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Interaction of a nonionic surfactant-based organogel with aqueous media

Sudaxshina Murdan, Gregory Gregoriadis, Alexander T. Florence *

Centre for Drug Delivery Research, School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK

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Abstract

In an attempt to explain the rather short half-life of molecules at the injection site after their intra-muscular administration in a sorbitan monostearate organogel, in vitro studies were carried out to study the effects of an aqueous medium (simulating interstitial fluid at injection site) on the physical form of the organogel. When the gel mass comes in contact with an aqueous phase, the latter penetrates into the organic gel via the sorbitan monostearate tubular network, resulting in gel breakdown into smaller fragments. The surfactant tubular network act as a conduit for water penetration into the gel. Meanwhile, emulsification, aided by the surfactants present in the gel, also occurs at the gel surface between the organogel and the aqueous phase. This leads to a gradual erosion of the gel as oil droplets bud off from the gel mass. From these in vitro observations, we speculate that after gel administration in vivo, dynamic interactions occur between the local interstitial fluid and the gel mass: fluid penetration into the gel and emulsification at the gel surface is thus responsible for gel breakdown and so a relatively short duration of drug at the injection site.

Keywords: Organogel; Interactions with aqueous media; Short depot

1. Introduction

We have previously reported the gelation of a number of organic solvents e.g. hexane, hexadecane, isopropyl myristate, vegetable oils by the non-ionic surfactant, sorbitan monostearate (Yoshioka and Florence, 1994; Murdan et al., 1996). The latter is a small (MW 431), hydrophobic (HLB 4.1) molecule (Fig. 1) which gels the above (and several other, but not all) organic solvents at concentrations as low as 1–10% w/v. The organogels are prepared by dissolving/dispersing the sorbitan monostearate in a particular solvent at 60°C and allowing the solution/suspen-

* Corresponding author. Tel.: +44-171-753-5819; fax: +44-171-837-5092.

E-mail address: a.t.florence@ulsop.ac.uk (A.T. Florence)

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sion which is formed to cool and thereby set to the gel state. Cooling the sol phase results in a reduction in the gelator solubility in the solvent and the consequent decrease in solvent–gelator interactions causes the surfactant molecules to self-assemble into what we believe to be tubular aggregates. The latter associate with one another, junction points are formed and a three-dimensional network is established which immobilises the solvent. The resulting physical gels are opaque, thermoreversible, with a smooth 'silky' feel. Light microscopy reveals the gels to consist of an interconnected network of tubular aggregates dispersed in the liquid medium (Fig. 2).

A hydrophilic surfactant, polysorbate 20 (polyoxyethylene sorbitan monolaurate) was included in some organogel formulations as it increases gel stability in long-chain ($C > 14$) solvents (Murdan et al., 1996). Polysorbate 20 enhances the solubility of sorbitan monostearate in these solvents, perhaps via the formation of mixed inverse micelles. The enhanced solubility of the gelator in the liquid dispersing medium seems to favour stable gel formation. It is anticipated that upon cooling the sol phase (sorbitan monostearate/polysorbate 20/solvent), the polysorbate molecules are most likely to be incorporated within the bilayer membranes of the tubular aggregate network, the most favourable location for the hydrophilic polysorbate molecules (HLB 16.7) in the non-aqueous oil medium. As a result, the interior of the surfactant tubules would acquire a more hydrophilic nature.

We have proposed that these sorbitan monostearate organogels can be used as delivery vehicles for hydrophilic and hydrophobic drugs and vaccines. The gels may also provide sustained release of appropriate active entities after intramuscular and subcutaneous administration. Oily vehicles are localised at the site of injection and some form a pea-shaped depot following intramuscular or subcutaneous administration (Shaffer, 1929), unlike aqueous formulations which spread along the muscle fibres. Organogels were expected to behave similarly, to form a localised depot and gradually release drug or vaccine to the surrounding medium after injection. In an attempt to explain the rather short duration of the drug at the injection site, we have studied the effects of an aqueous medium on the physical form of the organogel.

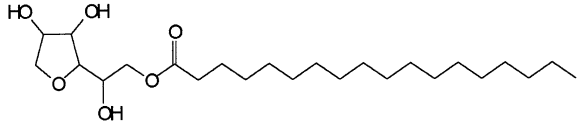

Fig. 1. Molecular structure of sorbitan monostearate, the organogelator in this study.

