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EVALUATION OF CARBOPOL 934 AS A SUSPENDING AGENT FOR SULPHADIMIDINE SUSPENSIONS

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SUMMARY

The suitability of carbopol 934 as a suspending agent was investigated by continuous shear and creep analysis using a concentric cylinder air turbine viscometer. Apparent viscosities determined from the apices of flow curves at a constant shear rate of 87 s^{-1} varied little with temperature over the range of 10–50°C. Decrease in pH from 8 to 6 caused a reduction in apparent viscosity. Non-Newtonian, pseudoplastic-like flow curves with little hysteresis were obtained for 0.1–3% w/v neutralized carbopol 934 dispersions, the magnitude of their apparent static yield value being linearly related to the polymer concentration. Analysis of creep compliance curves for carbopol dispersions showed that the material was a viscoelastic liquid at 0.5 and 1% and a viscoelastic solid at 3%.

Suspensions containing 10% w/v sulphadimidine and variable concentration of carbopol 934 gave qualitatively similar rheological results. Permanent suspensions after 6 months storage at room temperature were obtained for sulphadimidine suspensions using 0.3% or greater carbopol 934. Accelerated sedimentation tests on sulphadimidine–carbopol suspensions involving centrifugal techniques correlated well with the results of long-term sedimentation studies. Measurement of apparent static yield values and apparent viscosities at 87 s^{-1} of such suspensions were also found useful for predicting their long-term sedimentation appearance.

INTRODUCTION

An ideal pharmaceutical suspension should be uniform in content and readily pourable from its final container. Any sedimentation which does occur during storage should be easily redispersed on agitation. The two major approaches utilized either alone or in combination to formulate physically stable suspensions involve either controlled flocculation procedures (Jones et al., 1970; Matthews and Rhodes, 1968) or rheological modification of the suspension (Catacalos and Wood, 1964; Farley and Lund, 1976). Flocculated suspensions settle rapidly to form large loose sediments which are readily dispersed. Pseudoplastic vehicles are generally used for the rheological modification of suspensions

and decrease the rate of sedimentation but eventually allow the formation of a compact sediment which is difficult to redisperse.

We have criticized (Bhagwan et al., 1971) the rapid appearance of a large supernatant and the caking tendencies of sulphadimidine mixture, paediatric B.P.C. prepared containing either compound tragacanth powder or sodium carboxymethylcellulose as suspending agent. Subsequently we have shown (Holly et al., 1974) that it is possible to enhance the physical stability of sulphadimidine suspensions by use of controlled particle size, wetting, flocculating and suspending agents. In an attempt to reduce the number of adjuvants it was decided to use carbopol 934 as suspending agent to achieve non-sedimenting suspensions of sulphadimidine. Carbopol 934 is a carboxyvinyl polymer which has been reported to produce pseudoplastic or plastic dispersions in water. Initially carbopol dispersions were rheologically evaluated by continuous shear and creep testing with particular regard to plasticity, thixotropy and stability to temperature and pH variation, which are of importance in a suspending agent. Further studies were then carried out using rheological, long-term and accelerated physical stability testing to determine the suitability of this material as a suspending agent for 10% w/v sulphadimidine suspensions.

MATERIALS AND METHODS

Materials and their preparation

Sulphadimidine B.P. (Osmonde Bros. Ltd.) was milled in a ball mill (Erweka Ltd.) for 3 h and passed through a 180 μm sieve before use. The mean particle size was 29 μm, determined using a Coulter Counter, model B (Coulter Electronics Ltd.). Dispersions of carbopol 934 (Goodrich Chemical Co. Ltd., pharmaceutical grade) in deionized water were prepared as recommended by the manufacturers using a mechanical stirrer at 500 rev min^{-1} and neutralization with 10% sodium hydroxide solution. The final pH of dispersions was determined using a pH meter (Radiometer Ltd.). Suspensions of 10% sulphadimidine in variable concentration carbopol 934 dispersions were prepared using a mortar and pestle.

