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Viscosity prediction of lipophilic semisolid emulsion systems by neural network modelling

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Abstract

Previously published data (Gašperlin et al., 1998) on viscoelastic behaviour of lipophilic semisolid emulsion systems and the prediction of their physical stability by neural network modelling are analysed in further detail. Most attention has been paid to viscosity, which with storage (G′) and loss modulus (G″), is one of the most important rheological parameters influenced by structure. Complex dynamic viscosity (η^*) was measured by oscillatory rheometry. The viscosity dependence of the lipophilic semisolid emulsions on the ratio of the particular components was defined by the neural network (error back-propagation algorithm), linear and incomplete polynomial models of higher orders. Polynomial models were used to complement the neural network model and to determine the relationship between variables. Since the viscosity was expressed in the whole measured frequency range, modelling was more complex and indirect modelling was introduced. The determined models were tested and the results confirm their usefulness for the explanation and prediction of the rheological characteristics of emulsion systems. The trained and tested neural network model proved to be a highly effective and applicable tool for predicting the viscosity of a lipophilic semisolid emulsion system of given composition.

Keywords: Emulsions; Silicone surfactant; Rheology; Viscosity; Modelling; Neural networks

1. Introduction

Alkyl glycol siloxanes are very effective surfactants in W/O emulsion systems for cosmetic use (Starch, 1990), but they are also gaining importance in the pharmaceutical field (Müller-Goymann, 1992; Gašperlin et al., 1994). They possess a unique combination of properties which makes them highly effective. Their ternary molecule structure allows them to migrate at the interface and lower interfacial tension. Furthermore, the polymeric character enables them to remain at the interface and stabilise the emulsion by steric repulsion, and finally, the very flexible siloxane

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backbone allows all alkyl and glycol substituted groups to be presented at their best (De Smedt et al., 1996).

Most semisolid emulsion systems, represented by a large number of pharmaceutical preparations like ointments, creams or lotions, are very heterogeneous systems and have a complex flow behaviour. They are one of the most complicated systems for rheological evaluation because they simultaneously possess viscous and elastic characteristics, reflecting their internal structure. They are viscoelastic gels in which a surfactant or its blends interact with themselves and/or with the hydrophilic or lipophilic phase, to form a gel network (Eccleston, 1986). Such an internal structure decisively influences appearance, physical stability and drug transport.

The flow characteristics of these systems are clearly among some of the most important physical properties from both the fundamental and applied point of view. At the fundamental level, the rheology of an emulsion is a direct manifestation of the various forces of interaction that occur in the systems. At an applied level rheology is vital in some industrial applications because it is a very useful property for quantitative analysis of raw materials or final products and for checking customer acceptance (Tadros, 1994). Hence, the ability to measure, adjust and predict rheological properties is essential. Rheology, especially oscillatory rheometry, is one of the most effective methods for the characterisation of the gel network of emulsions. At rest this network helps to stabilise the emulsion, therefore a measurement of this strength will help to predict stability (Förster and Herrington, 1997). Moreover, the differences between strong and week gels can be clearly evidenced by means of oscillatory flow measurements (Lapasin and Pricl, 1995).

Neural networks still represent a rather new method in the area of modelling. The selection of the learning algorithm (back-propagation, counter propagation, Kohonen) for the neural network depends upon use. They can be used for empirical modelling, grouping and recognition (Zupan and Gasteiger, 1993). In the field of pharmacy the application of artificial neural network methodology has recently gained importance (Hussain et al., 1995; Bourquin et al., 1997). The potential applications are dosage form design and analysis, biopharmacy, drug design, epidemiology and clinical pharmacy (Archanta et al., 1995).

Previously published articles (Leskovšek et al., 1995; Gašperlin et al., 1998) included empirical models for the explanation of the relationship between rheological behaviour, expressed as a ratio between G''/G' and the composition of the selected mixture, where treated responses were only at selected frequency values. In the present case the responses are at the whole frequency range and, consequently, the modelling process is very complex. We employ so-called indirect modelling.

The purpose of this article was to discover the dependence of a rheological parameter, complex dynamic viscosity (η^*) on the composition of lipophilic semisolid emulsion systems, and particularly the influence of the individual components (silicone surfactant, hydrophilic and lipophilic phase). The error back-propagation neural network and polynomial models were used to prove our findings concerning viscosity dependence immediately after preparation and during the ageing process.

2. Materials and methods

2.1. Formulation of lipophilic semisolid emulsion systems

The lipophilic semisolid emulsion systems were prepared according to our own prescription. They contain silicone surfactant, white petrolatum as lipophilic and purified water as hydrophilic phase. The ratio of all above mentioned components were chosen according to a preliminary experimental design. The constrained mixture design was chosen where the sum of all three components was equal to 100%. The content of components was varied: silicone surfactant — x_1 (1–5%), purified water — x_2 (40–90%), and white petrolatum — x_3 (5–59%) (Fig. 1). The technological procedure has already been described (Gašperlin et al., 1998).

2.2. Materials

The polymeric silicone surfactant is a mixture of polysiloxane-polyalkylen-polyether copolymer and non-ionic surfactants, commercially known as ABIL WE 09® (Th. Goldschmidt, Essen, Germany). It is a pale yellow liquid which has hydroxyl value of 25–50, acid value max. 4, refractive index 1.447 ± 0.005 and specific density at 25°C 0.91 ± 0.02 g/cm^3. In all experiments the same batch was used. White petrolatum and purified water meet the requirements of DAB (1998).

2.3. Rheology

Rheological measurements were performed using an oscillatory viscometer (Rheolab MC 100, Paar-Physica, Stuttgart, Germany) coupled with the cone and plate measuring system KP 22 (diameter = 25 mm, $\alpha = 1°$, cone-plate distance = 50 μm) at a constant temperature (20 ± 0.2°C). In order to determine the linear viscoelastic area the experiments were carried out at constant frequency (1 Hz) in an amplitude range from 0.05 to 10 (deformation sweep). Once this region was established, the frequency sweep was performed at an amplitude within the linear region (0.2) and the frequency range from 0.01 to 50 Hz. The complex dynamic viscosity — η^* (Pas) obtained from mechanical spectra by oscillatory measurements is defined as:

$$\eta^* = \frac{G^*}{\omega} \quad (1)$$

G^* complex modulus (Pa); $\omega = 2\pi\nu$ angular frequency (rad/s); ν frequency (Hz). It is a measure of the total response of the sample:

