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Amphiphilogels as drug carriers: effects of drug incorporation on the gel and on the active drug

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Abstract

Amphiphilogels (a subset of organogels) are being studied as drug carriers in our laboratories. In this paper, the effects of drug incorporation on the drugs and the gels are discussed. Amphiphilogels were prepared by heating a mixture of the gelator (sorbitan monostearate or sorbitan monopalmitate) and the liquid (e.g. Tweens or liquid Spans) to form a solution/dispersion, which was cooled to the gel state. Drugs were dissolved by heating a mixture of the drug and the gel and cooling the resulting solution. Hydrophilic gels (composed of hydrophilic Tweens as the liquid) were more effective solvents than hydrophobic ones (composed of hydrophobic Span 20 or 80 liquids). The latter's solvent capacity could, however, be increased by the inclusion of co-solvents, such as propylene glycol and ethanol. Drug incorporation at 10% w/w did not cause any detrimental changes in gel stability, while the drug's release rate was dependent on its concentration and on the nature of the gel's liquid component (which influences drug solubility), but not on gelator concentration or on the method of drug incorporation. This study shows the importance of the nature of the gels' liquid component and the possibility of using hydrophilic amphiphilogels as solvents for poorly water-soluble drugs.

Introduction

In recent years, interest in organogels has increased dramatically with the (often serendipitous) discovery and synthesis of a very large number of diverse molecules that gel a range of organic solvents at low concentrations (typically a few weight percent). Most of the organogelators are relatively small molecules (MW 3000 Da) and they have been called low-molecular-weight organogelators (LMOGs). The latter and related organogels have been reviewed by a number of authors (Hinze et al 1996; Terech & Weiss 1997; Abdallah & Weiss 2000; Van Esch & Feringa 2000; Gronwald et al 2002; Murdan 2005). One of the drivers of the growing research on organogelators and their gels is the range of potential applications, including drug delivery, immobilisation of enzymes for biocatalysis, synthesis and transformation of toxic wastes, separation technology, temperature sensors, flatbed displays, recovery of oil spills, templates for the creation of inorganic structures, etc.

In our laboratories, we have formulated novel organogels where the liquid component is a surfactant, and have termed these amphiphilogels, based on the amphiphilic nature of the liquid component (Murdan et al 1998). The non-ionic sorbitan ester surfactants, sorbitan monostearate (Span 60) or sorbitan monopalmitate (Span 40), have been used as the gelators, while polysorbates (Tweens) and liquid sorbitan esters have been used as the liquid component. Depending on the hydrophilicity/hydrophobicity of the gel's liquid component, hydrophilic or hydrophobic amphiphilogels can be produced. These gels are being investigated as oral and transdermal delivery vehicles for drugs and antigens. Their physico-chemical properties, skin irritancy and potential as oral vehicle have been investigated (Jibry & Murdan 2004; Jibry et al 2004; Murdan et al 1999, 2005). The gels caused little irritancy to the skin (in mice and in man) when applied twice a day for five consecutive days, while in-vivo experiments in rats and dogs showed good oral bioavailability of the poorly water-soluble drug ciclosporin when the latter was solubilised within amphiphilogels.

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Drug incorporation in organogels affects the drug (e.g., the solubility of certain drugs, such as broxaterol and nifedipine in lecithin gels was enhanced compared with the neat liquid (Willimann et al 1992)). Drug incorporation can also change the gel's properties (e.g., the viscosity of Eudragit and lecithin gels was found to decrease with increasing drug content, while addition of high concentrations of indometacin and diclofenac destroyed lecithin organogels (Goto et al 1991; Dreher et al 1997)). Care must be taken, therefore, when drugs are dissolved or suspended in organogels and the drug-containing formulations must be thoroughly characterised. Currently, the literature on the influence of drug incorporation on the physico-chemical properties of organogels is limited.

In this paper, we report the effects of drug incorporation on the properties of the amphiphilogels and of the active entity. The solubility of model hydrophobic drugs, enhancement of solubility by the inclusion of co-solvents (ethanol, propylene glycol), drug release from the gel and the effects of drug incorporation on the gel properties are discussed. Aspirin, paracetamol, ibuprofen and hydrocortisone were used as model hydrophobic drugs.

Materials and Methods

Materials

Sorbitan monostearate (Span 60), sorbitan monopalmitate (Span 40), sorbitan monolaurate (Span 20), sorbitan monooleate (Span 80), polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan monopalmitate (Tween 40), polyoxyethylene sorbitan monooleate (Tween 80), ibuprofen and hydrocortisone were purchased from Sigma-Aldrich (UK) and used as received. Paracetamol and aspirin were obtained from BASF Pharma (UK) and Rhone-Poulenc (UK), respectively. Phosphate-buffered saline (PBS), pH 7.4, was prepared using sodium chloride, disodium hydrogen orthophosphate 12-hydrate and potassium dihydrogen orthophosphate, all from BDH (UK). Visking cellulose dialysis tubing, size 8, with a molecular-weight cut-off point of 12000–14000 Da was from Medicell International Ltd (UK). Distilled water was used throughout.