Rheological assessment

A modification of a concentric cylinder air turbine viscometer having a series of interchangeable cups and bobbins was built and calibrated as described by Davis et al. (1968). A particular advantage of the instrument for use in the assessment of structured vehicles suitable for pharmaceutical suspensions is that, because the independent variable is shear stress, apparent yield values may be determined directly rather than by extrapolation techniques. Experiments were performed at 20°C unless otherwise indicated. Flow curves shown were based on the mean of 5 determinations. A maximum shear rate of 87 s^{-1} was employed in all continuous shear work.

Physical stability assessment

Sedimentation heights of suspensions were recorded as the ratio of their ultimate settled height (h_u) to their original height (h_o) for 100 ml samples stored in 100 ml graduated cylinders at room temperature (about 20°C) for 6 months, as recommended by Martin (1961). Accelerated testing of 30 g samples of suspensions in 50 ml tubes was

carried out using a thermostatted centrifuge (Measuring and Scientific Instruments Ltd.) set at 20°C by determining the minimum rev. min^{-1} required to just produce visible signs of sedimentation. The results obtained were expressed as multiples of the acceleration due to gravity as estimated at the mid-point of centrifuged samples.

RESULTS AND DISCUSSION

Fig. 1 shows the influence of varying temperature over the range 10–50°C on flow curves for samples of 1% w/v neutralized carbopol 934 dispersions. The flow curves suggest that the carbopol gel varies very little in apparent viscosity over normal ranges of storage temperature. Fig. 2 shows an Arrhenius-type plot from which the apparent activation energy for flow was calculated to be 1.7 kcal mol^{-1}. This value is in good agreement with the value of 2 kcal mol^{-1} obtained by Barry and Meyer (1974) for neutralized carbopol 940 and 941 dispersions. The usefulness of Arrhenius-type plots has been questioned by Barry and Grace (1971). However the low value for the activation energy obtained does indicate the rheological stability of the carbopol 934 dispersion over normal storage temperature, which is a desirable feature of a suspending agent.

It is apparent from the flow curves shown in Fig. 3 that as the pH drops from 8.14 to 6.25 there is a reduction in apparent viscosity. The method of preparation of what are termed neutralized carbopol dispersions, as detailed by the manufacturers, allow for the pH of the final dispersions to be in the range 7.0–7.8. Flow curves constructed for carbopol dispersions in this pH range were intermediary between those obtained at pH 8.14 and 6.25, though not significantly different from each other. Similar results were reported by Fisher et al. (1961) who studied carbopol dispersions over a wider pH range.

Nine different concentrations of neutralized carbopol 934 dispersions over the range 0.1–3%, which should be suitable for most pharmaceutical applications, were examined

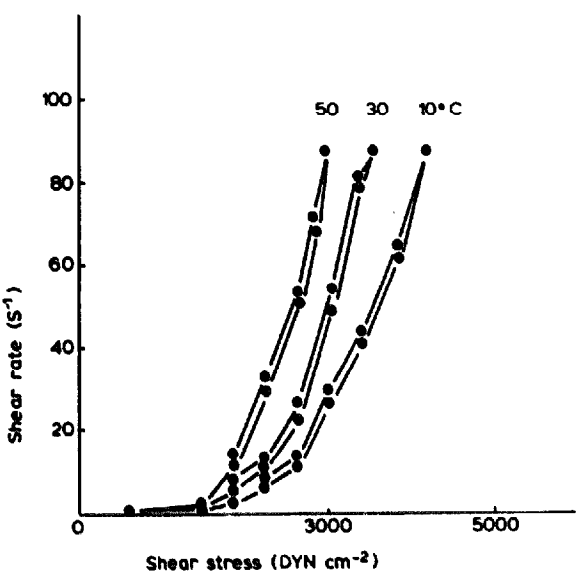

Fig. 1. Effect of variation in temperature on 1% w/v neutralized carbopol 934 dispersions.

