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METHODS FOR FORECASTING THE USEFULNESS OF PERFLUOROCARBONS FOR BLOOD SUBSTITUTES

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SUMMARY

It is shown that the development of more efficient perfluorocarbon (PFC) emulsions for blood substitution depends mainly on the application of improved PFCs, the most important PFC-properties being emulsion stability and excretion rate. As a basis for synthesis strategy the estimation of the latter, from the structural formulas alone, has already been reported. For the prediction of the emulsion stability, quantitative structure-stability relationships of several PFCs have now been investigated. It was found that the molar volumes of the PFCs, estimated by means of Lawson's group additivity system, correlate well with their emulsion stability (high molar volume corresponds to high emulsion stability). These findings support Ostwald-ripening as being the main process of PFC-emulsion deterioration.

INTRODUCTION

Perfluorocarbon (PFC) emulsions have attracted much research activity because of their potential use as blood substitutes or, more generally, as oxygen transporting pharmaceutical agents. From a medical viewpoint such emulsions ought to be nontoxic, stable under different storage conditions as well as in the blood stream, able to transport high amounts of oxygen and of carbon dioxide, and should be excreted from the body within a reasonable time.

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It will be shown that all these properties depend mainly on the perfluorocarbon emulsified.

The toxicity of an emulsion results from its components and from the particle size (diameters below 200 nm are claimed). Particle size is linked with storage stability which has been up to now a major problem. The most serious disadvantage of the well-known Fluosol DA 20 is that it must be stored frozen to prevent deterioration of emulsion particles. To enhance emulsion stability it is common practice in colloid chemistry to use a more surface active emulsifier. However, with blood substitutes there is very limited room for such measures because of direct relation between surface activity and toxicity of emulsifying agents [1]. The oxygen transport capacity of proposed PFC blood substitutes reaches the level of whole blood at elevated oxygen partial pressure only. To improve this capacity one has either to use more efficient PFCs - these are very unlikely - or to increase the PFC content of the emulsion. So that the oxygen transport problem is also dependent on emulsion stability. As the importance of excretion rate of the used PFC is obvious, one is justified to say that all the significant emulsion properties depend on the perfluorocarbon. Accordingly, the main efforts regarding improvements in PFC-emulsions for blood substitutes have been concentrated on selection or syntheses of more useful PFCs. Faced also with this task, we were looking for relationships between structural parameters of PFCs and their oxygen solubility, excretion rate and emulsion stability.

EXPERIMENTAL

PFC data were taken from the literature cited. The computations were done on a Robotron A 5120 microcomputer.

DISCUSSION AND RESULTS

The aim of our investigations was the prediction of these properties even for hypothetical compounds as guiding principles for the working preparative chemist.
Here we report the state of predictability of PFC-properties.

Oxygen solubility: Lawson et al. [2] developed a group additivity system for the estimation of energy of vaporization and molar volume of PFCs by which they could also estimate oxygen solubility. Using this system we could show [3] that oxygen solubilities of useful (also hypothetical) PFCs lie within a narrow range not exceeding about 50 % as maximum. Therefore, this parameter is not very important in the development of a synthesis strategy.

Excretion rate: Because of the importance of the excretion rate, many attempts have been made to correlate this property with other PFC-parameters, as e.g. vapour pressure [4], molar weight [5], and critical solution temperature [6]. On the basis of thorough experimental work Yamanouchi et al. [7] studied a number of possible correlations. They found, among others, a very close relationship between half-life ($\tau_{1/2}$) of PFC within test animals and the number of carbon atoms (NOC) as well as the number of fluorine atoms (NOF) expressed by eqn. 1 (obviously, heteroatoms are less important in this respect).

$$\log \tau_{1/2} = 0.254\ (\pm 0.035)\ NOF - 0.151\ (\pm 0.077)\ NOC - 2.19\ (\pm 1.06) \qquad (1)$$

By Eqn. 1 we calculated the NOC and NOF, respectively, which fit the half-life values of 5, 10, 20 and 30 days (Table 1).