Gel preparation

The amphiphilogels were prepared by weighing the gelator (10 or 20% w/w sorbitan monopalmitate (Span 40) or sorbitan monostearate (Span 60)) and the liquid (liquid Spans or Tweens) in glass jars, which were closed and placed in a water bath at 60°C. The solid was dissolved/dispersed in the liquid to obtain a solution/dispersion. The latter was cooled by standing at room temperature overnight, whereupon it set into an opaque, semi-solid gel.

Co-solvents (ethanol, propylene glycol) were included in amphiphilogels to enhance the solubility of the poorly water-soluble drugs. These gels were prepared by weighing appropriate quantities of the co-solvent and the amphiphilogel into a glass vessel, which was placed in a water-bath at 60°C until the gel melted. The mixture was mixed, then allowed to cool as described above. Ethanol and propylene glycol were included at maximum 5 and 15% w/w, respectively, in 20% w/w Span 60 in Span 20 gels, as greater concentrations resulted in the loss of the gel state.

Solubility of hydrophobic drugs in amphiphilogels

To determine whether the amphiphilogels could be suitable vehicles for poorly water-soluble drugs, the solubility of the model drugs aspirin, paracetamol, ibuprofen and hydrocortisone in a number of gels was determined. Hydrophilic amphiphilogels (where the liquid component was Tween 20, 40 or 80), hydrophobic amphiphilogels (where the liquid was Span 20 or 80) and hydrophobic gels containing the co-solvents ethanol and propylene glycol were tested. The gelator (Span 40 or Span 60) was present at 10 or 20% w/w. Drug solubility was determined by equilibrating, in separate vessels, increasing amounts of drug in gel and determining the highest concentration of drug that could be dissolved (James 1986). Because of the opacity of the gels, the extent of drug dissolution could not be determined by visually examining the gels for undissolved drugs. Therefore, the sol state was used. Drug–gel mixtures of pre-planned drug concentrations (e.g., 0.5, 1, 1.5% w/w), increasing by 0.5% w/w increments, were prepared and incubated at 60°C for 24 h, before the solution/suspensions were examined for undissolved drug. This method of solubility determination does not yield an exact value of solubility, but gives an underestimate by a maximum of 0.5% w/w. Five replicates of each drug–gel system were prepared, except for when the gel included ethanol and propylene glycol, when 3 replicates were produced. The cooled drug–gel systems were examined by light and polarised light microscopy to confirm drug dissolution and the absence of drug crystals.

The solubility of the drug in the neat liquids and in water was also tested. Solubility in the neat liquid was determined as described above. Aqueous solubility of paracetamol and aspirin was determined by the preparation of saturated drug solutions, filtration and measurement of UV absorbance using a UV spectrophotometer (Pharmacia Biotech Ultraspec 2000). The aqueous solubilities of ibuprofen and hydrocortisone were too low to be determined by this method and the literature values were used (Lund 1994; British Pharmacopoeia 2002).

Effect of drug incorporation on gel microstructure and on gelation temperature

The effect of drug dissolution on gels was tested by examining drug-loaded gels microscopically and investigating changes in gelation temperatures, if any, gelation temperatures being an indication of gel stability. The drug was dissolved by weighing appropriate quantities of drug and gel in a vial, which was placed in a water-bath at 60°C, whereupon the gel melted and the drug dissolved. The resulting solution was then cooled and it set into an opaque, semi-solid gel. Eight different gels (composed of Span 40 or Span 60 gelator at 10 or 20% w/w, in Tweens 20, 40 or 80, as shown in Table 2), loaded with 10% w/w paracetamol, aspirin or ibuprofen, were

prepared to determine the influence of drug and gel natures on changes in gel stability. To determine influence of drug concentration, 20% Span 60 in Tween 20 gels were loaded with paracetamol, aspirin or ibuprofen at 2, 4, 6, 8, 10 and 15% w/w.

Gel microstructure was determined by light and crossed polarised microscopy. A thin smear of the gel was placed on a microscope slide, covered with a cover slip and observed under a Nikon Microphot-FXA (Japan) light microscope equipped with a Linkham hot-stage and camera (Nikon FX-35DX, Japan).

Gelation temperatures (temperature at which gel-to-sol or sol-to-gel transition occurs) were measured using a Bibby Stuart Scientific Melting Point SMP1 apparatus. The gel was introduced into a capillary tube (100 mm length, 1.3–1.4 mm o.d.) by dipping the tube into the semi-solid (some gel would rise up the tube by capillary action) to obtain a sample of approximately 5 mm in length within the tube. The sample was then drawn up the tube to approximately 3 mm from the lower end of the tube using a syringe. The gel-filled tubes were placed in the melting point apparatus and the temperature was increased by $1°C\,min^{-1}$. Gel melting point (gelation temperature) was taken as the temperature at which the gels melted into an isotropic liquid that flowed down the capillary tube. The melting temperatures of five samples were measured for each gel, and a mean was calculated.

