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Research paper

Rapid assessment of sedimentation stability in dispersions using near infrared transmission measurements during centrifugation and oscillatory rheology

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Abstract

We used the LUMiFuge® 114 particle separation analyser to investigate the sedimentation kinetics of bentonite/xanthan gum mixtures through pH 2–7 during centrifugation. This new technique monitors timed near infrared transmission profiles of different samples in the centrifugal field. Statistical analysis of the data then identifies the formulations with minimal clarification tendency.

All mixtures were characterised by rotational and oscillatory rheology. Various rheological parameters correlated with the LUMiFuge clarification data, most notably the relaxation exponent, n and loss tangent, tan δ. We devised a combined desirability function for the different mixtures, defining maximal desirability as the minimal values for the two oscillatory parameters. The results matched those of separation analysis in the centrifugal field.

We conclude that the experimental design is suitable for selecting formulations with optimal sedimentation stability whether combined with LUMiFuge analysis or oscillatory measurements. The method can be used to screen formulations for optimal long-term stability test performance, with significant potential savings and minimal sedimentation risk after prolonged storage.

Keywords: Dispersion stability; Sedimentation; LUMiFuge; Rheology; Bentonite; Xanthan gum

1. Introduction

The critical parameters in early formulation development are time, resources and availability of drug substance. It is therefore vital to enter as few formulations as possible into conventional long-term stability tests at different temperatures. Such formulations should be preselectable for stability throughout the anticipated shelf-life. This can only be achieved by rapid and effective physical screening.

This paper focuses on the sedimentation stability of dispersions using a recently introduced separation analyser – the LUMiFuge® 114 (LUM Ltd., Berlin, Germany) [1–3]. The system measures near infrared (NIR) transmission profiles continuously during centrifugation. Separation kinetics can thus be studied under accelerated conditions and eight samples run in parallel using volumes >2 ml.

Our primary aim was to apply the LUMiFuge® method to mixtures of Veegum® and xanthan gum at acidic to neutral pH values. Ciullo originally investigated the specific effects of Veegum® and xanthan gum using a traditional controlled rate rheometer [4], while Luckham and Rossi [5] recently viewed the general aspects of polymer adsorption on smectite clays. The pharmaceutical purpose behind such gum combinations is to obtain physically stable clay dispersions which exhibit thixotropic flow behaviour and can be used in acidic environments. Such a vehicle could for example be used to formulate ad hoc drug suspensions, thus facilitating the administration of oral formulations mostly in toxicology studies.

Our secondary aim was to correlate the LUMiFuge® data with parameters from static and dynamic rheology to elucidate their significance in terms of sedimentation stability.

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2. Materials and methods

2.1. Raw materials and dispersion manufacture

Using a rapid hydrating bentonite and xanthan gum (Veegum® HS and Vanzan® NF, R.T. Vanderbilt Inc, Norwalk, CT 06856-5150, USA), we manufactured 15 vehicles with Veegum® 1–3% (w/w) and xanthan gum 0.1–0.7% (w/w) at pH values ranging from 2 to 7 (Table 1). Veegum® and xanthan gum were weighed, blended and then sprinkled into demineralised water during continuous stirring for 30 min using a Viscojet mixer (Viscojet Ltd., Switzerland) at 800 rpm. The pH was adjusted to the target value, followed by an additional 5 min stirring and overnight equilibration.

2.2. Methods

2.2.1. Sedimentation analysis

Phase separation analysis was performed using the automated LUMiFuge® 114 system, an analytical centrifuge with an opto-electronic sensor system that measures NIR transmission profiles along horizontally inserted sample tubes [6].

The 2 ml sample volume (in a 1.15 cm diameter tube) forms a rather shallow suspension sample compared to the distance from the axis of rotation to the base of the tube (11.5 cm), thereby minimising the lateral particle movement that could invalidate the analogy with gravitational settling [7]. The 3000 rpm rotor speed is equivalent to 1200 g acceleration with reference to the base of the tube. NIR transmission profiles were recorded continuously every 150 s during the 9 h separation process (Fig. 1). For clarity of presentation, only every 10th transmission profile was displayed. With an evaluation range of 90–109 mm neither the CCD sensor tip nor reflections from the base of the tube could interfere with data evaluation. The change of decline in transmission illustrated in Fig. 1, representing the movement of the interface (separation of the clear phase) over time, is typical of the sedimentation process.

