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Combined use of partially fluorinated alkanes, perfluorocarbon liquids and silicone oil: an experimental study

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Abstract *Background*: Partially fluorinated alkanes (FALKs) are a new class of substances which can be used in vitreoretinal surgery as an intraoperative tool and as a long-term tamponade. The aim of this in vitro study was (1) to investigate the solubility of FALKs in silicone oil during direct exchange, (2) to study their combined use and solubility in PFCLs, (3) to evaluate their lipophilic properties and (4) to investigate the possibility of preparing "heavy silicone oil". *Methods*: (1) Four different FALKs (F_6H_6, F_6H_8, O_{44} and O_{62}) were directly exchanged with silicone oil (5,000 mPas). The dissolved amount of fluorocarbons in the removed silicone oil was determined by gas chromatography and by gravimetry. Furthermore, the diffusion phenomena during the exchange process were studied. (2) The behaviour of FALKs in PFCLs was investigated and the solubility of the resulting mixtures in silicone oil was measured. (3) The solubility of FALKs and PFCLs in native olive oil was analysed. (4) Different FALKs were added to silicone oil and measurements of the resulting specific gravity and the viscosity were performed. *Results*: (1) FALKs dissolved in silicone oil up to the following values: F_6H_6=45 m%, F_6H_8=54 m%, O_{44}=100 m%, O_{62}=18 m%. (2) FALKs dissolved in PFCL, thereby changing the physicochemical properties of PFCL depending on the type of FALK and ratio used. (3) The lipophilic properties of FALKs and PFCLs could be characterized by their dissolution in native olive oil (F_6H_8=23.4 m%, O_{44}=16.7 m%, F_6H_6=12.3 m%, O_{62}=5.3 m%, PFD=1.1 m%, PFO=0.6 m%). (4) It was possible to prepare "heavy silicone oil" e.g. by adding 30 vol% F_6H_8, resulting in a specific gravity of 1.08 g/ml, or by adding 80 vol% O_{44}, resulting in a specific gravity of 1.25 g/ml, but decreasing the viscosity of the mixtures dramatically. *Conclusion*: (1) If FALKs are used as an intraoperative tool, a direct exchange with silicone oil should be avoided owing to their capacity to dissolve in silicone oil, resulting in a mixture with unpredictable properties. (2) A combined use with PFCLs and silicone oil is possible, if the right ratio is chosen. (3) The solubility of FALKs in native olive oil may be an indicator for their tissue penetration and may render feasible their use as a long-term tamponade. (3) "Heavy silicone oil" preparation using FALKs is possible, but the mixture needs further evaluation in terms of emulsification, mobilization of oligosiloxanes, tissue penetration and long-term stability.

Introduction

Silicone oil and perfluorocarbon liquids (PFCLs) are well-known substances, and many experimental and clinical studies have classified their properties and their role in the management of retinal detachments [1, 18,19]. In the past decade PFCLs have become increasingly popular as intraoperative tools in vitreoretinal surgery and have facilitated the surgical management of complicated retinal detachments [2, 29]. PFCLs have also been tested experimentally as a long-term vitreous substitute, showing retinal damage in several studies [3, 4, 33]. Recently, a new class of partially fluorinated alkanes (FALKs) [20, 32] was approved (CE-marked) in Europe for intraocular use [21]. Compared with PFCLs, FALKs have a different structure, a significantly lower specific gravity and a higher potential to dissolve several lipophilic substances and silicone oil [22]. They have been already investigated as a solvent for silicone oil adhesions on intraocular lenses [8, 9,15] and are recommended as a wash-out solution after silicone oil removal. Recent studies have proven their intraocular tolerance as a long-term endotamponade experimentally [6, 14, 37] and clinically [12, 30].

PFCLs and silicone oil show no clinically significant interactions during combined use. This clinical experience and the used intraoperative techniques cannot be transferred to the new class of partially fluorinated alkanes. The exact knowledge of their interactions with silicone oil and PFCL is essential for their combined use in vitreoretinal surgery.

The presented in vitro study had the following aims: (1) To characterize the solubility of four selected FALKs in silicone oil, which is an important property if a direct exchange is intended; (2) to study their interaction with PFCLs evaluating their capability to function as a tool during macular translocation; (3) to measure the solubility of FALKs in native olive oil as a marker for lipophilicity and tissue penetration capability; (4) to evaluate the possibility of preparing "heavy silicone oil" by mixing different FALKs with silicone oil and to assess the influence of the FALKs on the chemical properties of the resulting substance.