Release of hydrophobic drugs from gels

Release experiments were conducted to determine the effects of drug nature (paracetamol, aspirin, ibuprofen) and concentration (5 or 10% w/w), the method of drug incorporation (simple mixing into gel or dissolution into the sol state) and the nature of the gel on drug release rates. Drugs were dissolved in the gels as described in the previous section. Mixing allowed drug incorporation into hydrophobic Span 20 and Span 80 gels where drug solubility was low. To mix the drug in the gel, the required amounts of drug and gel were weighed in a glass vial and mixed using a glass rod. In this case, drug particles were dispersed within the gel. Release studies were carried out at $22 \pm 1°C$ using Franz-type vertical diffusion cells and a Visking membrane. The receptor chamber was filled with PBS and 1 g of gel sample was placed in the donor chamber, which was then closed with a screw-cap. The experiment was conducted for 6 h; 0.5-mL samples of the receptor phase were taken hourly and analysed for drug content by UV, at 239 nm for paracetamol, 267 nm for aspirin and 216 nm for ibuprofen. An equal volume of fresh PBS replaced the samples taken out. Adjustments were then made in the calculations to account for the samples taken out. The experiments were repeated 3 times for each formulation of paracetamol and aspirin, and five times for each formulation of ibuprofen. Blank gel samples were also run simultaneously to check for any interference with UV absorbance.

Statistical methods

Two-way analysis of variance, followed by post-hoc Tukey HSD tests, was conducted to analyse the influence of the nature of the solvent and that of the gelator and their concentrations on drug solubility. The same statistical tests were used to analyse the effects of drug incorporation at 10% w/w, drug concentrations (0–15% w/w) and natures of drug and of the gel on gelation temperatures. Drug release rates were analysed by Kruskal–Wallis test, followed by Nemenyi's tests to determine the effects of drug concentration in donor, the method of drug incorporation (simple mixing into gel or dissolution into the sol state), the nature of the gel (hydrophilicity/hydrophobicity, nature of liquid) and gelator concentration on release rates. All the experiments were replicated 5 times, except for release studies with aspirin- and paracetamol-loaded gels, which were repeated 3 times.

Results and Discussion

Amphiphilogel formation and microstructure

Amphiphilogels were prepared using a very simple method; the gelator (Span 60 or Span 40) and the liquid (e.g. Tween 20) were mixed and heated until the gelator dissolved or dispersed in the latter. The sol state was then cooled and it set to an opaque, smooth, semi-solid gel. Light microscopy revealed tubular structures arranged in clusters (Figure 1). Cooling of the sol phase results in reduced gelator solubility in the solvent and, consequently, reduced gelator–solvent affinities. As a result, gelator molecules come out of solution and self-assemble into aggregates, which interact (via junction points) and form a 3-dimensional network that immobilises the liquid component. It is expected that some (probably very little) gelator will remain dissolved in the liquid, depending on solubility. This simple method of organogel preparation, based on gelator solubility in the liquid at high temperatures and insolubility at room temperature, is commonly used in the preparation of the majority of organogels (Murdan 2005).

The amphiphilogels have previously been investigated using light, polarised light and scanning electron microscopy (SEM), as well as small-angle neutron scattering (SANS) (Jibry et al 2004). SEM showed the existence of connections among gelator aggregates; these connections

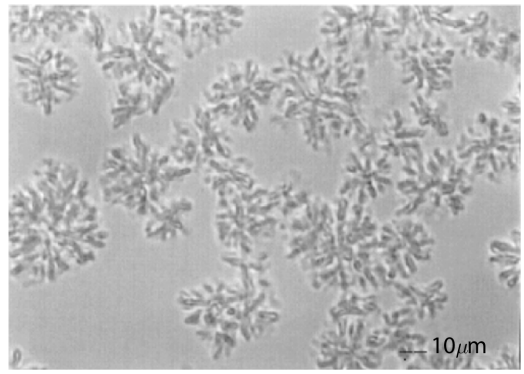

Figure 1 Light micrograph of a 20% w/w Span 60 in Span 85 amphiphilogel. Gel microstructure consists of tubular clusters. Bar = 10 μm.

allow a 3-dimensional network to be formed, while SANS indicated that the tubules seen in Figure 1 are composed of stacks of bilayers of gelator molecules and that each bilayer is separated from adjacent ones by a layer of the liquid component. Polarised light microscopy has shown crystallinity of the tubular structures, but not of the liquid. Crystallinity of the tubules is thought to be related to a liquid crystalline nature of the gelator bilayers that make up the tubules.

