European Journal of Ophthalmology / Vol. 10 no. 3, 2000 / pp. 189-197

Review

Semifluorinated alkanes – A new class of compounds with outstanding properties for use in ophthalmology

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Semifluorinated alkanes, R_FR_H, have a perfluorocarbon and a hydrocarbon segment in the molecule. R_FR_H are physically, chemically and physiologically inert, colorless, laser stable liquids with substantially reduced densities - between 1.1 and 1.7 g/cm^3 - and very low surface and interface tensions. R_FR_H are useful for unfolding a retina or for permanent tamponade. They are soluble in perfluorocarbon liquids (PFCL), hydrocarbons and silicone oils. For the first time residues of silicone oil can be extracted from the eye because R_FR_H are solubilizers for PFCLs and silicone oils, so they can be used as solvents or solubilizers for drugs and medicaments. Therefore R_FR_H are excellent candidates for use in the ophthalmic field. (Eur J Ophthalmol 2000; 10: 189-97)

KEY WORDS. *Semifluorinated alkanes, Perfluorocarbons, Biocompatibility, Silicone oil, "Heavy" silicone oil, Silicone oil solvent*

Accepted: June 12, 2000

INTRODUCTION

PFCL are insoluble in water and poorly soluble in silicone oils and hydrocarbons. Studies in recent years have shown that retinal damage occurs when PFCL are used as long-term vitreous replacements (1-6). In addition, PFCL are not tolerated in the anterior chamber, causing corneal edema (7). Therefore, after unfolding a retina, the PFCL have to be removed from the eye and replaced by another medium of lower density, for example silicone oil. We have patented a new class of biocompatible compounds, semifluorinated alkanes of the type R_FR_H and $R_FR_HR_F$, which have lower densities, excellent surface and interface tensions and solubility in silicone oils (8).

MATERIALS AND METHODS

We synthesized and examined type R_FR_H and $R_FR_HR_F$ semifluorinated compounds from commercially available precursors, or used commercially available substances (13-15). We determined toxic byproducts by measuring cleavable fluoride, then by gas chromatography followed by mass spectrometry. Depending on the results the substances were treated with strong bases and high-efficiency distillation according to known procedures for extreme purification (16), resulting in compounds without any impurities. All substances used for clinical investigation or toxicity measurements were heat-sterilized, filtered sterile (filter 0.2 µm), and subsequently steam-sterilized in an autoclave (EN 554).

Cell toxicological values are determined at the University of Tübingen on MonoMac 6, Molt 4, Hela and Raji cell-cultures. Infrared spectroscopy (IR), ultraviolet spectroscopy (UV) and nuclear magnetic resonance (1H-nmr, 19F-nmr) was done at the University of Ulm; temperature-dependent measurements on mixtures of R_FR_H with silicone oils, and the preparation of solutions with medicaments, was done at the Fluoron company. Clinical examinations with F6H8 and mixtures of F6H8 with perfluorodecalin on rabbits and

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30 patients were done at RWTH Aachen (17, 18). A multicenter study on F6H8 as long-term vitreous substitute was conducted under the direction of the Eye Clinic RWTH Aachen (32).

Behaviour and properties of perfluorocarbons used in vitreo-retinal surgery

Up to now PFCL are the most widely used intraoperative unfolding liquids in ophthalmic retinal surgery. They offer exceptional chemical stability, high oxygen solubility and low surface tension. PFCL are of medical interest because they undergo neither catabolism nor metabolism in the human body.

On these accounts, and because of their high specific gravity, PFCL are used for temporary tamponade and mechanical fixation of the retina. Their high specific gravity breaks the micro-membranes on the surface of the retina and provides a good quality smooth surface.

All PFCL are interface-active, leading to the formation and adhesion of a thin PFCL film on the tissue. This effect is stronger the less the surface of the organic material is covered with a layer of moisture, mainly water. Therefore, after application and withdrawal of PFCL with a cannula and hypodermic needle this residual film may remain inside the eye and with time small PFCL bubbles form. Of course, PFCL bubbles may also result from incomplete withdrawal of the unfolding liquid. These small bubbles may join up with larger ones or become emulsified by surrounding plasma or cell constituents. It is not easy to remove the PFCL without residue, as perfluorocarbons cannot be removed or diluted with conventional solvents.

