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Research paper

Oil-in-water-emulsion gels: determination and mathematical treatment of flow properties

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Abstract

Flow properties of oil-in-water (o/w)-emulsion gels are determined for two experimental designs using common Searle-type rotating viscometers. Samples were characterized after preparation as well as real time and stress stability testing. Model emulsions contained Newtonian oil phases and cross-linked acrylic acid polymers and carboxymethylcellulose sodium as aqueous thickener. Varying two factors, concentration of gelling agent in the aqueous phase and amount of phase fraction ϕ, a series of formulations was obtained ranging from liquid o/w-lotions to semi-solid o/w-emulsion gels. Robust data evaluation is done applying Herschel, Bulkley, Van-Wazer (HBW) power law function and determination of rheological area under the curve (AUC) parameters. Factors were calculated by means of a power law function and a modified Taylor-series. Second order multiple regression and the method of Kriging were applied to describe summarized response surfaces. O/w-emulsion gels are (pseudo)plastics without rheotropic effects. Flow properties can be assessed by choosing an appropriate concentration and type of gelling agent. The influence of the Newtonian oil phase vanishes in a dominant thickened aqueous phase. Consistency of liquid o/w-lotions on the other hand is primarily controlled by ϕ. © 1998 Elsevier Science B.V. All rights reserved

Keywords: Oil-in-water emulsion gel; Rotating viscosimetry; (Pseudo)plastic flow properties; Area under the curve; Multiple regression; Kriging method

1. Introduction

O/w-emulsion gels are oil-in-water systems containing a gum solution as thickened aqueous outer phase. Since the mid 80's emulsion gels have been of growing concern in the field of pharmaceutical semi-solid dosage forms. In cosmetics such hydrophilic systems have already been known for a longer period. Despite their common applications few references are found in the literature about the physical properties of emulsion gels.

In pharmaceutical development and quality control destructive rheological investigations are used as an important tool. Nevertheless, description of flow properties of emulsion gels is rare and insufficient. In addition, data interpretation and evaluation has not been standardized so far. Different authors and laboratories have taken individual approaches.

The aim of the present investigation is to describe flow properties of o/w-emulsion gels by means of two different experimental designs. Common rotational viscosimeter data is to be reduced to area under the flow curve parameters. Systematic description of formulation field includes transition of o/w-emulsion gels to o/w-lotions. Formulations containing different concentrations of aqueous gum solutions and amounts of liquid lipophilic phase are to be examined following accelerated as well as real time stability testing.

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2. Materials and methods

2.1. Chemicals

Isopropyl myristate (IPM), polysorbate 60 (Tween® 60) and sorbitan monolaurate (Span® 20) were purchased from Fluka Chemie AG, Buchs, Switzerland. Coco-Caprylate/Caprate (Cetiol® LC) was purchased from Henkel, Düsseldorf, Germany. Trometamol was bought from Merck, Germany. Carbomer 934 P (Carbopol® 974 P) was kindly supplied by BF Goodrich, Dr. Buser Rohstoffe AG, Zürich, Switzerland. Carboxymethylcellulose sodium (Blanose® 7HOF) was a gift from Aqualon/Hercules, Fischer Chemicals AG, Zürich, Switzerland. The exact specifications were: degree of substitution 0.89, content of water 8%, pH 7.7, content of NaCl 0.07%.

Polyoxyl 35 castor oil (Cremophor® EL) was kindly provided by BASF, Ludwigshafen, Germany. All chemicals were used without further purification. Gelling agents were dried at 60°C overnight.

2.2. Viscometer

Viscosity measurements of emulsion gels containing carbomer 934 and ionic carboxymethylcellulose sodium (CMC Na) were performed using a Searle-type coaxial cylinder viscometer RHEOMAT 30, Contraves AG, Zürich, Switzerland. A set of different rotational cylinders was mounted covering a shear rate range of 0.575 to 1740 s^{-1}.

2.3. Data recording

RHEOMAT 30 scale readings were noted for each velocity stage, and data was transferred into corresponding shear rate and shear stress values using factors listed in a table supplied with the measuring device [1]. The following standard procedure was used to record RHEOMAT 30 data:

- thermostatting of samples overnight at 20°C, thermostatting during measurement;
- equilibration of sample following loading of viscosimeter;
- ascendant and descendent curve: readings for each velocity stage from 15 to 30 and 30 to 15, respectively;
- ramp time for each velocity stage ascending and descending curve: reading after 30 s;
- ramp time at highest velocity stage: 60 s, readings after 30 and 60 s.

2.4. Data evaluation

(Pseudo)plastic data were fitted with power law function Eq. (1). Describing plastic flow properties model proposed by Herschel, Bulkley and Van-Wazer (HBW) is considering a yield value τ_0 [2]. As τ_0 cannot be determined easily yield value is calculated for 1/1000 D_{max} (e.g. $\tau_{0.1}$ for $D = 0.1\ s^{-1}$) following double logarithmic transformation to give best estimation (see Eq. (2)) [2].

$$\tau = \tau_0 + k_2 \times D^{n_O} \quad \text{HBW} - \text{equation} \tag{1}$$

where $D = \dot{\gamma}$ = shear rate (s^{-1}); τ = shear stress (Pa); τ_0 = yield stress, yield value (Pa); k_2 = index of consistency; n_O = index of structure break-down, Ostwald index.

$$\log(\tau - \tau_0) = \log k_2 + n_O \times \log D \tag{2}$$

Values of k_2 and n_O are determined performing iteration with the program SYSTAT 5.0 and its Pseudo-Newton algorithm. Application and comparison of different fitting models is discussed in Ref. [3]. Lack of fit of HBW-model is avoided by defining a rheological area under the curve (AUC) (see Eq. (3)). Comparing data obtained with different cylinders or spindles, a unit range of D is chosen: $0 \le D \le 98\ s^{-1}$, $D = 98\ s^{-1}$ being the largest common shear rate for all rotational bobs used. Although there are difficulties in obtaining sufficient data inside this range of D when mounting large measuring systems, authors favour intrapolation of flow curve rather than extrapolation. Eq. (4) shows the dimension energy/volume. In a τ/D-plot AUC can be determined either by planimetration, calculation using the method of trapezoids, or integration of HBW-model in case of good fit (see Eq. (3)). Application and validation of the different methods is presented in Ref. [3].