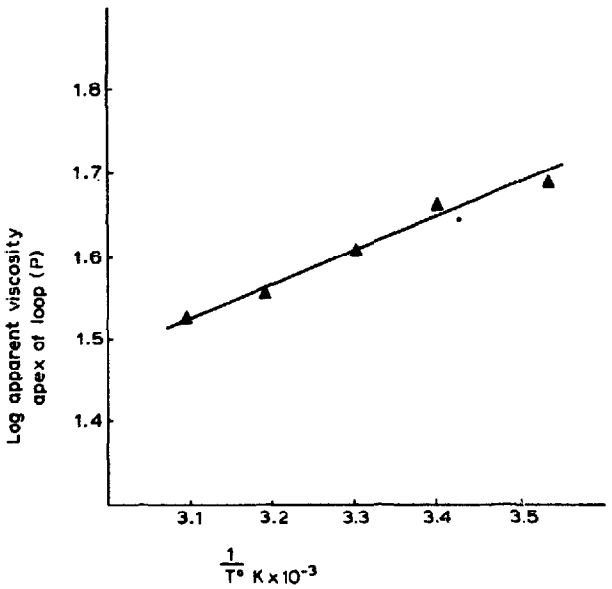

Fig. 2. Arrhenius-type plot.

in continuous shear. Fig. 4 shows 4 of the flow curves obtained. The plots were all non-Newtonian showing pseudoplastic flow. The magnitude of the apparent static yield value and apparent viscosity at 87 s^{-1} both increased progressively with increasing concentration of polymer used. Their correlation coefficients for linear fits were highly significant ($r = 0.988$, n = 7, $P = <0.001$; $r = 0.995$, n = 7, $P = <0.001$, respectively) and greater than for exponential, logarithmic or power curve fits. This result was unexpected as it was anticipated that both these rheological properties of the carbopol dispersions would

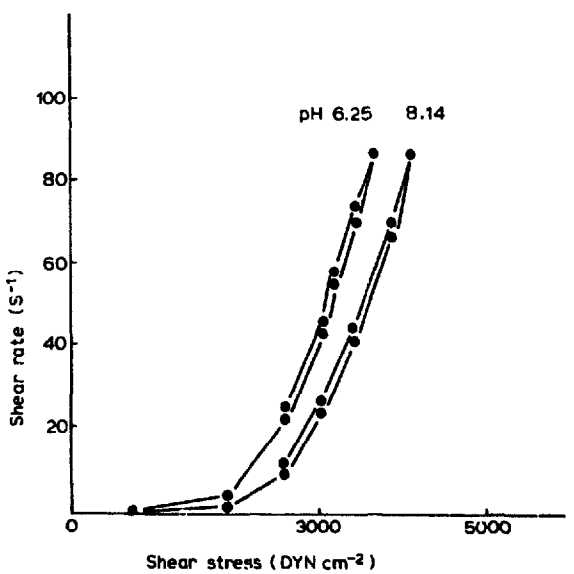

Fig. 3. Effect of variation in pH on 1% w/v carbopol 934 dispersions at 20°C.

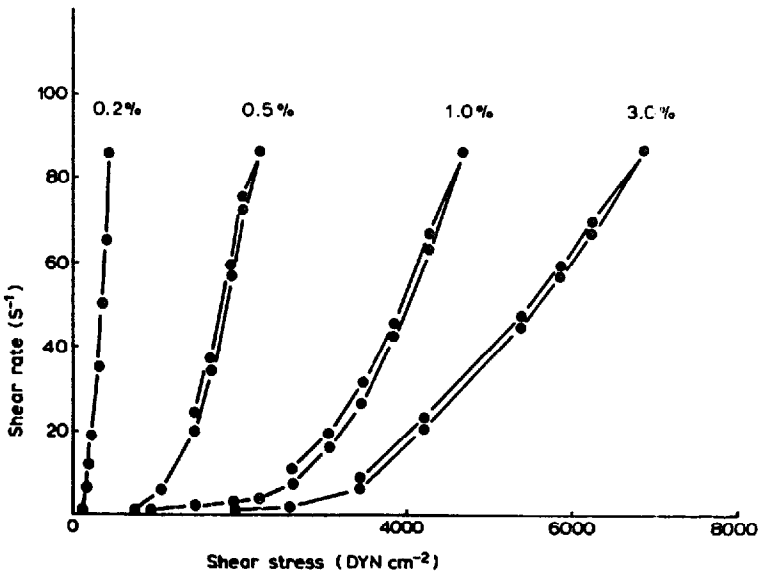

Fig. 4. Effect of concentration (% w/v) of neutralized carbopol 934 at 20°C.

increase disproportionately with increase in concentration due to increasing interaction between constituent groups. The level of hysteresis observable was always small, declining to negligible amount at concentrations lower that 0.3% which indicates loss of the small polymer interaction with reducing concentration.