$$\eta^* = \eta' + i\eta'' \quad (2)$$

and can be divided into its real (η') and imaginary (η'') part. The real part of viscosity is usually given the name dynamic viscosity and stands for viscous behaviour:

$$\eta' = G''/\omega \quad (3)$$

where G'' (Pa) is called loss modulus and represents a viscous contribution. The imaginary part of the viscosity is given no special name, but stands for elastic behaviour:

$$\eta'' = G'/\omega \quad (4)$$

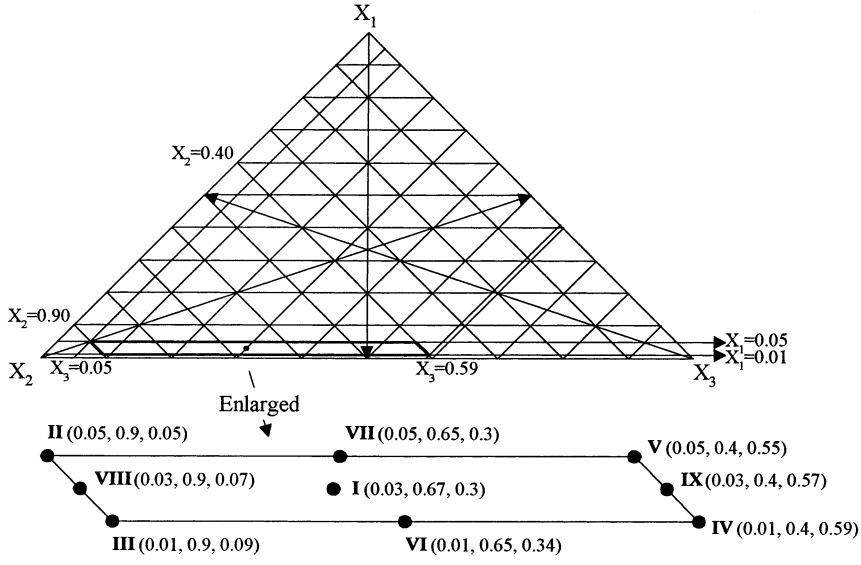

Fig. 1. Systematically planned experiments for modelling with the constrained mixture design. The permissible region for the experiments is enlarged. The ratio of components (silicone surfactant–x_1, water–x_2, white petrolatum–x_3) are written with the selected samples numbered from I to IX.

where G' (Pa) is called storage modulus and represents the elastic behaviour.

In order to obtain viscosity changes during ageing the systems were followed for 12 weeks. Rheological measurements were performed following preparation, and then after 1, 2, 3, 4, 6, 8, 10 and 12 weeks.

2.4. Modelling

The main problem was how to represent the whole frequency curve of the mechanical spectrum which shows the dependence between complex dynamic viscosity (η^*) and frequency (v). In this case indirect modelling seems to be very useful.

The procedure of indirect modelling is as follows:

1. First step models: the calculation of the natural logarithm of viscosity values (responses) and frequencies (factors) for nine emulsion systems (experimentally prepared). This means the calculation of parameters α (slopes) and β (sections) of a straight line for 81 linear polynomial models.
2. Second step models: parameters α (the basis for the calculation of A) and β (the basis for the calculation of B) represent responses, while the contents of silicone surfactant-x_1, water-x_2 and white petrolatum-x_3 are factors. The factors values were chosen according to the selected experimental design (Fig. 1). The empirical models were of three types: linear polynomial models for three factors, incomplete polynomial models of higher orders, and neural network models (error back-propagation algorithm).

The first experiment was replicated six times because the error of the measurements was set as the limit when the neural network model must stop training (over-training problems). At this point the RMS (root mean square of the difference between indirect and direct calculated responses: parameters A and B) was the same as the RMS_m (root mean square of the difference between the particular experimental value and mean experimental value).

The polynomial models are accepted on the basis of the statistical (values of F_{lof}, F_{reg}, CC, DC, RMS, RMS_m) and graphical (close inspection of calculated contours) analysis. F_{lof} is Fisher's ratio or lack-of-fit. F_{reg} is statistic F or observed F value. CC is the correlation coefficient and DC the coefficient of determination. RMS is the root mean square of the difference between simulated and indirect calculated parameters A or B according to its lowest and highest values of the particular parameter as a percentage. RMS_m represents the indirect calculated values of the particular parameter according to its lowest and highest value as a percentage (Draper and Pukelsheim, 1996).

2.4.1. First step models: linear polynomials

First, the natural logarithms (ln) of the entire function representing the dependence between the complex dynamic viscosity (η^*) and the frequency (v) (index k) for nine different emulsion systems (index j) (Fig. 1) are calculated with respect to the ageing plan (index i): after preparation, after 1, 2, 3, 4, 6, 8, 10 and 12 weeks:

$$q_{ijk} = \alpha_{ij} p_{ijk} + \beta_{ij} \tag{5}$$

$$\text{Response:} \qquad q_{ijk} = \ln \eta^*_{ijk} \tag{6}$$

$$\text{Factor:} \qquad p_{ijk} = \ln v_{ijk} \tag{7}$$

$$\text{Follows:} \qquad \ln \eta^*_{ijk} = \alpha_{ij} \ln v_{ijk} + \beta_{ij} \tag{8}$$

where q_{ijk} is a viscosity value (index k: from 1 to 20; set of 20 experimental points uniformly distributed on the ln frequency scale were taken for the calculations) for a particular emulsion system (index j: from 1 to 9; because of the selection of nine different emulsion systems from the selected constrained mixture design shown in Fig. 1) regarding the ageing plan (index i: from 1 to 9; after the preparation, after 1, 2, 3, 4, 6, 8, 10 and 12 weeks).

p_{ijk} is a frequency value (index k: from 1 to 20) for a particular emulsion system (index j: from 1 to 9) regarding the ageing plan (index i: from 1 to 9 different observation times), α_{ij} is a slope of the line; β_{ij} is a section of the line.

Values of α_{ij} and β_{ij} are included as responses in the determination of second step models.

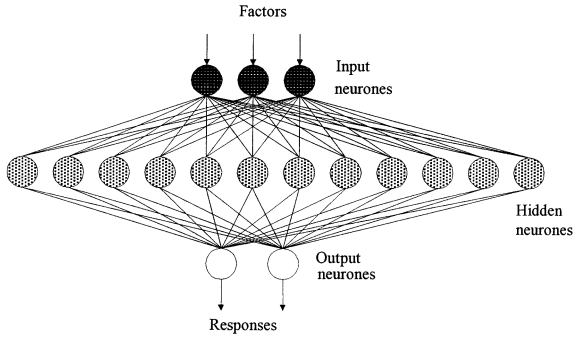

Fig. 2. Architecture of the used two-level error back-propagation neural network with one hidden layer.