With one perfluoro-perhydrophenanthrene, Vitreon®, there is a double problem: on account of its viscosity, this PFCL is difficult to withdraw from the eye. Then too, it has the same refractive index (1,334 at 20°C) as water (1,333 at 20°C). In this case, residual droplets must inevitably remain, which cannot be distinguished from the wet background or the liquor. Therefore, to be visible during surgery, the PFCL should have a refractive index different from water.

According to Chang (9), the long-term effects of these small amounts of PFCL are uncertain. According to Eckardt, PFCL (F-Octane, F-Ether like Hostinert®) are well tolerated in the rabbit eye for a short time, but after some weeks there is significant damage to the retina, caused by a mechanical interaction between the heavy liquid and the vitreous body (4).

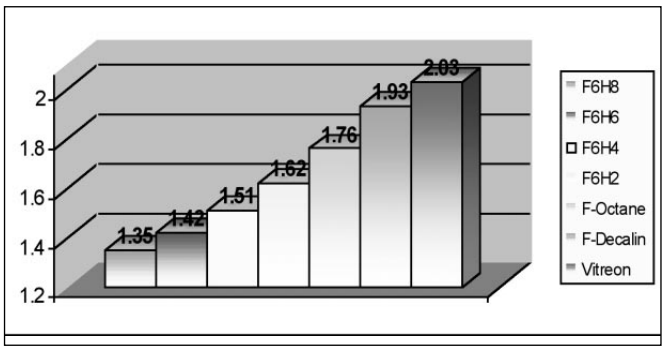


Fig. 1 - *Density of selected semifluorinated alkanes and perfluorocarbons.*

Many similar results are reported (10) (Fig. 1).

The long-term biocompatibility is limited by the specific gravities of PFCL (density), which are between 1.7 and 2.1 g/cm^3, almost double that of the natural eye components. A long-term perfluorocarbon tamponade can set up quite high pressure on the choroid beneath the retina, so that the blood supply to the capillary system is impaired.

According to Velikay, toxic effects of PFCL left inside the eye mainly result from impurities in these liquids (11,12). There is no evidence of toxicity for pure perfluorocarbons. Whenever toxicity was observed, it could be traced either to some unfavourable physical characteristics, or to the presence of impurities. Minute amounts of not completely fluorinated substances still containing hydrogen result in intramolecular splitting of hydrogen fluoride under the formation of toxic fluoro-olefinic C=C bonds. A measure of toxic components is the concentration of fluoride ions released by reaction with a secondary amine.

Gas chromatography combined with mass spectrometry is an essential and fast method for checking purity. Hydrogen and double-bond containing compounds are determined by nuclear magnetic resonance (^{1}H-nmr) and infrared spectroscopy. The purity of PFCL or the toxicity of impurities can also be checked by cell cultures.

In morphological tests the limit of non-toxicity was established at a fluoride ion concentration of 10^{-5} mol/L, but the growth of L-, HEP2 or Molt4-cells was already inhibited at 10^{-3} mol/L.

Semifluorinated alkanes for ophthalmology

To exclude the effect of excessive density and to preserve the favourable properties, such as biocompatibility, high fluidity and gas solubility, favourable interface activities etc., we synthesized and tested compounds for application in ophthalmology, referred to as semifluorinated alkanes (13-15, 20). An example is shown in Figure 2.

Semifluorinated alkanes of the type R_FR_H and $R_FR_HR_F$ have the general formula:

$$F(CF_2)_n(CH_2)_mH$$

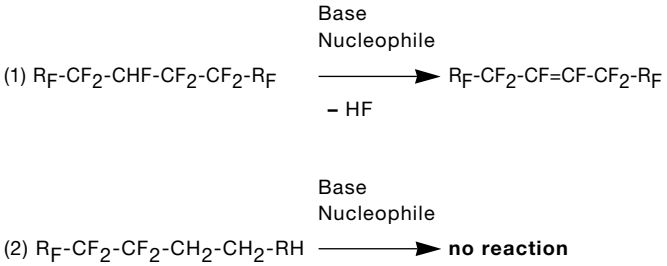
$$F(CF_2)_n(CH_2)_m(CF_2)_nF$$

with n= 3-20 and m = 3-20

These compounds can be linear or branched, and their structure is different from that of perfluorocarbons. In the R_FR_H type the hydrocarbon segment is bonded to the perfluorinated segment. In the $R_F(CH_2)_nR_F$ type the hydrocarbon-alkane group is between both terminal perfluorocarbon segments.

