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Pharmaceutical Technology: Drug Delivery, Formulation, and Process Research

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Abstract: This paper describes in the introduction the actual research trends in the area of pharmaceutical technology and the impact of FDA's PAT (Process Analytical Technology) Initiative on this research field. These new FDA requirements concerning a science-based approach in the area of pharmaceutical formulations and processes will boost this research field in academia and industry. There is a special need for a research initiative in the field of pharmaceutical powder technology, which is the basis for *ca*. 80% of all drug delivery systems on the market, *i.e.* solid dosage forms. Pharmaceutical formulations are complex systems which are difficult to model and analyse. For this purpose special tools such as the percolation theory, concept of fractal dimensions, dielectric spectroscopy, *etc.* are necessary. In this context, typical results obtained with these novel tools are presented.

Keywords: Dosage form design · Drug delivery systems · Percolation theory · Powder technology · Process technology

1. Introduction to the Research Topics

1.1. *Hazards Arising from an Unsuitable Drug Delivery System or Dosage Form*

If the dosage form (drug carrier, drug delivery system, formulation, galenical vehicle, vector) does not deliver the drug precisely with the right quantity in the right quality at the right site of the body of the patient, undesirable side-effects can occur, which depend on the nature of the drug substance.

Already Paracelsus was aware several hundred years ago that it depends on the quantity, whether a drug substance is a poison or a beneficial medication. Paracelsus could not measure the bioavailability of the drug substance and could not monitor the drug concentration in the blood plasma of a patient. More specifically, he could not measure whether the drug concentration in the plasma was above the minimum effective and below the maximum tolerable concentration, *i.e.* within the therapeutic window (Fig. 1). An optimal drug delivery system shows an optimal therapeutic effect and a minimum of side-effects.

In case of theophylline, higher doses overshadow the beneficial effect for asthma patients (broncho-dilation), and can induce severe side-effects leading to heart arrhythmias or even to a status epilepticus (grand mal seizure). For a complete documentation on theophylline see Theophylline CAS N°: 58-55-9 [1]. Fortunately, not every drug shows such a narrow therapeutic window. It has to be realized on the other hand that the occurrence of toxic side-effects does not depend only on the absolute quantity of the plasma drug concentration, but may also depend on the rate of increase of the drug concentration. Thus, a careful design of the dosage form is essential. In case of a long acting drug delivery system for a 'once a day' treatment to avoid a 'three times per day' prescription, the triple unit dose needs to be released under a strict time control.

1.2. *The Complex Task of Designing a Suitable Drug Delivery System or Dosage Form*

The design of a dosage form can be compared to the design of an aircraft, which

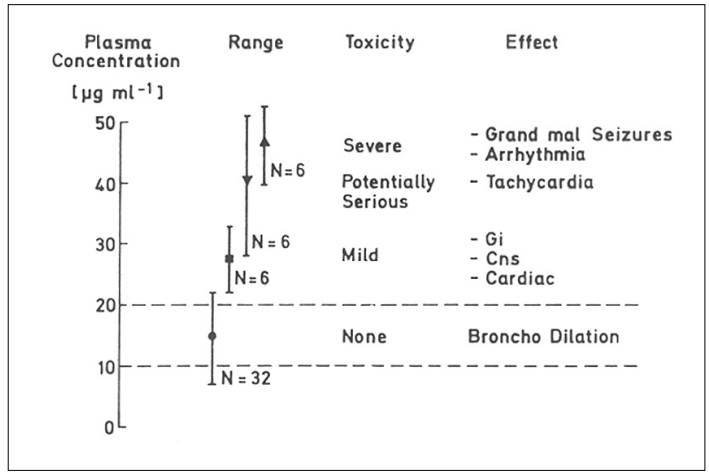

Fig. 1. Plasma concentrations of theophylline related directly to the appearance of adverse reactions. Bronchodilation is the therapeutic effect of this drug. The narrow therapeutic window is indicated.