2.4.2. Second step models: neural network

For empirical modelling a one- (no hidden layer) and two-level (one hidden layer) neural network is employed with the error back-propagation supervised learning algorithm. The squashing function is sigmoidal. The learning term is 0.5 and the momentum term 0.9. The architecture of the two-level neural network can be seen in Fig. 2. It has 12 neurones on the hidden layer. The contents of the individual emulsion components x_{ij1}, x_{ij2}, x_{ij3} represent the factors while the responses are values of parameters α_{ij} and β_{ij}. The meaning of indices i and j is the same as in the case of the first step models. Two neural network models are determined: one for parameter A_{ij} (on the basis of value α_{ij} as responses) and one for parameter B_{ij} (on the basis of value β_{ij} as responses).

The most proper neural network was selected according to the statistical and graphical analysis. For the statistical analysis the RMS value was used and for graphical the examination of the calculated contours.

Because the interpretation of coefficients cannot be determined with the neural network, polynomial models were involved. The comparison between models (neural network and incomplete quadratic polynomials) was performed statistically and graphically. For the successful statistical comparison the RMS values of both models must be in the same order of magnitude. The calculated contours of responses given by both models must be similar for almost all selected values of the third factor (the same tendencies of contours and positions of maximum and minimum points).

2.4.3. Second step models: linear polynomials

For the determination of the second step models the contents of the individual emulsion components x_{ij1}, x_{ij2}, x_{ij3} represent the factors and the values of parameter α_{ij} and β_{ij} responses. Two types of polynomials were determined: one for parameter A_{ij} (on the basis of α_{ij} values as responses) and one for parameter B_{ij} (on the basis of β_{ij} values as responses).

$$A_{ij} = a_{i1}x_{ij1} + b_{i1}x_{ij2} + c_{i1}x_{ij3} \quad (9)$$

$$B_{ij} = a_{i2}x_{ij1} + b_{i2}x_{ij2} + c_{i2}x_{ij3} \quad (10)$$

2.4.4. Second step models: incomplete polynomials of higher orders

The main point of the procedure for the determination of the incomplete polynomial models of higher orders is to determine the most important higher order terms from the complete polynomial models: in our case from the second (Eq. (11)) and third (Eq. (12)) order. The main reason for the use of incomplete polynomial models is of a practical nature: they require fewer experiments.

Similar to the procedure used for linear models, two types of higher order polynomials were also determined in this case: one for parameter A_{ij} (on the basis of α_{ij} values as responses) and one for parameter B_{ij} (on the basis of β_{ij} values as responses). For the parameter A_{ij} the terms of second polynomials are included (Eq. (11)). The number of all possible combinations of second polynomial terms (x_1x_2, x_1x_3, x_2x_3) added to the linear polynomial (Eq. (9)) was 7 in this case:

1. x_1, x_2, x_3, x_1x_2;
2. x_1, x_2, x_3, x_1x_3;
3. x_1, x_2, x_3, x_2x_3;
4. $x_1, x_2, x_3, x_1x_2, x_1x_3$;
5. $x_1, x_2, x_3, x_1x_2, x_2x_3$;
6. $x_1, x_2, x_3, x_1x_3, x_2x_3$;
7. $x_1, x_2, x_3, x_1x_2, x_1x_3, x_2x_3$.

Among the above models only one was statistically and graphically acceptable. The inclusion of the third order terms was unnecessary. The quadratic polynomial model is as follows:

$$A_{ij} = a_{i1}x_{ij1} + b_{i1}x_{ij2} + c_{i1}x_{ij3} + d_{i1}x_{ij1}x_{ij2} + e_{i1}x_{ij1}x_{ij3} + f_{i1}x_{ij2}x_{ij3} \quad (11)$$

In the case of the determination of the incomplete polynomial model for parameter B_{ij} it was found that some cubic terms must be included (Eq. (12)). The number of possible combinations in this case is much higher, 696. The number 696 is a sum of combinations of 16 different terms; x_1x_2, x_1x_3, x_2x_3, x_1x_1, x_2x_2, x_3x_3, $x_1x_2x_3$, $x_1x_1x_1$, $x_2x_2x_2$, $x_3x_3x_3$, $x_1x_1x_2$, $x_1x_1x_3$, $x_2x_2x_1$, $x_2x_2x_3$, $x_3x_3x_1$, $x_3x_3x_2$ added to the linear polynomial (Eq. (10)). For example:

1. x_1, x_2, x_3, x_1x_2;
2. x_1, x_2, x_3, x_1x_3;
3. x_1, x_2, x_3, x_2x_3;
4. x_1, x_2, x_3, x_1x_1;
5. x_1, x_2, x_3, x_2x_2;
6. x_1, x_2, x_3, x_3x_3;
7. $x_1, x_2, x_3, x_1x_2x_3$;

...

17. $x_1, x_2, x_3, x_1x_2, x_1x_3$;
18. $x_1, x_2, x_3, x_1x_2, x_2x_3$;
19. $x_1, x_2, x_3, x_1x_3, x_2x_3$;
20. $x_1, x_2, x_3, x_1x_2, x_1x_3, x_2x_3$,

...

696. $x_1, x_2, x_3, x_1x_2, x_1x_3, x_2x_3, x_1x_1, x_2x_2, x_3x_3, x_1x_2x_3, x_1x_1x_1, x_2x_2x_2, x_3x_3x_3, x_1x_1x_2, x_1x_1x_3, x_2x_2x_1, x_2x_2x_3, x_3x_3x_1, x_3x_3x_2$.