Material and methods

Substances

The four different partially fluorinated alkanes used were F_6H_6, F_6H_8, O_{44} and O_{62}. F_6H_6 (perfluorohexylhexane) and F_6H_8 (perfluorohexyloctane) are already certified for medical use and commercially available (Fluoron, Neu-Ulm, Germany; Geuder, Heidelberg, Germany). O_{44} (perfluorobutylbutane) and O_{62} (üperfluorohexylethane) are still in clinical trials (Bausch&Lomb Surgical, Munich, Germany; Pharm Pur, Augsburg, Germany). Chemical and physical properties of the four different FALKs are listed in Table 1. As perfluorocarbon liquids, ADATO OCTA (perfluorooctane, PFO) and ADATO DECA (perfluorodecalin, PFD) were used. They were obtained from Bausch &Lomb Surgical. Their properties are listed in Table 1 as well. All studies were performed using silicone oil with a viscosity of 5,000 mPas (ADATO SIL-OL; Bausch &Lomb Surgical).

Experiments

Direct exchange of FALKs for silicone oil

The reduced specific gravity of FALKs compared with PFCLs has significant advantages during certain vitreoretinal manoeuvres [10]. However, in selected clinical situations such as severe traction retinal detachment a direct exchange for silicone oil might be preferred to avoid retinal slippage [36]. This experiment was performed to investigate the solubility of the different FALKs in silicone oil during direct exchange. In order to determine the mixing ratio during direct exchange and to estimate the resulting risks, the maximum solubility of FALKs in silicone oil and vice versa was determined (a). The concentration reached during the exchange was simulated under clinical conditions (b). Spontaneously occurring diffusion phenomena during direct contact were investigated (c).

(a) Measurement in cylindrical vials. In order to determine the respective saturation concentrations the substances in question were mixed in 5-ml cylindrical glass vials. The solubility of two substances in each other depends on concentration and temperature. The most common way to characterize the solubility is by a so-called solubility diagram. The solubility of each FALK in silicone oil, and vice versa, was measured using cylindrical vials. Silicone oil was added to the selected FALK, and the selected FALK to silicone oil, in small increments. The temperature at which the transition opacification occurred was determined for each ratio, creating the solubility diagram. The temperature of the mixtures was changed until they became opaque or cleared again. Solutions in a molecular ratio which can be described as "FALK in silicone oil"

Table 1 Chemical and physical properties of semifluorinated alkanes (O_{62}, O_{44}, F_6H_6, F_6H_8) and PFCLs (PFO, PFD)

	PFO (perfluoro-octane)	PFD (perfluoro-decalin)	O_{62} (perfluoro-hexylethane)	O_{44} (perfluoro-butylbutane)	F_6H_6 (perfluoro-hexylhexane)	F_6H_8 (perfluoro-hexyloctane)
Purity	>99%	>99%	>99%	>99%		
Boiling point (°C)	104°	142°	113.7°	102.8°	187	223
Density (g/cm³)	1.78	1.92	1.62	1.24	1.42	1.35
Refractive index (nD)	1.27	1.31	1.29	1.31	1.32	1.34
Viscosity (mPas)	1.4	5.53	0.75	0.77	1.85	2.5
Surface tension/air (mN/m)	14.0	17.6	14.7	17.4	20.0	21.0
Molecular weight (g/mol)	438	462	348	276	404	432

form so-called ideal solutions, whereas the ratio "silicone oil in FALK" is characterized by formation of aggregation systems. Both forms of solution are transparent and cannot be differentiated macroscopically. The determination whether the mixture created was an ideal solution or just an aggregated system was performed by means of light scattering using a laser pointer (wavelength: 630–660 nm, power:< 1 mW). At least two determinations were performed.

(b) Measurements in a glass eye model. To simulate clinical conditions optimally, a slow manual direct exchange in a glass eye model was performed, avoiding turbulences and maintaining a controlled temperature of 37°C. The glass eye had two "sclerotomies" to which syringes or infusion lines could be connected. The exchange processes were identical to the clinical manoeuvres. After filling the glass eye with balanced salt solution (BSS) using the infusion line and subsequent exchange with one of the different FALKs by injection through the second opening, substitution of FALK by silicone oil (5,000 mPas) was performed with a suction cannula. To minimize the influence of turbulence during the exchange process and to simulate intraoperative conditions, the silicone oil was removed from the model eye after waiting 15 min. Removal was performed by aspiration using a syringe connected to the "sclerotomy site" and by injection of BSS via the infusion line. The dissolved fluorocarbon molecules in the silicone oil were detected using gas chromatography.

(c) Diffusion experiment in plastic syringes. This experimental set-up was chosen to create defined geometrical conditions and to investigate different interactions between fluorocarbons and silicone oil. Plastic syringes (5 ml) were placed in an upright position and filled with PFD, O_{44} and O_{62}, then cooled down to temperatures below 0°C. Subsequently silicone oil was added and the temperature was increased to 37°C. Fifteen minutes later the temperature was decreased again to "freeze" the diffusion profile. Samples at different heights were taken using syringes and 20-gauge cannulas. The amount of fluorocarbons in the different layers of the mixture was measured by a head-space sampler (HS40 Perkin-Elmer) coupled with gas chromatography (Shimadzu GC 17AQP5000). This machine measures samples from a gas phase which is in equilibrium with an underlying liquid phase. This technique allows detection of volatile compounds in silicone oil qualitatively and quantitatively.