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needs to deliver all passengers at the right time to the right destination. However, there is an important difference: The 'goods' to be delivered (the drug), cannot be described as easily as a 'normalised' passenger with a mean weight and a mean size. The broad range of therapeutic drugs contains drugs with very different properties such as molecular weight, lipophilicity, wettability, solubility in gastro-intestinal juices, physical and chemical stability in bulk or dissolved in water at different pH-values, compatibility with excipients *etc*. Moreover there can be huge differences between the biopharmaceutical properties of drugs such as the intrinsic permeability of the drug substance through a biological membrane (absorption step), the accumulation of the drug in different organs of the body (distribution), the metabolic pattern of the drug substance (metabolism including the liver first pass effect), the residence time of the drug in the body (elimination kinetics), and last but not least, the amount of drug to be delivered which, in general, can range between 0.1 mg and 1 g per unit dose.

Some of the properties can be also decisive for the type of administration of a drug. Thus as an example, insulin needs to be injected with a syringe subcutaneously because of its instability in the gastro-intestinal juices and absorption problems due to the large molecular weight.

Fig. 2 shows topics and hurdles related to pharmaceutical technology designing a drug delivery system fit for the market place. In addition, it has to be kept in mind that the dosage form is optimised during the search for the optimal dose in early clinical studies using a formulation manufactured on small-scale equipment. Unfortunately, the formulation cannot be changed at a later stage. Thus, the quality obtained with small-scale batches needs to be the same for large-scale batches. This is an extra challenge for the pharmacist working in industry on the design of robust formulations.

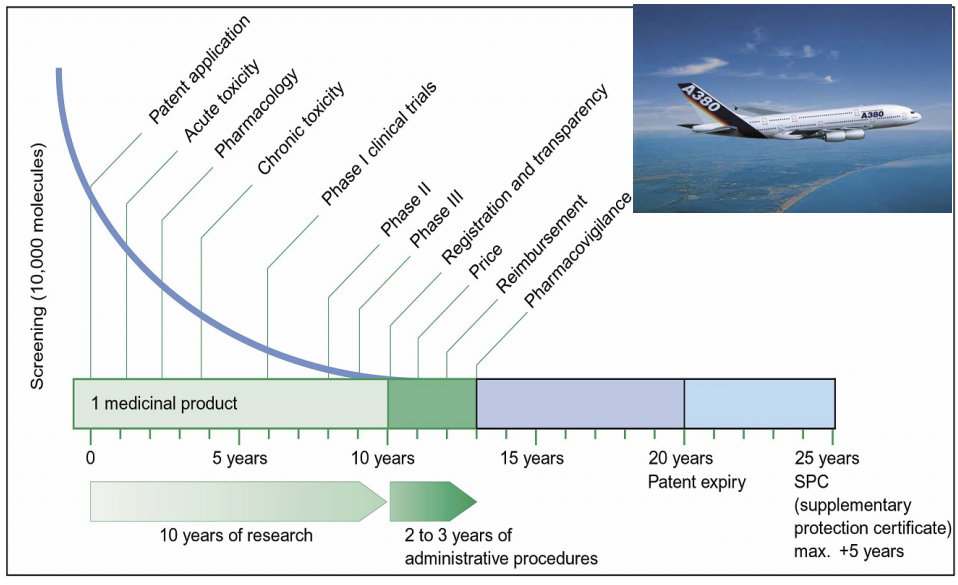

Fig. 2. From a promising molecule to a marketed product. Topics and hurdles related to pharmaceutical technology designing a drug delivery system fit for the market place: drug solubility, drug release, physical, microbiological and chemical stability, bioavailability, liver first pass effect, scale-up! Identical quality of the first small batches for clinical studies with the large production batches in the market.

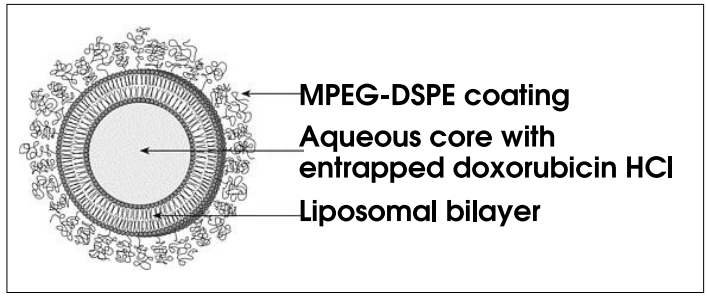

Fig. 3. Stealth®-liposome (100 nm size) Doxil® loaded with doxorubicin HCl, an anticancer drug. The Stealth® liposome carriers are composed of N-(carbonyl-**m**ethoxy**p**oly**e**thylene **g**lycol 2000)-1,2-**d**istearoyl- **s**n -glycero-3-**p**hospho**e**thanolamine sodium salt (MPEG-DSPE) [2][3].