Solubility of model hydrophobic drugs in amphiphilogels

To determine whether the amphiphilogels could be used as carriers for poorly water-soluble drugs, the solubility of 4 model drugs (paracetamol, aspirin, ibuprofen and hydrocortisone) in various hydrophilic and hydrophobic gels, in the corresponding neat liquids and in water was measured (Table 1). The latter shows the low aqueous solubility of all four drugs, the low solubility of hydrocortisone in all the gels and the poor solvent capacity of hydrophobic gels and of the corresponding neat Span 20 and Span 80 for all 4 drugs.

In contrast, the hydrophilic amphiphilogels and the corresponding neat Tweens dissolved paracetamol, aspirin and ibuprofen to appreciable extents. Examination by light and polarised light microscopy of gels containing drugs below the saturation solubility revealed no drug precipitation. This shows that the drugs dissolved in the sol state at 60°C remained dissolved within the gel upon cooling. The solubility of paracetamol, aspirin and ibuprofen in the hydrophilic solvents (liquid Tweens and hydrophilic gels) was analysed by two-way analysis of variance, followed by post-hoc Tukey HSD tests to determine the influence of solvent (gel/liquid Tweens), and of gelator nature (Span 60 or 40) and concentration (10 or 20% w/w) on drug solubility. Statistically significant main effects of drug nature ($F(2, 132) = 14006.17$; $P < 0.0005$) and of solvent ($F(10, 132) = 128.15$, $P < 0.0005$), as well as an interaction effect between drug nature and solvent ($F(20, 132) = 10.66$; $P < 0.0005$) were found. That is, drug solubility in the various solvents was dependent on both the nature of the solvent and of the drug.

Solubility of paracetamol, aspirin and ibuprofen in the hydrophilic gels and the corresponding neat Tweens and insolubility in the hydrophobic gels and corresponding neat Spans (Table 1) indicates the importance of the liquid component of the gel as the solvent for drug dissolution. This was confirmed by the fact that solubilisation of ibuprofen, aspirin and paracetamol was greater in the neat Tweens 20, 40 and 80 than in the corresponding gels ($P < 0.0005$). This is due to the presence of greater amount of the solvent (100% for the neat liquids compared with 80 or 90% w/w in the gels (gelator making up the rest of the gel)). In addition, increasing gelator concentrations (10–20% w/w in Tween 40 gels; i.e. decreasing the liquid concentration) resulted in decreased drug solubility ($P < 0.0005$). The nature of the gelator (i.e. Span 40 or Span 60) on the other hand did not have any effect on drug solubility ($P > 0.01$). We can deduce, therefore, that the drugs are mainly dissolved in the liquid part of the hydrophilic amphiphilogels.

When the influence of the nature of the Tween (i.e. Tween 20, 40 or 80) on drug solubility was analysed by two-way analysis of variance separately for each drug, no obvious relationship between the nature of the Tween and drug solubility was found, except for the statistically significant higher solubility of ibuprofen in Tween 80 (compared with Tween 20 and 40), which was reflected in the statistically significant differences between ibuprofen solubility in Tween 80 gels compared with those of Tweens 20 and 40 ($P < 0.01$). Tween 80 and its gels proved to be better solvents for ibuprofen, but not for aspirin and paracetamol whose solubility was similar in the three Tweens.

The low solvent capacity of Span 20 and Span 80 gels for the model drugs was mentioned earlier (Table 1). The low

Table 1 Solubility of model drugs paracetamol, aspirin, ibuprofen and hydrocortisone

Solvent	Drug solubility (% w/w)			
	Paracetamol	Aspirin	Ibuprofen	Hydrocortisone
Water	1.78 ± 0.12	0.33 ± 0.03	<0.01	<0.01
Tween 20	14.00 ± 0.71	20.70 ± 0.45	29.70 ± 0.57	0.80 ± 0.27
20% Sp40/Tw20	11.50 ± 0.35	19.50 ± 0.35	26.70 ± 0.57	0.50 ± 0.35
20% Sp60/Tw20	11.00 ± 0.35	17.90 ± 0.55	26.80 ± 0.45	0.50 ± 0.35
Tween 40	14.40 ± 0.42	20.40 ± 0.42	30.60 ± 0.55	0.70 ± 0.45
10% Sp40/Tw40	12.80 ± 0.57	17.80 ± 0.57	27.50 ± 0.35	0.30 ± 0.27
10% Sp60/Tw40	12.60 ± 0.55	18.00 ± 0.35	27.50 ± 0.35	0.50 ± 0.35
20% Sp40/Tw40	10.50 ± 0.35	17.50 ± 0.35	25.90 ± 0.55	0.30 ± 0.27
20% Sp60/Tw40	10.80 ± 0.45	17.30 ± 0.57	27.20 ± 0.57	0.40 ± 0.22
Tween 80	13.70 ± 0.76	21.50 ± 0.00	32.00 ± 0.71	1.00 ± 0.00
20% Sp40/Tw80	12.10 ± 0.65	20.20 ± 0.57	28.90 ± 0.65	0.50 ± 0.35
20% Sp60/Tw80	12.60 ± 0.22	19.50 ± 0.35	30.10 ± 0.65	0.40 ± 0.22
Span 20	0.40 ± 0.22	0.00 ± 0.00	1.30 ± 0.27	0.20 ± 0.27
20% Sp40/Sp20	0.50 ± 0.00	0.10 ± 0.22	0.80 ± 0.27	0.00 ± 0.00
20% Sp60/Sp20	0.10 ± 0.22	0.00 ± 0.00	0.70 ± 0.27	0.10 ± 0.22
Span 80	0.00 ± 0.00	0.00 ± 0.00	1.50 ± 0.00	0.00 ± 0.00
20% Sp60/Sp80	0.10 ± 0.22	0.20 ± 0.27	0.70 ± 0.45	0.00 ± 0.00

