International Journal of Pharmaceutics, 24 (1985) 287–296
Elsevier

IJP 00828

Formulation studies on certain oily injection products

Edward E. Sims* and Harry E.C. Worthington

Pharmaceutical Research Department, Roche Products Ltd., Welwyn Garden City, Herts AL7 3AY (U.K.)

(Received September 24th, 1984)
(Modified version received December 18th, 1984)
(Accepted January 4th, 1985)

Key words: injections – oily injections – aluminium monostearate – processing factors – suspensions – fluorouracil

Summary

The effects of different processing methods on the rheology of a sterile oily injectable have been studied. The interaction of processing variables with different formulation changes has also been examined. Dry heat sterilization of Miglyol 812N based preparations is considered feasible. Vehicles prepared using Miglyol 812N together with aluminium monostearate as a suspending agent were found to be satisfactory from a resuspendability point of view, but addition of a model drug (5-fluorouracil) did produce a significant reduction in vehicle viscosity.

Introduction

Controlled release parenteral dosage forms are usually designed for intramuscular or subcutaneous administration, although recently (McLaughlin and Goldberg, 1983) their intralesional application has been described. The physical methods used to achieve controlled delivery have been reviewed (Lee and Robinson, 1978). More recently a review of long-acting parenteral drug formulations has appeared (Chien, 1981) and a review of the release of drugs from lipid-based parenteral dosage forms has also been published (Armstrong and James, 1980). Oily parenteral preparations

* *Present address:* Wyeth Research (UK) Ltd., Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, U.K.
Correspondence: H.E.C. Worthington, Pharmaceutical Research Department, Roche Products Ltd., P.O. Box 8, Welwyn Garden City, Herts AL7 3AY, U.K.

may be presented as solutions or suspensions and the vehicles most commonly used include sesame oil, castor oil, arachis oil, olive oil and cottonseed oil. Drug release from an oily solution is reported to be through partitioning (Ballard, 1968), and this may also apply to an oil suspension, although absorption and removal of the oil from the injection site and exposure of particles of drug for dissolution will also contribute to the effect.

Formulation of oily parenteral products may involve the use of a gelling agent, in some cases to provide good drug suspending properties, but also to increase viscosity and localize the preparation in the tissues. This could be expected to enhance sustained or controlled release. Aluminium monostearate has been used as a thickening agent in oily preparations and its use to achieve a sustained effect has been reported for pollen extract compositions (British Patent, 1952; U.S. Patent, 1954), antitoxins (Coles et al., 1965), procaine penicillin G (Buckwalter and Dickison, 1948) and LH-RH analogues (British Patent Application, 1981). It is generally known that the properties of aluminium monostearate/oil gels ('organogels') depend on the method of preparation and conditions should be standardized to obtain a reproducible result (Morrison and Stephens, 1967). Organogels have been reported to consist of two phases (Rideal, 1950); i.e. a network of solvated material and interstices filled with saturated solution. The aluminium salts of fatty acids are reported (Ekwall et al., 1972) to give long chain-like aggregates in non-polar organic solvents, being held together by intermolecular bonds involving free hydroxyl groups or coordinate linkages between metal, metal ions and carboxylate oxygen. These authors refer to deaggregation on stirring with some spontaneous reformation and liken the system to one containing high-polymer fibrous aggregates rather than surfactant molecules. Application of stress (thermal or mechanical) would be expected to cause some degree of structural modification and therefore the conditions used for preparation of gels, and their subsequent treatment (e.g. heat sterilization processes) may ultimately determine the characteristics of the product and hence influence its performance. With respect to suspending properties the crucial role of trace amounts of water has been noted (Attwood and Florence, 1983), and this factor particularly will be affected by processing conditions.

Materials and Methods

The aluminium monostearate U.S.N.F. was supplied by Mallinckrodt, U.S.A. through Aynchem, London. The material conformed to the U.S.N.F. specification and gave a loss on drying of 1.2–1.5% by weight. Analysis by GLC of a methylated ether-soluble extract of an acid hydrolyzed sample showed the sample to consist of stearate (31%) together with quantities of myristic (4%), palmitic (24%), arachidic (25%) and behenic (15%) components. Microbiological testing revealed the absence of pathogens and a total aerobic viable count of less than 100 org/g. Oily vehicles initially assessed included Miglyol 812N (Dynamit Nobel, Slough, U.K.), sesame oil (Alembic Products, Manchester, U.K.) and arachis oil (Evans Medical, Liverpool, U.K.). Only one batch of each of these oils was used in the work described.