1.3. *The Search for a Targeted Delivery System of a Drug Substance*

The comparison of the design of a drug delivery system with the design of a civil aircraft can be extended to include missiles and military aircrafts such as the famous stealth bombers, which cannot be detected by an enemy radar system. In fact, thanks to a stealth-type liposomal formulation (Fig. 3) [2], which is administered as an intravenous injection, the residence time of the drug substance in the systemic circulation could be significantly extended.

The stealth effect [2] was obtained by connecting to the surface of the liposome hydrophilic PEG (polyethylene glycol) chains, which look like tentacles shielding the liposomal core containing the drug from detection by mononuclear phagocytes of the immune defence system. Another approach concerns the concept of cruise missiles equipped with a path-finding system for a direct targeting. So far, the design of 'cruise missile' type liposomal drug carriers for a targeted delivery avoiding collateral damage did not fulfil the high expectations at all, despite 30 years of intensive research. Some accumulation of liposomes in tumours could be realized [3] to a similar extent as in case of chelate complexes with ^{99m}Tc loaded for diagnostic purposes, or with other radioactive isotopes such as rhenium for therapeutic use [4].

The problem is that liposomal drug carriers accumulate mainly in the liver, spleen and lungs. This research area is still gaining momentum especially in academia with the replacement of the very bio-friendly liposomal systems with polymeric drug carriers of similar size in the range of nano- to micrometers.

This momentum is a result of the current megatrend in nanoscience and nanotechnology [5]. So far, the only true organ-specific targeted delivery systems are parenteral injections, which are injected directly into the respective organ such as the heart muscle, the eye, the spinal cord, *etc*.

1.4. *The Champion of All Drug Delivery Systems*

Every patient would prefer a tablet to a painful injection. Tablets are solid dosage forms, which have overwhelming competitive advantages such as a higher chemical, physical and microbiological stability; possibilities for an exact dosing, for time-controlled delivery, for taste masking, for a delivery of multiple unit doses (*e.g.* pellets in capsules), for mass production, *etc*. Approximately 80% of all drug delivery systems such as tablets, film tablets, controlled release formulations, pellets, instant soluble preparations, powders for nasal, bronchial or pulmonal administration are solid dosage forms. Solid dosage forms are based on the application of powder technology and physical pharmacy [6]. The science of powder technology is however still in a state of infancy, and a special research

initiative is needed to develop a rigorous scientific framework [7].

1.5. *Research Focus of the Institute of Pharmaceutical Technology*

The research focus is centred on pharmaceutical powder technology and themes which represent, according to the FDA, the hottest topics. For the latter, additional research effort is needed to better overcome the hurdles mentioned in Fig. 2. In fact, the research topics are derived from the actual needs of the industry, covering basic research themes, where industry has no time to look in depth. The international peer review committee characterized in 2003 the research focus of the Institute of Pharmaceutical Technology as follows: "*This field is highly relevant to the pharmaceutical industry, but enjoys little interest in the academic pharmaceutical research centres: Many departments were closed over the last twenty years, not because of lack of importance of the subject, but because of the move to more biological topics*". This trend to follow more biological topics was fuelled by the fact that generations of European pharmacists received a postdoctoral training in the United States in the area of biopharmacy, and not in the area of formulation and process technology, which is the core activity of the pharmacist in industry [8]. Biopharmacy is an important and necessary complement to pharmaceutical technology, but cannot replace it. In this context, research topics such as the design of liposomal drug delivery systems with the goal of targeted delivery described in Section 1.3 became very popular. It has to be emphasised that biopharmaceutical topics, such as the effect of the type of formulation on absorption are an integral part of research in pharmaceutical technology done at the University of Basel by the research group of Georgios Imanidis. His group focuses mainly on topics that are related to the drug transport through a biological membrane such as intestine, skin (see contribution of G. Imanidis *et al.* [9] in this issue).

