J. Pharm. Pharmacol. 1983, 35: 275–278
Received September 20, 1982

0022–3573/83/050275–04 $02.50/0

Rheological and sedimentation studies on Instant Clearjel and Primojel suspensions

K. SABRA AND P. B. DEASY*

Department of Pharmaceutics, Trinity College, University of Dublin, Shrewsbury Road, Dublin 4, Ireland

The suitability of Instant Clearjel and Primojel for use as extemporaneous suspending agents has been investigated by continuous shear and creep analysis using a specially constructed air turbine viscometer. Aqueous dispersions of both of the modified starches exhibited non-Newtonian, pseudoplastic flow with little thixotropy and some irreversible shear breakdown. Apparent viscosities, determined from the apices of flow curves obtained at constant maximum shear rate, decreased progressively with increase in temperature over the range 10–50 °C. An Arrhenius plot gave a low apparent activation energy of flow for Primojel. The two modified starches showed a marked rise in apparent viscosity with rise in pH from 3 to 11 of the dispersion medium. Only Instant Clearjel dispersions exhibited a linear viscoelastic region in creep testing, studies which confirmed that this system behaved as a viscoelastic liquid. Sedimentation studies on 10% w/v sulphadimidine suspensions containing varying concentrations of either suspending agent indicated that 3% w/v Primojel could form permanent suspensions even after 6 months storage at room temperature. The significance of these results in relation to the usefulness of these starch derivatives as suspending agents is discussed.

Various hydrophilic polymers have been proposed as extemporaneous suspending agents for pharmaceutical suspensions intended for internal use. A disadvantage of commonly used agents like tragacanth and sodium carboxymethylcellulose is that they delay rather than prevent sedimentation occurring, and redispersal may be very difficult (Bhagwan et al 1971). Permanent suspensions can be achieved using an agent like carbopol (Berney & Deasy 1979), which, however, is not suitable for extemporaneous use as it requires a high speed stirrer and neutralization with alkali.

Instant Clearjel, which is a pregelatinized maize starch, and Primojel, which is a sodium starch glycolate prepared from potato starch, have been reported by Farley & Lund (1976) to be satisfactory suspending agents for a range of pharmaceutical suspensions. Their in-vivo degradation products should be harmless and they are typical of a range of similar modified starches now available. This investigation is concerned with a rheological evaluation of aqueous dispersions of both of these products, to establish their suitability for use as suspending agents. Sulphadimidine suspensions containing them have been studied with a view to producing permanent systems that undergo negligible caking during long term storage.

* Correspondence.

MATERIALS AND METHODS

Materials and their preparation

Sulphadimidine B.P. (Osmonde Bros. Ltd) was milled in a ball mill (Erweka Ltd) for 4 h and passed through a 180 μm sieve before use. The median diameter oversize was found to be 9·7 μm, determined using a Coulter Counter, model B (Coulter Electronics Ltd). Instant Clearjel was obtained from Laing National Ltd, U.K. and Primojel from Verenigde Zet., De Bijenkorf, The Netherlands. Dispersions of the modified starches were prepared in deionized water. Suspensions of 10% w/v sulphadimidine in variable concentrations of either compound were prepared using a mortar and pestle.

Rheological assessment

A modification of the air turbine viscometer described by Davis et al (1968) was constructed which had a series of interchangeable cups and bobbins to allow apparent viscosities to be measured over a wider range. The instrument is particularly suitable for the determination of yield values directly in continuous shear operation, as the independent variable is shear stress. It may also be readily modified for creep testing. The instrument was calibrated in the vertical or use position as the horizontal calibration method of Davis et al (1968) was observed to produce unwanted friction in the turbine bearing. Experiments were performed at 25 °C unless otherwise indicated. Samples were allowed to rest after loading for 30 min in continuous shear testing and overnight for creep testing before being examined. Flow curves shown are based on the mean of 5 determinations. A maximum shear rate of 150 s^{-1} was employed in all continuous shear work.

Sedimentation assessment

Sedimentation heights of suspensions were determined from 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 (15–20 °C) for periods up to six months, as recommended by Martin (1961).