$$\text{AUC} = \int_0^{D_{max}} \left\{\tau_{0.1} + k_2 \times D^{n_O}\right\} dD \tag{3}$$

$$\text{AUC} = \tau \times D \left(\frac{\text{N} \times \text{m}}{\text{m}^2 \times \text{s} \times \text{m}}\right) = \left(\frac{\text{N} \times \text{m}}{\text{s}} \times \frac{1}{\text{m}^3}\right) = \left(\text{Watt} \times \text{m}^{-3}\right) \tag{4}$$

Simple reduction of data is achieved as flow properties are described by the following AUC parameters:

A_T = total area for $D = 0 \ldots D_{98}$,
$A_F = A_T - \tau_{0.1} \times D_{98}$) Area of flow
A_N = Newtonian area of flow

$$R = \frac{A_F}{A_N} = \frac{A_F}{\frac{1}{2}(\tau_{98} - \tau_{0.1}) \times D_{98}} = \text{AUC} - \text{relation},$$

degree of deviation from Newtonian behaviour:

$R = 1$ Newtonian, Bingham behaviour respectively
$R > 1$ Casson solid, $R < 1$ dilatant system

$$A_{rel} = \frac{AUC_{emulsion}}{AUC_{acqueous\ phase}}$$

= relative AUC, measure of influence of ϕ

$$HR = \frac{AUC_{ascending\ curve}}{AUC_{descending\ curve}}$$

= relation of hysteresis, measure of rheotropic effects

The effects of changing the concentration of polymeric thickener and the amount of lipophilic phase are calculated by use of different models. Among them are a power law function (Eq. (5)), a modified Taylor-series (Eq. (6)), a second order model (Eq. (7)) and a matrix approach (Eqs. (8) to (11)).

$$A_{rel} = a \times b^{c_{gelling\ agent}} \quad (5)$$

where a = levelling factor $a \geq 1$, for $a > 1$: o/w-emulsion gel, for $a = 1$: no levelling, pure hydrogel; b = factor of reinforcement, proportional to formulation's amount of hydrogel for $0 < b < 1$: o/w-emulsion gel, for $b = 1$: pure hydrogel.

$$A_{rel} = 1 + a\phi + b\phi^2 + c\phi^3 + \ldots \quad (6)$$

$$AUC_T : Y(z) = b_0 z_0 + b_1 z_1 + b_2 z_2 + b_{12} z_{12} + b_{11} z_{11} + b_{22} z_{22} \quad (7)$$

where $Y(z)$ = modelled response criterion AUC_T; z_i = controlled factors (ϕ and $c_{gelling\ agent}$); b_i = calculated effects of ϕ and $c_{gelling\ agent}$.

$$Y = X \times b \quad (8)$$

$$Y \times X^T = X \times b \times X^T \quad (9)$$

$$(X^T \times X)^{-1} \times Y \times X^T = X \times b \times X^T \times (X^T \times X)^{-1} \quad (10)$$

$$b = (X^T \times X)^{-1} \times X^T \times Y \quad (11)$$

where X = matrix of controlled factors (ϕ and $c_{gelling\ agent}$); X^T = transpose of matrix X; X^{-1} = inverse of matrix X; Y = matrix of calculated response A_T.

Eq. (7) and Eqs. (8) to (11) have been used earlier in empirical studies to calculate and plot relationships between one or more measured responses such as tablet-crushing strength, friability or tablet-disintegration time, on the one hand, and a number of input variables such as amount of compounding substances magnesium stearate, lactose and microcrystalline cellulose, on the other. In the analysis of experimental results it is not sufficient to look at variation of one factor at a time. Every combination of the different factors must be examined in order to determine the effect of each dependent variable and the possible way in which each single factor can be influenced by the variation of the others.

2.5. Stability testing

Stability of formulations is tested by performing different stress tests. For semi-solid formulations different procedures have been described earlier by various authors and the Arbeitsgemeinschaft Pharmazeutischer Verfahrenstechnik (APV) [4–7]. Among those are:

- temperature cycle test, change between 4°C and 40°C every 24 h, 2 weeks;
- freeze-thaw-storage, slow freezing and storage at −16°C, 2 weeks.

In addition samples were stored at room temperature (RT) for 4 months and 18 months, respectively to examine real time stability. Flow properties were measured after each stability test and data were compared with values obtained shortly after emulsion preparation.

2.6. Emulsion preparation

Samples were prepared using a laboratory emulsifying unit (IKA-Laborreaktor LR 250, ULTRA-TURRAX T25, Jahnke and Kunkel, Staufen, Germany) suitable for batch sizes of 250 g. Preparation conditions were standardized and kept as indicated below. For gums used in formulation, gel-temperature was well above 70°C as gels could be autoclaved by means of super-heated steam at 121°C without any optical changes:

- separate preparation of aqueous and lipophilic stock phase dispersing of gum in water, neutralization of Carbopol® solutions to pH 6.5 with Trometamol;
- mixing all-in-one pot: adding emulsifiers, gum solution, oil phase;
- heat-up time to reach 70°C:~15 min, T-shaped stirrer 20 UpM;
- emulsifying time: homogenizator 135 000 UpM, T-shaped stirrer 100 UpM, evacuation of mixing chamber (400 hPa), 5 min;
- cooling phase: homogenizator 135 000 UpM, T-shaped stirrer 100 UpM, water cooling, 10 min;
- stirring at RT: T-shaped stirrer 50 UpM, turning off water cooling and homogenizator, 2 min;
- ventilation and filling of storing vessels.