The LUMiFuge® software – SEPView V.3.2. (L.U.M. Ltd.) – calculates the integral of every transmission curve over the chosen sample radius. Integral transmission increases linearly as a function of time in the initial sedimentation phase. This linear range provides a slope of integral transmission, or so-called *clarification*, $\Delta T_{int}/\Delta t$ (%/1000 s) [8], calculated by the software using correlation coefficients all exceeding 0.98. Clarification serves as a surrogate marker of sedimentation velocity in highly polydisperse systems and as a discriminating measure of separation instability [8].

Table 1
Box-Behnken study design (brackets: coded factor levels)

No.	X_1 Veegum HS %, w/w	X_2 Xanthan gum %, w/w	X_3 pH
1	3.0 (+1)	0.1 (−1)	4.5 (0)
2	3.0 (+1)	0.7 (+1)	4.5 (0)
3	2.0 (0)	0.1 (−1)	2.0 (−1)
4	1.0 (−1)	0.4 (0)	2.0 (−1)
5	1.0 (−1)	0.7 (+1)	4.5 (0)
6	2.0 (0)	0.7 (+1)	2.0 (−1)
7	2.0 (0)	0.7 (+1)	7.0 (+1)
8	3.0 (+1)	0.4 (0)	7.0 (+1)
9	2.0 (0)	0.4 (0)	4.5 (0)
10	3.0 (+1)	0.4 (0)	2.0 (−1)
11	2.0 (0)	0.4 (0)	4.5 (0)
12	2.0 (0)	0.4 (0)	4.5 (0)
13	1.0 (−1)	0.4 (0)	7.0 (+1)
14	1.0 (−1)	0.1 (−1)	4.5 (0)
15	2.0 (0)	0.1 (−1)	7.0 (+1)

2.2.2. Rheology

A rotational/oscillatory viscometer (CSL 500, Carri-Med/TA Instruments, New Castle, DE, US) was used. All measurements were performed with a stainless steel cone-plate sensor (6 cm diameter and 2° angle) at 25 ± 0.1°C. Viscosity, η, was obtained from the down-curve of rotational measurements at a shear rate of 100 s^{-1}; the yield point, σ_Y, was calculated from the up-curve using Casson extrapolation [9]. The flow curve was also used to calculate the corresponding thixotropic area, ΔA (Pa/s), from the hysteresis curve.

Strain sweep measurements at 1 Hz were made with all samples to determine a strain amplitude within the linear viscoelastic range. Subsequent oscillatory measurements were performed at a frequency range of 0.1–10 Hz employing a displacement of 0.001 rad. Storage modulus G' (Pa), loss modulus G'' (Pa), loss tangent (or damping factor), tan δ and dynamic viscosity (or in-phase component of the complex viscosity), η' (Pas) were calculated using a specific computer program (TA Instruments, Alzenau, Germany). These parameters were evaluated at a fixed oscillatory frequency (0.5 Hz) to serve as response variables in the statistical design.

The relaxation exponent, n [10], was calculated in Microsoft® Excel 97 based on the G' values obtained as a power law of the frequency.

2.2.3. Statistical design and optimisation using a desirability function

Statgraphics® Plus software (version 5.0, Quality and Design Edition, Manugistics, MD 20850, USA) was used for all statistical calculations. The study was planned using a Box-Behnken design, with 15 compositions and the following coded factor levels: X_1 – concentration of Veegum® HS (w/w), X_2 – concentration of xanthan gum (w/w), and X_3 – pH (Table 1). Three compositions (9, 11 and 12) marked the centre points of the factor space. A significance level of $P < 0.05$ was used in all tests.