The cubic model is as follows

$$B_{ij} = a_{i2}x_{ij1} + b_{i2}x_{ij2} + c_{i2}x_{ij3} + d_{i2}x_{ij1}x_{ij2} + e_{i2}x_{ij1}x_{ij3} + f_{i2}x_{ij2}x_{ij3} + g_{i2}x_{ij1}x_{ij2}x_{ij3} + h_{i2}x_{ij1}x_{ij1}x_{ij1} + i_{i2}x_{ij2}x_{ij2}x_{ij2} + j_{i2}x_{ij3}x_{ij3}x_{ij3} + k_{i2}x_{ij1}x_{ij1}x_{ij2} + l_{i2}x_{ij1}x_{ij1}x_{ij3} + m_{i2}x_{ij2}x_{ij2}x_{ij1} + n_{i2}x_{ij2}x_{ij2}x_{ij3} + o_{i2}x_{ij3}x_{ij3}x_{ij1} + p_{i2}x_{ij3}x_{ij3}x_{ij2} \quad (12)$$

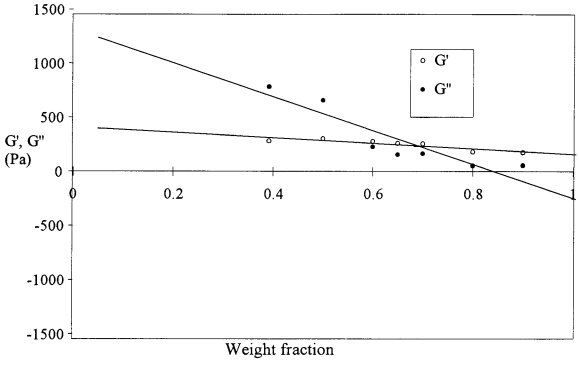

Fig. 3. Changes of G' and G'' in dependence on weight fraction of inner water phase of tested lipophilic semisolid emulsions (amplitude 0.2, frequency 1.38 Hz). The weight fraction of silicone surfactant is kept constant = 0.05.

3. Results and discussion

Lipophilic semisolid emulsion systems (nine different samples) containing a silicone surfactant were prepared as described according to the selected constrained mixture experimental design shown in Fig. 1. The resulting semisolid emulsions can be divided into three main groups:

- highly concentrated-samples II, III and VIII with 0.90 weight fraction of inner water phase;
- concentrated-samples I, VI, VII with weight fraction of water phase of ≈ 0.65; and
- least concentrated-samples IV, V, and IX with 0.40 weight fraction of water phase.

With regard to the previously published results concerning $\tan\delta$ for the prediction of physical stability of the investigated emulsion systems, only the water/white petrolatum ratio was found to be decisive (Gašperlin et al., 1998). The changes of storage — G' and loss modulus — G'' by constant amplitude and frequency of deformation in dependence of weight fraction of the inner water phase are shown in Fig. 3. The transition from predominantly elastic to predominantly viscous behaviour is evident when the weight fraction of the inner water phase exceeds 0.7.

Table 1
The calculated values of parameter α_{ij} for tested lipophilic semisolid emulsion systems[a]

Emulsion system	α_{1j}	α_{2j}	α_{3j}	α_{4j}	α_{5j}	α_{6j}	α_{7j}	α_{8j}	α_{9j}
1a[c]	−0.7873	−0.7905	−0.6929	−0.7245	−0.7230	−0.7050	−0.7247	−0.6962	−0.7175
1b	−0.7287	−0.7464	−0.7292	−0.7319	−0.7335	−0.7495	−0.7257	−0.7203	−0.7404
1c	−0.7195	−0.7485	−0.7297	−0.6925	−0.7301	−0.7230	−0.7197	−0.7247	−0.7192
1d	−0.7004	−0.7542	−0.7385	−0.6923	−0.7281	−0.7082	−0.7199	−0.7181	−0.7116
1e	−0.7318	−0.7376	−0.7280	−0.7269	−0.7227	−0.7148	−0.6979	−0.7041	−0.7298
1f	−0.7167	−0.7663	−0.7234	−0.7186	−0.7288	#[b]	−0.7095	−0.6977	−0.6801
2	−0.8235	−0.8503	−0.7728	−0.7434	−0.7676	−0.7868	−0.7495	−0.7181	−0.7095
3	−0.8330	−0.8991	−0.8548	−0.8412	−0.8306	−0.8426	−0.8383	−0.8284	−0.8195
4	−0.5594	−0.6307	−0.5837	−0.5895	−0.6137	−0.6142	−0.6180	−0.5802	−0.6093
5a	−0.6879	−0.6771	−0.6387	−0.6519	−0.6680	−0.6299	−0.6335	−0.6188	−0.6139
5b	−0.6903	−0.6754	−0.6571	−0.6576	−0.6443	−0.6575	−0.6294	−0.6425	−0.5229
6	−0.7351	−0.7328	−0.7402	−0.7281	−0.7329	−0.7253	−0.7453	−0.7260	−0.7509
7	−0.7880	−0.7391	−0.7468	−0.8023	−0.7309	−0.7104	−0.7111	−0.7203	−0.6984
8	−0.8547	−0.8250	−0.7992	−0.7939	−0.8063	−0.7879	−0.7599	−0.8145	−0.7803
9	−0.6783	−0.6419	−0.6513	−0.5965	−0.5964	−0.6219	−0.6292	−0.5518	−0.6417

[a] Index i varies from 1 to 9 according to the ageing plan, index j varies from 1 to 9 according to the sequential number of the particular emulsion system in the selected constrained mixture experimental design.
[b] Experimental error.
[c] 1a–1f: six replicas of the first experiment.

3.1. Modelling and viscosity predicting

3.1.1. First step models

The calculated α_{ij} and β_{ij} values are given in Tables 1 and 2. These values represent the responses for the second step modelling. The η^* profiles versus v for the tested emulsion systems clearly show a non-linear behaviour while the logarithm (ln) dependence is linear.

Table 2
The calculated values of parameter β_{ij} for tested lipophilic semisolid emulsion systems[a]

Emulsion system	β_{1j}	β_{2j}	β_{3j}	β_{4j}	β_{5j}	β_{6j}	β_{7j}	β_{8j}	β_{9j}
1a[c]	4.7476	4.9582	4.0288	4.1003	4.1025	4.0129	4.1629	4.2649	4.0941
1b	4.3224	4.4003	4.3387	4.4390	4.2399	4.4957	4.4955	4.2695	4.4604
1c	4.3037	4.3654	4.3157	4.1786	4.2418	4.4423	4.4546	4.3704	4.5183
1d	4.1275	4.3406	4.3801	3.8586	4.1971	4.3310	4.3179	4.3148	4.4223
1e	4.2297	4.2216	4.1371	4.1565	4.2133	4.2670	4.3186	4.2963	4.3594
1f	4.2314	4.0941	4.3071	4.3076	4.2382	#[b]	4.2217	4.2512	4.0090
2	4.8082	4.7729	3.3444	3.1707	3.2519	3.3860	3.0400	3.0314	2.8262
3	4.8092	4.8920	3.7096	3.7864	3.6796	3.5709	3.7939	3.7866	3.6431
4	4.9508	5.2307	5.0576	5.1051	5.1317	5.2667	5.2582	5.2528	5.1247
5a	4.7898	4.9195	4.8225	4.8046	4.7269	4.8049	4.8209	4.9429	4.8670
5b	4.8001	4.9478	4.5983	4.6078	4.8127	4.7368	4.8122	5.0103	4.8253
6	5.0363	5.0439	4.7094	4.6002	4.7422	4.6893	4.6738	4.6576	4.6891
7	4.7395	4.0216	4.0134	5.5556	4.0422	4.0746	4.1134	4.1361	4.2698
8	4.7495	3.6905	3.4390	3.4762	3.4909	3.4226	3.2689	3.3687	3.2705
9	5.0735	4.7632	4.9028	4.2832	5.0640	4.9571	5.0011	4.9884	5.0563