The FDA became interested in the current research focus of the Institute of Pharmaceutical Technology as a result of the PAT (Process Analytical Technology) initiative, and its generalisation described in the paper 'Innovation or Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products' [10]. In this context, the peer review committee mentions that the Institute of Pharmaceutical Technologies "*was instrumental in setting up the Industrial Pharmacy Lab, where indeed scale-up research can be performed. This is a unique achievement.*" (See contribution of G. Betz [11] in this issue).

In order to achieve high-quality pharma products and a high number of registered products, the FDA emphasises the need for a rigorous scientific understanding of complex pharmaceutical formulations and processes. For this purpose, novel research tools are needed such as the application of percolation theory, the concept of fractal dimensions, and the use of artificial neural networks, *etc.* which play an important role in the research activities of the institute. The goal is to climb up the knowledge pyramid described in Fig. 4 (courtesy of FDA, Dr. A. Hussain), which is an important task of academia.

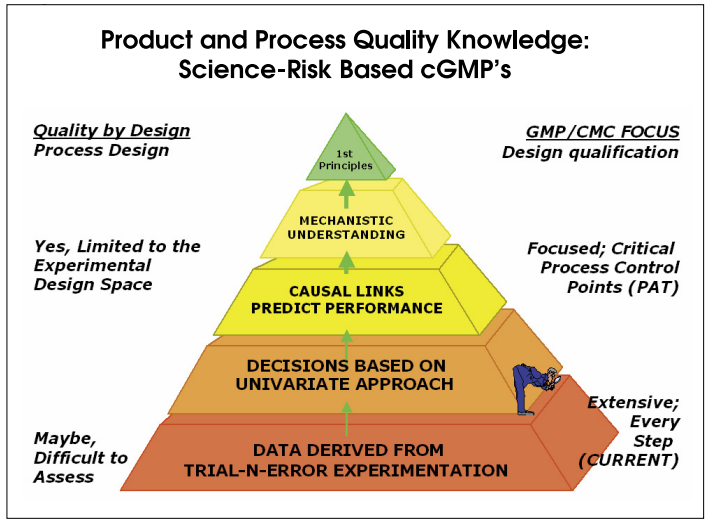

Fig. 4. Knowledge Pyramid (Courtesy of FDA, Dr. A. Hussain)

It is the merit of the peer review committee (2003) to realize that formulation and powder process technology research offers excellent models for studying 'complex systems'. The understanding of complex systems is the most current research trend in systems biology [12]. In conclusion, the peer review committee recommends "*to maintain and strengthen the position in pharmaceutical technology at the University of Basel in the future, when Prof. H. Leuenberger retires*".

2. A Digest of Typical Results in Formulation and Process Research

2.1. *The Design of Nanocomposite Micropellets for Poorly Water Soluble Classical Drugs and Therapeutic Proteins*

The majority of the recently discovered novel highly potent drugs show poor water solubility. Fortunately, the poor water solubility of a drug substance can be significantly enhanced by taking into account the results from nanoscience [13], and by using the right choice of hydrophilic excipients in the formulation. According to the Eqn. of Kelvin, the solubility $S(r)$ of a substance is related to its particle size r as follows:

$$\ln \frac{S(r)}{S_o} = \frac{2\sigma \quad V}{r \quad RT} \qquad (1)$$

σ = surface tension, r = particle size (radius), V = molar volume, T = temperature, R = gas constant, S_o = solubility of a coarse particle (r>>10 μm)

Due to their high specific surface, nanoparticles show a very high solubility but at the same time the problem of chemical and physical stability. Thus, the drug particles need to be stabilized in an inert hydrophilic matrix forming a nanocomposite structure. For this purpose, a novel process technology was developed: spray-freeze drying at atmospheric pressure. These droplets of a drug formulation dissolved in water are frozen at –50 °C and

