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A comparison of the physical properties of some sulphacetamide eye ointments commercially available in the U.K.

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Summary

The rheology, particle size distribution and drug release, measured by dissolution and agar diffusion techniques, of 5 eye ointments containing sulphacetamide sodium has been studied. Although the particle size distributions of 2 B.P. products (6% strength) were similar (mean particle sizes of 13.5 and 14.7 μm) their consistency and drug release patterns were different. All ointments exhibited shear breakdown during continuous shear rheology. A linear relationship was found between the quantity of drug released by agar diffusion techniques and the amount dissolved after 60 min by dissolution. The B.P. ointments released their drug more slowly and, in most cases, to a lesser extent than the other 3, non-official ointments studied (strengths of 2.5, 6 and 10% w/w). The 2.5% strength ointment (w/o emulsion) was considered equivalent to the B.P. products.

Introduction

Drug release from ophthalmic ointments is dependent upon several factors, in particular: (a) drug particle size; (b) vehicle viscosity and rheological type; (c) partitioning; and (d) drug type. Konning and Mital (1978) showed that particle size was important by demonstrating that as the particle size of benzoic and salicyclic acids decreased, their release correspondingly increased. Vehicle viscosity and rheo-

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logical type are known to play a controlling role in drug release, especially after application to the eye. Abel and Leopold (1980) considered that ocular delivery by ointment rather than drops should prolong contact times and therefore increase absorption. Patton and Robinson (1975), in considering the influence of rheological property on corneal contact time, stated that the ocular use of Newtonian vehicles would lead to a loss of solution through tear drainage that was inversely proportional to vehicle viscosity. Pseudoplastic and thixotropic systems would undergo shear during blinking and would consequently thin and drain from the eye reducing corneal contact time.

The rheology of an ideal eye ointment is such that it can be easily applied and spreads uniformly over the corneal and scleral surfaces but subsequently reassumes its structure. That is, it should flow when subject to shear but regain structure when the forces are removed in order to prolong contact time and minimize drainage from the eye. Mixing problems between ophthalmic ointments and tears have been reported (Sieg and Robinson, 1974, 1975) and consequently a partitioning parameter may affect drug release between ointments and tears. The chemical nature of the drug may also influence ocular availability since a sustained effect was observed using an ointment containing fluorometholone but not with an ointment containing pilocarpine (Sieg and Robinson, 1975, 1977). This was due to different solubilities of the two drugs in the ointment basis.

Apart from suggesting Simple Eye Ointment B.P. as a suitable base, the British Pharmacopoeia (1980) offers little guidance in the choice or viscosity of a suitable eye ointment base. Only for Sulphacetamide Eye Ointment B.P. is the base specified. This report, therefore, outlines the comparative in vitro assessment of various sulphacetamide eye ointments commercially available in the U.K. The viscosity and particle size of these products have been examined together with estimations of sulphacetamide release measured by dissolution and agar diffusion.

Materials and methods

Five commercially available sulphacetamide eye ointments were studied. A and B (B.P. products, 6% w/w), were dispersions of sulphacetamide sodium crystals. Ointments C, D and E were 2.5, 6 and 10% w/w, respectively. C and D were w/o emulsions and E an o/w emulsion.

Particle size analysis

Small quantities of ointments A, B or D were placed on microscope slides and gently streaked out using a clean camel-hair brush. Cover-slips were not used in order to minimize particle distortion, and aggregate breakdown. Size ranges were estimated using a Double Image Shearing Microscope (Flemming Instruments). The lower limit of resolution was 0.2 μm and a minimum of 625 particles were counted for each ointment. Aggregates were defined as containing more than 3 individual particles.

Rheology

Rheograms were obtained using a Ferranti-Shirley cone and plate viscometer, at 37°C with a 1200 g · cm spring and a cone of 7 cm diameter (0.006173 radians). A maximum rate of shear of 100 rpm was employed with a total sweep time of 2 min.

In vitro release

(a) Agar diffusion technique. Sulphacetamide release was estimated against *Sarcina lutea* (NCTC 196). 18-hour cultures were used, grown in Mueller Hinton Broth (Oxoid CM405), centrifuged and washed twice before resuspension in sterile water, in order to avoid antagonism of sulphacetamide by sulphonamide antagonists which may have formed during incubation. For the study Mueller Hinton agar, seeded 2% v/v with the resuspended culture, was used. Either 150 mg of the ointments (A–E) or 0.05 ml of standard solutions were placed into wells, 9 mm in diameter cut in the agar.

