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The formulation and sterilization of a surgical lubricant gel based on carboxypolymethylene

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A lubricant gel of optimal consistency containing a local anaesthetic (lignocaine) has been formulated which can be sterilized by gamma irradiation. A rheological specification was obtained by examination of some currently used preparations. The variation in their consistency was large but all exhibited pseudoplastic flow with a yield value. Gels based on tragacanth, the methylcelluloses and the Carbopols were suitable as lubricants before sterilization and after autoclaving, but on gamma irradiation the gel structure was destroyed. Ethanol (5–10%) protected the Carbopol formulations. Irradiation of lignocaine solutions caused some cloudiness and a small drop in pH. Ethanol and metabisulphite acted as protective agents. A final formulation was developed consisting of a Carbopol gel (1%) neutralized by lignocaine base (2%) and the biological availability of the local anaesthetic was assessed using an *in vitro* method.

Lubricants are used to overcome friction in procedures such as catheterization. A variety of substances have been used; for example, glycerol, propylene glycol, emulsions, fixed oils and gels (Levy & Schwarz, 1957a). In particular, the lubricant gel has been found convenient because it will remain *in situ* without dripping. The product must be sterile but even with aseptic precautions an infection rate as high as 30% has been reported for a single catheterization (Kass, 1957, Slade & Linton, 1960).

Proprietary sterile lubricant gels are usually available in collapsible metal tubes fitted with a screw cap. The nozzle for application is supplied separately. And, recently, the Interim Report of the Steering Committee for the Standardisation of Supplies from Central Sterile Supply Departments has recommended the supply of a sterile single use container of anaesthetic gel with an integral nozzle (Cunliffe, 1970). Such a unit pack must be suitably sterilized and gamma irradiation offers the most advantages if the gel is included in a pack since the complete pack can be routinely sterilized.

We have attempted to formulate a lubricant gel of optimal consistency and stability, containing a suitable anaesthetic that could be sterilized by gamma irradiation in its pack.

Little information is available on the desired properties of a lubricant gel and the methods by which these may be measured quantitatively. Some features have been summarized by Levy & Schwarz (1957b): it should be water soluble, non-irritating,

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easily spreadable and of high lubricating capacity. The gel should not contain greases or oils (which may be harmful to rubber) or any other water-insoluble or non-metabolizable components that cause foreign body reactions. Ideally it should be transparent, adhere well to instruments and resist being removed by body fluids.

Although, Levy & Schwarz (1957a,b) demonstrated a lack of correlation between 'viscosity' and lubricant effect for oils, organic liquids and gels, we believe the usefulness of a gel as a medicinal lubricant will be largely influenced by its rheological properties. It should have a low enough viscosity to be squeezed from the container through the nozzle and to be spread, whilst being viscous enough and having a yield strength so that it remains in the region to which it has been applied. In this work, we have obtained a rheological specification by examining some lubricant gels currently in use.

MATERIALS AND METHODS

Apparatus

The Ferranti-Shirley Cone and Plate Viscometer was used as described by McKennell (1960). This instrument's use and limitations with pharmaceutical preparations have been discussed by Davis, Shotton & Warburton (1968). The instrument was fitted with an automatic flow curve recorder unit. It was used at a temperature of 25° and a sweep time of 120 s. A maximum shear rate of 725 s^{-1} was used. The U tube viscometer was used as decribed in the British Standard (1957).

Sterilization by autoclaving was carried out using a small laboratory autoclave at 10 lb in^{-2} pressure for 1 h. Gamma irradiation was performed at the Atomic Energy Research Establishment, Harwell, using a Spent Fuel Pond and ^{60}Co Hotspot. The total dose used was 3 Mrad and the temperature of irradiation about 25°. Pre and post irradiation storage was at ambient temperature.

In vitro release rates of lignocaine were followed using an arrangement similar to that described by Billups & Patel (1970). 15 g of the gel was placed in a small diffusion cell and covered with a Cellophane dialysis membrane. The release of lignocaine into 475 ml of phosphate buffer was followed using a spectrophotometer with flow cell assembly at a wavelength of 262 nm.

Materials

Sodium carboxymethyl cellulose (high and low viscosity) and general laboratory chemicals were obtained from British Drug Houses Ltd. Carboxypolymethylene (Carbopols 934, 940, 941) were kindly supplied by Honeywell-Stein, London. Lignocaine hydrochloride and base were from the Pharmaceutical Manufacturing Company.