Combined use of FALKs, PFCL and silicone oil

FALKs were introduced into vitreoretinal surgery because of their reduced specific gravity compared with PFCLs and have shown advantages for the macular rotation manoeuvre. As FALKs and silicone oil are miscible, a direct exchange of one of these two substances for the other should be avoided. Therefore, before use in surgery FALKs are mixed with PFCLs to avoid their dissolution in silicone oil.

The solubility of mixtures of the four different FALKs in PFO was analysed by adding the FALK/PFO mixtures to silicone oil at a controlled temperature of 37°C until opacification, an indicator of saturation, occurred. The substances were stirred until saturation was achieved. The amount of fluorocarbon mixtures dissolved in silicone oil was measured gravimetrically. Furthermore, the solubility of different ratios of FALK/PFO mixtures in silicone oil was analysed in order to determine a combination and a ratio which allows a direct exchange with silicone oil.

Lipophilicity of FALKs and PFCLs

The lipophilicity of a substance can be used as an indicator for its tissue penetration properties. Since FALKs are lipophilic substances, their penetration into the retina may be possible, particularly if they are used as long-term tamponades. Therefore we determined the lipophilicity of F_6H_6, F_6H_8, O_{44} and O_{62}.

The current standard for determining the lipophilicity of fluorocarbons for biomedical applications is the measurement of the CTSH value (*c*ritical *t*emperature for *s*olubility in n-*h*exane – the lower this temperature, the higher the lipophilicity). Because visual observation of the opacification point served as an indicator for lipophilicity of FALKs with CTSH values below 0°C, the precision of this subjective method was not sufficient to determine the lipophilic properties of such compounds. In consequence, the solubility of the selected FALKs and of PFCLs was measured in native olive oil, another method for characterization of lipophilicity behaviour.

Recent studies have shown that solubility in olive oil may serve as a model for biological tissue penetration capability [16]. The measurements were performed at room temperature by adding the characterized substance to native olive oil in cylindrical vials under constant mechanical stirring, until irreversible opacification occurred. Subsequently, an additional amount of fluorocarbon was added to this mixture and it was evaluated at which temperature the native olive oil became clear again [16]. The solubility was detected gravimetrically.

"Heavy silicone oil"

Due to the solubility of FALKs in silicone oil, "heavy silicone oil" can theoretically be created. Its higher specific gravity could have marked advantages in the treatment of complicated retinal detachments, especially if inferior breaks or retinotomies are present. The increased viscosity compared with FALKs could be advantageous with respect to droplet formation and applicability.

Therefore, changes in the specific gravity of silicone oil (5,000 mPas) were measured after adding different amounts of F_6H_6, F_6H_8 and O_{44}. The viscosity was determined in a rheoviscometer according to Höppler. GC/MS was performed using a Shimadzu GC 17AQP5000 coupled with a head space sampler (HS40 Perkin-Elmer).

Results

Direct exchange of FALKs with silicone oil

(a) Measurement in cylindrical vials

The solubility of O_{44}, F_6H_8, F_6H_6 and O_{62} was measured using cylindrical vials by adding silicone oil to the selected FALK, and the selected FALK to silicone oil, in small increments. The solubility diagram for F_6H_8 is shown in Fig. 1. Only at a certain temperature are defined ratios of FALK and silicone oil miscible [22, 23]. Outside these defined ratios the two substances are immiscible, creating a so-called mixture gap. At mixture gaps the solutions opacified, because they were not stable, and the two substances separated to single phases again. Another characteristic point is the change of the solution structure at a molecular ratio of approximately 50%. Molecular ratios which can be described as "FALK in silicone oil solutions" form so-called ideal solutions, whereas "silicone oil in FALK solutions" are characterized by the formation of aggregation systems. That could be demonstrated with the beam of a laser pointer: a solution of “silicone oil in FALK” (silicone oil:FALK ratio <1) showed a Tyndall phenomenon and differed markedly from a solution of “FALK in silicone oil” (silicone oil:FALK ratio >1), where no Tyndall phenomenon could be observed. If the temperature of the “silicone oil in FALK” solution was increased the Tyndall phenomenon disappeared, and if the temperature was diminished, the phenomenon reoccurred, a typical indicator for self-organization. Further cooling lead to the formation of two separate phases. This behaviour illustrates the complex interactions of the different components in such mixtures, and it has to be considered that the individual molecular structure of the FALK that is used has an important influence on the stability of the formed solutions.