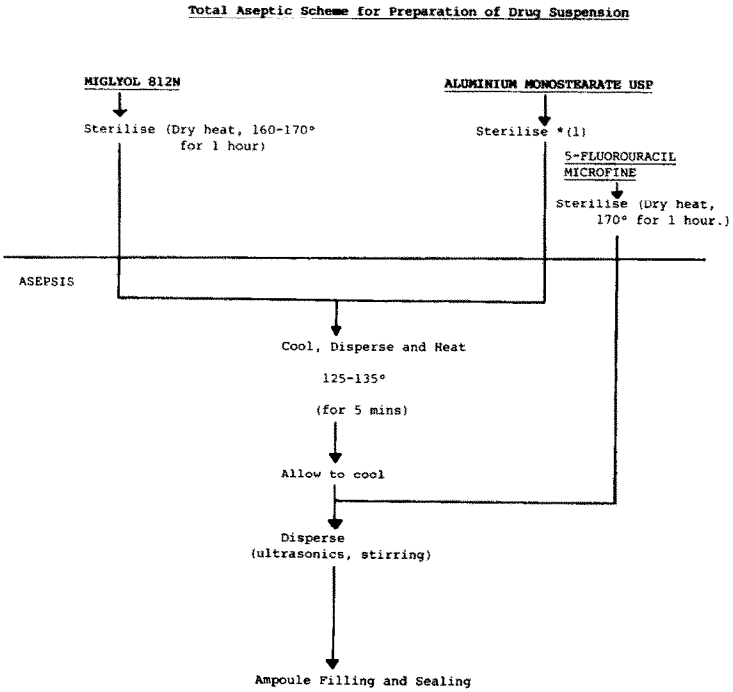
Preparation of the gels

The gels were prepared in accordance with the methods reported in the manufacturer's literature for aluminium monostearate. The weighed quantity of aluminium monostearate was carefully dispersed in the cold oil and continuously stirred by a magnetic follower. The mixture was heated to 125–130°C with continued stirring, using a heating rate of approximately 5°C/min. At temperatures in excess of 100°C gel formation was characterized by a change in physical appearance of the preparation from an opaque dispersion to a semi-transparent gel, accompanied by an increase in viscosity. The gels were held at maximum temperature (130°C) for 5 min before removing from the heat source and allowing to cool at rest. This standard preparation technique was used to prepare all gels used in the study.

Sterilization methods

Two processes were designed for the preparation of the oily injection vehicles for incorporation of a thermolabile drug. Fig. 1 describes the use of sterile components and aseptic gel preparation while Fig. 2 outlines a process for the heat sterilization of a prepared gel.

Samples of aluminium monostearate powder for use in the process as described by Fig. 1 were subjected to a range of treatments to achieve sterility.



*(1) Ethylene oxide gas sterilisation, or γ-irradiation or dry heat.

Fig. 1.

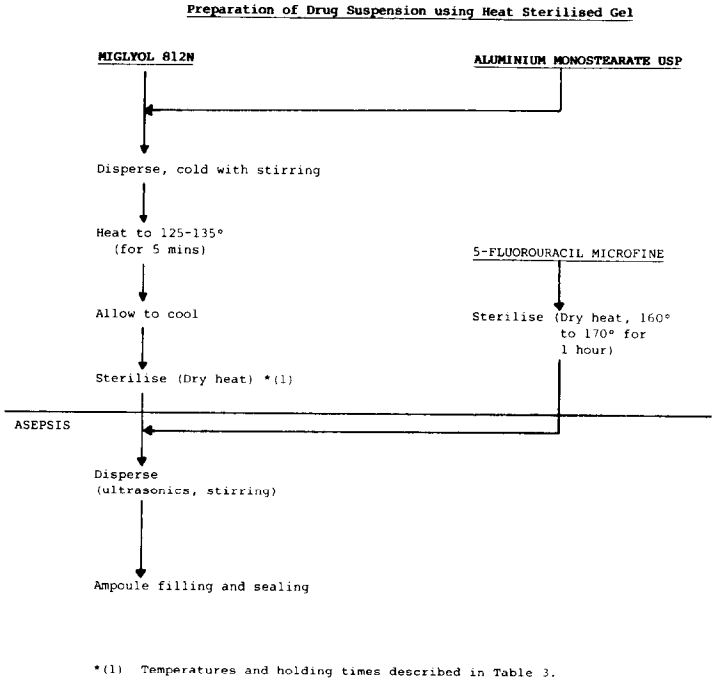


Fig. 2.