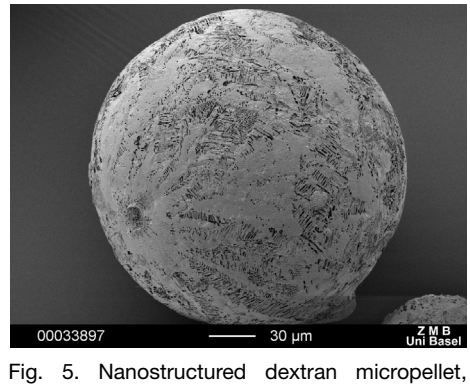

Fig. 5. Nanostructured dextran micropellet, combining the advantages of micro- and nanotechnology [7]

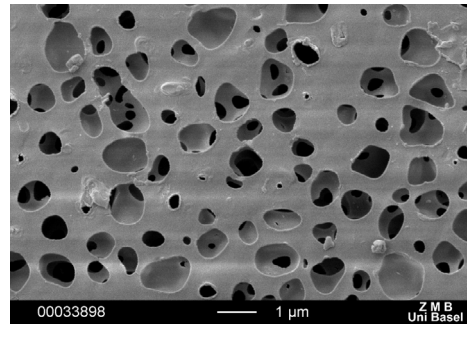

Fig. 6. Surface texture of nanostructured dextran micropellet, combining the advantages of micro- and nanotechnology [7]

subsequently lyophilised in a fluidised bed system.

Fig. 5 shows a dextran nanocomposite micropellet with an excellent flowability due to its shape and size and an excellent instant solubility due to its high internal surface and a porosity of 85%. Fig. 6 shows the surface structure of the nanoparticle pellet with the pores. The drug substance needs to be chemically compatible with the matrix substance forming a nano-dispersion or a solid solution.

Such micropellets can be also used as carriers for therapeutic proteins such as interferon, insulin, *etc*. Under shear forces, suitable micropellets can disintegrate in a metered dose powder inhaler to the desired aerodynamic size distribution for pulmonary administration (1–6 μm). A mechanistic model for the spray-freeze drying unit operation was developed in collaboration with the Mendeleyev University of Chemical Technology of Russia.

2.2. *The Application of Percolation Theory for a Better Understanding of the Behaviour of Complex Systems*

Percolation theory is one of the few tools used to study on a scientific firm basis the behaviour of complex formulations [14]. For a better understanding, drug formulation can often be analysed as a two-component, *i.e.* drug/matrix carrier system. The basic equation of percolation theory is a simple power law:

$$X = S(p-p_c)^q \quad (2)$$

X = system property, S = scaling factor, p = occupation probability (site percolation), p_c = percolation threshold, q = critical exponent

The percolation threshold p_c depends on the microstructure of the system, *i.e.* on the underlying coordination number. The critical exponent q depends only on the Euclidean dimension of the process studied and is, for a number of processes, a universal constant introducing a strange order in a chaotic system. Thus in the case of controlled release of the drug substance from a matrix-type retard system for oral use, the release is governed by the effective diffusion coefficient D_{eff}, which is related to Eqn. (2) in the case of a three-dimensional matrix as follows:

$$D_{eff} = D(p-p_c)^2 \quad (3)$$

D = diffusion coefficient of the drug substance in the extracting solvent, p = drug concentration (drug load) in the carrier matrix consisting of a water-insoluble excipient, p_c = critical drug concentration (percolation threshold), where the drug particles start to form an 'infinite' cluster (a continuous phase), connecting all surfaces of the matrix tablet exposed to the intestinal fluids.

The critical exponent (q) is equal to 2 for three dimensions. Percolation theory is related at the same time to the concept of fractal dimension [15].

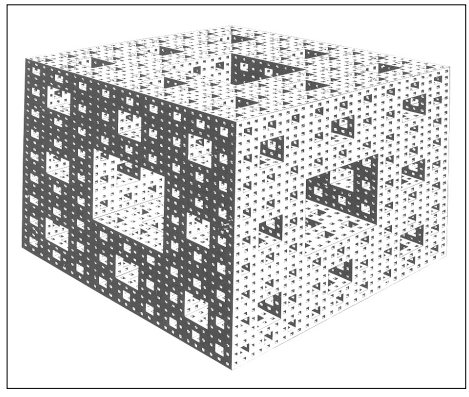

Fig. 7. Menger sponge with a fractal dimension of 2.63 [15]

Fig. 7 shows as a model a Menger sponge with a fractal dimension of 2.63, and Fig. 8 a matrix-controlled release system with water-soluble caffeine as a model drug and ethylcellulose as a water-insoluble matrix material [16].