Liquid semifluorinated alkanes are physically, chemically and physiologically inert, colorless and laser-stable with densities reduced to between 1.1 and 1.7 g/cm^3.

With the exception of compounds with the short perfluorinated parts CF_3- and C_2F_5- semifluorinated alkanes are completely biocompatible. Another important point is their chemical stability. They might eliminate hydrogen fluoride. The basic mechanism of cleaning fluorocarbons is given below (21).



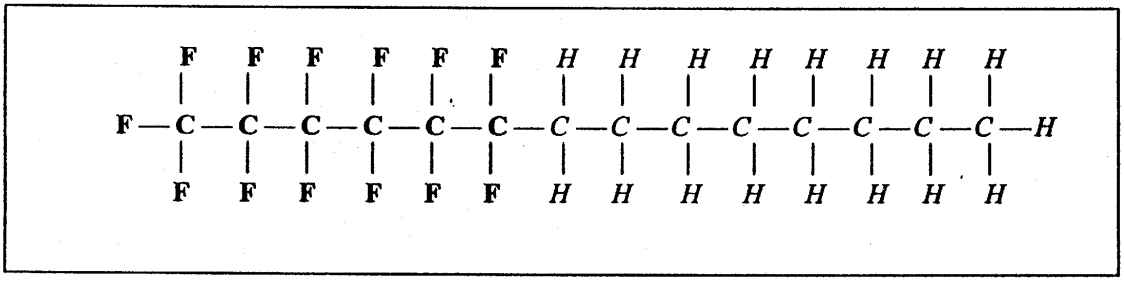
Impurities containing hydrogen in the form of a CHF-group eliminate hydrogen fluoride in the presence of bases (equation 1). The same reaction occurs in the body and the resulting alkenes pose toxicity problems. But semifluorinated linear alkanes do not react according to the mechanism described above (equation 2). They are stable under cleaning-up conditions for perfluorocarbons.

In spite of the $-CF_2$-CH_2-linkage, which inserts an element of discontinuity into the structure, semifluorinated alkanes show high chemical and biological stability that enables them to be used in the biological field.

The influence of semifluorinated alkanes on *in vitro* proliferation of carcinoma cells was tested (22), in comparison with perfluorodecalin, the hydrocarbon de-

Nomenclature

Example:



Chemical Formula: **$F(CF_2)_6$-$(CH_2)_8H$** or $C_6F_{13}C_8H_{17}$
Chemical Name: 1-Perfluorohexyloctane
Abbreviation: F6H8

Fig 2 - *F6H8 as an example of the nomenclature of semifluorinated alkanes.*

cane, and hexafluoropropene (Tab. I). Perfluorodecalin has no influence on cell proliferation but decane reduces it. The toxicity of semifluorinated alkanes should be somewhere between these two compounds. Hexafluoropropene was chosen as a toxic perfluoroalkene to prove the sensitivity of the cells. Cell proliferation was not inhibited by the purified compounds of the homologous series of C_6F_{13}-C_nH_{2n+1} with n = 2,4,6,8,10. But the longer the alkyl chain, the closer were the semifluorinated alkanes' properties to the alkanes. Because cell proliferation is inhibited by hydrocarbons, semifluorinated alkanes with short perfluoroalkyl chains $-CF_3$ and $-C_2F_5$ and a long alkyl chain might be toxic too.

The differences in toxicity for short alkyl chains might be due to the different solubility of lecithin in decane and semifluorinated alkanes. Decane dissolves more than 5% (w/w) of lecithin whereas the compounds of the homologous series C_6F_{13}-C_nH_{2n+1} (n = 2,4,6,8,10) dissolve less than 0.2% (w/w) lecithin. To influence proceedings inside a cell a compound does not have to destroy the cell membrane: something already happens when it is incorporated into the membrane (23). Thus decane reduces cell proliferation but does not destroy the cell membrane, whereas semifluorinated alkanes are not incorporated sufficiently into the membrane to have any influence inside the cell.

Compounds of the homologous series RFC_2H_5 were also examined, but none of these inhibited cell proliferation.

Semifluorinated alkanes are of medical interest because they undergo neither catabolism nor metabolism in the human body (13-16). Purified semifluorinated alkanes cause no inhibition of proliferation concerning DNS- and protein synthesis, as proved in HeLa, Molt4 and HEP2 cell cultures.