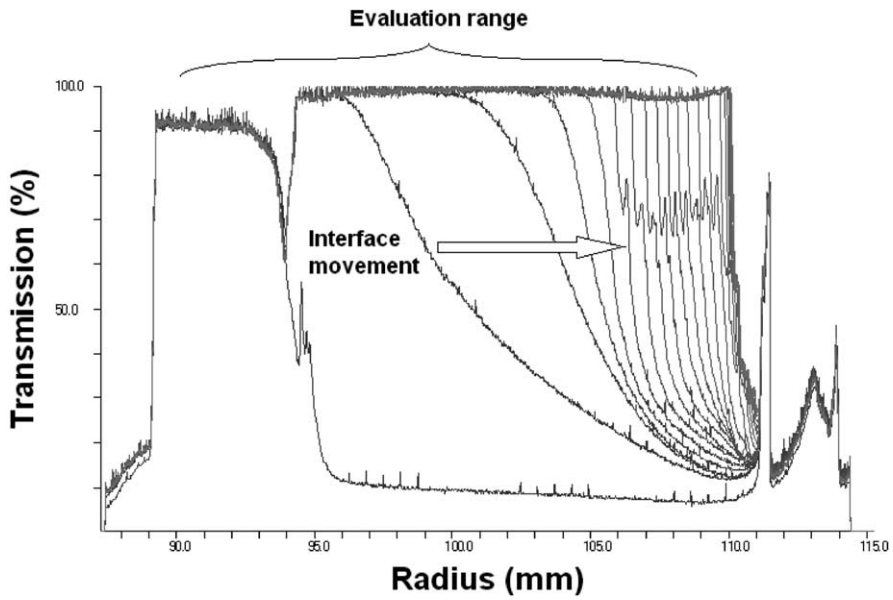

Fig. 1. Plot of NIR transmission (every 10th transmission profile) versus tube radius (sample 15).

The various response surfaces were calculated using the following equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{11} X_1^2 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{22} X_2^2 + \beta_{23} X_2 X_3 + \beta_{33} X_3^2$$

Analysis of variance (ANOVA) was followed by an F-test of the individual factors and interactions.

Pearson product moment correlation coefficients were determined to correlate $\Delta T_{int}/\Delta t$ with the individual rheological parameters, i.e. η, σ_Y, ΔA, G', G'', tan δ, η', n.

The concept of a desirability function [11] was applied to the significant dynamic rheological parameters to obtain a function d_1 for tan δ and another desirability function d_2 for n, where a standard weight of $s = 1$ in both cases. Combined desirability, D, was calculated by the software program using the harmonic mean of d_1 and d_2. Further details of the software calculation are available from the software developer [12].

3. Results and discussion

The colloidal structure of the model system remains incompletely understood. Veegum®, a sodium montmorillonite, is a 2:1 layer clay mineral. Its particles carry a negative electrical double layer on the faces caused by isomorphous substitution [13]. The platelet edges are different where the lattice is disrupted and the double layer charge depends on pH, being positive in acidic environment [14,15]. This opposite charge favours edge-to-face interaction between the clay particles and potentially also interaction between the clay edges and an anionic polyheterosaccharide like xanthan gum. This combination of Veegum® and xanthan gum was first investigated by Ciullo [4] using a conventional spindle rheometer. The flow behaviour indicated that some blends might be effective in stabilising dispersions.

The clarification results from our accelerated separation study using the Box-Behnken design are shown in Table 2 and Fig. 2. Increasing concentrations of Veegum® from 1 to 3% (w/w) impaired clarification. The β_1 coefficient indicated significant stabilisation ($P < 0.05$; Table 2). Even less phase separation was obtained in combination with xanthan gum up to a level of about 0.6% (Fig. 2), so that a considerable part of the response surface predicts absent clarification. Between 0.6 and 0.8% xanthan gum, however, clarification appeared to reincrease slightly, suggesting that the stabilising polymer concentration was optimal. Although an optimal polymer concentration is expected in terms of the extent of flocculation, given the experimental data obtained with clays and different polymers [14,16],

Table 2
Clarification and viscosity coefficients of the mathematical models (eq. (1))

Coefficients	First model and P values (brackets) Y_1: $\Delta T(\%)/\Delta t$[a,b]	Second model and P values (brackets) Y_2: $\eta(100\ s^{-1})$[a,b]
β_0	95.88	−9.62
β_1	−49.56 (0.040**)	45.42 (0.001***)
β_2	−168.26 (0.015**)	227.20 (0.000***)
β_3	0.78	−20.80 (0.001***)
β_{11}	4.66	1.93
β_{12}	40.07 (0.031**)	43.05 (0.102)
β_{13}	1.56	−8.72 (0.020**)
β_{22}	103.39 (0.078*)	58.60
β_{23}	−6.45	−24.93 (0.034**)
β_{33}	−0.12	3.85 (0.016**)

[a] X_1, Veegum® HS; X_2, Xanthan gum; X_3, pH.
[b] P values of significant factors and interactions calculated by F-test after ANOVA.