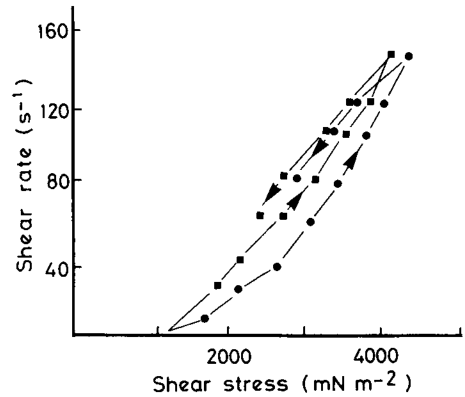

FIG. 2. Testing for true thixotropy and/or irreversible shear breakdown for 3% w/v Primojel. Time zero (●), 30 min (■), 210 min (■) and 900 min (■).

RESULTS AND DISCUSSION

To determine whether Instant Clearjel and Primojel dispersions exhibit reversible or irreversible shear breakdown it was necessary to test for recovery of structure on resting. Figs 1 and 2 show the non-Newtonian flow curves obtained after variable time intervals using the same samples of each suspending agent. Since the shear stress-shear rate values obtained at 30,210 and 900 min after the beginning of the experiments did not differ significantly from each other, they were represented by a single loop which was displaced to the left of the loop obtained at time zero. The results indicated a degree of irreversible breakdown in that the materials did not recover their original levels of structure in the time scale of the experiments. However, both systems exhibited a little thixotropy in that they recovered the same level of structure at 210 or 900 min as they had at 30 min, but their hysteresis loop area was small.

These results are in agreement with the observation that many time-dependent rheological phenomena in aqueous dispersions of hydrophilic colloids are a combination of reversible and irreversible effects, which are normally not distinguishable from each other in the conventional drawing of rheograms.

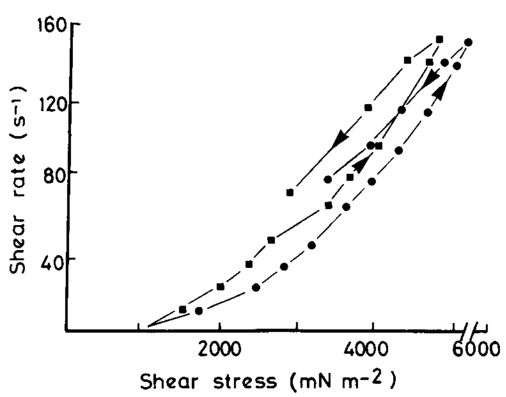

FIG. 1. Testing for true thixotropy and/or irreversible shear breakdown for 3% w/v Instant Clearjel. Time zero (●), 30 min (■), 210 min (■) and 900 min (■).

The influence of varying temperature over the range 10–50 °C on flow curves for samples of 3% w/v Instant Clearjel and Primojel was studied. The flow curves obtained suggested that both suspending agents varied little in apparent viscosity over normal ranges of storage temperature. This impression was confirmed in Fig. 3 which shows Arrhenius-type plots of the log apparent viscosity at the shear rate of 150 s^{-1} against the reciprocal of the absolute temperature. From these plots the apparent activation energy of flow were calculated to be 3·9 and 1·3 kcal mol^{-1} (16·3 and 5·4 $kJmol^{-1}$) for Instant Clearjel and Primojel respectively. These values are not greatly dissimilar from the value of 2·0 kcal-mol^{-1} (8·4 kJ mol^{-1}) reported by Barry & Meyer (1974) for carbopol 940 and 941 dispersions which

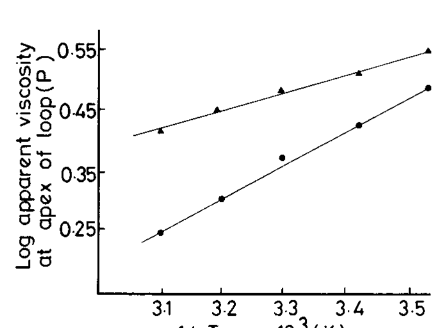

FIG. 3. Arrhenius-type plots. ▲ Primojel. ■ Instant Clearjel.

are known to alter little in rheological properties over normal storage temperatures. The particularly low value associated with Primojel is indicative of lack of segmental flow in its polymer chains during testing, which should make it suitable for use as a suspending agent where chain rigidity is desirable to effectively support sedimenting particles.