The solubility of the different FALKs in silicone oil (5,000 mPas) over the whole temperature range was: $O_{44} > F_6H_8 > F_6H_6 > O_{62}$. If the temperature was reduced, the solubility in silicone oil of all FALKs used was decreased. Assuming that the clinical exchange process is performed at room temperature (25°C), the measured values were: O_{44}=100 m%, F_6H_8=54 m%, F_6H_6=45 m% and O_{62}=18 m%. There was a correlation between the solubility in silicone oil, the lipophilicity and the molecular structure of the FALKs. These values are the results of double tests; therefore, no standard deviation is given. The detected values are the upper limits of solubility of FALKs in silicone oil during a direct exchange.

(b) Measurements in the glass eye model

The quantity of FALKs measured dissolving in the silicone oil samples was influenced markedly by the unsuitable surface properties of the glass eye, which showed a considerable amount of visible FALK remnants after the exchange process. Due to the adhesion forces of FALKs and silicone oil to the glass surface, in contrast to clinical conditions exact evaluation of the position of the interface shift during the exchange was not possible. Various modifications of the glass surface failed to improve its unsuitable properties for this experiment. The measured values were not reproducible and showed huge differences of more than 100% deviation. Visually the conditions influencing the mixture could be described (Fig. 2), but quantification was not possible.

(c) Diffusion experiment in plastic syringes

In the diffusion experiment a shift in the position of the interfaces could be observed as a clear indication of a dissolution process. The direction in which the dissolution occurred could be described. After adding PFO to silicone oil only a minimal shift of the interface to the silicone oil was seen and the mixing phase appeared as a thin layer. However, if FALKs were added, a marked shift towards the silicone oil phase occurred and a larger mixing phase or interfacial layer developed (Fig. 3). The diffusion profile for PFD, O_{62} and O_{44} is shown in Fig. 4. The steepness of the concentration gradient and the diffusion distance from the former phase boundary are strongly correlated with the solubility of the different fluorocarbons in silicone oil.

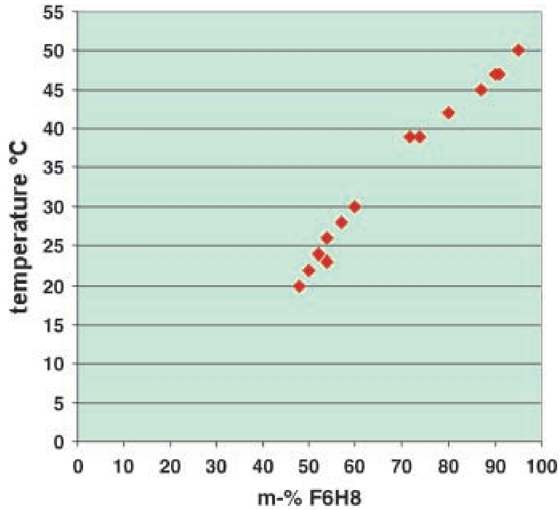

Fig. 1 Solubility diagram indicating the mixture gap in the system ADATO SIL-OL 5000 and F6H8

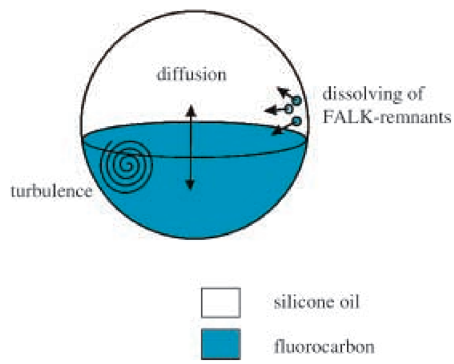

Fig. 2 Mechanisms involved in direct exchange of FALKs and silicone oil

Combined use of FALKs, PFCLs and silicone oil

Initially, after adding the different FALKs to PFCL, inhomogeneities could be detected with the naked eye which disappeared after a few seconds without stirring. The substances dissolved completely without later separation of the phases. The resulting mixtures showed the same behaviour as PFCL in BSS, but revealed different chemical properties, including a higher solubility for silicone oil. There-