It is often sufficient to study the impact of percolation theory qualitatively, without the quantitative evaluation of Eqn. (2), as illustrated by the following examples.

Fig. 9 describes the granule particle size distribution of a corn starch–lactose formulation, which is often used in industry. There is a critical ratio between the two ingredients – a percolation threshold – where corn starch starts to dominate leading to a different shape of the normalized size distribution. It is known that the percolation threshold depends on the size distribution of the starting material [17]. To avoid such catastrophic changes it is important to design a robust formulation far from a percolation threshold.

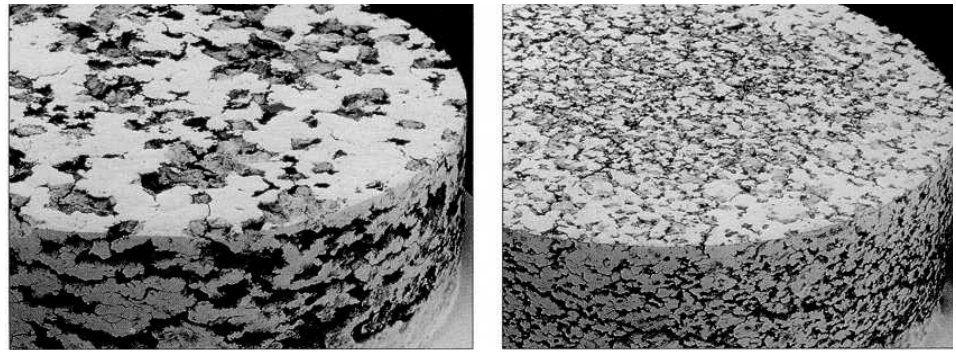

Fig. 8. Matrix-controlled release system [16] after erosion of 60% (w/w) of well soluble caffeine from an ethylcellulose matrix

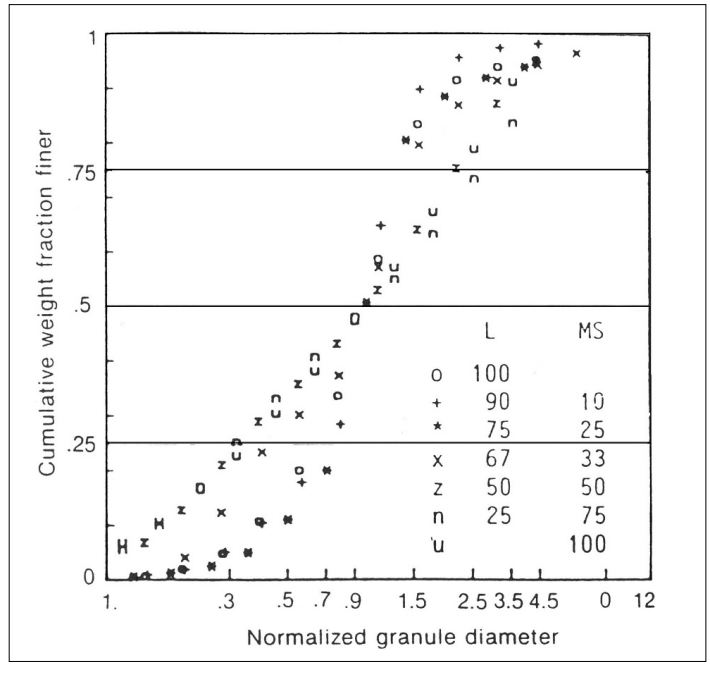

Fig. 9. Normalized granule size distribution of corn starch/lactose formulations [14]