Figs 4 and 5 shows the effect of variation in pH on the flow curves for 3% w/v Instant Clearjel and Primojel respectively. As the pH rose from 3 to 11

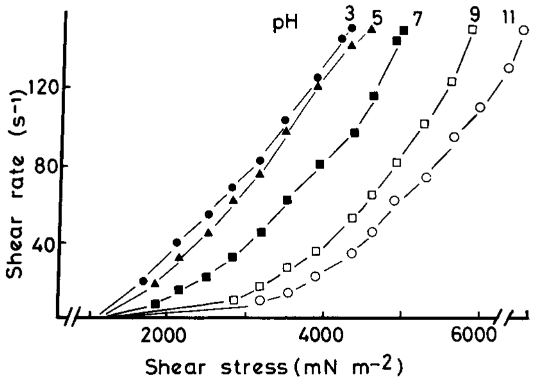

FIG. 4. Effect of variation in pH on 3% w/v Instant Clearjel.

there was an increase in the apparent viscosity of both polymer dispersions. These starch derivatives are largely composed of the branched polysaccharide, amylopectin, and the linear polysaccharide, amylose, whose chains have been forced apart either by prior hydrolysis in the case of Instant Clearjel, or the introduction of bulky sodium carboxymethyl substituents in the case of Primojel, to render both compounds more cold water-soluble. Increase in pH would increase the dissociation of

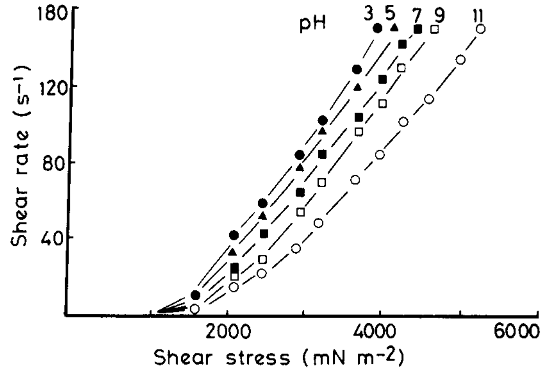

FIG. 5. Effect of variation in pH on 3% w/v Primojel.

their exposed carboxyl and/or hydroxyl groups, aiding polymer uncoiling and greater water solubility. These effects would be shown as a rise in apparent viscosity with increase in pH of the dispersion medium as seen in Figs 4 and 5. However the effect of variation in pH on apparent viscosity over the range which might be encountered in a pharmaceutical suspension was small and confirms the general suitability of both materials, but particularly Primojel, for use as suspending agents.

Barry & Meyer (1974) have discussed the limitations of continuous shear work because of its destructive effect for the rheological examination of materials with structure and viscoelastic components. Creep analysis is a more fundamental method of examining semi-solid materials because this method does not significantly alter the rheological ground state of the test material. Fig. 6 shows the creep compliance curve obtained for a 5% w/v Instant Clearjel dispersion determined in the limited linear viscoelastic region. The plot obtained is typical of that associated with a viscoelastic liquid, so confirming that the system was pseudoplastic and not plastic. Recovery on removal of the shear stress was

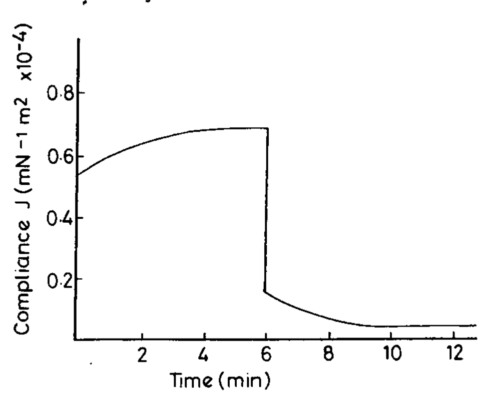

FIG. 6. Creep compliance curve for 5% w/v Instant Clearjel.

almost complete which is indicative of Hookean behaviour. The discrete spectral method of analysis as described by Warburton & Barry (1968) was applied to the creep data. The results shown in Table 1 indicate that a satisfactory model representation was a Maxwell unit in series with three Voigt units. The determination of an unretarded viscosity value indicated that yield values noted in continuous shear work were only apparent because any stress, however small, must eventually cause an observable flow provided the period of observation is long enough. It would be preferable if Instant Clearjel had an absolute yield value whose magnitude could

Table 1. Model analysis for 5·0% w/v Instant Clearjel (n = o − t). J_o, initial compliance; J_1, J_2, J_3, retarded shear compliances; η_o, residual shear viscosity; η_1, η_2, η_3, viscosities associated with retarded regions.