Data are expressed as mean ± s.d., n = 5. Sp, Span; Tw, Tween.

drug solubility can, however, be increased by the inclusion of organic solvents, such as ethanol and propylene glycol, which results in an increased solvent capacity of the gel for the solute. For example, a 20% Span 60 in Span 20 gel containing 15% w/w propylene glycol dissolved aspirin and ibuprofen at 5 and 27% w/w, respectively, compared with 0 and 5% w/w in the absence of propylene glycol. Similarly, inclusion of 3% w/w ethanol in the same parent hydrophobic gel enhanced solubility of aspirin and ibuprofen to 2 and 8% w/w, respectively. Increasing the concentration of ethanol resulted in increased solvent capacity of the gel and, consequently, in increased drug solubility. Thus, inclusion of 5% w/w ethanol enabled the dissolution of 3 and 11% w/w of aspirin and ibuprofen, respectively. For all the gels, the solubility experiment was conducted in triplicate and all three gave the same values for solubility.

The extent to which drug solubility in hydrophobic amphiphilogels can be enhanced by inclusion of a co-solvent is limited by the amount of co-solvent that may be incorporated before the gel state is lost. For example, propylene glycol and ethanol can be incorporated at maximum 15 and 5% w/w, respectively, within a 20% w/w Span 60 in Span 20 amphiphilogel. Addition of these co-solvents changes the gel microstructure as well as its consistency. Light and polarised light microscopy reveal the presence of fewer gelator aggregates (data not shown). This results in fewer interactions between aggregates and a less cohesive 3-dimensional gelator network, which traps and immobilises the liquid to a lesser degree, and this leads to the gel becoming softer and more liquid-like. Such changes in the gel, followed by gel breakdown at higher co-solvent concentrations, are due to the changed nature of the liquid component. For example, when a co-solvent, such as ethanol, is included in the amphiphilogel, the solubility of the gelator (e.g. Span 60) in the liquid (e.g. Span 20 + ethanol) is increased, ethanol being a solvent for the Span 60 gelator. The importance of gelator solubility in the liquid component at high temperature and insolubility at room temperature for gelator self-assembly and gel formation at room temperature was discussed above. When the solvent capacity of the liquid for the gelator is increased, fewer gelator molecules self-assemble into aggregates upon cooling of the sol state. At high co-solvent concentrations, the number of gelator aggregates formed is insufficient to form a connected network and the gel state is lost.

Such a disruptive effect of ethanol on gelation has also been reported for the organogelator, *N*-lauroyl-L-alanine methyl ester, and it is being exploited to form gels in-situ as drug delivery vehicles. A gel is formed at the injection site following the subcutaneous injection of a gelator/liquid/ethanol solution upon ethanol diffusion away from the formulation into the surrounding tissues (Couffin-Hoarau et al 2004).

Effect of drug incorporation on amphiphilogels

Solubilisation of paracetamol, aspirin and ibuprofen in hydrophilic amphiphilogels at 10% w/w (below the saturation solubility limit) caused no obvious changes in gel microstructure (data not shown), but did cause small, statistically significant, changes in the gelation temperatures (Table 2). To analyse the effects of drug presence (at 10% w/w), drug nature and gel type on the gelation temperatures, the latter were analysed by two-way analysis of variance. Statistically significant main effects of drug presence and nature ($F(3, 128) = 43.03$; $P < 0.0005$) and of gel type ($F(7, 128) = 364.92$, $P < 0.0005$), as well as an interaction effect between solubilisation of drug and its nature and gel type were found ($F(21, 128) = 1.739$; $P = 0.03$)). Post-hoc comparisons using the Tukey HSD tests indicated that drug incorporation resulted in a statistically significant change in gelation temperatures for all 3 drugs ($P < 0.0005$). From Table 2, it can be seen that the gelation temperatures of drug-loaded gels were slightly higher than those of the corresponding blank gels, except for ibuprofen in 20% Span 40 in Tween 20 gel. The increases in gelation temperature are relatively small and show that paracetamol, ibuprofen and aspirin can be loaded in the amphiphilogels in Table 2 at 10% w/w, without any major change in gel stability, gelation temperature being one indication of gel stability. The possible reasons for the slight increase in gelation temperature upon drug dissolution and the influence of drug nature are discussed in the following paragraph.