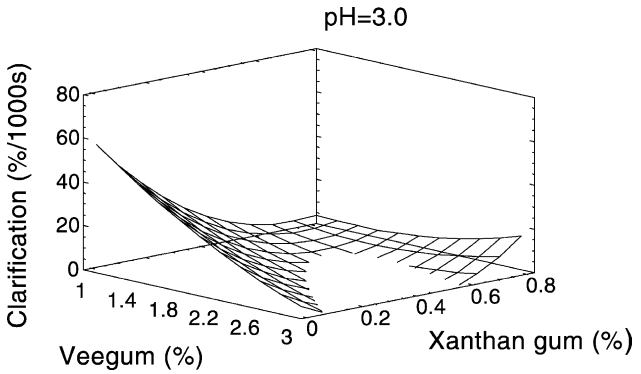

Fig. 2. Clarification response surface (%/1000 s) versus concentrations of Veegum® (%, w/w) and xanthan gum (%, w/w) at pH 3.

this is not equivalent to optimal sedimentation stability. The bridging flocculation which is involved may increase the average floc size, followed by even greater subsidence rates for the individual aggregates. This explains why the β_{12} interaction coefficient was positive. In concentrated flocculated systems, however, a coherent network is formed that entraps all available liquid and thus prevents phase separation. In their study of polyvinyl alcohol addition to clay suspensions, Chang et al. provided an instructive demonstration and discussion of this crucial aspect of separation stability in colloidal systems [17].

It must also be kept in mind that a network of polymer flocculated particles may coexist with the individual networks of the gelling agents Veegum® and xanthan gum. The latter had a significant effect ($P < 0.05$), with a marked negative value for β_2. Interestingly, the pH coefficient, β_3, hardly affected separation stability. The network of bentonite particles flocculated with xanthan gum was obviously less sensitive to pH than a structure based on clay particles alone.

The second model in Table 2 was calculated from the viscosity data under shear (100 s^{-1}). Again, it was xanthan gum which had the main effect, within the concentration range chosen. Veegum® affected viscosity only slightly within the test range (Fig. 3). A minimal clay concentration of about 1.6% (w/w) at pH 3.0 was required for any impact

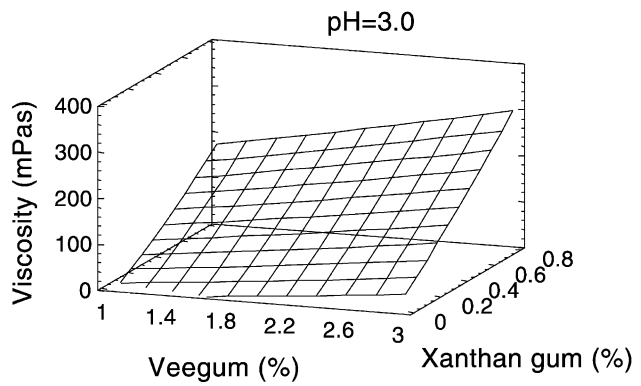

Fig. 3. Viscosity under shear (mPas) response surface versus concentrations of Veegum® (%, w/w) and xanthan gum (%, w/w) at pH 3.

on viscosity. The entire viscosity response surface, in contrast to that for clarification, was rather flat at pH 3. Although again the effect of pH was not pronounced, it was found to be significant, as indicated by β_3 in Table 2.

Fig. 4 shows a slight decrease in viscosity as pH changed from acidic to neutral, especially at higher concentrations of Veegum®. This was probably due to the loss of double layer charge at the edges of the montmorillonite platelets (the isoelectric point is known to be around pH 7) [14,15]. General pH dependence was only moderate, however, compared to the effect of pH on a clay suspension without xanthan gum. This is a definite advantage in terms of the robustness of such a vehicle for drug dispersion.