The limitations of continuous shear work, particularly in the rheological examination of materials with structure and viscoelastic components, have been discussed by Barry and Meyer (1974). The parameters measured, though adequate and commonly used for examining rheological variation between closely related systems like suspending agents at high shear, are not fundamental as their magnitude depends to some extent on the test instrument and on its manner of use. Creep testing is a more fundamental method of examining semi-solid materials like higher concentrations of carbopol 934 dispersions, as the method of testing does not significantly alter the rheological ground state of the test material.

Fig. 5 shows creep compliance curves for 0.5, 1 and 3% w/v neutralized carbopol 934 dispersions determined in the linear viscoelastic region, which was very limited. Table 1 shows the model analysis of the creep curves into a Maxwell unit in series with a Voigt unit, as determined by the discrete spectral method described by Warburton and Barry (1968). It is evident from the creep curves and the values of residual viscosity that the carbopol dispersions behave as viscoelastic liquids at concentrations of 0.5 and 1%, and as a viscoelastic solid at 3%. The presence of unretarded viscosity in the lower concentrations of carbopol means that the static yield values obtained for such concentrations in continuous shear experiments are only apparent because any stress, however small, must eventually cause an observable flow, provided the period of observation is long enough. Therefore lower concentrations of carbopol suitable for use as suspending agents for mixtures are pseudoplastic and higher concentrations suitable for use as ointment gels are

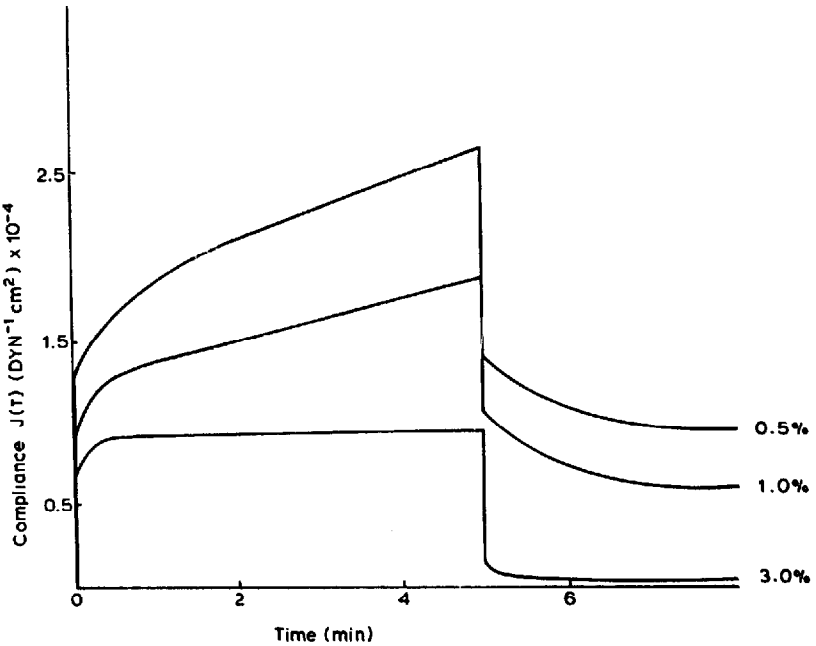

Fig. 5. Creep compliance curves for neutralized carbopol 934 at 20°C.

plastic-like.

Results of a determination of the viscoelastic properties of 3% w/w carbopol 940 and 941 gels using a concentric cylinder creep viscometer were presented by Barry and Meyer (1974). They reported that their creep curves approached Hookean behaviour, a finding similar to that observed in this work with 3% w/v neutralized carbopol 934, where recovery on removal of the stress was almost complete. Values in Table 1 obtained for instantaneous compliance J_0 were of the same order of magnitude as those reported by Barry and Meyer (1974), who represented their system by a Maxwell unit in series with 3 Voigt units.