RESULTS AND DISCUSSION

Rheological specification for a lubricant gel

The lubricant gels examined are listed in Table 1. These all showed pseudoplastic behaviour with a yield value; that is the viscosity of the system decreased with increase in rate of shear. This type of flow is often produced by solutions of long chain hydrocolloid molecules (Martin, Swarbrick & Cammarata, 1969). To characterize the lubricant gels, the following values were calculated:— The apparent viscosity at

Table 1. *Rheological characteristics of some lubricant gels.*

Sample	Viscosity at 518 s^{-1} (Poise)	Apparent viscosity (Poise)	Yield value (Dyne cm^{-2})*a*
K-Y	1·23	4·72	1333
Lignocaine Gel 2% ..	1·37	2·24	32
'Lidothesin'	2·96	5·58	282
Lignocaine Gel 2% ..	2·52	5·37	282
Lignocaine Gel 2% ..	2·39	5·14	235
'Xylocaine Gel'	2·79	6·54	512
Catheter Lubricant.. ..	2·49	4·10	94
Catheter Lubricant.. ..	2·11	3·14	47

(*a*) 1 dyne cm^{-2} = 0·1 Nm^{-2}.

maximum shear rate, the viscosity at an arbitrary shear rate of 518 s^{-1} and the yield value (Table 1).

It was clear that the lubricant gels commonly in use are pseudoplastic systems which show a wide range in the values of their viscosity and yield. Therefore, a satisfactory formulated lubricant gel should also show pseudoplastic flow and have a value for viscosity and yield which would fall into this range.

Suitable agents for the preparation of the base of the gel

Aqueous solutions of polymers, including a large number of pharmaceutical thickening agents such as the natural and synthetic gums exhibit pseudoplastic flow properties. Three different types of material were considered for the base of the lubricant gel; tragacanth, the methylcelluloses and carboxypolymethylene. The rheological properties of the gels were examined before and after sterilization by autoclaving or gamma irradiation, using the Ferranti-Shirley Viscometer (and where necessary, the U tube viscometer).

Tragacanth and methylcellulose gels (Table 2). These gels were pseudoplastic with a yield value when prepared (Table 3) but as expected, there was a marked decrease in viscosity and yield value of the tragacanth gels after autoclaving (See Gralen & Karrholm, 1950). However, the gel containing 3% w/v of tragacanth and the

Table 2. *Composition of gels prepared from published formulae on lubricants.*

Constituents	Formulation (% weight in volume)						
	A	B	C	D	E	F	G
Tragacanth					2·29		3·0
Glycerol	6·26				25·0		31·25
Alcohol (90%)					2·5		
Hydroxypropylmethyl cellulose						1·0	
Sodium carboxymethyl cellulose H/V				1·5			
Sodium carboxymethyl cellulose L/V	5·0	5·0	1·5				
Carbopol 934						0·3	
Propylene glycol		25·9	25·9	25·9		20·7	
Hydroxybenzoates			0·15	0·15			
Water to	100	100	100	100	100	100	100

Details of the Lubricants were taken from Martindale, The Extra Pharmacopoeia 25th Edn. The Pharmaceutical Press, London, 1967.

Table 3. *Rheological properties of the lubricants based on tragacanth, the methylcelluloses and carbopols.*

Formulation (Table 2)		Before sterilization: Apparent viscosity (Poise)	Before sterilization: Yield value (dyne cm^{-2})	After autoclaving: Apparent viscosity (Poise)	After autoclaving: Yield value (dyne cm^{-2})	After irradiation: Apparent viscosity (Poise)
Tragacanth	D	3·52	705	1·82	35	0·19
	F	6·78	2118	3·40	382	0·45
Methylcelluloses	A	11·14	1175	9·96	940	0·47
	B	11·94	1659	10·22	940	1·30
	C	1·59	24	1·54	23	0·07
	G	4·72	376	3·52	188	0·16
	E	5·65	799	4·85	612	0·55
Carbopols	934	9·23	1308	6·03	1099	0·019
	940	8·47	1691	8·04	1388	0·02
	941	4·06	306	3·69	306	0·014

methylcellulose gels still maintained values of viscosity and yield strength after autoclaving within the ranges suitable for lubricant gels. In contrast, after gamma irradiation all formulations lost their gel structure and became Newtonian liquids of reduced viscosity. Similar effects of gamma irradiation on aqueous solutions of sodium carboxymethylcelluloses have been reported by Rasero & Skauen (1967).