LD50 values for purified perfluorinated and semifluorinated liquids are extremely high and confirm their biocompatibility. In the case of F6H6 and F6H8 LD50 of 2000 mg/kg rat demonstrate the low toxicity (Tab. II).

Semifluorinated alkanes, especially of the R_FR_H type, are amphiphilic compounds, due to the oleophobic or lipophobic R_F segment and the oleophilic or lipophilic R_H segment. A measure of the lipophilic or oleophilic behaviour of a substance is its critical temperature of solubility in n-hexane (CTSH). The CTSH depends on the molecules' chemical structure. Lipophobia rises with the length of the R_F segment, whereas lipophilia rises with the length of the R_H segment. Perfluorocarbons are lipophobic/oleophobic substances, with CTSH higher than +42°C, whereas semifluorinated

TABLE I - PROLIFERATION OF CARCINOMA CELLS IN CONTACT WITH DIFFERENT COMPOUNDS

(Percentages of the proliferation of reference cells not in contact with the compounds). Proliferation > 90 % means no inhibition: those compounds are non-toxic.

	(%)
Perfluorodecalin	98
n-Decane, $C_{10}H_{22}$	19
Hexafluoropropene, C_3F_6	0
F6H10	99
F6H8	95
F6H6	96
F6H4	96
F6H2	97
F8H2	96
F10H2	100

TABLE II - CELL TOXICITY

Substance	Hemolysis R.L./Ser.	IL1β-Suppression	IL1β-Induction	HELA-underfloor 3HTDR	RAJI 3HTDR	HELA Trypan % dead cells 4h/24h	RAJI Trypan % dead cells 4h/24h	MonoMac Trypan % dead cells 4h/24h
Perfluorodecalin	neg/neg	4 %	neg	neg	neg	3/4	0/0	0/0
Ringer-lactate	neg/neg	neg	neg	neg	neg	1/0	2/0	2/4
F6H8	neg/neg	24 %	neg	neg	neg	0/12	0/0	5/5

alkanes are lipophilic/oleophilic compounds, with CTSH values significantly lower than 0°C.

Semifluorinated alkanes have the excellent properties of perfluorocarbons as regards low interface tensions against water (50-58 mN/m at 20°C) and very low surface tensions against air (15-22 mN at 20°C).

R_FR_H are statistically isotopic fluids but, depending on the length and linear structure of their R_F and R_H segments, there may be F...H bridges between the R_F and the R_H segments of neighbouring molecules. This leads to the formation of alternate lamellar arrangements between the molecules in relation to the R_F and R_H segments.

Semifluorinated alkanes similarly to perfluorocarbons or hydrocarbons, are not soluble in water. They are soluble in perfluorocarbons or their derivatives and in hydrocarbons or their derivatives. The solubility in perfluorocarbons rises with the length of the R_F part, whereas the solubility in hydrocarbons rises with the length of the R_H part.

Depending on the length of the R_F and R_H segments R_FR_H form micelles (13,24), when dispersed in either perfluorocarbon or hydrocarbon solvents. In general, the solubility of R_FR_H in PFCL is good, depending on the length of the R_F and R_H segments. The R_FR_H may be arranged to the PFCL in form of organized species, eventually forming micelles (13, 28). Micelles or fibrous gels are formed in solutions or dispersions of R_FR_H in hydrocarbons (19, 28-30) (Tab. III).

R_FR_H-silicone oil systems

Until now there was no biocompatible solvent or diluent for silicone oils. For the semifluorinated alkane's, however, a biocompatible solvent or diluent exists, meaning that remainders of silicone oil can be extracted from the eye or dissolved from a lens.

Consequently we examined binary systems of semifluorinated alkanes and silicone oils. The longer the RH group in the semifluorinated alkane and the lower the viscosity of the silicone oil, the better the solubility in each other.

The starting components can be homogenized by strong shaking or sonication. In addition, the solubility of R_FR_H in silicone oils rises with the temperature (Tab. IV). Consequently, homogenous mixtures without dullness cannot be achieved within the eye.