3. Results and discussion

3.1. Variation of Carbopol® concentration and phase fraction ϕ

Based on a model formulation (Table 1) flow properties of o/w-emulsion gels yielding o/w-lotions are investigated varying two factors, the amount of gelling agent and ϕ. Carbopol® is known to be a very effective thickener of aqueous solutions producing plastic, transparent hydrogels

Table 1

Model o/w-emulsion gel with carbomer

Isopropyl myristate	5.0-40.0
Cremophor® EL + Span® 20 4 + 1	6.0
Trometamol (pH 6.5)	q.s.
Carbopol® 974 P + Aqua conservans 0.8 + 99.2	ad 100.0

even at very low concentrations of 0.5%. Carbopol polymers are made of acrylic acid crosslinked with allyl sucrose or allylpentaerythritol, polymerization being carried out in a non-toxic solvent ethylacetate. Elastic properties are due to its closely tailored microgel structures described by Ketz et al. [8] and Taylor and Bagley [9]. Bremecker proposes Trometamol as an alternative organic neutralizing agent for viscosity build up as diethylamine or triethylamine can give rise to cancerogenic nitrosamine residues [10]. Maximum viscosity is found to be between pH 6.5 and 8. Preservation is achieved by Aqua conservans DAC 1986 (methyl-, propylparabenes 7 + 3, 0.1%).

Easy spreading IPM serves as a solvent agent for many lipophilic drugs and as a penetration enhancement. Investigating only physical properties, a possible comedogenic action is accepted [11].

A combination of Cremophor® EL and Span® 20 is used as an emulsifying agent. Mixed emulsifying agents can reduce surface tension to a minimum to yield thermodynamically stable systems [12]. In order to minimize possible rheological changes due to a rise in consistency caused by solid surfactants, liquid or waxlike emulsifiers were chosen for a model formulation. For both surfactants sufficient compatibility with Carbopol® gels was assumed as addition of surfactants to gels did not give rise to precipitation or a drop in consistency. HLB-optimization was done preparing o/w-lotions containing no gelling agent with ϕ IPM = 0.3. Physical stability was tested briefly storing emulsions at elevated temperatures for a week. Emulsions containing 6% of a mixture of Cremophor® EL (HLB 12.5) and Span® 20 (HLB 8.6) 4 + 1 gave the best results. Assuming additive properties the emulsion's HLB totals to 11.7.

Table 2 displays the experimental design. As formulations contain different concentrations of aqueous gelling agent and fractions of lipophilic phases emulsions cannot be compared directly. Relating rheological parameters to each aqueous phase, separate aqueous and non-aqueous phases were prepared and measured as reference values. Simulating idealized conditions, o/w-surfactants are considered to be a part of the outer phase, w/o-surfactants belong to the inner phase.

Table 2

Experimental design

ϕ Isopropyl myristate	Carbopol® 974 P (%) in aqueous phase			
	0	0.2	0.4	0.6
0.05	01	05	09	13
0.1	02	06	10	14
0.2	03	07	11	15
0.4	04	08	12	16
Row	I	II	III	IV

Numbers refer to batches, batch size 250 g.

RHEOMAT 30 measurements revealed lipophilic phases to behave as Newtonian liquids as w/o-surfactant was completely soluble in IPM. Increasing amounts of Span® 20 gave rise to higher viscosities η. Relationship between Span® 20 and η was not linear however.

According to Table 3 non-thickened aqueous phases containing Cremophor® EL in concentrations corresponding to the experimental design up to 8.2% are Newtonian liquids. All Carbopol® solutions showed (pseudo)plastic flow behaviour without rheotropic effects such as thixotropy, rheodestruction, or rheopexy. A transition from pseudoplastic to plastic systems is observed for Carbopol® concentrations between 0.4 and 0.6%. Addition of o/w-surfactant Cremophor® EL resulted in a slight drop in consistency. Competitive hydration between both surfactant ether-oxygens and polymer carboxyl groups might give rise to this interaction. Reduced hydration of carbomer causes closely tailored microgel structures to form a dispersion of smaller microgel particles in a continuous phase. Increased values for n_O provide support for this theory, indicating a deflocculation and orientation to Newtonian flow behaviour. For a constant Carbopol® concentration (0.6) an increase in Cremophor® concentration (5.1-8.2) n_O remains more or less constant whereas for a constant Cremophor® concentration (6.1) the increase of Carbopol® concentration (0.6-0.2) decreases n_O.

Table 4 lists results of rheological investigation after preparation. Batches of rows I (Carbopol® concentration 0%) and II (Carbopol® concentration 0.2%) are typical o/w-lotions revealing pseudoplastic flow behaviour without rheotropic effects. Consistency is controlled by ϕ as values for A_T are rising for increasing amounts of inner phase. Rows III and IV (Carbopol® concentration 0.4 and 0.6%) contain pseudoplastic and plastic o/w-emulsion gels with a

Table 3

Representative parameters of aqueous reference phases and ascendant curves

$c_{\text{Carbopol® 974 P}}$ (%)	$c_{\text{Cremophor® EL}}$ (%)	A_T	τ_0 (Pa)	n_O	R
0.6	0	6744	14.7	0.40	1.42
0.6	5.1	3578	8.3	0.51	1.32
0.6	5.4	3453	7.6	0.51	1.32
0.6	6.1	3491	7.8	0.51	1.32
0.6	8.2	3041	5.9	0.53	1.31
0.4	0	1792	4.2	0.50	1.32
0.4	6.1	848	1.1	0.60	1.25
0.2	0	136	0.2	0.74	1.15
0.2	6.1	118	0.1	0.80	1.11
0.0	0	5	0	1.00	1.00
0.0	6.1	10	0	1.01	1.00

Data are mean of two experiments.