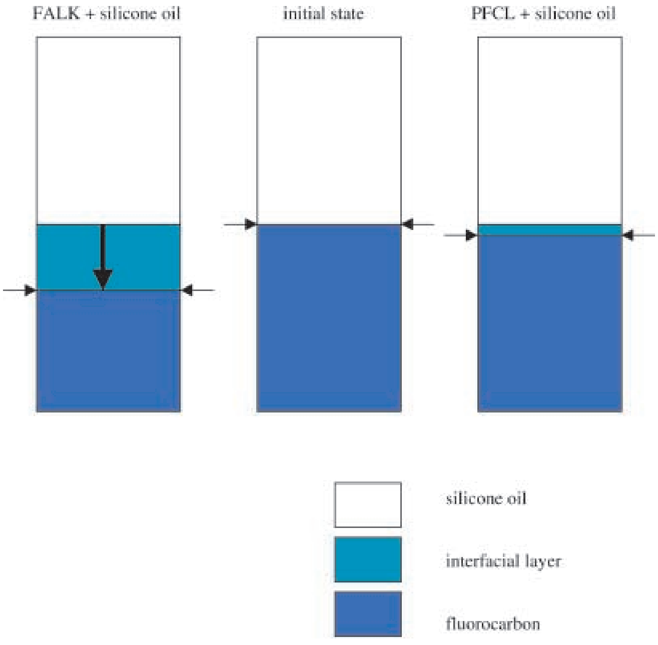

Fig. 3 Interaction of silicone oil and FALK or silicone oil and PFCL

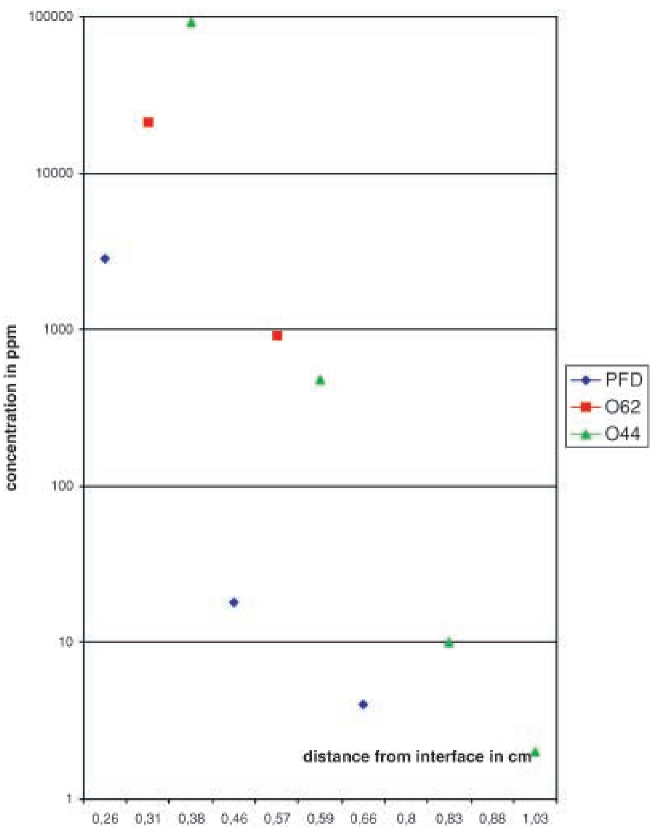

Fig. 4 Diffusion profile of PFD, O_{62} and O_{44} in ADATO SIL-OL 5000

Table 2 Solubility of PFCLs (PFD, PFO) with 10 vol% FALK (O_{62}, O_{44}, F_6H_8) in silicone oil (5,000 mPas) in contrast to the pure FALK

	PFD (perfluoro-octane)	PFO (perfluoro-decalin)	Pure FALKs
O_{44} (perfluorobutylbutane)	6.2 m%	3.9 m%	100 m%
O_{62} (perfluorohexylethane)	5.8 m%	3.7 m%	18 m%
F_6H_8 (perfluorohexyloctane)	6.4 m%	4.1 m%	54 m%

fore the solubility of FALK/PFCL mixtures in silicone oil was measured. Several ratios of FALK and PFCLs were chosen. The resulting solubilities of the mixtures in a ratio of "PFCL/FALK in silicone oil" ranged between the values of the pure components. In contrast to the pure FALKs, silicone oil was not miscible with mixtures of PFCL/FALKs. The reason for this additional mixture gap was that the addition of the PFCL destroyed the solvent structure of silicone oil in FALK. Therefore, an addition of PFCLs to stable "silicone oil in FALK" mixtures but also to "PFCL/FALK in silicone oil" mixtures led to a spontaneous opacification or phase separation. Stable mixtures existed only in a limited range of "PFCL/FALK in silicone oil" ratios, provided the sequence of addition of the single components had been correct.

The results of solubility measurements for a ratio of 90 vol% PFO or PFD and 10 vol% FALK (O_{44}, O_{62}, F_6H_6 and F_6H_8) are presented (Table 2). For this ratio the solubility for silicone oil was nearly the same as for pure PFCLs (below 7 m%). In comparison, PFO could be dissolved up to 3.7–4.4 m% and PFD up to 5.8–6.4 m% in silicone oils of different viscosities. Only PFCL/FALK mixtures with nearly the same solubilities as the PFCLs allowed a direct exchange with silicone oil, i.e. the FALK concentration in the mixtures had to be 10% or less.

Lipophilicity of FALKs and PFCL

The solubility of PFO in native olive oil was 0.6 m% and of PFD 1.1 m% respectively. The values measured for FALKs were markedly higher: F_6H_8=23.4 m%, O_{44}=16.7 m%, F_6H_6=12.3 m% and O_{62}=5.2 m%. The corresponding molecular fraction correlated with their solubility in silicone oil.