TABLE 1

Relation between PFC half-life (retention in a body) $\tau_{1/2}$ and structural data NOC and NOF

NOC	NOF for given NOC and wanted $\tau_{1/2}$ [days]			
	$\tau_{1/2} = 5$	$\tau_{1/2} = 10$	$\tau_{1/2} = 20$	$\tau_{1/2} = 30$
8	16.1*	17.3	18.5	19.2
10	17.3	18.5	19.7	20.4
12	18.5	19.7	20.9	21.6
14	19.7	20.9	22.1	22.8
16	20.9	22.1	23.2	23.9

*decimal numbers are given for orientation only

From Table 1 one can see that a perfluorochemical with e.g. 10 carbon atoms and 18 fluorine atoms is more likely to exhibit a short retention time ($\tau_{1/2}$ between 5 and 10 days) than another compound with 10 carbon atoms but 20 fluorine atoms, which according to Table 1 should have a $\tau_{1/2}$ in the range from 20 to 30 days.

Emulsion stability: There are three main mechanisms which can contribute to stepwise destabilization of emulsions. These are coagulation, coalescence and Ostwald ripening. The latter two result in larger droplets of the perfluorocarbon emulsified, whereas coagulation results in aggregates of unchanged particles which can be reversibly dispersed by comparatively low mechanical forces. Soviet researchers emphasize Ostwald ripening as the decisive process [8, 9]. Following their argumentation we tried to estimate emulsion stability of any PFCs by calculating their solubilities in water. From Hildebrand's solubility theory the following expression for PFC solubility in water can be derived (eqn. 2):

$$\log x_2 = \log \frac{v_1}{v_2} + 0.43 \left[\frac{v_2}{v_1} - (\delta_2 - \delta_1)^2 \cdot \frac{v_2}{RT} - 1 \right] \qquad (2)$$

with $\delta = (-E/v)^{1/2}$

x_2 = molar fraction of PFC in water; v = molar volume; δ = Hildebrand's solubility parameter; subscript 1 = water; subscript 2 = PFC; E = energy of vaporization

We estimated the molar volumes and solubility parameters of some PFCs by again using Lawson's group additivity system and consequently calculated their water solubilities according to eqn. 2. The PFC-solubilities obtained this way are plotted against emulsion stability for some PFCs in Fig. 1. The necessary stability values are taken from Rozenberg and Makarov [11] (quantitative values) as well as from Riess and LeBlanc [12] and Yokohama et al. [13] (qualitative values).From Fig. 1 two conclusions are evident: firstly,the solubility values are too low to have physical significance and secondly, they reflect nevertheless roughly the order of emulsion stability. The correlation between Rozenberg's sta-

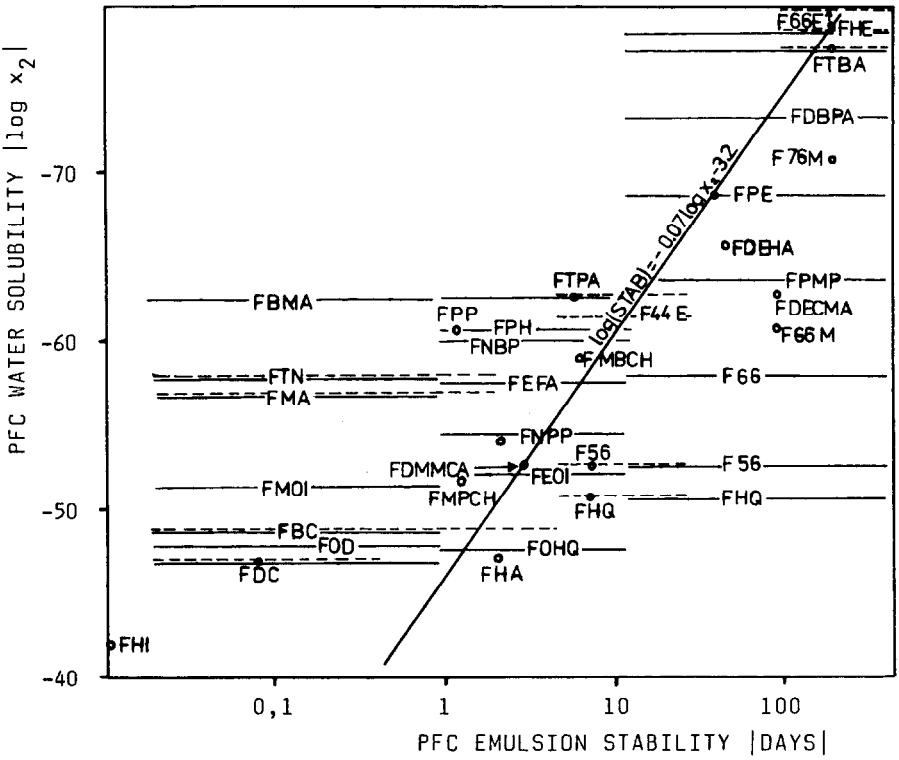

Fig. 1. Emulsion stability (exper.) and water solubility (calc.) of some PFCs (abbreviations see Table 2)
Stability data: o from [11]; quantitative evaluation:
--- from [12] ("poor, fair, good, very good, excellent"),
—— from [13] ("fair, good, excellent")