After allowing 2 h at room temperature for diffusion of the sulphonamide, the assay plates were incubated at 37°C for 18 h when the clear zones of inhibition were measured. Sulphacetamide release was calculated (in μg) against standards. Preliminary results indicated a linear response between zone size and log applied sulphacetamide between 10 and 2000 μg. Therefore standards of 10 and 200 μg and 1000 and 2000 μg were used for ointments A–D and E, respectively.

(b) Dissolution studies. The ointments (A–E) were carefully placed into aluminium vial covers (2 cm internal diameter) and the excess was removed to leave a flat surface level with the cover edge. A 3.0 cm^2 piece of "Celgard" water-wettable polypropylene film (Type 3401) was placed over the surface and held flat in position using a perspex O-ring which was also used to mount the upturned disc onto the lower surface of the top part of the B.P. dissolution apparatus. The disc surface was centrally positioned in a 150 ml flat-bottomed flask and rotated at 100 rpm approximately 2 mm below the surface of the dissolution fluid (100 ml of 0.9% w/v aqueous sodium chloride) maintained at 37°C. Sulphacetamide sodium content was determined spectrophotometrically at 255 nm using flow-through facilities.

Results and discussion

Continuous shear rheograms of products A, B and D are given in Fig. 1. Each displayed anticlockwise hysteresis loops, indicative of structural breakdown by shear and may be regarded as pseudoplastic. Such systems may undergo shear in the eye (caused by blinking); they then thin and consequently drain from the eye, therefore reducing the contact time (Patton and Robinson, 1975). It is apparent from Fig. 1 that of the two B.P. products, ointment B was more viscous than ointment A. Barry (1970) pointed out that soft paraffin is a heterogenous and variable material and rheograms of even different batches of white soft paraffin may vary considerably (Barry and Grace, 1970). Since Sulphacetamide Eye Ointment B.P. contains considerable quantities of soft paraffin, such variations in Fig. 1 in the rheograms of A and B are therefore not unexpected.