The gel type, which had a significant effect on gelation temperature, depends on the nature of the gelator (Span 40 or Span 60), its concentration in the gel (10 or 20% w/w) and the nature of the liquid (Tween 20, 40 or 80). The post-hoc Tukey tests showed significantly different gelation temperatures of drug-loaded Span 60 and Span 40 gels ($P < 0.005$). Span 60 gels have higher gelation temperatures than Span 40 gels

Table 2 Gelation temperatures of gels (blank and loaded with paracetamol, aspirin or ibuprofen at 10% w/w)

Gel	Gelation temperature (°C)			
	No drug	Paracetamol	Aspirin	Ibuprofen
20% Sp40/Tw20	40.8 ± 0.8	42.4 ± 0.9	42.4 ± 0.5	40.4 ± 0.5
10% Sp40/Tw40	33.0 ± 1.0	35.0 ± 1.0	35.6 ± 1.7	34.6 ± 2.1
20% Sp40/Tw40	38.0 ± 0.7	40.8 ± 1.8	41.0 ± 1.2	41.4 ± 1.8
20% Sp40/Tw80	37.6 ± 0.9	40.2 ± 1.3	40.8 ± 0.8	40.8 ± 0.8
20% Sp60/Tw20	48.8 ± 0.8	51.0 ± 1.4	50.6 ± 1.3	50.6 ± 0.5
10% Sp60/Tw40	43.0 ± 1.0	46.2 ± 1.8	45.0 ± 1.0	44.0 ± 1.6
20% Sp60/Tw40	46.2 ± 0.8	50.2 ± 0.8	48.6 ± 1.3	47.2 ± 0.8
20% Sp60/Tw80	42.0 ± 1.2	45.0 ± 1.2	44.6 ± 0.9	43.2 ± 0.8

Data are expressed as mean ± s.d., n = 5. Sp, Span; Tw, Tween.

(Table 2). This is related to the higher melting point of Span 60 gelator (55.2°C compared with 47.8°C of Span 40) and reflects the higher amount of energy needed to disrupt the forces of attraction between and within the Span 60 aggregates. Increasing gelator concentration also caused significant differences in gelation temperatures ($P < 0.005$), as more energy was needed to disrupt the forces of interaction among a greater number of gelator aggregates. As far as the nature of the liquid was concerned, no obvious trend could be detected between the nature of the liquid and gelation temperature. This shows that gel melting is mainly determined by the solid component of the gels. From this, one could conclude that the small increases in gelation temperatures observed upon drug incorporation (Table 2) could be due to small increases in the number of gelator aggregates formed upon cooling a drug-loaded sol state. More gelator aggregates might be formed as a greater number of gelator molecules come out of solution and self-assemble into aggregates in the presence of drug molecules, which could be competing for the solvent. The fact that different drug molecules have different solubilities in the liquid component and hence different competing ability against the gelator means that different amounts of gelator molecules will come out of solution and self-assemble into aggregates, depending on the nature of the drug. Hence the change in gelation temperature upon drug inclusion depends on the nature of the drug.

Drug loading at 10% w/w did not seem to affect the gel stability adversely, as indicated by the gelation temperatures. To investigate whether a higher drug loading was possible without affecting gel stability and to investigate the effect of drug concentration on gelation temperature, the gelation temperatures of a 20% w/w Span 60/Tween 20 gel loaded with paracetamol, aspirin and ibuprofen at 2, 4, 6, 8, 10 and 15% w/w were determined (Table 3). When two-way analysis of variance was used to explore the effects of drug nature and concentration on the gelation temperatures, statistically significant main effects of drug nature ($F(2, 96) = 19.77$; $P < 0.0005$) and of concentration ($F(7, 96) = 5.85$, $P < 0.0005$), as well as an interaction effect between the nature of drug and its concentration, were found ($F(14, 96) = 11.03$; $P < 0.0005$). Post-hoc comparisons using the Tukey HSD tests at the 0.05 significance level indicated that the effect of increasing paracetamol concentration on gelation temperature was significantly different to the effects of aspirin and of ibuprofen, while the latter two were not significantly different from each other. Increasing paracetamol concentration led to increasing gelation temperatures, while the effects of increasing aspirin and ibuprofen were less straightforward. These analyses show that incorporation of different drugs affects the gel stability in different ways depending on drug nature and that knowledge gained from the solubilisation of one drug is not transferable to other drugs.