Table 4
Rheological parameters obtained after preparation

Batch	$c_{(Carbopol®)}$ (%)	ϕ	A_T	A_{rel}	HR	τ_0 (Pa)	n_O	R
Ref.[a]	0	0	8	1.00	1.00	0	1.00	1.00
01	0	0.05	10	1.28	1.03	0	1.00	1.00
02	0	0.10	11	1.42	1.00	0.1	1.00	1.00
03	0	0.20	20	2.52	1.02	0	0.97	1.02
04	0	0.40	61	7.62	1.01	0	0.82	1.10
Ref.[a]	0.2	0	103	1.00	0.99	0.1	0.80	1.11
05	0.2	0.05	124	1.20	1.01	0.1	0.81	1.10
06	0.2	0.10	148	1.44	1.00	0	0.76	1.14
07	0.2	0.20	187	1.82	1.00	0	0.75	1.14
08	0.2	0.40	374	3.65	0.95	0	0.69	1.19
Ref.[a]	0.4	0	863	1.00	1.00	1.1	0.60	1.25
09	0.4	0.05	915	1.06	1.04	1.1	0.63	1.23
10	0.4	0.10	727	0.84	1.01	0.5	0.66	1.20
11	0.4	0.20	863	1.00	1.00	0.9	0.65	1.21
12	0.4	0.40	1273	1.47	0.98	2.2	0.62	1.23
Ref.[a]	0.6	0	3493	1.00	1.00	7.8	0.51	1.32
13	0.6	0.05	3294	0.94	1.00	5.7	0.54	1.30
14	0.6	0.10	3047	0.87	1.00	4.0	0.56	1.29
15	0.6	0.20	3550	1.02	0.99	7.0	0.54	1.30
16	0.6	0.40	3624	1.04	0.98	8.0	0.57	1.28

[a]Aqueous phase + 6.1% Cremophor® EL.
Data are mean of two experiments.

consistency ranging from very thick to soft semi-solid. Again no rheotropic effects were detected as values for HR agreed well with 1.00. Compared to rows I and II, flow behaviour of batches 09–16 is primarily controlled by consistency of a thickened aqueous phase. For batches with $\phi = 0.05$ and 0.1 a drop of A_T was observed. Viscosities were reported to be even lower than the corresponding aqueous phase as values of $A_{rel} < 1$ were found. This effect is compensated for $\phi > 0.2$ as structural resistance increases with a higher amount of oil phase. For row IV flow properties of o/w-emulsion gels seem to be independent of ϕ. Deflocculation of IPM drops is controlled by Carbopol® gel causing n_O to remain relatively constant.

Using Eq. (5), A_{rel} can be calculated as a power law function of the gum's concentration in the aqueous phase and ϕ (Table 5). In Fig. 1 the dominant effect of concentration of aqueous gelling agent on emulsion's viscosity is shown. Responding to an increase of viscosity of aqueous phase, values for A_{rel} are calculated approximating 1.

For concentrated emulsions, that is formulations with a large amount of lipophilic inner phase, a relationship between η_{rel} and ϕ can be expressed by Eq. (6) [13]. Fig. 2 and Table 6 show calculated results for a modified Taylor-series, substituting η_{rel} by A_{rel}. Determining $A_{rel} \times a$ value for $a = 2.5$ which is often quoted in literature could not be found for emulsion gels with $0.05 \leq \phi \geq 0.4$.

Surface methodology is a powerful strategy to optimize and validate production as well as development processes [14–17]. Experimental response can be summarized using a second order model as given by Eq. (7). Calculation of multiple regression is performed using MATHCAD 6.0 (MathSoft, Cambridge, MA, USA). Estimation of regression coefficients is based on a matrix approach Eq. (8) Eq. (9) Eq. (10) Eq. (11).

Regression coefficients, statistics and calculated response values of A_T are listed in Tables 7 and 8.

Comparing original and calculated values of A_T it becomes obvious that response surface for o/w-lotions is

Table 5
Calculation of levelling effect

ϕ	a	b	r^2	SS_{res}
0	1.000	1.000	1.000	0
0.05	1.298	0.598	1.000	0.068
0.1	1.496	0.377	0.985	0.081
0.2	2.515	0.165	0.993	0.082
0.4	7.620	0.023	0.998	0.111

SS_{res}, sum of square of residues.

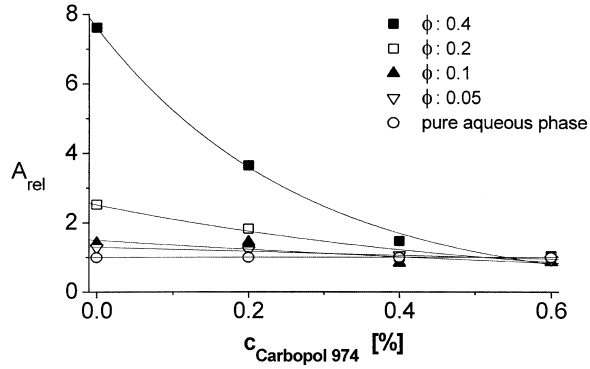

Fig. 1. Effect of concentration of aqueous gelling agent on emulsion's A_{rel}, points are mean of two experiments, lines correspond to Eq. (5).

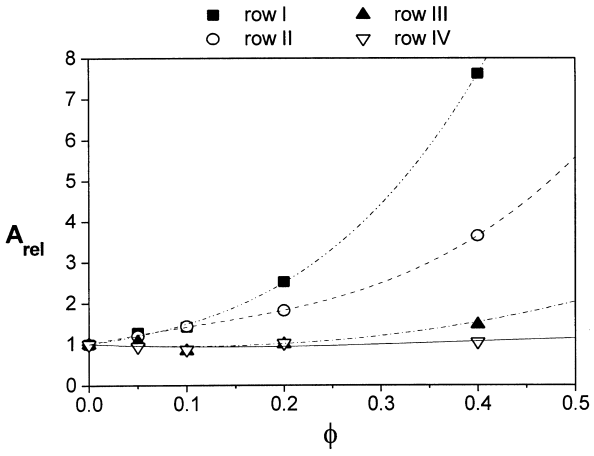

Fig. 2. Approach of modified Taylor-series, dominant effect of Carbopol® concentration on viscosity of emulsions, points are mean of two experiments, lines correspond to Eq. (6).

only poorly described by Eq. (7). Errors calculated for this part of the experimental design have a large influence on small values of A_T. This is not surprising as the fitting function ranges over three decades of A_T.