Viscosity under shear correlated with clarification using the Pearson product moment correlation r (−0.52). On theoretical grounds we expect the sedimentation rate of a single spherical particle in a centrifugal field to be inversely proportional to viscosity in a Newtonian fluid [18]. Even in the case of a polydisperse pharmaceutical drug suspension, with complex flow behaviour, one intuitively expects some inverse proportionality between viscosity and settling rate under centrifugation. This has been shown experimentally with drug microsuspensions containing sodium carboxymethylcellulose gelling agent [19]. However, in the present case, clarification was quantified instead by an average settling rate; the colloidal systems tested also differed from a microsuspension. Mean hydrodynamic floc size in a centrifugal field may not be equivalent to the mean aggregate size that occurs under the shear of flow measurements. This may explain the absence of a closer correlation between clarification and viscosity under shear.

Nor were the other flow experiment parameters closely associated with clarification. The hysteresis area of the flow curve showed no significant correlation with clarification ($r = -0.26$), whereas the extrapolated yield point had an r of −0.54. The scatterplot of clarification versus yield point (Fig. 5) shows that once the system withstood a critical

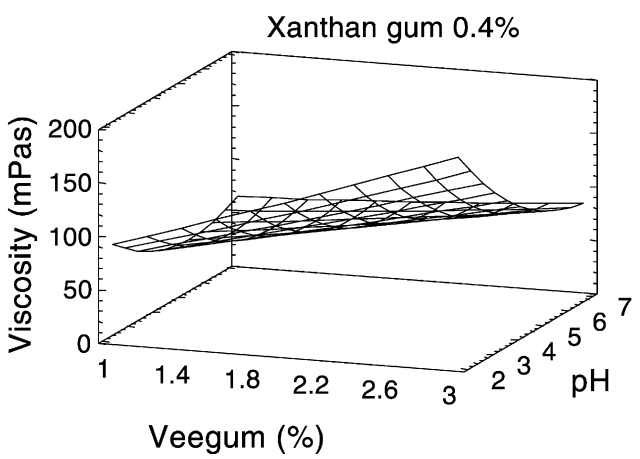

Fig. 4. Viscosity under shear (mPas) response surface vs. concentrations of Veegum® (%, w/w) and pH at constant xanthan gum concentration (0.4%, w/w).

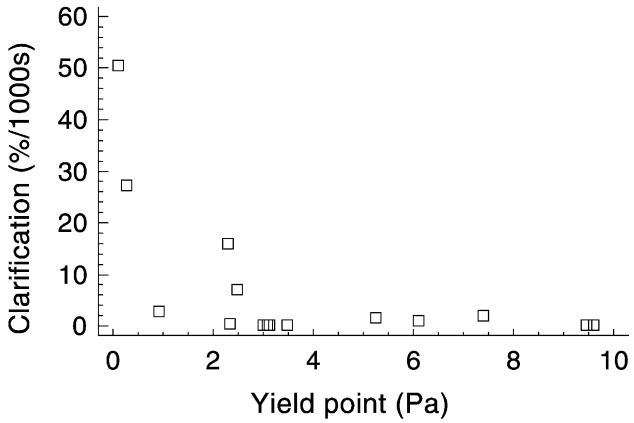

Fig. 5. Scatterplot of clarification (%/1000 s) versus yield point (Pa).

shear stress exceeding some 3 Pa, clarification stayed minimal under test conditions. Correlation occurred mainly at low yield point values where clarification values were high, indicating rapid separation. This feature, i.e. stabilisation of a disperse system by a minimal yield point, can be described theoretically by calculating the force equilibrium acting on a particle [20]. However, since the average settling unit in small particle systems is generally an aggregate, such a calculation would greatly underestimate the minimal stabilising yield point if only primary particles were considered. On the other hand, the centrifugal LUMiFuge® data tend to overestimate the minimal yield point needed to stabilise a dispersion [19]. It seems convenient to stabilise a dispersion by adjusting the yield point. For the sake of robustness, one should target a yield point exceeding the theoretical minimum to keep the particles homogenous. Thus formulators may find that determining an overestimated minimal yield point in a centrifugal field is a useful guide for being on the safe side with sufficient gel structure.