Table 3 Effect of drug loading on gelation temperature of a 20% w/w Span 60/Tween 20 gel

Drug concn (% w/w)	Gelation temperature (°C)		
	Paracetamol	Aspirin	Ibuprofen
0	48.8 ± 0.8	48.8 ± 0.8	48.8 ± 0.8
1	47.0 ± 1.6	49.0 ± 0.7	51.8 ± 0.4
2	47.6 ± 1.1	50.4 ± 1.1	51.2 ± 1.3
4	48.0 ± 1.6	49.8 ± 1.3	52.2 ± 1.3
6	48.8 ± 0.8	49.0 ± 0.7	50.4 ± 0.5
8	49.0 ± 1.2	51.0 ± 1.2	51.0 ± 1.2
10	51.0 ± 1.4	50.6 ± 1.3	50.6 ± 0.5
15	51.8 ± 1.3	52.2 ± 0.4	47.6 ± 0.5

Data are expressed as mean ± s.d., n = 5. Sp, Span; Tw, Tween.

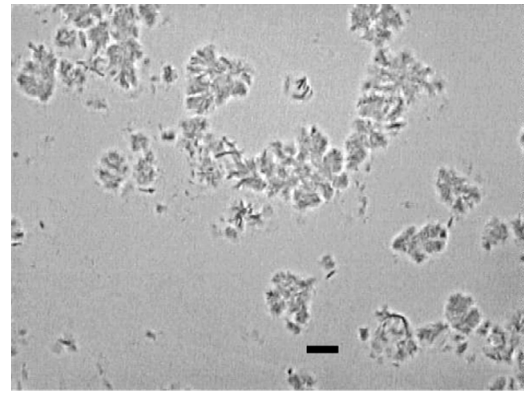

Figure 2 Light micrograph of a 20% w/w Span 60 in Tween 20 amphiphilogel, containing 20% w/w ibuprofen. Bar = 30 μm.

The results in Table 3 show a decrease in gelation temperature (and hence stability) of gels loaded with more than 10% w/w of ibuprofen. Indeed, when ibuprofen was loaded at 20% w/w, the gel state was lost due to the fact that far fewer gelator aggregates were formed, as shown in Figure 2. Insufficient interactions between the aggregates leads to the absence of a cohesive 3-dimensional gelator network to immobilise the liquid and hence loss of the gel state. The paucity of gelator aggregates at high drug loading could be due to the failure of the gelator to dissolve in the liquid at high temperatures (possibly due to competing drug solute for the same solvent) before the gelator molecules can self-assemble into aggregates at low temperature. This shows the importance of keeping drug loadings sufficiently low to maintain gel integrity.

Release of hydrophobic drugs from amphiphilogels

Following the application of topical dosage forms, the drug must be released from the carrier before it can contact the skin surface and permeate into the latter (Guy et al 1986). The in-vitro studies were conducted with PBS as the receptor phase. Over the course of the experiment, the drug diffused out of the gel into the receptor medium. At the same time, it is expected that water from the receptor medium might diffuse into the gel as a water gradient arises between the donor and receptor media; this would result in structural changes in the gel, which would affect drug release mechanisms over the course of the experiment. In our studies, the donor gels were examined microscopically at the end of the release experiments and were not found to have changed significantly. The

Table 4 Release rates of drugs from different amphiphilogels

Drug	Concn (% w/w) and state of drug in gel	Release rates (mg cm$^{-2}\sqrt{h}^{-1}$) from gel				
		10% Sp 60/Tw 40 (Gel 1)	20% Sp 60/Tw 40 (Gel 2)	20% Sp 60/Tw 80 (Gel 3)	20% Sp 60/Sp 20 (Gel 4)	20% Sp 60/Sp 80 (Gel 5)
Paracetamol	5 sol	1.52 ± 0.30	1.76 ± 0.36	1.28 ± 0.32		
	5 mix	2.01 ± 0.28	1.91 ± 0.39	1.89 ± 0.48	1.26 ± 0.04	1.07 ± 0.14
	10 sol	2.43 ± 0.50	2.54 ± 0.51	2.23 ± 0.40		
	10 mix	3.56 ± 0.68	3.71 ± 0.37	3.29 ± 1.07	1.56 ± 0.11	1.8 ± 0.08
Aspirin	5 sol	1.25 ± 0.39	0.94 ± 0.42	2.08 ± 0.39		
	5 mix	1.77 ± 0.23	1.27 ± 0.33	2.33 ± 0.71	0.77 ± 0.09	0.81 ± 0.10
	10 sol	2.34 ± 0.21	1.90 ± 0.47	2.83 ± 0.47		
	10 mix	2.51 ± 0.43	2.17 ± 0.28	3.74 ± 1.40	1.23 ± 0.07	1.26 ± 0.10
Ibuprofen	5 sol	0.21 ± 0.03	0.24 ± 0.09	0.17 ± 0.05		
	5 mix	0.21 ± 0.08	0.22 ± 0.03	0.19 ± 0.05	0.13 ± 0.03	0.13 ± 0.03
	10 sol	0.31 ± 0.06	0.33 ± 0.06	0.31 ± 0.06		
	10 mix	0.35 ± 0.10	0.37 ± 0.08	0.35 ± 0.07	0.23 ± 0.03	0.25 ± 0.07