We examined mixtures of silicone oils with perfluoro hexylhexane (F6H6) and perfluorohexyloctane (F6H8). In F6H8, the R_H segment consists of a lin-

TABLE III - SOLUBILITY OF SEMIFLUORINATED ALKANES (25°C)

	n-Decan, $C_{10}H_{22}$
F6H8	miscible in all ratios
F6H6	miscible in all ratios
F6H2	miscible in all ratios
F12H2	not miscible
F8H8F8	not miscible

	Silicone Oil 1000 cSt
F2H8	miscible in all ratios
F4H5	miscible in all ratios
F6H8	73% F6H8 (m/m) soluble
F6H6	36% F6H6 (m/m) soluble
F8H2	not miscible
F6H2	not miscible
F4H8F4	not miscible
F8H8F8	not soluble

	F-Decalin, $C_{10}F_{18}$
F6H8	miscible in all ratios
F6H6	miscible in all ratios
F2H8	miscible in all ratios

	F-Octane, $C_{10}F_{20}$
F6H8	miscible in all ratios
F6H6	miscible in all ratios
F2H8	miscible in all ratios

	Perfluorophenanthrene,$C_{14}F_{24}$
F2H8	miscible in all ratios
F4H8F4	miscible in all ratios
F8H8F8	not soluble

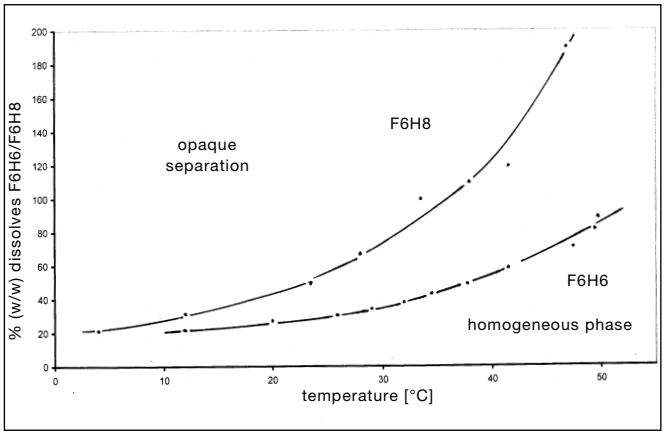


Fig. 3 - *Temperature-dependent mixtures of F6H6 and F6H8 with silicone oil 5000 cSt.*

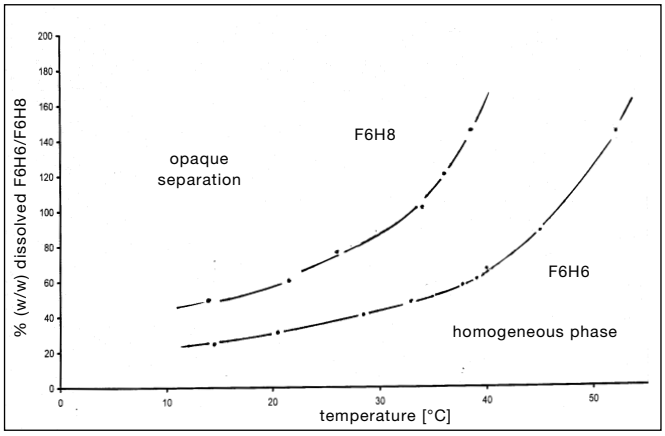


Fig. 4 - *Temperature-dependent mixtures of F6H6 and F6H8 with silicone oil 1000 cSt.*

ear chain of eight hydrogen saturated carbon atoms; in F6H6 the R_H segment consists of six carbon atoms, since the R_F segment is constant. These two additional CH_2-groups in the R_H chain of F6H8 compared to F6H6 increase the solubility in silicone oils considerably. For example, at 20°C the solubility of F6H6 in silicone oil (5000 cSt) amounts to 28% (m/m), and the solubility of F6H8 amounts to 44% (m/m). The solubilities of F6H6 and F6H8 in silicone oils with viscosities of 1000 and 5000 cSt at different temperatures are indicated in Figures 3 and 4.

As mentioned before the solubility of R_FR_H in the binary system R_FR_H/silicone oils increases with decreasing viscosity of the silicone oil. Thus, at a given temperature the solubility of F6H6 and F6H8 can be enhanced by 10 to 20% if silicone oil of viscosity 1000 cSt is used instead of viscosity 5000 cSt.

The solubilities of semifluorinated alkanes in silicone oils also rise with the temperature. At 37°C the RFRHs investigated were about twice as soluble as at room temperature. For example, we observed 60% solubility (m/m) for F6H8 in silicone oil (1000 cSt) at 21.5°C and 120% (m/m) at 36°C.