(1) Dry heat. A range of temperatures and holding times were tried with limited success, as melting of the solid resulted in cake formation and material which could not be used for gel preparation. A temperature of 140°C was eventually selected and samples (10 g) were placed in 250 ml conical flasks and covered with aluminium foil prior to placing in the hot air sterilizing oven (L.T.E., Greenfield, Oldham). Warm up times were estimated from thermometer readings to ensure that samples were held at the correct temperature for the stated time period for all heat treatment methods.

(2) γ-Irradiation. Samples were packed in clean, low density polypropylene containers and sealed. Sterilization was effected by exposure to 25 kGy from a Co^{60} source (Irradiated Products).

(3) Ethylene oxide. 20 g samples of aluminium monostearate were sealed in Sterilok gas sterilization bags (3M Company, Medical Products Division) and placed in an ethylene oxide sterilization unit (Medical Supply Association). Sterilization was effected by exposure to ethylene oxide gas under the following conditions: pressure 712 mm Hg; R.H. 60%; temperature 55°C, exposure time 1 h. Sterilization was monitored by appropriate chemical indicators.

Oils used in the initial investigations into the characteristics of aluminium monostearate gels were not sterilized. All sterilized preparations were made using Miglyol 812N as the oil component, which is stable to heat sterilization processes. Dry heat sterilization at up to 170°C for 2 h did not cause any chemical changes

indicative of rancidity. Changes in peroxide value (as determined in the B.P. 1980), from < 1 to 25 were observed on sterilization but other characteristics of the oil remained unchanged.

All experiments involving incorporation of a drug were carried out using sterile, microfine, 5-Fluorouracil (Roche) as a model substance.

Rheological determinations

A Contraves RM30 rheometer fitted with an Advances HR-2000 recorder (Contraves AG, Zurich) was used for the rheological measurements. Samples were allowed to stand on the equipment for 15 min at 25°C and the rheograms were plotted directly using a sweep time of 60 s with a hold time of 120 s at the maximum shear rate to investigate any effects due to thixotropy or structural modification under shear. The cup and bob system provided a range of shear rates from 2.15 to 157.90 s^{-1}, and the cone and plate 53.6 to 3950 s^{-1}.

Results and Discussion

Rheograms for the arachis oil, sesame oil and Miglyol 812N were linear over the range of shear rates used in the initial rheological characterization tests, indicative of Newtonian character. The incorporation of aluminium monostearate (loss on drying ~ 1.5%) with subsequent heating to induce gel formation resulted in anticlockwise hysteresis loops, characteristic of shear induced structural breakdown. The upcurves were typically pseudoplastic and the apparent viscosity and loop area were dependent upon the concentration of aluminium monostearate and the oil used (Table 1). The apparent viscosities quoted in Table 1 were read for the upcurve at the maximum shear rate ($D = 157.90\ s^{-1}$). Loop areas were determined using a microprocessor controlled digitizing platen (MOP-1, Kontron), by tracing the outline of the curve. The results were output directly in mm^2 and represent the mean value for three separate determinations. Limiting viscosities were calculated by taking the reciprocal of the slope of the linear portion of the downcurve (Davis and Khanderia, 1980).

The results in Table 1 show that increasing concentration of aluminium monostearate produces gels of increasing viscosity and imparts a greater degree of structure to the gel. Inspection of the viscosities of 2% aluminium monostearate products shows a decrease in the order arachis oil greater than sesame oil greater than Miglyol 812 N. This difference is attributed to the differing compositions of the oils (Morrison and Stephens, 1967). Syneresis was detected at aluminium monostearate concentrations of 3 and 4% w/w in Miglyol 812N. Investigation of this phenomenon using 3% w/w aluminium monostearate gels revealed a limited ($< 10\%$ of loop area) contribution to rheological character. In order to investigate the effects of sterilization on the gels samples were agitated to eliminate any contribution due to irreversible structural breakdown.