Carboxypolymethylene (Carbopol) gels. Three grades of Carbopol at 1% concentration were examined. Before sterilization and after autoclaving the samples were pseudoplastic systems with a yield value. Some loss of viscosity occurred on autoclaving, however, after gamma irradiation the samples were Newtonian liquids of considerably reduced viscosity (Table 3).

Protection of gels from gamma irradiation. The methylcelluloses and the Carbopols were considered to be suitable as possible starting materials since formulated gels had the desired rheological properties before they were subjected to gamma irradiation, but after irradiation the gel structure was lost. Charlesby (1967) has pointed out that in aqueous solutions of polymers, the agents effective in protecting the solutions from irradiation effects show a close correlation to those effective in radiobiological protection. Consequently, such agents (sulphydryl compounds, hydrosulphites, metabisulphites, nitrites and hydroxy compounds including alcohols and glycols) were considered and, of these, ethanol was found to be a good protective agent for Carbopol gels.

Three grades of Carbopol and two grades of sodium carboxymethylcellulose (low viscosity and high viscosity) were investigated. The Carbopol gels were prepared as before using 1% of the polymer and ethanol concentrations from 0·5 to 20% (v/v). The sodium carboxymethylcellulose gels were prepared using 1·5% of the high or low viscosity grades, propylene glycol 25% v/v and ethanol 10% v/v.

The rheograms of the sodium carboxymethylcellulose gels after irradiation were Newtonian liquids of much reduced viscosity and while ethanol reduced the viscosity loss it was not effective in protecting the gel structure. On the other hand, the incorporation of the ethanol into the Carbopol gel formulations had a dramatic effect in

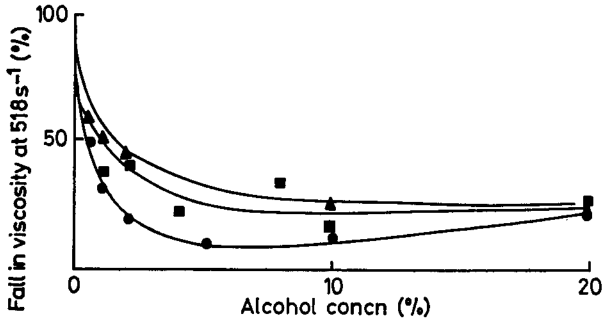

FIG. 1. The change in the viscosity at $518s^{-1}$ of gamma irradiated Carbopol gels ●, 934; ■, 940; ▲, 941, containing different quantities of ethanol as a protective agent.

protecting the gel structure. The rheograms produced after irradiation were still pseudoplastic. The results, expressed as a % fall in viscosity, are summarized in Fig. 1. Although there is some scatter in the results (possibly due to the gels not being irradiated together) it is clear that the addition of 5–10% ethanol reduces the viscosity loss to about 20%.

Thus, a satisfactory concentration of ethanol for inclusion in the Carbopol lubricant gel formulation would be 5–10% v/v.

Effects of sterilization on the local anaesthetic

Lignocaine is commonly included in lubricant gels as a local anaesthetic and the stability of aqueous solutions of the hydrochloride to sterilization by autoclaving has been well established (Bullock & Grundy, 1955, Whittet, 1954, Katz, 1966). After gamma irradiation of aqueous solutions of lignocaine Pandula, Farkas & Racz (1967) found a lowering in pH of a 2% solution but no changes in the ultraviolet spectrum, or new spots on paper chromatography. Later, Pandula & Farkas (1970) showed that oxidative changes occurred and that these could be eliminated by antioxidants such as potassium pyrosulphite.

In our work, solutions of lignocaine hydrochloride B.P. were packed into 10 ml glass ampoules and irradiated solutions were compared with non-irradiated solutions. The irradiated solutions showed some degree of cloudiness and a decrease in pH (from 5·0 to 3·5) absent in the non-irradiated samples and an increase in ultraviolet absorption and a new absorption in the range 280–325 nm. Preliminary studies using thin-layer paper and gas chromatography and mass spectrometry have failed to reveal the nature of the breakdown products.