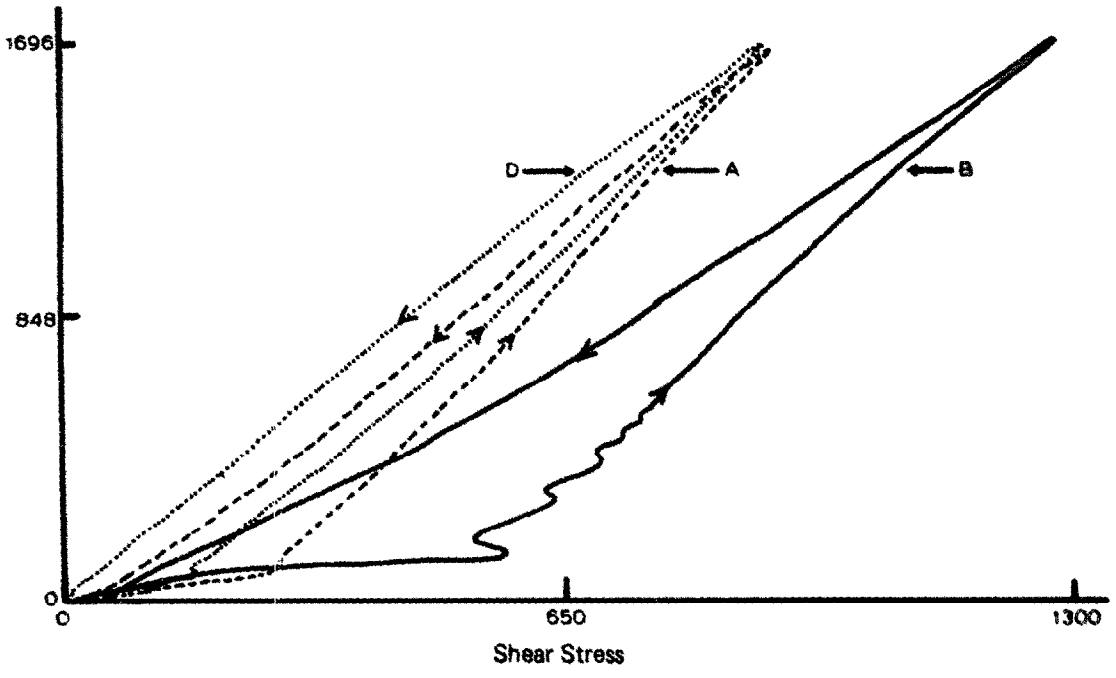

Fig. 1. Continuous shear rheograms of ointments containing 6% w/w sulphacetamide sodium. A: Ointment A; B: Ointment B; D: Ointment D. Ordinate: shear rate (s^{-1}); abscissa: shear stress ($dyne \cdot cm^{-2}$).

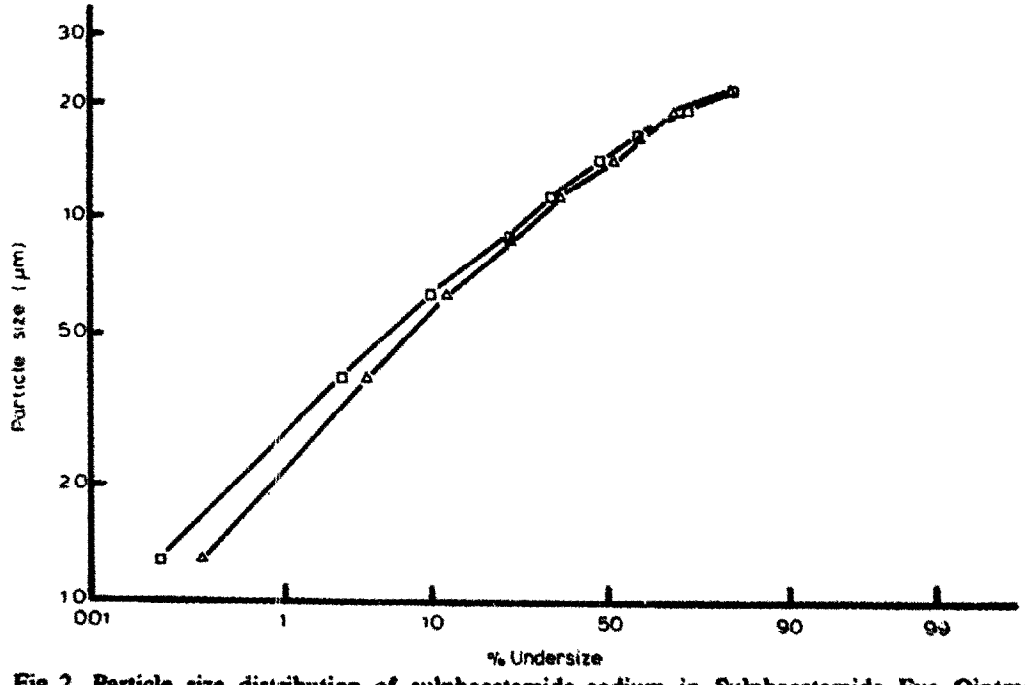

Fig. 2. Particle size distribution of sulphacetamide sodium in Sulphacetamide Eye Ointments. B.P. determined by image shearing microscopy. □: Ointment A; △: Ointment B. Ordinate: particle size in μm (log. scale); abscissa: % undersize (probit. scale).

The particle size data of sulphacetamide sodium in A and B are shown in Fig. 2. The particle size distributions were similar and median particle diameters of 14.5 μm and 13.7 μm were found for A and B, respectively; 15.3% of the particles counted in A were aggregates ranging in size from 6 to 25 μm and 65% of these aggregates were > 10 μm. Similarly, in B, 12.3% of the particles were aggregates ranging in size from 6 to 15 μm; 58% of these aggregates were > 10 μm. In a study on corticosteroid ointments, Orr et al. (1980) pointed out that skewed drug content distribution was undesirable because of the increased chance of administering doses of drug substantially higher (and consequently lower!) than the labelled strength. This is especially important with antibiotic preparations where bacteriostatic levels of the antibiotic should be maintained. The particle size distributions appeared to be near log-normally distributed (Fig. 2). The dispersed phase of product D did not show aggregation, and the droplets were all less than 2.5 μm in diameter. Consequently the risk of obtaining variable ophthalmic sulphacetamide levels due to inhomogenous drug dispersion in the ointment is lower in D than ointments A and B.