[a] Index i varies from 1 to 9 according to the ageing plan, index j varies from 1 to 9 according to the sequential number of the particular emulsion system in the selected constrained mixture experimental design.
[b] Experimental error.
[c] 1a–1f: six replicas of the first experiment.

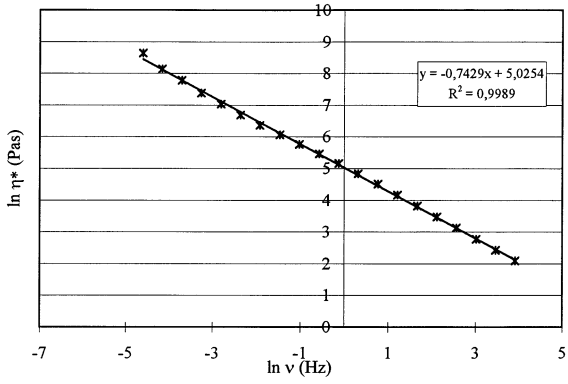

Fig. 4. The linear relationship between $\ln \eta^*$ and $\ln \nu$ for the sample VI after preparation.

With the frequency range explored, the relationship $\ln \eta^*$ versus $\ln \nu$ is fairly well described by a straight line, having a slope in the interval between 0.6 and 0.9 and a correlation coefficient of about 0.99. The illustration of such a relationship for a selected emulsion system is given in Fig. 4. All points were close to the regression line, so the linear relationship between selected factors and responses was strong (correlation coefficient 0.9989).

The remaining question is what is the physical meaning of the slope (parameter α_{ij}) and the section (parameter β_{ij}). On the basis of Eqs. (1)–(4) the following equations are carried out, which might represent an answer:

$$\eta^* = \frac{G^*}{\omega} = \frac{G'' + iG'}{\omega} = \frac{G'(1 + i \cdot tg\delta)}{\omega}$$

$$= \frac{G'}{\omega} + \frac{iG' tg\delta}{\omega} = \frac{G'}{\omega}(1 + itg\delta)$$

$$tg\delta = \frac{G''}{G'}$$

$$\ln \eta^* = \ln \frac{G'}{\omega} + \ln(1 + itg\delta)$$

$$\alpha_{ij} = \ln \frac{G'}{\omega}$$

$$\beta_{ij} = \ln(1 + itg\delta)$$

3.1.2. Second step models for A_{ij} and B_{ij}

From the statistical analysis of the linear polynomial models (Eqs. (9) and (10)) for parameters A_{ij} and B_{ij}, according to F_{reg}, F_{lof}, CC, DC and RMS (RMS values are stated in Tables 3 and 4), it was found that these models do not properly represent the systems (higher values of RMS in comparison with RMS_m). Consequently, higher-order polynomials must be used.

The values of A_{ij} and B_{ij} calculated with a one-level neural network (no hidden layer) are too high or too low, so the RMS values are much

Table 3
The RMS values (as a percentage) of the selected empirical models for the parameter A_{ij}[a]

	Response	One−level neural network	Linear polynomials	Two−level neural network	High order polynomials	Indirect calculation
A_{1j}	After preparation	10.607	10.725	7.766	8.911	7.990
A_{2j}	After 1 week	7.943	8.157	5.475	6.140	5.559
A_{3j}	After 2 Week	9.171	9.226	4.966	6.142	4.919
A_{4j}	After 3 Week	13.688	13.826	6.053	11.029	5.558
A_{5j}	After 4 Week	8.141	8.4879	3.247	5.085	2.897
A_{6j}	After 6 week	7.534	7.9492	5.152	5.528	6.733
A_{7j}	After 8 week	8.303	8.4031	3.314	5.595	3.847
A_{8j}	After 10 week	9.754	11.365	8.088	7.473	4.129
A_{9j}	After 12 week	11.062	9.783	4.901	9.629	9.421
	Common response	9.755		5.667		

[a] Index j varies from 1 to 9 according to the sequential number of the emulsion system in the selected constrained mixture experimental design.

Table 4
The RMS values (as a percentage) of the selected empirical models for the parameter B_{ij}[a]

	Response	One−level neural network	Linear polynomials	Two−level neural network	High order polynomials	Indirect calculation
B_{1j}	After preparation	30.992	35.402	15.959	25.241	18.155
B_{2j}	After 1week	24.027	23.902	13.799	19.795	15.262
B_{3j}	After 2 week	6.477	7.223	5.22	5.353	7.124
B_{4j}	After 3 week	18.212	18.037	6.645	9.486	6.837
B_{5j}	After 4 week	3.582	4.304	2.543	2.514	2.524
B_{6j}	After 6 week	7.155	7.536	5.284	5.572	7.649
B_{7j}	After 8 week	5.391	6.261	3.453	4.540	4.589
B_{8j}	After 10 week	7.626	4.792	5.378	2.074	1.731
B_{9j}	After 12 week	3.796	8.838	2.512	5.809	7.201
	Common response	15.192		8.152		

[a] Index j varies from 1 to 9 according to the sequential number of the emulsion system in the selected constrained mixture experimental design.

higher (Tables 3 and 4) in comparison to RMS_m values calculated with the indirect models. The most proper values of parameters A_{ij} and B_{ij} are calculated with the two-level neural network (one hidden layer), which is reflected in the RMS values being in the same order of magnitude as the RMS_m values.