bility values and PFC water solubility is poor (r = 0.64) and the differences between Yokoyama's stability classes ("fair", "good", "excellent") are, with respect to the corresponding water solubilities, even not statistically significant (t - test; 95 % significance level). It looks as if the water solubility of a PFC could be the basis for the estimation of its emulsion stability. To prove this we looked for more accurate emulsion stability data. The most accurate data we found in the literature are from Aprosin and Kolpachkova[14].They introduced as measure for PFC emulsion stability the rate of particle growth,extrapolated to

TABLE 2

Abbreviations of perfluorocarbons used in Fig. 1

F66E	Bis-F-hexylethene
FHE	F-dihexylether
FTBA	F-tributylamine
FDBPA	F-dibutylpropylamine
F76M	F-N-(p-methylcyclohexyl)hexamethylenimine
FPE	F-dipentylether
FDEHA	F-diethylhexylamine
FPMP	F-2-methoxy-2-pentoxypropane
FTPA	F-tripropylamine
FBMA	F-dibutylmethylamine
FPP	F-N-pentylpiperidine
F44E	bis-F-butylethene
FDECMA	F-N,N-diethyl-(p-methylcyclohexyl)amine
FPH	F-3-propoxy-2-methylpentane
FNBP	F-N-butylpipecoline
F66M	F-N-(p-methylcyclohexyl)piperidine
FMBCH	F-1-methyl-4-tert. butylcyclohexane
FTN	F-trimethyl-bicyclo|3.3.1|nonane
FEFA	F-N,N-diethyltetrahydrofurfurylamine
F66	F-N-cyclohexylpiperidine
FMA	F-N,N-dimethylcyclohexylmethylamine
FNPP	F-N-propylpipecoline
F56	F-N-cyclohexylpyrrolidine
FDMMCA	F-N,N-dimethyl-(p-methylcyclohexyl)amine
FMOI	F-N-methyloctahydroisoindole
FEOI	F-N-ethyloctahydroisoindole
FMPCH	F-1-methyl-4-isopropylcyclohexane
FHQ	F-N-methyldecahydroquinoline
FBC	F-bicyclo-[5.3.0]decane
FOD	F-1-oxadecalin
FOHQ	F-octahydroquinolizine
FDC	F-decalin
FHA	F-decahydroacenaphthene
FHI	F-perhydroindane

the time the emulsion was prepared (w_o in nm per 24 hrs). Table 3 shows for some PFCs the w_o-values taken from Aprosin, together with water solubilities, calculated according to eqn. 2, and additionally molar volumes.
The correlation between stability and water solubility is much better (r = 0.936) than with Rozenberg's data; however, there exists an even closer relationship to a much simpler parameter, i.e. molar volume. This relation is plotted in Fig. 2 and can by expressed by eqn. 4:

$$\log w_o = -0.020\ v + 6.315 \quad (r = 0.941) \qquad (4)$$

TABLE 3

Comparison of emulsion stability w_o (rate of particle growth extrapolated to time zero, taken from Aprosin [14]), water solubility (according eqn. 2), and molar volumes (calculated according to Lawson [2], see Table 4) for some PFCs

PFC	w_o	log x_2	v
F-decalin (FDC)	97.6	-46.9	234.6
F-decahydroacenaphthene (FHA)	64.3	-46.7	242.3
F-1,3-dimethylcyclohexane (FDMCH)	150	-43.5	211.9
F-1-methyl-4-tert.butylcyclohexane (FMBCH)	18.8	-58.9	283.2
F-2-methyldecalin (FMDC)	5.3	-53	251.3
F-5-isopropylperhydroindane (FPI)	5.9	-55.2	265.8
F-tripropylamine (FTPA)	6.3	-62.6	286.7
F-dibutylmethylamine (FBMA)	4.82	-62.6	286.7
F-tributylamine (FTBA)	0*	-77.3	356
F-dibutylether (FBE)	11.1	-59.2	267.2
F-dipentylether (FPE)	1.3	-69	313.4
F-dihexylether (FHE)	0*	-78.8	359.6
F-N-propylpipecoline (FNPP)	8.7	-54.1	256.8
F-N-(p-methylcyclohexyl)piperidine (F66M)	3	-60.5	296.2
F-N,N-dimethylcyclohexylamine (FDMCA)	35	-49.1	233.7
F-dimethylaminoperhydroindane (FDMAI)	4.1	-53.7	264.5
F-N,N-diethyl-(p-methylcyclohexyl)amine (FDECMA)	2.1	-62.1	296.6