In solutions of R_FR_H in silicone oils the optically clear homogeneous phase is limited to a certain concentration of R_FR_H, above which the mixture separates into opaque phases (Figs. 3 and 4).

"Heavy" silicone oils

Optically clear mixtures of semifluorinated alkanes (e.g. F6H8) with silicone oils (1000–5000 cSt) with densities between 1.0 and 1.3 g/cm^3 can be obtained (Tab. V).

These mixtures are suitable for use in ophthalmology. Mixtures of semifluorinated alkanes with silicone oils should be preferred to silicone oils in which the RH

TABLE IV - SELECTED SURFACE TENSIONS, INTERFACE TENSIONS AND VISCOSITIES

	Surface tension (mN/m) at 25°C against air	Interface tension (mN/m) at 25°C against water	Viscosity (mPas) at 25°C	Density (g/cm^3) at 25°C
Silicone oil (1000 cSt)	22	23.3	1000	0.97
Silicone oil (5000 cSt)	21	35.4	5000	0.97
F6H8	21.0	49.1	2.5	1.35
F6H6	20.0	49.6	1.85 (37 °C)	1.42
Perfluorodecalin	19.0	57.8	5.1	1.93
Perfluorooctane	14.0	55.0	1.4	1.76
Water	72.0		0.89	1.00

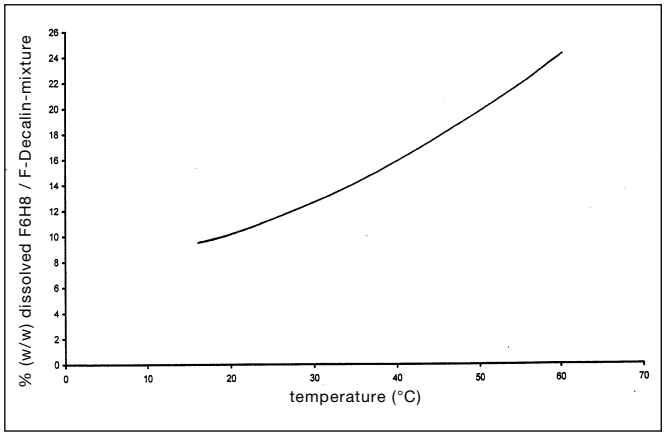


Fig. 5 - *Mixtures of F6H8 and perfluorodecalin (50:50) in silicone oil 1000 cSt.*

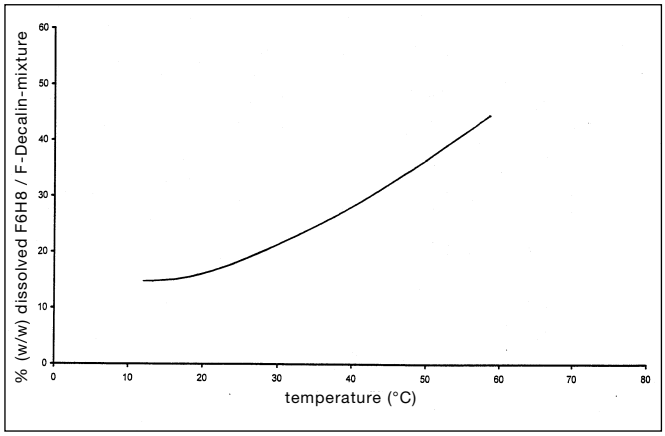


Fig. 6 - *Mixtures of F6H8 and perfluorodecalin (70:30) in silicone oil 1000 cSt.*

groups are substituted by R_F groups (e.g. CF_3 or C_2F_5). Silicone oils with this substitution, where RF groups are a component of the polymer, are rarely produced on a technical scale in the same quality as the unsubstituted silicone oils. Therefore fluorine-substituted silicone oils can be excluded.

R_FR_H-PFCL mixtures

PFCL are scarcely soluble in silicone oils. Therefore, if perfluorocarbons are exchanged for silicone oil, it is very likely that PFCL droplets will remain in the eye for a long time. Strong shaking, sonication or heating of silicone oil-PFCL mixtures are needed to reach a maximal concentration of 2.7% (w/w) perfluorooctane or 4.5% (w/w) perfluorodecalin (20°C), independent of the viscosity of the oil.