For the determination of the higher order polynomials for parameter A_{ij}, the terms of the second order polynomials were added to the linear polynomials. There were seven possible models for a particular A_{ij}; from among 63 models (7×9) the one statistically and graphically acceptable for all responses was selected:

$$A_{ij} = a_{i1}x_{ij1} + b_{i1}x_{ij2} + c_{i1}x_{ij3} + d_{i1}x_{ij1}x_{ij2} \quad (13)$$

The parameter values a_{i1}, b_{i1}, c_{i1} and d_{i1} can be seen in Fig. 5. It is evident that ageing has no significant influence on the relationships between variables. The statistical analysis of the selected model (Eq. (13)) showed that the incomplete quadratic models properly represent parameter A_{ij} according to the selected factors (Table 5). The relationship between A_{ij} and variables x_1 and x_2 was found to be the largest of all.

For the determination of parameter B_{ij}, the terms of the third order polynomial were included. For example, the determination of B_{5i} required 696 incomplete models of the third order. Among them 28 models were statistically acceptable, although only 15 models met the requirements of the graphical analysis. Finally, one model was selected, which also was appropriate for responses B_{3j}, B_{5j}, B_{8j} and B_{9j}. This model is the following:

$$B_{ij} = a_{i2}x_{ij1} + b_{i2}x_{ij2} + c_{i2}x_{ij3} + d_{i2}x_{ij3}x_{ij3} + e_{i2}x_{ij2}x_{ij3} + f_{i2}x_{ij3}x_{ij3}x_{ij2} \quad (14)$$

The index i value is 3, 5, 8, 9 for 2, 4, 10 and 12 weeks after preparation according to the ageing plan. The values of statistical parameters for all responses for selected model (Eq. (14)) are given in Table 6. The parameter values a_{i2}, b_{i2}, c_{i2}, d_{i2},

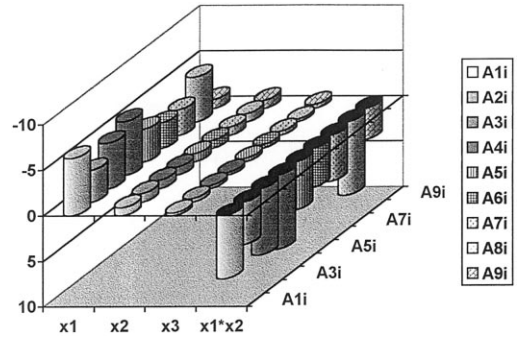

Fig. 5. The size of the terms of higher order polynomials of parameter A_{ij} (slope of the straight line) calculated by Eq. (13).

Table 5
Statistical evaluation of polynomial models (Eq. (13)) for parameter A_{ij}[a]

	Responses	F_{reg}	F_{lof}	CC	DC	RMS	RMS_m
A_{1j}	After preparation	24.304	1.599	0.860	0.890	8.911	7.989
A_{2j}	After 1week	66.804	1.545	0.952	0.962	6.140	5.559
A_{3j}	After 2 week	51.322	2.307	0.893	0.916	6.142	4.919
A_{4j}	After 3 week	18.201	7.660	0.781	0.828	11.029	5.558
A_{5j}	After 4 week	96.508	5.731	0.966	0.973	5.085	2.897
A_{6j}	After 6 week	83.674	0.348	0.964	0.973	5.528	6.733
A_{7j}	After 8 week	74.750	3.559	0.915	0.933	5.595	3.847
A_{8j}	After 10 week	41.368	6.171	0.900	0.921	7.473	4.129
A_{9j}	After 12 week	17.379	1.150	0.682	0.75	9.629	9.421

[a] Index j varies from 1 to 9 according to the sequential number of the emulsion in the selected constrained mixture experimental design. $F_{regcrit} = 3.587$; $F_{lofcrit} = 4.387$.

Table 6
Statistical evaluation of polynomial models (Eq. (14) for B_{3j}, B_{5j}, B_{8j} and B_{9j}, Eq. (15) for B_{4j}, Eq. (16) for B_{6j} and Eq. (17) for B_{7j})[a]

	Responses	F_{reg}	F_{lof}	CC	DC	RMS	RMS_m
B_{3j}	After 2 week	50.412	0.118	0.950	0.968	5.353	7.124
B_{4j}	After 3 week	11.433	5.220	0.911	0.943	9.486	6.837
B_{5j}	After 4 week	224.554	1.721	0.999	0.999	2.514	2.524
B_{6j}	After 6 week	42.819	0.102	0.934	0.959	5.572	7.649
B_{7j}	After 8 week	81.071	1.253	0.952	0.966	4.540	4.589
B_{8j}	After 10 week	288.458	3.382	0.973	0.983	2.074	1.731
B_{9j}	After 12 week	38.577	0.441	0.960	0.974	5.809	7.201

[a] Index j varies from 1 to 9 according to the sequential number of the emulsion in the selected constrained mixture experimental design. For B_{3j}, B_{4j}, B_{5j}, B_{8j} and B_{9j}: $F_{regcrit} = 3.482$; $F_{lofcrit} = 4.757$. For B_{6j}: $F_{regcrit} = 3.688$; $F_{lofcrit} = 5.409$. For B_{7j}: $F_{regcrit} = 3.478$; $F_{lofcrit} = 4.534$.

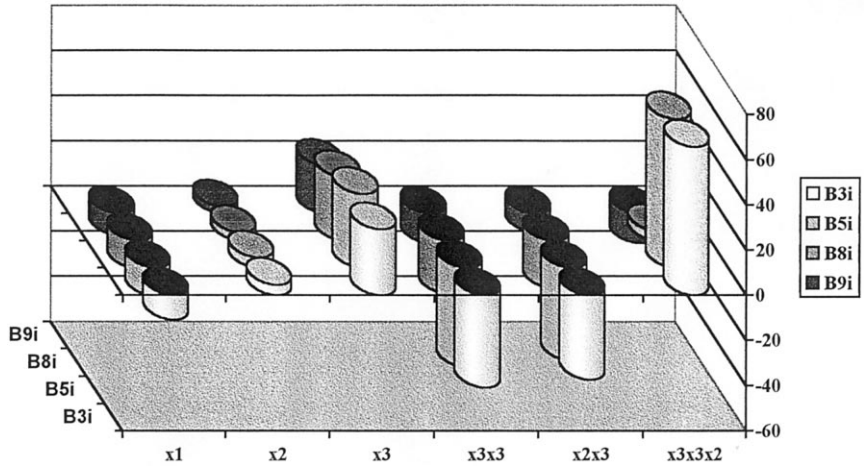

Fig. 6. The size of the terms of higher order polynomials of parameter B_{ij} (section of the straight line) calculated by Eq. (14).

e_{i2} and f_{i2} are given in Fig. 6. It is also evident that during ageing (index i) the relationship between the variables is almost unchanged. The important relationship is between response B_{ij} and x_3 and between B_{ij} and x_1.