A preliminary investigation into the effect of dry heat sterilization (B.P., 1980 and USP XX, 1980) on prepared organogels revealed a marked reduction in the ability of the gels to maintain dispersed solid in suspension under static conditions. This led to

TABLE 1

EFFECT OF ALUMINIUM MONOSTEARATE CONCENTRATION AND OIL SOURCE ON RHEOLOGICAL PARAMETERS OF CORRESPONDING ORGANOGELS

Preparation	Newtonian viscosity (Pa·s)	Apparent viscosity η_{app} at D_{max} (Pa·s)	Loop area (mm^2)	Limiting viscosity η_{lim} (Pa·s)
Arachis oil	6.47×10^{-2}			
Sesame oil	5.43×10^{-2}			
Miglyol 812N	2.47×10^{-2}			
2% w/w aluminium monostearate/sesame oil		1.15×10^{-1}	1308.6	1.02×10^{-1}
2% w/w aluminium monostearate/Miglyol 812N		0.72×10^{-1}	1562.0	0.61×10^{-1}
4% w/w aluminium monostearate/Miglyol 812N		2.24×10^{-1}	4895.4	1.69×10^{-1}
1% w/w aluminium monostearate/arachis oil		1.05×10^{-1}	659.9	0.98×10^{-1}
2% w/w aluminium monostearate/arachis oil		1.46×10^{-1}	2053.8	1.28×10^{-1}
3% w/w aluminium monostearate/arachis oil		1.90×10^{-1}	2678.6	1.56×10^{-1}

Measuring system — Contraves MS-B.
$D_{max} = 157.90\ s^{-1}$.

TABLE 2

EFFECT OF STERILIZING CONDITION FOR ALUMINIUM MONOSTEARATE ON GELS PREPARED WITH MIGLYOL 812N

Concentration of aluminium monostearate in Miglyol 812N (% w/w)	Treatment condition for aluminium monostearate	η_{app} at D_{max} (mPa·s)	Loop area (mm^2)	Limiting viscosity η_{lim} (mPa·s)
1	DH 140°C 3 h	25.4	343.9	23.6
2	DH 140°C 3 h	31.4	1847.8	28.4
2	DH 140°C 5 h	32.3	452.1	29.0
1	γ	18.1	599.1	17.9
2	γ	22.8	732.0	20.0
3	γ	35.5	4452.4	30.1
1	EtO	17.7	449.9	16.6
2	EtO	22.5	573.5	21.1
3	EtO	34.9	3954.5	29.2

Measuring system — Contraves KP-1.
D_{max} = 3950 s^{-1}; DH = dry heat; h = time (h); γ = γ-irradiation, 25 kGy; EtO = ethylene oxide sterilization.

the consideration and investigation of less stressful processes, with the overall objective of producing gels with good suspending characteristics.

The effect of sterilization processes on gel component materials

Aluminium monostearate samples were subjected to a range of conditions designed to either sterilize the materials or to reduce bacterial loading. Gels were prepared from the treated samples, and the treatment parameters and viscosity results are described in Table 2. The gels were of similar appearance when compared to untreated samples, and 'setting' was evident at the higher concentration of 3% w/w aluminium monostearate.

Results for gel apparent viscosities and D_{max} and η_{lim} for the γ-irradiated and ethylene oxide sterilized samples were similar. Differences were observed in the loop area measurements where the ethylene oxide-treated material gives lower values, indicative of reduced thixotropic character at the 2 and 3% w/w concentrations. Dry heat treatment at temperatures in excess of 140°C resulted in melted samples which would not disperse or gel in the oil using the standard preparation method. Exposure to 140°C for 5 h resulted in some discolouration, and longer exposure times were not deemed feasible. The results indicate that exposure for 3 h gives material producing a gel of increased viscosity and thixotropic character. Extension to 5 h results in substantial loss in thixotropic character. These effects may be due to drying of the aluminium monostearate, followed by particle aggregation and melting resulting in discrete localized differences in aluminium monostearate concentration and subsequent reduction in contribution to structure. The results also indicate that the overall viscosities as shown by the values for η_{app} at D_{max} and η_{lim}, are not substantially changed by an increase of exposure time from 3 to 5 h.