* estimated value for ln w_o = -2

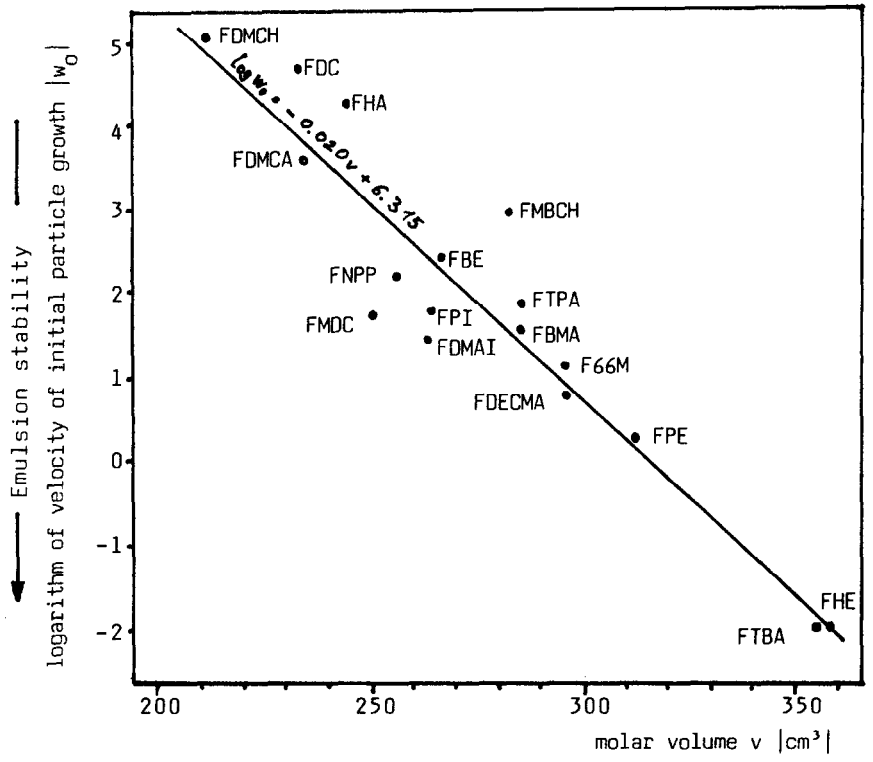

Fig. 2. Correlation between emulsion stability (expressed in term of velocity of initial particle growth) and molar volume of some PFCs(abbreviations see Table 3). Stability data from [14]; molar volumes estimated according to [2] (see Table 3).

According to eqn. 4 high emulsion stability of a PFC,that is low rate of particle growth, is linked with high molar volume. An explanation for this phenomenon can be given on the basis of Ostwald-ripening. Ostwald-ripening is a process of emulsion coarsening by transferring perfluorocarbon (or more generally, emulsified liquid) from smaller droplets to larger droplets. The driving force of this process is the difference in vapour pressures: smaller droplets have higher vapor pressures than larger

TABLE 4

Partial contributions of structural elements to PFC molar volume (taken from Lawson et al. [2])

structural element	v
— CF_3	54.8
— CF_2 —	23.1
— CF —	-15.0
— C —	-38.3
— N —	-16.3
— O —	19.0
5-ring	37.7
6-ring	39.9

ones. However, it can only proceed if PFC molecules are able to penetrate the water layer between emulsified PFC droplets. Thus, the diffusion rate of PFC through water should determine the rate of emulsion deterioration. Larger PFC molecules should exhibit smaller diffusion rates and give more stable emulsions.

Our aim was the prediction of the most important properties of PFCs for blood substitutes as a possible basis for synthesis strategy. As excretion rate and emulsion stability are most important, one has to search for PFCs with a small ratio of number of fluorine atoms to number of carbon atoms (as exemplified in Table 1) as well as a high molar volume (equal to or larger than 290 cm^3/Mol, as shown in Fig. 2). Obviously, such compounds are preferably cyclic and contain oxygen atoms (see Table 4).

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