The oscillation rheology data are of special interest as these experiments were performed in the linear viscoelastic range. Fig. 6 displays a frequency sweep from a comparatively stable sample (no. 10). The storage modulus dominated the loss modulus over the frequency range tested. In this case both moduli were only slightly affected by frequency. This dependence can be much greater if

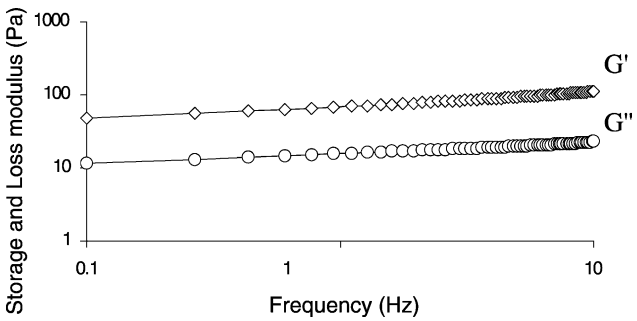

Fig. 6. Scatterplot of storage (diamonds) and loss (circles) moduli versus oscillatory frequency (sample 10).

polymer entanglement makes a major contribution to the network structure. Since a change in moduli is known to reflect physical cross-linking in the network structure [21], we evaluated the so-called *relaxation exponent*, n of G' [22], with the different formulations. The coefficient of correlation with clarification was 0.96, showing a close association between the two parameters. Coefficients were much lower between clarification and dynamic viscosity ($r = 0.50$), storage modulus ($r = 0.41$), and loss modulus ($r = 0.50$).

The plot of clarification against the relaxation exponent (Fig. 7) points to a subtle underlying physical relationship. The more stable formulations had a relaxation exponent close to a limiting value of 0.3, whereas higher relaxation exponents produced an almost linear increase in clarification.

The phase angle, δ, indicates whether a viscoelastic formulation approximates more to a perfectly elastic system in which $\delta = 0°$ or to a perfectly viscous system in which $\delta = 90°$. It is useful to calculate the loss tangent, tan δ, because it equals the ratio between the loss and storage moduli (G''/G'), which is known to be a relevant measure of physical stability [21]. Gašperlin et al. even attempted to predict physical separation stability in lipophilic dispersions from tan δ alone [23].

The correlation coefficient between tan δ and clarification was $r = 0.84$. The corresponding scatterplot again showed two ranges (Fig. 8). As long as G' exceeded G'' by a factor ≥ 2, tan δ was < 0.5 and the dispersions were least susceptible to de-mixing.

As a result the LUMiFuge® data – in terms of dispersion clarification – correlated best with the relaxation exponent n and tan δ. The G''/G' ratio indicates the proportion of applied stress whose energy is dissipated compared to the energy elastically stored in the gel network. On the other hand, the relaxation index, n, differentiates the quality of contact points in a gel by taking into account the frequency dependence of the proportion of elastically stored stress. Since the two dynamic rheological parameters involve complementary information, they should be considered

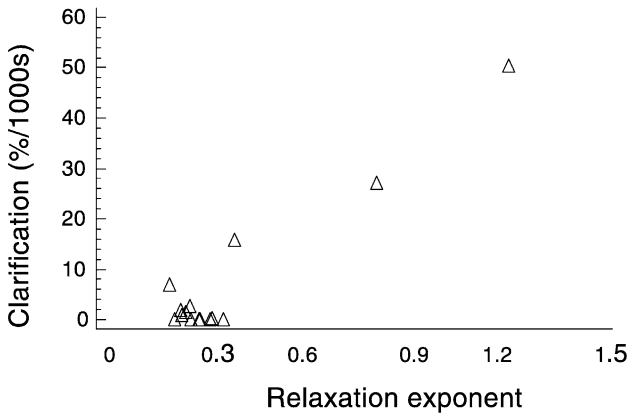

Fig. 7. Scatterplot of clarification (%/1000 s) versus relaxation exponent.