TABLE 1

MODEL ANALYSIS FOR CARBOPOL 934 DISPERSIONS

J_0, initial shear compliance; J_R, retarted shear compliance; η_R, viscosity associated with retarded region; T_R, retardation time; η_0, residual shear viscosity; J_t total compliance at time 300 s.

Conc. of carbopol 934 (%w/v)	$J_0 \times 10^{-4}$ (dyn^{-1} cm^2)	$J_R \times 10^{-5}$ (dyn^{-1} cm^2)	$\eta_R \times 10^6$ (p)	$T_R \times 10^0$ (s)	$\eta_0 \times 10^7$ (p)	$J_t \times 10^{-4}$ (dyn^{-1} cm^2)
3.0	0.731	1.34	18.20	243.90	$\rightarrow \infty$	0.920
1.0	0.862	2.78	3.99	110.98	1.935	1.846
0.5	1.235	5.00	2.57	128.53	1.363	2.657

TABLE 2

SEDIMENTATION AND RHEOLOGICAL DATA USED IN CURVE FIT DETERMINATIONS FOR 10% W/V SULPHADIMIDINE SUSPENSIONS CONTAINING VARIABLE CONCENTRATIONS OF CARBOPOL 934

Conc. of carbopol 934 (%w/v)	Sedimentation height after 6 months (h_u/h_0)	Accelerated centrifugal test (×g)	Apparent static yield value (dyn cm^{-2})	Apparent viscosity at 87 s^{-1} (p)
0.10	0.28	1.0	9.67	0.73
0.15	0.85	23.7	51.08	2.49
0.20	0.93	155.6	135.38	6.39
0.25	0.99	648.6	218.70	8.33
0.30	1.00	920.9	311.30	11.31
0.35	1.00	1431.2	434.40	16.23

Suspensions of 10% w/v sulphadimidine containing the same 9 concentrations of carbopol 934 over the range 0.1–3% w/v as previously discussed were also subjected to continuous shear. The flow curves obtained were displaced to the right of the corresponding flow curves for the carbopol dispersions at equivalent polymer concentration, having approx. 72 and 73% higher apparent static yield value and apparent viscosity at 87 s^{-1}, respectively. However both series of flow curves did not differ appreciably in shape, which indicates little polymer–sulphadimidine interaction.

Table 2 shows sedimentation height data after 6 months storage for 10% sulphadimidine suspensions containing varying concentrations of carbopol 934. The corresponding accelerated stability test data, apparent static yield values and apparent viscosities at 87 s^{-1} of recently prepared suspensions, are also shown. It is apparent from the sedimentation data that suspensions containing 0.3% carbopol or greater remain completely uniform over long-term storage. At such low concentrations of carbopol the suspensions were rapidly pourable and so this polymer is obviously highly suitable for the preparation of pharmaceutically acceptable suspensions. Meyer and Cohen (1959) reported similar results in that concentrations as low as 0.18% carbopol 934 produced permanent dispersions of silica sand.

A significant correlation existed between the sedimentation height and accelerated test data ($r = 0.913$, $n = 4$, $P = 0.01–0.02$) for a power curve fit of the form $y = ax^b$. This indicates that one may conveniently and rapidly predict the sedimentation height after long-term storage of such suspensions from the results of a simple accelerated test. Presumably similar correlations could be developed for other suspension systems and could be very useful for predicting the effect on long-term sedimentation height of minor formulation modifications within such systems.

Highly significant correlations also existed between the sedimentation height data and both apparent static yield values ($r = 0.952$, $n = 4$, $P = 0.001–0.01$) and apparent viscosities ($r = 0.938$, $n = 4$, $P = 0.001–0.01$) for a logarithmic curve fit of the form $y = a + b \ln X$. This suggests that by suitable modification of either of these rheological parameters it should be possible to produce suspensions which remain permanent over an adequate

shelf life.

The results collectively presented in this paper indicate the suitability of carbopol 934 as a pharmaceutical suspending agent, and this is confirmed by its usage in the production of a non-sedimenting, readily pourable suspension of 10% sulphadimidine.

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