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Fig. 10 shows percolation phenomena in binary fully miscible hydrophilic solvents. The application of the modified Clausius-Mossotti-Debye Eqn. permits characterization with the parameter E_i/E hydrophilic polar solvents and solvent mixtures [18]. This modified equation defines E_i/E as follows:

$$\frac{\varepsilon-1}{3\frac{E_i}{E}+(\varepsilon+2)}\frac{M}{\rho}=\frac{N_A}{3\varepsilon_0}\left(\alpha+\frac{\mu_g^2}{3kT}\right) \quad (4)$$

M = molecular weight, ρ = density, N_A = Avogadro number, k = Boltzman constant, α = polarizability, μ_g = dipole moment, ε = relative static dielectric constant, ε_o = dielectric constant of the vacuum

E_i is equal to the mean local internal electric field in the close neighbourhood of molecules and E is the externally applied electric field used for the determination of the relative static dielectric constant ε. Fig. 10 shows E_i/E values for 1,4-dioxane–water and for DMSO–water mixtures. In the case of 1,4-dioxane–water mixtures, the lower percolation threshold of water is expected to be in the range of 31% (v/v) to 43% (v/v) which corresponds to a coordination number of 6 respectively 4. The inflexion point in Fig. 10 is located at 38% (v/v) of water, which corresponds to a coordination number between 4 and 6. Due to the absence of a dipole moment in 1,4-dioxane, the upper percolation threshold is not visible. As DMSO and water have a dipole moment, both percolation thresholds in DMSO–water mixtures [19] can be determined: the lower at *ca.* 32% v/v water, where water starts to percolate, the upper at 26% (v/v) DMSO (74% (v/v) water), where DMSO starts to percolate the system indicating a 'quasi lattice' structure with a dynamic coordination number between 4 and 6 [19]. Large negative values of E_i/E describe strong dipole–dipole interactions and low values indicate their absence. In this context, it has to be kept in mind that 1,4-dioxane has no intrinsic dipole moment and is fully miscible with water due to hydrogen bonding. High frequency dielectric spectroscopy reveals how the structure of water is changed by adding a co-solvent. The structure of water is still not fully elucidated, but it is assumed that liquid water consists of nano-icebergs, which are continuously dissolved and reformed with a coordination number close to 4. Interestingly, pure water and pure DMSO can be characterised by a single relaxation time τ of their dipole moment with the Debye Eqn. A single Debye process has the following well-known frequency dependence of the complex dielectric permittivity $\varepsilon^* = \varepsilon'$, ε'' as a function of the frequency ω, split into real and imaginary part:

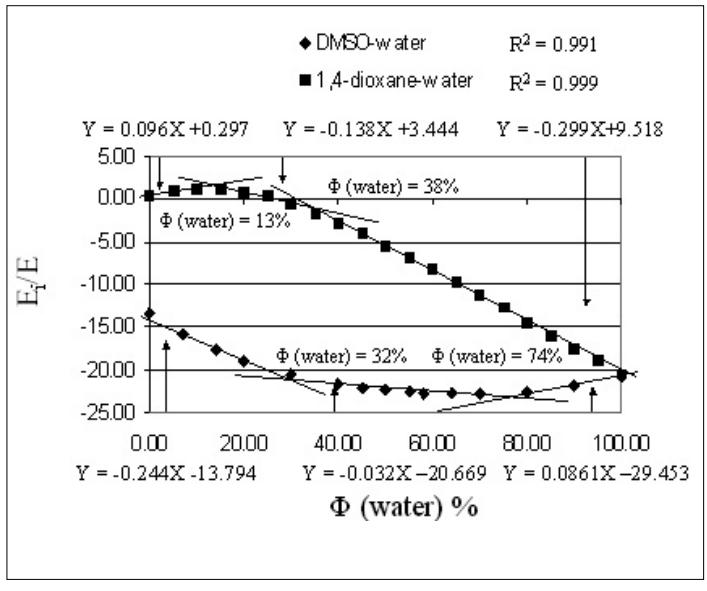

Fig. 10. E_i/E values for 1,4-dioxane–water and DMSO–water mixtures showing the lower percolation threshold for water in the case of 1,4-dioxane-water mixture and both percolation thresholds for the DMSO-water mixtures [15]

$$\varepsilon'(\omega)=\varepsilon_\infty+(\varepsilon-\varepsilon_\infty)\frac{1}{1+\omega^2\tau^2}, \quad (5)$$

$$\varepsilon''(\omega)=(\varepsilon-\varepsilon_\infty)\frac{\omega\tau}{1+\omega^2\tau^2}. \quad (6)$$

with ε = relative quasi-static dielectric permittivity and with ε_∞ = permittivity at $\omega \rightarrow \infty$