For B_{1j} and B_{2j} the differences between the first and the second step model were too high. The RMS for B_{1j} was 18.2% and for B_{2j} 15.3%, therefore the empirical models are less useful. Responses B_{4j} (3 weeks after preparation), B_{6j} (6 weeks after preparation) and B_{7j} (8 weeks after preparation), are of different types (another combination of terms).

$$B_{4j} = -12.8701x_{4j1} + 2.82307x_{4j2} + 9.06916x_{4j3} + 0.63827x_{4j2}x_{4j2}x_{4j2} + 4091.25025x_{4j1}x_{4j1}x_{4j3} - 413.4177x_{4j3}x_{4j3}x_{4j1} \quad (15)$$

$$B_{6j} = -22.49777x_{6j1} + 3.66615x_{6j2} + 16.25679x_{6j3} - 19.99744x_{6j3}x_{6j3}x_{6j3} + 25.48371x_{6j2}x_{6j2}x_{6j1} - 16.11646x_{6j2}x_{6j2}x_{6j3} \quad (16)$$

$$B_{7j} = -7.94341x_{7j1} + 2.94224x_{7j2} + 16.94202x_{7j3} - 26.13457x_{7j3}x_{7j3}x_{7j1} - 40.65831x_{7j3}x_{7j3}x_{7j2} \quad (17)$$

The simulated values of A_{id} and $B_{ij\text{ou}}$ by the two-level neural network models with one hidden layer are entirely comparable with the α_{ij} and β_{ij} values calculated by the first step models (Tables 1 and 2). Such a comparison is possible regarding Tables 3 and 4. The RMS values calculated on the basis of incomplete models of high orders and the two-level neural network are close enough to the RMS_m. Thus, the explanation of the relationship between variables can be regarded as reliable. Fig. 7 shows the graphical comparison of the calculated contours, based on the neural network and incomplete quadratic model for response A_{ij}. The tendency and the shape of lines in the contours were found to be practically the same. On the basis of this comparison for the calculation of parameters A_{ij} and B_{ij}, the neural network models were found to be more accurate. These methods gave us the possibility of approaching the calculated values to the experimental values to the size of the error without knowing whether the relations between variables are linear or non-linear.

From Tables 1 and 2 it can also be seen that the measurements immediately (B_{1j}) and 1 week (B_{2j}) after preparation are less reliable (higher RMS values), therefore the simulated values were also less accurate. The measurements and the simulated values with the two-level neural network are quite comparable in all other ageing periods.

The two-level neural network was then tested with several new experiments (Fig. 8), not included

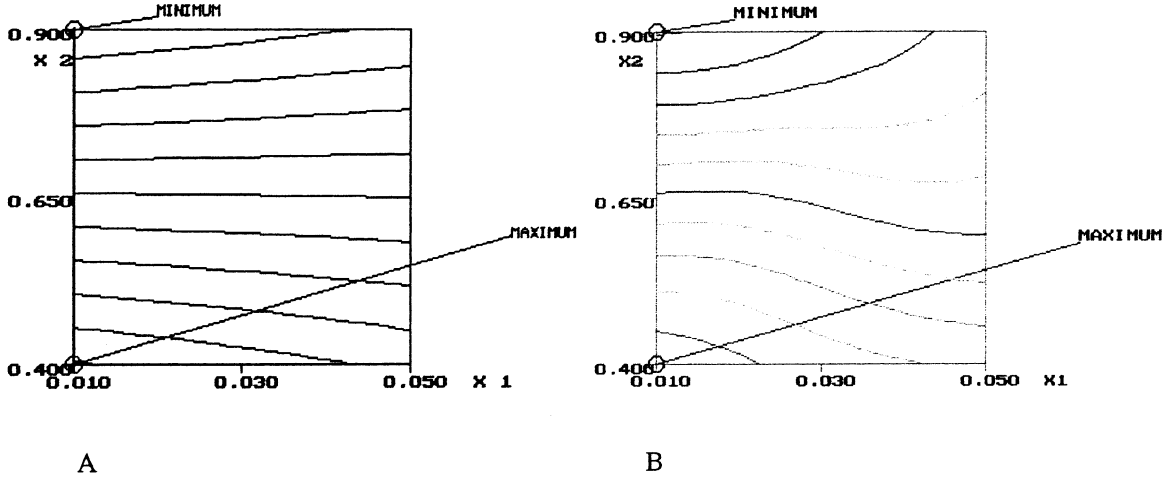

Fig. 7. Comparison of the calculated contours of the incomplete polynomial models $A_{5j} = a_{51}x_{5j1} + b_{51}x_{5j2} + c_{51}x_{5j3} + d_{51}x_{5j1}x_{5j2}$ (A) and two-level neural network (B) which shows the dependence between A_{5j} ($i = 5$ or after 4 weeks) and x_{5j1} (content of silicone surfactant) and x_{5j2} (content of purified water). The content of the white petrolatum was 0.3.

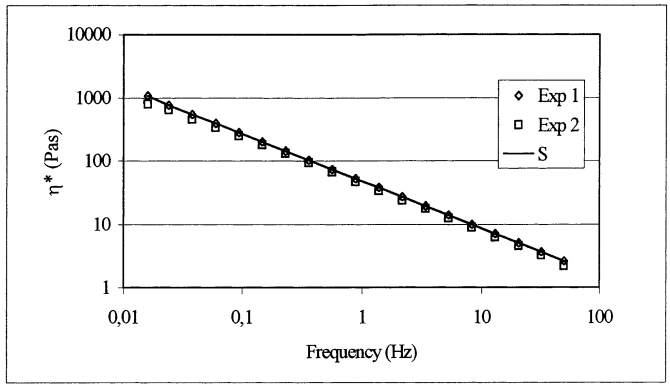

Fig. 8. Testing the two-level neural network model by comparison between experimentally obtained and predicted values of η^* calculated for the following formulation: $x_1 = 0.05$; $x_2 = 0.70$; $x_3 = 0.25$ which was not included in the experimental design (after 2 weeks).

in the training process, but placed in the area of the experimental design. The procedure for testing models was the following: the values of parameters A_{ij} and B_{ij} were simulated first, next the straight line was drawn, and finally the comparison between the calculated and the experimentally obtained line was performed.

On the basis of the trained and tested neural network, the following actions can be taken:

1. prediction of the complex dynamic viscosity for a selected formulation and time dependent changes during ageing.
2. coincidental search of optimal formulations; the optimal formulation can be calculated with the trained neural network according to our request (viscosity range).
3. the study of influences of particular factors with the inspection of the calculated counters.