Data are expressed as mean ± s.d., n = 3–5. sol, drug solubilised; mix, drug mixed in gel; Sp, Span; Tw, Tween

release rates of the model drugs from the different amphiphilogels were thus calculated (as the slope of the straight line obtained when the cumulative amount of drug released per unit area (mg cm^{-2}) was plotted against the square root of time ($\sqrt{h}$); Shah et al 1999) (Table 4). Kruskal–Wallis statistical tests, followed by post-hoc Nemenyi's tests were performed to determine the effects of drug concentration in donor, the method of drug incorporation (simple mixing into gel or dissolution into the sol state), the nature of the gel (hydrophilicity/hydrophobicity, nature of liquid) and gelator concentration on release rates. The following findings were made.

As expected, increasing the concentration of drug in the gel led to increased release rates as the drug diffused along the greater concentration gradient ($P < 0.05$).

The method of drug incorporation (i.e. mixing the drug in the gel or dissolving the drug in the sol phase) in the hydrophilic gels (Gels 1–3) resulted in similar release rates ($P > 0.05$). This was surprising, as the need for dissolution of the mixed drug particles in the gel before the dissolved drug molecules could diffuse through the barrier membrane was expected to reduce the rate of drug release compared with the gels where the drug was already solubilised in the gel. The results suggest that the process of drug dissolution in the hydrophilic gels was not a rate-limiting step for drug release.

When the drug was mixed in the gels, drug release rates from hydrophilic amphiphilogels (Gels 1–3) were significantly different ($P < 0.05$) to those from hydrophobic ones (Gels 4, 5). Post-hoc analysis showed that this applied for all three drugs, at both concentrations. A higher release rate occurred from hydrophilic gels (Table 4). This may be explained by the greater drug solubility in the hydrophilic gels compared with the hydrophobic ones (Table 1). Following mixing, the drug had to dissolve in the gel before it could be released into the receptor medium. Poor drug solubility in the hydrophobic gel limited the extent of drug dissolution and, consequently, the release rate. When hydrophilic gels were compared with one another, the drug release rates were not significantly different ($P > 0.05$). This is probably due to similar affinities of the hydrophilic Tweens 40 and 80 gels for the drug, which influence drug release into the aqueous receptor compartment. Drug release rates from hydrophobic gels were also not significantly different from each other ($P > 0.05$), again probably due to similar affinities of the two hydrophobic gels for the drug.

Increasing the gelator concentration (from 10 to 20% w/w) in Span 60/Tween 40 gels did not affect drug release rate rates, for all three drugs, whether they were solubilised or mixed in the gel ($P > 0.05$). A greater gelator concentration leads to an increased number of gelator aggregates and a denser solid network (Jibry et al 2004). The latter did not, however, affect drug movement through the gel as the drug was mainly dissolved in the gel's continuous phase, which made up the bulk of the gel.

Conclusions

In this paper, the application of amphiphilogels as carriers for hydrophobic drugs has been explored. Hydrophilic amphiphilogels dissolved appreciable amounts of model drugs ibuprofen, paracetamol and aspirin, but not hydrocortisone. In contrast, the hydrophobic gels were poor solvents for these drugs. Solubility of aspirin, ibuprofen and paracetamol in the hydrophilic gels and insolubility in the hydrophobic ones was reflected in their solubility in hydrophilic liquids and insolubility in the hydrophobic ones, which indicated the gels' liquid component as the solvent for drug dissolution. The low drug solubility in hydrophobic gels could be enhanced by the inclusion of co-solvents, such as propylene glycol and ethanol. However, increase in drug solubility is limited by the amount of co-solvent that can be incorporated in a gel, while maintaining the latter's integrity. Drug dissolution (at 10% w/w, below the drug's saturation solubility) in hydrophilic gels did not cause any major changes in the gel's

microstructure, or in the gelation temperatures, which indicated that at 10% w/w drug loading, the gel stability was not compromised. However, the changes in gelation temperatures upon drug loading, though small, were statistically significant and were found to depend on the natures of the drug and of the gel. Drug release rates from the amphiphilogels were influenced by drug concentration (as expected) and the hydrophilic or hydrophobic nature of the gel (which influences drug solubility). Surprisingly, the method of drug inclusion in the gel (dissolution in sol phase or simple mixing of solid drug in the gel state) did not influence drug release rates. Neither did increasing gelator concentration from 10 to 20% w/w, as the drug was dissolved in the gel's liquid component.

This study has shown the major role of the gels' liquid component when amphiphilogels (a type of organogels) are used as drug delivery vehicles for poorly water-soluble drugs. The liquid component is the site of drug dissolution, hence influences the amount of drug that can be dissolved in gels. Through its effect on drug solubility, the fluid phase influences drug release rates.

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