Fig. 11 shows the result of the high frequency dielectric spectroscopy for DMSO–water and 1,4-dioxane–water mixtures. In case of 1,4-dioxane–water mixtures, the system cannot be described with a single relaxation time τ. A much better description is obtained by taking into account a Cole-Davidson distribution function. The Cole-Davidson distribution is defined as follows:

$$\varepsilon'(\omega)=\varepsilon_\infty+(\varepsilon-\varepsilon_\infty)(\cos\phi)^\beta\cos\beta\phi, \quad (7)$$

$$\varepsilon''(\omega)=(\varepsilon-\varepsilon_\infty)(\cos\phi)^\beta\sin\beta\phi, \quad (8)$$

$$\text{with } \phi=\arctan(\omega\tau_0) \quad (9)$$

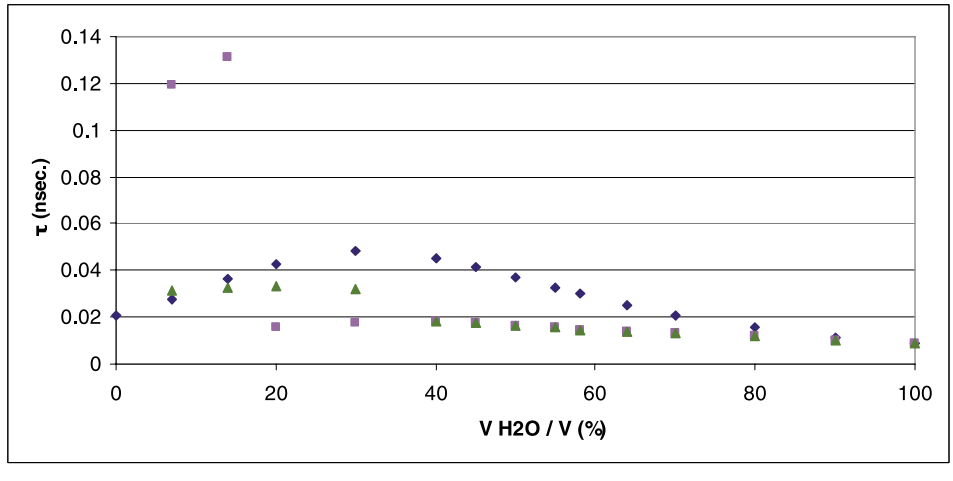

Fig. 11. Characteristic relaxation time behaviour of DMSO–water mixtures (♦) and 1,4-dioxane–water mixtures (■, ▲). In case of 1,4-dioxane mixtures for a better description of the relaxation behaviour a superposition of the Debye Eqn. with a Cole-Davidson τ-distribution (▲) with $\tau = \tau_o$ is needed. Interestingly the DMSO–water mixtures can be described with a single τ (Eqn. (5) resp. (6)).

with β = parameter describing the distribution of τ centred around τ_0.

The different behaviour of 1,4-dioxane and DMSO leads to the conclusion that 1,4-dioxane seems to disrupt the original water structure in a more significant way. Thus, surprisingly DMSO does not strongly disturb the water structure even at concentrations above the percolation threshold of DMSO, *i.e.* the characteristic relaxation time τ varies to a certain extent but can still be described by the simple Debye model based on a single τ. Thus, the question arises whether this effect is responsible for the fact that DMSO is an ideal carrier for a drug in early pharmacological studies, because it passes easily through biological membranes. Similar results (unpublished data) can be obtained in the case of PEG (polyethylene glycol)–water mixtures, which may explain the effect of PEG as an ideal shield in case of the 'stealth®' liposomes (Fig. 3).

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