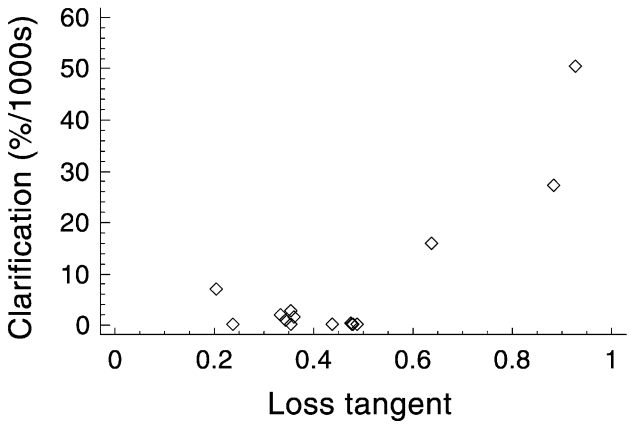

Fig. 8. Scatterplot of clarification (%/1000 s) versus loss tangent.

together in choosing an optimal formulation. The response surfaces for the two parameters were used to calculate a combined desirability function in a way that minimised values for both parameters. A reference pH was arbitrarily chosen since pH significantly influenced neither n ($P = 0.27$) nor tan δ ($P = 0.068$). The combined desirability response surface (pH 3.0) shown in Fig. 9 was practically the inverse surface of its clarification counterpart (Fig. 2). This result implies that an optimally stabilised formulation can be determined from either the LUMiFuge or oscillation data. The mathematical model showed minimal clarification (at reference pH 3) with 3.0% (w/w) Veegum® and 0.33% xanthan gum. The desirability functions of the two oscillation parameters gave an almost identical result. Desirability was maximal with a mixture of 3.0% Veegum® and 0.27% xanthan gum (at pH 3).

4. Conclusions

The clarification parameter yielded by the centrifugal separation analysis discriminated well between the various test formulations. Data evaluation from an experimental design helped to identify the optimal concentrations of the excipients Veegum® and xanthan gum. Rapid assessment of physical stability is extremely valuable in preselecting formulations for conventional pharmaceutical stability testing. More focussed long-term stability testing creates considerable savings while minimising the risk of separation problems emerging at a late phase of formulation development.

Rheological methods have the potential to screen physically stable systems. Formulators may, however, find it difficult to choose a relevant parameter of settling stability from the multiplicity of rheological properties that can be determined using the different methods. Also, rheological parameters remain only an indirect measure of physical stability; what is important is correlation with a real separation process.

The results of this study indicate that rotational rheometry provides the requisite characterisation of flow, but appears less suited to mirroring separation processes in a centrifugal field. Whereas formulators gain only some guidance from inspecting the yield point on the flow curve, special analysis of the linear viscoelastic range, e.g. by oscillation, adds considerable information. This study showed good correlation between clarification and both the relaxation exponent and loss tangent. Both these dynamic rheology parameters involve complementary information about the linkages of the stabilising network and should therefore be evaluated together. Both were consequently used to calculate a combined desirability function that showed good qualitative agreement with the clarification response surface. An optimal formulation could therefore be chosen from either the clarification or combined desirability response surfaces of tan δ and n, resulting in practically the same mixture of Veegum® and xanthan gum. In this study the dynamic rheological method provided an alternative to the LUMiFuge® method. More experimental work is needed to determine whether the two procedures remain equivalent in other model systems for preselecting formulations for long-term stability testing.

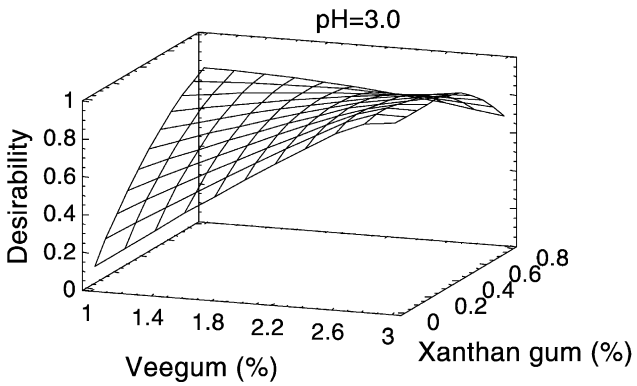

Fig. 9. Combined desirability surface of parameters tan δ and n versus concentrations of Veegum® (%, w/w) and xanthan gum (%, w/w) at pH 3.

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