Sieg and Robinson (1975) considered that particles inserted into the eye should ideally be less than 10 μm in diameter to minimize irritation which is likely to stimulate tear secretion causing the administered dose to be washed away. Both products A and B contained considerable numbers of particles in excess of 10 μm in diameter.

Table 1 summarizes the agar diffusion from the 5 ointments. The B.P. products A and B gave the poorest release, less even than C which was only 2.5% w/w. The dissolution from ointments (Fig. 3) gave the same ranking of release as agar diffusion, namely $E > D > C > B > A$. Drug concentration plays an important role in the release of drugs from ointment bases; for example, Ayres and Lasker (1974) have shown that release of benzocaine from ointments was concentration dependent. Thus, product E, an aqueous-based ointment containing 10% w/w sulphacetamide sodium, gave higher releases than the 6% and 2.5 w/w greasy-based products (D and C). However, both Fig. 3 and Table 1 indicate the marked superiority in release from emulsion-based products compared to that from suspensions of the drug in an ointment base. Sieg and Robinson (1979) showed that shear facilitated the release of

TABLE 1

THE RELEASE OF SULPHACETAMIDE SODIUM FROM EYE OINTMENTS ASSESSED BY AGAR DIFFUSION AGAINST *SARCINA LUTEA*

Ointment	μg released
A	21.7 ± 5.3
B	43.8 ± 6.2
C	89
D	114 ± 10.7
E	1798

Results are expressed as μg ± S.D. of 10 determinations for ointments A, B and D, but only the mean of 3 determinations for ointments C and E.