2. Materials and methods

2.1. Materials

Sorbitan monostearate was purchased from Sigma (UK) and used as received. Like most sorbitan esters, sorbitan monostearate is a mixture of sorbitan esters, with the stearate and palmitate esters predominating. Polysorbates 20 and hexadecane were purchased from Fluka (UK). The organic solvent, hexadecane, was dried in a vacuum oven (Gallenkemp, UK) at room temperature overnight, to ensure the absence of any moisture which might affect gelation. Oil-Red-O dye was from Sigma while toluidine blue was from Raymond A. Lamb, waxes and general laboratory supplies, London.

2.2. Gel preparation

Sorbitan monostearate (10% w/v) and polysorbate 20 (2% w/v) were weighed into a glass vial. Hexadecane was added and the vial incubated in a water-bath at 60°C for a few minutes. The surfactants dissolved in the organic liquid and a clear, transparent solution was obtained. On cooling to room temperature, the solution set to an opaque, semi-solid, thermoreversible organic gel.

2.3. In vitro studies

The organogel was placed on a microscope slide and a drop of aqueous phase (water/toluidine blue solution) was made to contact the gel (with/without dissolved Oil-Red-O dye), using a Pasteur

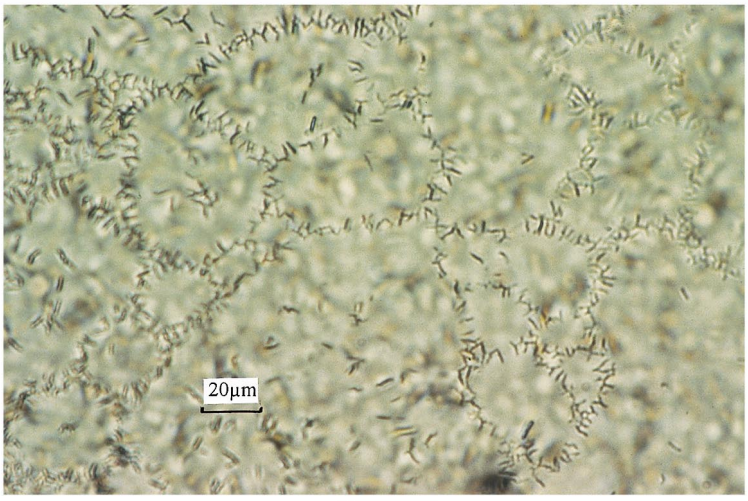

Fig. 2

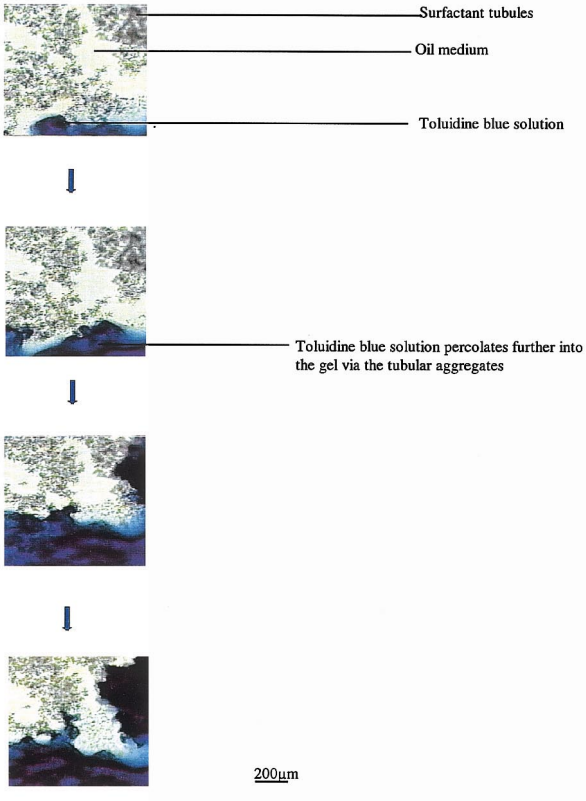

Fig. 3

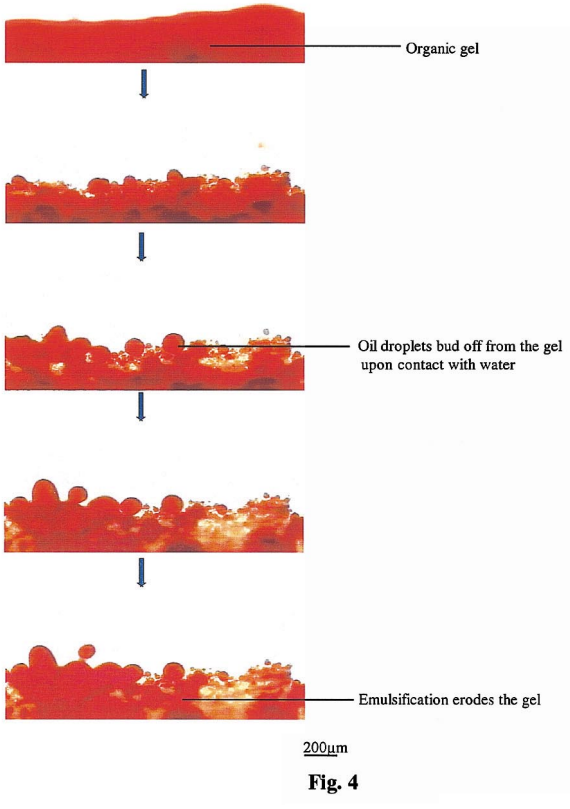

Fig. 4

Fig. 2. An interconnected network of tubular aggregates in sorbitan monostearate/isopropyl myristate organogel.
Fig. 3. Video stills showing the penetration of aqueous phase (toluidine blue solution) into the organogel (sorbitan monostearate/polysorbate 20/hexadecane) through the tubular network. The whole sequence took approximately 1 min. Scale bar: 200 μm.
Fig. 4. Video stills showing emulsification occurring between the oil phase, hexadecane (containing Oil-Red-O dye) and water at the gel surface. The gel consequently erodes. The whole sequence took approximately 20 s. Scale bar: 200 μm.

pipette. The inclusion of the water-soluble toluidine blue and the oil-soluble Oil-Red-O dyes enable the recognition of the aqueous and the organic phase respectively. The events subsequent to contact between the gel and the aqueous phase were followed and recorded using a light microscope (Nikon, Microphot-FXA, Japan) attached to a video recorder (Samsung, Japan) via a camera (Panasonic F15, Japan).

3. Results and discussion