$J_n \times 10^{-4}$ dyn^{-1} cm^2		$\eta_n \times 10^5$ (P)	
J_0	0·56	η_0	2·01
J_1	0·38	η_1	2·60
J_2	0·44	η_2	1·83
J_3	0·12	η_3	1·73

be adjusted by choice of concentration to effect permanent suspension of dispersed solids. However, common suspending agents, such as tragacanth and sodium carboxymethylcellulose, are pseudoplastic and those like carbopol, which have been reported as plastic based on continuous shear results, are in fact pseudoplastic in concentrations in normal use when examined by the more sensitive creep testing method (Berney & Deasy 1979).

Primojel dispersions did not show a linear visco-elastic region and consequently were not subjected to creep testing. However, because of their chemical similarity with Instant Clearjel and sodium carboxymethylcellulose it is probable that they are also pseudoplastic in the concentration range suitable for use in suspensions, which must still flow adequately to permit delivery of the product from its container.

In an attempt to ascertain if the rheological properties of Instant Clearjel and Primojel dispersions could be related to their ability to suspend drug particles and thus be of use in the formulation of uniform non-sedimenting suspensions, a range of suspensions containing 10% w/v sulphadimidine and varying concentration of Instant Clearjel or Primojel (1–3% w/v) was prepared. These suspensions were not suitable for direct rheological examination because of sedimentation and irregular flow in the gap between the concentric cylinders of the viscometer. Table 2 shows the sedimentation height recorded at specified intervals over a six month storage period at room temperature. Suspensions containing 3% Primojel remained completely uniform over long term storage and quite pourable, so this starch derivative has obvious value in the preparation of pharmaceutically acceptable suspensions. In contrast suspensions containing the same concentrations of Instant Clearjel showed rapid sedimentation. Higher concentrations were not suitable because of the difficulty in pouring the products. Redispersal of suspensions containing either Instant Clearjel or Primojel which had sedimented was easily achieved even after six months storage.

Table 2. Sedimentation heights of 10% sulphadimidine suspensions, made with varying concentrations of either Instant Clearjel or Primojel, determined after stated time intervals (mean of five determinations).

	Sedimentation heights H_u/H_o					
	Instant Clearjel			Primojel		
Time	1%	2%	3%	1%	2%	3%
1 h	0·6	1·0	1·0	0·52	0·81	1·0
6 h	0·58	0·98	1·0	0·50	0·79	1·0
1 day	0·58	0·9	0·98	0·45	0·71	1·0
2 days	0·57	0·85	0·98	0·44	0·70	1·0
7 days	0·55	0·75	0·98	0·44	0·70	1·0
4 weeks	0·35	0·42	0·53	0·44	0·70	1·0
16 weeks	0·35	0·42	0·46	0·44	0·70	1·0
6 months	0·32	0·40	0·46	0·44	0·70	1·0

H_o = original height.
H_u = ultimate height.

The results collectively presented in this paper indicate the suitability of Primojel in particular as a pharmaceutical suspending agent. Farley & Lund (1976) evaluated this material as an alternative to tragacanth for the extemporaneous preparation of paediatric chalk and sulphadimidine mixtures. Sedimentation and ease of redispersal data indicated that at 1% concentration it was superior to other modified starches including Instant Clearjel and various other suspending agents such as cellulose, alginate or silicate derivatives and tragacanth. However, with aromatic and chalk mixture Instant Clearjel produced better suspensions than Primojel indicating the importance of testing such agents under conditions of intended usage. The model suspensions studied in this report had a very simple formulation unlike the usual multicomponent preparations which may also contain other drugs, flavourings and preservatives, which may affect the suspending agent.

REFERENCES

Barry, B. W., Meyer, M. C. (1974) J. Pharm. Pharmacol. 26: Suppl. 129P–130P
Berney, B., Deasy, P. B. (1979) Int. J. Pharm. 3: 73–80
Bhagwan, L. B., Deasy, P. B., Timoney, R. F. (1971) J. Pharm. Pharmacol. 23, Suppl. 251S–252S
Davis, S. S., Deer, J. J., Warburton, B. (1968) J. Sci. Inst. 2: 933–936
Farley, C. A., Lund, W. (1976) Pharm. J. 216: 562–566
Martin, A. N. (1961) J. Pharm. Sci. 50: 513–517
Warburton, B., Barry, B. W. (1968) J. Pharm. Pharmacol. 20: 255–268