TABLE 3

EFFECT OF DRY HEAT TREATMENT ON RHEOLOGICAL CHARACTERISTICS OF 3% w/w ALUMINIUM MONOSTEARATE/MIGLYOL 812N GELS

Temperature (°C)	Holding time (min)	η_{app} at D_{max} (mPa·s)	Loop area (mm^2)	Limiting viscosity η_{lim} (mPa·s)
Initials	–	34.0	4068.0	30.5
140	30	31.1	2146.2	27.1
140	120	31.4	1926.9	28.0
140	180	28.2	1308.2	25.6
140	300	27.3	955.8	24.7
160	15	34.1	1775.2	27.6
160	30	26.6	1242.6	23.6
160	60	31.1	840.1	28.0
180	20	28.5	1411.2	25.9

Measuring system — Contraves KP-1.
$D_{max} = 3950\ s^{-1}$.

The effect of dry heat treatment on prepared gels

Preliminary experiments revealed a substantial loss of consistency when gels were subjected to dry heat sterilization processes. Gels consisting of 3% w/w aluminium monostearate in Miglyol 812N were subjected to a range of temperatures and holding times, as shown in Table 3. Increasing time and temperatures resulted in gradual reduction in opacity. In general a reduction in viscosity was observed, but the most pronounced effect of heat treatment on the gel is shown in the hysteresis loop area values. Allowing the samples to stand for up to 24 h did not result in any recovery of structure. Separation of gel was observed, with a denser opaque white layer and transparent layer separated by a visually well defined boundary. Redispersion was readily achieved by agitation.

The effect of dispersion of micronized drug on gel characteristics

The processes described in Figs. 1 and 2 make provision for the incorporation of the thermolabile drug into the organogel vehicle. Micronized 5-fluorouracil was used as model drug (although not thermolabile), and calculated quantities were incorporated into 20 g of gel to give a final concentration of 26.25 $mg \cdot ml^{-1}$. Incorporation was effected by a combination of low energy ultrasonics and gentle agitation using a magnetic stirrer until a visually even dispersion was observed. Samples were removed for rheological testing both prior to addition of drug and after incorporation. The standard rheological testing method was followed and the results are presented in Table 4. The effects of drug addition were seen most dramatically for heat-treated aluminium monostearate samples as demonstrated by the result for 3% w/w aluminium monostearate gel. The incorporation of the drug resulted in a significant loss in viscosity and thixotropy and it would appear that the effects seen are not due to changes brought about by the mechanical action used for drug incorporation, since control experiments showed that such agitation minus drug had little effect on rheological properties. Therefore some fundamental differences between heat-treated

TABLE 4

EFFECT OF DISPERSION OF MICRONIZED 5-FLUOROURACIL (26.25 $mg \cdot ml^{-1}$) IN ALUMINIUM MONOSTEARATE/MIGLYOL 812N GELS

Gel	Aluminium monostearate concentration (% w/w)	η_{app} at D_{max} (mPa·s)	Loop area (mm^2)	η_{lim} (mPa·s)
Irradiated AlSt	1	18.1	599.1	17.9
Irradiated AlSt and drug	1	16.8	300 *	16.3
EtO-treated AlSt	1	17.7	449.9	16.6
EtO-treated AlSt and drug	1	16.8	379.3	15.7
Irradiated AlSt	2	22.8	732.0	20.0
Irradiated AlSt and drug	2	21.2	888.1	19.2
Heat-treated gel, 140°C, 30 min	3	31.1	2146.2	27.1
Heat-treated gel, 140°C, 30 min and drug	3	19.6	503.2	17.9

Measuring system — Contraves KP-1
$D_{max} = 3950\ s^{-1}$; AlSt = aluminium monostearate.
* Below instrument sensitivity.

gels and non-heat-treated gels are apparent on incorporation of microfine drug particles. The results suggest physical interaction between drug and vehicle.