Mixtures of FALK in silicone oil – "heavy silicone oil"

The theoretically achievable changes in specific gravity of silicone oil (5,000 mPas) by addition of different

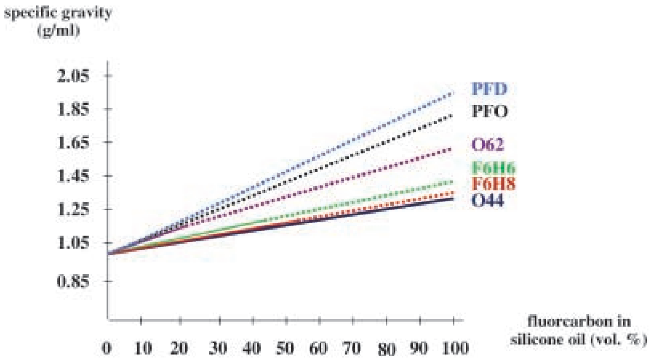

Fig. 5 Theoretical changes of specific gravity by addition of different fluorocarbons to ADATO SIL-OL 5000: (....) indicates the mixture gap of each fluorocarbon

FALKs (F_6H_8, O_{44} and O_{62}) are shown in Fig. 5. The use of the FALK with the highest specific gravity (O_{62}) yields mixtures with a specific gravity as high as possible. However, the achievable increase in specific gravity is limited by the solubility of FALKs in silicone oil. Theoretically, an increase of specific gravity to 1.01 g/ml should be sufficient to obtain "heavy silicone oil", but the subsidence in water-containing media is also influenced by surface tension and adhesion forces of surrounding tissues. This could be observed in experiments with 20 vol% F_6H_8 in silicone oil, which was adequate to obtain a specific gravity of 1.02 g/ml, but showed an instability of the phase separation between "heavy silicone oil" and BSS, with floating and hovering of parts of the oily phase after moving the vial. To guarantee a stable tamponade which is heavier than water, a specific gravity of at least 1.06 should be achieved in order to obtain a safe subsidence and phase separation inert tamponade. Therefore, if F_6H_8 is used, a mixture near the saturation limit is necessary for safe intraoperative use.

After addition of FALK the silicone oil changes its refractive index and its original viscosity. An addition of 10 vol% O_{62} to silicone oil (5,000 mPas) resulted in a specific gravity of 1.04 g/ml and a decrease in viscosity from 5,000 to 2,852 mPas. An addition of 30 vol% F_6H_8 resulted in a specific gravity of 1.08 g/ml and a decrease in viscosity to 1,136 mPas. Increasing the amount of FALK leads to further decrease in viscosity of the resulting mixture and thus may influence the risk of emulsification.

Discussion

Direct exchange of FALKs with silicone oil

Vitreoretinal surgeons are used to perfluorocarbon liquids and silicone oil as intravitreal substances which do not show significant clinical interactions and are not soluble in one another. In former studies the different specific gravity of the two substances was used concomitantly for combined long-term tamponade of the lower and upper retina [28, 31]. In these studies no interaction among PFCLs and silicone oil was noted. This situation has changed markedly with the introduction of the so-called partially fluorinated alkanes which are able to form mixtures with silicone oil [22, 23]. The solubility of the different FALKs in silicone oil varies significantly. Therefore, exact knowledge of the different properties of these new substances is extremely important if the vitreoretinal surgeon is to profit from their benefits and avoid complications if a combined usage of FALKs and silicone oil is intended.

Regarding solubility properties in the system FALK/silicone oil, it has to be taken into account that solutions of "FALKs in silicone oil" or "silicone oil in FALK" show different effects. Usually the transition of a "FALK in silicone oil" to a "silicone oil in FALK" solution happens by a sudden change in solubility. This indicates that at this concentration structural changes in the solution occur. In contrast to the purified PFCLs, the lipophilic behaviour, expressed as the solubility of several FALKs in silicone oil, cannot be predicted by the CTSH value. The solubility in native olive oil is a better measure of the lipophilicity of FALKs [16], although structural influences in the solution have to be taken into account. Especially in the case of small amounts of silicone oil, the solubility can be dominated by structural influences. No simple correlation exists between the length of the fluorinated or non-fluorinated part of the FALK and the solubility in silicone oil. Nevertheless, the ratio of length and molecular structure of both parts is of great importance for the stability of the resulting solutions and the dimension of the mixture gap in the system FALK/silicone oil. With decreasing solubility of FALK in silicone oil and of silicone oil in FALK, mixtures are stable at higher temperatures only. During the exchange process when the mixture ratios might be changed a segregation may occur.

The following mechanisms may influence the amount of dissolved FALKs in silicone oil during their direct exchange (see Fig. 2): (A) Diffusion through the contact interface of the two substances and (B) the dissolution by contact of silicone oil and FALK remnants on the retinal surface. This is enhanced by (C) turbulences during the exchange process.