Fig. 3a,b shows response contour plots for the method of Kriging (ORIGIN 4.0, Microcal Software, Northampton, MA, USA) and calculated values of A_T using multiple regression. Kriging involves construction of a weighted moving average equation which is used to estimate the true value of a regionalized variable at successive points of a grid. All measured mean values are points of the contour plot. Algorithms and application are discussed in Ref. [18]. For the spectrum of lotions and emulsion gels investigated, both methods of calculation are appropriate to show the different effect of the controlled variables ϕ and $c_{\text{gelling agent}}$ on a rheological response surface. Here consistency of formulations is primarily controlled by Carbopol® concentration.

Temperature cycle testing and storing for 4 months proved the excellent physical stability of all emulsions except batch 04 and 08 (high ϕ, low thickener concentration). Both formulations suffered separation into two phases. For all other formulations rheological parameters remained relatively constant. In comparison stability during freeze-thaw-storage was rather poor. Here conditions caused either a detectable drop of consistency or a macroscopic separation of phases. Flow properties of batches 09-11 and 13-15 with a small ϕ and a thickened aqueous phase were the only ones to remain unchanged. With respect to structure break down and ageing of emulsions, although theories are discussed in Refs. [19,20], experimental testing of hypothesis was however not possible. Stability profile of formulations with Carbopol® 974 P 0.6% is shown in Fig. 4.

Table 6

Calculation of modified Taylor-series

Row	a	b	c	r^2	SS_{res}
I	3.51	7.44	62.92	1.000	0.011
II	5.08	−13.37	45.49	1.000	0.001
III	−1.84	4.80	2.76	0.997	0.020
IV	−1.02	4.40	−3.62	0.998	0.012

Table 7

Regression coefficients of calculated summarizing equation

Coefficient	Meaning of effect	Value
b_0	Index of consistency, shift of plane to base x_1,x_2	105
b_1	Main effect: ϕ	−1401
b_2	Main effect: thickening of aqueous phase	−3523
b_{12}	Interaction: ϕ and thickening of aqueous phase	366
b_{11}	Squared effect of ϕ	4482
b_{22}	Squared effect of thickening of aqueous phase	15290
SS_{res}	Sum of square of residues	809182
MST	Mean square: SS_{res}/degrees of freedom	57799
r^2	Multiple correlation coefficient	0.980

3.2. Variation of Blanose® concentration in aqueous phase and ϕ

Demonstrating universal application of methods for emulsion(gel) systems a second experimental design investigated flow properties of o/w-emulsions containing varying concentrations of Blanose® 7HOF in the aqueous phase. In pretests ionic cellulose derivative showed excellent short time stability at elevated temperatures. Compatibility with non-ionic o/w-surfactants was recorded to be good as no flocculation or other physical change occurred.

Specifications of Blanose® 7HOF was as given earlier. Optimizing stability of new model o/w-emulsion gel oil

Table 8

Comparison of original and calculated values for A_T

Batch	A_T	$A_T$calc.	Residues
Ref.[a]	9	105	+96
01	9	46	+38
02	11	9	−2
03	18	4	−14
04	63	261	+198
Ref.[a]	101	12	−90
05	122	−44	−165
06	154	−76	−230
07	193	−75	−268
08	389	197	−192
Ref.[a]	893	1142	+249
09	914	1090	+176
10	751	1061	+310
11	894	1070	+176
12	1323	1357	+34
Ref.[a]	3957	3495	−462
13	3384	3447	+63
14	3142	3422	+280
15	3649	3438	−211
16	3725	3740	+15

[a]Aqueous phase containing 6.1% Cremophor® EL.

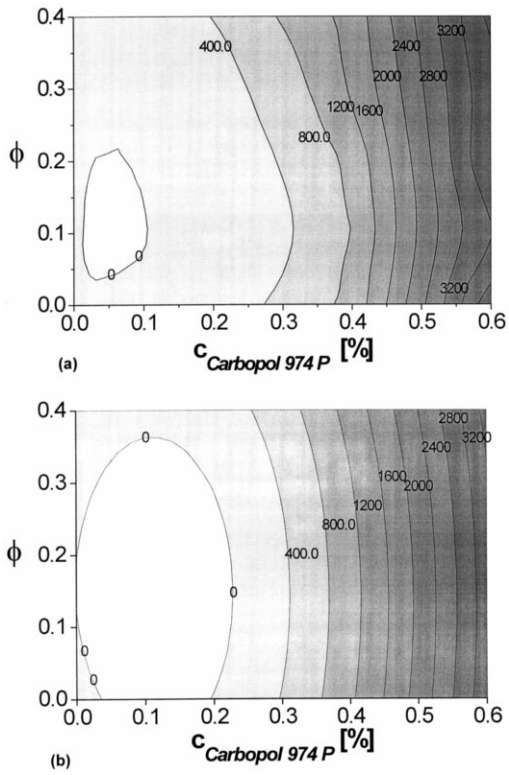

Fig. 3. Contour plot for calculated values of A_T (a) method of Kriging and (b) multiple regression.

phase and o/w-surfactant were changed. Surfactant mixture was composed of Tween® 60 and Span® 20 1.3 + 1.7. Total HLB was 11.4 assuming additive properties. Concentration of mixed surfactant was kept constantly at 6% and ϕ of Cetiol® LC ranged from 0.05 to 0.6. Tables 9 and 10 list experimental design and composition of formulations and reference phases.

Two hundred and fifty gram sized batches of emulsions and 100 g sized batches of reference phases were prepared and stored as described in Sections 2.5 and 2.6.

Investigation of reference phases showed Newtonian flow behaviour of oil phases for all concentrations of Span® 20.