Upon contact with the gel, the toluidine blue solution penetrates into the organic gel mass as illustrated in the sequential pictures in Fig. 3. The movement of the aqueous solution seems to occur solely through the tubular surfactant network which will provide convenient hydrophilic pathways within the organogel. The surfactant tubules act as conduits for water penetration into the gel. Such an invasion by the aqueous phase into the gel results in the gradual break-up of the gel mass into smaller fragments as the gel skeleton is compromised.

Meanwhile, emulsification, aided by the surfactants present in the gel, occurs at the gel surface between the organogel and the aqueous phase. Oil droplets are seen to bud off from the gel surface causing the gel to slowly erode (Fig. 4). The two processes, of water penetration into the gel and emulsification at the gel surface occur simultaneously when the gel is in contact with water.

From these in vitro observations, we speculate that after gel administration in vivo, interstitial fluid present in the surrounding tissue penetrates the organogel via the surfactant tubular network and the gel fragments. Emulsification between the interstitial fluid and the organogel also occurs, resulting in gel surface erosion. An oil-in-water (o/w) emulsion may thus be produced in situ after intramuscular/subcutaneous administration of the organogel. These events may, however, occur at a slow rate in vivo, considering the small amount of interstitial fluid present in muscle/subcutaneous tissue. After the organic gel has broken down, the o/w emulsion formed in situ (together with any drug solubilised in the organogel) may persist at the site of injection for some time. Active entities solubilised in the organogel may thus be initially released from the gel but subsequently from the emerging o/w emulsion.

These in vitro investigations have given us some insight into the dynamic interactions which may occur after gel administration in vivo. The higher apparent bulk viscosity of the gels (compared to the parent oils) may suggest a more compact-shaped depot at the injection site and a subsequently a slower release rate of drugs compared to those produced by simple oil solutions or suspensions. These investigations have shown, however, that the organogel formulations discussed here are likely to drastically change through interactions with the host. The nature of the gel, which comprises surfactant tubules with hydrophilic interiors, promotes the movement of tissue fluids into the gel and is finally responsible for its breakdown and the rather short-lived depot.

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