The silicone oil/FALK-mixtures described above could be reduced if a larger volume of silicone oil would pass the eye. However, this cannot be performed in clinical routine without the risk of uncontrolled increase of intraocular pressure.

In the diffusion experiment the penetration depth of the different FALKs correlated with their solubility. A significant difference between PFCL and FALK could be observed with a marked shift of the FALK/silicone oil interface compared with the PFCL/silicone oil interface. However, this shift is also the prerequisite for a direct exchange, because opacifications are minimized this way.

With increasing solubility of FALKs in silicone oil, the direct exchange becomes more difficult. If the exchange process is not conducted fast enough, complete exchange can become impossible. Only O_{62}, the FALK with the lowest solubility in silicone oil, might be used if a direct exchange cannot be avoided.

Generally, an exchange from FALK to air should be preferred to avoid any dissolving of FALK in silicone oil during the exchange process. However, it has to be kept in mind that even if a clinically complete exchange of FALK with air is assumed, a small amount of FALK may remain as a transparent layer on the retinal surface. This was already described for PFCL by Winter et al. [34]. Since the enthalpy of the different FALKs is not known, the exact vapour pressure at 37°C cannot be given. Using fluorocarbons with a boiling point of 115°C at body temperature results in a vapour pressure between 40 and 60 mbar. PFO, with a boiling point of 104°C and a vapour pressure of 43 mbar at 37°C, shows markedly better evaporation than PFD, which has a boiling point of 142°C and a vapour pressure of 8.8 mbar. The FALKs with a boiling point below 115°C have evaporation behaviour similar to that of PFO and they are therefore more suitable if an air exchange must be performed to minimize remnants in the gas phase.

Therefore, the most suitable FALKs for an air exchange are O_{44} and O_{62}. However, it has to be kept in mind that an intraoperative fluid–air exchange is often impossible in cases of severe tractional retinal detachment. In these situations a PFCL should still be used.

Combined use of FALKs, PFCLs and silicone oil

FALKs and PFCLs can be mixed intraoperatively and dissolve in each other. However, if a direct exchange of the resulting mixture to silicone oil is planned, the sequence of substances should guarantee that the solubility of the PFCL for silicone oil has not increased. The use of such mixtures could be considered during the macular rotation procedure when a direct exchange is desired to avoid retinal slippage [36]. To take advantage of the specific properties of a small bubble of FALK during the rotation, its volume should not exceed 10 vol% of the subsequently added PFCL. In this case the solubility of PFCL is not markedly affected and complete direct exchange of the resulting mixture with silicone oil is guaranteed. As compared with PFD analogues their solubility in silicone oil is low, PFO and PFO/FALK mixtures are favourable. If a larger amount (>10 vol%) of FALK is used, precipitations and opacifications during the direct exchange occur, which may cause severe complications during the exchange process. An alternative method is the use of O_{62} alone. F_6H_6 has a lower specific gravity than O_{62}, but O_{62} shows the lowest solubility of the examined FALKs in silicone oil. This is favourable for a direct exchange procedure and allows a clinically complete exchange.

However, O_{62} has the highest specific gravity (1.62 g/ml) among the presented FALKs. It seems that properties of FALKs other than specific gravity are of importance, especially interfacial tensions which facilitate the rotation manoeuvre. Further investigations will have to clarify, whether the specific gravity is the critical property for the macular rotation procedure.

Nevertheless, a lower specific gravity is favourable. The reduction of specific gravity of fluorocarbon can be achieved by replacement of the fluorine atoms by hydrogen atoms only. This, however, leads to a more hydrocarbon type substance which shows a higher potential for solubility in silicone oil. The properties “low specific gravity” and “high potential for solubility in silicone oil” coincide; thus, the substances F_6H_8 and O_{44} are not suitable for combined use with silicone oil.

Therefore, some general rules for the exchange procedure have to be followed:

a) If PFCL is to be added to FALK intraoperatively, the resulting mixture should consist of at least 90% PFCL before replacement with silicone oil is performed.
b) Even the least soluble FALK (O_{62}) dissolves in silicone oil more easily than PFCLs. Despite the fact that the resulting silicone oil shows no visual differences from “clean” silicone oil, viscosity and lipophilicity are influenced in an unpredictable manner. Therefore, direct exchange of FALK with silicone oil should be considered with the least soluble FALK (O_{62}) only.
c) If FALKs are already in contact with silicone oil, any further contact between PFCLs and both other substances should be avoided.

Lipophilicity and tissue penetration capability of PFCLs and FALKs

The lipophilic properties of FALKs are important during their use as an intraoperative tool or vitreous substitute, because lipophilic compounds may penetrate ocular tissue like the retina or the optic nerve, as already shown for silicone oil[5, 11, 13,26]. It has been shown that the determination of solubility of FALKs in olive oil can be an adequate model for their tissue penetration capability [16].