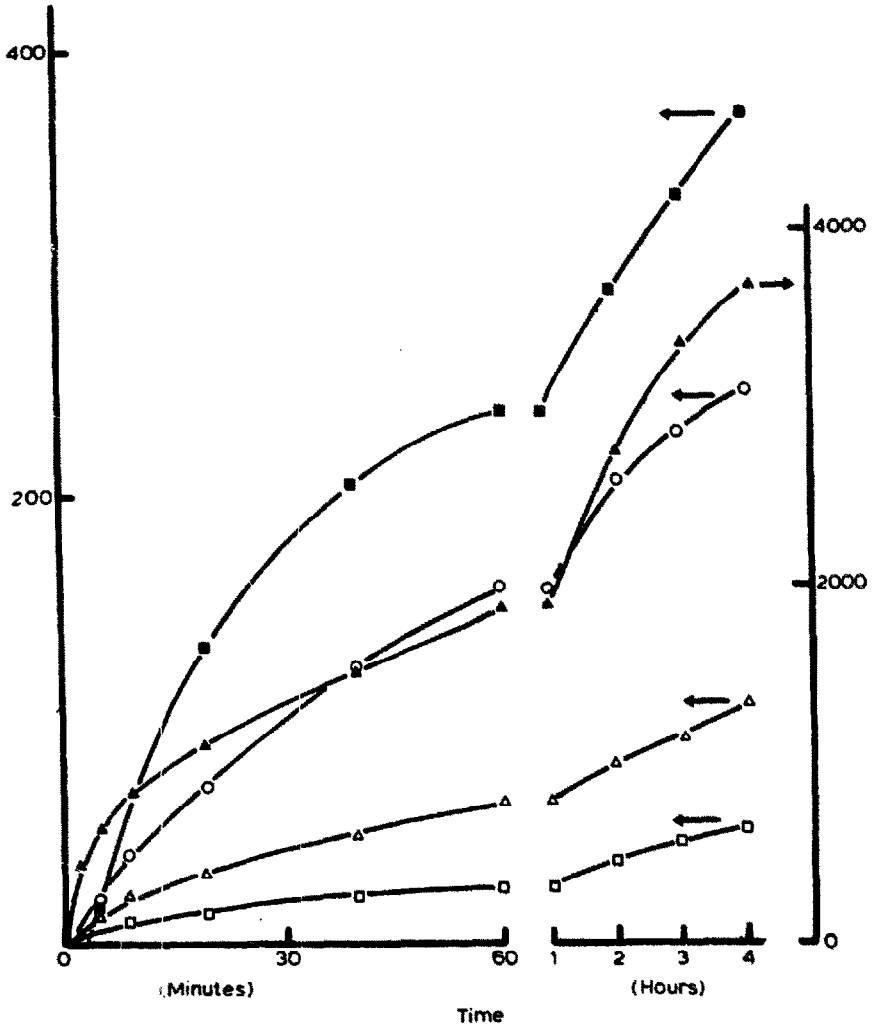

Fig. 3. Dissolution profiles of sulphacetamide sodium from sulphacetamide eye ointments into 0.9% w/v aqueous sodium chloride at 37°C. □: Ointment A (B.P.); △: Ointment B (B.P.); ○: Ointment C (2.5%); ■: Ointment D (6.0%); ▲: Ointment E (10%). Ordinate: μg of sulphacetamide sodium; abscissa: time (min).

pilocarpine from w/o emulsions as shear disrupted emulsion structure causing dispersed droplet rupture. This should further increase the in situ release from the emulsified products compared with the B.P. products. It has not always been easy to correlate results obtained from agar diffusion techniques with those obtained by dissolution methodology. However, Fig. 4 demonstrates that a linear relationship existed between agar diffusion release (μg) and the quantity of sulphacetamide sodium released after 60 min by the dissolution method.

It is essential in the correct use of antimicrobial agents that drug levels are maintained at or above their minimum inhibitory concentration. The effect of viscosity and rheological properties on ocular drug release are difficult to assess. However, drug release from ointments is probably the rate-limiting step in their bioavailability. Sieg and Robinson (1974) pointed out that drugs in ophthalmic

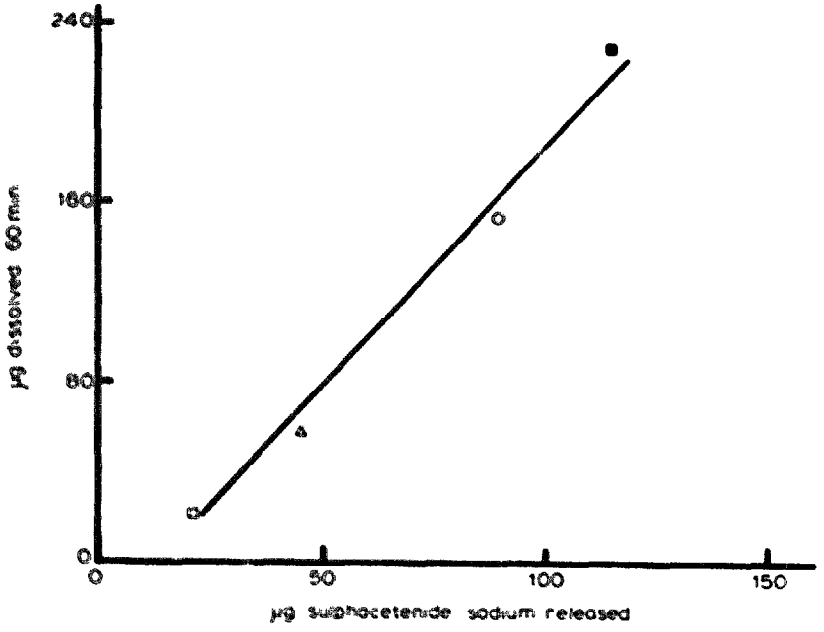

Fig. 4. Graph showing relationship between the amount of sulphacetamide sodium released after 60 min by dissolution (µg: ordinate) and the amount released by agar diffusion against *Sarcina lutea* (µg: abscissa). □: Ointment A; △: Ointment B; ○: Ointment C; ■: Ointment D.

ointments, irrespective of their solubility or diffusion characteristics in the vehicle, will have to partition into the tear film or epithelium directly in order for corneal absorption to occur. It is probable that the differences in drug release measured during the study may potentially affect bioavailability and cause clinical problems. Therefore, it is likely during the next decade that efforts will have to be made to standardize release from ophthalmic ointments. Based on drug release only, it would appear that the official B.P. (6%) ointments may only be equivalent to a 2.5% w/w strength of a w/o emulsion-based product.

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