viability and oxidative stress were assessed. Rat models of ischemic stroke were induced by middle cerebral artery occlusion (MCAO). The effects of GOLD and normobaric hyperoxia on infarct volume, neurological function, and oxidative stress were evaluated. In vitro studies demonstrated that GOLD and normobaric hyperoxia significantly improved neuronal cell viability and reduced oxidative stress following OGD. In vivo studies showed that GOLD and normobaric hyperoxia significantly reduced infarct volume, improved neurological function, and attenuated oxidative stress in MCAO-induced stroke rats. Their results suggested that GOLD technology, in combination with normobaric hyperoxia, has significant therapeutic potential for the treatment of acute stroke. This approach can potentially improve stroke outcomes by enhancing oxygen delivery to the penumbra, reducing oxidative stress, and promoting neuroprotection.

## 4. Conclusions

PFCs have emerged as promising oxygen-dissolving and delivering agents, offering a unique approach to addressing oxygen deficiency in various medical conditions. PFCs have demonstrated efficacy in treating hypoxic conditions associated with stroke, heart attack,

trauma, and respiratory disorders. Their ability to enhance oxygen delivery has the potential to improve tissue perfusion, reduce organ damage, and promote healing. PFC-based therapies are being investigated in various forms, including emulsions, liposomes, nanoparticles, etc. However, despite their promising therapeutic potential, PFCs also present potential drawbacks, such as accumulation in the body and potential toxic effects. Further research is necessary to understand and address these concerns fully, ensuring the safe and effective utilization of PFCs in clinical settings. Overall, PFCs are promising to revolutionize oxygen delivery strategies and improve outcomes for patients with oxygen-deprived conditions.

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## Conflicts of Interest

The authors declare no conflict of interest.

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