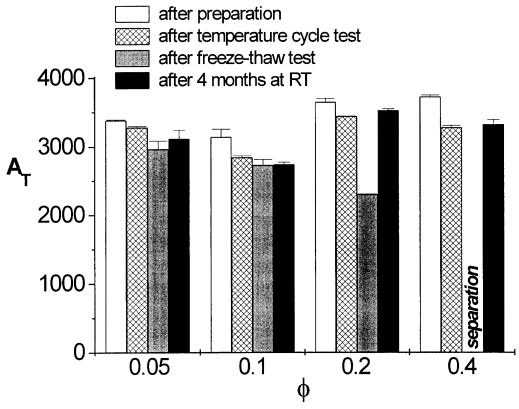

Fig. 4. Stability of o/w-emulsion gels containing 0.6% of Carbopol® 974 P in the aqueous phase, data are mean of two experiments.

Table 9

Model o/w-emulsion gel with carboxymethylcellulose sodium (CMC Na)

Cetiol® LC	5.0–60.0
Tween® 60 + Span® 20 1.3 + 1.7	6.0
Blanose® 7HOF + Aqua conservans 2.3 + 97.7	ad 100.0

Thickened aqueous phases included pseudoplastic properties for gum concentrations $< 2.3\%$ and plastic properties at 2.3% of CMC Na. Addition of Tween® 60 did not influence consistency of hydrogels.

In Table 11 representative data of rheological testing after preparation are listed for formulations of rows I, III and V. For other rows congruent parameters were obtained. Response of parameters agreed well with results found for experimental design 1. O/w-lotions with $\phi < 0.2$ in good approximation behaved like Newtonian liquids whereas other systems were pseudoplastic and plastic. As expected, values of n_O dropped below 1 as ϕ of emulsion was rising. For systems containing a thickened aqueous phase n_O seemed to be almost unaffected by ϕ. Yield stresses around 15 and 25 Pa were determined for o/w-emulsion gels with a gum concentration of 2.3% (row V). It is worth mentioning that theoretical yield values below 15 Pa can be neglected as emulsions are still pourable and will not be regarded as semi-solid or plastic o/w-emulsion gel during application. Values of HR agreed well with 1.0 for all formulations, revealing that no rheotropic effects occurred.

Evaluation of rheological data confirms the dominating effect of a thickened aqueous phase as it was already found for o/w-emulsion gels containing carbomer 934. Influence of Newtonian liquid vanishes as concentration of hydrophilic gelling agent is increased in the continuous phase. On the other hand consistency of o/w-lotions containing no thickened aqueous phase (row I) primarily is a function of ϕ. Raising ϕ, mobility of oil drops is decreased and inner resistance expressed as A_T becomes larger during process of shearing. For those systems values of A_{rel} and n_O are varying.

In row V value for A_T of formulation with $\phi = 0.2$ is lower compared to the value for the corresponding aqueous

Table 10

Experimental design

ϕ Cetiol® LC	Blanose® 7HOF (%) in aqueous phase				
	0	0.7	1.2	1.7	2.3
0.05	01	08	15	22	29
0.1	02	09	16	23	30
0.2	03	10	17	24	31
0.3	04	11	18	25	32
0.4	05	12	19	26	33
0.5	06	13	20	27	34
0.6	07	14	21	28	35
Row	I	II	III	IV	V

Numbers refer to batches.

Table 11

Row I, III and V: rheological parameters after preparation

Batch	$c_{(Blanose®)}$ (%)	ϕ	A_T	A_{rel}	HR	τ_0 (Pa)	R	n_O
Ref.[a]	0	0	7	1.00	1.04	0	1.00	1.00
01	0	0.05	8	1.86	1.03	0	1.00	1.00
02	0	0.10	9	2.10	1.01	0	1.01	0.99
03	0	0.20	18	2.87	1.02	0	1.03	0.94
04	0	0.30	31	4.32	1.03	0	1.05	0.91
05	0	0.40	100	10.10	1.04	0	1.08	0.85
06	0	0.50	292	26.75	1.04	0	1.14	0.76
07	0	0.60	737	44.66	0.99	0	1.15	0.74
Ref.[a]	1.2	0	1975	1.00	1.01	0.3	1.22	0.63
15	1.2	0.05	2822	1.43	1.01	1.0	1.29	0.55
16	1.2	0.10	2896	1.47	1.01	0.9	1.28	0.56
17	1.2	0.20	2890	1.38	1.01	1.5	1.31	0.53
18	1.2	0.30	3311	1.49	1.01	1.8	1.31	0.52
19	1.2	0.40	3998	1.71	1.00	2.0	1.30	0.54
20	1.2	0.50	4631	1.75	0.99	2.1	1.29	0.56
21	1.2	0.60	5772	1.80	0.99	2.5	1.26	0.58
Ref.[a]	2.3	0	12735	1.00	1.04	11.1	1.38	0.45
29	2.3	0.05	13997	1.10	1.02	17.5	1.42	0.41
30	2.3	0.10	13096	1.03	1.05	16.3	1.42	0.41
31	2.3	0.20	12361	0.99	1.01	15.4	1.41	0.42
32	2.3	0.30	14127	1.11	1.01	20.0	1.42	0.41
33	2.3	0.40	15330	1.20	1.00	21.4	1.41	0.42
34	2.3	0.50	16382	1.28	0.99	21.8	1.41	0.42
35	2.3	0.60	17869	1.29	0.98	24.0	1.40	0.43

[a]Corresponding aqueous phase + 2.9% Tween® 60.
Data are mean of two experiments.