All published results indicate that the examined FALKs may have the capacity to penetrate tissue. As a result retinal damage might occur during long-term use. However, it remains speculative whether penetration through the inner limiting membrane (ILM) of the retina takes place. The hydrated character of the ILM, which is classified as the basal membrane of the Müller cells, should prevent a marked penetration of lipophilic FALKs.

The increased lipophilicity of FALKs compared with PFCLs also has advantages. Intraocularly retained FALKs can dissolve in silicone oil better than the PFCLs, which have significantly lower lipophilicity. Small FALK bubbles should vanish in this way, resulting in a better optical performance of the silicone oil. It has been reported that PFCL remnants can be mobilized by adding lipophilic FALKs [22]. Higher amounts of FALKs (>10 vol%) markedly raise the solubility of PFCLs, but unfortunately the risks caused by the instability of the mixtures so formed rise proportionally, as mentioned above. Based on our observations concerning lipophilicity and segregation processes, preliminary tests on diffusion mechanisms between different silicone oil/FALK mixtures and aqueous solution like tissue culture media (DMEM) have been performed. First results indicate that lipophilic components leach into aqueous media and form the basis for tissue penetration experiments using retinal cultures.

Mixtures of FALK and silicone oil – "heavy silicone oil"

A vitreous tamponade heavier than water would have marked advantages in the treatment of complicated detachments of the lower retina, especially if large inferior breaks or retinotomies are present. The use of PFCLs in vitreoretinal surgery is limited mainly to a temporary tamponade, and removal at the end of surgery is recommended. Changes in the retinal architecture were observed in animal studies using PFCLs as a long-term vitreous substitute [2, 3, 33]. Since these changes were found mainly in the lower retina, the high specific gravity of the PFCLs was thought to be the reason for this finding. Therefore FALKs, which have markedly lower specific gravity, may offer advantages not only during certain vitreoretinal manoeuvres but also as a long term vitreous substitute [10]. Other disadvantages of PFCLs, such as the combination of low viscosity and high specific gravity with the tendency toward emulsification and dispersion, cannot be overcome by the use of FALKs. A new class of hydrofluorocarbons formed by oligomerization of FALK may solve this problem [14].

Peyman et al. reported successful treatment of three patients with fluorosilicone oil, which has a specific gravity of 1.31 g/ml [27]. However, toxic reactions after use of this oil were observed in experimental studies [24]. An alternative preparation of "heavy silicone oil", which leads to a physical mixture and not to a chemical compound, can be achieved by the addition of FALKs to silicone oil [7,35]. Wolf et al. reported about the successful use of such a mixture (Oxane HD) in a small series of patients with inferior retinal pathologies. We found that the use of approximately 30 vol% F_6H_8 resulted in a mixture with a specific gravity of 1.08 g/ml. However, this led also to a change in other properties, including a significant reduction in viscosity and a marked decrease in the refractive index. It is not yet known whether the resulting mixture remains stable or whether it may lose its higher specific gravity by emigration of the lipophilic alkane. Due to lipophilic properties of the FALK/silicone oil solution, the capability of tissue penetration is unknown and the anatomical and functional consequences during a long-term tamponade can not be predicted. Finally, the mobilization of toxic oligosiloxanes in silicone oil [25] by the addition of FALKs cannot be excluded. This hypothesis is supported by a study on the release of low-molecular-weight siloxanes and platinum from silicone breast implants [17]. These compounds are much more soluble in FALKs than silicone oil. Therefore, experimental in vivo studies are needed to evaluate this issue.

Conclusion and clinical consequences

The new class of partially fluorinated alkanes offers promising substances for vitreoretinal surgery, which provide a variety of new properties. Basing on the results presented in this study the following conclusions can be drawn:

a) This new class of vitreous substances cannot adequately replace perfluorocarbon liquids in all their current functions. Vitreoretinal surgeons should not use them as if they were only another PFCL. Generally, direct replacement of FALKs by silicone oil should be avoided.
b) O_{44}, the FALK with complete solubility in silicone oil seems to be the best candidate as a wash-out solution for silicone oil remnants which are not covered by hydrophobic substances.
c) A combined use of PFCLs and FALKs, allowing direct replacement of the resulting mixture by silicone oil, is possible only if the right ratio of 9:1 is chosen. This property is advantageous during macular rotation if subsequent replacement by silicone oil is necessary.
d) FALKs are lipophilic compounds and their tissue penetration capability is still unclear. Therefore, their use as a heavy long-term vitreous tamponade should be restricted to clinical studies at this time.
e) The preparation of "heavy silicone oil" by the addition of FALKs to silicone oil is possible, but a marked reduction in viscosity and a shift in the refractive index occur. The long-term stability, the tissue penetration capability and the toxicity of the mixture have not been sufficiently evaluated yet. The mixtures of FALKs and silicone oil described need further research.
f) Future clinical studies will have to define the exact indications for the use of the FALKs presented here.

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