3.2. Viscosity investigation from different aspects

For pharmaceutical or cosmetic semisolid preparation viscosity is undoubtedly one of the most characteristic rheological parameters. Therefore most attention has been focused on it here.

η^*, representing the complex vector sum of the partial components η' and η'', is shown in Fig. 9. Since the content of the silicone surfactant has no significant role in rheological behaviour, only one representative of each group is presented. The slope of the lines is almost identical for the creams containing the same amount of the water phase and different surfactant concentration. The differences become evident only when the amount of silicone surfactant is kept constant and the ratio between water and white petrolatum is changed. Within the frequency range explored, the relationship ln η^* versus ln v [ln $\eta^* = f(\ln \nu)$] is well approximated by a straight line (Table 1, Fig. 4). The analysis of the measured mechanical spectra has shown that with increasing v, η^* decreases. This is a result of the arrangement, or more precisely of water droplet deformation. Because of the shear force acting, the friction among the droplets was decreased and observed as a non-Newtonian, shear thinning behaviour, which is a desirable property of a cream.

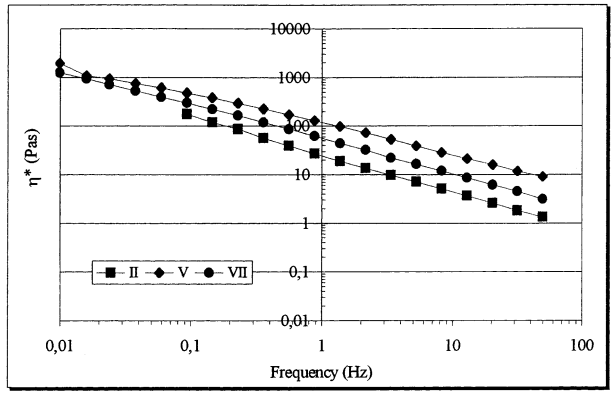

Fig. 9. The relationship between ln η^* and ln v for emulsion systems with different weight fractions of inner water phase (II — 0.90; VII — 0.65; V — 0.40); 1 month after preparation.

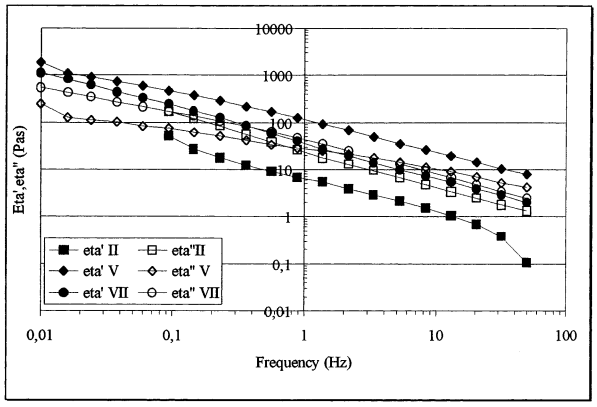

Fig. 10. Viscoelastic behaviour for emulsion systems with different weight fractions (II — 0.90; VII — 0.65; V — 0.40), expressed in values of η′ and η″, 1 month after preparation.

More detailed analysis is evident in Fig. 10, where η' and η'' are exposed. The results correlate well with previously published data. For the highly concentrated sample II elastic behaviour prevails (values of η'' are higher throughout the whole frequency range). For the concentrated system VII, a viscous behaviour prevails in the low frequency regime and elastic at the higher ones. On the contrary, for the least concentrated system, V, viscous characteristics, expressed in η', prevailed in the whole frequency range.

The values of η^* at constant frequency (5.32 Hz) and amplitude of deformation (0.2) for all prepared semisolid emulsions during ageing are shown in Fig. 11. These values are indirectly reflected in calculated parameter B_{ij}. It is evident, that the lowest values of η^* are exhibited for high concentrated systems II, III, VIII, followed by concentrated (I, VI, VII) and least concentrated ones (IV, V, IX). Sometimes deviated initial values (viscosity, measured immediately after preparation) are the consequence of the fact that emulsion systems need some time for equilibration, but thereafter, values stay more or less constant. For these reasons calculated values of parameter β_{ij} immediately after preparation and after one week were found to be less reliable and were not included in the modelling.

4. Conclusions

The determination of the dependence of complex dynamic viscosity on the content of individual components has confirmed no important role for the silicone surfactant concentration, but it is decisively influenced by the hydrophilic/lipophilic phase ratio.

The use of indirect modelling enables the investigation of the relationship between viscosity and the composition of the tested emulsions from different aspects. From empirical models it was determined that parameter A_{ij} depends mainly on the content of particular components of the emul-

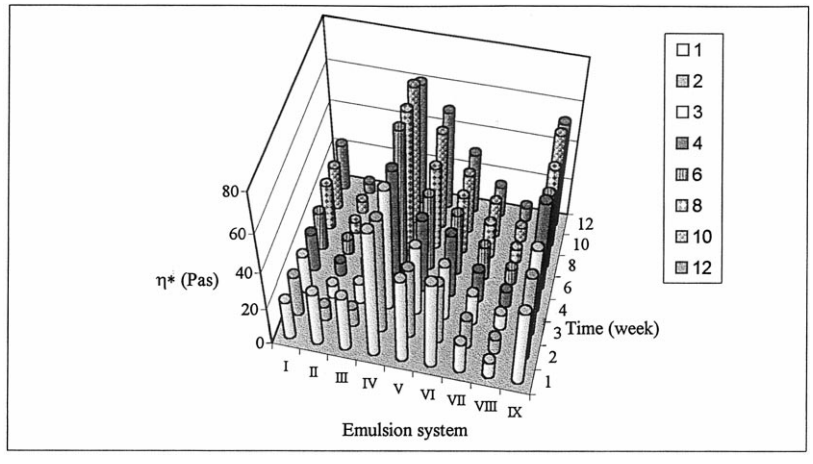

Fig. 11. The values for η^* for all prepared emulsion systems during ageing. $v = 5.32$ Hz, amplitude = 0.2.

sion and on the interaction between x_1–silicone surfactant and x_2–water. The relationship between variables is more complex for parameters B_{ij} where the contents of all particular components are still important. The interactions of high orders between x_2 and x_3–white petrolatum, x_1 and x_3, and x_2 and x_3 are also important.

The trained and tested neural network model proved to be a highly effective and applicable tool for predicting the viscosity of the composition of a lipophilic semisolid emulsion system.

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