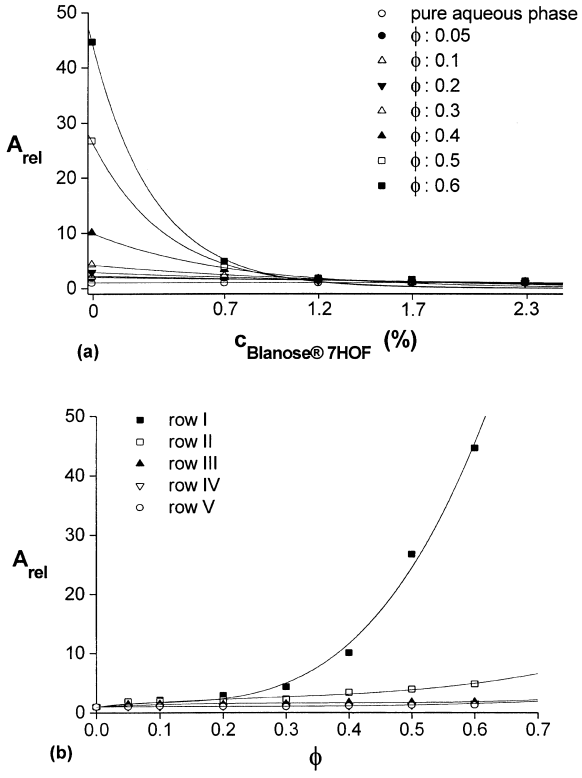

Fig. 5. Dominant effect of thickened aqueous phase on emulsions' consistency expressed as reduction of A_{rel} (a) power law approach (Eq. (5)) and (b) approach of modified Taylor-series (Eq. (6)), points are mean of two experiments.

phases. This might be due to disturbance of gum's hydration.

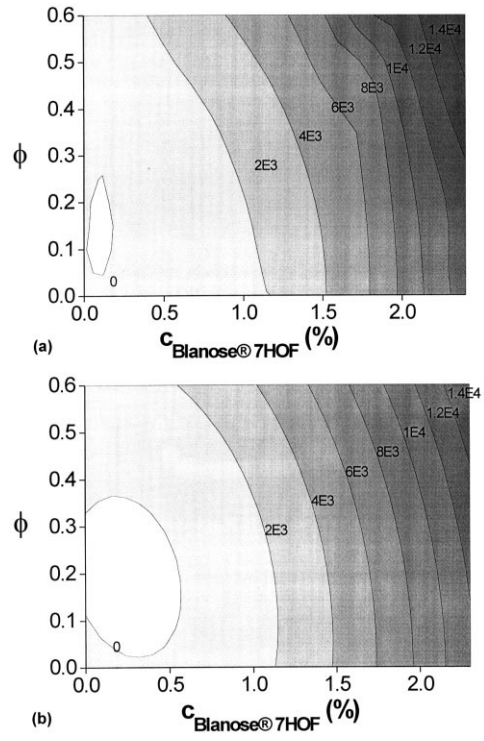

Fig. 6. Response contour plot for A_T (a) values for A_T calculated using the method of Kriging and (b) values for A_T calculated using multiple regression (Eq. (7)).

Table 12

Calculation of levelling effect

ϕ	a	b	r^2	SS_{res}
0	1.000	1.000	1.000	0
0.05	1.965	0.757	0.990	0.116
0.10	2.186	0.704	0.993	0.089
0.20	2.880	0.587	0.996	0.063
0.30	4.215	0.459	0.992	0.238
0.40	10.014	0.241	0.993	0.845
0.50	26.709	0.076	0.996	2.809
0.60	44.635	0.047	0.998	3.869

Table 14

Regression coefficients of calculated summarizing equation (Eq. (7))

Coefficient	Value
b_0	386
b_1	–4804
b_2	–1994
b_{12}	2564
b_{11}	11220
b_{22}	3180
SS_{res}	13775120
MST	353208
r^2	0.987

Estimated response for A_T and A_{rel} data is given in Figs. 5 and 6 and Tables 12–14.

Compared to the experimental design in Section 3.1, systems containing Blanose® 7HOF and Cetiol® LC revealed rather poor stability [21]. Systems with a large ϕ and a high concentration of hydrophilic thickener showed the best physical stability for all storage conditions investigated. For lotions with a small ϕ phase separation was reported within 2 weeks storing samples at RT. Generally, values of A_T dropped following temperature cycle testing and storing at RT for 4 months. The corresponding rise for values of n_O indicated a shift of flow behaviour towards Newtonian properties. Freeze-thaw testing on the other hand resulted in relatively constant AUC parameters. It is worth mentioning that stress stability tests however did not give the same results as real time stability testing. Following 2 years of shelf-life at RT phase separation occurred for a larger number of emulsions than was reported after submitting samples to temperature stress. Representative values of A_T are shown in Fig. 7 for row IV containing 1.7% Blanose® 7HOF in the aqueous phase.

4. Conclusion

Investigation of flow properties of o/w-emulsions was carried out for two experimental designs to show universal application of mathematical treatment of response data. O/w-emulsion gels with carbomer 934 and ionic CMC as aqueous thickener and Isopropyl myristate and Coco/Caprylate-Caprate as non-thickened Newtonian fatty phase proved to be suitable model formulations. Varying two factors (i) concentration of gum and (ii) amount of lipophilic phase ϕ a spectrum of o/w-emulsions is obtained to cover transition from common o/w-lotions to o/w-emulsion gels. Physical properties can be described in a systematic way reducing rotational viscosity data to non-linear HBW power law fitting function and rheological AUC parameters. In addition influence of different formulation factors can be calculated as a power law function, and a modified Taylor-series. For optimization of formulation criteria summarized A_T response surfaces can be calculated and plotted using second order multiple regression and the method of Kriging.

As a result all o/w-emulsion gels investigated in this part of research were (pseudo)plastics without rheotropic effects such as thixotropy, rheodestruction, or rheopexy. Flow properties of emulsions can be assessed by choosing appropriate gum concentration in the aqueous phase. This is of practical importance finding appropriate consistency of dosage forms for consumer's application, industrial pumping, or filling action. For o/w-emulsion gels the influence of a Newtonian oil phase vanishes in a dominant thickened aqueous phase. With respect to dissolution of lipophilic drugs, the formulator is free to choose amount of fatty phase as consistency of dosage form remains relatively unchanged for $\phi < 0.4$. Consistency of common liquid o/w-lotions on the other hand is primarily controlled by ϕ. Calculation of surface methodology proved to be an appropriate tool to analyze the different effects of the controlled variables.