Better results can be achieved with mixtures of PFCL with R_FR_H as unfolding liquids. Because of the good dissolving capacity of semifluorinated alkanes for silicone oils, there is a much better transition to the oil. For example, 10.5 % (w/w) of a mixture of 50% F6H8 and 50% F-Decalin can be dissolved in silicone oil at 20°C. At 37°C the solubility is 14.5% (w/w). In general, larger amounts of semifluorinated alkanes in these mixtures lead to better solubilities in silicone oils (Figs. 5 and 6).

R_FR_H as solubilizers for drugs and medicaments

Semifluorinated alkanes are amphiphilic, non-aqueous liquids. These compounds, especially the R_FR_H type, with a long R_H segment, can therefore be used as solvents or solubilizers for selected drugs and medicaments. In R_FR_H drugs and medicaments can be dissolved in their basic form, i.e. the form in which the drug is physiologically effective.

For example, in the case of 5-fluorouracil (5-FU) the basic, physiologically effective, substance can be used instead of its modified, water-soluble hydrochloride. We determined the solubility of 5-FU in F6H8 by UV measurements and found it was 450 mg/L at room temperature.

TABLE V - SURFACE TENSIONS, INTERFACE TENSIONS, VISCOSITIES AND DENSITIES OF "HEAVY" SILICONE OILS

	Surface tension (mN/m) at 25°C against air	Interface tension (mN/m) at 25°C against water	Viscosity (mPas) at 25°C	Density (g/cm³) at 25°C
Silicone oil (5000 cSt) with 17.4% (w/w) F6H8	19.2	34.5	1886	1.02
Silicone oil (5000 cSt) with 33% (w/w) F6H8	18.9	32.8	1275	1.07

Application of R_FR_H in ophthalmology

Semifluorinated alkanes, especially the R_FR_H type, are potentially useful for unfolding or reapplying a retina, for long-term tamponade and also as a vitreous humor substitute in ophthalmology. A multicenter study (32) directed by the University Eye Clinic of RWTH Aachen found F6H8 was a good long-term vitreous substitute for up to three months. Now this product is commercially available for ophthalmic purposes.

In view of their low densities, the semifluorinated alkanes are suited for innovative techniques for retinal translocations (macular relocation) (31).

CONCLUSIONS

Liquid semifluorinated alkanes are physically and chemically inert, colorless, laser- stable compounds with low densities, between and 1.1 and 1.7 g/cm^3.

Semifluorinated alkanes have excellent properties as regards low interface tensions, and very low surface tensions. Semifluorinated alkanes, especially of the RFRH type, are amphiphilic compounds, given by the oleophobic or lipophilic RF-segment and the oleophilic or lipophilic RH segment.

Lipophobia rises with the length of the R_F-segment, whereas lipophilia rises with the length of the R_H segment. Semifluorinated alkanes are soluble in perfluorocarbons or their derivatives and in hydrocarbons or derivatives of hydrocarbons. The solubility in perfluorocarbon systems rises with the length of the RF part, whereas the solubility in hydrocarbon systems rises with the length of the RH part.

Semifluorinated alkanes are the first biocompatible solvents for silicone oils. The longer the RH group in the semifluorinated alkane and the lower the viscosity of the silicone oil, the better is the solubility in each other. The starting components can be homogenized by intensive shaking, sonication or warming. Consequently, homogeneous mixtures without dullness cannot be achieved within the eye. In solutions of RFRHs in silicone oils the optically clear homogeneous phase is limited depending on the respective RF and RH portion and by a definite concentration of RFRHs. Above this concentration, separation into opaque phases occurs. Though F6H8 is preferable for use in ophthalmology (see below) it cannot be dissolved in silicone oil 5000 cSt indefinitely.

By means of RFRH remainders of silicone oil can be removed from the vitreous cavity and intraocular lenses can be cleaned after a silicone oil tamponade.

Optically clear mixtures of semifluorinated alkanes with silicone oils with densities variable between 1.0 and 1.3 g/cm^3 can be obtained.

Semifluorinated alkanes, especially of the RFRH type with a long RH segment, may be used as solvents or solubilizers for selected drugs and medicaments.

ACKNOWLEDGEMENTS

We thank Prof. Dr. B. Kirchhof, Dr. D. Zeana, Dr. S. Langefeld, PD Dr. N. Schrage, Dr. R. D. Hilgers (RWTH Aachen), Dr. D. Wong (Royal Liverpool Hospital), Dr. J. C. van Meurs, (Rotterdam Eye Hospital) for clinical investigations. Cytotoxic examinations were performed by Prof. Dr. H. Northoff (University of Tübingen).

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