Assessment of 5-fluorouracil / organogel formulations in glass ampoules

Miglyol 812N was selected in preference to other oils because of its lower viscosity (Table 1) making syringeability easier. Gels containing 26.25 $mg \cdot ml^{-1}$ 5-fluorouracil prepared by the various described methods were filled into 2 ml (nominal) glass ampoules and sealed. Filling was carried out using a manually operated syringe unit fitted with a 2-way valve (A R Horwell) and wide bore (2 mm) filling needle. Samples were stored at ambient temperature for 3 months, and subjectively assessed after 1 week, 1 month and 3 months. The sedimentation condition of the 5-fluorouracil was assessed by comparison with a control containing no aluminium monostearate, and the ease of redispersion was assessed by inversion and gentle shaking of the ampoule, and comparison with the controls. The thixotropic nature of the gels manufactured from irradiated and ethylene oxide treated aluminium monostearate did not prevent sedimentation of drug particles. An element of retardation was observed, and hence the higher aluminium monostearate concentrations were more effective in this respect. The sediment was tightly packed and difficult to redisperse.

In contrast to this the heat treated gels showed gradual sedimentation, although their viscosity values were less than the irradiated and ethylene oxide samples.

Redispersion of the drug in the heat-treated gels was also relatively easy and the samples showed some separation of components, as described previously.

The results indicate the heat-treated gels to be less structured than the gels prepared from treated components, but to be more effective in providing a suitable vehicle to achieve a readily dispersible product. In the control samples, the 5-fluorouracil formed a cake at the bottom of the ampoule, which did not readily disperse on shaking.

Finally, the work described illustrates the complexity of aluminium monostearate–oil systems and in particular the sensitivity of formulations to processing conditions. Nevertheless, such vehicles do provide opportunities for development of drug suspensions having satisfactory physical stability characteristics and controlled drug delivery.

Acknowledgements

The technical assistance of Miss Karin J. Humes in the preparation of gels and suspensions and carrying out of some of the rheological work is gratefully acknowledged. Thanks are also due to Mr. A. Kern for the GLC analysis.

References

Armstrong, N.A. and James, K.C., Drug release from lipid based dosage forms. Int. J. Pharm., 6 (1980) 185–193.

Attwood, D. and Florence, A.T., Surfactant Systems, Chapman and Hall, London, 1983, 594 pp.

Ballard, B.E., Biopharmaceutical considerations in subcutaneous and intramuscular drug administration. J. Pharm. Sci., 57 (1968) 357–378.

Bristol Laboratories, British Patent 665367, 1952.

Bristol Laboratories, U.S. Patent 2690414, 1954.

Buckwalter,F.H. and Dickison, H.L., A new absorption delaying vehicle for penicillin. J. Amer. Pharm. Assoc., Sci. Ed., 37 (1948) 472–474.

Chien, Y.W., Long-acting parenteral drug formulations. J. Parenteral Sci. Technol., 35 (1981) 106–139.

Coles, C.L.T., Heath, K.R., Hilton, M.L., Lees, K.A., Muggleton, P.W. and Walton, C.A., Adjuvant effect of aluminium monostearate paraffin gels on antitoxin response. J. Pharm. Pharmacol., 17 (1965) 87S–91S.

Davis, S.S. and Khanderia, M.S., Rheological characterisation of plastibases and the effect of formulation variables on the consistency of these vehicles. Int. J. Pharm. Tech. Prod. Mfr., 1 (1980) 11–17.

Ekwall, P., Danielsson, I. and Stenius, P., Aggregation in surfactant systems. In Kerker, M. (Ed.), International Review of Science, Physical Chemistry, Series 1, Vol. 7, Butterworths, London, 1972, pp. 97–145.

Lee, V.H.L. and Robinson, J.R., Methods to achieve sustained drug delivery. The physical approach: oral and parenteral dosage forms. In Robinson, J.R. (Ed.), Sustained and Controlled Release Drug Delivery Systems, Marcel Dekker, New York, 1978, pp. 123–209.

McLaughlin, C.A. and Goldberg, E.P., Local chemo- and immuno-therapy by intratumour injection: Opportunities for polymer–drug compositions. In Goldberg, E.P. (Ed.), Targeted Drugs, John Wiley and Sons, New York, 1983, pp. 231–268.

Morrison, J.C. and Stephens, J.S., Some properties and applications of aluminium stearate gels. Amer. Perfum. Cosmet., 82 (1967) 53–56.

Rideal, E.K., A discussion on the physics and chemistry of hydrocarbon gels, Proc. Roy. Soc. B, 200 (1950) 136.

Syntex (USA) Inc., U.K. Patent Application 20052258A, 1981.