Accelerated stability testing of samples included stress

Table 13

Calculation of modified Taylor-series

Row	a	b	c	r^2	SS_{res}
I	14.50	– 107.55	344.80	0.997	9.276
II	9.40	– 21.41	27.77	0.993	0.467
III	4.78	– 12.90	12.19	0.994	0.112
IV	0.67	– 3.27	6.07	1.000	0.242
V	0.23	– 0.56	1.80	0.998	0.020

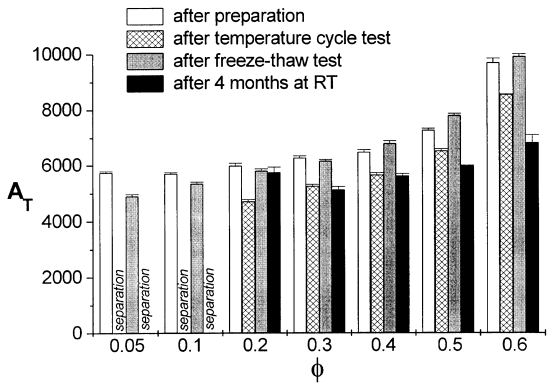

Fig. 7. Stability of o/w-emulsion gels containing 1.7% of Blanose® 7HOF in the aqueous phase (row IV), data are mean of two experiments.

conditions such as temperature cycle and freeze-thawing-storage. In addition samples were stored at RT for 4 months and 18 months, respectively to examine real time stability. Non-conforming results revealed that rheological measurements after stress testing obviously could neither simulate nor predict long term stability of semi-solid multi-phase preparations. Ageing of o/w-lotions containing a liquid fatty phase however resulted in a drop of consistency easily detectable e.g. by A_T.

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References

[1] Contraves AG, Rheomat 30 – Laborgerät zur Ermittlung des Flie\usverhaltens von Flüssigkeiten und Pasten, Instruction manual, Zürich, Switzerland, 1975.
[2] W. Herschel, R. Bulkley, Konsistenzmessungen von Gummi-Benzollösungen, Kolloid Ztsch. 39 (1926) 291–300.
[3] D. Marquardt, R. Pedrussio, B. Herzog, H.B. Sucker, Determination of (pseudo)plastic flow properties of pharmaceutical semi solids using rheological AUC parameters, Pharm. Dev. Technol. 2 (1997) 123–133.
[4] F.J. Gohlke, L. Fiquet, Standardisierte Stabilitäts-Charakterisierung von Emulsionen, Tenside Deterg. 21 (1984) 28–33.
[5] S.A. Hill, K.A. Khan, Protocols for stability testing, Int. J. Pharm. 8 (1981) 73–80.
[6] R. Hüttinger, D. Billek, E. Charlet, L. Hoenen, K. Kuczera, L. Motitschke, J. Quack, K. Seib, I. Umbach, K.-P. Wittern, G. Wolff, Zur Prüfung der Stabilität kosmetischer Emulsionen. Erfahrungen aus einem Ringtest, Parfüm. Kosmet. 61 (1980) 41–47.
[7] H.J. Jörs, Qualitätskontrolle von Grundlagen und Fertigprodukten, in: Dermatika III, Arbeitsunterlagen für den APV Fortbildungslehrgang, Mainz, 1974.
[8] R.J.Ketz Jr., , R.K. Prud'homme, W.W. Graessley, Rheology of concentrated microgel solutions, Rheol. Acta 27 (1988) 531–539.
[9] N.W. Taylor, E.B. Bagley, Rheology of dispersions of swollen gel particles, J. Polym. Sci. (Polym. Phys. Edition) 13 (1975) 1133–1144.
[10] K.-D. Bremecker, Tromethamine – an alternative in carbomer-gels containing amines, Pharm. Ind. 51 (1989) 199–202.
[11] R. Campell, R. Bruce, Comparative dermatotoxicology: direct comparison of rabbit and human primary skin irritation responses to IPM, Toxicol. Appl. Pharmacol. 59 (1981) 555–563.
[12] W. Pohler, Mikroemulsionsgele, Strukturuntersuchungen und galenische Eigenschaften, Doctoral Thesis, Erlangen, Germany, 1983.
[13] P. Sherman, The flow properties of emulsions – review article, J. Pharm. Pharmacol. 16 (1964) 1–25.
[14] G.E. Box, N.P. Draper, Empirical Model-Building and Response Surfaces. Wiley, New York, 1987, pp. 205–243.
[15] G.E. Box, W.G. Hunter, J.S. Hunter, Response surface methods, in: G.E. Box, W.G. Hunter, J.S. Hunter (Eds.), Statistics for Experimenters, Wiley, New York, 1978, pp. 510–539.
[16] O.L. Davies, Design an Analysis of Industrial Experiments, Oliver and Boyd, London, pp. 290–366.
[17] M. Sergent, D. Mathieu, R. Phan-Tan-Lieu, G. Drava, Correct and incorrect use of multilinear regression, Chemometrics Intell. Lab. Syst. 27 (1995) 153–162.
[18] J.C. Davies, Statistics and Data Analysis in Geology, Wiley, New York, 1986, pp. 383–390.
[19] I. Erös, E. Ugri-Hunyadvári, Theoretische und praktische Fragen der strukturrheologischen Forschung an Salben. 4. Mitteilung: Untersuchung der Konsistenzstabilität, Pharmazie 32 (1977) 784–787.
[20] T.F. Tadros, B. Vincent, Emulsion stability, in: P. Becher, Encyclopedia of Emulsion Technology, Vol. 1, Marcel Dekker, New York, 1983, pp. 129–286.
[21] D. Marquardt, O/W-Emulsionsgele – Ein Beitrag zur rheologischen Charakterisierung und Abgrenzung, Doctoral Thesis, Berne, Switzerland, 1996.