The irradiation changes were almost totally eliminated by the addition of 10% v/v ethanol or 1% w/v sodium metabisulphite.

The final formulation

From a consideration of the results described above a formulation of Carbopol 1% lignocaine HCl 2% and ethanol (95%) 5 to to 10% was proposed. But all attempts to prepare a satisfactory gel to this specification failed, since addition of the lignocaine hydrochloride solution produced a white precipitate and the gel structure was immediately lost.

Replacement of the hydrochloride with the base to neutralize the acid Carbopol (Saski, 1960) gave gels from each grade of Carbopol. These were examined rheo-

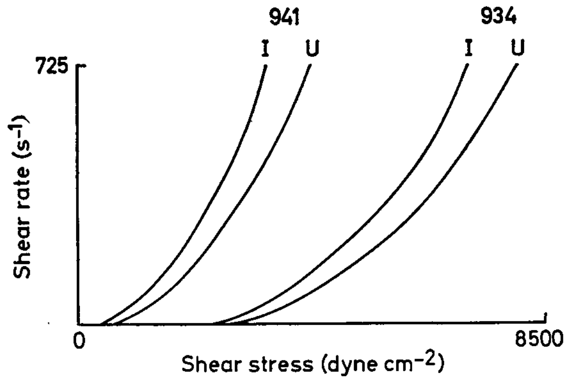

FIG. 2. The rheograms for the final Carbopol gel formulation. U = unirradiated. I = gamma irradiated.

logically before and after gamma irradiation and the rheograms were pseudoplastic (Fig. 2) and showed only slight reduction in viscosity (11 to 18%) after irradiation.

Biological availability tests

The release rates of lignocaine from the three Carbopol formulations were measured using the *in vitro* diffusion cell and were similar and marginally less than that found for a commercial product (xylocaine—2% lignocaine) (Fig. 3). Thus, we conclude that the formation of a lignocaine-Carbopol salt should not seriously affect the *in vivo* availability of the anaesthetic. This has been confirmed clinically (Kershaw, private communication, 1972).

Other considerations

Schwarz & Levy (1958) reported an oxidative degradation of Carbopol gels with age—a process probably catalysed by trace metals, while Saski (1960) found that a

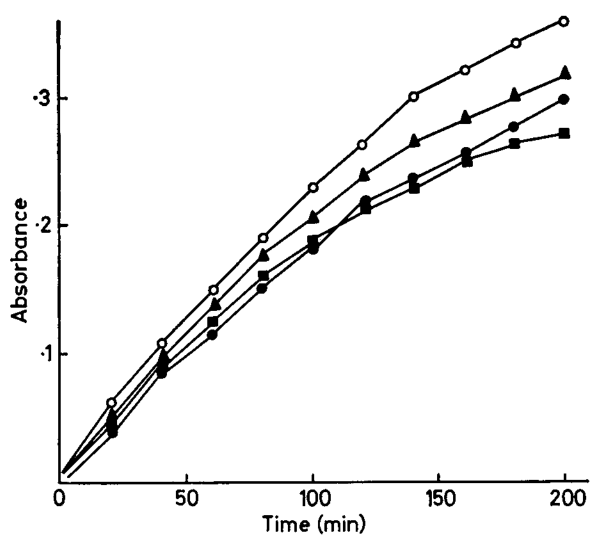

FIG. 3. The release of lignocaine from lubricant gel formulations (37°, pH = 6·8). Carbopo gels: ●, 934; ■, 940; ▲, 941; xylocaine gel, ○.

Carbopol gel prepared with an alkaloidal base as neutralizing agent showed no significant viscosity changes upon storage. Our lubricant gel prepared from Carbopols is likely to have a satisfactory stability since no evidence of instability has been detected over 12 months.

The toxicity of the Carbopols is negligible and Carbopol 934 has been approval for oral use (Moes, 1972). However, it would still be necessary to make a toxicological evaluation of the final sterile gel since irradiation produces some small changes, even in the presence of ethanol.

Thus, it is possible to produce a gel using Carbopol neutralized by lignocaine base. This has suitable rheological properties even after sterilization by gamma irradiation. Ethanol added to the formulation is effective in protecting the gel structure and lignocaine against degradation.

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